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SYNTHESIS OF (+)- AND (-)-BENZO[a]PYRENE 7,8-OXIDE

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The concept of stereoselectivity during monooxygenase catalyzed addition of an oxygen atom to the stereoheterotopic faces of a polycyclic aromatic hydrocarbon (PAH) was initially proposed[1] on the basis of (a) liver microsomal metabolism studies on naphthalene and (±)-naphthalene 1,2-oxide and (b) synthesis of partially resolved naphthalene 1,2-oxide. Synthesis of optically pure naphthalene- and anthracene 1,2-oxide was subsequently achieved by a combination of short-column chromatography and recrystallization of the trans-2-bromo-1-menthyloxyacetoxy-1,2,3,4-tetrahydro diastereomers of naphthalene and anthracene.[2,3] Recent studies of the metabolically formed trans-dihydrodiols of the potent carcinogen benzo[a]pyrene (B[a]P) have indicated that a high degree of stereoselectivity occurs during their formation.[4] The trans-7,8-dihydrodiol obtained by liver microsomal metabolism of B[a]P via BP 7,8-oxide was >90% optically pure, whereas enzymatic hydration of (±)-BP 7,8-oxide produced (-)-BP 7,8-dihydrodiol with lower optical purity. Introduction of asymmetry into the PAH ring system during the initial oxygen atom addition at the 7,8-bond to form BP 7,8-oxide, therefore, can control the absolute stereochemistry (and thus, mutagenicity or carcinogenicity)[5,6] of the subsequent metabolites.

The present report describes the synthesis of the optically pure enantiomers of BP 7,8-oxide in order to test the theoretical predictions that these enantiomers do not readily become racemic[7] and to examine the tumorigenicity of the individual enantiomers. Reaction of the acid chloride of (-)-menthyloxyacetic acid with trans-7-hydroxy-8-bromo-7,8,9,10-tetrahydroB[a]P in pyridine (7 days) provided the required mixture of diastereomers (1a,b) in 86% yield (Scheme I) as a viscous mass. Partial separation of the diastereomers was achieved by passing 10 g of the mixture through a short column of silica gel (1 kg of Kiesel gel G type 60 in a 12 cm column eluted with 10% ether in petroleum ether, bp 40-60°). Multiple recrystallizations (5x) of the early portion (from CH_2Cl_2-CH_3OH) and late portion (from cyclohexane) of the eluted peak provided homogeneous samples of each diastereomer (10% recovery). The diastereomers were more conveniently separated by passage of 1 g of the mixture through a 1" x 4' column of 10 μ silica gel eluted with 2%

ether in cyclohexane. The column was pumped at a flow rate of 40 ml/min. More than 90% of the material was recovered in two fractions which were each >95% diastereomerically pure and were easily recrystallized to homogeneity with high recovery. Analytical high-pressure liquid chromatography (6.2 mm x 25 cm Du Pont Zorbax SIL column eluted with 5% ether in cyclohexane) proved useful in analysis of mixtures of the less polar (1a, k' = 1.68) and more polar (1b, k' = 2.04) diastereomers (Figure 1). The nmr spectra (220 MHz, C_6D_6) of the diastereotopic protons H_A and H_B in 1a and 1b are quite diagnostic; in 1a protons H_A and H_B appear as a singlet (4.12δ) while in 1b protons H_A and H_B appear as an AB quartet (centered at 3.98 and 4.20 δ) with J = 16.3 Hz

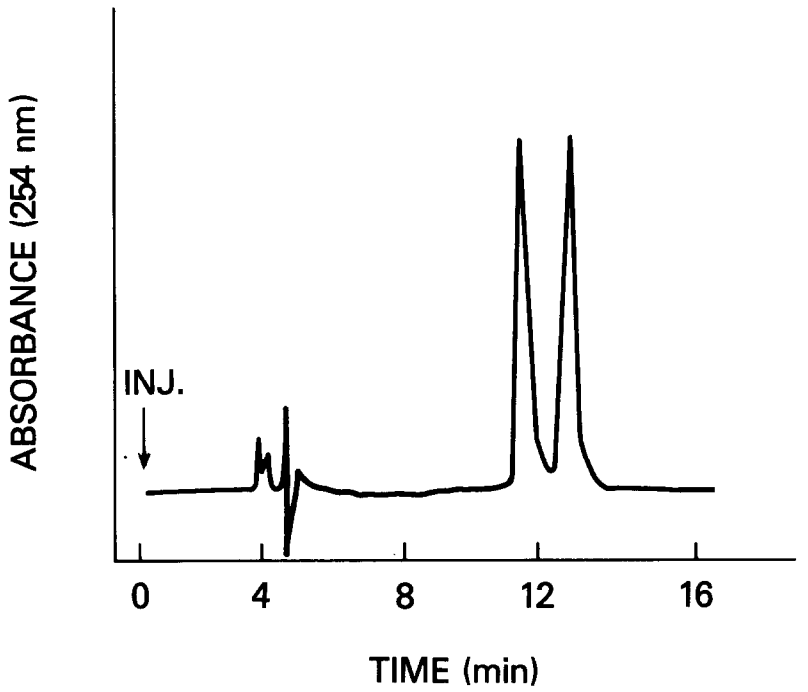
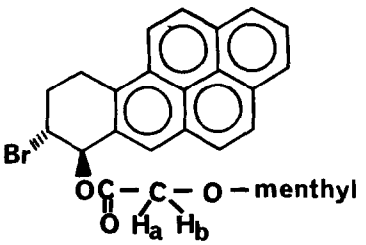
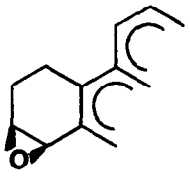


Figure 1. Analytical separation of diastereomers 1a and 1b on a Du Pont Zorbax SIL column (α = 1.2) eluted with 5% ether in cyclohexane.

Absolute stereochemistry was assigned on the basis of a configurational correlation between diastereomer 1a and diol 3a. Thus, treatment of diastereomer 1a with dry $NaOCH_3$ in ether for 24 hr produced 7,8-epoxy-7,8,9,10-tetrahydroB[a]P (2a. Scheme I) in 89% yield. Hydrolysis of 2a with 0.5 N KOH in 50% t-BuOH in water at reflux for 24 hr provided (-)-trans-(7S,8S)-dihydroxy-7,8,9,10-tetrahydroB[a]P (3a) of known absolute stereochemistry[8] in 50% yield. Similarily, 1b was converted into (+)-3b. The fact that the 3a formed above is only ∿80% optically pure suggests that the hydrolysis was not totally regioselective in that ∿10% of the attack by hydroxide had occurred at the non-benzylic position C-8. This absolute stereochemical assignment for 1a [7R,8R] follows the general trend previously observed for analogous structures in other members of the PAH series; i.e., the less polar diastereomer shows a large negative $[\alpha]_D$ ($CHCl_3$) value and [R] configuration at the chiral benzylic center.[2,3,7]

SCHEME I. Reaction sequence and absolute stereochemistry for the a-series of enantiomers and diastereomers. Rotations were measured in $CHCl_3$ except in the cases of 3a and 7a which were measured in THF. Optical rotations for the b-series were of opposite sign and of identical magnitude (within the limit of experimental error) of those in the a-series. Except for 1a and 1b, melting points in both series were identical.

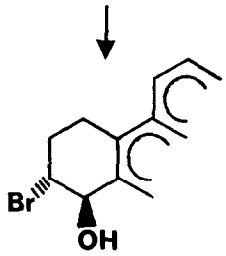




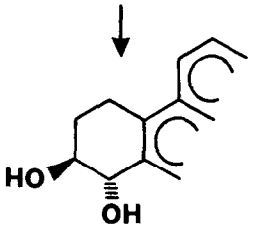
1a: (less polar), $[\alpha]_D$ - 112°, mp 143-144°

1b: (more polar), $[\alpha]_D$ + 36°, mp 135-136°

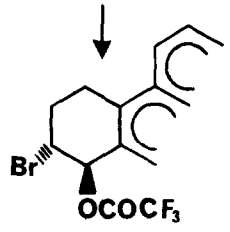
2a: $[\alpha]_D$ + 114°, mp 135-136°



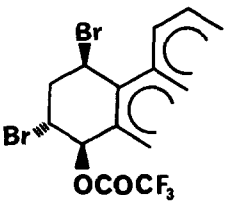
4a: $[\alpha]_D$ + 68°, mp 170-171°



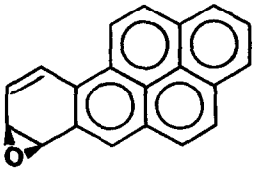
3a: $[\alpha]_D$ - 63°, mp 215°, [7S:8S]



5a: $[\alpha]_D$ - 122°, mp 132-133°



6a: $[\alpha]_D$ - 712°, mp 181-182°



7a: $[\alpha]_D$ + 100°, [7R,8S]

The diastereomers 1a and 1b were individually treated with B_2H_6 in THF for 3 days to produce trans-7-hydroxy-8-bromo-7,8,9,10-tetrahydroB[a]P ((+)-4a and (-)-4b) in 70% yield. Each of these enantiomers was converted into B[a]P 7,8-oxide by methods described for racemic material[9] as shown in Scheme I. Yields were comparable to those previously reported, and the optically active compounds gave microanalytical and spectral data which were satisfactory. The sequence in Scheme I establishes that (-)-7R,8R-1a is converted into (+)-B[a]P 7R,8S-oxide (7a).

That the arene oxide enantiomers 7a and 7b could be prepared optically pure and that they were found to have configurational stability over the period of observation (several hours) at ambient temperature in both $CHCl_3$ and in THF is in concurrence with predictions of optical stability based upon PMO calculations. Thus, B[a]P 7,8-oxide (7) does not exist in a state of tautomeric equilibration with its oxepin form. The present resolution technique makes enantiomerically homogeneous samples of 7a and 7b available for biological studies. Since (-)-7R,8R-dihydroxy-7,8-dihydroB[a]P is much more tumorigenic than its (+)-enantiomer[6] and since epoxide hydrase prefers to attack B[a]P 7,8-oxide with inversion of configuration at C-8,[4b,c] (+)-B[a]P 7R,8S-oxide (7a) is anticipated to be the more tumorigenic enantiomer.

References

1. D. R. Boyd, D. M. Jerina and J. W. Daly, J. Org. Chem., 35, 3170 (1970).
2. M. N. Akhtar and D. R. Boyd, Chem. Commun., 916 (1975).
3. M. N. Akhtar, D. R. Boyd and J. G. Hamilton, manuscript in preparation.
4. a) D. R. Thakker, H. Yagi, H. Akagi, M. Koreeda, A. Y. H. Lu, W. Levin, A. W. Wood, A. H. Conney and D. M. Jerina, Chem.-Biol. Interact., 16, 281 (1977).
   b) D. R. Thakker, H. Yagi, W. Levin, A. Y. H. Lu, A. H. Conney and D. M. Jerina, J. Biol. Chem., 232, 6328 (1977).
   c) S. K. Yang, P. P. Roller and H. V. Gelboin, Biochem., 16, 3680 (1977).
5. A. W. Wood, R. L. Chang, W. Levin, H. Yagi, D. R. Thakker, D. M. Jerina and A. H. Conney, Biochem. Biophys. Res. Commun., 77, 1389 (1977) and references therein.
6. W. Levin, A. W. Wood, P. G. Wislocki, J. Kapitulnik, H. Yagi, D. M. Jerina and A. H. Conney, Cancer Res., 37, 2721 (1977).
7. D. R. Boyd, J. D. Neill and M. E. Stubbs, J. Chem. Soc. Chem. Commun., 873, 1977.
8. K. Nakanishi, H. Kasai, H. Cho, R. Harvey, A. Jeffrey, K. Jennette and I. Weinstain, J. Am. Chem. Soc., 99, 258 (1977); H. Yagi, H. Akagi, D. R. Thakker, H. D. Mah, M. Koreeda and D. M. Jerina, J. Am. Chem. Soc., 99, 2358 (1977).
9. H. Yagi and D. M. Jerina, J. Am. Chem. Soc., 97, 3185 (1975).