bridge carbon (i.e., 15–20°; see Table I). Hence these observations are quite consistent with Gorenstein's[15] interpretation of the "gauche" NMR effect in terms of bond angle distortions.

As one would expect, a pe substituent on one bridge carbon has little effect on the chemical shift of the second bridge carbon across the ring. However, a pa group does produce a ca. 1.0 ppm upfield shift, and this appears quite reasonable for the expected δ effect.[16]

Substituent Carbons. The difference in chemical shifts at the α-carbon of pe and pa ethyl substituents is about 8 ppm. A similar value is observed for the isopropyl group. This is best interpreted as an upfield shift of the pe CH_2CH_3 carbon due to two γ effects[16] from the "ortho" positions on the adjacent aromatic rings. The net upfield shift is a little smaller than that observed for a pe methyl in solid-state *trans*-9,10-dimethyl-9,10-dihydroanthracene (13.2 ppm).[2] This may be due to the difference in the relevant dihedral angles for the two systems.

Experimental Section

Proton NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer with tetramethylsilane as reference and $CDCl_3$ as solvent. NOE experiments were conducted on deoxygenated samples. Carbon NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer with $CDCl_3$ as solvent and lock and internal tetramethylsilane as reference. Variable-temperature experiments were carried out on both instruments, but $\Delta G^{\ddagger}$ calculations were performed with the proton data with temperature measurements made with a methanol temperature calibration sample.

Calculations were performed with the Allinger MM2 molecular mechanics program.[13] Aromatic carbons were defined in terms of the optimum C=C bond length (1.397 Å) and the C=C force constant (8.067 mdyn/Å).

We have recently reported the preparation of 7-alkyl- and 7,12-dialkyl-7,12-dihydropleiadenes.[7] This was accomplished by reaction of *n*-butyllithium (2.1 mmol) with the DHP in THF at 0 °C for 30 min followed by the addition of excess alkyl halide.

7-Methylene-12-isopropyl-7,12-dihydropleiadene (4). *n*-Butyllithium (2.09 mmol) in hexane was added to *trans*-7-methyl-12-isopropyl-7,12-dihydropleiadene (150 mg, 0.52 mmol) in dry cyclohexane (7 mol) containing TMEDA (0.32 mL, 2.09 mmol). The mixture was heated at reflux for 23 h, cooled, and poured into water. The product was isolated by ether extraction, and *GLPC* indicated ca. 40% 4 and 60% starting material. Pure 4, mp 108–109 °C, was isolated by chromatography on 230–400 mesh silica gel (Merck) with petroleum ether/carbon tetrachloride/ethyl acetate (98:1:1): NMR ($CDCl_3$) δ 0.72 (6 H, d; expansion reveals 2 d separated by 1.2 Hz), 2.8 (1 H, m), 3.45 (1 H, d), 5.5 (2 H, AB q, vinyl), 7.4 (10 H, m, aryl); mass spectrum, *m/e* 284 (M^+).

Anal. Calcd for $C_{22}H_{23}$:[17] C, 92.96; H, 7.04. Found: C, 92.57; H, 6.96.

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Registry No. EtDHP, 15529-85-8; *i*-PrDHP, 14529-25-0; *cis*-Et_2DHP, 100021-40-7; *trans*-Et_2DHP, 100021-41-8; *cis*-MeEtDHP, 100021-36-1; *trans*-MeEtDHP, 100021-37-2; *trans*-Me-*i*-PrDHP, 100021-39-4; *trans*-Et-*i*-PrDHP, 100021-43-0; *trans*-*i*-Pr_2DHP, 100021-44-1; methylene-*i*-PrDHP, 102683-33-0; DHP, 4580-70-5; MeDHP, 7119-78-0; *trans*-Me_2DHP, 17430-42-1.

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Hydrolysis and Rearrangement of O^6-Substituted Guanosine Products Resulting from Reaction of Guanosine with Styrene Oxide

Robert C. Moschel,* Kari Hemminki, and Anthony Dipple

Laboratory of Chemical and Physical Carcinogenesis, LBI-Basic Research Program, NCI-Frederick Cancer Research Facility, Frederick, Maryland 21701

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The preparation and properties of four diastereomeric O^6-substituted guanosines which result from reaction between guanosine and styrene oxide are described. While the two diastereomers for O^6-(2-hydroxy-2-phenylethyl)guanosine (**1bI** and **1bII**) are reasonably stable under mildly acidic aqueous conditions, the two diastereomers for O^6-(2-hydroxy-1-phenylethyl)guanosine (**1aI** and **1aII**) undergo acid-catalyzed hydrolysis to cleave the O^6-aralkyl ether linkage. In neutral and alkaline aqueous conditions **1aI** and **1bI** or **1aII** and **1bII** interconvert. An equilibrium is established between the isomers such that at equilibrium the ratio of **1bI**/**1aI** or **1bII**/**1aII** is 2.0. The rate of equilibration is first-order in hydroxide ion although the equilibrium constant is independent of pH over the range 7.5–12. The configuration about the α-carbon of the substituted phenylethyl side chain is retained during isomer equilibration.

Styrene oxide is a mammalian metabolite of styrene, a widely produced monomer used in the production of plastics and rubber products. The oxide is mutagenic[1,2] and carcinogenic,[3] and it has been shown to react at the 7-position of DNA guanine residues.[2,4,5] In later investigations of its reactions with guanosine under totally aqueous conditions, products derived from reaction at the exocyclic N^2- and O^6-position were detected in addition

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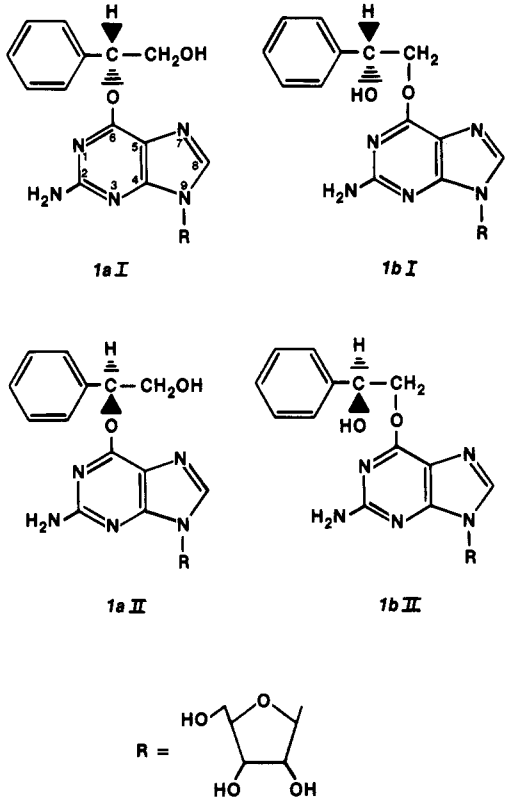
0022-3263/86/1951-2952$01.50/0

to 7-substituted products.[6] However, the extents of reaction of these exocyclic sites with either the α- or β-carbon of the oxide could not be determined accurately. In order to make these determinations, we sought to prepare markers for all the anticipated products arising from reaction between the racemic oxide and guanosine, i.e., two diastereomers for each of 7-(2-hydroxy-1-phenylethyl)-guanosine, 7-(2-hydroxy-2-phenylethyl)guanosine, N^2-(2-hydroxy-1-phenylethyl)guanosine, O^6-(2-hydroxy-1-phenylethyl)guanosine (**1aI** and **1aII**), and O^6-(2-hydroxy-2-phenylethyl)guanosine (**1bI** and **1bII**). Our studies of the stability of the latter four O⁶-substituted diastereomers revealed both expected and unexpected results. Details of their preparation and properties are described herein.



Results and Discussion

From synthetic reactions between the sodium alkoxides of (±)-1-phenyl-1,2-ethanediol ((±)-styrene glycol) and 2-amino-6-chloropurine riboside, the mixture of diastereomers for O^6-(2-hydroxy-1-phenylethyl)guanosine (**1aI** and **1aII**) and O^6-(2-hydroxy-2-phenylethyl)guanosine (**1bI** and **1bII**) was resolved by a combination of Sephadex LH-20 and high-performance liquid chromatography (HPLC). The order of elution of these isomers from an analytical HPLC column is **1aI**, **1bI**, **1aII**, and **1bII**, and they were formed in a ratio of 1:2:1:2, respectively (Experimental Section). The UV absorption spectrum and the molecular weight as determined by negative ion fast atom bombardment mass spectrometry were the same for these four derivatives, and they were consistent with their assignments as O⁶-substituted guanosines.[7-9] The ^1H NMR spectra for the related **1aI** and **1aII** and for **1bI** and **1bII** were also very similar and consistent with their structures, although the spectra for diastereomers **1a** were readily distinguishable from those for diastereomers **1b**. In particular, the resonance for the methinyl α-proton of the side chain of derivatives **1aI** and **1aII** ($\delta \sim 6.38$) appears at much lower field than that for derivatives **1bI** and **1bII** (δ 5.01), and the former lies beneath the resonance for the exchangeable amino protons of the base. The methylene protons adjacent to the α-methine proton in **1aI** and **1aII** are nonequivalent and appear at higher field than those of derivatives **1bI** and **1bII**, where their chemical shifts are very similar.

Table I. Observed Rate Constants (k_{obsd}) for Hydrolysis of O⁶-Substituted Guanosines 1aI and 1aII in Methanol/H_2O (5:95) at 40 °C as a Function of pH

	1aI		1aII	
pH	10^2k_{obsd}, min^{-1}	$t_{1/2}$	10^2k_{obsd}, min^{-1}	$t_{1/2}$, min
0.3	140	0.5	139	0.5
0.7	49.6	1.4	50.1	1.4
1.1	46.8	1.5	47.5	1.5
1.4	26.7	2.6	27.6	2.5
1.7	19.7	3.5	19.6	3.5
2.05	9.83	7.0	9.68	7.1
2.61	4.28	16.2	4.44	15.6
3.22	1.65	42.0	1.52	45.5

Table II. Observed Forward (k_f) and Reverse (k_r) Rate Constants for the Equilibration of 1aI ⇄ 1bI in Methanol/H_2O (5:95) at 40 °C as a Function of pH

pH	10^3k_f, min^{-1}	10^3k_r, min^{-1}	$t_{1/2}$, min
12.0	1790	890	0.26
11.2	309	154	1.5
9.3	4.4	2.2	105
7.5	0.31	0.15	1500

Because O^6-aralkylguanosines are known to hydrolyze in acidic aqueous solution,[7,8] we anticipated that diastereomers **1aI** and **1aII** would be hydrolytically unstable and considerably less stable than the isomers **1bI** and **1bII** where linkage to O⁶ is through a nonbenzylic carbon. In preliminary comparisons of the UV absorption spectra for these products at pH 2.6, 40 °C, the spectra for **1bI** and **1bII** were essentially unchanged over a 40-min incubation period while the spectra for **1aI** and **1aII** changed to that of guanosine with a half-time of conversion of approximately 16 min. This indicated that hydrolysis of the O^6-aralkyl ether linkage had occurred as has been observed with related derivatives.[7,8] To determine if there were any significant reactivity differences between diastereomers **1a** at other pH values, more extensive rate vs. pH measurements were carried out for both **1aI** and **1aII** at 40 °C. A tabular summary of the observed first-order rate constants (k_{obsd}) for hydrolysis of the O^6-aralkyl ether linkage of these diastereomers appears in Table I. As is apparent, both diastereomers hydrolyze at nearly identical rates over the range of pH examined. Plots of log k_{obsd} vs. pH for these data resemble those reported for O^6-benzylguanosine,[8] indicating that the hydrolysis is first order in acid and that the rate-determining step involves dissociation of the aralkyl group from the protonated nucleoside. Under identical solvent conditions, **1aI** and **1aII** hydrolyze an order of magnitude more rapidly than the O^6-benzyl analogue. This is consistent with dissociation of O⁶ from a secondary benzylic carbon rather than a primary benzylic carbon as in O^6-benzylguanosine.

As the data of Table I suggest the hydrolytic stability of diastereomers **1a** is markedly increased under neutral or alkaline aqueous conditions. However, under these conditions we observed an unexpected equilibration of **1aI**

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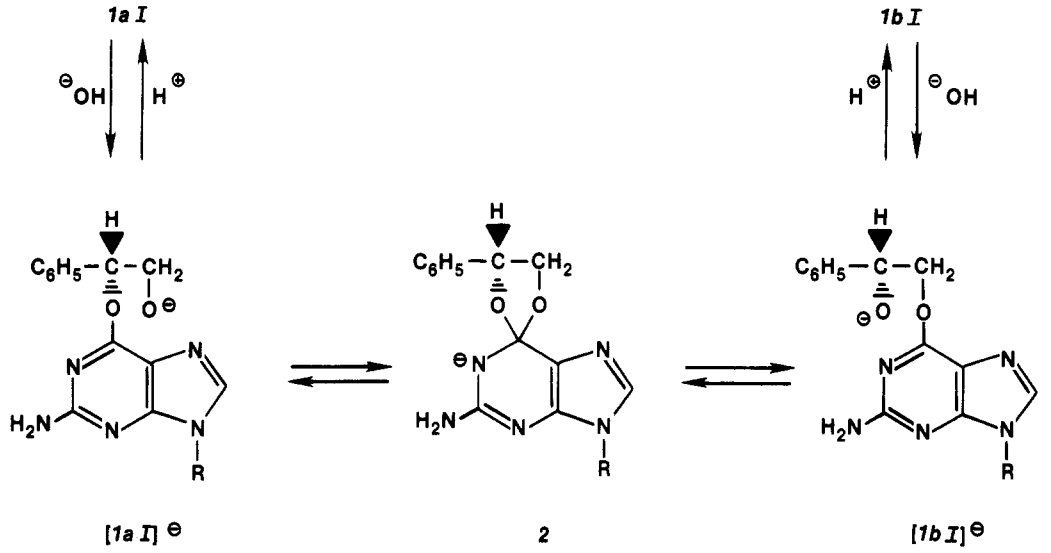
Scheme I



and **1bI** and of **1aII** and **1bII**. The rate of equilibration is first order in hydroxide ion over the range of pH 7.5–12, but the magnitude of the equilibrium constant is independent of pH in the neutral and alkaline range (i.e., K_{eq} = [**1b**]/[**1a**] = 2.0). Rate constants for the overall forward (k_f, **1aI** → **1bI**) and reverse (k_r, **1aI** ← **1bI**) reactions in the equilibrium **1aI** ⇄ **1bI** at 40 °C are presented as a function of pH in Table II. Identical data were obtained with either **1aI** or **1bI** as starting material. The half-time for equilibration is ~24 h at pH 7.5 and decreases to 15 s at pH 12. Rates are too fast to be conveniently measured under more alkaline conditions. At pH 9.5 and 11, equilibrium was also established between **1aII** and **1bII** over the same time period required for equilibration of **1aI** and **1bI**, indicating that no significant diastereomeric rate differences exist in the equilibration.

To establish the stereochemistry about the α-carbon of the 1-phenyl-1,2-ethanediol side chain in the equilibrating isomers, two syntheses of the O⁶-substituted diastereomers were carried out with (±)-1-phenyl-1,2-ethanediol enriched in either (*R*)-(−)- or (*S*)-(+)-1-phenyl-1,2-ethanediol.[10,11] From these syntheses (Experimental Section) it was established that **1aI** and **1bI** are derived from the *S*-(+) enantiomer of the diol, while **1aII** and **1bII** are derived from the *R*-(−)-enantiomer. Thus, the correct chemical representation for **1aI**, **1aII**, **1bI**, and **1bII** is as illustrated. Since **1aI** (**1aII**) is converted to **1bI** (**1bII**) in the equilibration, it is apparent that the configuration about the α-carbon in the 1-phenyl-1,2-ethanediol side chain is retained.

The simplest mechanism for this equilibration which accounts for the equilibration rates (Table II) and retention of configuration in the side chain is suggested for the equilibration of, e.g., **1aI** and **1bI** in Scheme I. The increased rates of equilibration with increasing pH (Table II) lead us to postulate proton abstraction by hydroxide ion from the weakly acidic β-hydroxyl group of **1aI** to afford the anion [**1aI**]⁻. Intramolecular addition of this β-alkoxide to carbon 6 of the guanine residue would lead to a Meisenheimer complex[12] shown as the anion of the ketal derivative **2**. This could rearomatize by expulsion of the α-alkoxide function to form anion [**1bI**]⁻. Protonation of [**1bI**]⁻ would generate the neutral nucleoside **1bI** from **1aI** with overall retention of configuration about the α-carbon of the side chain.

To our knowledge this is the first report of isomerization of guanine nucleosides substituted at the O⁶-position by a β-hydroxyethyl derivative. If the mechanism proposed for this isomerization (Scheme I) is substantially correct, then it is likely that other O⁶-substituted guanine nucleosides bearing similar functional groups would also isomerize. Likely candidates would be O⁶-substituted products derived from guanine nucleoside reactions with other alkyl or aralkyl epoxides. Additionally, a degenerate rearrangement might be observable with O⁶-substituted products derived from hydroxyethylating agents such as *N*-nitroso-*N*-hydroxyethylurea[13] or potential hydroxyethylating agents such as *N*-nitroso-*N*,*N*-bis(2-chloroethyl)urea.[13-15]

Experimental Section

(±)-1-Phenyl-1,2-ethanediol (styrene glycol), (*R*)-(−)- and (*S*)-(+)-mandelic acid, borane–methyl sulfide complex, and 2-amino-6-chloropurine riboside were purchased from Aldrich Chemical Co., Milwaukee, WI. (*R*)-(−)- and (*S*)-(+)-1-phenyl-1,2-ethanediol were synthesized by reduction of (*R*)-(−)- and (*S*)-(+)-mandelic acid with borane–methyl sulfide complex instead of $LiAlH_4$ as described previously.[10,11] UV absorption spectra and kinetic measurements were obtained with a Gilford Model 250 spectrophotometer equipped with a temperature-controlled cell compartment. ^1H NMR spectra were recorded on a Varian XL 200 instrument interfaced to an Advance data system. Samples were dissolved in dimethyl-d_6 sulfoxide with tetramethylsilane as an internal standard. Negative ion (-ve) fast atom bombardment (FAB) mass spectra (MS) were obtained with a reversed geometry VG Micromass ZAB-2F spectrometer interfaced to a VG 2035 data system. A mixture of glycerol and *N*,*N*-dimethylformamide (1:1, v/v) was used as the FAB matrix. HPLC was carried out on an LDC Constametric system with an LKB gradient master.

Preparation of the Diastereomers of *O*⁶-(2-Hydroxy-1-phenylethyl)guanosine (1aI and 1aII) and *O*⁶-(2-Hydroxy-2-phenylethyl)guanosine (1bI and 1bII). To 18 g of molten (±)-1-phenyl-1,2-ethanediol was added 0.3 g of finely divided Na with stirring for 5 h at 80 °C. 2-Amino-6-chloropurine riboside (0.5 g) was added, and the homogeneous solution was stirred at

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80 °C under N_2 for 18 h. At the end of the incubation the solution was cooled to room temperature, and the solid residue was dissolved in a minimum volume of methanol. This solution was diluted to 500 mL with diethyl ether with constant stirring. The precipitate that formed was collected and redissolved in 40 mL of methanol/H_2O (1:1), and this was loaded on a 2.8 × 70 cm Sephadex LH-20 column eluted with methanol/H_2O (1:1). The flow rate was 1 mL/min. UV absorption was continuously monitored at 254 nm and fractions (10 mL) were collected. The mixture of four diastereomeric O^6-substituted guanosine products eluted together in fractions 85–125. Earlier fractions were rich in diastereomers **1aI** and **1aII**. Fractions 85–125 were pooled and evaporated to dryness and the residue was again loaded on the Sephadex LH-20 column, which was eluted as before. The positional isomers were better resolved on rechromatography. O^6-(2-Hydroxy-1-phenylethyl)guanosine (**1aI** and **1aII**) eluted in fractions 77–92. O^6-(2-Hydroxy-2-phenylethyl)guanosine (**1bI** and **1bII**) eluted in fractions 93–115. Fractions containing the respective products were routinely diluted 5:1 with 2-propanol and evaporated to dryness. The yield for combined **1aI** and **1aII** was 0.132 g (19%), and for combined **1bI** and **1bII** it was 0.254 g (37%). Resolution of the individual diastereomers **1aI** and **1aII** was accomplished by loading portions (~0.03 g) of the mixture on a 10 × 250 mm Spherisorb ODS-2 column eluted isocratically with methanol/H_2O (4:6) at a flow rate of 1.5 mL/min. UV absorption was continuously monitored at 254 nm, and fractions (4.5 mL) were collected. Diastereomer **1aI** eluted in fractions 11–15: UV λ_{max} (pH 6.9) 247, 284 nm; NMR δ 8.12 (s, 1, H-8), 7.36 (m, 5, C_6H_5), 6.38 (dd, 1, α-CH), 6.37 (s, 2, NH_2, exchange with D_2O), 5.76 (d, 1, H-1′), 3.87 (m, 1, β-CH) 3.76 (m, 1, β-CH); -ve FAB MS, m/z 402 ($[M - H]^-$). Diastereomer **1aII** eluted in fractions 17–20: UV λ_{max} (pH 6.9) 248, 284 nm; NMR δ 8.10 (s, 1, H-8), 7.36 (m, 5, C_6H_5), 6.36 (dd, 1, α-CH), 6.31 (s, 2, NH_2, exchange with D_2O), 5.76 (d, 1, H-1′), 3.88 (m, 1, β-CH), 3.74 (m, 1, β-CH); -ve FAB MS, m/z 402 ($[M - H]^-$). The diastereomers **1bI** and **1bII** were resolved by loading portions (~0.01 g) of the mixture on the same Spherisorb ODS-2 column eluted isocratically with methanol/H_2O (35:65). The earlier eluting isomer **1bI** eluted in fractions 30–33: UV λ_{max} (pH 6.9) 247, 284 nm; NMR δ 8.12 (s, 1, H-8), 7.39 (m, 5, C_6H_5), 6.46 (s, 2, NH_2, exchange with D_2O), 5.79 (d, 1, H-1′), 5.01 (dd, 1, α-CH), 4.42 (m, 2, β-CH_2); -ve FAB MS, m/z 402 ($[M - H]^-$). The later eluting diastereomer **1bII** eluted in fractions 35–37: UV λ_{max} (pH 6.9) 248, 284 nm; NMR δ 8.14 (s, 1, H-8), 7.40 (m, 5, C_6H_5), 6.45 (s, 2, NH_2, exchange with D_2O), 5.78 (d, 1, H-1′), 5.01 (dd, 1, α-CH), 4.43 (m, 2, β-CH_2); -ve FAB MS, m/z 402 ($[M - H]^-$).

For analytical purposes, the four diastereomers were separated from one another on a 4.6 × 250 mm Ultrasphere ODS column (Beckman), which was eluted at 1 mL/min with a linear gradient of 0.01 M Na_2HPO_4 adjusted to pH 6.0 with HCl to 25% methanol in the aqueous buffer over 60 min, followed by isocratic elution with the same solvent mixture for 30 min, and finally with a linear gradient from 25% to 35% methanol in the aqueous buffer over 96 min. The retention times for **1aI**, **1bI**, **1aII**, and **1bII** under these conditions were 109, 143, 148, and 151 min, respectively.

Reaction of 2-Amino-6-chloropurine Riboside with (±)-1-Phenyl-1,2-ethanediol Enriched in the Respective Enantiomers of the Diol. To 0.2 g molten (*R*)-(−)-1-phenyl-1,2-ethanediol[10,11] was added 0.009 g of Na. When the Na had dissolved, 0.05 g of 2-amino-6-chloropurine riboside was added followed by 0.20 g of racemic (±)-1-phenyl-1,2-ethanediol. The reaction was stirred at 95 °C for 18 h. At the end of this incubation an aliquot (25 μL) of the reaction solution was diluted to 1 mL with 0.01 M Na_2HPO_4 buffer adjusted to pH 6.0. The sample was loaded on the analytical HPLC system described above. The ratio ([**1aI**] + [**1bI**])/([**1aII**] + [**1bII**]) (determined from peak areas) was 0.37 and close to the theoretical value of 0.33 expected from the proportion of (*R*)-(−)- and (*S*)-(+)-1-phenyl-1,2-ethanediol present in the synthetic reaction. From a similar synthesis with (*S*)-(+)-1-phenyl-1,2-ethanediol in excess, the product mixture was enriched in **1aI** and **1bI**. Thus, **1aI** and **1bI** exhibit *S* stereochemistry about the α-carbon while the configuration about the α-carbon in **1aII** and **1bII** exhibits *R* stereochemistry.

Kinetics of Hydrolysis of 1aI and 1aII. An aliquot (100 μL) from a 2.5 × 10^{-3} M stock solution of either diastereomer in methanol/H_2O (1:1) was added to 0.90 mL of aqueous buffer at the indicated pH (Table I). Rates of disappearance of either product were measured from the time-dependent increase in absorbance of these solutions at 251 nm. Values of k_{obsd} (Table I) were calculated from the slopes of plots of ln ($OD_\infty - OD_t$) vs. time and the k_{obsd} values are the average of at least three determinations.

Kinetics of Equilibration of 1aI and 1bI. An aliquot (0.1 mL) from a 2.5 × 10^{-3} M stock solution of **1aI** or **1bI** in methanol/H_2O (1:1) was added to 0.9 mL of aqueous 0.01 M K_2HPO_4 adjusted to the indicated pH (Table II). At various times, 0.10 mL of the solution was withdrawn and mixed with 0.90 mL of methanol/H_2O (45:55). The resulting solution was chromatographed on the Ultrasphere ODS column eluted isocratically at 1 mL/min with methanol/H_2O (45:55). The retention times for **1aI** and **1bI** under these conditions were 6 and 8 min, respectively. The concentration of **1aI** and **1bI** was determined from peak areas. The sum of the rate constants for the forward (k_f) and reverse (k_r) reactions for the equilibration was determined from the slopes of plots of ln (([**1aI**]$_t$ − [**1aI**]$_\infty$)/([**1aI**]$_{t_0}$ − [**1aI**]$_\infty$)) vs. time.[16] Values for k_f and k_r (Table II) were calculated from this slope and the equilibrium relationship k_f/k_r = 2.0.

Acknowledgment. We are indebted to Drs. G. Chmurny and Y. Tondeur for determining the ^1H NMR and mass spectral data, respectively, to Dr. R. Kupper for advice on the use of borane–methyl sulfide complex, and to A. Shirey for technical assistance. The research was undertaken during the tenure of an Eleanor Roosevelt Fellowship of the International Union Against Cancer awarded to K.H. This research was sponsored by the National Cancer Institute, DHHS, under Contract N01-CO-23909 with Litton Bionetics, Inc. The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products, or organizations imply endorsement by U.S. Government.

Registry No. **1aI**, 102830-38-6; **1aII**, 102830-39-7; **1bI**, 102830-40-0; **1bII**, 102830-41-1; (±)-1-phenyl-1,2-ethanediol, 7138-28-5; 2-amino-6-chloropurine riboside, 2004-07-1; (*R*)-(−)-1-phenyl-1,2-ethanediol, 16355-00-3; (*S*)-(+)-1-phenyl-1,2-ethanediol, 25779-13-9.

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