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A General Synthetic Method for Non-K-Region Arene Oxides

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Abstract: A general method has been developed for the synthesis of non-K-region arene oxides of polycyclic aromatic hydrocarbons. The procedure involves construction of a halohydrin ester at the desired position of a saturated ring in the hydrocarbon, bromination of the unsubstituted benzylic position with *N*-bromosuccinimide, and direct treatment of the resulting dibromo ester with dry sodium methoxide. Cyclization to form the oxirane ring and dehydrohalogenation to introduce the double bond occur in a single step. Syntheses of naphthalene 1,2-oxide, phenanthrene 1,2- and 3,4-oxides, and benzo[*a*]pyrene 7,8- and 9,10-oxides were achieved in high yield.

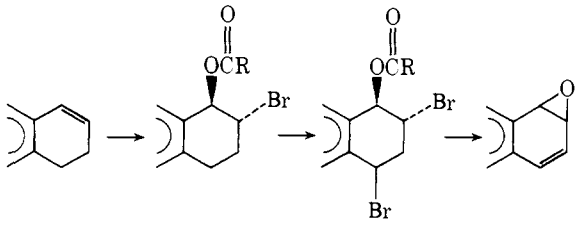
Since the initial demonstration of an arene oxide as an obligatory intermediate in the metabolism of naphthalene by mammals,[1] substantial interest has developed in the chemistry, biochemistry, and pharmacology of arene oxides.[2] Subsequent reports have implicated arene oxides in the metabolism of several other polycyclic aromatic hydrocarbons. Arene oxides are capable of transforming cells in culture and are potent frameshift mutagens in bacterial test systems. In addition, substantial evidence has accumulated which implicates metabolically formed arene oxides as the causative agents which account for the toxicity of several aromatic hydrocarbons. The broad spectrum of biological activity displayed by arene oxides has prompted the exploration of convenient synthetic routes into this class of compounds.

For polycyclic aromatic hydrocarbons, both K-region and non-K-region arene oxides are possible. Enhanced stability of K-region versus non-K-region arene oxides with regard to isomerization to phenols in the neutral and basic pH regions[3] has permitted more flexibility in the choice of synthetic routes to K-region arene oxides. Thus, closure of the corresponding dialdehydes with tris(dimethylamino)phosphine,[4] dehydration of *trans*-dihydrodiols with the dimethylacetal of dimethylformamide,[5] and cyclization of *trans*-halohydrin acetates[6] have all proved useful in the synthesis of K-region arene oxides. Unavailability of requisite starting materials and overly vigorous reaction conditions have precluded the use of these routes for the preparation of non-K-region arene oxides.

Vogel and coworkers[7] have devised a dehydrohalogenation route to non-K-region arene oxides in which HBr is eliminated from bromotetrahydro epoxides to generate the necessary double bonds in the final step. Conversion of 1,2-epoxy-4,5-dibromocyclohexane to benzene oxide with dry sodium methoxide and of 1,2-epoxy-4-bromotetralin to naphthalene 1,2-oxide with diazabicyclononene are typical examples.[8] Although elegantly conceived, this approach suffers from a serious drawback in that the tetrahydro epoxides of polycyclic hydrocarbons are relatively unstable to the conditions of bromination with NBS (*N*-bromosuccinimide) and suffer extensive polymerization and isomerization to ketones. The low yields and difficulties in purification at this step[8c,9] prompted a search for efficient and convenient alternatives.

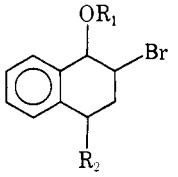
The optimum situation for synthesis of labile non-K-region arene oxides requires the preparation of a stable, easily purified immediate precursor which can be converted into the desired arene oxide in high yield under mild conditions. Bromination of tetrahydro epoxides results in a mixture of stereoisomers which are difficult to separate from impurities by crystallization. In marked contrast, bromination of *trans*-bromohydrin trifluoroacetates with NBS has been found to proceed in excellent yield and with high stereoselectivity.[10] Bromohydrin esters were employed rather than the free benzylic alcohols in order to avoid oxidation to ketones. Labile trifluoroacetates were selected as blocking groups for the benzylic alcohol since they could be removed in the presence of the reactive bromine introduced at the other benzylic position. Elimination of 2 mol of HBr with dry sodium methoxide in tetrahydrofuran cyclized the bromohydrin to an oxirane and introduced the final double bond to produce the desired arene oxides in excellent yield and high purity. While the halohydrin ester route as initially described[10] has proved most effective in the synthesis of labile arene oxides, there are inherent disadvantages in that an ester blocking group must be introduced and later removed and in that certain dibromo esters are not readily hydrolyzed without loss of the benzylic bromine. Subsequent studies of the halohydrin ester route have shown that the above disadvantages can be avoided. Dihydroaromatic hydrocarbons can be converted to bromohydrin acetates in a single step with *N*-bromoacetamide in acetic acid, brominated at the benzylic position with NBS, and converted directly to the desired arene oxide without an intervening hydrolysis step. Since separate steps are not required for the introduction and later removal of a blocking group, the halohydrin ester route becomes a classic example of latent functionality[11] in the synthesis of arene oxides. The procedure is exemplified by the synthesis of naphthalene, phenanthrene, and benzo[*a*]pyrene oxides. The basic scheme is

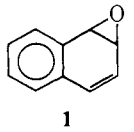
shown below. A discussion of the ^1H NMR spectra and relative stereochemistry of the dibromo esters appears at the end of the Discussion.



Discussion

Synthesis of naphthalene 1,2-oxide (**1**) was examined as a model for the more complex hydrocarbons. Both the acetate (**3b**) and trifluoroacetate (**3a**) of *trans*-1-hydroxy-2-bromotetralin (**2**)[9] are stereoselectively brominated (NBS) in high yield at the free benzylic position to produce the dibromo esters **4a** (87%) and **4b** (82%). On treatment with





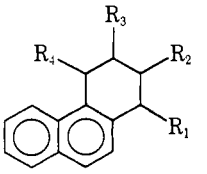
1

2, $R_1 = R_2 = H$
3a, $R_1 = COCF_3$; $R_2 = H$
b, $R_1 = COCH_3$; $R_2 = H$
4a, $R_1 = COCF_3$; $R_2 = Br$
b, $R_1 = COCH_3$; $R_2 = Br$
5, $R_1 = H$; $R_2 = Br$

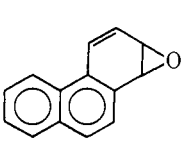
dry sodium methoxide in tetrahydrofuran, both the epoxide ring and the double bond were generated to produce naphthalene 1,2-oxide (**1**) in excellent yield (**4a**, 92%; **4b**, 97%). No particular advantage was found by prior hydrolysis of **4a** to **5** and subsequent treatment with methoxide to produce **1**. The present procedures realized 68–79% overall conversions from **2** to **1** while the earlier route[9] via the tetrahydro epoxide only provides 14% of **1** from the same starting material.

Synthesis of the two possible[2a] non-K-region arene oxides of phenanthrene (**13a,b**) was examined next. Both routes proceed from the appropriate tetrahydrophenanthrenones (**6a,b**)[12] which were reduced to alcohols (**7a,b**), dehydrated to dihydrophenanthrenes (**8a,b**), brominated (**9a,b**), and hydrolyzed at the benzylic positions to provide the requisite bromohydrins (**10a,b**). Acetates, trichloroacetates, and trifluoroacetates (**11a–e**) of **10a** and **10b** were stereoselectively brominated with NBS at the free benzylic position to provide the dibromo esters **12a–e** in high yields. Phenanthrene 1,2- and 3,4-oxides (**13a,b**) were obtained in greater than 90% yield from these esters. Incorporation of the additional hydrolysis step to convert the dibromo ester **12e** to the alcohol **12f** followed by dehydrobromination to the 3,4-oxide (**13b**) proceeded in 70% overall yield for the two steps. In marked contrast, attempts to selectively hydrolyze the ester group in **12a** and **12b** were without success. The bromine at C-4 in these esters exists in a highly axial environment (see later) due in part to steric hindrance at the "bay position"[13] of the phenanthrene ring system and thus undergoes side reactions prior to hydrolysis of the ester.

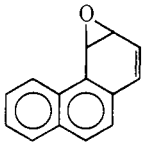
For comparison, synthesis of **13a** and **13b** was attempted via bromination of tetrahydro epoxides and subsequent dehydrohalogenation. The bay position in the tetrahydro epoxide **14a** serves to good advantage in that the axial hydrogen is readily replaced by bromine to form the bromotetrahydro epoxide **14b**. Overall conversion of **14a** to the 1,2-



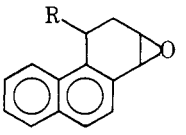
6a, R_1 = ketone; $R_2 = R_3 = R_4 = H_2$
b, $R_1 = R_2 = R_3 = H_2$; R_4 = ketone
7a, R_1 = OH; $R_2 = R_3 = R_4 = H_2$
b, $R_1 = R_2 = R_3 = H_2$; R_4 = OH
8a, $R_1 = R_2 = H$; $R_3 = R_4 = H_2$
b, $R_1 = R_2 = H_2$; $R_3 = R_4 = H$
9a, $R_1 = R_2$ = Br; $R_3 = R_4 = H_2$
b, $R_1 = R_2 = H_2$; $R_3 = R_4$ = Br
10a, R_1 = OH; R_2 = Br; $R_3 = R_4 = H_2$
b, $R_1 = R_2 = H_2$; R_3 = Br; R_4 = OH
11a, $R_1 = OCOCF_3$; R_2 = Br; $R_3 = R_4 = H_2$
b, $R_1 = OCOCl_3$; R_2 = Br; $R_3 = R_4 = H_2$
c, $R_1 = R_2 = H_2$; R_3 = Br; $R_4 = OCOCH_3$
d, $R_1 = R_2 = H_2$; R_3 = Br; $R_4 = OCOCl_3$
e, $R_1 = R_2 = H_2$; R_3 = Br; $R_4 = OCOCF_3$
12a, $R_1 = OCOCF_3$; $R_2 = R_4$ = Br; $R_3 = H_2$
b, $R_1 = OCOCl_3$; $R_2 = R_4$ = Br; $R_3 = H_2$
c, $R_1 = R_3$ = Br; $R_2 = H_2$; $R_4 = OCOCH_3$
d, $R_1 = R_3$ = Br; $R_2 = H_2$; $R_4 = OCOCl_3$
e, $R_1 = R_3$ = Br; $R_2 = H_2$; $R_4 = OCOCF_3$
f, $R_1 = R_3$ = Br; $R_2 = H_2$; R_4 = OH



13a



13b



14a, R = H_2
b, R = Br

oxide (**13a**) proceeds in 61% yield. In contrast, attempted bromination of 3,4-epoxy-1,2,3,4-tetrahydrophenanthrene was completely without success. In this instance, the proximate bay position sufficiently destabilizes the starting epoxide that it does not withstand the conditions of bromination and rearranges extensively to ketone. For this same reason, the 3,4-oxide (**13b**) is markedly less stable than the 1,2-oxide (**13a**).

The biologically interesting 7,8- and 9,10-oxides of the environmental carcinogen benzo[*a*]pyrene have been synthesized[8c] via the basic procedure[9] developed for **1**. In light of the preceding studies on the phenanthrene ring system, it is not surprising to note that they were obtained in low yield and impure state. Instability of the oxides prevented substantial purification at the final stage. The halohydrin ester route has proved highly successful in the preparation of these challenging compounds.

The dihydrobenzo[*a*]pyrenes required for the synthesis of both arene oxides have been obtained[14] from 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one.[15] Reduction of the ketone to the 7-alcohol followed by dehydration has provided a satisfactory route to 9,10-dihydrobenzo[*a*]pyrene (**17b**).[14] Conversion of **17b** to the bromohydrin (**20b**) was as described.[8c] 7,8,9,10-Tetrahydrobenzo[*a*]pyrene (**15**) is conveniently prepared by reduction of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one. In the course of examining the free radical acetoxylation of **15** with lead tetraacetate, Kon and Roe[14] identified 7,8-dihydrobenzo[*a*]pyrene (**17a**) as a major product which presumably arose by selective acetoxylation at C-10 (**16**) and subsequent ester pyrolysis in the medium. Column chromatography must be employed to separate the several products. A second major product has now been identified as 6-acetoxy-7,8-dihydrobenzo[*a*]pyrene (**18**) by dehydrogenation to the known 6-acetoxybenzo[*a*]pyrene

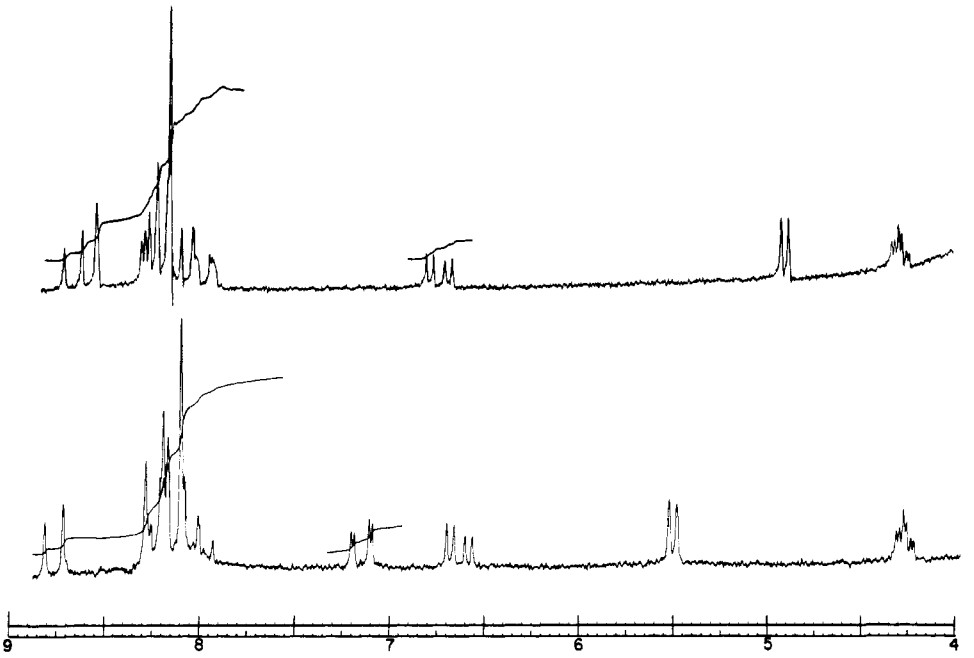
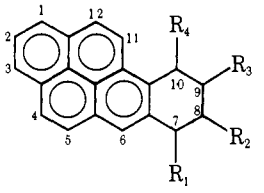
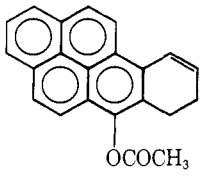


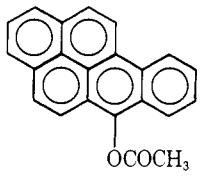
Figure 1. ^{1}H NMR spectra of benzo[*a*]pyrene 7,8-oxide (**22b**, top) and 9,10-oxide (**22a**, bottom) in deuteriotetrahydrofuran measured at 10° and 100 MHz.



15, $R_1 = R_2 = R_3 = R_4 = H_2$
16, $R_1 = R_2 = R_3 = H_2$; $R_4 = OCOCH_3$
17a, $R_1 = R_2 = H_2$; $R_3 = R_4 = H$
b, $R_1 = R_2 = H$; $R_3 = R_4 = H_2$
20a, $R_1 = R_2 = H_2$; $R_3 = Br$; $R_4 = OCOCH_3$
b, $R_1 = OH$; $R_2 = Br$; $R_3 = R_4 = H_2$
c, $R_1 = OCOCF_3$; $R_2 = Br$; $R_3 = R_4 = H_2$
d, $R_1 = OCOCH_3$; $R_2 = Br$; $R_3 = R_4 = H_2$
21a, $R_1 = R_3 = Br$; $R_2 = H_2$; $R_4 = OCOCH_3$
b, $R_1 = OCOCF_3$; $R_2 = R_4 = Br$; $R_3 = H_2$



18



19

(**19**).[16] Careful control of reaction conditions allows the direct crystallization of pure **16** from the reaction medium in 82% yield. Elimination of acetic acid from **16** and direct conversion of the resultant **17a** into the bromohydrin acetate (**20a**) with *N*-bromoacetamide in acetic acid occurred in 96% yield for the two steps.

Bromination of the unsubstituted benzylic positions in the bromohydrin acetate **20a** and the bromohydrin trifluoroacetate **20c** with NBS proceeded in 70% yield to produce the stable, crystalline dibromo esters **21a** and **21b**, respectively. The choice of ester employed in these sequences is critical. The bromohydrin acetate **20d** (ester at C-7) fails to undergo bromination at C-10 for unknown reasons. The trifluoroacetate analog of **20a** (ester at C-10) could not be isolated due to spontaneous elimination of trifluoroacetic acid, presumably because of its quasi-axial conformation in the hindered bay position. Dehydrohalogenation of the dibromo

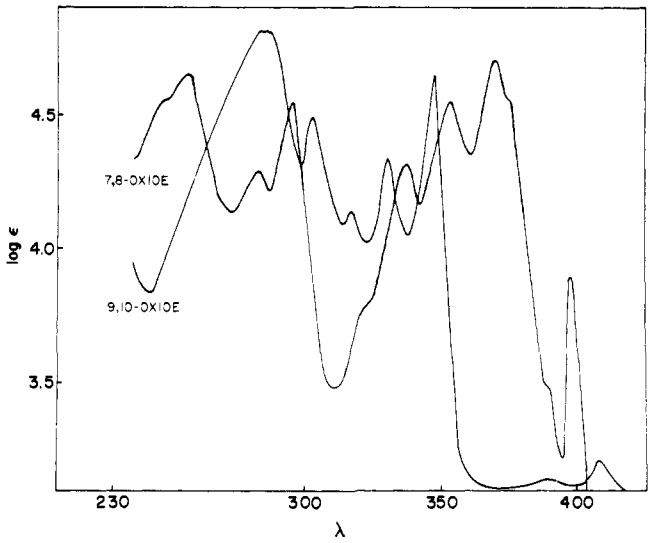
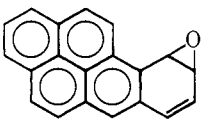
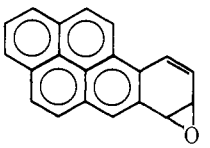


Figure 2. Ultraviolet spectra of benzo[*a*]pyrene 7,8- (**22b**) and 9,10-oxides (**22a**) in tetrahydrofuran at room temperature.

esters **21a** and **21b** with dry sodium methoxide in tetrahydrofuran cleanly produced the desired benzo[*a*]pyrene 9,10- and 7,8-oxides (**22a** and **22b**) in 95 and 93% yield, respectively. Their ^{1}H NMR and uv spectra (Figures 1 and 2) are consistent with the structures assigned.



22a



22b

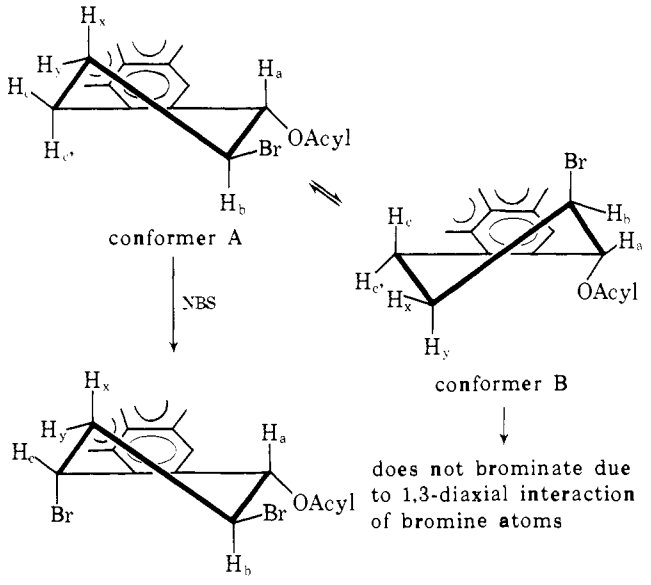
Much of the success of the halohydrin ester route to arene oxides can be attributed to the stereoselectivity for the bromination step with NBS. The highly crystalline dibromo esters are preponderantly single stereoisomers which can readily be obtained quite pure prior to generation of the arene oxide. Inspection of the ^{1}H NMR spectra of the halohydrin esters and the resulting dibromo esters (Table I)

Table I. ^{1}H NMR Spectrum of Dibromo Esters

Compd	Methylene protons	Acetyl proton	Methine protons: Acyl	Methine protons: Nonbenzylic	Methine protons: Benzylic	Aromatic proton
4a[a,c]	2.77 (H_{3ax}), 3.0 (H_{3eq})		6.45 (H_1)	4.82 (H_2)	5.51 (H_4)	7.0–7.6
	$^3J_{1,2}$ = 8.5, $^3J_{2,3ax}$ = 10.5, $^3J_{2,3eq}$ = $^3J_{4,3ax}$ = $^3J_{4,3eq}$ = 4.3, $^2J_{3eq,3ax}$ = 15.5					
4b[b]	2.6–3.2 ($2H_3$)	2.22	6.33 (H_1)	4.75 (H_2)	5.52 (H_4)	7.0–7.6
	$^3J_{1,2}$ = 8.5, $^3J_{2,3ax}$ = 10.5, $^3J_{2,3eq}$ = $^3J_{4,3ax}$ = $^3J_{4,3eq}$ = 4.3					
12a[a]	2.6–3.3 ($2H_3$)		6.71 (H_1)	5.08 (H_2)	5.91 (H_4)	7.0–8.2
	$^3J_{1,2}$ = 9, $^3J_{2,3ax}$ = 12, $^3J_{2,3eq}$ = 3.0, $^3J_{4,3ax}$ = $^3J_{4,3eq}$ = 4.3					
12b[b]	2.6–3.3 ($2H_3$)		6.68 (H_1)	5.12 (H_2)	5.95 (H_4)	7.0–8.2
	$^3J_{1,2}$ = 9, $^3J_{2,3ax}$ = 12, $^3J_{2,3eq}$ = 3.0, $^3J_{4,3ax}$ = $^3J_{4,3eq}$ = 4.3					
12c[b]	2.8–3.2 ($2H_2$)	2.12	6.75 (H_4)	4.61 (H_3)	5.76 (H_1)	7.4–8.1
	$^3J_{4,3}$ = 3.0, $^3J_{3,2ax}$ = $^3J_{3,2eq}$ = 4.0, $^3J_{1,2}$ = 9.0, $^3J_{1,2'}$ = 8					
12d[b]	2.8~3.2 ($2H_2$)		6.74 (H_4)	4.75 (H_3)	5.75 (H_1)	7.4–8.1
	$^3J_{4,3}$ = 3.0, $^3J_{3,2ax}$ = $^3J_{3,2eq}$ = 4.0, $^3J_{1,2}$ = $^3J_{1,2'}$ = 7.5					
12e[b]	2.8–3.15 ($2H_2$)		6.92 (H_4)	4.67 (H_3)	5.75 (H_1)	7.4–8.1
	$^3J_{4,3}$ = 3.5, $^3J_{3,2ax}$ = $^3J_{3,2eq}$ = 4.0, $^3J_{1,2}$ = $^3J_{1,2'}$ = 8.0					
21a[b]	2.9–3.3 ($2H_8$)	2.10	7.06 (H_{10})	4.72 (H_9)	6.10 (H_7)	7.8–8.5
	$^3J_{10,9}$ = 3.5, $^3J_{9,8ax}$ = $^3J_{9,8eq}$ = 4.0, $^3J_{7,8}$ = 9.0, $^3J_{7,8'}$ = 8.0					
21b[a]	2.6–3.4 ($2H_9$)		6.88 (H_7)	5.18 (H_8)	6.22 (H_{10})	7.6–9.0
	$J_{7,8}$ = 10, $^3J_{8,9ax}$ = 12, $^3J_{8,9eq}$ = 3.0, $^3J_{10,9ax}$ = $^3J_{10,9eq}$ = 4.0					

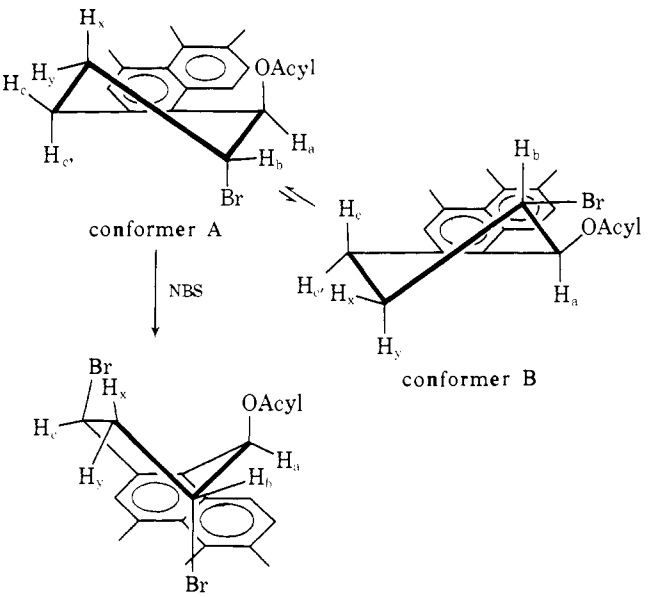
[a] Varian HA-100. [b] Varian A-60 in $CDCl_3$. [c] Chemical shifts (δ) are reported in ppm downfield from internal TMS, and coupling constants (J) are in Hz.

suggests that this stereoselectivity is a consequence of axial attack on the least hindered ring conformer. Halohydrin esters **3a, 3b, 11a, 11b,** and **20c,** which *do not* have the bulky ester substituent at the benzylic portion of a hindered bay position, show the following ^{1}H NMR spectra: benzylic methylene protons H_c and $H_{c'}$ as an A_2B_2-type triplet due to coupling ($J \sim 7$ Hz) to the methylene protons H_x and H_y, H_a as a doublet with $J_{a,b} = 4$, and $J_{b,y} = 3$ Hz. The A_2B_2 triplet requires that conformers A and B (see below)



are present in comparable amounts. The ^{1}H NMR spectra of the resulting dibromo esters **4a, 4b, 12a, 12b,** and **21b** show $J_{a,b}$ = 8.5–10, $J_{b,x}$ = 10.5–12, $J_{b,y}$ = 3, and $J_{c,x} = J_{c,y}$ = 3 Hz indicative that axial attack had occurred on conformer A as confirmed by the large value of $J_{a,b}$ and the equality of $J_{c,x}$ and $J_{c,y}$. A general preference for axial attack and possible steric hindrance of the periaromatic hydrogen to equatorial attack may also be factors in the selectivity. When the benzylic position to be brominated is part of a hindered bay position in the hydrocarbon (i.e., **11a, 11b,** and **20c**), the brominations proceed more readily and with even higher stereoselectivity. The special role of the bay position is dramatically emphasized by the highly selective attack of lead tetraacetate on tetrahydrobenzo[*a*]pyrene (**15**) to produce **16** in over 80% yield without detectable amounts of attack at the other benzylic position.

When the bulky ester group of the halohydrin ester resides at the benzylic portion of a hindered bay position (**11c, 11d, 11e,** and **20a**), the molecule prefers conformation A (see below) in which the ester occupies a quasi-axial posi-



tion: benzylic methylene protons H_c and $H_{c'}$ as a complex ABXY-type multiplet, H_a as a doublet with $J_{a,b} \sim 3$, and H_b as a quartet with $J_{b,x} = J_{b,y} \sim 3$ Hz. The very small value of $J_{a,b}$ requires that the ester group resides in an axial environment nearly all the time. Bromination of these esters to form **12c, 12d, 12e,** and **21a** occurs at a markedly reduced rate, and the products have both bromine atoms in quasi-axial environments: H_a as a doublet with $J_{a,b}$ = 3–3.5, H_b as a quartet with $J_{b,x} = J_{b,y}$ = 4.0 and H_c as a quartet in **12c** and **21b** with $J_{c,x}$ = 9 and $J_{c,y}$ = 8 and as a triplet in **12d** and **12e** with $J_{c,x} = J_{c,y}$ = 7 Hz. The large values of $J_{c,x}$ and $J_{c,y}$ suggest the half boat form shown. The unusual conformation suggested for these dibromo esters is a consequence of the molecule attempting to maintain axial attack and, at the same time, avoid severe 1,3-diaxial interactions between bromine atoms.

The biochemistry of the arene oxides prepared in this study is currently under investigation. The role of the arene oxides **22a** and **22b** in the metabolism of benzo[*a*]pyrene by liver preparations has been described.[17] The action of epoxide hydrase[18] and the kinetics of isomerization[3] for the phenanthrene oxides **13a** and **13b** have also been reported.

Experimental Section

Infrared spectra were taken on Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. The proton NMR spectra were taken with Varian A-60 and HA-100 instruments and chemical shift data are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (J) in hertz. Mass spectra were run on a Hitachi Perkin-Elmer RMU-7 with an ionizing potential of 70 eV unless otherwise indicated. High pressure liquid chromatographic (HPLC) analyses were carried out with Chromatronix 3500 high pressure liquid chromatograph equipped with a Varian MicroPak alumina column (0.5 m × 0.6 cm, 10 μ particles): 10% methylene chloride in hexane containing 0.2% methanol and 1% triethylamine as mobile phase at a flow rate of 2.4 ml/min.

2-Bromo-1-trifluoroacetoxytetralin (3a). A mixture of 2 g of 2-bromo-1-hydroxytetralin (**2**),[9] 2 ml of trifluoroacetic anhydride, and 10 ml of chloroform was stirred at 10° for 0.5 hr. After evaporation of solvent under reduced pressure, 50 ml of dry ether and 5 g of anhydrous K_2CO_3 were added to the residue and the mixture was stirred for 2 hr. Solids were removed by filtration, and the solvent was evaporated to leave 2.4 g (84%) of colorless oil which was purified by distillation: bp 100–105° (0.2 mm); ^{1}H NMR (60 MHz, $CDCl_3$) 2.0–3.2 ($H_{3,4}$), 4.5 (H_2), 6.3 ($^3J_{1,2}$ = 5, H_1), and 7.0–7.5 (H_{5-8}).

Anal. Calcd for $C_{12}H_{10}BrF_3O_2$: C, 44.61; H, 3.12. Found: C, 44.86; H, 3.08.

1-Acetoxy-2-bromotetralin (3b). To a cooled solution of 4 g of the bromohydrin (**2**)[9] in 30 ml of pyridine was added dropwise 3.2 ml of acetic anhydride with stirring. The reaction mixture was stirred at room temperature for 24 hr, acidified with cold 10% HCl, and extracted with chloroform. The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to leave 4.7 g (99%) of colorless crystals which were recrystallized from ether–petroleum ether to give colorless prisms: mp 96–97°; ^{1}H NMR (60 MH_2, $CDCl_3$) 2.1 (CH_3CO), 2.15–2.7 (H_3), 2.8–3.2 (H_4), 4.5 ($^3J_{2,3}$ = 3.5, $^3J_{2,3'}$ = 6.5, H_2), 6.21 ($^3J_{1,2}$ = 5, H_1), and 7.10–7.40 (H_{5-8}).

Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: C, 53.48; H, 5.07.

2,4-Dibromo-1-trifluoroacetoxytetralin (4a). A mixture of 2.4 g of **3a**, 1.6 g of *N*-bromosuccinimide, 5 mg of α,α'-azoisobutyrodinitrile, and 50 ml of CCl_4 was irradiated with a sun lamp and stirred under a current of nitrogen at 50–60°. After a short induction period, reaction commenced vigorously and was completed in 15–30 min. After filtration to remove precipitated succinimide, the filtrate was evaporated to leave crystals which were recrystallized from petroleum ether to give 2.6 g (87%) of colorless prisms: mp 89–90°; ^{1}H NMR (see Table I).

Anal. Calcd for $C_{12}H_9Br_2F_3O_2$: C, 35.85; H, 2.25. Found: C, 35.81; H, 2.09.

1-Acetoxy-2,4-dibromotetralin (4b). The conversion of **3b** (3 g) into **4b** was accomplished in 82.5% yield according to the procedure described above for **3a**. The dibromide **4b** was obtained as colorless needles: mp 114–115° (ether–petroleum ether); ^{1}H NMR (see Table I).

Anal. Calcd for $C_{12}H_{12}Br_2O_2$: C, 41.41; H, 3.47. Found: C, 41.43; H, 3.36.

2,4-Dibromo-1-hydroxytetralin (5). A mixture of 1 g of **4a**, 0.4 ml of 40% aqueous diethylamine, and 15 ml of acetonitrile was stirred at 0° for 0.5 hr. The reaction mixture was diluted with 30 ml of water and extracted with methylene chloride (100 ml × 2). The extract was washed with water, dried (K_2CO_3), and evaporated to leave 680 mg (90%) of crystals which were recrystallized from ether–petroleum ether to give colorless prisms: mp 109–110°; ^{1}H NMR (100 MHz, $CDCl_3$), 2.35–3.20 (H_3), 2.50 (OH), 4.76 ($^3J_{2,1}$ = 9.5, $^3J_{2,3}$ = 10.5, $^3J_{2,3'}$ = 4, H_2), 5.0 ($^3J_{1,2}$ = 9.5 H_1), and 5.52 ($^3J_{4,3}$ = $^3J_{4,3'}$ = 4, H_4).

Anal. Calcd for $C_{10}H_{10}Br_2O$: C, 39.25; H, 3.29. Found: C, 39.26; H, 3.28.

Naphthalene 1,2-Oxide (1).[19] A mixture of 200 mg of **4a**, 200 mg of dry sodium methoxide, and 4 ml of dry tetrahydrofuran was stirred at 0–2° for 20 hr under nitrogen. The reaction mixture was poured into 50 ml of cold ether, washed with water (20 ml × 2), dried (K_2CO_3), and evaporated to leave 80 mg (92%) of colorless crystals which were recrystallized from ether–petroleum ether to give colorless prisms; the ^{1}H NMR spectrum was superimposable with that of the authentic material.[9] The conversion of **4b** (174 mg) and **5** (670 mg) into **1** was accomplished in 95 and 97% yield, respectively, according the procedure described above for **4a**.

1-Hydroxy-1,2,3,4-tetrahydrophenanthrene (7a). To a suspension of 1 g of 1,2,3,4-tetrahydro-4-oxophenanthrene (**6a**)[12] in 100 ml of methanol was added 1.5 g of sodium borohydride in portions with stirring. The stirring was continued for 1 hr. The reaction mixture was evaporated, and the residue was treated with 50 ml of water and extracted with chloroform (50 ml × 2). The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to leave crystals which were recrystallized from ether–petroleum ether to give 1.0 g of colorless feathers, mp 99–100°.

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.83; H, 7.23.

3,4-Dihydrophenanthrene (8a). A mixture of 4.5 g of **7a**, 4 drops of concentrated hydrochloric acid, and 25 ml of acetic acid was heated at 90° for 1 hr. After cooling, 100 ml of water was added and the reaction mixture was extracted with chloroform (100 ml × 2). The chloroform extract was washed with saturated sodium carbonate solution and water, dried (K_2CO_3), and evaporated to leave an oil which was purified by evaporative distillation to give 3.8 g of colorless oil: bp 90° (0.1 mm); ^{1}H NMR (60 MHz, $CDCl_3$), 6.1 ($^3J_{2,1}$ = 10 and $^3J_{2,3}$ = $^3J_{2,3'}$ = 4, H_2), and 6.6 ($^3J_{1,2}$ = 10, $^4J_{1,3}$ = $^4J_{1,3'}$ = 1.5, H_1).

Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.31; H, 6.54.

1,2-Dibromo-1,2,3,4-tetrahydrophenanthrene (9a). To a stirred solution of 2 g of **8a** in 50 ml of carbon tetrachloride was added a solution of 0.85 ml of bromine in 10 ml of carbon tetrachloride at −30°. The solvent was evaporated after stirring for 30 min, and the residue was recrystallized from ether–petroleum ether to give 3 g of colorless prisms, mp 81–83°.

Anal. Calcd for $C_{14}H_{12}Br_2$: C, 49.44; H, 3.56. Found: C, 49.16; H, 3.61.

2-Bromo-1,2,3,4-tetrahydro-1-hydroxyphenanthrene (10a). A mixture of 2.7 g of **9a**, 1.5 g of magnesium carbonate, 40 ml of acetone, and 10 ml of water was refluxed for 5 hr. After the insoluble inorganic salts were removed by filtration, the filtrate was evaporated and extracted with ether (100 ml × 2). The ethereal extract was washed with water, dried (K_2CO_3), and evaporated to leave crystals which were recrystallized from chloroform–petroleum ether to give 2.0 g of colorless feathers: mp 152–153°; ^{1}H NMR (60 MHz, $CDCl_3$) 4.42 (H_2) and 5.02 ($^3J_{1,2}$ = 7, H_1).

Anal. Calcd for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.68; H, 4.98.

2-Bromo-1-trifluoroacetoxy-1,2,3,4-tetrahydrophenanthrene (11a). The conversion of **10a** (1.5 g) into **11a** was accomplished in 90% yield according to the procedure described above for **3a**. The bromohydrin trifluoroacetate **11a** was obtained as colorless needles: mp 88–89° (ether–petroleum ether); ^{1}H NMR (60 MHz, CCl_4) 2.3–2.8 ($2H_3$), 3.37 (A_2B_2-type triplet, $^3J_{4,3}$ = 7, $2H_4$), 4.58 ($^3J_{2,3}$ = 6, $^3J_{2,3'}$ = 3, $^3J_{2,1}$ = 4, H_2), 6.42 ($^3J_{1,2}$ = 4, H_1), and 7.2–8.2 (H_{5-10}).

Anal. Calcd for $C_{16}H_{12}BrF_3O_2$: C, 51.50; H, 3.24. Found: C, 51.45; H, 3.10.

2-Bromo-1-trichloroacetoxy-1,2,3,4-tetrahydrophenanthrene (11b). The bromohydrin **10a** (1.5 g) was esterified in 83.5% yield using trichloroacetic anhydride according to the procedure described as for **3a**. The trichloroacetate (**11b**) was obtained as colorless prisms: mp 111–112° (ether–petroleum ether); ^{1}H NMR (60 MHz, $CDCl_3$) 2.3–2.8 ($2H_3$), 3.37 (A_2B_2-type triplet, $^3J_{4,3}$ = 7, $2H_4$), 4.78 ($^3J_{2,3}$ = 6, $^3J_{2,3'}$ = 3, $^3J_{2,1}$ = 4, H_2), and 6.82 ($^3J_{1,2}$ = 4, H_1).

Anal. Calcd for $C_{16}H_{12}BrCl_3O_2$: C, 45.46; H, 2.86. Found: C, 45.20; H, 2.82.

2,4-Dibromo-1-trifluoroacetoxy-1,2,3,4-tetrahydrophenanthrene (12a). The conversion of **11a** (1 g) into **12a** was accomplished in

80% yield according to the procedure described above for **4a**. The dibromide **12a** was obtained as colorless needles: mp 127–128° (ether–petroleum ether); ^{1}H NMR (see Table I) mass (*m/e*, 15 eV) M^+ (450, 452, 454).

Anal. Calcd for $C_{16}H_{11}Br_2F_3O_2$: C, 42.51; H, 2.45. Found: C, 42.48; H, 2.45.

2,4-Dibromo-1-trichloroacetoxy-1,2,3,4-tetrahydrophenanthrene (12b). The bromination of **11b** (460 mg) was accomplished in 53% yield according to the procedure described above for **4a**. The dibromide **12b** was obtained as colorless feathers: mp 145–146° (chloroform–petroleum ether); ^{1}H NMR (see Table I).

Anal. Calcd for $C_{16}H_{11}Br_2Cl_3O_2$: C, 41.28; H, 2.38. Found: C, 41.15; H, 2.35.

1,2-Epoxy-1,2,3,4-tetrahydrophenanthrene (14a). To a stirred solution of 1.65 g of the bromohydrin **10a** in 20 ml of absolute methanol was added a solution of 640 mg of dry sodium methoxide in 10 ml of absolute methanol over a period of 10 min at 0°. The mixture was stirred for an additional 1 hr at 0°, treated with 10 ml of cold water, and extracted with methylene chloride (100 ml × 2). The extract was washed with water, dried (K_2CO_3), and evaporated to leave 1.15 g of colorless crystals which were recrystallized from ether–petroleum ether to give colorless prisms: mp 90–91°; ^{1}H NMR (60 MHz, CCl_4) 3.70 (H_2) and 3.83 ($^3J_{1,2}$ = 4.5, H_1).

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.93; H, 5.94.

4-Bromo-1,2-epoxy-1,2,3,4-tetrahydrophenanthrene (14b). The tetrahydro epoxide **14a** (1 g) was brominated according to the procedure described above for **3a**. The bromide **14b** (1.38 g) was obtained as a pale brown oil which was used in the following reaction without further purification: ^{1}H NMR (60 MHz, CCl_4) 3.67 (H_2), 3.81 ($^3J_{1,2}$ = 4.5, H_1), and 5.82 ($^3J_{4,3}$ = $^3J_{4,3'}$ = 6, H_4).

Phenanthrene 1,2-Oxide (13a). A mixture of 1 g of the bromo epoxide **14b**, 3 g of dry sodium methoxide, and 30 ml of dry tetrahydrofuran was stirred at 0–2° for 15 hr. The reaction mixture was worked up the same way as in the case of **1** to give 440 mg (61% overall yield from **14a**) of crystals which were recrystallized from ether to give colorless prisms, mp 110°. Similar treatment of **12a** (363 mg) and **12b** (500 mg) gave **13a** in 90 and 92% yield, respectively: ^{1}H NMR (60 MHz, $CDCl_4$) 4.25 ($^3J_{2,1}$ = $^3J_{2,3}$ = 4.0, $^4J_{2,4}$ = 1.5, H_2), 4.67 ($^3J_{1,2}$ = 4.0, H_1), 6.63 ($^3J_{3,4}$ = 10.0, $J_{3,2}$ = 4.0, H_3), and 7.30–8.40 ($H_{4\text{-}10}$), mass (*m/e*) M^+ (194), M^+ − 16 (178), $M^+ - H_2O$ (176), and M^+ − CHO (165).

Anal. Calcd for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.66; H, 5.00.

1-Hydroxy-1,2,3,4-tetrahydrophenanthrene (7b). The conversion of **6b**[12] (2 g) into **7b** was accomplished in 99% yield according to the procedure described above for **7a**. The alcohol **7b** was obtained as colorless needles, mp 125–126° (ether–petroleum ether).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.65; H, 7.13.

1,2-Dihydrophenanthrene (8b). The conversion of **7b** (2 g) into **8b** was accomplished in 84% yield according to the procedure described above for **8a**. The dihydrophenanthrene **8b** was obtained as a colorless oil: bp 110–115° (0.3 mm); ^{1}H NMR (60 MHz, $CDCl_3$) 6.27 ($^3J_{3,4}$ = 10, $^3J_{3,2}$ = $^3J_{3,2'}$ = 4, H_3).

3,4-Dibromo-1,2,3,4-tetrahydrophenanthrene (9b). The conversion of **8b** (3 g) into **9b** was accomplished in 79% yield according to the procedure described above for **9a**. The dibromide **9b** was obtained as colorless prisms, mp 81–83° (ether–petroleum ether).

Anal. Calcd for $C_{14}H_{12}Br_2$: C, 49.44; H, 3.56. Found: C, 49.62; H, 3.74.

3-Bromo-1,2,3,4-tetrahydro-4-hydroxyphenanthrene (10b). The conversion **9b** (3 g) into **10b** was accomplished in 91% yield according the procedure described for **10a**. The bromohydrin **10b** was obtained as colorless feathers: mp 157–158° (chloroform–petroleum ether); ^{1}H NMR (60 MHz, $CDCl_3$) 4.75 (H_3) and 5.63 ($^3J_{4,3}$ = 3.5, H_4).

Anal. Calcd for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found: C, 60.40; H, 4.83.

4-Acetoxy-3-bromo-1,2,3,4-tetrahydrophenanthrene (11c). The bromohydrin **10b** (1 g) was acetylated in 95% yield according to the procedure described for **3b**. The acetoxybromohydrin **11c** was obtained as colorless needles: mp 127–128° (ether); ^{1}H NMR (60 MHz, $CDCl_3$) 2.05 (CH_3CO), 2.10–2.80 ($2H_2$), 2.90–3.40 (m, $2H_1$), 4.71 ($^3J_{3,4}$ = $^3J_{3,2}$ = $^3J_{3,2'}$ = 3, H_3), 6.77 ($^3J_{4,3}$ = 3, H_4), and 7.20–7.70 ($H_{5\text{-}10}$).

Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.39; H, 4.75. Found: C, 60.21; H, 4.70.

3-Bromo-4-trichloroacetoxy-1,2,3,4-tetrahydrophenanthrene (11d). The bromohydrin **10b** (2 g) was esterified in 78% yield using trichloroacetic anhydride according to the procedure described for **3a**. The trichloroacetoxybromohydrin **11b** was obtained as colorless prisms: mp 125–127° (ether–petroleum ether); ^{1}H NMR (60 MHz, $CDCl_3$) 2.10–2.75 (m, $2H_2$), 3.0–3.45 (m, $2H_1$), 4.80 ($^3J_{2,1}$ = $^3J_{2,3}$ = $^3J_{2,3'}$ = 3, H_3), and 6.85 ($^3J_{1,2}$ = 3, H_4).

Anal. Calcd for $C_{16}H_{12}BrCl_3O_2$: C, 45.46; H, 2.86. Found: C, 45.30; H, 2.84.

3-Bromo-4-trifluoroacetoxy-1,2,3,4-tetrahydrophenanthrene (11e). The bromohydrin **10b** (2 g) was esterified in 89% yield according to the procedure described for **3a**. The trifluoroacetate **11e** was obtained as colorless needles: mp 115° (ether–petroleum ether); ^{1}H NMR (100 MHz, $CDCl_3$) 2.2–2.7 (m, H_2), 2.9–3.5 (m, H_1), 4.76 ($^3J_{3,4}$ = $^3J_{3,2}$ = $^3J_{3,2'}$ = 3.5, H_3), 6.95 ($^3J_{4,3}$ = 3.5, H_4). The coupling between the H_3 and H_4 protons was confirmed by decoupling.

Anal. Calcd for $C_{16}H_{12}BrF_3O_2$: C, 51.50; H, 3.24. Found: C, 51.34; H, 3.20.

4-Acetoxy-1,3-dibromo-1,2,3,4-tetrahydrophenanthrene (12c). The conversion of **11c** into **12c** was accomplished in 54% yield according to the procedure described above for **4a**. The dibromide **12c** was obtained as colorless prisms: mp 157–158° (chloroform–petroleum ether); ^{1}H NMR (see Table I); mass (*m/e*, 15 eV) M^+ (396, 398, 400).

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.21; H, 2.51. Found: C, 48.18; H, 2.48.

1,3-Dibromo-4-trichloroacetoxy-1,2,3,4-tetrahydrophenanthrene (12d). The conversion of **11c** (923 mg) into **12d** was accomplished in 82% yield according to the procedure described above for **4a**. The dibromide **12d** was obtained as colorless prisms: mp 127–128° (ether–petroleum ether); ^{1}H NMR (see Table I).

Anal. Calcd for $C_{16}H_{11}Br_2Cl_3O_2$: C, 41.28; H, 2.38. Found: C, 41.08; H, 2.17.

1,3-Dibromo-4-trifluoroacetoxy-1,2,3,4-tetrahydrophenanthrene (12e). The conversion of **11c** (900 mg) into **12e** was accomplished in 91.5% yield according to the procedure described above for **4a**. The dibromide **12e** was obtained as colorless needles: mp 112–113° (ether–petroleum ether); ^{1}H NMR (see Table I); mass (*m/e*, 15 eV) M^+ (454, 452, 450).

Anal. Calcd for $C_{16}H_{11}Br_2F_3O_2$: C, 42.51; H, 2.45. Found: C, 42.35; H, 2.35.

1,3-Dibromo-1,2,3,4-tetrahydro-4-hydroxyphenanthrene (12f). The hydrolysis of **12d** (630 mg) was carried out in the same way as for **5**. The hydroxy compound **12f** was obtained as an oil: ^{1}H NMR (60 MHz, $CDCl_3$) 4.64 (H_3), 5.57 ($^3J_{4,3}$ = 5, H_4), and 5.64 ($^3J_{1,2}$ = $^3J_{1,2'}$ = 5, H_1). The oil was used directly in the following reaction without further purification.

Phenanthrene 3,4-Oxide (13b). A mixture of 400 mg of **12f**, 0.6 ml of 1,5-diazabicyclo[4.3.0]non-5-ene, and 15 ml of dry tetrahydrofuran was stirred at −5° for 16 hr. The reaction mixture[19] was added to 100 ml of cold ether, washed with cold water (20 ml × 3), dried (K_2CO_3), and concentrated below −5° to leave crystals which were recrystallized from 15 ml of ether–petroleum ether (1:1) by cooling to −70° to provide 170 mg (70% overall yield from **12d**) of colorless prisms. This compound was unstable at room temperature and had an indefinite melting point: ^{1}H NMR (60 MHz, CS_2 at 10°) 4.07 ($^3J_{3,4}$ = $^3J_{3,2}$ = 3.5, $^4J_{3,1}$ = 1.5, H_3), 5.02 ($^3J_{4,3}$ = 3.5, H_4), 6.44 ($^3J_{2,1}$ = 9, $^3J_{2,3}$ = 3.5, H_2), 6.80 ($^3J_{1,2}$ = 9, $^4J_{1,3}$ = 1.5, H_1), and 7.20–8.40 ($H_{5\text{-}10}$). The dibromides **12c**, **12d**, and **12e** were converted to **13b** with sodium methoxide according to the procedure described in **1** in 93, 89.5, and 92% yields, respectively.

Anal. Calcd for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.66; H, 5.00.

Acetoxylation of 7,8,9,10-Tetrahydrobenzo[*a*]pyrene (15).[14] **(a).** The reaction was carried out using 2.5 g of 7,8,9,10-tetrahydrobenzo[*a*]pyrene following the method reported by Kon and Roe.[14] The crude chloroform extract was chromatographed on alumina using petroleum ether (bp 60–100°) and benzene. The first petroleum ether eluent gave the starting tetrahydrobenzo[*a*]pyrene (0.3 g). The second petroleum ether–benzene (8:2) eluent gave 1.2 g of 7,8-dihydrobenzo[*a*]pyrene (**17a**), mp 126–128° (recrystallized from ethanol). The third benzene eluent gave 1 g of 6-acetoxy-

7,8-dihydrobenzo[*a*]pyrene (**19**) as pale yellow needles: mp 178–179° (methanol–acetone); ^{1}H NMR (100 MHz, $CDCl_3$) 2.5 ($CH_3C{=}O$), 2.25–2.6 (H_8), 3.0 (H_7), 6.36 ($^3J_{9,10}$ = 10, $^3J_{9,8}$ = 4, H_9), 7.50 ($^3J_{10,9}$ = 10, $^3J_{10,8}$ = 1.6, H_{10}), and 7.80–8.32 ($H_{1\text{-}5}$ and $H_{11,12}$); mass (*m/e*) M^+ (312).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.54; H, 4.87.

(**b**). A mixture of 7 g of 7,8,9,10-tetrahydrobenzo[*a*]pyrene (**15**), 14 g of lead tetraacetate (recrystallized from acetic acid and dried over P_2O_5), 300 ml of benzene, and 200 ml of acetic acid was heated at 50–60° for 7 hr. After addition of 20 ml of ethylene glycol, the benzene layer was washed with water (200 ml × 3), 10% ammonium hydroxide, water and dried (K_2CO_3). Evaporation of the solvent gave reddish crystals which were recrystallized from ethanol to give 7.0 g (81.5%) of **16** as colorless plates: mp 174–175° (lit.[14] 174–175°); ^{1}H NMR (60 MHz, $CDCl_3$) 1.85–2.60 ($H_{8\text{-}9}$), 2.06 ($CH_3C{=}O$), 3.02–3.45 (H_7), H_{10} 6.88 ($^3J_{10,9}$ = $^3J_{10,9'}$ = 3, H_{10}), and 7.65–8.22 (aromatic protons).

6-Acetoxybenzo[*a*]pyrene (19). A mixture of 150 mg of **18,** 15 mg of palladium black, and 4 ml of xylene was reluxed under nitrogen gas for 48 hr. The reaction mixture was filtered, and the filtrate was cooled to give 70 mg of yellow needles which was recrystallized from benzene to give yellow needles, mp 208–209° (lit.[16] mp 208.5–209.5°). This compound was identified by mixture melting point and by comparison of ^{1}H NMR and ir spectra with an authentic sample.[16]

10-Acetoxy-9-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene (20a). A mixture of 4 g of **16,** 300 ml of acetic acid, and 5 drops of concentrated hydrochloric acid was heated at 110° under argon gas in the dark for 20 min. After cooling, 4.9 g of lithium acetate was added. Then 1.76 g of *N*-bromoacetoamide (freshly recrystallized from methylene chloride–*n*-hexane) was added portionwise with stirring at 20° under argon gas. After stirring for 3 hr, the product began to precipitate. The reaction mixture was poured into 700 ml of water, and the resulting crystals were collected by filtration, dissolved in 200 ml of chloroform, washed with water, dried (K_2CO_3), and evaporated to leave colorless crystals which were recrystallized from chloroform–petroleum ether to give 4.8 g (96%) of colorless needles: mp 162–164°; ^{1}H NMR (100 MHz, $CDCl_3$) 2.0 (CH_3CO), 2.0–2.75 ($2H_8$), 3.10–3.80 (m, $2H_7$), 4.80 ($^3J_{9,10}$ = $^3J_{9,8}$ = $^3J_{9,8'}$ = 3.0, H_9), 7.05 ($^3J_{10,9}$ = 3.0, H_{10}), and 7.8–8.3 (aromatic protons).

Anal. Calcd for $C_{22}H_{17}BrO_2$: C, 67.19; H, 4.36. Found: C, 66.93; H, 4.41.

10-Acetoxy-7,10-dibromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene (21a). The conversion of **20a** (832 mg) into **21a** was accomplished in 65% yield according to the procedure described above for **4a.** The dibromide **21** was obtained as colorless prisms: mp 113–115° dec (ether); ^{1}H NMR (see Table I); ir ($CHCl_3$) 1730 cm^{-1} (C=O); mass (*m/e*, 15 eV) M − HOAc (410, 412, 414).

Anal. Calcd for $C_{22}H_{16}Br_2O_2$: C, 55.96; H, 3.42. Found: C, 55.90; H, 3.71.

7-Bromo-8-trifluoroacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (20c). The conversion of **20b**[8c] (2.0 g) into **20c** was accomplished in 86.4% yield as described for **3a.** The trifluoroacetoxybromohydrin (**20c**) was obtained as colorless needles: mp 130–132° dec (chloroform–petroleum ether); ^{1}H NMR (60 MHz, $CDCl_3$) 2.12–2.80 (H_9), 3.40 (A_2B_2-type triplet, $^3J_{10,9}$ = $^3J_{10,9'}$ = 6.5, H_{10}), 4.53 ($^3J_{8,9}$ = 6, $^3J_{8,9'}$ = 3, $^3J_{8,7}$ = 4, H_8), 6.54 ($^3J_{7,8}$ = 4, H_7), 7.60–8.20 (eight aromatic protons); mass (*m/e*, 15 eV) M^+ (446 and 448).

Anal. Calcd for $C_{22}H_{14}BrF_3O_2$: C, 59.08; H, 3.15. Found: C, 58.85; H, 2.94.

8-Acetoxy-7-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene (20d). The conversion of 7-hydroxy-1,2,3,4-tetrahydrobenzo[*a*]pyrene (2 g) into **20d** was accomplished in 90% yield according to the procedure described above for **20a.** The acetoxy derivative **20d** was obtained as colorless needles: mp 169–170° (chloroform–ethanol); ^{1}H NMR (100 MHz, $CDCl_3$) 2.10 ($CH_3C{=}O$), 2.12–2.85 (H_9), 3.42 (A_2B_2-type triplet, $^3J_{10,9}$ = $^3J_{10,9'}$ = 7, H_{10}), 4.58 ($^3J_{8,9}$ = 6, $^3J_{8,9'}$ = 3, $^3J_{8,7}$ = 4, H_8), 6.55 ($^3J_{7,8}$ = 4, H_7), and 7.70–8.20 (eight aromatic protons).

Anal. Calcd for $C_{22}H_{17}BrO_2$: C, 67.19; H, 4.36. Found: C, 67.10; H, 4.25.

8,10-Dibromo-7-trifluoroacetoxy-7,8,9,10-tetrahydrobenzo-[*a*]pyrene (21b). The conversion of **20c** (2.86 g) into **21b** was accomplished in 70% yield according to the procedure described for **4a.** The dibromide **21b** was obtained as pale yellow needles: mp 176–178° (benzene); ^{1}H NMR (see Table I); ir (KBr) 1795 cm^{-1} (C=O); mass (*m/e*, 15 eV) $M^+ - Br_2$ (364).

Anal. Calcd for $C_{22}H_{13}Br_2F_3O_2$: C, 50.22; H, 2.49. Found: C, 49.97; H, 2.26.

Benzo[*a*]pyrene 9,10-Oxide (22a). To a stirred suspension of 350 mg of dry sodium methoxide in 5 ml of dry tetrahydrofuran was added portionwise a solution of 350 mg of **21a** in 5 ml of dry tetrahydrofuran under cooling with Dry Ice. The reaction mixture was stirred at 0–4° and monitored by TLC (Eastman Chromatogram sheet 6060, silica gel; benzene:chloroform:ethyl acetate (1:1:1) with 5% triethylamine) and uv spectra. At 24 hr starting material could not be detected by either TLC or uv. Cold ether (100 ml) was added, and the organic phase was washed with water (50 ml × 4) and dried (K_2CO_3). Evaporation of the solvent below 5° gave yellowish crystals which were recrystallized from tetrahydrofuran–petroleum ether to give 184 mg (92.7%) of slightly yellow prisms that were unstable at room temperature and has an indefinite melting point: ^{1}H NMR (see Figure 1); uv, see Figure 2; TLC [R_f 0.55, conducted as described above]; and HPLC R_t 3.7 min.

Anal. Calcd for $C_{20}H_{12}O$: C, 89.53; H, 4.51. Found: C, 89.27; H, 4.60.

Benzo[*a*]pyrene 7,8-Oxide (22b). The conversion of **21b** (350 mg) into **22b** was accomplished in 94.7% yield according to the procedure described above for **22a.** The oxide **22b** was obtained as pale yellow prisms which had an indefinite melting point: ^{1}H NMR (see Figure 1); uv (see Figure 2); TLC [R_f 0.55, conducted as described for **22a**]; and HPLC R_t 4 min.

Anal. Calcd for $C_{20}H_{12}O$: C, 89.53; H, 4.51. Found: C, 89.72; H, 4.59.

Stability of 22a and 22b. As with other non-K-region arene oxides, both **22a** and **22b** show a marked tendency to rearrange to phenols: preponderantly the 9-hydroxybenzo[*a*]pyrene and 7-hydroxybenzo[*a*]pyrene, respectively. In acetone solution, **22a** is >50% decomposed after 15 min at 4°. Both arene oxides survive several hours at room temperature in acetone containing a trace of concentrated NH_4OH. Approximate half-lives in aqueous buffer at pH 7.4 and 37° are about 15 min. When TLC is conducted on these arene oxides (see above), the portion of the plate where the solution is applied must be pretreated with triethylamine. Neither arene oxide survives HPLC on Du Pont ODS columns eluted with methanol–water gradients at room temperature.[17]

The selective isomerization of **22b** to 7-hydroxybenzo[*a*]pyrene is reminiscent of the isomerization of naphthalene 1,2-oxide (**1**) predominantly to 1-naphthol,[2a] where the greater stability of the allylic versus the benzylic carbonium ion directs the opening of the arene oxide. Notably, the allylic carbonium ion resulting from **22b** can be delocalized into the pyrene residue at the same ring positions to which delocalization occurs when pyrene undergoes electrophilic substitution at the 1 position. The failure of pyrene to undergo electrophilic substitution at the 2 position may be reflected in the fact that **22a** isomerizes mainly to 9-hydroxybenzo[*a*]pyrene. The allylic carbonium ion from **22a** which would lead to 10-hydroxybenzo[*a*]pyrene may not be effectively stabilized by the pyrene residue. The unusual direction for the isomerization of **22a** does not seem to be due to the proximate bay position since **13b** gives mainly 4-hydroxyphenanthrene.[3]

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Chemical Transformations of Penicillins and Cephalosporins. Mechanism and Stereochemistry of the Interconversions of Penam and Cepham Systems[1]

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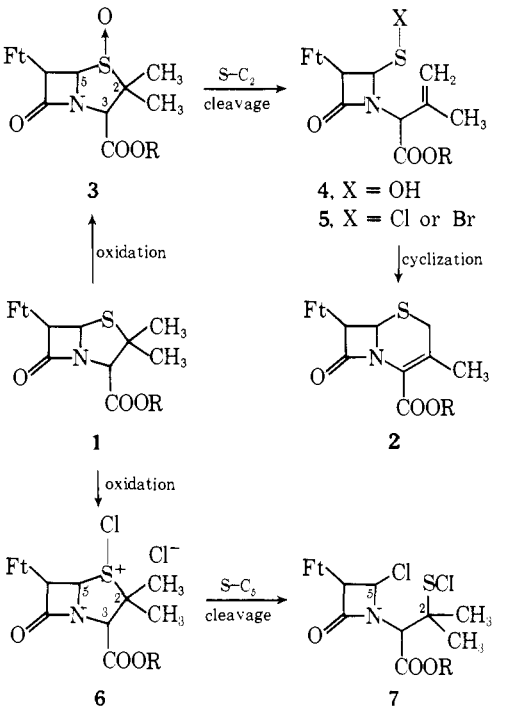
Abstract: Isomeric penam and cepham compounds have been prepared and isolated. It has been established that a thiiranium ion is a common intermediate in the interconversions of penam and cepham systems. The mechanism and stereochemistry of these interconversions have been studied in detail. A new synthesis of deacetoxycephalosporin starting from substituted penams and cephams is reported.

In the last decade the chemical modifications of azetidinone antibiotics (penicillins and cephalosporins) have been studied very actively. Since cephalosporins have been shown to be very effective antibiotics, the conversion of penicillins **1** to cephalosporins **2** has received considerable attention.[2] The difference between these two classes of compounds is in the nature of a heterocyclic ring attached to the four-membered azetidinone. In order to make **2** from **1**, an oxidative enlargement of the thiazolidine system in **1** has to be performed. Such a ring expansion has been realized by the following sequence of reactions, i.e., (a) oxidation of sulfur, (b) the cleavage of the $S-C_2$ bond, and (c) the cyclization to a six-membered dihydrothiazine. In this process the intermediate sulfenic acid **4** is formed, as was first suggested by Morin et al.[3] and later confirmed by Cooper and Barton et al.[4]

During studies of the electrophilic opening of the thiazolidine ring in penicillins, we have carried out a similar set of reactions (oxidation and the cleavage of an S-C bond).[5] However, in contrast to the $S-C_2$ bond cleavage reported in the formation of **4**, we observed the cleavage of an $S-C_5$ bond and formation of the sulfenyl chloride (**7**). Thus, oxidation of penicillin **1** with chlorine affords a chlorosulfonium chloride intermediate **6** which rearranges to the more stable sulfenyl chloride **7**. Since compounds having the sulfenyl halide group attached directly to the azetidinone ring, such as in **5**, are attractive intermediates for synthesis of deacetoxycephalosporins, other possibilities for making compounds of type **5** were explored.

A logical approach for the preparation of **5** would be to generate **4** by thermolysis of sulfoxide **3** and subsequently convert it to **5** by standard methods for the preparation of acid halides. Indeed, treatment of penicillin sulfoxide **3** (R = CH_3) with thionyl chloride and triethylamine in boiling carbon tetrachloride gives the highly reactive intermediate **5** which immediately cyclizes to isomeric penams **8** and **9** in the ratio of ca. 3:4.[6] Similarly, treatment of the sulfenic acid **4** (R = *p*-NB) with phosphorus tribromide in dichloromethane at room temperature gave **10** and **11** in the ratio of ca. 1:1.



3 4, X = OH 5, X = Cl or Br
1 2
6 7

a, R = CH_3; b, R = $CH_2C_6H_4$-*p*-NO_2 (*p*-NB);
c, R = $CH_2C_6H_4$-*p*-OCH_3 (*p*-MB); Ft = phthalimido

The structure and the stereochemistry of these isomers could not be established unequivocally on the basis of ir, NMR, and mass spectra alone. At the outset of our studies, we had some difficulties in distinguishing the isomeric 2-halomethylpenam and 3-halocepham derivatives, because the ir, NMR, and mass spectra are not discernible and especially since the AB quartet signals for methylene protons in the NMR spectra are nondistinctive. Chemical evidence was, therefore, required to substantiate the configuration and conformation of these isomeric products. Since Spry[7] has described 2-acetoxymethylpenam sulfoxides, it seemed