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SYNTHESIS AND REACTIVITY OF DIOL EPOXIDES DERIVED FROM NON-K-REGION TRANS-DIHYDRODIOLS OF BENZO[a]ANTHRACENE

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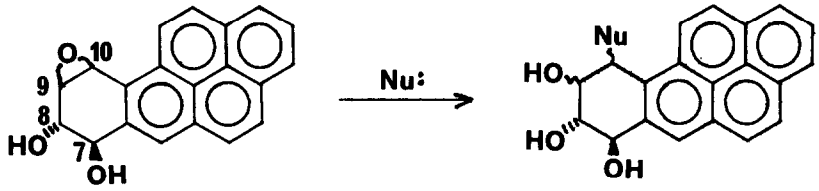
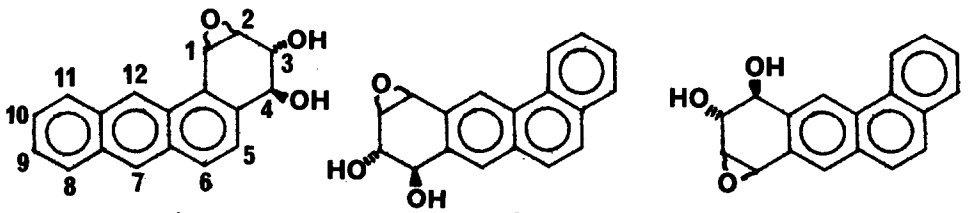
The diastereomeric 7,8-diol-9,10-epoxides (1a,b) of the environmental carcinogen benzo[a]-pyrene (BP) are highly reactive, potent alkylating agents that combine with nucleophiles at the benzylic carbon atom of the oxirane ring.[1] They are potent mutagens[2] and may be ultimate



1 a,b

carcinogenic forms of BP. Both cis and trans opening of the oxirane ring of 1 in water[1c] suggested carbonium ions (at C_{10}) as intermediates and prompted perturbational molecular orbital (PMO) calculations. The calculations[3] predict that diol epoxides for a number of polycyclic aromatic hydrocarbons (PAH's) should vary greatly in S_N1 reactivity and that those in which the oxirane ring forms part of a "bay region" (such as 1) should be the most reactive for a given PAH.[3a] The calculated relative ease of carbonium ion formation was suggested as an index by which the relative mutagenicity could be predicted for a series of positional isomers of



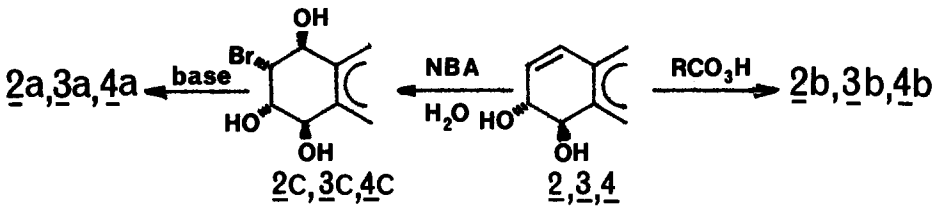
2 a,b 3 a,b 4 a,b

a series: oxirane oxygen and benzylic OH on same face of saturated ring.

b series: oxirane oxygen and benzylic OH on opposite faces of saturated ring.

diol epoxides derived from a given PAH.[3a] For example, diol epoxides 2a, 3a and 4a derived from the weak carcinogen benzo[a]anthracene (BA) have calculated values of ΔE_{deloc}[3b] for the formation of benzylic carbonium ions of 0.766β, 0.526β and 0.572β, respectively, which suggests that the predicted reactivity and mutagenicity should be 2a >> 4a ∿ 3a. Metabolic activation of dihydrodiols 2-4 (presumably to 2a,b-4a,b), other dihydrodiols of BA, and BA established that 2 caused >7-fold more mutations that the other substrates[4] and supported this prediction.

To determine whether the metabolic activation studies provided a true reflection of inherent mutagenicity rather than differences in rates of metabolism, synthesis and testing of diol epoxides from BA was required. The diol epoxides were prepared from the corresponding dihydrodiols[5] by routes analogous to those used for the preparation of the naphthalene diol epoxides and



partial structures for: 3,4-dihydroxy-3,4-dihydrobenzo[a]anthracene, 2; 8,9-dihydroxy-8,9-dihydrobenzo[a]anthracene, 3; 10,11-dihydroxy-10,11-dihydrobenzo[a]anthracene, 4.

1[1]. Treatment of the dihydrodiols with m-chloroperoxybenzoic acid in THF produced diol epoxides 2b-4b in yields of 60,52 and 80%, respectively. In a typical experiment, an excess of m-chloroperoxybenzoic acid (1 g) was added to a solution of dihydrodiol (100 mg) in anh. THF (20 ml) under argon. After 1 hr, EtOAc (150 ml) was added, and the organic phase was extracted (10% NaOH), dried ($MgSO_4$), and concentrated to yield a white solid which was purified by trituration with acetone. The diastereomeric diol epoxides 2a-4a were prepared in two steps by conversion of the dihydrodiols to the bromotriols 2c-4c with N-bromoacetamide in aq. THF (yields of 62,67 and 70%, respectively) followed by cyclication of the bromotriols either with Amberlite (OH-form) in anh. THF (for 2a, 95% yield) or with $KOBu^t$ in anh. THF (for 3a and 4a, yields of 77% and 38%, respectively). In a typical experiment, bromotriols were prepared by adding HCl (one drop) to a solution of NBA (64 mg), and the dihydrodiol (100 mg) in THF/H_2O (16 ml/4 ml) and stirring under argon at 0° for 2 hr. EtOAc was added and the organic phase was extracted with H_2O, dried, filtered and concentrated to give the product which was recrystallized from ethanol. In the cyclization with Amberlite, the bromotriol (100 mg) and resin (5 g) were stirred in anh. THF under N_2 for 1 hr. The resin and solvent were removed to give the product which was purified by trituration. Alternatively, $KOBu^t$ (36 mg) was added to a solution of bromotriol (44 mg) in anh. THF (5 ml) under argon. After 1 hr, 20 ml THF was added and the mixture was filtered through florisil which was eluted with EtOAc to give the diol epoxide as a white solid on concentration of the eluent. The diol epoxides are formed stereospecifically in each case, due to the directing effects of the hydroxyl groups[1] as shown by the NMR specta in the Table. Significant upfield shifts of the benzylic hydroxyl protons, a

consequence of shielding due to the influence of the oxirane ring, are observed for 2a-4a and are most pronounced for 3a and 4a as expected by analogy with chemical shifts observed in the spectra of the diastereomeric diol epoxides of naphthalene and of BP (1a,b).[1a,b]

Second-order rate constants were measured for the reaction between the BA diol epoxides (added in 0.05 ml of DMSO) and sodium p-nitrothiophenolate in dry $HOBu^t$ (3.0 ml) at 30° as previously described.[1b] In the a series which is more reactive due to anchimeric assistance by the intramolecular hydrogen bond between the benzylic hydroxy group and the oxirane oxygen, rate constants of 53 $M^{-1}sec^{-1}$ (2a), 14 $M^{-1}sec^{-1}$ (3a), and 9 $M^{-1}sec^{-1}$ (4a) were observed. The corresponding diastereomers in the b series were 60 to 130 times less reactive. As anticipated from the calculations of ΔE_{deloc}, the diol epoxides of 2 were 4 to 6-fold more reactive compared to those of 3 or 4 within each series. Results of testing for mutagenic activity were even more dramatic. Diol epoxides 2a,b were >14 times more active than 3a,b and 4a,b.[6] Very little difference in mutagenicity was found when diastereomeric pairs from the a and b series were compared. Diol epoxides of other hydrocarbons are being examined to determine the generality of the "bay region" concept[7] and its importance to PAH-induced carcinogenesis.

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TABLE. MELTING POINTS AND NMR SPECTRA OF BENZO[a]ANTHRACENE DIOL EPOXIDES AND BROMOTRIOLS.

Compound (MP)	100 MHz NMR SPECTRA[a]						
	epoxy protons		carbinol protons		hydroxyl protons		aromatic protons
	benzylic	non-benzylic	benzylic	non-benzylic	benzylic	non-benzylic	
2a (173-175,dec)	H_1 4.81	H_2 3.80	H_4 4.71	H_3 3.91	OH_4 5.07	OH_3 5.61	7.4-8.3(6H); 8.60
		$J_{1,2}$ = 4.3; $J_{2,3}$ = 2.0; $J_{3,4}$ = 7.0; $J_{H_3,OH}$ = 5.0; $J_{H_4,OH}$ = 7.0					9.02(H_7,H_{12})
2b (180-182,dec)	H_1 5.11	H_2 3.80	H_4 4.50	H_3 3.89	OH_4 5.74	OH_3 5.59	7.4-8.3(6H); 8.58,
		$J_{1,2}$ = 4.7; $J_{3,4}$ = 8.5; $J_{H_3,OH}$ = 5.0: $J_{H_4,OH}$ = 6.5					9.16(H_7,H_{12})
3a (122-124)	H_{11} 4.37	H_{10} 3.85	H_8 4.65	H_9 4.30	OH_8 4.40	OH_9 5.54	7.6-8.1(6H); 8.90(H_1);
		$J_{8,9}$ = 3.2; $J_{9,10}$ = 2.5; $J_{10,11}$ = 4.0; $J_{8,10}$ = 1.3; J_{H_8,OH_8} = 8.0					9.07(H_{12})
3b (210-215,dec)	H_{11} 4.35	H_{10} 3.76	H_8 4.60	H_9 3.82	OH_8 5.70	OH_9 5.58	7.6-8.2(6H); 8.86;
		$J_{8,9}$ = 9.0; $J_{9,10}$ = 1.0; $J_{10,11}$ = 4.4; J_{H_8,OH_8} = 6.0; J_{H_9,OH_9} = 5.0					(H_1); 9.00(H_{12})
4a (134-136)	H_8[b]	H_9 3.85	H_{11} 4.78	H_{10}[b]	OH_{11}[b]	OH_{10} 5.46	7.6-8.3(6H); 8.70-
	$J_{8,9}$ = 4.0; $J_{9,10}$ = 2.4; $J_{10,11}$ = 3.0; $J_{9,11}$ = 1.6; $J_{H_{10},OH_{10}}$ = 5.0; $J_{H_{11},OH_{11}}$ ~ 8.0						8.95(H_1,H_{12})
4b (180-184,dec)	H_8 4.25	H_9 3.73	H_{11} 4.63	H_{10} 3.82	ca. 5.7		7.6-8.2(6H); 8.72(H_1);
			$J_{8,9}$ = 4.2; $J_{9,10}$ = 1.0; $J_{10,11}$ = 9.0				8.93(H_{12})

For the bromotriols (mp, NMR spectrum): 2c (152-153,dec), 4.18(H_3), 4.6-4.8(H_2,H_4), 5.64(OH_3), 5.70(H_1), 5.83, 6.35(OH_2,OH_3), 7.4-8.2(6H), 8.54-8.82(H_7,H_{12}), $J_{1,2}$ = 3.2, $J_{2,3}$ = 2.8, $J_{3,4}$ = 8.1, J_{H_3,OH_3} = 4.6; 3c (153-155,dec), 4.22(H_{10}), 4.68(H_9), 4.75(H_{11}), 5.12(H_8), 5.62(OH_{10}), 5.72(OH_{11}), 6.13(OH_8), 7.6-8.1(6H), 8.74(H_1), 8.84(H_{12}), $J_{8,9}$ = 6.5, $J_{9,10}$ = 2.0, $J_{10,11}$ = 6.0, J_{H_8,OH_8} = 6.0, $J_{H_{10},OH_{10}}$ = 4.0, $J_{H_{11},OH_{11}}$ = 5.5; 4c (144-147,dec), 4.26(H_9), 4.70(H_{10}), 4.84(H_8), 5.05(H_{11}), 5.5-6.1($OH_{8,10,11}$), 7.5-8.1(6H), 8.75(H_1), 8.80(H_{12}), $J_{8,9}$ = 5.4, $J_{9,10}$ = 2.0, $J_{10,11}$ = 7.0

[a] Reported in delta units, obtained in d_6-DMSO with TMS as internal standard. For purpose of comparison, see reference 1b.

[b] The absorptions of the indicated protons overlap at 4.15-4.40 δ.