The (2-benzo[b]thienyl)phenylglycolic ester **21** was also obtained in 39% yield along with 8% of the dione by using 2-benzo[b]thienylmagnesium bromide instead of the lithium derivative.

Reaction of Ethyl (2-Benzo[b]thienyl)phenylglycolate with $AlCl_3$ in Benzene. Treatment of ethyl (2-benzo[b]thienyl)phenylglycolate (0.5 g, 1.6 mmol) in 45 mL of dry benzene at 0 °C with 3 molar excess of sublimed $AlCl_3$ (0.64 g, 4.8 mmol) followed by reflux overnight gave upon the usual workup a red-brown oil (0.40 g) which was sublimed (110 °C, 0.04 mm) to yield 0.1 g (21%) of bright yellow crystals, which were recrystallized twice from cyclohexane to given an analytical sample of ethyl 6H-benz[b]indeno[1,2-d]thiophene-6-carboxylate (**23**) as white needles: mp 94-95 °C; IR (KBr) 1728 (s), 1220 (m), 1028 (m), 763 (s), 630 cm^{-1} (w); NMR ($CDCl_3$) δ 8.10-7.00 (m, 8, aromatic), 4.81 (s, 1, CH), 4.18 (q, 2, CH_2), 1.26 (t, 3, CH_3). Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.33; H, 4.70, S, 10.95.

Reaction of Ethyl (2-Benzo[b]thienyl)phenylglycolate with $AlCl_3$ in Carbon Disulfide. Reaction of the glycolate ester **21** with $AlCl_3$ in carbon disulfide using the same as solvent but without any benzene gave a 67% yield of closed ester **23** which was chromatographed over silica gel 60 and eluted with 1:1 benzene-hexane to yield 0.63 g of yellow-orange solid (mp 89-92 °C). Yellow fluffy solid (0.40 g, mp 93.5-95 °C) was obtained on recrystallization from heptane and was shown to be identical with an authentic sample of ethyl 6H-benz[b]indeno[1,2-d]-thiophene-6-carboxylate described above by comparison of their NMR and IR spectra.

Saponification of Ethyl 6H-Benz[b]indeno[1,2-d]-thiophene-6-carboxylate (23). Recrystallized ethyl 6H-benz-[b]indeno[1,2-d]thiophene-6-carboxylate (0.40 g, 1.36 mmol) was saponified to give a dark red-brown solid (0.11 g, mp 80-85 °C) which was sublimed at 108 °C (0.1 mm) to give a yellow solid (60 mg, 20%, mp 106-108 °C). Recrystallization from pentane afforded an analytical sample of 6H-benz[b]indeno[1,2-d]thiophene as pale yellow platelets: mp 109.5-110.5 °C; IR (KBr) 1470 (m), 1420 (m), 1380 (m), 1290 (w), 1225 (w), 1170 (m), 760 (s), 720 (s), 710 (s), 620 cm^{-1} (m); NMR (CCl_4) δ 7.9-6.79 (m, 8, aromatic), 3.59 (s, 2, CH_2). Anal. Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 81.08; H, 4.57; S, 14.60.

A mixture melting point of this product with synthetic 6H-benz[b]indeno[1,2-d]thiophene showed no depression and the NMR and IR spectra were identical.

6H-Benzo[b]indeno[1,2-d]thiophene (25). Reaction of sodium thiophenoxide from thiophenol (11.0 g, 0.10 mol) in aqueous THF solution with 2-bromo-1-indanone[14] (21.0 g, 0.1 mol) at 20 °C with vigorous stirring for 1 h gave upon extraction with ether a yellow oil which was crystallized from hexane to afford 16.7 g (69%) of 2-(thiophenoxy)-1-indanone, mp 77-67 °C. Anal. Calcd for $C_{15}H_{12}OS$: C, 74.96; H, 5.04; S, 13.34. Found: C, 75.16; H, 5.13; S, 13.42.

To a mixture of 30 g of 85% H_3PO_4 and 30 g of P_4O_{10} at 70 °C was added 2-(thiophenoxy)-1-indanone (6.0 g, 0.025 mol) with stirring. The mixture was maintained at 100 °C for 15 min and poured into ice and water followed by extraction with ether. The residue obtained from the ether extraction was an oil (3.86 g) which was dissolved in benzene and chromatographed over alumina with pentane as eluant to give 1.12 g of a waxy solid (mp 80-85 °C). Two recrystallizations from pentane gave 0.7 g (13%) of 6H-benzo[b]indeno[1,3-d]thiophene (**25**): mp 111-112 °C; NMR (CCl_4) 7.8-6.8 (m, 8, aromatic), 3.58 (s, 2, CH_2). Anal. Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 80.92; H, 4.43; S, 14.25.

(14) H. O. House, V. Paraganian, R. S. Ro, and D. J. Wlunka, *J. Am. Chem. Soc.*, **82**, 1452 (1960).

Isomeric Phenols of Benzo[e]pyrene

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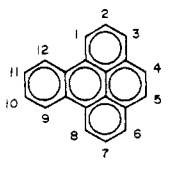
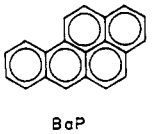
Convenient syntheses of the complete set of isomeric phenols of benzo[e]pyrene, 1-, 2-, 3-, 4-, 9-, and 10-hydroxybenzo[e]pyrene, are described. The structural assignments are supported by high-resolution 270-MHz proton NMR spectra in which the chemical shifts and coupling constants of the aromatic protons are fully assigned. Ultraviolet absorption and fluorescence spectral data for the isomeric benzo[e]pyrene phenols are also presented.

Benzo[e]pyrene (BeP) is a widespread environmental pollutant present in the atmosphere, soil, automobile exhaust, cigarette smoke, and foods.[1] In contrast to the isomeric benzo[a]pyrene which is a potent carcinogen, BeP is only a weak tumor initiator.[2]



BeP



BaP

In connection with biological studies designed to probe the nature of this striking difference in biological activity,[3,4] we required authentic samples of the isomeric phenols of BeP as standards for identification of the metabolites of this hydrocarbon. Since only one of the six isomeric phenols of BeP (4-HO-BeP) appears to have been syn-

(1) International Agency for Research on Cancer. "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds"; World Health Organization: Geneva, Switzerland, 1973; Vol. 3.

(2) Scribner, J. D. *J. Natl. Cancer Inst.* **1973**, *50*, 1717.

(3) Recent studies have implicated a diol epoxide metabolite, *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (*anti*-BPDE), as the principal active form of benzo[a]pyrene.[4] Significant levels of carcinogenic activity are also exhibited by certain other metabolites of benzo[a]pyrene, notably the 4,5-oxide and 2-, 9-, 11-, and 12-HO-BaP's.[5]

(4) Reviews: (a) Gelboin, H. V., Ts'o, P. O. P. Eds.; "Polycyclic Hydrocarbons and Cancer"; Academic Press: New York, 1978; (b) Harvey, R. G. In "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens"; Walters, D. B., Ed.; Ann Arbor Science Publishers, Inc.: Ann Arbor, MI, 1980; (c) Harvey, R. G. *Acc. Chem. Res.*, in press.

(5) Slaga, T. J.; Bracken, W. M.; Dresner, S.; Levin, W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 678. Flesher, J. W.; Harvey, R. G.; Sydnor, K. L. *Int. J. Cancer* **1976**, *18*, 351.

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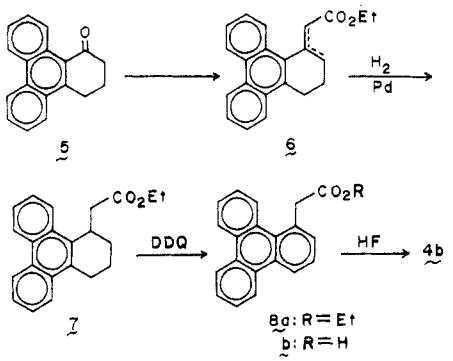
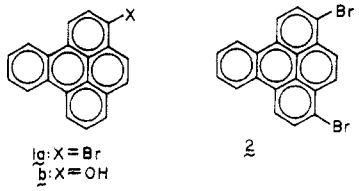
Scheme I



thesized and partially characterized,[6] we undertook to synthesize the complete set of isomers. We report herein synthesis of 1-, 2-, 3-, 4-, 9-, and 10-hydroxybenzo[e]pyrene.

Results

3-Hydroxybenzo[e]pyrene. Surprisingly, virtually nothing is known[7] concerning the patterns of electrophilic substitution of BeP, aside from the report by Lang and Zander[8] that bromination with excess bromine affords 3,6-dibromobenzo[e]pyrene (**2**). We reasoned that if bromination could be controlled to afford 3-Br-BeP (**1a**), the latter could serve as a convenient synthetic precursor of 3-hydroxybenzo[e]pyrene (3-HO-BeP).

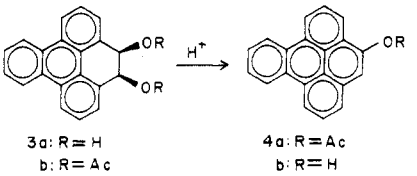


Bromination of BeP with *N*-bromosuccinimide gave a mixture of isomeric monobromo and dibromo derivatives (by HPLC analysis) which proved difficult to separate by column chromatography. Bromination of BeP with 1 molar equiv of bromine furnished a monobromo derivative identified as **1a** accompanied by a lesser amount of a dibromo derivative (~30%) identical with the 3,6-Br_2-BeP (**2**) previously characterized by Lang and Zander by IR spectral analysis.[8] Bromination of BeP with excess Br_2 afforded exclusively **2**. Bromination of BeP with *o*-chloranil and HBr by the method of Wilk and Hoppe[9] also afforded **1a** rather than 4-Br-BeP as previously assumed by these investigators on the basis of IR spectral analysis. The NMR spectrum of this compound proved identical with that of **1a** synthesized above and a mixture melting point failed to depress. The high-resolution 270-MHz proton NMR spectra of **1a** and **2** were consistent with these structural assignments (cf. Discussion).

Conversion of 3-Br-BeP to 3-HO-BeP (**1b**) was accomplished through reaction of the Grignard reagent of **1a** with diborane, followed by treatment of the resulting arene–borane intermediate with alkaline H_2O_2. The NMR spectrum of **1b** was in good agreement with the assigned structure and different from that of authentic 4-HO-BeP synthesized below, further confirming the assignment of **1a** as 3-Br-BeP.

4-Hydroxybenzo[e]pyrene. Synthesis of 4-HO-BeP was accomplished via two approaches, one from BeP and the second from 1-oxo-1,2,3,4-tetrahydrotriphenylene (Scheme I).

The former sequence affords 4-HO-BeP (**4b**) from BeP smoothly in four steps. Reaction of BeP with osmium tetraoxide by the procedure utilized earlier for BaP[10] furnished *cis*-4,5-dihydroxy-4,5-dihydrobenzo[e]pyrene (**3a**)[6] isolated as the diacetate (**3b**) by chromatography on



Florisil. The latter on heating in refluxing benzene in the presence of *p*-toluenesulfonic acid underwent elimination of acetic acid to furnish 4-OAc-BeP (**4a**). Acid-catalyzed methanolysis of **4a** provided pure **4b** in good overall yield (53%).

While the forgoing synthesis of 4-HO-BeP is attractive in its simplicity, the starting compound, BeP, is itself relatively expensive. Therefore, an alternative synthetic approach based on 1-oxo-1,2,3,4-tetrahydrotriphenylene (**5**)[11,12] was also investigated (Scheme I); this method has the advantage that it is adaptable to the synthesis of other BeP derivatives (e.g., 4-CH_3-BeP). Reformatsky reaction of **5** provided ethyl (1-hydroxy-1,2,3,4-tetrahydro-1-triphenylenyl)acetate. The latter underwent acid-catalyzed dehydration to a mixture of the conjugated and unconjugated esters **6**. Hydrogenation of **6** over 5% Pd/C afforded quantitatively the ethyl 1,2,3,4-tetrahydro compound **7**, dehydrogenation of which with DDQ followed by alcoholysis gave 1-triphenylenylacetic acid (**8b**). The NMR spectrum of **8b** exhibited five bay-region aryl protons ($H_{4,5,8,9,12}$) at low field (δ 8.5–8.8) and six additional aromatic protons at δ 7.6–7.9, confirming the presence of the substituent in the bay region 1-position. Cyclization of **8b** in liquid HF provided a phenol, the 270-MHz NMR spectrum and melting point of which were identical with those of 4-HO-BeP obtained via the former synthetic route. The overall yield of **4b** from **5** was 54%, virtually identical with that obtained via the alternative method.

9- and 10-Hydroxybenzo[e]pyrenes. The syntheses of 9- and 10-HO-BeP are based on 9-oxo-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]pyrene (**9**), an intermediate in the synthesis of the 9,10-dihydro diol of BeP previously[11] described.

Synthesis of 9-HO-BeP (**10b**) was conveniently achieved through conversion of **9** to its enol acetate by reaction with isopropenyl acetate followed by dehydrogenation with DDQ to 9-acetoxy-BeP (**10a**). Acid-catalyzed methanolysis of **10a** provided pure 9-HO-BeP.

Several synthetic approaches to 10-HO-BeP (**17b**) were investigated (Scheme II). Since 1,2,3,6,7,8,9,10-octahydrobenzo[e]pyrene (**12**) is readily available from **9** through reduction with $NaBH_4$ and dehydration,[11] it was initially attempted to convert **12** to 10-oxo-

(6) Synthesis of 4-HO-BeP through dehydration of *cis*-4,5-dihydroxy-4,5-dihydrobenzo[e]pyrene was reported by Sims (*Biochem. Pharmacol.* **1970**, *19*, 285) without experimental details and characterized only by UV spectrum.

(7) Clar, E. "Polycyclic Hydrocarbons"; Academic Press: New York, 1964; Vol. 2.

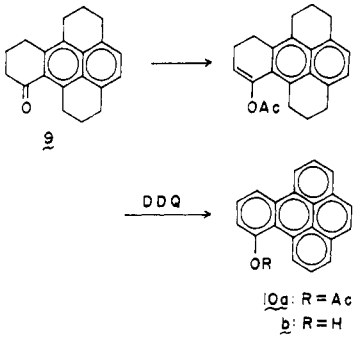
(8) Lang, K. F.; Zander, M. *Chem. Ber.* **1964**, *97*, 218.

(9) Wilk, M.; Hoppe, U. *Justus Liebigs Ann. Chem.* **1969**, 727, 81. The assignment of the monobromo BeP isomer obtained by these authors is unclear due to confusion in the nomenclature and ring numbering system employed (cf. Experimental Section).

(10) Harvey, R. G.; Goh, S. H.; Cortez, C. *J. Am. Chem. Soc.* **1975**, *97*, 3468.

(11) Harvey, R. G.; Lee, H. M.; Shyamasundar, N. *J. Org. Chem.* **1979**, *44*, 78, 5006.

(12) Bergmann, E.; Blum-Bergman, O. *J. Am. Chem. Soc.* **1937**, *59*, 1441.



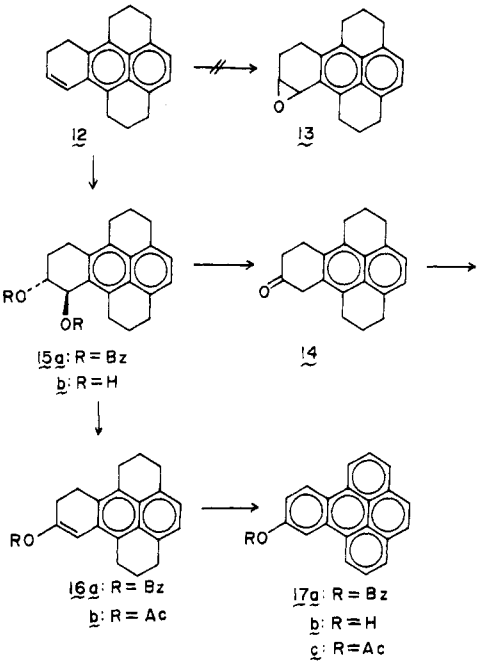
1,2,3,6,7,8,9,10-octahydrobenzo[e]pyrene (14) via epoxidation to 13 and BF_3-catalyzed rearrangement, a method successfully employed previously in the synthesis of 9-oxo-8,9,10,11-tetrahydrobenz[a]anthracene.[13] However, 13 could not be obtained from reaction of 12 with *m*-chloroperbenzoic acid. On the other hand, Prevost reaction of 12 furnished pure *trans*-9,10-bis(benzoyloxy)-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]pyrene (**15a**,[11] 90%) which underwent acid-catalyzed elimination of benzoic acid in refluxing benzene to provide the enol benzoate **16a** (71%) accompanied by a minor amount of 14, readily separable by chromatography on Florisil. The integrated proton NMR spectrum of **16a** confirmed this structural assignment, exhibiting a characteristic singlet vinylic signal at δ 6.75 in addition to aliphatic, allylic, benzylic, and aromatic peaks in the expected ratio. Aromatization of **16a** with DDQ in refluxing benzene provided 10-(benzoyloxy)benzo[e]pyrene (**17a**) in 77% yield. Acid-catalyzed methanolysis of **17a** gave pure 10-HO-BeP (**17b**) in 91% yield.

Prior to development of this successful approach to 10-HO-BeP, an alternative procedure involving initial basic methanolysis of **15a** to the free diol **15b** was investigated. Dehydration of **15b** to the ketone 14, followed by formation of the enol acetate **16b**, aromatization with DDQ, and methanolysis provided **17b** in slightly lower overall yield.

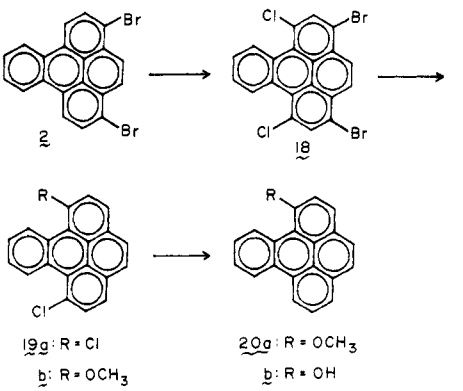
1-Hydroxybenzo[e]pyrene. Synthesis of 1-HO-BeP presented a more difficult challenge. An attractive approach was through chlorination of 3,6-Br_2-BeP. Although bromination of BeP stops at the dibromo stage, chlorination proceeds to 1,3,6,8-Cl_4-BeP.[8] It was reasoned that if 1-Cl-3,6-Br_2-BeP could be obtained, selective debromination would afford 1-Cl-BeP which could be converted to 1-HO-BeP. However, chlorination of 2 exhibited a strong tendency to proceed beyond the monochloro stage to afford predominantly 3,6-Br_2-1,8-Cl_2-BeP (18) under all conditions (Scheme III). Since 18 was easily accessible, it was thought to utilize it as the precursor of 1-HO-BeP (**20b**). Debromination of 18 was accomplished by treatment with *n*-butyllithium and hydrolysis to afford 1,8-Cl_2-BeP (**19a**). Reaction of the dichloro compound with sodium methoxide in hexamethylphosphoramide by the method of Shaw et al.[14] provided 1-MeO-8-Cl-BeP (**19b**). Dechlorination of **19b** with *n*-butyllithium and hydrolysis gave 1-methoxybenzo[e]pyrene (**20a**). Demethylation of **20a** with sodium thioethoxide gave pure 1-HO-BeP (**20b**) as a white crystalline solid. The proton NMR spectra of **20b** and all intermediates were consistent with the structural assignments.

2-Hydroxybenzo[e]pyrene. Two synthetic approaches to 2-HO-BeP were explored. One of these involved cine substitution of 3-Br-BeP with sodamide in liquid ammonia to generate a mixture of 2- and 3-NH_2-BeP (7:3 by HPLC) via a benzyne-type intermediate. The amines were purified by conversion to the corresponding acetamides and chromatography. High-resolution 270-MHz NMR spectral analysis of the major isomer unequivocally confirmed the structure as 2-(AcNH)-BeP (**21**). However, all attempts to convert 2-NH_2-BeP to 2-Br-BeP via diazotization and

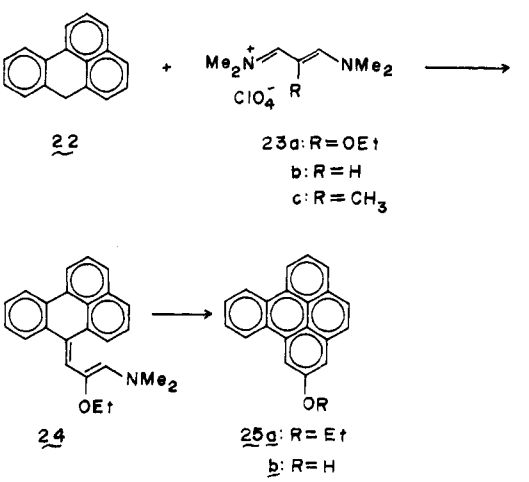
Scheme II



Scheme III



Scheme IV



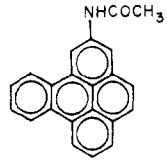
(13) Fu, P. P.; Cortez, C.; Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4265.
(14) Shaw, J. E.; Kunerth, D. C.; Swanson, S. B. *J. Org. Chem.* **1976**, *41*, 732.

Table I. Ultraviolet Absorption Data for the Phenols of Benzo[e]pyrene[a]

isomer	absorption maxima (molar extinction coefficients), nm ($10^{-4}\epsilon_{max}$)
1-HO-BeP	225 (3.08), 230 (2.54), 263 (2.49), 280 (2.38), 295 (2.76), 350 (1.41)
2-HO-BeP	215 (3.19), 263 (389), 275 (2.63), 287 (3.69), 330 (2.22)
3-HO-BeP	225 (3.42), 238 (2.86), 280 (2.90), 295 (3.42), 340 (2.43)
4-HO-BeP	225 (3.10), 268 (4.17), 295 (2.01), 330 (9.66)
9-HO-BeP	225 (3.27), 245 (2.52), 280 (2.85), 295 (3.19), 330 (2.27)
10-HO-BeP	226 (3.79), 288 (6.66), 340 (1.89)

[a] Spectra were measured in ethanol on a Varian Techtron Model 635 spectrometer with a slit width of 2.0 mm. The measurements were carried out on approximately 2×10^{-5} M solutions.

Sandmeyer reaction failed to afford any appreciable yield of 2-Br-BeP.



21

The alternative synthetic approach involved reaction of benzanthrene (**22**) with the appropriately substituted "vinamidinium salt" **23a**[15] by the method of Jutz.[16] The resulting 1-(dialkylamino)-2-ethoxy diene intermediate **24** (Scheme IV) on being heated in refluxing quinoline underwent electrocyclic ring closure with elimination of dimethylamine to furnish 2-EtO-BeP (**25a**). Dealkylation with sodium thioethoxide gave pure crystalline 2-HO-BeP (**25b**). The ultraviolet spectrum of **25b** matched rather closely that of BeP and differed markedly from that of benzo[a]pyrene or perylene, confirming the presence of the BeP aromatic ring system. The NMR spectra of **25a** and **25b** further supported these structural assignments (cf. Discussion).

Since ultraviolet absorption and fluorescence spectra are commonly employed as the principal methods of detection and characterization of hydrocarbon metabolites in biological studies, UV and fluorescence spectral data on the isomeric phenols of BeP are presented in Tables I and II.

Discussion

The foregoing syntheses provide convenient methods for the preparation of the complete set of isomeric phenols of BeP.

The 270-MHz NMR spectra of the six isomeric phenols of BeP were analyzed and the chemical shifts and coupling constants of the aromatic protons fully assigned (Table III). Decoupling was employed to aid in the chemical shift assignments. In the NMR spectrum of BeP the H_1, H_8, H_9, and H_{12} hydrogens in the bay region appear at lowest field due to their repulsive van der Waals interaction.[17] Introduction of hydroxyl groups into BeP resulted in upfield shifts of the ortho, meta, and para protons in the same ring of 0.43–0.68, 0.17–0.32, and 0.46 ppm, respectively. A pronounced downfield shift ($\Delta\delta \approx 1.0$ ppm) was also observed for the bay region hydrogens of 1- and 9-HO-BeP. The magnitudes of the observed coupling constants were in the typical range for polyarenes,[17] J_{ortho} = 5.2–8.9 Hz and J_{meta} = 2.0–3.5 Hz. Longer range couplings between para protons and protons on adjacent rings were generally too small to permit accurate assignment. The NMR spectra of all compounds were entirely consistent with their structural assignments.

Table II. Fluorescence Spectral Data for the Phenols of Benzo[e]pyrene[a]

isomer	maxima, nm	rel intens
1-HO-BeP	390	28
2-HO-BeP	390	55
3-HO-BeP	397	37
4-HO-BeP	397	12
9-HO-BeP	394	18
10-HO-BeP	397	25

[a] Spectra were measured in ethanol on a Perkin-Elmer Model 512 spectrometer at an excitation wavelength of 330 nm in the energy mode with slit width settings of 3 nm for the emission monochromators.

The structural assignments of 3-Br-BeP (**1a**), 3-HO-BeP (**1b**), and 3,6-Br_2-BeP (**2**) are deserving of additional comment. The structure of **1a** was initially based on its conversion to the known **2** and analysis of its proton NMR spectrum. However, the structure of **2** was previously based solely on IR spectral evidence.[8] Confirmation of the structure of **1a** is provided by its conversion to **1b**, differing in its physical properties and NMR spectrum from the remaining isomeric phenols of BeP, and by conversion of **1a** to 3-methylbenzo[e]pyrene, identical with an authentic sample synthesized by an unequivocal route.[18]

The integrated proton NMR spectra of these compounds were consistent with their assigned structures (Table IV). The symmetry of substitution of the dibromo compound **2** is clearly indicated by the presence of only five types of protons. The two pairs of bay-region protons $H_{1,8}$ and $H_{9,12}$ appear at lowest field (δ 8.74 and 8.77, respectively), displaced minimally from the analogous protons of BeP (δ 8.83 and 8.78, respectively). The K-region protons $H_{4,5}$ appear as a singlet at δ 8.53 shifted downfield ($\Delta\delta$ = –0.54 ppm) from the related protons of BeP (δ 7.99), consistent with their peri relationship to the bromo substituents. The $H_{2,7}$ protons adjacent to the bromo substituents appear as a doublet shifted downfield ($\Delta\delta$ = –0.31 ppm) to δ 8.28. The protons $H_{10,11}$ located furthest from the site of substitution exhibit expected minimal displacement. The NMR spectrum of **1a** differs minimally from that of the parent hydrocarbon at positions 5–11 in the lower half of the molecule remote from the site of substitution. The meta H_1 proton in the substituted ring shows an upfield shift ($\Delta\delta$ = 0.31 ppm), while the ortho H_2 and the peri H_4 protons exhibit downfield shifts ($\Delta\delta$ = –0.15 and –0.31 ppm, respectively). The observed splitting patterns of **1a** and **2** were also entirely consistent with these assignments.

The NMR spectra of the other halobenzo[e]pyrenes **18** and **19a** confirm their structural assignments. Thus the spectrum of 1,8-dichloro-3,6-dibromobenzo[e]pyrene (**18**) is relatively simple, revealing only four types of protons. The $H_{9,12}$ protons appear at lowest field (δ 9.40, $\Delta\delta$ = –0.62 ppm relative to the $H_{9,12}$ protons of BeP), consistent with their location in the sterically crowded bay region. Also, the $H_{2,7}$ protons appear as a singlet at δ 8.32, confirming the absence of protons in the adjacent ring positions. The $H_{9,12}$ protons of 1,8-dichlorobenzo[e]pyrene (**19a**) and 1,3,6,8-tetrachlorobenzo[e]pyrene (TCBP), like those of

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Table III. 270-MHz Proton NMR Spectral Data for the Isomeric Phenols of Benzo[e]pyrene[a]

isomer	chemical shift, δ											
	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{11}	H_{12}
BeP	9.06 d	8.09 t	8.28 d	8.14 s	8.14 s	8.28 d	8.09 t	9.06 d	8.99 m	7.79 m	7.79 m	8.99 m
1-HO-BeP		7.62 d	7.96 d	7.85 d[b]	7.72 d[b]	8.00 d	7.85 d	8.79 d	8.79 m	7.55 m	7.55 m	9.90 m
	$J_{2,3}$ = 8.3, $J_{4,5}$ = 8.8, $J_{6,7} = J_{7,8}$ = 7.6, $J_{9,10} = J_{11,12}$ = 6.4, $J_{9,11} = J_{10,12}$ = 3.5 Hz											
2-HO-BeP	8.49 d		7.70 d	7.96 d[b]	8.05 d[b]	8.19 d	7.96 t	8.97 d	8.97 m[c]	7.76 m	7.76 m	8.84 m[c]
	$J_{1,3}$ = 2.3, $J_{4,5}$ = 9.0, $J_{6,7} = J_{7,8}$ = 7.7, $J_{9,10} = J_{11,12}$ = 5.2, $J_{9,11} = J_{10,12}$ = 2.0 Hz											
3-HO-BeP	8.86 d	7.63 d		8.19 d	8.03 d	8.43 d	8.01 t	8.95 d	8.89 m[b]	7.67 m[c]	7.70 m[c]	8.80 m[b]
	$J_{1,2}$ = 8.5, $J_{4,5}$ = 7.5, $J_{6,7} = J_{7,8}$ = 8.5, $J_{9,10} = J_{11,12}$ = 7.8, $J_{9,11} = J_{10,12}$ = 2.1 Hz											
4-HO-BeP	9.11 d	8.13 t	8.67 d		7.51 s	8.05 d	7.98 t	8.84 d	8.99 t	7.79 t	7.79 t	8.99 t
	$J_{1,2} = J_{2,3}$ = 7.9, $J_{6,7} = J_{7,8}$ = 7.85, $J_{9,10} = J_{11,12}$ = 6.03, $J_{9,11} = J_{10,12}$ = 3.17 Hz											
9-HO-BeP	8.99 d	8.02 t[b]	8.23 d[c]	8.09 s	8.09 d	8.20 d[c]	8.01 t[b]	10.18 m		7.36 m	7.56 m	8.53 m
	$J_{1,2} = J_{2,3}$ = 7.9, $J_{6,7} = J_{7,8}$ = 8.1, $J_{10,11} = J_{11,12}$ = 8.1 Hz											
10-HO-BeP	8.90 d	8.04 t[b]	8.17 d[c]	8.10 s	8.10 s	8.24 d[c]	8.02 t[b]	8.90 d	8.31 s		7.34 d	8.82 d
	$J_{1,2} = J_{7,8}$ = 7.3, $J_{2,3} = J_{6,7}$ = 8.3, $J_{9,11}$ = 2.4, $J_{11,12}$ = 8.9 Hz											

[a] All spectra were measured in acetone-d_6; chemical shifts are relative to tetramethylsilane. [b,c] In these pairs of signals, distinction between the two protons was not possible; the assigned chemical shifts may possibly be interchanged.

Table IV. 270-MHz Proton NMR Spectra of Halobenzo[e]pyrenes[a]

	BeP	1a	2	18	19a	TCBP[b]
H_1	8.83	8.52	8.74			
H_2	7.97	8.12	8.28	8.32	7.99	8.13
H_3	8.13				7.99	
H_4	7.99	8.30	8.53	8.43	7.93	8.46
H_5	7.99	7.99	8.53	8.43	7.93	8.46
H_6	8.13	8.08			7.99	
H_7	7.97	7.95	8.28	8.32	7.99	8.13
H_8	8.83	8.76	8.74			
H_9	8.78	8.69	8.77	9.40	9.54	9.42
H_{10}	7.69	7.66	7.77	7.66	7.67	7.66
H_{11}	7.69	7.66	7.77	7.66	7.67	7.66
H_{12}	8.78	8.61	8.77	9.40	9.54	9.42

[a] All spectra are in $CDCl_3$; chemical shifts are relative to tetramethylsilane. [b] TCBP = 1,3,6,8-tetrachlorobenzo[e]-pyrene.

18, show a substantial downfield shift ($\Delta\delta$ = −0.76 and −0.64 ppm, respectively), confirming the presence of the chlorine substituents in the 1,3-positions. The chemical shifts and coupling patterns of the remaining protons are also consistent with these assignments.

Exclusive formation of 2-ethoxybenzo[e]pyrene (**25a**) from the Jutz reaction of benzanthrene (**22**) was unexpected, since analogous reaction of **22** with the related unsubstituted vinamidinium salt **23b** is reported to furnish benzo[e]pyrene and benzo[a]pyrene in 2:1 ratio.[16] However, careful reinvestigation of the latter reaction gave only BeP with no detectable trace of benzo[a]pyrene (NMR or TLC). In related studies conducted in our laboratory[18,19] the analogous reaction of the methyl-substituted vinamidinium salt **23c** was also reinvestigated, and contrary to previous claims[16] only 2-methylbenzo[e]pyrene unaccompanied by 2-methylbenzo[a]pyrene was found. In the earlier studies[16] the benzo[a]pyrene isomers were not isolated and characterized but were inferred to be present on the basis of a color test with H_2SO_4 and the broad melting range of the product. In our hands, the color test with the authentic isomers showed no clearly distinctive difference. We conclude that the base-catalyzed condensation of **23** with benzanthrene is essentially regiospecific, providing only the BeP derivatives and none of the isomeric benzo[a]pyrene derivatives under the conditions employed herein.

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Experimental Section

General Methods. 1,2,3,6,7,8,9,10-Octahydrobenzo[e]pyrene (**12**), 1-oxo-1,2,3,4-tetrahydrotriphenylene (**5**), 9-oxo-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]pyrene (**9**), and *trans*-9,10-bis(benzoyloxy)-1,2,3,6,7,8,9,10,11,12-decahydrobenzo[e]-pyrene (**15a**) were synthesized as previously described.[11,12] 1,3,6,8-Tetrachlorobenzo[e]pyrene was synthesized by the method of Lang and Zander.[8] *N*-Bromosuccinimide (NBS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were purchased from the Arapahoe Chemical Co.; NBS was recrystallized from water prior to use. Benzanthrene was synthesized through reduction of benzanthrone with $LiAlH_4$ and $AlCl_3$.[20] The NMR spectra were obtained on a Varian T60 or a Bruker HX-270 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$ unless specified otherwise. Melting points are uncorrected. All new compounds gave satisfactory microanalyses for C and H within ±0.3% and/or mass spectra consistent with the assigned structures.

Benzo[e]pyrene. Commercial samples of BeP were found to sometimes contain significant amounts of BaP. It is recommended, therefore, that the identity and purity of samples of BeP purchased from commercial sources be verified before use. The BeP employed herein was synthesized through catalytic dehydrogenation of 9-hydroxy-1,2,3,6,7,8,9,10,11,12-decahydrobenzo-[e]pyrene obtained through reduction of **9** with $NaBH_4$ as described.[11] Dehydrogenation of the alcohol (3.6 g, 13 mmol) over a 10% Pd/C catalyst (72 mg, 2.6 mmol) at 300–320 °C for 2 h gave BeP (3.0 g, 86%); a sample recrystallized from benzene had a melting point of 180–181 °C (lit.[21] mp 178–179 °C).

3-Bromobenzo[e]pyrene (1a). To a solution of BeP (126 mg, 0.5 mmol) in 20 mL of chlorobenzene was added bromine (88 mg, 0.55 mmol) dropwise. The solution was stirred at ambient temperature for 30 min, the solvent was evaporated, and the residue was crystallized from benzene. The product was shown by high-resolution 270-MHz NMR analysis in comparison with the authentic compounds to be a mixture (7:3) of **1a** and **2**. Recrystallization from benzene gave **2** (29 mg, mp 264–265 °C), and concentration of the mother liquors afforded **1a** (50 mg) as long white needles (mp 164–166 °C) and a second crop of less pure **1a** (45 mg). The NMR spectra of **1a** and **2** (Table IV) matched those of the authentic compounds synthesized herein by the methods described.[8,9]

Compound **1a** (mp 168–169 °C, lit.[9] mp 169 °C) was also synthesized by reaction of BeP with *o*-chloranil and HBr by the method of Wilk and Hoppe.[9] There is some confusion in the nomenclature and ring numbering system employed by these authors, who apparently assign the structure as 4-bromobenzo-[e]pyrene, misnaming it 6-bromobenzo[a]pyrene.

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3-Hydroxybenzo[*e*]pyrene (1b). To a solution of **1a** (165 mg, 0.5 mL) in tetrahydrofuran (50 mL) were added Mg (15 mg, 0.625 mmol), diborane (1.5 mL of a 1 M solution in THF), and 2 drops of bromoethane, and the solution was heated at reflux overnight until all the Mg dissolved. The solution was cooled, a solution of 10% NaOH (2 mL) and 70% H_2O_2 (0.5 mL) was added with caution, and reflux was continued for 20 min. The reaction mixture was cooled, quenched with water, acidified with a few drops concentrated HCl, and worked up in the usual manner to afford crude **1b** which was purified by passage through a short column of Florisil eluted with benzene to give **1b**: 100 mg (74%); mp 246–248 °C (benzene); NMR, Table III.

***cis*-4,5-Diacetoxy-4,5-dihydrobenzo[*e*]pyrene (3b).** To a solution of BeP (1 g) in dry benzene (20 mL) was added to a solution of OsO_4 (1 g) in anhydrous pyridine (5 mL), and the resulting solution was stirred in the dark for 5 days under N_2. Workup by the usual method[10] afforded the crude *cis*-dihydro diol **1a** which was acetylated with acetic anhydride (20 mL) and pyridine (5 mL),[10] and the crude diacetate (1.2 g) was chromatographed on Florisil. Elution with benzene gave pure **3b**: 1 g (68%); mp 206–207 °C; NMR δ 8.35–8.65 (m, 4, $H_{1,8,9,12}$), 7.5–7.8 (m, 6, aromatic), 6.65 (s, 2, $H_{4,5}$), 2.10 (s, 6, CH_3). Similar reaction conducted under somewhat different conditions over a longer period (42 days) was reported to afford **3a** in lower yield (50%) with a lower melting point (194–195 °C).[22]

4-Hydroxybenzo[*e*]pyrene (4b). A solution of **3b** (50 mg) in benzene (15 mL) was heated at reflux with *p*-toluenesulfonic acid (5 mg) for 2 h. Conventional workup furnished **4a**: 40 mg (95%); mp 173–174 °C; mass spectrum, *m/e* 311 (M^+); NMR δ 8.7–8.9 (m, 3, H_{1or8}, $H_{9,12}$), 8.2 (d, 1, H_{1or8}), 6.8–7.1 (m, 6, aromatic), 7.30 (s, 1, H_5), 2.6 (s, 3, CH_3).

A solution of **4a** (120 mg) was heated in refluxing methanol (20 mL) with *p*-toluenesulfonic acid (12 mg) for 4 h. Conventional workup provided crude **4b** which was purified by chromatography on a short column of Florisil. Elution with benzene and recrystallization from this solvent gave pure **4b**: 85 mg (82%); mp 242–243 °C; M^+ mass spectrum, *m/e* 268 (M^+); NMR Table III.

Ethyl 1-(1,2,3,4-Tetrahydrotriphenylenyl)acetate (7). A solution of **5** (2 g) and ethyl bromoacetate (2 mL) in dry benzene (50 mL) and anhydrous ether (20 mL) was heated at reflux with activated zinc (4 g) and a crystal of iodine for 8 h. The reaction mixture was poured into 5% hydrochloric acid (200 mL); the organic layer was separated and worked up conventionally to provide the crude β-hydroxy ester (2.2 g). The latter was dehydrated directly to a mixture (by NMR) of the conjugated and unconjugated esters **6** by being heated at reflux in benzene (50 mL) with *p*-tosic acid (20 mg) for 2 h. The resulting oil (2 g) was dissolved in ethanol (50 mL) and hydrogenated over a 5% Pd/C catalyst (400 mg) at room temperature and low pressure. The usual workup provided the ester 7 as an oil: 2 g (77% yield from 5); NMR δ 7.0–8.6 (m, 8, aromatic), 4.1 (q, 2, CH_2CH_3), 2.6–2.9 (m, 3, $H_{1,4}$), 2.6–3.1 (m, 6, $H_{2,3}$ and CH_2CO_2), 1.2 (t, 3, CH_3).

1-Triphenylenylacetic Acid (8b). A solution of **7** (500 mg) was heated with DDQ (910 mg) in refluxing benzene for 4 h. Conventional workup afforded the fully aromatic ester **8a**: 450 mg (91%); NMR δ 8.0–8.6 (m, 5, $H_{4,5,8,9,12}$), 7.0–7.6 (m, 6, $H_{2,3,6,7,10,11}$), 3.8–4.2 (m, 4, CH_2), 0.9 (t, 3, CH_3).

Hydrolysis of **8a** with 5% alcoholic KOH furnished the free acid **8b** (395 mg, 96%) recrystallization of which from benzene gave pure **8b** as colorless needles: mp 186–187 °C; NMR δ 8.5–8.8 (m, 5, $H_{4,5,8,9,12}$), 7.6–7.9 (m, 6, $H_{2,3,6,7,10,11}$), 4.4 (s, 2, CH_2).

4-Hydroxybenzo[*e*]pyrene (4b). A solution of **8b** (200 mg) in liquid HF (10 mL) was allowed to evaporate to dryness in a hood. The crude phenol was recrystallized from benzene to afford pure **4b** (150 mg, 80%; mp 242–243 °C) identical by NMR with that obtained via the alternative synthetic approach.

9-Hydroxybenzo[*e*]pyrene (10b). A solution of the ketone **9** (250 mg) in isopropenyl acetate (20 mL) and acetic anhydride (2 mL) was heated at reflux in the presence of *p*-tosic acid (25 mg) under N_2 for 14 h. Conventional workup provided the crude enol acetate which was chromatographed on Florisil. Elution with benzene–CH_2Cl_2 furnished pure 9-acetoxy-1,2,3,6,7,8,11,12-octahydrobenzo[*e*]pyrene: 255 mg (88%); 138–139 °C; NMR δ 6.95 (s, 2, $H_{4,5}$), 5.81 (t, 1, H_{10}, $J_{10,11}$ = 5 Hz), 2.61–3.3 (m, 10, $H_{1,3,6,8,12}$), 2.10 (s, 1, OAc), 1.8–2.58 (m, 6, $H_{2,7,11}$).

A solution of the enol acetate and DDQ (1.1 g) in benzene (100 mL) was heated at reflux for 4 h under N_2. The crude phenol acetate was chromatographed on Florisil and eluted with benzene to provide **10a**: 200 mg (80%); mp 179–180 °C; NMR δ 9.4 (dd, 1, H_8), 8.8 (m, 2, $H_{1,12}$), 7.3–8.1 (m, 8, aromatic), 2.4 (s, 1, CH_3).

Methanolysis of **10a** (200 mg) in refluxing methanol (50 mL) in the presence of *p*-tosic acid (20 mg) for 4 h furnished the free phenol **10b**. The latter was purified by chromatography on Florisil. Elution with benzene and crystallization from benzene gave pure **10b**: 146 mg (84%); mp 210 °C; mass spectrum, *m/e* 268 (M^+); NMR, Table III.

10-(Benzoyloxy)-1,2,3,6,7,8,11,12-octahydrobenzo[*e*]pyrene (16a). A solution of **15a**[11] (1.28 g, 2.55 mmol) and *p*-tosic acid (120 mg) in benzene (200 mL) was heated at reflux for 4 h. Conventional workup followed by chromatography on Florisil eluted with benzene afforded **16a** (663 mg, 71%). Recrystallization from ethyl acetate gave pure **16a**: mp 161–162 °C; NMR δ 1.7–2.3 (m, 4, aliphatic), 2.4–3.3 (m, 12, benzylic and allylic), 6.75 (s, 1, H_9), 7.0 (s, 2, $H_{4,5}$), 7.2–8.2 (m, 5, aromatic).

10-Hydroxybenzo[*e*]pyrene (17b). A solution of **16a** (610 mg, 1.6 mmol) and DDQ (1.5 g, 6.6 mmol) in benzene (100 mL) was heated at reflux for 2 h. The reaction mixture was poured onto a column of Florisil and eluted with benzene–ether (4:1) to provide 10-(benzoyloxy)benzo[*e*]pyrene (**17a**; 535 mg, 77%). Recrystallization from THF gave pure **17a**: mp 213–214 °C; NMR δ 7.4–8.4 (m, 12, aromatic), 8.5–8.95 (m, 4, $H_{1,8,9,12}$). Analogous reaction of the enol acetate **16b** furnished the corresponding phenol acetate **17c**.

A suspension of **17a** (306 mg, 0.82 mmol) and *p*-tosic acid monohydrate (28 mg) in methanol (50 mL) was heated at reflux for 2 h. Conventional workup gave the crude phenol **17b** (220 mg). Chromatography on Florisil eluted with benzene gave **17b**: 200 mg (91%); mp 239–240 °C; NMR, Table III. Analogous reaction of **17c** (120 mg) gave **17b**: 80 mg (84%); mp 239–240 °C.

10-Oxo-1,2,3,5,6,7,8,9,10,11,12-decahydrobenzo[*e*]pyrene (14). Sodium methoxide (200 mg) was added to a solution of **15a** (1 g) in THF (30 mL) and methanol (15 mL) under N_2, and the solution was heated at reflux for 1 h. The usual workup afforded the free diol which was triturated with ether–hexane (1:1) to yield pure **15b** (600 mg). The latter was taken up in acetic acid (20 mL), concentrated HCl (0.5 mL) was added, and the solution was refluxed for 30 min. The usual workup gave the crude ketone (400 mg) which was purified by chromatography on Florisil. Elution with benzene gave **14**: 350 mg; NMR δ 7.0 (s, 2, aryl), 3.6 (s, 2, H_9), 3.2–3.0 (m, 10, benzylic), 1.8–2.2 (m, 6, aliphatic).

10-Acetoxy-1,2,3,6,7,8,11,12-octahydrobenzo[*e*]pyrene (16b). A solution of **14** (150 mg) in isopropenyl acetate (15 mL) and acetic anhydride (1.5 mL) was heated at reflux in the presence of *p*-tosic acid (15 mg) for 14 h. Conventional workup followed by chromatography on Florisil eluted with benzene furnished the pure enol acetate **16b**: NMR δ 7.1 (br s, 2, aryl), 5.1 (s, 1, vinylic), 3.1–3.3 (m, 10, benzylic), 2.6–2.1 (m, 6, aliphatic), 2.10 (s, 3, CH_3).

3,6-Dibromobenzo[*e*]pyrene (2). To a solution of BeP (1 g, 4 mmol) in 20 mL of chlorobenzene was added Br_2 (3.64 g, 23 mmol) dropwise at room temperature. The solution was stirred for 15 min, the solvent was evaporated, and the residue was crystallized from chlorobenzene to provide **2**: 1.28 g (78%); mp 264–266 °C (lit.[8] mp 264–265 °C); NMR, Table IV.

3,6-Dibromo-1,8-dichlorobenzo[*e*]pyrene (18). Chlorine gas was bubbled through a solution of **2** (3.32 g, 8.1 mmol) in trichlorobenzene (60 mL) for 20 min at room temperature. The resulting suspension was diluted with hexane and the precipitate filtered, affording pure **18**: 3.53 g (91%); mp 264–266 °C; NMR, Table IV.

1,8-Dichlorobenzo[*e*]pyrene (19a). To a suspension of **18** (5.68 g, 11.8 mmol) in anhydrous ether was added a solution of *n*-butyllithium (26 mmol) in hexane under N_2. The suspension was heated at reflux for 30 min, cooled, and quenched with water. The usual workup followed by crystallization from benzene and chromatography on a column of Florisil eluted with hexane gave pure **19a**: 3.6 g (95%); mp 173–174 °C; NMR, Table IV.

1-Methoxybenzo[*e*]pyrene (20a). A solution of **19a** (2.84 g, 9 mmol) and NaOMe (540 mg, 10 mmol) in HMPA (60 mL) was

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held at 100 °C for 20 h. The product was worked up conventionally and chromatographed on Florisil eluted with benzene to furnish 1-methoxy-8-chlorobenzo[e]pyrene (**19b**, 1.7 g) as a white solid: NMR δ 4.0 (s, 3, OCH_3), 7.3–7.9 (m, 8, aromatic), 9.3–9.7 (m, 2, $H_{9,12}$).

A solution of **19b** (1.7 g) and *n*-butyllithium (20 mmol) in ether was heated at reflux for 30 min and then quenched with water to afford crude **20a**, 1.67 g (66%). Chromatography on a column of Florisil eluted with benzene followed by crystallization from benzene afforded pure **20a**: mp 206–208 °C; NMR δ 4.0 (s, 3, OCH_3), 7.4–8.2 (m, 8, aromatic), 8.55–8.9 (m, 2, $H_{8,9}$), 9.6–9.9 (m, 1, H_{12}).

1-Hydroxybenzo[e]pyrene (20b). A solution of ethanethiol (434 mg, 7 mmol) in dimethylformamide (1 mL) was added to a suspension of NaH (340 mg of a 50% oil dispersion) in DMF (1 mL) under N_2. The mixture was stirred for 5 min, **20a** (200 mg, 0.7 mmol) in DMF (1 mL) was added, and the solution was heated at reflux for 3 h. Conventional workup and passage through a column of Florisil eluted with benzene gave **20b**: 198 mg (99%); white solid; mp 180–181 °C (benzene); NMR, Table III.

2-Ethoxybenzo[e]pyrene (25a). A solution of benzanthrene (320 mg, 1.5 mmol), NaOMe (89 mg, 1.65 mmol), and 1,3-bis(dimethylamino)-2-ethoxytrimethinium perchlorate[15] (407 mg, 1.5 mmol) in pyridine (10 mL) was heated at 100 °C for 5 h under N_2. The pyridine was then replaced by quinoline (5 mL), and the solution was heated at reflux overnight. Conventional workup and passage through a column of Florisil eluted with benzene–hexane (1:1) gave **25a**: 142 mg (32%); white solid; mp 120–122 °C; NMR δ 1.5 (t, 3, CH_3), 4.2 (q, 2, CH_2), 7.4–8.1 (m, 7, aromatic), 8.22 (d, 1, H_1, $J_{1,3}$ = 2 Hz), 8.5–8.8 (m, 3, $H_{8,9,12}$).

2-Hydroxybenzo[e]pyrene (25b). Dealkylation of **25a** (140 mg, 0.47 mmol) was conducted by the procedure employed for the analogous reaction of **20a** to afford **25b**: 130 mg (99%); white solid; mp 229–230 °C (benzene); NMR, Table III.

2-Acetamidobenzo[e]pyrene (21). Potassium metal (98 mg, 2.5 mmol) and $FeCl_3$ (10 mg) were added to refluxing anhydrous liquid ammonia to generate KNH_2. Solid **1a** (166 mg, 0.5 mmol) was added to this solution over 15 min, and ether (50 mL) was added as a cosolvent. The deep red solution was stirred for 1 h, decomposed by addition of NH_4Cl, and worked up in the usual manner to afford crude 2-aminobenzo[e]pyrene (123 mg) as a yellow solid. Acetylation with acetic anhydride (10 mL) and pyridine (1 mL) gave **21** (150 mg) which was purified by chromatography on silica gel. Initial elution with benzene removed impurities (10 mg). Elution with $CHCl_3$ gave **21** (120 mg, 78%) contaminated with 6–7% (by HPLC) of an isomeric product, apparently 3-(AcNH)-BeP, which could not be removed by recrystallization. The analytical sample of **21** melted at 265–270 °C: NMR (Me_2SO-d_6, 270 MHz) δ 2.30 (s, 3, CH_3), 7.66 (m, 2, $H_{10,11}$), 7.88 (t, 1, H_7, $J_{6,7} = J_{7,8}$ = 8 Hz), 7.97 (d, 2, $H_{4,5}$, $J_{4,5}$ = 6.6 Hz), 8.11 (d, 1, H_6), 8.41 (s, 1, H_3), 8.58 (d, 1, H_8), 8.83 (m, 2, $H_{9,12}$), 8.99 (s, 1, H_1).

Anal. Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.49; H, 4.91; N, 4.51.

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Registry No. **1a**, 26105-52-2; **1b**, 77508-02-2; **2**, 77508-03-3; **3a**, 24909-10-2; **3b**, 66788-07-6; **4a**, 77508-04-4; **4b**, 28318-40-3; **5**, 68151-17-7; **5** β-hydroxy ester, 77508-05-5; *endo*-**6**, 77508-06-6; *exo*-**6**, 77508-07-7; **7**, 77508-08-8; **8a**, 77508-09-9; **8b**, 77508-10-2; **9**, 68151-08-6; **9** enol acetate, 77508-11-3; **10a**, 77508-12-4; **10b**, 77508-13-5; **14**, 77508-14-6; **15a**, 68151-11-1; **15b**, 77508-15-7; **16a**, 77508-16-8; **16b**, 77508-17-9; **17a**, 77508-18-0; **17b**, 77508-19-1; **17c**, 77508-20-4; **18**, 77508-21-5; **19a**, 77508-22-6; **19b**, 77508-23-7; **20a**, 77508-24-8; **20b**, 77508-25-9; **21**, 77508-26-0; **22**, 199-94-0; **23a**, 42784-01-0; **25a**, 77508-27-1; **25b**, 77508-28-2; BeP, 192-97-2; 2-aminobenzo[e]pyrene, 77508-29-3.

Synthesis of *trans*-3,4-Dihydroxy-3,4-dihydrobenz[a]- and -[c]acridines, Possible Proximate Carcinogenic Metabolites of Polycyclic Azaarenes

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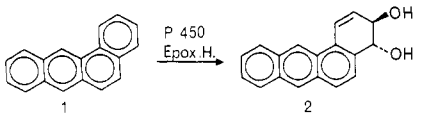
The vicinal *trans*-3,4-dihydro 3,4-diols of benz[a]- and -[c]acridine have been synthesized via modified Birch reduction of the parent heterocycles. Thus the pyridine moiety and the angular benzene ring could be reduced selectively. Controlled reoxidation re-formed the stable acridine part, leaving the angular ring partially hydrogenated. Isomerization of the isolated double bond led to 1,2-dihydrobenzacridines as key intermediates of the synthesis. Prêvost reaction, bromination, dehydrobromination, and hydrolysis of the 3,4-dihydrodioldiacetates in the angular ring did not interfere with the basic acridine moiety. This strategy has been applied to both series, i.e., benz[a]- and -[c]acridine. In some reaction steps the product ratio and total yield were strongly influenced by the position of nitrogen, indicating intrinsic differences in the chemical reactivity of the two systems. The new title compounds which have not been prepared previously are presumably the proximate carcinogenic metabolites of benzacridines. The benzacridines were chosen as model compounds of polycyclic azaarenes (PAA) which impose an increasing environmental risk with the industrial processing of synthetic fuel from shale and oil.

Studies with benz[a]anthracene (1), a model system for the carcinogenic polycyclic aromatic hydrocarbons (PAH), have clearly demonstrated that oxidative metabolism at the bay region (i.e., via the 3,4-dihydro diol 2) accounts



1 2

for its mutagenic and carcinogenic properties.[2] The carcinogenic polycyclic azaarenes (PAA) have not yet thoroughly been investigated in terms of their biological activity. Recently there has been renewed interest in this class of compounds as investigations of marine sediments

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(2) P. G. Wislocki, J. Kapitulnik, W. Levin, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Cancer Res.*, **38**, 693 (1978).

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