# Synthesis and Reactions of Heterocyclic Methyl 2-Propenoates and 2,3-Epoxypropanoates with Nucleophiles



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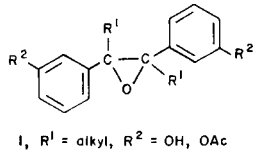
Received April 18, 1984

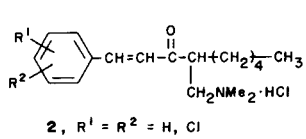
Reaction of 2-(3-,4-)pyridinecarboxaldehydes **5** with carbomethoxymethylene triphenylphosphorane afforded predominantly *E*-methyl-3-(pyridinyl)-2-propenoates **7**. Oxidation of **7a-c** with *m*-chloroperbenzoic acid gave methyl *E*-3-(1-oxidopyridinyl)-2-propenoates **8a-c** in high yield. The Darzen's reaction of **5a-c** with methyl bromoacetate yielded a mixture of stereoisomers *cis*-**9a-c** and methyl *trans*-3-(pyridinyl)-2,3-epoxypropanoates **10a-c** in a ratio of 2:1. Oxidation of *cis*-**9a-c** and *trans*-**10a-c** afforded the corresponding *cis*-**11a-c** and methyl *trans*-3-(1-oxidopyridinyl)-2,3-epoxypropanoates **12a-c** in good yield. The reaction of **11a** and **12a** with cyclic amines as piperidine gave the respective *threo*-**13** and methyl *erythro*-2-(1-piperidino)-3-hydroxy-3-(1-oxido-2-pyridino)propanoate **14**. The sodium borohydride reduction of the *N*-alkoxylcarbonyl pyridinium salts of **9c** and **10c** afforded the corresponding *N*-alkoxycarbonyl-1,2-dihydropyridyl derivatives **15** and **16**. A number of selected compounds (**7a-c, 9a-c, 10a, 10c, 11a-c** and **12a, 12c**) were found to be inactive in the P388 Lymphocytic screen. Compounds **9-12** did not react with the model nucleophile ethanethiol in phosphate buffer at 37°.

*J. Heterocyclic Chem.*, **22**, 65 (1985).

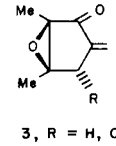
There has recently been a considerable degree of pharmacological interest in 3,3[1]-diacetoxy-$\alpha,\beta$-dialkylstilbene oxides **1** [1], Mannich bases **2** [2], methenomycins **3** [3] and arylsulfonylhydrazones of 2-formylpyridine *N*-oxide **4** [4] as antineoplastic agents. In an earlier report, we described the synthesis of 1-[1-oxido-2-(3-,4-)pyridinyl]-2-methyloxiranes and their reaction with sulfur, oxygen and nitrogen nucleophiles [5,6]. It was therefore of interest to extend this study to include activated heterocyclic $\alpha,\beta$-unsaturated esters and oxiranes, which may react with cellular thiols, for evaluation as antitumor agents. We now describe the synthesis of some pyridinyl methyl 2-propenoates and 2,3-epoxypropanoates and their reaction with model nucleophiles.



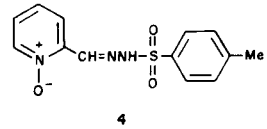
1, $R^1$ = alkyl, $R^2$ = OH, OAc



2, $R^1 = R^2$ = H, Cl



3, R = H, COOH



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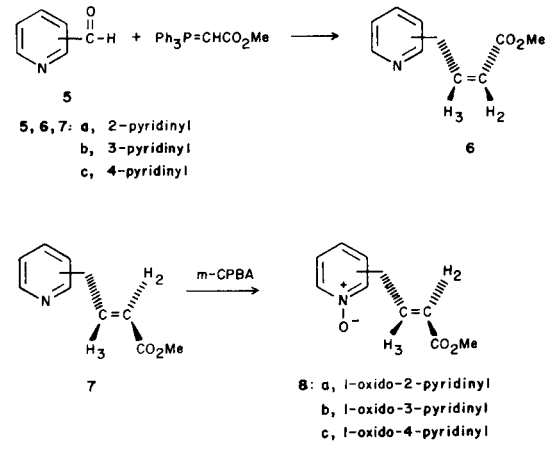
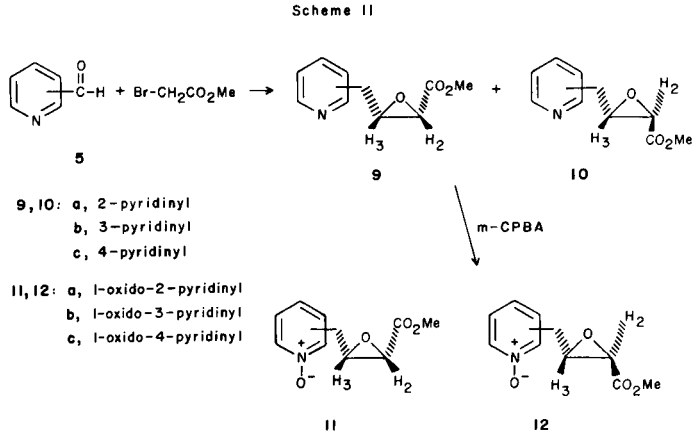
Reaction of 2-pyridinecarboxaldehyde (**5a**) with the Wittig reagent carbomethoxymethylene triphenylphosphorane afforded a 10:90 mixture (88%) of stereoisomers *Z*-**6a** and methyl *E*-3-(2-pyridinyl)-2-propenoate (**7a**) which were separated by preparative silica gel tlc (Scheme I). The ratio of **6a:7a** was determined ($^1$H nmr) by integration of the $H_2$ and $H_3$ vicinal protons which appeared at $\delta$ 6.2 and 7.03 (**6a**) as a doublet ($J_{2,3}$ = 12.5 Hz) and at $\delta$ 6.93 and 7.8 (**7a**) as a doublet ($J_{2,3}$ = 16 Hz) respectively. Similar reactions of 3-pyridinecarboxaldehyde (**5b**) and 4-pyridinecarboxaldehyde (**5c**) yielded predominantly **7b** (90%) and **7c** (92%). Oxidation of methyl *E*-3-(2-pyridinyl)-2-propenoate (**7a**) with excess *m*-chloroperbenzoic acid in methylene chloride afforded *E*-**8a** in 84% yield. Similar oxidations of olefins **7b** and **7c** gave *E*-**8b** (92%) and *E*-**8c** (75%) respectively. It is interesting to note that oxidation with *m*-chloroperbenzoic acid afforded *N*-oxides **8** rather than methyl *E*-3-[1-oxido-2-(3-,4-)pyridinyl]-2,3-epoxypropanoates **12** [6]. Attempts to prepare **12** by oxidation of **7a-c** using sodium hydrogen peroxide or sodium *t*-butylhydroperoxide were unsuccessful.

Scheme I



The Darzen's reaction of 2-pyridinecarboxaldehyde (**5a**) with methyl bromoacetate in the presence of potassium *t*-butoxide in *t*-butanol afforded a 2:1 mixture (68%) of stereoisomers *cis*-**9a** and methyl *trans*-3-(2-pyridinyl)-2,3-epoxypropanoate (**10a**) along with the corresponding *trans* esterified ($CO_2$-*t*-Bu) products (Scheme II). The stereoisomers **9a** and **10a** were separated from the *trans* esterified products by preparative hplc. The ratio of stereoisomers **9a** and **10a** was calculated from the integrals of the $H_3$ protons which appeared at $\delta$ 4.43 and 4.3 respectively. Stereoisomers **9a** and **10a** were separated by fractional crystallization from hexane-ether. A similar reaction of **5b** and **5c** with methyl bromoacetate afforded a mixture of stereoisomers **9b** and **10b** (41%) and **9c** and **10c** (34%) respectively. The ratio of **9b:10b**, after hplc separation as described above, as determined by integration of the $H_3$ protons at $\delta$ 4.35 and 4.2 respectively was also 2:1. Repeated attempts to separate **9b** and **10b** by fractional crystallization or column chromatography were unsuccessful although **9c** and **10c** could be separated by fractional crystallization from ether. Oxidation of the methyl-2,3-epoxypropanoates **9** and **10** gave the respective *cis*-**11** and *trans*-**12** *N*-oxide analogs which were routinely purified by elution from a neutral aluminum oxide column to remove excess *m*-chloroperbenzoic and *m*-chlorobenzoic acid.

Scheme II




The stereospecific reaction of *cis*-**11a** and methyl *trans*-3-(1-oxido-2-pyridinyl)-2,3-epoxypropanoate (**12a**) with nucleo-

Table I

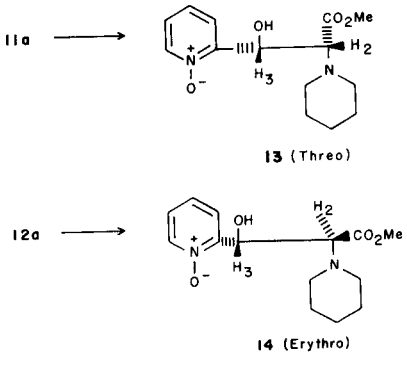
Physical Constants of Heterocyclic Methyl 2-Propenoates **6-8** and Methyl 2,3-Epoxypropanoates **9-12, 15-16**

| Compound No. | C-3 Substitutent | Stereo-isomer | Coupling constant $J_{2,3}$ (Hz) | Method of Prepa-ration | Yield % | Mp, °C | Formula | Analysis % Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | 2-pyridinyl | *Z* | 12.5 | A | 8.8 | oil | $C_9H_9NO_2$ | 66.24 | 5.56 | 8.58 | 66.14 | 5.50 | 8.48 |
| **7a** | 2-pyridinyl | *E* | 16 | A | 79.2 | oil | $C_9H_9NO_2$ | 66.24 | 5.56 | 8.58 | 66.09 | 5.54 | 8.50 |
| **7b** | 3-pyridinyl | *E* | 16 | A | 90 | 40-41 | $C_9H_9NO_9$ | 66.24 | 5.56 | 8.58 | 66.11 | 5.48 | 8.52 |
| **7c** | 4-pyridinyl | *E* | 16 | A | 92 | 72 [a] | $C_9H_9NO_2$ | 66.24 | 5.56 | 8.58 | 66.18 | 5.48 | 8.46 |
| **8a** | 1-oxido-2-pyridinyl | *E* | 16 | B | 83.8 | 123-124 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.26 | 5.04 | 7.86 |
| **8b** | 1-oxido-3-pyridinyl | *E* | 16 | B | 91.2 | 150 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.06 | 5.09 | 7.74 |
| **8c** | 1-oxido-4-pyridinyl | *E* | 16 | B | 75.9 | 146 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.02 | 5.06 | 7.79 |
| **9a** | 2-pyridinyl | *cis* | 4.5 | C | 45.3 | 73 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.23 | 5.16 | 7.73 |
| **10a** | 2-pyridinyl | *trans* | 1.5 | C | 22.7 | 68 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.25 | 5.13 | 7.78 |
| **9b** | 3-pyridinyl | *cis* | 4.5 | C | 27.3 [b] | oil | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 59.96 | 5.09 | 7.86 |
| **10b** | 3-pyridinyl | *trans* | 1.5 | C | 13.7 [b] | oil | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 59.96 | 5.09 | 7.86 |
| **9c** | 4-pyridinyl | *cis* | 4.5 | C | 22.33 | 78 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.07 | 4.99 | 8.07 |
| **10c** | 4-pyridinyl | *trans* | 1.5 | C | 11.17 | 80 | $C_9H_9NO_3$ | 60.33 | 5.03 | 7.82 | 60.58 | 5.21 | 7.47 |
| **11a** | 1-oxido-2-pyridinyl | *cis* | 4.5 | D | 78.7 | 116 | $C_9H_9NO_4$ | 55.38 | 4.62 | 7.18 | 55.25 | 4.66 | 7.13 |
| **12a** | 1-oxido-2-pyridinyl | *trans* | 1.5 | D | 67.4 | 117 | $C_9H_9NO_4$ | 55.38 | 4.62 | 7.18 | 55.50 | 4.69 | 7.07 |
| **11b** and **12b** | 1-oxido-3-pyridinyl | *cis-trans* mixture | 4.5<br>1.5 | D<br>E | 63.3 [c] | 131 | $C_9H_9NO_4$ | 55.38 | 4.62 | 7.18 | 55.17 | 4.76 | 7.20 |
| **11c** | 1-oxido-4-pyridinyl | *cis* | 4.5 | D | 78.8 | 139-140 | $C_9H_9NO_4$ | 55.38 | 4.62 | 7.18 | 55.24 | 4.61 | 7.32 |
| **12c** | 1-oxido-4-pyridinyl | *trans* | 1.5 | D | 30 | 122 | $C_9H_9NO_4$ | 55.38 | 4.62 | 7.18 | 55.17 | 4.61 | 6.93 |
| **15a** | 4-(1-methoxycarbonyl-1,2-dihydropyridyl) | *cis* | 4.5 [d] | E | 75 | 60-61 | $C_{11}H_{13}NO_5$ | 55.23 | 5.43 | 5.85 | 55.61 | 5.57 | 5.77 |
| **15b** | 4-(1-phenoxycarbonyl-1,2-dihydropyridyl) | *cis* | 4.5 [e] | E | 63 | 125 | $C_{16}H_{15}NO_5$ | 63.78 | 4.98 | 4.65 | 63.81 | 5.07 | 4.73 |
| **16a** | 4-(1-methoxycarbonyl-1,2-dihydropyridyl) | *trans* | 1.5 | E | 50 | 60 | $C_{11}H_{13}NO_5$ | 55.23 | 5.43 | 5.85 | 54.97 | 5.25 | 5.60 |
| **16b** | 4-(1-phenoxycarbonyl-1,2-dihydropyridyl) | *cis* | 1.5 | E | 59.8 | 120 | $C_{16}H_{15}NO_5$ | 63.78 | 4.98 | 4.65 | 63.43 | 5.05 | 4.64 |

[a] Lit [13] mp 74-77°. [b] These yields were determined from integration of the $H_3$ protons in **9b** and **10b**. [c] A pure sample of **11b** (25%) was obtained by trituration and crystallization from ether. [d] Partially overlapped by the two methoxyl resonances at $\delta$ 3.8 and 3.84. [e] Partially overlapped by the methoxyl resonance at $\delta$ 3.76.

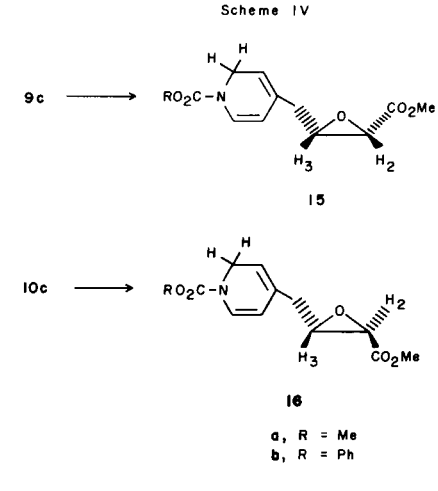
philes as amines afforded the respective *threo* (2*R*,3*R*/2*S*,3*S*) and *erythro* (2*R*,3*S*/2*S*,3*R*) β-aminoalcohols diastereoisomers [6,7] (Scheme III). Thus reaction of *cis*-**11a** with piperidine at 50° gave methyl *threo*-2-(1-piperidino)-3-hydroxy-3-(1-oxido-2-pyridinyl)propanoate (**13**, 90%) whereas reaction with *trans*-**12a** gave rise to *erythro*-**14** (85%). The amination reaction was regiospecific since no product arising from attack by piperidine at C-3 of **11a** or **12a** was detected [6].

Scheme III

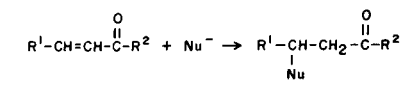



Reaction of *cis*-**9c** with methyl chloroformate and sodium borohydride in methanol [8] at −65° afforded methyl *cis*-3-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)]-2,3-epoxypropanoate (**15a**, 75%) (Scheme IV). Similar reactions of **10c** with methyl chloroformate and **9c** and **10c** with phenyl chloroformate afforded **16a** (50%), **15b** (63%) and **16b** (60%) respectively.

Scheme IV




The antineoplastic activity of compounds containing the α,β-unsaturated structural moiety has been attributed to their reaction with cellular nucleophiles [9-11]. Nucleophilic attack by anions on α,β-unsaturated carbonyl compounds is known as the Michael reaction and has been studied extensively primarily due to its synthetic usefulness




[2]. It was expected that oxiranes having electron attracting methoxycarbonyl and pyridinyl or 1-oxidopyridinyl substituents would be highly activated toward attack by cellular nucleophiles. On this basis, activated oxiranes may be useful antineoplastic agents. Although the activated *cis*-**11a** and **12a** reacted readily with piperidine to yield *threo*-**13** and *erythro*-**14** respectively, the methyl *E*-2-propenoates **8** and the 2,3-epoxypropanoates **10-12** were all inactive in the P388 Lymphocytic Leukemia screen. This lack of tumor inhibiting activity prompted us to investigate the reaction of selected compounds **9-12** with the model thiol ethanethiol. No reaction was observed when a solution of **9a** in acetonitrile-aqueous phosphate buffered to *p*H 7 was treated with ethanethiol at 37° for 24 hours. In a related experiment, it was also shown that no reaction occured when a solution of **9a** and ethanethiol containing a catalytic quantity of piperidine in benzene was heated at reflux for 24 hours. Similar results were obtained for **10a**, **11a** and **12a**. The lack of tumor inhibiting activity for **8** and **10-12** is likely due to their inability to act as biological alkylating agents.

## EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide unless otherwise indicated) were taken on a Perkin-Elmer 267 or Nicolet 5DX FT spectrometer. Nuclear magnetic resonance spectra were determined for solutions in deuteriochloroform unless otherwise stated with TMS as internal standard using a Brucker AM-300 or Varian EM-360/A spectrometer. Preparative hplc was performed using a Water's Prep LC/System 500A chromatograph using Prep Pak 500 silica cartridges. All the products described gave rise to a single spot on tlc using three different solvent systems of low, medium and high polarity. Carbomethoxymethylene triphenylphosphorane was prepared by the literature method [12].

Methyl *Z*-3-(2-Pyridinyl)-2-propenoate (**6a**) and Methyl *E*-3-(2-Pyridinyl)-2-propenoate (**7a**). Procedure A.

A solution of 2-pyridinecarboxaldehyde (**5a**, 4.17 g, 39 mmoles) in 10 ml of methylene chloride was added dropwise to a solution of carbomethoxymethylene triphenylphosphorane (12 g, 36 mmoles) in 30 ml of methylene chloride with stirring. The reaction mixture was heated at reflux for 4 hours and then about half of the methylene chloride was removed by distillation. Petroleum ether (bp 40-60°, 100 ml) was added to the residual solution which was then cooled to −5° and the precipitated triphenylphosphine oxide was removed by filtration. Removal of the solvent *in vacuo* afforded a mixture of **6a** and **7a** (5.56 g, 88%) as a yellow oil in a ratio of 10:90. The stereoisomers **6a** and **7a** were separated on 20 × 20 cm silica gel plates, 0.75 mm in thickness, using ether as the development solvent. Extraction with methanol of the lower band having $R_f$ 0.6 gave **6a** and the higher band having $R_f$ 0.75 gave **7a**. Stereoisomer **6a** had $^1$H nmr: δ 3.78 (s, 3H, OMe), 6.2 (d, $J_{2,3}$ = 12.5 Hz, 1H, $H_2$), 7.03 (d, $J_{2,3}$ = 12.5 Hz, 1H, $H_3$), 7.32 (d, $J_{4,5}$ = 8 Hz, of d, $J_{5,6}$ = 5 Hz, 1H, pyridinyl $H_5$), 7.8 (m, 2H, pyridinyl $H_3$, $H_4$), 8.7 (d, $J_{5,6}$ = 5 Hz, 1H, pyridinyl $H_6$). Stereoisomer **7a** had $^1$H nmr: δ 3.8 (s, 3H, OMe), 6.93 (d, $J_{2,3}$ = 16 Hz, 1H, $H_2$), 7.1-7.8 (m, 3H, pyridinyl $H_3$, $H_4$, $H_5$), 7.8 (d, $J_{2,3}$ = 16 Hz, 2H,

$H_3$), 8.7 (d, $J_{5,6}$ = 5 Hz, 1H, pyridinyl $H_6$).

Similar reactions of **5b** and **5c** yielded predominantly **7b** (90%) and **7c** (92%) respectively.

Methyl *trans*-3-(1-Oxido-2-pyridinyl)-2-propenoate (**8a**). Procedure B.

A solution of **7a** (1.63 g, 10 mmoles) in 10 ml of methylene chloride was added dropwise to a solution of 85% *m*-chloroperbenzoic acid (2.22 g, 11 mmoles) in 60 ml of methylene chloride at 0° with stirring. This solution was stirred for 30 minutes at 0° and then heated at reflux for 24 hours. The reaction mixture was cooled to 25° and filtered to remove any solids present. Removal of the solvent *in vacuo* and elution of the product from a neutral aluminum oxide column (2.5 × 40 cm) using 2% methanol in chloroform as eluant gave **8a** (1.5 g, 84%) as a white solid, mp 123-124°; ir 1720 (CO), 1640 (C=C), 1240 $cm^{-1}$ (*N*-oxide); $^1H$ nmr: $\delta$ 3.88 (s, 3H, OMe), 7.08 (d, $J_{2,3}$ = 16 Hz, 1H, $H_2$), 7.2-7.75 (m, 3H, 1-oxido-2-pyridinyl $H_3$, $H_4$, $H_5$), 8.2 (d, $J_{2,3}$ = 16 Hz, 1H, $H_3$), 8.38 (m, 1H, 1-oxido-2-pyridinyl $H_6$).

A similar oxidation of **7b** and purification of the product by elution from a neutral alumina column using 3% methanol in chloroform as eluant afforded **8b** as a white solid (91%). The 1-oxido-4-pyridinyl analog **8c** (76%) was similarly prepared and purified.

Methyl *cis*-3-(2-Pyridinyl)-2,3-epoxypropanoate (**9a**) and Methyl *trans*-3-(2-Pyridinyl)-2,3-epoxypropanoate (**10a**). Procedure C.

A solution of potassium *t*-butoxide, prepared by dissolution of potassium (4.5 g) in dry *t*-butyl alcohol (100 ml), was added dropwise during 2 hours to a mixture of **5a** (12.3 g, 115 mmoles) and methyl bromoacetate (17.57 g, 115 mmoles) with stirring and cooling under an atmosphere of nitrogen at such a rate that the reaction temperature did not exceed 15°. The reaction was allowed to proceed for a further 1 hour at 15° at which time tlc indicated the absence of **5a**. The *t*-butyl alcohol was removed *in vacuo* and 100 ml water was added to the residue. Extraction with methylene chloride (4 × 50 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gave a solid (21 g) which was eluted from a 5.0 × 45 cm silica gel column using ether as eluant to afford a mixture (20 g) of **9a** and **10a** and the *trans* esterified (*t*-Bu) product in a ratio of 70:30 as indicated by $^1H$ nmr. Preparative hplc using 5% hexane in ether as eluant at a flow rate of 250 ml $min^{-1}$ gave the *trans* esterified product (6 g) in the 700-1300 ml fraction and a mixture of **9a** and **10a** (14 g, 68%) in the 1300-2100 ml fraction. The stereoisomers **9a** and **10a** were separated by fractional crystallization from 20% hexane in ether. The less soluble *cis*-**9a** was obtained in the first crop of crystals. Stereoisomer **9a** had ir: 1750 (CO), 1220 $cm^{-1}$ (oxirane); $^1H$ nmr: $\delta$ 3.65 (s, 3H, OMe), 3.95 (d, $J_{2,3}$ = 4.5 Hz, 1H, $H_2$), 4.43 (d, $J_{2,3}$ = 4.5 Hz, 1H, $H_3$), 7.12-7.95 (m, 3H, pyridinyl $H_3$, $H_4$, $H_5$), 8.6 (d, $J_{5,6}$ = 5 Hz, 1H, pyridinyl $H_6$). Stereoisomer **10a** had ir: 1760 (CO), 1210 $cm^{-1}$ (oxirane); $^1H$ nmr: $\delta$ 3.78 (d, $J_{2,3}$ = 1.5 Hz, 1H, $H_2$), 3.88 (s, 3H, OMe), 4.3 (d, $J_{2,3}$ = 1.5 Hz, 1H, $H_3$), 7.32 (m, 2H, pyridinyl $H_3$, $H_5$), 7.75 (d, $J_{4,5}$ = 8 Hz of d, $J_{3,4}$ = 6 Hz, 1H, pyridinyl $H_4$), 8.68 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 2 Hz, 1H, pyridinyl $H_6$).

A similar reaction of **5b** and separation of the reaction mixture by preparative hplc using 10% hexane in ether as eluant gave a mixture of **9b** and **10b** (11 g, 41%) and *trans* esterified product (6 g). The ratio of **9b:10b**, after hplc separation as determined by integration of $H_3$ at $\delta$ 4.35 and $\delta$ 4.2 respectively was 2:1. Repeated attempts to separate **9b** and **10b** by column chromatography or fractional crystallization were unsuccessful.

Reaction of **5c** with methyl bromoacetate as described above gave a mixture of **9c** and **10c** and the *trans* esterified product in a ratio of 55:45 as calculated from the $^1H$ nmr integrals of the OMe and *t*-Bu resonances. Separation by preparative hplc using 5% hexane in ether as eluant gave a mixture of **9c** and **10c** (9 g, 34%). Fractional crystallization from ether gave **9c** (3 g), **10c** (1.5 g) and a mixture of **9c** and **10c** (4 g) containing predominantly **10c**. The less soluble **9c** was obtained in the first crop of crystals.

Methyl *cis*-3-(1-Oxido-2-pyridinyl)-2,3-epoxypropanoate (**11a**). Procedure D.

A solution of *m*-chloroperbenzoic acid (1.11 g of 85%, 5.5 mmoles) in 30 ml of methylene chloride was added dropwise to a solution of **9a** (0.895 g, 5 mmoles) in methylene chloride (20 ml) at 0° with stirring. The reaction mixture was then stirred at 0° for 30 minutes, 1 hour at 25° followed by heating at reflux for 24 hours. The volume was reduced by 50% and the reaction mixture was cooled and filtered. Removal of the solvent from the filtrate gave a residue which was purified by elution from a neutral aluminum oxide column using 3% methanol in chloroform to afford **11a** (0.768 g, 79%); ir 1755 (CO), 1255 (*N*-oxide), 1220 $cm^{-1}$ (oxirane); $^1H$ nmr: $\delta$ 3.66 (s, 3H, OMe), 4.1 (d, $J_{2,3}$ = 4.5 Hz, 1H, $H_2$), 4.73 (d, $J_{2,3}$ = 4.5 Hz, 1H, $H_3$), 7.2-7.8 (m, 3H, 1-oxido-2-pyridinyl $H_3$, $H_4$, $H_5$), 8.26 (d, $J_{5,6}$ = 5 Hz of d, $J_{4,6}$ = 2 Hz, 1H, 1-oxido-2-pyridinyl $H_6$).

Oxidation of **10a** as described above gave **12a** (67%); $^1H$ nmr: $\delta$ 3.53 (d, $J_{2,3}$ = 1.5 Hz, 1H, $H_2$), 3.87 (s, 3H, OMe), 4.84 (d, $J_{2,3}$ = 1.5 Hz, 1H, $H_3$), 7.4 (m, 3H, 1-oxido-2-pyridinyl $H_3$, $H_4$, $H_5$), 8.38 (m, 1H, 1-oxido-2-pyridinyl $H_6$).

Oxidation of a mixture of **9b** and **10b** followed by column chromatography as described above gave a mixture of **11b** and **12b** (63%). Trituration of **11b** and **12b** (1.27 g) with 20 ml of ether and storage at −5° for 72 hours afforded **11b** (0.768 g, 25%). A pure sample of **12b** could not be obtained. Similar oxidations of **9c** and **10c** followed by column purification as described above gave **11c** (79%) and **12c** (30%) respectively.

Methyl *threo*-2-(1-Piperidino)-3-hydroxy-3-(1-oxido-2-pyridinyl)propanoate (**13**).

Reaction of **11a** (0.18 g, 0.92 mmole) with piperidine (0.234 g, 2.76 mmoles) at 50° for 2 hours and removal of excess piperidine yielded a semi-solid. Recrystallization from acetone afforded **13** (0.23 g, 90%), mp 158°; ir: 1730 $cm^{-1}$ (CO); $^1H$ nmr: $\delta$ 1.6 (m, 6H, piperidino $H_3$, $H_4$, $H_5$), 2.84 (m, 4H, piperidino $H_2$, $H_6$), 3.75 (s, 3H, OMe), 3.92 (d, $J_{2,3}$ = 8 Hz, 1H, $H_2$), 5.4 (m, 2H, $H_3$, OH, hydroxyl exchanges with deuterium oxide), 7.45 (m, 3H, 1-oxido-2-pyridinyl $H_3$, $H_4$, $H_5$), 8.22 (m, 1H, 1-oxido-2-pyridinyl $H_6$).

*Anal.* Calcd. for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14; N, 10.00. Found: C, 59.80; H, 7.17; N, 9.87.

Methyl *erythro*-2-(1-Piperidino)-3-hydroxy-3-(1-oxido-2-pyridinyl)propanoate (**14**).

Reaction of **12a** (0.18 g, 0.92 mmole) with piperidine (0.234 g, 2.76 mmoles) at 50° for 2 hours and removal of the excess piperidine gave a semi-solid residue. Recrystallization from acetone yielded **14** (0.22 g, 85%), mp 147°; ir 1745 $cm^{-1}$ (CO); $^1H$ nmr: $\delta$ 1.4 (m, 6H, piperidino $H_3$, $H_4$, $H_5$), 2.55 (m, 4H, piperidino $H_2$, $H_6$), 3.8 (s, 3H, OMe), 4.13 (d, $J_{2,3}$ = 9 Hz, 1H, $H_2$), 5.3 (d, $J_{2,3}$ = 9 Hz, 1H, $H_3$), 6.32 (broad s, 1H, OH, exchanges with deuterium oxide), 7.35 (m, 3H, 1-oxido-2-pyridinyl $H_3$, $H_4$, $H_5$), 8.25 (m, 1H, 1-oxido-2-pyridinyl $H_6$).

*Anal.* Calcd. for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14; N, 10.00. Found: C, 60.20; H, 7.25; N, 10.18.

Methyl *cis*-3-[4-(1-Methoxycarbonyl-1,2-dihydropyridyl)]-2,3-epoxypropanoate (**15a**). Procedure E.

A solution of methyl chloroformate (0.189 g, 2 mmoles) in 2 ml of dry ether was added dropwise to **9c** (0.268 g, 1.5 mmoles) and sodium borohydride (0.074 g, 2 mmoles) in 2 ml of absolute methanol precooled to −65° with stirring. The rate of addition was controlled so that the temperature of the reaction mixture did not exceed −65°. The reaction was allowed to proceed at −65° with stirring for 2 hours and then poured into ice-water. Sufficient water was added to dissolve the inorganic salts and the separated solid was filtered. Recrystallization from ether-hexane gave **15a** (0.27 g, 75%), mp 60-61°; ir: 1715 and 1765 $cm^{-1}$ (CO); $^1H$ nmr: $\delta$ 3.66-3.9 (m, 8H, $H_2$, $H_3$, OMe), 4.4 (d, $J_{gem}$ = 4 Hz, 2H, 1,2-dihydropyridyl $H_2$), 5.18 (d, $J_{4,5}$ = 8 Hz, 1H, 1,2-dihydropyridyl $H_5$), 5.68 (m, 1H, 1,2-dihydropyridyl $H_3$), 6.78 (d, $J_{5,6}$ = 8 Hz, 1H, 1,2-dihydropyridyl $H_6$).

A similar reaction of **9c** and **10c** with phenyl chloroformate and recrystallization of the product from chloroform-ether gave **15b** (63%) and **16b** (60%) respectively.

Reaction of **10c** with methyl chloroformate and sodium borohydride as described above followed by recrystallization of the product from ether-hexane gave **16a** (50%), mp 60°.

Treatment of Methyl 2,3-Epoxypropanoates **9-12** with Ethanethiol. In Phosphate Buffer at *p*H 7.4.

Solutions of ethanethiol (22.3 mg, 0.286 mmole) in 1 ml of distilled water, monobasic sodium phosphate monohydrate (15.8 mg) in 1.7 ml of water, dibasic sodium phosphate heptahydrate (59 mg) in 3.3 ml of water and 3.5 ml of acetonitrile (to effect dissolution of the methyl-2,3-epoxypropanoates **9-12**) were added to the selected methyl 2,3-epoxypropanoate **9-12** (0.094 mmole). The *p*H of the resultant solution was 7.4. This solution was maintained at 37 ±0.5° for 24 hours. Examination of this solution using micro silica gel G or neutral aluminum oxide plates did not show the presence of any product other than the selected methyl 2,3-epoxypropanoate **9-12** and ethanethiol. Removal of the water *in vacuo* gave a gummy residue for which the $^1$H nmr spectrum and the chromatogram (as above) showed the presence of only the selected methyl 2,3-epoxypropanoate **9-12** and ethanethiol.

In Benzene at Reflux.

A solution of **9a** (0.136 mmole), ethanethiol (10.6 mg, 0.136 mmole) and one drop of piperidine in 10 ml of benzene was heated under reflux for 24 hours. Removal of benzene and piperidine *in vacuo* gave a gummy residue for which the $^1$H nmr spectrum and tlc chromatogram (as above) showed the presence of only **9a** and ethanethiol.

A similar reaction of **10a** with ethanethiol did not show the presence of any product ($^1$H nmr, tlc) other than **10a** and ethanethiol.

Antitumor Screening.

The screening was performed by the Drug Evaluation Branch of the NCI using the P388 Lymphocytic Leukemia screen. A once daily dose (6.25-400 mg/kg range) in saline was administered by ip injection for a total of nine doses. The % T/C (% T/C = treated/control × 100) was calculated for the different doses administered. Compounds **8**, **9**, **10**, **11** and **12** were considered to be inactive since the % T/C remained close to 100 for all compounds tested.

Acknowledgement.

We are grateful to the Medical Research Council of Canada (Grant MT-4888) for financial support of this work and to the Alberta Hertiage Foundation for Medical Research for a Fellowship to one of us (K.C.A.).

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