336,[17] 45 ml of saturated KCl solution, and some solid KCl were added. After stirring for 24 h at room temperature the benzene solution was passed through a short column of alumina (to remove the Aliquat-336). After the usual workup there was obtained 3.0 g (90%) of **9**:[18] mp 175–176 °C; *m/e* 366, 368; NMR δ 2.33 and 2.46 (s, 6 each, $ArCH_3$), 3.47 (s, 6, OCH_3), 4.34 (s, 4, CH_2Cl), 7.1 (s, 2, ArH).

2,2′-Di(bromomethyl)-6,6′-dimethoxy-3,3′,5,5′-tetramethylbiphenyl* (10). In reactions involving KBr similar to the above preparation of **9**, about 80% yields of **10**, mp 145–146 °C, *m/e* 454, 456, 458, after recrystallization of the distilled product from benzene–petroleum ether were obtained.

4,5-Dimethoxy-1,3,6,8-tetramethylphenanthrene[4] (11). In the best of many experiments sodium amide was prepared from 2 g of sodium in 100 ml of liquid NH_3.[19] This mixture (stirred with an iron stirrer) was cooled to about −70 to −65 °C by an external dry ice bath and then 150 ml of toluene followed (after cooling) by 5.8 g of **9** were added. After 2 h at −70 to −65 °C the cooling bath was removed and the reaction mixture was left under reflux (dry ice condenser) overnight. After the usual workup (initial treatment of the reaction mixture with 20 g of solid NH_4Cl) the crude product showed only one spot on TLC. Crystallization from ethanol afforded 4.45 g (95%) of **11**, mp 129–130 °C (lit.[4] mp 130–131 °C).

9,10-Dihydro-9,10-dimethoxy-1,3,6,8-tetramethylphenanthrene (12). A solution of 1.70 g of **10** in 10 ml of ether was added to the C_6H_5Li prepared from 0.2 g of Li and 1.75 g of C_6H_5Br in ether. After 2 h at reflux the reaction products were chromatographed over silica gel to yield a small amount of **12**, mp 101–102 °C *m/e* calcd 296.1776, found[16] 296.1782.

4,5-Dihydroxy-1,3,6,8-tetramethylphenanthrene (1). In the best of several attempts at demethylation of **11**, a solution of 1.0 g of **11** and 4.0 g of Na_2S[9] (dried at room temperature to constant weight in a desiccator over P_2O_5) in 10 ml of pure NMP[20] was held at reflux for 3.5 h. The reaction mixture was poured into water and the product isolated as usual to give a slightly yellow solid in 91% yield (in other attempts on heating with $C_5H_5N{\cdot}HCl$[10] high yields of similar product having darker colors were obtained). Various samples of this material melted in the 240–249 °C range. The analytical sample [mp 246.5–248.0 °C; *m/e* 266; NMR (Me_2SO-d_6) δ 2.40 (s, 6, $ArCH_3$, C_3, C_6), 2.59 (s, 6, $ArCH_3$, C_1, C_8), 7.43 (s, 2, ArH), 7.70 (s, 2, ArH)] was obtained by recrystallization from ethanol. The diol, **1**, was converted into the corresponding diacetate:* mp 224–225 °C; IR (KBr) 1750, 1760, cm^{-1}; NMR δ 2.23 (s, 6, $ArCH_3$), 2.30 (s, 6, $ArCH_3$), 2.65 (s, 6, CH_3CO_2), 7.26 (s, 2, ArH), 7.71 (s, 2, ArH).

Registry No.—**1**, 60935-38-8; **1** diacetate, 60935-46-8; **4**, 50790-68-6; **5**, 60935-39-9; **6**, 60935-40-2; **7**, 60935-41-3; **8**, 60935-42-4; **9**, 60935-43-5; **10**, 60935-44-6; **11**, 50790-66-4; **12**, 60935-45-7.

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(2) Postdoctoral Research Associate.
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(12) R. N. Adams, "Voltammetry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969.
(13) D. C. Tse, R. L. McCreery, and R. N. Adams, *J. Med. Chem.* **19**, 37 (1976).
(14) All melting points and boiling points are uncorrected. IR spectra were recorded using a Perkin-Elmer Infracord using NaCl disks (neat liquids) or KBr pellets. NMR spectra were recorded on a Varian A-60 instrument and are reported as δ units (Me_4Si, 0) in $CDCl_3$ unless otherwise noted. The phrase "worked up in the usual way" means that an ether–benzene solution of the products was washed with dilute acid and/or base, with saturated NaCl solution. The ether–benzene solution was then filtered through a cone of $MgSO_4$ and the solvent was removed on a rotary evaporator. All compounds marked with an asterisk gave elemental analytical data consistent (±0.3%) with the theoretical values, which were submitted for review. Analyses were by M-H-W Laboratories, Garden City, Mich.
(15) The present procedure represents an improvement over that described in "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 329.
(16) Mass spectra were determined on an Associated Electrical Industries, Ltd., instrument by Mr. R. Weisenburger.
(17) Aliquat 336 is methyltricaprylammonium chloride, obtainable from the McKerson Corp., Minneapolis, Minn.
(18) The analytical sample was kindly prepared by Dr. R. Kannan.
(19) The technique and apparatus are described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, p 145.
(20) We thank the General Aniline and Film Corp. for a generous gift of NMP.

Synthesis and Properties of the Vicinal Trans Dihydrodiols of Anthracene, Phenanthrene, and Benzo[*a*]anthracene

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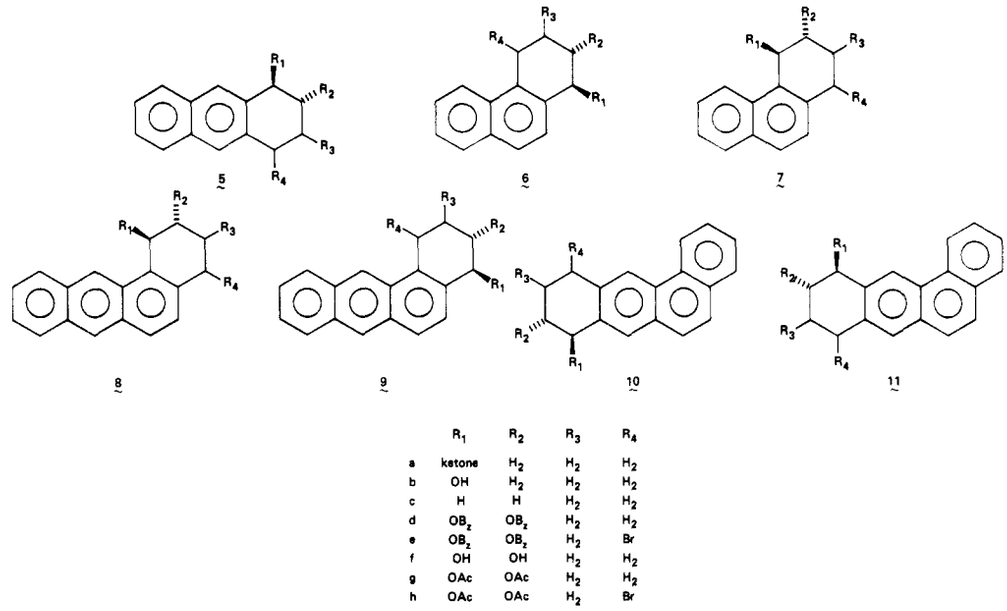
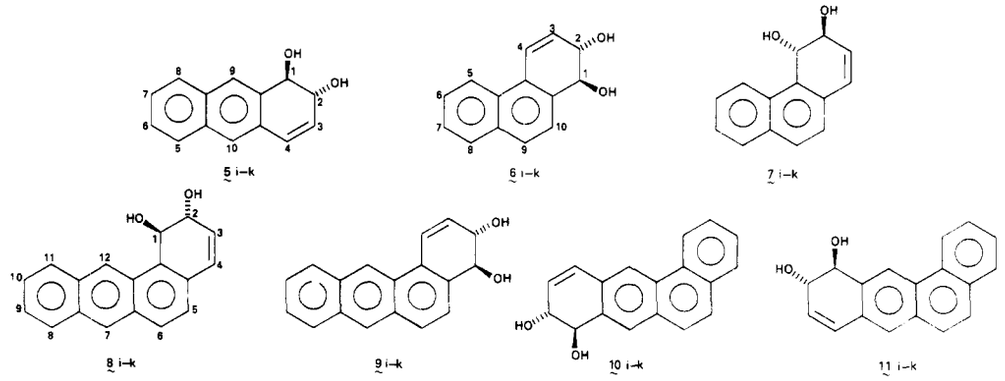
The vicinal, trans, non-K-region dihydrodiols of anthracene, phenanthrene, and benzo[*a*]anthracene have been synthesized by a common approach involving bromination, dehydrobromination, and hydrolysis of the appropriate tetrahydrodiesters of the parent aromatic hydrocarbons. Utilization of tetrahydrodiacetate derivatives proved important for successful preparation of dihydrodiols in angular benzo rings, whereas tetrahydrodibenzoates served as appropriate precursors in all other cases. The NMR spectra of the dihydrodiols and dihydrodioldiesters are discussed. Of the dihydrodiols, only 3,4-dihydroxy-3,4-dihydrobenzo[*a*]anthracene (**9k**) could be metabolically activated to species highly mutagenic to bacteria, although 8,9-dihydroxy-8,9-dihydrobenzo[*a*]anthracene and 10,11-dihydroxy-10,11-dihydrobenzo[*a*]anthracene could be activated to weakly mutagenic species. The much greater biological activity of metabolically activated **9k** is in accord with the enhanced reactivity predicted by PMO calculations for the benzylic positions of many intermediate diol epoxides in which the oxirane ring occupies a bay region.

Vicinal, trans dihydrodiols, both at K-region and non-K-region (**1**, Scheme I) positions, are common metabolites of polycyclic aromatic hydrocarbons in mammals.[1] Their formation consists of initial oxidation of the hydrocarbons to arene oxides[2] which are then hydrated by the enzyme epoxide hydrase to trans dihydrodiols that are often optically active.[3] Recently, substantial interest has developed in dihydrodiols since they can be metabolically activated to diol epoxides[4] (**2**,



	R_1	R_2	R_3	R_4
a	ketone	H_2	H_2	H_2
b	OH	H_2	H_2	H_2
c	H	H	H_2	H_2
d	OB_z	OB_z	H_2	H_2
e	OB_z	OB_z	H_2	Br
f	OH	OH	H_2	H_2
g	OAc	OAc	H_2	H_2
h	OAc	OAc	H_2	Br

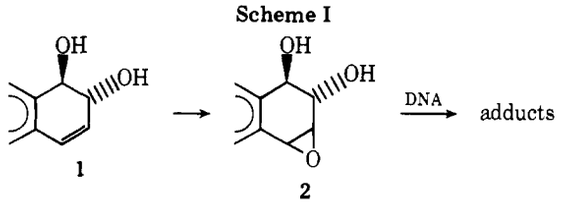
Figure 1.

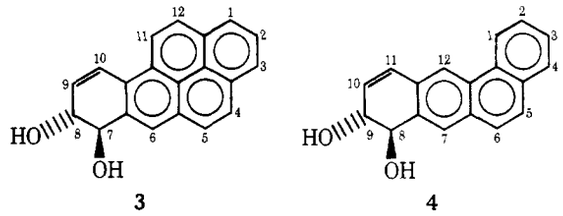


i: dihydrodiols as benzoate derivatives
j: dihydrodiols as acetate derivatives
k: dihydrodiols

Figure 2.

Scheme I



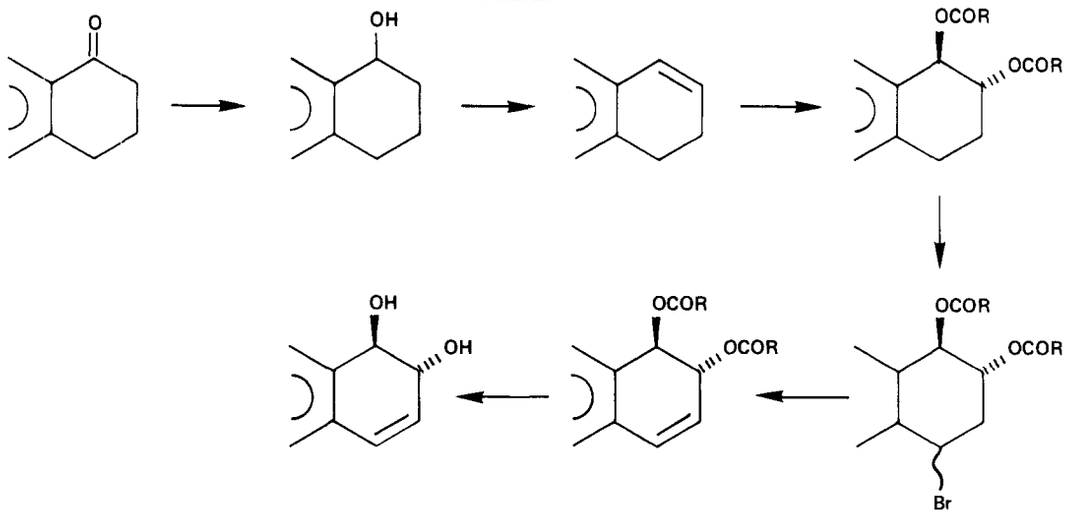


Scheme I). Stereoisomeric diol epoxides of *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (**3**),[4a,5] for example, appear to account for much of the covalent binding of benzo[*a*]pyrene (BP) to the DNA of mouse skin in vivo[6] and are highly mutagenic toward bacterial[7a–e] and mammalian cells.[4b,7a–d,f] In addition, **3** is a potent transforming agent toward cultured mammalian cells which possess drug metabolizing activity.[8] These results, taken together with the facts that BP 7,8-oxide[9] and BP 7,8-dihydrodiol (**3**)[10] are potent carcinogens on mouse skin, strongly indicate that BP 7,8-diol-9,10-epoxides may be the long sought ultimate carcinogenic forms of the ubiquitous environmental carcinogen BP.

At present, relatively little information is available as to which positional isomers of dihydrodiols from a given hydrocarbon can be metabolically activated to diol epoxides with high biological activity. Although BP 7,8-dihydrodiol (**3**) can be activated to potent mutagens, BP 4,5-, 9,10-, and 11,12-dihydrodiols are weak or inactive as mutagens after metabolic activation.[11] For benzo[*a*]anthracene (BA), the 8,9-dihydrodiol (**4**) could be activated to mutagens whereas the 5,6- (K-region) dihydrodiol could not.[7e] The present study describes the synthesis of vicinal, trans dihydrodiols of anthracene, phenanthrene, and benzo[*a*]anthracene at non-K-region positions (Figure 2) to enable the examination of their carcinogenicity and metabolic activation to mutagens. The procedure is general and can be applied to a wide range of unsubstituted hydrocarbons. Synthetic K-region dihydrodiols are available through existing methods (cf. ref 12).

Previously, trans dihydrodiols were prepared by metal hydride reduction of the corresponding *o*-quinones.[13] However, recent application of the approach to the non-K-region trans dihydrodiols of anthracene and phenanthrene resulted in very low yields of the desired products.[14] More recently, *cis*- and *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene have

Scheme II



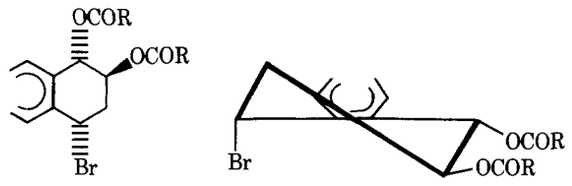
been prepared by an alternate approach involving bromination, dehydrobromination, and hydrolysis of vicinal tetrahydrodiesters of aromatic hydrocarbons.[5b,15] The present study establishes the generality of the latter approach, as well as modifications that are occasionally required.

Results and Discussion

The synthetic sequence utilized for the preparation of the dihydrodiols is outlined in Scheme II. The ketonic starting materials (**5a–11a**, Figure 1) are available by succinylation of smaller aromatic hydrocarbons, reduction of the resulting keto acids to aryl butyric acids, and cyclization. Their conversion to the desired dihydroaromatic hydrocarbons, previously described for **5c–7c**, could be routinely achieved by reduction of the ketones to alcohols with $NaBH_4$ in methanol and dehydration of the alcohols with catalytic quantities of HCl in glacial HOAc.[16] The alkenes could be isolated in good yield (80–90%), but in some cases they appear to be air sensitive in solution. 3,4-Dihydrobenzo[*a*]anthracene (**8c**) appeared to be especially labile during purification attempts and was used without purification.

Synthesis of Dihydrodiols from Dihydroaromatics. The dihydroaromatic compounds, **5c–11c**, were converted to trans tetrahydro diesters via the Prévost reaction, with either silver benzoate (**5d, 7d–11d**) or silver acetate (**6g**) and iodine in benzene.[17] Yields ranged from 32 to 76% for the reactions with silver benzoate whereas the trans diacetate **6g** was obtained in 51% yield. An attempt to prepare diacetate **9g** by the Prévost reaction, however, was not successful. Thus, the trans diacetates **7g, 8g,** and **9g** were prepared by the sequence dibenzoate → diol → diacetate (the reason for preparing dibenzoates in some cases and diacetates in others will be described later). The dibenzoates were hydrolyzed with NaOH in methanolic THF and the resulting diols were acetylated with Ac_2O/pyridine. Good overall conversions of the dibenzoates to the diacetates were achieved in that fashion (73–82%).

Bromination of the trans diesters was effected with *N*-bromosuccinimide (NBS) in CCl_4 at temperatures below 70 °C. The yields of bromo diesters were high in most cases, but mixtures of stereoisomers usually resulted. The crude reaction products were obtained as oils, but purification was readily achieved by the addition of ether, which precipitates the major isomer. In those cases (**5e, 6h, 9h, 10e, 11e**) where the nuclear magnetic resonance (NMR) spectrum permitted an assignment of structure (see Experimental Section for NMR data), the major isomer possessed the relative stereochemistry shown in **12**, where the benzylic ester and the bromine atom are cis. As indicated, the predominant conformation of **12** is that in



12

which the bromine atom is quasi-axial. This observation is in accord with previous results obtained in the bromination of analogous bromohydrin esters with NBS.[16a] Only for the bromination product of **7g** and **8g** were NMR data inadequate to permit an unequivocal structure assignment. In these cases, the benzylic ester moieties (groups R_1) in **7** and **8** occupy "bay region" positions,[18] and steric interactions force them to be quasi-axial, with consequent effects upon the conformation of the molecules and their NMR spectra.[14]

All bromo diesters were thermally dehydrobrominated in boiling toluene or xylene to which $NaHCO_3$ had been added to neutralize HBr. The water formed was continually removed as an azeotrope. Yields varied from 25 to 65%. The use of bromodibenzoates in some series (**5, 10, 11**) and bromodiacetates in others (**6, 7, 8, 9**) requires comment. It appears that bromodibenzoates are reliable substrates for thermal elimination of HBr when the ring being modified has no "bay region" positions. Thus, dehydrobromination in systems **5, 10,** and **11** proceeds in over 60% yield. However, attempts to effect the analogous conversions, **6e → 6i** and **7e → 7i**, in the phenanthrene series were unsuccessful. Thus, **6i** could not be isolated after pyrolysis of **6e**, and a very low yield of **7i** was obtained from **7e**. Respectable yields of the desired dihydrodiol diesters **6j** and **7j** were obtained, however, on thermal dehydrohalogenation of the analogous bromodiacetates. Although the basis for the observed difference in behavior is not known, there is evidence that the desired dihydrodiol dibenzoates were formed from **6e** and **7e**, but aromatized under the reaction conditions by further elimination of benzoic acid since fully aromatic products were isolated.

An alternative procedure for the elimination of HBr proved effective for the preparation of dihydrodiol diacetates **7j** and **8j**. In these cases, treatment of the bromo diesters with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in anhydrous THF at 0 °C afforded high yields of the desired products. This alternative is especially valuable in the case of **8j**, where the yield obtained thermally is low (25%). Reaction of the crude bromo diester mixture, rather than the pure isomer, also resulted in higher yields of the dihydrodiol diesters (based upon tetrahydrodiester) in the syntheses of **5i** and **7j** by the DBN route.

Table I. NMR Spectra of Dihydrodiol Diesters[a]

Registry no.	Compd	Carbinol ester hydrogens		Vinyl hydrogens		Acetyl hydrogens	Aromatic hydrogens
		Benzylic	Nonbenzylic	Benzylic	Nonbenzylic		
60967-83-1	*trans*-1,2-Dibenxoyloxy-1,2-dihydroanthracene (**5i**)	H_1 6.78	H_2 6.07 ($J_{1,2}$ = 7.0; $J_{2,3}$ = 3.7; $J_{3,4}$ = 9.8; $J_{2,4}$ = 1.2)	H_4 6.89	H_3 6.20		7.27–8.18
60890-34-8	*trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**6j**)	H_1 6.29	H_2 5.61 ($J_{1,2}$ = 5.6; $J_{2,3}$ = 4.2; $J_{3,4}$ = 10.0)	H_4[b]	H_3 6.22	2.11, 2.04	7.43–8.23 (6 H, H_4[b])
61009-15-2	*trans*-3,4-Diacetoxy-3,4-dihydrophenanthrene (**7j**)	H_4 6.80	H_3 5.40 ($J_{3,4}$ = 1.6; $J_{2,3}$ = 5.4; $J_{1,2}$ = 9.6)	H_1 6.88	H_2 6.05	2.02, 1.98	7.27–8.09
60967-84-2	*trans*-1,2-Diacetoxy-1,2-dihydrobenzo[*a*]anthracene (**8j**)	H_1 6.95	H_2 5.47 ($J_{1,2}$ = 1.8; $J_{2,3}$ = 5.5; $J_{3,4}$ = 9.5; $J_{1,3}$ = 0.8)	H_4 6.87	H_3 6.31	1.99, 1.94	7.24–8.10 (6 H) 8.40, 8.50 (H_7, H_{12})
60967-85-3	*trans*-3,4-Diacetoxy-3,4-dihydrobenzo[*a*]anthracene (**9j**)	H_4 6.37	H_3 5.69 ($J_{3,4}$ = 6.1; $J_{2,3}$ = 4.3; $J_{1,2}$ = 10.4; $J_{1,3}$ = 1.1)	H_1[b]	H_2 6.28	2.10, 2.02	7.2–8.2 (6 H, H[b]) 8.64, 8.34 (H_7, H_{12})
60967-86-4	*trans*-8,9-Dibenzoyloxy-8,9-dihydrobenzo[*a*]anthracene (**10i**)	H_8 6.85	H_9 6.14 ($J_{8,9}$ = 7.0; $J_{9,10}$ = 3.6; $J_{10,11}$ = 9.3; $J_{9,11}$ = 1.2)	H_{11} 6.95	H_{10} 6.24		7.2–8.2 (16 H) 8.45 (H_{12}), 8.65 (H_1)
60967-87-5	*trans*-10,11-Dibenzoyloxy-10,11-dihydrobenzo[*a*]anthracene (**11i**)	H_{11} 6.84	H_{10} 6.07 ($J_{10,11}$ = 6.2; $J_{9,10}$ = 4.0; $J_{8,9}$ = 9.8; $J_{8,10}$ = 1.0)	H_8 6.91	H_9 6.26		7.2–8.2 (16 H) 8.56 (H_1), 8.71 (H_{12})

[a] NMR spectra were recorded in $CDCl_3$, with Me_4Si as internal standard. For **5i**, **6j**, and **7j** spectra were recorded at 220 MHz; for **8j**, **9j**, **10i**, and **11i**, spectra were recorded at 100 MHz. [b] The resonance of the indicated bay region hydrogens occurs within the aromatic absorption envelope owing to edge deshielding by the proximate aromatic ring.

Table II. NMR Spectra of Dihydrodiols[a]

Registry no.	Compd	Carbinol hydrogens		Vinyl hydrogens		Aromatic hydrogens
		Benzylic	Nonbenzylic	Benzylic	Nonbenzylic	
4841-37-6	*trans*-1,2-Dihydroxy-1,2-dihydroanthracene (**5k**)	H_1 4.83	H_2 4.42 ($J_{1,2}$ = 10.0; $J_{2,3}$ = 2.2; $J_{3,4}$ = 9.7; $J_{2,4}$ = 2.2; $J_{1,Ar}$ = 1.3[c])	H_4 6.60	H_3 6.02	7.3–8.1
60917-41-1	*trans*-1,2-Dihydroxy-1,2-dihydrophenanthrene (**6k**)	H_1 4.91	H_2 4.50 ($J_{1,2}$ = 11.4; $J_{2,3}$ = 2.3; $J_{3,4}$ = 10.4; $J_{2,4}$ = 2.3)	H_4 7.25	H_3 6.21	7.4–8.3
569-20-0	*trans*-3,4-Dihydroxy-3,4-dihydrophenanthrene (**7k**)	H_4 5.37	H_3 4.36 ($J_{3,4}$ = 2.0; $J_{2,3}$ = 5.4; $J_{1,2}$ = 9.6; $J_{2,4}$ = 10.)	H_1 6.69	H_2 6.22	7.3–8.4
60967-88-6	*trans*-1,2-Dihydroxy-1,2-dihydrobenzo[*a*]anthracene (**8k**)	H_1 5.56	H_2 4.45 ($J_{1,2}$ = 1.7; $J_{2,3}$ = 5.4; $J_{3,4}$ = 9.5; $J_{1,3}$ = 0.8)	H_4 6.73	H_3 6.30	7.27–8.30 (6 H); 8.48, 8.93 (H_7, H_{12})
60967-89-7	*trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*a*]anthracene (**9k**)	H_4 4.96	H_3 4.56 ($J_{3,4}$ = 11.5; $J_{2,3}$ = 2.3; $J_{1,2}$ = 10.1; $J_{1,3}$ = 2.3)	H_1[b]	H_2 6.28	7.30–8.30 (6 H, H_1[b]); 8.86, 8.52 (H_7, H_{12})
34501-24-1	*trans*-8,9-Dihydroxy-8,9-dihydrobenzo[*a*]anthracene (**10k**)	H_8 4.90	H_9 4.50 ($J_{8,9}$ = 10.0; $J_{9,10}$ = 2.0; $J_{10,11}$ = 10.0; $J_{9,11}$ = 2.4)	H_{11} 6.75	H_{10} 6.10	7.55–8.20 (6 H); 8.52 (H_{12}); 8.80 (H_1)
60967-90-0	*trans*-10,11-Dihydroxy-10,11-dihydrobenzo[*a*]anthracene (**11k**)	H_{11} 4.75	H_{10} 4.50 ($J_{10,11}$ = 10.4; $J_{9,10}$ = 2.2; $J_{8,9}$ = 10.0; $J_{8,10}$ = 2.4)	H_8 6.63	H_9 6.06	7.5–8.0 (6 H); 8.77 (H_1); 8.95 (H_{12})

[a] Spectra were recorded in acetone-d_6, with Me_4Si as internal standard. All spectra were recorded at 100 MHz except for that of **8k**, which was recorded at 220 MHz. [b] The resonance of the indicated bay region hydrogens occurs within the aromatic absorption envelope. [c] Due to sharp signals for H_3, $J_{1,Ar}$ probably represents coupling to H_9 which suggests that H_1 is predominantly axial.

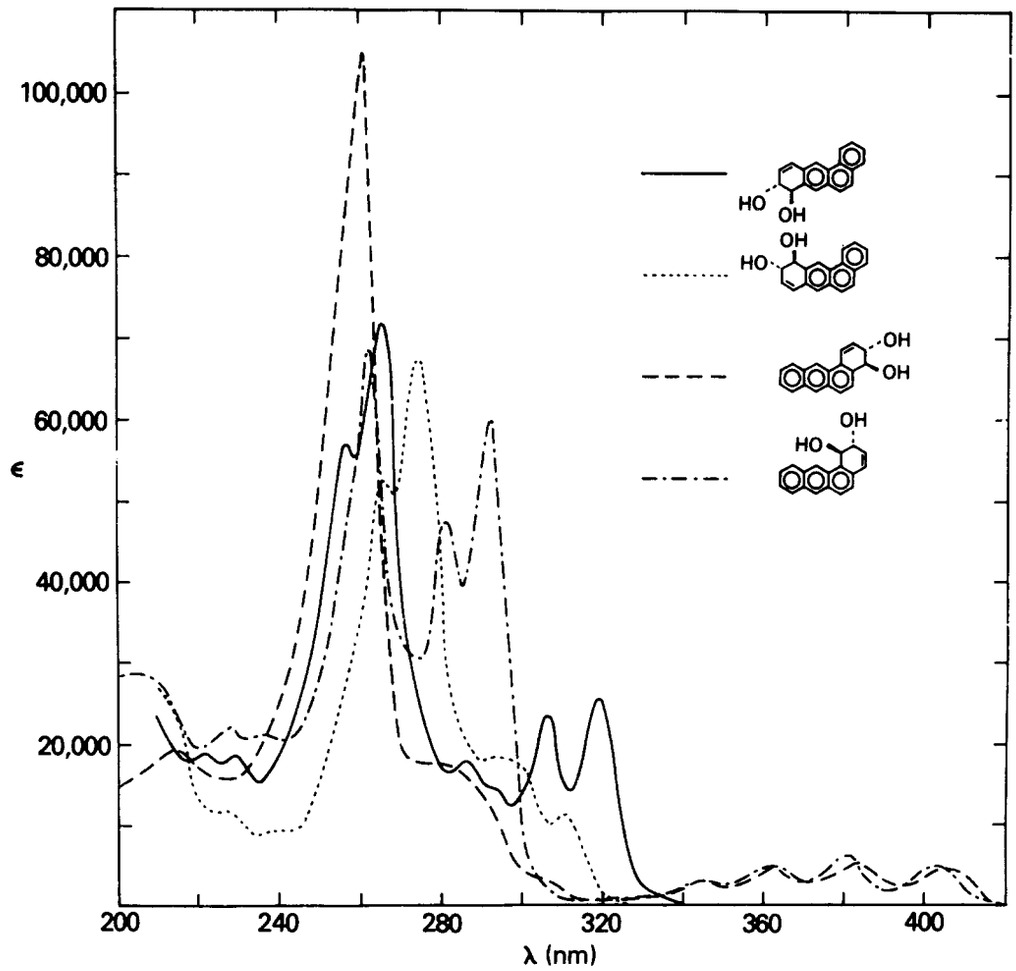


Figure 3. Ultraviolet spectra (in absolute EtOH) of the vicinal, trans, non-K-region dihydrodiols of benzo[*a*]anthracene. Selected maxima and extinction coefficients are cited in the Experimental Section. For comparison, the K-region isomer, *trans*-5,6-dihydroxy-5,6-dihydrobenzo[*a*]anthracene, had the following spectrum in absolute EtOH (λ_{max}, ϵ_{max}): 216 (33 100); 247 (32 200); 258 (39 800); 266 (41 800); 298 (16 400); 309 (14 800); 336 (700).

The conditions required for hydrolysis of the dihydrodiol diesters to dihydrodiols depended upon whether benzoates or acetates were hydrolyzed. Thus, conversion of the dihydrodiol diacetates **6j, 7j, 8j,** and **9j** to the corresponding dihydrodiols was readily achieved with dry ammonia in methanol. Hydrolysis of the dibenzoates was achieved with sodium methoxide in THF/MeOH. Yields of the dihydrodiols ranged from 54 to 89%.

Spectral Properties of the Dihydrodiols and Dihydrodiol Diesters. The NMR spectra of the dihydrodiol diesters and dihydrodiols are recorded in Tables I and II. Noteworthy are the substantial downfield shifts expected for protons in bay regions of the dihydrodiols and their diesters (H_4 in **6j, 6k** and **7j, 7k**; H_1 in **8j, 8k** and **9j, 9k**). Further, the coupling constants between the carbinol hydrogens in the bay region dihydrodiols (J_{diol}) and dihydrodiol diesters (J_{ester}) are very low when they are in bay regions (J_{diol} = 1.8 ± 0.2; J_{ester} = 1.7 ± 0.1 Hz). The values for the bay region substituted compounds are those expected for a predominant quasi-diaxial relationship of the diol and diester functionalities. Further evidence for the quasi-axial conformation of the benzylic hydroxyl groups in the bay region diols is the observed $J_{2,4}$ = 1.0 Hz for **7k** and $J_{1,3}$ = 0.8 Hz for **8k.** This conformation-dependent W coupling was not observed in the other cases. The large values of J_{diol} (10.7 ± 0.8 Hz) for the non-bay region dihydrodiols indicate that the vicinal hydroxyl groups are predominantly quasi-diequatorial. The decrease of this coupling constant in the dihydrodiol diesters (J_{ester} = 6.4 ± 0.8 Hz) is consistent with a conformational change toward a diaxial relationship of these substituents and is in accord with previous observations.[14]

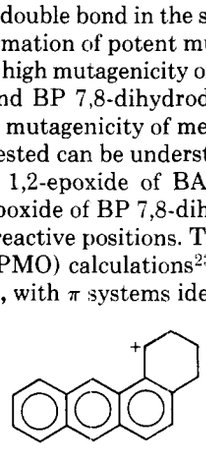
The ultraviolet spectra of the four synthetic non-K-region *trans*-benzo[*a*]anthracene dihydrodiols are shown in Figure 3. The UV spectrum of **10k** agrees with that reported by Sims for BA 8,9-dihydrodiol isolated from metabolism studies.[19] Dihydrodiols substituted in the angular ring of BA (**8k** and **9k**) are yellow and exhibit long-wavelength absorptions in the visible region (~345–405 nm) that are lacking in **10k** and **11k.** In **8k** and **9k,** the double bonds of the dihydrodiols are conjugated with an anthracene nucleus whereas in **10k** and **11k,** they are conjugated with a phananthrene nucleus. The larger bathochromic shifts of the relatively weak p bands (ε ~4000–7000) observed for these vinyl anthracene derivatives are consistent with the larger shifts generally observed upon conjugation with the linearly annelated aromatic hydrocarbons (acenes) as contrasted with the shifts observed for conjugation with the angularly annelated aromatic hydrocarbons (phenes).[20]

Mutagenesis of Metabolically Activated Dihydrodiols. Neither the dihydrodiols synthesized in this work nor *trans*-1,2-dihydroxy-1,2-dihydronaphthalene nor the K-region trans dihydrodiols of phenanthrene or BA were mutagenic toward the histidine-dependent bacterial strain TA 100 without metabolic activation.[21] However, three of these dihydrodiols, the non-K-region dihydrodiols **9k, 10k,** and **11k** of BA, can be activated to mutagenic metabolites.[22] Significantly, the activity within the group of dihydrodiols which could be activated varies greatly. The metabolites of the BA 8,9- and

10,11-dihydrodiols are only weakly mutagenic, in contrast to the metabolites of the BA 3,4-dihydrodiol which are *ten times* as mutagenic as the metabolites obtained from benzo[a]anthracene.

The results of the testing of this complete series of dihydrodiols from several aromatic hydrocarbons allow structure–activity relationships to be assessed. First, it is important that the vicinal diol occupy a non-K region since the K-region dihydrodiols could not be activated. This is likely a consequence of the fact that all unsaturation in the K-region dihydrodiols is fully aromatic, whereas the non-K-region dihydrodiols possess a nonaromatic double bond in the substituted ring. Secondly, the structure of the highly mutagenic (after activation) BA 3,4-dihydrodiol is related to that of BP 7,8-dihydrodiol (**3**) in that both contain double bonds in "bay regions" of the hydrocarbons. In the latter case, the 9,10-epoxides of **3** are known to be formed metabolically[4b,c] and are potent mutagens.[4b,7] By analogy, the 1,2-epoxides of BA 3,4-dihydrodiol are probably the mutagenic metabolites formed from **9k.** Yet, the inability to activate the phenanthrene 1,2-dihydrodiol (**6k**) suggests that the presence of a bay region double bond in the substrate is insufficient to result in the formation of potent mutagens.

The high mutagenicity of the activated BA 3,4-dihydrodiol (**9k**) and BP 7,8-dihydrodiol (**3**) compared to the weak or absent mutagenicity of metabolites from the other dihydrodiols tested can be understood when it is recognized that C_1 of the 1,2-epoxide of BA 3,4-dihydrodiol and C_{10} of the 9,10-epoxide of BP 7,8-dihydrodiol are expected to be especially reactive positions. Thus, perturbational molecular orbital (PMO) calculations[23] indicate that carbonium ions **13** and **14,** with π systems identical with those which would be



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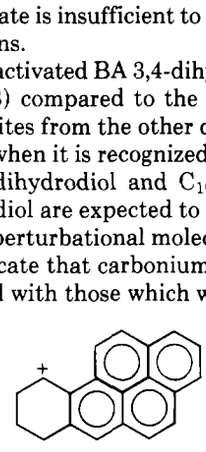

14

formed by heterolytic cleavage of the oxirane C–O bonds at C_1 and C_{10}, respectively, are considerably more stabilized by delocalization relative to their neutral precursors than are the carbonium ions analogous to those which would be formed from the diol epoxides of the other dihydrodiols examined. The calculations indicate that bay region carbonium ions are often especially stabilized by delocalization relative to their neutral precursors. The greater stability of these carbonium ions should result in an enhanced S_N1 component of reaction of the precursor diol epoxides and also should permit more binding to relatively weak nucleophilic sites such as those found in DNA and other macromolecules. The synthesis of the diol epoxides of the BA non-K-region dihydrodiols is in progress.

Since submission of this manuscript, the BA dihydrodiols **9k, 10k,** and **11k** have been converted into the three diastereomeric pairs of diol epoxides by introduction of the oxirane ring (cf. ref 5a) at the double bond of each dihydrodiol.[29] These pairs of diastereomers differ in that the oxirane ring is either cis or trans to the benzylic hydroxyl group. As had been previously shown for the diol epoxides of **3,**[5a] the cis isomers of the BA diol epoxides are substantially more reactive toward *p*-nitrothiophenolate in *tert*-butyl alcohol when compared to the corresponding trans isomers, presumably owing to anchimeric assistance to opening of the oxirane ring by the proximate benzylic hydroxyl group. Furthermore, the diol epoxides of **9k,** in which the oxirane ring forms part of a "bay region", are the most reactive as expected from the PMO calculations.[30] As anticipated from the metabolic activation studies on the BA dihydrodiols,[22] the pair of diol epoxides from **9k** are much more mutagenic than are the pairs from **10k** and **11k.**[31]

Experimental Section

Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Proton magnetic resonance spectra were recorded on Varian A-60, HA-100, and 220-MHz spectrometers. Unless noted otherwise, $CDCl_3$ was used as solvent. Coupling constants (J) are recorded in hertz and chemical shifts in parts per million (δ) with tetramethylsilane as internal standard. Melting points are uncorrected. The designations α and β are used to indicate relative stereochemistry.

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydroanthracene (5d).** Silver benzoate (8.60 g, 0.0376 mol) and iodine (4.45 g, 0.0175 mol) were added to dry benzene (70 ml). The mixture was stirred under N_2 until the red color disappeared. 1,2-Dihydroanthracene (3.0 g, 0.0167 mol)[24] was added and the mixture was stirred at 25 °C for 15 min, then was refluxed for 2.5 h. The reaction mixture was gravity filtered hot, and the filtrate was evaporated to leave a viscous orange oil that was crystallized from $CHCl_3$/petroleum ether to yield a light yellow solid (5.32 g, 76%). Recrystallization from ethanol gave **5d** as a white solid: mp 124–125.5 °C; ^{1}H NMR (60 MHz) δ7.2–8.2 (16 H, m), 6.70 (H_1, d), 5.49–5.77 (H_2), 3.03–3.40 (2 H), 2.13–2.60 (2 H), $J_{1,2}$ = 6 Hz.

4β-Bromo-1β,2α-dibenzoyloxy-1,2,3,4-tetrahydroanthracene (5e). A mixture of CCl_4 (50 ml), *N*-bromosuccinimide (NBS, 116 mg, 0.652 mmol), **5d** (250 mg, 0.592 mmol), and α,α'-azoisobutyrodinitrile (AIBN, 5 mg) was maintained at ca. 65 °C with a heat lamp for 15 min while a stream of N_2 was passed through the solution. The mixture was cooled and filtered, and the CCl_4 was removed under reduced pressure to leave a yellow, oily residue that crystallized upon addition of ether/hexane (130 mg, 44%). Recrystallization from benzene/hexane gave the bromo diester **5e** as a white solid: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 7.25–8.25 (16 H), 6.85 (H_1), 6.18 (H_2), 5.88 (H_4), 3.05 ($H_{3\beta}$), 2.71 ($H_{3\alpha}$) ($J_{1,2}$ = 8.0, $J_{2,3\alpha}$ = 10.1, $J_{2,3\beta}$ = 3.8, $J_{3\alpha,3\beta}$ = 14.5, $J_{3\alpha,4}$ = $J_{3\beta,4}$ = 4.6, $J_{1,x}$ = 1.0 Hz).

Anal. Calcd for $C_{28}H_{21}O_4Br$: C, 67.07; H, 4.22. Found: C, 66.70; H, 4.36.

***trans*-1,2-Dibenzoyloxy-1,2-dihydroanthracene (5i).** To a stirred mixture of boiling xylene (20 ml) and anhydrous $NaHCO_3$ (250 mg) was added bromodibenzoate **5e** (65 mg, 0.129 mmol). The mixture was heated, under Ar, for 15 min, with continuous removal of water. The mixture was cooled and filtered, and the xylene was removed under reduced pressure to leave a white solid that was recrystallized from ether to give **5i** (24 mg, 44%): mp 169–171 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{28}H_{20}O_4$: C, 79.98; H, 4.79. Found: C, 79.71; H, 4.99.

A better conversion to **5i** (46%, based upon tetrahydrodibenzoate **5d**) was obtained if the crude bromination product of **5d** was subjected to the above reaction conditions.

***trans*-1,2-Dihydroxy-1,2-dihydroanthracene (5k).** In the manner described for **10k,** dibenzoate **5i** (27 mg) was converted to dihydrodiol **5k.** Recrystallization of the crude product from EtOAc gave **5k** (11 mg, 61%) as colorless needles, ^{1}H NMR (see Table II).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (6g).** Benzene (150 ml), 3,4-dihydrophenanthrene (4.05 g, 0.0225 mol),[16a] and silver acetate (8.03 g, 0.0481 mol) were mixed under N_2. Iodine (5.99 g, 0.0236 mol) was added in portions over a 15-min period. After the red color disappeared, the reaction mixture was refluxed for 3 h, then was gravity filtered hot. The benzene was removed under reduced pressure, leaving an oily residue that was column chromatographed on Florisil using 5:95 EtOAc/hexane as developing solvent to give **6g** as a white solid (3.45 g, 51%): mp 118–119 °C; ^{1}H NMR (60 MHz) δ 7.16–8.10 (6 H), 6.20 (H_1, d), 5.07–5.40 (H_2), 2.97–3.36 (2 H), 1.80–2.40 (2 H), 2.06 (3 H, s), 1.94 (3 H, s), $J_{1,2}$ = 6.0 Hz.

4β-Bromo-1β,2α-diacetoxy-1,2,3,4-tetrahydrophenanthrene (6h). The reaction of **6g** (3,83 g), NBS (2.52 g), and AIBN (5 mg) in CCl_4 (150 ml) was effected as described for **5e.** Workup gave the rproduct as a darkened aerosol from which bromodiacetate **6h** was obtained as an off-white solid (3.40 g, 70%) by the addition of ether. Recrystallization from ether afforded **6h** as a white solid: mp 134–138 °C; ^{1}H NMR (220 MHz) δ7.16–8.30 (6 H), 6.49 (H_1), 6.04 (H_4), 5.94 (H_2), 2.83 ($H_{3\beta}$), 2.49 ($H_{3\alpha}$), 2.21 (3 H, s), 2.11 (3 H, s), $J_{1,2}$ = 8.5, $J_{2,3\beta}$ = 4.0, $J_{2,3\alpha}$ = 12.6, $J_{3\beta,4}$ = 3.4, $J_{3\alpha,4}$ = 3.6, $J_{3\alpha,3\beta}$ = 14.0 Hz. Anal. Calcd for $C_{18}H_{17}O_4Br$: C, 57.31; H, 4.54. Found: C, 57.08; H, 4.70.

***trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (6j).** The reaction of bromodiacetate **6h** (2.71 g) in xylene (250 ml) containing $NaHCO_3$ (13.5 g) was effected as described for **5i.** Workup gave a yellow oil that crystallized from ether (0 °C) to yield 0.69 g of **6j.** Preparative layer chromatography of the mother liquors (alumina,

1:9 EtOAc/hexane) afforded an additional 0.37 g of **6j** [total yield 1.06 g (50%)]. Recrystallization from ether/hexane gave **6j** as a white solid: mp 104–105 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.73; H, 5.40.

***trans*-1,2-Dihydroxy-1,2-dihydrophenanthrene (6k).** Dihydrodiol diacetate **6j** (50 mg) was dissolved in anhydrous MeOH (30 ml) and anhydrous NH_3 was bubbled through the solution for 15 min. The reaction vessel was capped and the reaction mixture was stirred at 25 °C for 2 h. The methanol was removed under reduced pressure, leaving a white solid that was dissolved in CH_2Cl_2 and water. The CH_2Cl_2 layer was extracted with water, dried (anhydrous Na_2SO_4), filtered, and concentrated, to give dihydrodiol **6k** as a white solid (32 mg, 89%): mp 164–165 °C; homogeneous by TLC (alumina, EtOAc as developing solvent); ^{1}H NMR (see Table II).

***trans*-3,4-Dibenzoyloxy-1,2,3,4-tetrahydrophenanthrene (7d).** The reaction of 1,2-dihydrophenanthrene (4.54 g),[16a] silver benzoate (13.01 g), and iodine (6.73 g) in benzene (200 ml) was effected as described for **5d.** Column chromatography of the crude product on Florisil using EtOAc/hexane (15:85) as developing solvent afforded slightly impure **7d,** which gave 3.4 g (32%) of white solid of mp 127–128 °C after recrystallization from ether/hexane: ^{1}H NMR (60 MHz) δ 7.0–8.1 (6 H), 6.97 (H_4), 5.76 (H_3, m), 2.9–3.4 (2 H), 2.2–2.6 (2 H), $J_{3,4}$ = 3.2 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (7g).** Dibenzoate **7d** (0.62 g) was dissolved in THF (35 ml) and MeOH (65 ml). To this solution was added 1 N NaOH (12 ml). A white solid separated after a few minutes. The mixture was stirred for 3 h at 25 °C. THF and MeOH were removed under reduced pressure to leave a white solid that was washed with water, isolated by suction filtration, and washed several times with cold water. The diol, **7f,** thus obtained (292 mg, 93%) was added to a mixture of Ac_2O (13 ml) and pyridine (3 ml). The solution was stirred at 25 °C for 12 h. Ethyl acetate (40 ml) was added to the solution and the EtOAc phase was extracted with H_2O (3 × 50 ml), dilute HCl (2 × 50 ml), saturated $NaHCO_3$ (50 ml), and H_2O (2 × 50 ml). The EtOAc layer was dried (anhydrous Na_2SO_4), filtered, and concentrated to leave a light yellow solid which was triturated twice with hexane. The resulting white tetrahydrodiacetate **7g** (329 mg, 81%) had mp 171–173 °C; ^{1}H NMR (60 MHz) δ 7.1–8.0 (6 H), 6.53 (H_4), 5.33 (H_3, m), 2.8–3.2 (2 H), 2.1–2.4 (2 H), 2.03 (3, s), 1.97 (3 H, s), $J_{3,4}$ = 3.2 Hz.

1-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrophenanthrene (7h). The reaction of tetrahydrodiol diester **7g** (230 mg), NBS (151 mg), and AIBN (5 mg) in CCl_4 (70 ml) was effected as described for **5e.** Workup gave a clear, oily residue which crystallized upon the addition of ether, yielding isomer I of **7h** (160 mg): ^{1}H NMR (60 MHz) δ 7.4–9.0 (6 H), 6.67 (H_4), 5.66 (H_1), 5.36 (H_3), 2.5–3.0 (2 H), 2.02 (6 H, br s), $J_{3,4} \sim J_{2,3} \sim J_{2',3} \sim 3$, $J_{1,2} \sim 5.5$, $J_{1,2} \sim 2.5$ Hz. Crystallization of the mother liquors from ether yielded a second solid (90 mg), that was recrystallized from ether to give isomer II of **7h:** mp 159–161 °C; ^{1}H NMR (100 MHz) δ 7.4–8.0 (6 H), (H_4), 5.45–5.70 (H_1, H_3), 2.65–2.85 (2 H), 2.07 (3 H, s), 1.98 (3 H, s). Anal. Calcd for $C_{18}H_{17}O_4Br$: C, 57.31; H, 4.54. Found: C, 57.30; H, 4.66.

***trans*-3,4-Diacetoxy-3,4-dihydrophenanthrene (7j).** The reaction of bromodiacetate **7h** (123 mg, isomer I) in xylene (70 ml) containing $NaHCO_3$ (2 g) was effected as described for **5i,** except that a 6-min heating period was used. Workup gave the product as an oil, which afforded crystalline **7j** (57 mg, 59%) of mp 166–167 °C after crystallization from EtOAc/hexane and recrystallization from benzene/hexane: ^{1}H NMR (see Table I). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.83; H, 5.49.

A much better conversion was achieved by reacting the crude bromodiacetate mixture **7h,** from 309 mg of tetrahydrodiacetate **7g,** in anhydrous THF (8 ml) at 0 °C, under N_2, with DBN (80 drops). The reaction mixture was maintained at 0 °C for 18 h. Ethyl acetate (50 ml) was added to the reaction mixture and the EtOAc phase was extracted with H_2O (2 × 40 ml), 0.1 N HCl (2 × 40 ml), dilute $NaHCO_3$ (1 × 40 ml), and H_2O (40 ml). The EtOAc phase was dried (anhydrous Na_2SO_4), filtered, and concentrated, leaving a yellow oil that was column chromatographed on Florisil with EtOAc/hexane (1:8) to give **7j** as a white solid (175 mg, 56% based on tetrahydrodiacetate **7g**).

***trans*-3,4-Dihydroxy-3,4-dihydrophenanthrene (7k).** Hydrolysis of dihydrodiol diacetate **7j** (40 mg) was effected as described for the preparation of **6k,** except that a reaction time of 18 h was employed and the crude product was dissolved in EtOAc rather than CH_2Cl_2. Crystallization of the crude product from EtOAc gave **7k** as a white solid (5 mg). Additional pure **7k** (16 mg) was obtained by column chromatography of the mother liquor on Florisil, using EtOAc/hexane (1:1) as developing solvent (total yield 72%). The product was chromatographically pure by TLC [silica gel, EtOAc/hexane (1:1)], ^{1}H NMR (see Table II).

1-Hydroxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8b). Ketone **8a** (6.0 g)[25] was dissolved in methanol (500 ml) and $NaBH_4$ (3.0 g) was added in portions. After 1 h, the MeOH was removed under reduced pressure and the residue was dissolved in EtOAc (250 ml) and H_2O (100 ml). The EtOAc phase was extracted with H_2O (3 × 100 ml), dried (anhydrous Na_2SO_4), filtered, and concentrated. The residue was crystallized from EtOAc/hexane, which gave **8b** as a light yellow solid (5.2 g, 86%).

***trans*-1,2-Dibenzoyloxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8d).** Alcohol **8b** (2.63 g) was added to a solution of HCl (4 drops) in glacial HOAc (200 ml). Nitrogen was bubbled through the solution and an atmosphere of N_2 was maintained throughout the reaction, as well as during the workup. The solution was heated at 55 °C for 3 h, then it was added to ice (150 g). The aqueous phase was extracted with benzene (200 ml). The benzene layer was extracted with H_2O (200 ml) and concentrated under reduced pressure. The resultant yellow solid, primarily 3,4-dihydrobenzo[*a*]anthracene (**8c**), was used in the subsequent step without further purification.

The reaction of 3,4-dihydrobenzo[*a*]anthracene (**8c,** crude reaction product vide supra), silver benzoate (5.46 g), and iodine (2.82 g) in benzene (150 ml) was effected as described for **5d.** The crude product was chromatographed on Florisil, using EtOAc/hexane (1:9) as developing solvent. Slightly impure **8d** (2.78 g) was obtained. It was recrystallized from MeOH to give tetrahydrodibenzoate (3.22 g, 64% based on alcohol **8b**) of mp 162–163 °C; ^{1}H NMR (60 MHz) δ 8.57, 8.27 (H_7, H_{12}, s), 5.87 (H_2), 6.75–8.15 (17 H), 2.2–3.5 (4 H).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8g).** Dibenzoate **8d** (2.84 g) was dissolved in THF (200 ml) and methanol (200 ml) and 1 N NaOH (24 ml) were added. The reaction mixture was stirred for 2 h, MeOH and THF were removed under reduced pressure, water was added, and the aqueous phase was extracted with EtOAc. The EtOAc phase was washed with H_2O, dried (anhydrous Na_2SO_4), filtered, and concentrated. The residue, primarily diol **8f,** was used without purification.

Diol **8f** (vide supra) was dissolved in Ac_2O (25 ml) and pyridine (5 ml). The acetylation was effected as described for the preparation of **7g.** The crude product was treated with EtOAc/hexane to give tetrahydrodiacetate **8g** as a white solid (1.71 g, 82% based on dibenzoate **8d**) of mp 175–176 °C; ^{1}H NMR (60 MHz) δ 8.35 (2 H, br s), 7.1–8.2 (6 H), 6.70 (H_1), 5.41 (H_2), 2.8–3.2 (2 H), 1.9–2.4 (2 H), 2.03 (3 H, s), 1.97 (3 H, s), $J_{1,2} \sim 3$ Hz.

4-Bromo-1α,2β-diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (8h). The reaction of **8g** (0.50 g), NBS (281 mg), and AIBN (5 mg) in CCl_4 (75 ml) was effected as described for **5e.** Addition of ether to the crude product yielded isomer I (334 mg) of **8h,** which was recrystallized from EtOAc/hexane to give isomer I of mp 163–164 °C; ^{1}H NMR (100 MHz) δ 8.45, 8.38 (H_7, H_{12}, s), 7.4–8.2 (6 H), 6.82 (H_1), 5.67 (H_4), 5.43 (H_2), 2.93–3.12 (1 H), 2.61–2.91 (1 H), 2.01 (6 H, br s), $J_{1,2}$ = 2.9, $J_{3,4}$ = 1.8, $J_{3',4}$ = 5.4, $J_{2,3} \sim J_{2,3} \sim 3.0$ Hz. Anal. Calcd for $C_{22}H_{19}O_4Br$: C, 61.84; H, 4.48. Found: C, 62.12; H, 4.67.

Crystallization of the mother liquors from EtOAc/hexane afforded isomer II (119 mg) of **8h** as a solid of mp 150–154 °C; ^{1}H NMR (100 MHz) δ 8.36 (2 H, br s), 7.3–8.2 (6 H), 6.77 (H_1), 5.43–5.70 (H_2, H_4), 2.70–2.90 (2 H), 2.06 (3 H, s), 1.98 (3 H, s), $J_{1,2}$ = 4.1 Hz.

***trans*-1,2-Diacetoxy-1,2-dihydrobenzo[*a*]anthracene (8j).** The reaction of bromodiacetate isomer I of **8h** (251 mg) in xylene (100 ml) containing $NaHCO_3$ (4 g) was effected as described for **5i,** except that a reaction time of 5 min was adequate. The crude reaction product, after workup, was column chromatographed on Florisil, using EtOAc/hexane (1:9) as developing solvent. The second compound to elute from the column was dihydrodiol diacetate **8j** (51 mg, 25%), which upon recrystallization from EtOAc had mp 182–183 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.26; H, 5.34.

Similar treatment of bromodiacetate isomer II of **8h** afforded a very low yield of **8j,** as judged by the NMR spectrum of the crude reaction product.

Both bromodiacetate isomers of **8h,** on the other hand, could be efficiently converted to dihydrodiol diacetate **8j** upon treatment with DBN in THF at 0 °C. Thus, isomer I of **8h** (50 mg), when reacted with DBN (15 drops) in THF (3 ml, 0 °C) as described for **7j,** yielded a crude reaction product composed almost entirely of **8j,** as judged by NMR. Treatment of the crude product with EtOAc led to the isolation of **8j** (21 mg, 51%). Similarly, isomer II of **8h** (30 mg), when reacted with DBN (15 drops) in THF (4 ml, 0 °C) as described for **7j,** yielded, upon workup, a crude reaction product whose NMR spectrum indicated it to be composed almost entirely of **8j.** The reaction mixture was not processed further. It is likely that best conversions to **8j** would be achieved by reacting the crude bromination product of tetrahydro diester **8g** with DBN in THF.

***trans*-1,2-Dihydroxy-1,2-dihydrobenzo[*a*]anthracene (8k).** Hydrolysis of dihydrodiol diacetate **8j** (49 mg) in MeOH (150 ml), THF (20 ml), and ammonia was effected as described for the preparation of **6k**, except that a reaction time of 24 h was used. Workup, as described previously, gave the product as a light yellow solid. Recrystallization of the solid from EtOAc/hexane afforded 20 mg (54%) of **8k**, mp 167–168 °C. The dihydrodiol diacetate, **8k**, was pure by TLC [silica gel, hexane/EtOAc (1:1), R_f ~0.4]: ^{1}H NMR (see Table II); UV spectrum (see Figure 2) λ_{max} (ϵ): 228 (22 323), 237 (21 325), 262 (69 238), 281 (47 731), 345 (2904), 361 (4809), 381 (6533), 403 (4809).

1,2-Dihydrobenzo[*a*]anthracene (9c). Ketone **9a** (6.0 g)[26] and $NaBH_4$ (9.0 g) were reacted in MeOH (500 ml), as described for the preparation of **8b**. The alcohol (**9b**) thus obtained was converted, without purification, to **9c**. Thus, the crude alcohol (**9b**) was dissolved in a solution of glacial HOAc (150 ml) and concentrated HCl (6 drops) and the mixture was heated at 90 °C for 1.5 h. The reaction mixture was cooled (25 °C), and H_2O (50 ml) was added. The product, **9c**, precipitated and was collected by filtration. Residual HOAc was removed by dissolving **9c** in CH_2Cl_2 and extracting with aqueous $NaHCO_3$. The product was obtained as a light yellow solid (5.0 g, 90% based on ketone **9a**) which, after recrystallization from EtOAc/hexane, had mp 176–178 °C; ^{1}H NMR (60 MHz) δ 8.48, 8.27 (H_7, H_{12}, s), 7.0–8.1 (6 H, m), 6.55 (H_4), 6.07 (H_3), 3.0–3.5 (2 H), 2.1–2.7 (2 H), $J_{2,3}$ = 3.8, $J_{2,4}$ = 1.9, $J_{3,4}$ = 9.7 Hz.

***trans*-3,4-Dibenzoyloxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9d).** The reaction of 1,2-dihydrobenzo[*a*]anthracene (**9c**, 5.0 g), silver benzoate (11.31 g), and iodine (5.85 g) in benzene (150 ml) was effected as described for **5d**. Crystallization of the crude product from acetone gave **9d** as a light yellow solid (5.51 g, 54%). Recrystallization gave **9d** as a light yellow solid (5.51 g, 54%). Recrystallization gave **9d** as a white solid: mp 187–188 °C; ^{1}H NMR (60 MHz) δ 8.57, 8.37 (H_7, H_{12}, s), 7.15–8.20 (16 H), 6.70 (H_4), 5.5–5.9 (H_3), 3.4–3.7 (2 H), 2.3–2.8 (2 H), $J_{3,4}$ = 6.0 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9g).** The conversion of dibenzoate **9d** (3.5 g) to diol **9f** in THF (200 ml), MeOH (100 ml), and 0.1 N NaOH (74.2 ml) was effected as described for the preparation of **7f**. The white, solid diol thus obtained (1.90 g, 97%) was used without characterization. Acetylation of **9f** (1.90 g) in Ac_2O (20 ml) and pyridine (3 ml) was effected as described for the preparation of **7g**, except that a 24-h reaction time was required. Workup, as described previously, gave the crude product as a solid, which was recrystallized from EtOAc/hexane to give diacetate **9g** as a clear solid (2.11 g, 84%) of mp 145–146 °C; ^{1}H NMR (60 MHz) δ 8.52, 8.37 (H_7, H_{12}, s), 7.1–8.2 (6 H), 6.22 (H_4), 5.15–5.50 (H_3), 3.2–3.6 (2 H), 2.0–2.6 (2 H), 2.14 (2 H, s), 2.03 (3 H, s), $J_{3,4}$ ~ 5.5 Hz.

1β-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene (9h). The reaction of tetrahydrodiacetate **9g** (1.83 g), NBS (1.03 g), and AIBN (5 mg) in CCl_4 (250 ml) was effected as described for **5e**. Crystallization of the crude product from ether (0 °C) gave **9h** (1.76 g, 78%) as a light yellow solid, which after recrystallization from CH_2Cl_2/hexane had mp 143–144 °C; ^{1}H NMR (100 MHz) δ 8.64, 8.35 (H_7, H_{12}, s), 7.06–8.20 (6 H, m), 6.47 (H_4), 6.11 (H_1), 5.96 (H_3), 2.89 ($H_{2\beta}$), 2.50 ($H_{2\alpha}$), 2.19 (3 H, s), 2.09 (3 H, s), $J_{1,2\beta}$ = 2.9, $J_{1,2\alpha}$ = 3.9, $J_{2\alpha,2\beta}$ = 14.3, $J_{2\alpha,3}$ = 12.3, $J_{2\beta,3}$ = 4.3, $J_{3,4}$ = 8.6 Hz. Anal. Calcd for $C_{22}H_{19}O_4Br$: C, 61.84; H, 4.48. Found: C, 62.23; H, 4.73.

***trans*-3,4-Diacetoxy-3,4-dihydrobenzo[*a*]anthracene (9j).** The reaction of bromodiacetate **9h** (145 mg) in xylene (70 ml) containing $NaHCO_3$ (2.0 g) was effected as described for **5i**, except that a reaction time of 10 min was employed. The crude product was chromatographed on Florisil with EtOAc/hexane (1:9). The second compound off the column was **9k** (39 mg, 33%), a yellow solid of mp 151–154 °C after recrystallization from EtOAc/hexane: ^{1}H NMR (see Table I). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.32; H, 5.54.

***trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*a*]anthracene (9k).** Hydrolysis of dihydrodiol diacetate **9j** (39 mg) in MeOH (50 ml) and NH_3 was effected as described for **6k**. The crude product was triturated with CH_2Cl_2/EtOAc to give **9k** as a yellow solid (22 mg, 73%) of mp 215–217 °C. The product was pure by TLC (1:1 EtOAc/hexane, R_f ~0.4): ^{1}H NMR (see Table I); UV (see Figure 2) λ_{max} (ϵ) 261 (104 950), 280 (17 327), 345 (2970), 363 (4554), 383 (5149), 405 (4257).

***trans*-8,9-Dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (10d).** To a mixture of 10,11-dihydrobenzo[*a*]anthracene (8.96 g)[16b,27] and silver benzoate (19.6 g) in benzene (500 ml) was added powdered iodine (10.9 g). The mixture was stirred for 10 min, then refluxed for 2 h. Workup was effected as described for **5d**. Recrystallization of the crude product from benzene/hexane (1:2) gave tetrahydrodibenzoate **10d** (13.8 g, 75%) as colorless needles: mp 153–154 °C; ^{1}H NMR (60 MHz) δ 8.60 (H_1, m), 8.46 (H_{12}, s), 7.20–8.25 (16 H), 6.75 (H_8, d), 5.70 (H_9, m), 3.37 (2 H, m), 2.2–2.8 (2 H, m), $J_{8,9}$ = 6.0 Hz.

11β-Bromo-8β,9α-dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (10e). The reaction of **10d** (6.1 g), NBS (2.54 g), and AIBN (5 mg) in CCl_4 (500 ml) was effected as described for **5e**, except that a heating period of 50 min was used. Treatment of the crude product with ether resulted in the crystallization of **10e**. Recrystallization from CH_2Cl_2/hexane (4:6) gave **10e** (5 g, 70%) as colorless needles: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 8.84 (H_{12}, s), 8.69 (H_1, m), 7.20–8.28 (16 H), 6.89 (H_8), 6.16 (H_9), 5.98 (H_{11}), 3.06 ($H_{10\beta}$), 2.74 ($H_{10\alpha}$), $J_{8,9}$ = 8.0, $J_{9,10\beta}$ = 4.0, $J_{9,10\alpha}$ = 10.0, $J_{10\alpha,11}$ = 4.4, $J_{10\beta,11}$ = 4.0, $J_{10\alpha,10\beta}$ = 14.5 Hz. Calcd for $C_{32}H_{23}O_4Br$: C, 69.70; H, 4.20. Found: C, 69.98; H, 4.26.

***trans*-8,9-Dibenzoyloxy-8,9-dihydrobenzo[*a*]anthracene (10i).** The reaction of bromodibenzoate **10e** (3.3 g) in xylene (80 ml) containing $NaHCO_3$ (10.0 g) was effected as described for **5i**, except that a reaction time of 30 min was employed. Recrystallization of the crude product from CH_2Cl_2/hexane (1:1) gave **10i** (1.84 g, 65%) as colorless needles: mp 167–168 °C; ^{H}NMR (see Table I). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.76; H, 4.92.

***trans*-8,9-Dihydroxy-8,9-dihydrobenzo[*a*]anthracene (10k).** Dibenzoate **10i** (1.5 g) was dissolved in deaerated THF (30 ml) and MeOH (30 ml), under argon. Freshly prepared $NaOCH_3$ (2.5 g) was added and the solution was stirred for 15 min. Ethyl acetate (200 ml) was added and the mixture was washed with H_2O (three times). The water layer was extracted with EtOAc (2 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Recrystallization of the crude product from acetone gave **10k** (580 g, 70%) as colorless prisms: mp 168–170 °C dec; ^{1}H NMR (see Table II); UV (see Figure 2) λ_{max} (ϵ) 229 (18 130), 256 (56 700), 265 (71 950), 286 (17 830), 306 (23 240), 319 (25 640).

8,9-Dihydrobenzo[*a*]anthracene (11c). Ketone **11a** (12.0 g)[28] and $NaBH_4$ (10.0 g) were reacted in methanol (900 ml), as described for the preparation of **8b**. Recrystallization of the crude product from EtOH gave alcohol **11b** (10.8 g, 89%) as colorless prisms: mp 119–120 °C; ^{1}H NMR (60 MHz) δ 8.66 (H_{12}, s), 8.50 (H_1, m), 7.40–7.90 (6 H), 4.90 (O–H), 2.85 (2 H, m), 1.6–2.2 (5 H, m).

Alcohol **11b** (10.0 g) was dissolved in a solution of HOAc (250 ml) and concentrated HCl (2 drops), and the mixture was heated at 100 °C, under argon, for 2 h. The reaction mixture was cooled (10 °C) and H_2O (150 ml) was added. The product **11c** precipitated and was collected by filtration. It was washed thoroughly with water and was dried (P_2O_5) under reduced pressure. Recrystallization from EtOH gave **11c** (8.8 g, 95%) as colorless needles: mp 99–100 °C; ^{1}H NMR (60 MHz) δ 8.55 (H_1, m), 8.20 (H_{12}, s), 7.35–7.90 (6 H), 6.70 (H_{11}), 6.07 (H_{10}), 2.91 (2 H, m), 2.36 (2 H, m), $J_{9,10}$ = 4, $J_{10,11}$ = 9.5 Hz.

***trans*-10,11-Dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (11d).** The reaction of **11c** (10 g), silver benzoate (22 g), and iodine (12.1 g) in benzene (500 ml) was effected as described for **10d**. Addition of EtOH to the crude reaction product led to the formation of a solid that was recrystallized from CH_2Cl_2/EtOH (4:1) to give **11d** (15.4 g, 75%) as colorless needles: mp 173–174 °C; ^{1}H NMR (60 MHz) δ 8.65 (H_{12}, s), 8.50 (H_1, m), 7.20–8.25 (16 H), 6.80 (H_{11}), 5.71 (H_{10}, m), 3.25 (2 H, m), 2.18–2.80 (2 H), $J_{10,11}$ = 5.5 Hz.

8β-Bromo-10α,11β-dibenzoyloxy-8,9,10,11-tetrahydrobenzo[*a*]anthracene (11e). The reaction of **11d** (7.6 g), NBS (3.16 g), and AIBN (5 mg) in CCl_4 (500 ml) was effected as described for **5e**, except that a heating period of 50 min was used. Treatment of the crude product with ether caused the precipitation of a solid which was recrystallized from CH_2/hexane (4:6) to give **11e** (5.8 g, 6) as colorless prisms: mp 137–138 °C; ^{1}H NMR (100 MHz) δ 8.64 (H_{12}, s), 8.49 (H_1, m), 7.20–8.27 (16 H), 6.90 (H_{11}), 6.13 (H_{10}), 5.85 (H_8), 3.05 ($H_{9\beta}$), 2.53 ($H_{9\alpha}$), $J_{8,9\beta}$ = 4.7, $J_{8,9\alpha}$ = 4.7, $J_{9\alpha,9\beta}$ = 14.5, $J_{9\beta,10}$ = 3.7, $J_{9\alpha,10}$ = 9.4, $J_{10,11}$ = 7.6 Hz. Anal. Calcd for $C_{32}H_{23}O_4Br$: C, 69.70; H, 4.20. Found: C, 69.95; H, 4.11.

***trans*-10,11-Dibenzoyloxy-10,11-dihydrobenzo[*a*]anthracene (11i).** The reaction of bromodibenzoate **11e** (1.1 g) in xylene (80 ml) containing $NaHCO_3$ (5.0 g) was effected as described for **5i**, except that a reaction time of 30 min was used. Recrystallization of the crude product from CH_2Cl_2/hexane (1:20) gave **11i** (0.660 g, 62%) as colorless prisms: mp 170–171 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.72; H, 4.93.

***trans*-10,11-Dihydroxy-10,11-dihydrobenzo[*a*]anthracene (11k).** The hydrolysis of dihydrodiol dibenzoate **11i** (300 mg) was effected as described for the preparation of **10k**. The crude product was recrystallized from EtOAc to give **11k** (109 mg, 65%) as colorless needles: mp 196–200 °C dec; ^{1}H NMR (see Table II); UV (see Figure 2) λ_{max} (ϵ) 227 (11 580), 265 (52 315), 274 (67 280), 294 (18 440), 210 (11 235).

Registry No.—**5d,** 60967-91-1; **5e** (R_4 = β), 60967-92-2; **6g,** 60967-93-3; **6h** (R_4 = β), 60967-94-4; **7d,** 60967-95-5; **7f,** 60967-96-6; **7g,** 60967-97-7; **7h** (R_4 = α), 60967-98-8; **7h** (R_4 = β), 60967-99-9; **8b,** 60968-00-5; **8c,** 60968-01-6; **8d,** 60968-02-7; **8f,** 60968-03-8; **8g,** 60968-04-9; **8h** (R_4 = α), 60968-05-0; **8h** (R_4 = β), 60968-06-1; **9a,** 38393-90-7; **9b,** 60968-07-2; **9c,** 60968-08-3; **9d,** 60968-09-4; **9f,** 60968-10-7; **9g,** 60968-11-8; **9h** (R_4 = β), 60968-12-9; **10d,** 60968-13-0; **10e** (R_4 = β), 60968-14-1; **11a,** 60968-15-2; **11b,** 60968-16-3; **11c,** 60968-17-4; **11d,** 60968-18-5; **11e** (R_4 = β), 60968-19-6; silver benzoate, 532-31-0; 1,2-dihydroanthracene, 58746-82-0; *N*-bromosuccinimide, 128-08-5; silver acetate, 563-63-3; 3,4-dihydrophenanthrene, 38399-10-9; 1,2-dihydrophenanthrene, 56179-83-0; ethyl acetate, 141-78-6; 10,11-dihydrobenzo[*a*]anthracene, 34501-50-3.

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Aporphines. 19.[1a] Mass Spectrometry of Nitrobenzylisoquinolines. Influence of Positional Isomerism on Fragmentation and Evidence for an Ionically Induced Intramolecular Migration Process[1b]

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The mass spectra of a series of nitro-substituted benzylisoquinolines were examined under both electron impact and chemical ionization conditions. A number of fragmentation processes have been observed which can be utilized for structural assignments to positional isomers. Isotopic labeling was used to confirm the mechanism of specific fragmentations. The procedures for synthesis of the title compounds are included.

The importance of 1-(2-nitrobenzyl)isoquinolines as key intermediates in the synthesis of aporphine alkaloids and other biologically active molecules has been well documented in the recent literature.[2] The Reissert[3] alkylation method via 2-benzoyl-1,2-dihydroisoquinaldonitriles is used to advantage for the synthesis of many benzylisoquinolines and 1-(2-nitrobenzyl)isoquinolines.[4] Thus, aporphine alkaloids can be conveniently prepared by the reduction of the isoquinolinium salts of 1-(*o*-nitrobenzyl)isoquinolines and Pschorr cyclization.[5,6]

As part of a program aimed at the preparation and biological testing of a variety of new aporphine derivatives, we have synthesized a series of benzylisoquinolines, **1a–h.** This report on the mass spectrometric properties—both under electron impact and chemical ionization conditions—has been prompted, in part, by the relative paucity of mass spectral