Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. David Singleton is also thanked for valuable technical assistance.

Registry No. 2a, 72553-35-6; **2b**, 7064-06-4; **2c**, 82149-99-3; **4a**, 82150-00-3; **4b**, 5381-93-1; **4c**, 82150-01-4; **6a**, 82150-02-5; **6a** ($R_1 = R_3 = n\text{-}C_3H_7$; R_2 = H), 82150-03-6; **6b**, 82150-04-7; **6b** (n = 2; R_1 = H; R_2 = Ph), 82150-05-8; **6c**, 82150-06-9; **7a**, 82150-07-0; **7a** [R_1, R_2 = $(CH_2)_4$; R_3 = H], 82150-08-1; **7a** [R_1, R_2 = $(CH_2)_3$; R_3 = H], 69423-36-5; **7b**, 26343-65-7; **7b** (n = 2; R_1 = H; R_2 = Ph), 42052-56-2; **7c**, 26343-67-9; **8a**, 53538-95-7; **8a** ($R_1 = R_3 = n\text{-}C_3H_7$; R_2 = H), 82150-09-2; **8b**, 82150-10-5; **8b** (n = 2; R_1 = Ph; R_2 = H), 82150-11-6; **8c**, 82150-12-7; **9a**, 53496-45-0; **9a** [R_1, R_2 = $(CH_2)_4$; R_3 = H], 82150-13-8; **9a** [R_1, R_2 = $(CH_2)_3$; R_3 = H], 32435-36-2; **9b**, 26343-66-8; **9b** (n = 2; R_1 = Ph; R_2 = H), 13161-18-7; **9c**, 26343-68-0; **10**, 82150-14-9; **11**, 82150-15-0.

(19) Other isoxazoline-based synthetic methodologies include conversion to α,β-unsaturated ketones via β elmination and oxime cleavage (Jäger, V.; Grund, H. *Angew Chem., Int. Ed. Engl.* **1976**, *15*, 50), conversion to β,γ-unsaturated oximes (Jäger, V.; Grund, H.; Schwab, W. *Ibid.* **1979**, *18*, 78), opening to β-hydroxy nitriles (Huisgen, R.; Cristl, M. *Chem. Ber.* **1973**, *106*, 3291. Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209. Kalvoda, J.; Kaufman, H. *Ibid.* **1976**, 210. Wade, P. M.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. Kozikowski, A. P.; Adamczyk, M., to be submitted for publication), cycloreversion to enol silyl ethers (Cunico, R. F. *J. Org. Met. Chem.* **1981**, *212*, C51).

Absolute Configuration of the *trans*-9,10-Dihydrodiol Metabolite of the Carcinogen Benzo[*a*]pyrene

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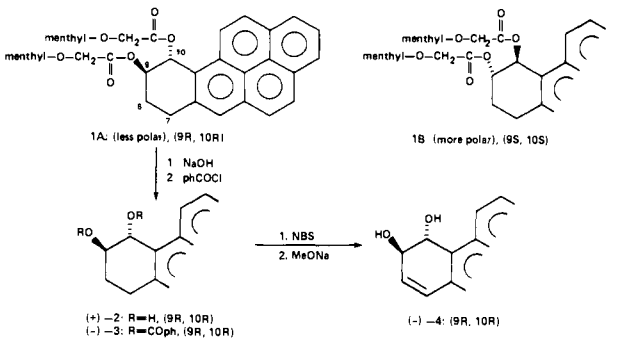
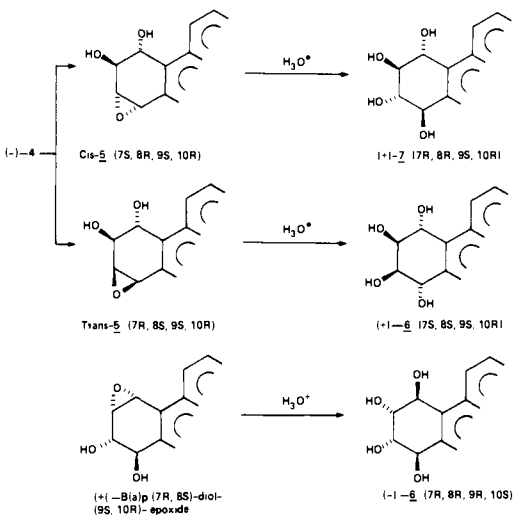
The cytochromes P-450 are the principal enzymes in liver that are responsible for the oxidative detoxification of nonpolar foreign compounds by mammals.[1] Among these enzymes, cytochrome P-450c[2] is particularly effective in catalyzing the oxidation of polycyclic aromatic hydrocarbons and accounts for 70% of the total cytochromes P-450 in the livers of rats that have been treated with the inducer 3-methylcholanthrene.[3] We have recently proposed a stereochemical model for the catalytic binding site of cytochrome P-450c that predicts the absolute configuration of arene oxides of many polycyclic hydrocarbons formed by this enzyme.[4] So that this model for the binding site of cytochrome P-450c could be tested, the present study assigns absolute configuration to the (+)- and (−)-enantiomers of benzo[*a*]pyrene 9,10-dihydrodiol which are formed by the action of epoxide hydrolase on their benzo[*a*]pyrene 9,10-oxide percursors. Configurational assignment was achieved through chemical correlation of the 9,10-dihydrodiol with the 7,8-dihydrodiol of known absolute configuration based on circular dichroism[5] as well as X-ray crystallographic studies.[6]

Scheme I



Scheme II



Enantiomers of the 9,10-dihydrodiol were obtained via resolution of *trans*-9,10-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene[7] as its diastereomeric bisesters (**1**, Scheme I) with (−)-menthoxyacetic acid. The diastereomeric bisesters were obtained in essentially quantitative yield by allowing the tetrahydrodiol to react with menthoxyacetyl chloride in pyridine at 50 °C for 24 h. Separation of the diastereomers was achieved by HPLC on a 2.5 × 120 cm column of 10-μm silica gel eluted with 12% ether in cyclohexane (α = 1.34):

1A: k' (less polar) = 2.00

$[\alpha]_D$ −99° (11 mg/mL, $CHCl_3$)

1B: k' (more polar) = 2.75

$[\alpha]_D$ −37° (12 mg/mL, $CHCl_3$)

Both diastereomers were colorless oils. Preliminary indication of the absolute configuration of these diastereomers was obtained from examination of their NMR spectra (100 MHz, C_6D_6). Previous studies[8] of the bis(menthoxy) esters of several *trans*-diol derivatives of polycyclic hydrocarbons have shown that the diastereotopic CH_2 hydrogens in the pair of $COCH_2O$ groups of the less polar bisester with the more negative $[\alpha]_D$ generally appear as a pair of singlets and have an *R,R* configuration whereas the

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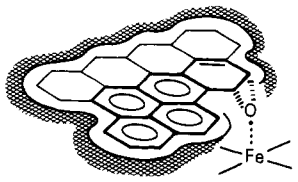

Figure 1. Estimated shape of the hydrophobic depression that constitutes the catalytic binding site of cytochrome P-450c. Only one of the heterotopic faces of benzo[*a*]pyrene can face the heme and fit into the site if the 9,10-bond of the hydrocarbon is epoxidized.

more polar (*S*,*S*)-diastereomers always show these hydrogens as a pair of AB quartets with $J_{gem} \sim 16$ Hz for each ester. In **1B** the hydrogens within each CH_2 group are nonequivalent and each CH_2 appears at a pair of AB quartets (centered at δ 3.72 and 3.93 and at δ 3.86 and 4.04 with $J_{gem} \sim 16$ Hz) suggestive of an *S*,*S* configuration. For **1A** these hydrogens appear as a sharp singlet (δ 3.98) and a weakly split AB quartet (major lines at δ 3.83 and 3.86) suggestive of an *R*,*R* configuration. After hydrolysis (50% 1 N NaOH in THF/MeOH (1:1), 18 °C, 2 h) of **1A**, the resultant free tetrahydrodiol (+)-**2** [mp 165 °C, $[\alpha]_D$ +55° (7 mg/mL, THF)] was benzoylated quantitatively (benzoyl chloride in pyridine, 10 °C, 18 h) to afford (−)-**3** [mp 145–146 °C, $[\alpha]_D$ −50° (30 mg/mL, $CHCl_3$)]. Bromination at C-7 with *N*-bromosuccinimide (in CCl_4) followed by dehydrohalogenation and hydrolysis with NaOMe [in THF/MeOH (1:1), 18 °C, 3 h] afforded (−)-**4** [mp 210 °C, $[\alpha]_D$ −294° (5 mg/mL, THF), HPLC on a Du Pont Zorbax ODS column (21.2 × 250 mm) eluted with 75% MeOH in water, $k' = 4.2$] in 77% overall yield for the above three steps (Scheme I). The circular dichroism spectrum of the (−)-9,10-dihydrodiol ((−)-**4**) was identical with that of 9,10-dihydrodiol formed metabolically from benzo[*a*]pyrene.[9]

Unequivocal assignment of the 9*R*,10*R* configuration to compounds **1A** and (−)-**4** (Scheme I) was achieved by (i) epoxidation of the dihydrodiol (−)-**4** to form a pair of diastereometrically related 9,10-diol 7,8-epoxides in which the benzylic 10-hydroxyl group is either cis or trans to the epoxide oxygen and (ii) acid-catalyzed hydrolysis of the trans isomer at C-7 to form a tetraol of known absolute configuration (Scheme II). Epoxidation of (−)-**4** with *m*-chloroperoxybenzoic acid as described for the racemic material[10] afforded a 2:3 mixture of the cis and trans diastereomers from which the trans isomer (*trans*-**5**) could be isolated in pure form by crystallization from tetrahydrofuran. The other diastereomer (*cis*-**5**) required HPLC for final purification.[11] Acid-catalyzed hydrolysis of *trans*-**5** (20% THF in 0.1 M $NaClO_4$ adjusted to pH 2.5 with $HClO_4$, 1 h, 18 °C) proceeded mainly by trans addition of water at C-7 to afford the *trans*,*cis*,*trans*-tetraol (+)-**6**, which was isolated in pure form by HPLC on a Du Pont Zorbax ODS column (21.2 × 250 mm^2) eluted with 60% methanol in water [$k' = 3.2$, $[\alpha]_D$ +51° (3 mg/mL in THF)]. The opposite enantiomer of the *trans*,*cis*,*trans*-tetrol [(−)-**6**: $[\alpha]_D$ −49° (3 mg/mL in THF), circular dichroism band $\Delta\epsilon_{340} = -1.32$ (methanol)] was obtained as the major product upon similar acidic hydrolysis but at C-10 of the known[5a] trans-diastereomer (+)-benzo[*a*]pyrene-(7*R*,8*S*)-diol (9*S*,10*R*)-epoxide. Acidic hydrolysis of *cis*-**5** by trans addition of water at the 7-position provided the *trans*,*trans*,*trans*-tetraols [(+)-**7**: $[\alpha]_D$ +110° (5mg/mL in THF), $k' = 3.9$]. Definitive structural assignments of the enanthiomeric tetraols rests on comparison of their HPLC retention time, UV spectra, mass spectra, and NMR spectra of their tetraacetates with the corresponding data for the racemic tetraol.[12]

The above correlations establish *trans*-**5** as the (9*S*,10*R*)-diol (7*R*,8*S*)-epoxide and *cis*-**5** as the (9*S*,10*R*)-diol (7*S*,8*R*)-epoxide. Furthermore, (−)-**4**, which is metabolically formed from benzo[*a*]pyrene,[9,13] must be the (−)-(9*R*,10*R*)-dihydrodiol. Since labeling studies have shown that the C-9 hydroxyl group derives from water and the C-10 hydroxyl group derives from air in the 9,10-dihydrodiol,[13,14] cytochrome P-450c must form predominantly the (9*S*,10*R*)-arene oxide which epoxide hydrolase[15,16] converts to the (−)-(9*R*,10*R*)-dihydrodiol.

On the basis of the known absolute configurations of several benzo[*a*]pyrene metabolites[5,9,17,18] and the assumption that a superimposition of all of these must fit into the active site of cytochrome P-450c in such a way that the double bond that is epoxidized lies directly over the heme iron, we have proposed[4] that the shape of the catalytic binding site for this enzyme is approximated by the hypothetical hydrocarbon shown in Figure 1. The model predicts that the (9*S*,10*R*)-arene oxide should be formed (dark outline in the hypothetical hydrocarbon skelton, Figure 1) and subsequently converted to the (9*R*,10*R*)-dihydrodiol by epoxide hydrolase, as confirmed by the present study. We felt that assignment of abolute configuration to the metabolically formed 9,10-dihydrodiol would provide a good test of this model since previous workers had erroneously predicted[13] that this dihydrodiol would have a 9*S*,10*S* absolute configuration.

Registry No. 1A, 81987-41-9; **1B**, 82041-88-1; (+)-**2**, 82041-89-2; (+)-**3**, 82041-90-5; (−)-**4**, 62600-11-7; *cis*-**5**, 64937-37-7; *trans*-**5**, 64937-38-8; (+)-6, 82041-91-6; (−)-**6**, 75110-13-3; (+)-**7**, 75110-16-6.

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(11) The THF mother liquor of crystallization from which the pure (9*S*,10*R*)-diol (7*R*,8*S*)-epoxide (*trans*-**5**) was removed was subjected to further purification by HPLC [Du Pont Zorbax SIL column (6.2 × 250 mm^2) eluted with 40% THF in hexane, recycled five times] to provide the pure (9*S*,10*R*)-diol (7*R*,8*R*)-epoxide (*cis*-**5**); NMR (100 MHz, acetone-*d*) δ 4.48 (H_7), 4.10 (H_8), 4.76 (H_9), 5.60 (H_{10}), with $J_{7,8} = 4.2$, $J_{8,9} = J_{9,10} = 2.5$, and $J_{9,10} = 2.5$ H_2. The NMR spectrum of *trans*-**5** was a previously reported.[10]

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2,6-Methano-2,6-dehydronorbornane: An Exceptionally Strained [3.1.1]Propellane[1]

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We report the first synthesis, characterization, and chemical behavior of a new [3.1.1]propellane, 2,6-methano-2,6-dehydronorbornane[2] (**2**). This is the most strained carbocyclic propellane that has been prepared.

Small-ring propellanes are tricyclic systems with three rings fused to a common, central bond containing two inverted carbon atoms.[3] Both the molecular orbital[4] and maximum overlap[5]

(1) Presented in part at the 10th Northeast Regional Meeting of the American Chemical Society, July 1980, Potsdam, NY, and at the 7th Meeting of Chemists of Croatia, February 1981, Zagreb, Yugoslavia.

(2) Tetracyclo[3.2.1.0.^{1,3}O^{3,7}]octane.

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