Synthesis of the Non-K-region and K-Region *trans*-Dihydrodiols of Benzo[*e*]pyrene

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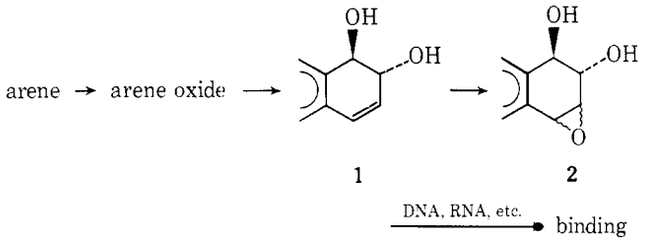
Syntheses of *trans*-9,10-dihydroxy-9,10-dihydrobenzo[*e*]pyrene (**14b**) and of *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*e*]pyrene (**17a**) are described. The preparation of the non-K-region *trans*-dihydrodiol **14b** proceeded via standard procedures from 9-oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (**7**), the synthesis of which is described. Intramolecular cyclization of methyl 4-pyrenylbutyrate (**6**) in HF produced primarily the undesired seven-membered ring ketone **8**, but cyclization in hot polyphosphoric acid gave the desired ketone **7** in good yield. Evidence is presented that **8** is the kinetic product of cyclization and that **7** is the more stable isomer which is produced under conditions of thermodynamic control. The NMR spectrum of the non-K-region dihydrodiol **14b** in acetone-d_6 indicates that the hydroxyl groups adopt a predominantly quasi-diaxial conformation. The trans-K-region dihydrodiol **17a** was prepared from benzo[*e*]pyrene [B(e)P] by a multistep procedure involving conversion of B(e)P to the *cis*-diol, oxidation to the quinone, and reduction of the quinone with KBH_4. The *trans*-diol **17a** easily oxidizes in the presence of air.

Recent studies of benzo[*a*]pyrene [B(a)P][1] and benz[*a*]anthracene (BA)[2] have provided strong evidence for the importance of the metabolic route: arene → arene oxide → dihydrodiol → diol epoxide in the activation of those polycyclic aromatic hydrocarbons to ultimate mutagenic and carcinogenic forms. Moreover, these studies have demonstrated that isomeric dihydrodiols (**1**) and diol epoxides (**2**)



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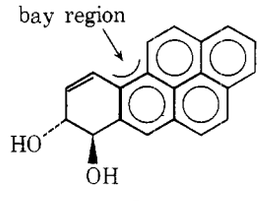
differ considerably in their properties, with dihydrodiols that can form "bay region"[3] diol epoxides being metabolically activated to a considerably greater extent than isomeric dihydrodiols that do not have a double bond that forms part of a bay region. Specifically, for B(a)P and BA, the derivatives **3** and **4** form highly mutagenic and tumorigenic diol epoxides.

We have described a theoretical approach[4] that rationalizes the high reactivity of the diol epoxides derived from **3** and **4**



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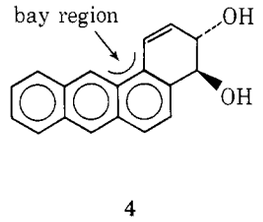

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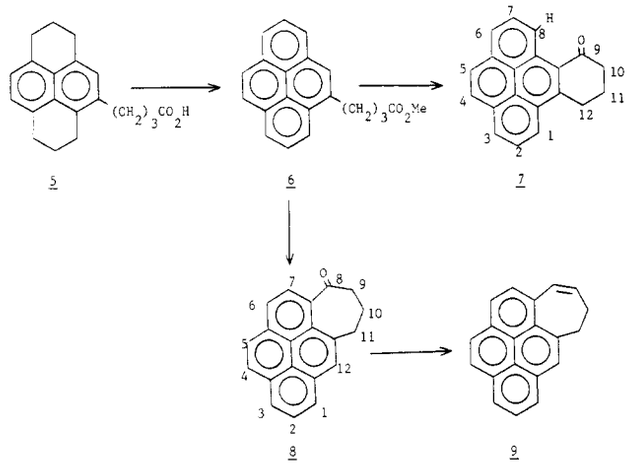
based upon their calculated relative ease of conversion to carbonium ions.[5] As part of our program to further test the predictive value of the calculations, we have synthesized the K- and non-K-region dihydrodiols of benzo[*E*]pyrene [B(e)P]. Although the tumorigenicity of B(e)P has been questioned, a recent report indicates that B(e)P has significant activity as a tumor initiator.[6] The non-K-region dihydrodiol derived from B(e)P, **14b** (Scheme II), has a double bond in a bay region, and its diol epoxide is calculated to be fairly reactive,

Scheme I



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although less reactive than those derived from **3** and **4** ($\Delta E_{deloc}/\beta$ values for **14b, 3,** and **4** are 0.713, 0.794, and 0.766, respectively). However, if metabolic activation of **14b** to a diol epoxide is important in the carcinogenesis of B(e)P, it may be anticipated that **14b** would be substantially more carcinogenic than B(e)P. Also, unlike other dihydrodiols of PAH thus far prepared, **14b** is unique in having *both* the benzylic hydroxyl group and the double bond form parts of bay regions.

Results and Discussion

Synthesis of 9-Oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (7). A general synthetic approach to the preparation of non-K-region dihydrodiols of PAH utilizes as starting material an appropriate tetrahydrobenzo ring ketone.[7] The required ketone (**7**, Scheme I) for the synthesis of **14b** has not been previously described in the literature. The ester, **6**, was prepared in 90% overall yield from γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyric acid (**5**)[8] by esterification followed by dehydrogenation. Cyclization of **6** in HF afforded two light yellow aromatic ketones, **7** and **8** (**7**/**8** = 1:7). The seven-membered ring ketone **8** was also the major product when the acid chloride derived from **6** was cyclized in $AlCl_3$/benzene.

The nuclear magnetic resonance (NMR) spectrum of **7** allowed its assignment as the desired six-membered ring ketone. Thus, the chemical shift of the proton at C_8 in **7** (δ 9.64) is significantly downfield from the other aromatic protons (δ

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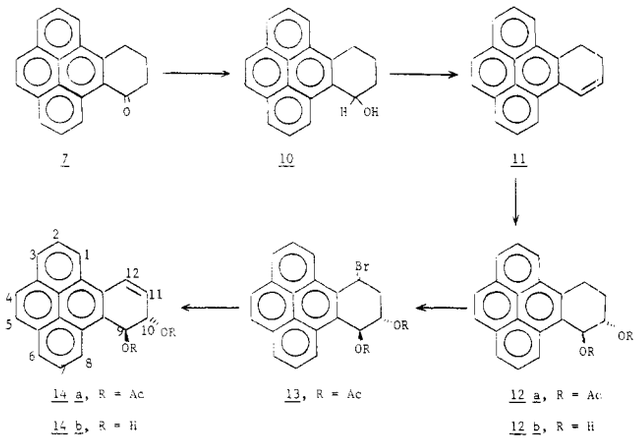
Scheme II



7.95–8.45), as expected for a hydrogen that is in a "bay region" and also in the plane of a carbonyl group. Similarly, H_5 in 4-oxo-1,2,3,4-tetrahydrophenanthrene is shifted downfield (δ 9.45) relative to the other aromatic proton absorptions (δ 7.25–7.95).[7] In contrast, the seven-membered ring ketone, **8**, has all aromatic proton absorptions in the range δ 7.9–8.3. As shown in Scheme II, reduction of **7** with $LiAlH_4$/THF gave alcohol **10** (94%), which was dehydrated in HOAc/HCl to alkene **11** (84%). Dehydrogenation of **11** over Pd/C at 220 °C gave B(e)P, which was identified by its UV spectrum and mixture melting point with an authentic sample. The structure of the seven-membered ring ketone, **8**, was assigned on the basis of consistency with spectral evidence (see Experimental Section) and the source of its production.

Good yields (86%) of the desired six-membered ring ketone, **7**, were obtained upon cyclization of **6** in polyphosphoric acid at 90–100 °C. In polyphosphoric acid at 100 °C, **8** is rapidly isomerized to **7**. Thus, it is likely that **8** is the kinetic product of cyclization, but that under the more forcing conditions in PPA, it is converted to **7**. The formation of seven-membered rather than six-membered rings in intramolecular acylation reactions is unusual. To our knowledge, only two other examples of this type have been reported,[9,10] and in one of those cases the position attacked was activated by a methoxyl group.[9] The kinetically controlled formation of the seven-membered ring ketone from **6** is understandable, in this case, as an intramolecular manifestation of the well-documented much greater reactivity of the C_1 position of pyrene toward Friedel–Crafts acylation relative to the other positions in pyrene.[11]

Attempts to convert the seven-membered ring ketone, **8**, to the unknown hydrocarbon, cyclohepta[*cd*]pyrene, have thus far been unsuccessful. The ketone can be converted to the dihydro compound, **9** (Scheme I), in good yield (86% overall), but both dehydrogenation with DDQ or Pd/C and bromination (NBS)/dehydrobromination (DBN) failed to yield isolable amounts of cyclohepta[*cd*]pyrene.

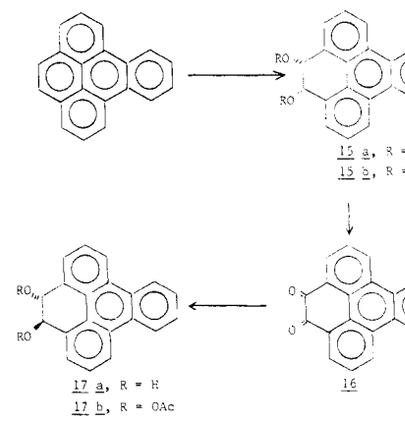
Synthesis of *trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*e*]pyrene, 14b. Ketone **7** was converted to alkene **11** in good yield, as described in the previous section. Conversion of **11** to *trans*-tetrahydrodiacetate **12a** was effected with $AgOAc/I_2$ in 63% yield. Although initial formation of the iodoacetate derivative of **11** was very rapid, prolonged heating at benzene reflux in the presence of excess AgOAc was required to effect formation of **12a**. The major identifiable byproduct of the reaction was B(e)P. The tetrahydrodiacetate, **12a**, was brominated with NBS in CCl_4 to give a high yield (91%) of a mixture of stereoisomeric bromodiacetates (**13**), which was directly dehydrobrominated with DBN in dry THF. Yields of the dihydrodiol diester, **14a**, were variable, ranging from virtually quantitative to very low. Good yields of **14a** seem to require avoidance of extended reaction periods and of high temperatures (an optimum yield was reached at 2.5 h and 0 °C) and careful handling of the crude product, which is very sensitive to acid. On several occasions, handling of a sample of **14a**, known to be pure by NMR, resulted in the formation of additional products, believed to be phenolic acetates based upon the chemical shift of the acetate protons (δ 2.45 and 2.53). Since virtually quantitative yields of **14a** were produced several times from the diastereomeric mixture (roughly 1:1), both stereoisomers evidently suffer dehydrobromination under these conditions.

Conversion of **14a** to dihydrodiol **14b** was effected in ammoniacal MeOH. The crude product was purified by column chromatography on Florisil, followed by crystallization from CH_2Cl_2. Although dihydrodiol **14b** was also sensitive to acid, it proved easier to purify than its precursor, **14a**. Consequently, in relatively large-scale preparations of **14b**, **12a** was converted to **14b** with only minimal purification at intermediate stages. When this approach was used, overall yields of 50–60% were typically achieved in the three-step sequence. Attempts to convert **12a** directly to **14a** with DDQ, by a recently described procedure,[12] were unsuccessful. The structure of dihydrodiol **14b** was firmly established by its spectral properties, most revealing of which was the NMR spectrum (see Experimental Section).

The coupling constant, $J_{9,10}$, between the carbinol hydrogens is not clearly visible in acetone-d_6 and is evidently <1.5 Hz. In Me_2SO-d_6, however, $J_{9,10}$ is measurable as ~0.8 Hz. These values indicate that the hydroxyl groups reside in a predominantly quasi-diaxial conformation, as has been observed for other dihydrodiols in which the benzylic hydroxyl group is in a "bay region".[7,13] In dihydrodiol diacetate **14a**, the immediate synthetic precursor of **14b**, $J_{9,10}$ = 2.2 Hz, again indicative of a predominant quasi-diaxial relationship of the acetoxyl groups. Previous attempts to prepare diol epoxides by direct epoxidation of benz[*a*]anthracene 1,2-dihydrodiol[14] and benzo[*a*]pyrene 9,10-dihydrodiol[15] proved exceedingly difficult because mixtures of products were formed. Like **14b**, these bay region dihydrodiols have hydroxyl groups that reside predominantly in the quasi-diaxial conformation, and they are not stereoselectively attacked on the face of the ring that bears the allylic hydroxyl group.[16] Although dihydrobenzo[*e*]pyrene, **11**, is smoothly epoxidized with *m*-chloroperoxybenzoic acid, dihydrodiol **14b** was converted to several products by a tenfold excess of *m*-chloroperoxybenzoic acid in THF at 0 °C.

Synthesis of *trans*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (17a). The K-region *trans*-dihydrodiol of benzo[*e*]pyrene, **17a**, was prepared in three steps from benzo[*e*]-pyrene, as shown in Scheme III. Oxidation of B(e)P with OsO_4 gave the *cis*-diol **15a**, which was purified by conversion to the diacetate with Ac_2O/pyridine (50% overall yield), followed by conversion back to **15a** (97% yield) in ammoniacal MeOH.

Scheme III



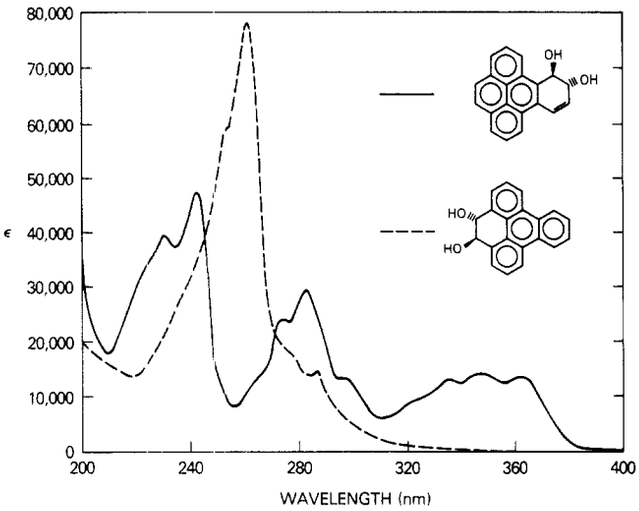


Figure 1. Ultraviolet spectra of *trans*-9,10-dihydroxy-9,10-dihydrobenzo[*e*]pyrene (in EtOH) and *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*e*]pyrene (in 85:15 = MeOH/H_2O).

Oxidation of the *cis*-diol **15a** to the quinone **16** was effected quantitatively with DDQ in dioxane. An attempt to prepare quinone **16** directly from B(e)P by oxidation with $Na_2Cr_2O_7$ in acetic acid was unsuccessful. Reduction of the quinone with KBH_4 gave the crude *trans*-diol **17a,** which was directly converted to the more easily purified *trans*-diacetate **17b.** Ammoniacal MeOH, under N_2, converted **17b** to the air-sensitive *trans*-diol **17a** in quantitative yield. The ultraviolet spectra of the K-region *trans*-dihydrodiol **17a,** and of the non-K-region *trans*-dihydrodiol **14b,** are presented in Figure 1.

Biological Activity. Metabolic activation of isomeric dihydrodiols from BA,[17] 7-methylbenz[*a*]anthracene,[18] chrysene,[19] dibenzo[*a,h*]anthracene,[20] and B(a)P[21] has resulted in the highest mutagenic response for those benzo-ring dihydrodiols which have bay region double bonds, presumably through metabolism to bay region diol epoxides. A major interest in benzo[*e*]pyrene dihydrodiol stems from the fact that it may not be metabolized to a diol epoxide. Benzo[*a*]pyrene 9,10-dihydrodiol, which also has quasi-axial hydroxyl groups, is metabolized almost entirely by hydroxylation of the aromatic nucleus.[15]

Experimental Section

Proton magnetic resonance spectra were recorded on Varian T-60, XL-100, and 220 MHz spectrometers. Unless otherwise noted, $CDCl_3$ was used as solvent. Coupling constants, J, are recorded in hertz and chemical shifts in parts per million (δ) with tetramethylsilane as internal standard. UV spectra were recorded on a Cary 16 spectrophotometer. Melting points are uncorrected. The designations α and β are used to indicate relative stereochemistry. Benzo[*e*]pyrene was obtained from Aldrich Chemical Co., Milwaukee, Wisc.

Methyl 4-Pyrenylbutyrate (6). γ-1,2,3,6,7,8-Hexahydro-4-pyrenylbutyric acid (**5;** 2.5 g)[8] was dissolved in MeOH (400 mL) and concentrated HCl (12 drops) was added. After 5 h at room temperature, the reaction was worked up in the usual manner, giving methyl γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyrate as a light yellow solid (2.62 g, 99%): mp 50–54 °C; ^1H NMR (60 MHz) δ 6.9–7.1 (3 H, m), 3.66 (3 H, s), 1.6–3.3 (12 H, m); M^+ 308. Methyl γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyrate (2.57 g) and 10% Pd/C (0.25 g) were mixed and heated at 220 °C under N_2 for 3 h. The residue was taken up in EtOAc and filtered through Celite. The EtOAc was removed, leaving a yellow oil which was crystallized from EtOAc/hexane to give **6** as a white solid (2.29 g, 91%): mp 48–50 °C; ^1H NMR (60 MHz) δ 7.8–8.4 (9 H, m), 3.66 (3 H, s), 3.1–3.5 (2 H, m), 2.2–2.6 (4 H, m); M^+ 302.

8-Oxo-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene (8). Liquid HF (20 mL) was added to ester **6** (1.0 g) in a polystyrene container at 0 °C. The mixture was stirred at room temperature for ~10 h, then H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and H_2O (20 mL). The usual workup left a yellow solid (0.86 g, 96%) of mp 172–174 °C after recrystallization from EtOAc/*i*-PrOH: ^1H NMR (220 MHz) δ 7.9–8.3 (8 H, m), 3.25 (2 H, t), 2.95 (2 H, t), 2.38 (2 H, quintet); M^+ 270. Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.77; H, 5.26.

9-Oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (7). A solution of ester **6** (6.06 g) in polyphosphoric acid (250 mL, Victor Chemical Co.) was stirred under N_2 for 2 h at 100 °C. The solution was cooled, H_2O (400 mL) was added, and the mixture was extracted with EtOAc (2 × 200 mL). The usual workup yielded a solid residue, which upon recrystallization from benzene/cyclohexane gave **7** as a yellow solid (4.65 g, 86%): mp 133–134 °C; ^1H NMR (220 MHz) δ 9.64 (H_8, dd), 7.95–8.45 (7 H, m), 3.52 (2 H, t), 2.90 (2 H, t), 2.35 (2 H, quintet), $J_{7,8}$ = 7.8, $J_{6,8}$ = 2.0 Hz. Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.61; H, 5.35.

10,11-Dihydrocyclohepta[*cd*]pyrene (9). Ketone **8** (300 mg) was added, under N_2, to a mixture of $LiAlH_4$ (40 mg) in freshly distilled THF (10 mL). The mixture was stirred for 5 min, then aqueous NH_4Cl (1 mL) was carefully added dropwise and the mixture was treated with CH_2Cl_2 (75 mL) and H_2O (10 mL) and was filtered. The usual workup gave 8-hydroxy-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene as a white solid (282 mg, 93%) which was used without further purification. The above alcohol (165 mg) was added, under N_2, to a mixture of glacial HOAc (50 mL) and concentrated HCl (2 drops) at 85 °C and the solution was stirred for 30 min. The reaction mixture was cooled and then poured onto ice (150 g). The white precipitate that formed was collected by filtration, washed extensively with saturated aqueous $NaHCO_3$ and H_2O, and dried to give **9** (143 mg, 93%): mp 113–114 °C; ^1H NMR (60 MHz) δ 7.6–8.2 (8 H, m), 6.85 (H_8, d), 6.26 (H_9, m), 3.2–3.6 (2 H, m), $J_{8,9}$ = 11.5, $J_{7,8}$ = 6.0 Hz. Anal. Calcd for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.17; H, 5.66. Conversion of **9** to the epoxide via the bromohydrin Amberlite route[16] as usual, except that 0 °C workup of the bromohydrin was required to avoid decomposition, afforded 8,9-epoxy-8,9,10,11-tetrahydrocyclohepta[*c,d*]pyrene as a light yellow solid: mp 149–151 °C (dec); ^1H NMR (100 MHz) δ 2.1–4.0 (5 H, m), 4.33 (H_8, d), 7.8–8.3 (8 H, m), $J_{8,9}$ = 4.5 Hz; M^+ 270 (base peak).

9-Hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (10). Ketone **7** (3 g) was dissolved in dry THF (30 mL) and added dropwise, under N_2, to a suspension of $LiAlH_4$ (0.153 g) in dry THF (30 mL). The mixture was stirred for 10 min, then aqueous NH_4Cl was added and the mixture was filtered. The collected solids were extensively washed with EtOAc and the solvents were removed under reduced pressure, leaving a yellow solid, which was dissolved in EtOAc (200 mL). The usual workup gave **10** as a yellow solid (2.84 g, 94%) which was used without further purification: ^1H NMR (60 MHz) δ 7.7–8.5 (8 H, m), 5.40 (H_9, m), 2.8–3.3 (2 H, m), 1.7–2.3 (2 H, m).

9,10-Dihydrobenzo[*e*]pyrene (11). Alcohol **10** (2.84 g) was dissolved, under N_2, in a mixture of glacial HOAc (150 mL) and concentrated HCl (4 drops) at 85 °C and the solution was stirred for 2 h. Ice was added to the mixture and **11** precipitated. The alkene was collected by filtration, washed extensively with saturated aqueous $NaHCO_3$ and H_2O, and dried to give **11** as a yellow solid (2.22 g, 84%), which melted at 120–122 °C after one crystallization from cyclohexane: ^1H NMR (60 MHz) δ 7.9–8.6 (8 H, m), 7.45 (H_{12}, m), 6.40 (H_{11}, m), 3.2–3.6 (2 H, m), 2.3–2.7 (2 H, m), $J_{11,12}$ = 10, $J_{10,12}$ = ~1, $J_{10,11}$ = 5 Hz. The reaction of **11** (80 mg) with *m*-chloroperoxybenzoic acid (550 mg) in anhydrous THF (15 mL) under N_2 for 1.5 h gave, after conventional workup, 9,10-epoxy-9,10,11,12-tetrahydrobenzo[*e*]-pyrene: mp 156–157 °C; ^1H NMR (100 MHz) δ 4.88 (H_9, d), 3.93 (H_{10}, m), $J_{9,10}$ = 4.5 Hz. Attempts to prepare the epoxide via the bromohydrin route were unsuccessful because of competitive formation of small amounts of ring-brominated tetrahydroepoxide, which could not be removed by fractional crystallization.

***trans*-9,10-Diacetoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (12a).** Iodine (1.71 g) was added to a suspension of AgOAc (2.29 g) in dry benzene (150 mL), under N_2. The mixture was stirred for 1 h, then alkene **11** (1.62 g) was added and the mixture was stirred at room temperature for 1 h and then was refluxed for 14 h. The reaction mixture was filtered hot and the solids were washed with hot benzene. The filtrate was concentrated to give a solid which upon recrystallization from CH_2Cl_2/EtOAc gave **12a** as a white solid (1.0 g) of mp 200–202 °C. Additional **12a** (0.5 g) was obtained by concentrating the mother liquor and chromatographing the residue on Florisil, with CH_2Cl_2 as solvent: total yield 1.5 g (63%); ^1H NMR (100 MHz) δ 7.7–8.4 (8 H, m), 6.68 (H_9, d), 5.42 (H_{10}, q), 3.2–3.6 (2 H, m), 2.2–2.6 (2 H, m), 2.10 (3 H, s), 1.96 (3 H, s), $J_{9,10}$ = $J_{10,11}$ = 3.0 Hz; M^+ 372. Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.35; H, 5.36.

12-Bromo-9α,10β-diacetoxy-9,10,11,12-tetrahydrobenzo[*e*]-pyrene (13). A mixture of CCl_4 (50 mL), *N*-bromosuccinimide (50

mg), **12a** (94 mg), and α,α'-azoisobutyrodinitrile (5 mg) was maintained at 65 °C with a heat lamp while a stream of N_2 was passed through the solution. Typical reaction times were 30 min, although the time of initiation varied from 10 min to 1 h, and was noted by the dissolving of the NBS. Workup in the usual manner gave the crude product (86 mg, 91%) as a roughly 1:1 mixture of diastereomeric bromodiacetates. Recrystallization from CCl_4 yielded one isomer: ^1H NMR (60 MHz) δ 8.0–8.8 (8 H, m), 6.87–6.96 (H_9, m), 6.1–6.3 (H_{12}, dd), 5.4–5.6 (H_{10}, m), 2.9–3.3 (2 H, m), 2.08 (3 H, s), 2.05 (3 H, s). Recrystallization of the mother liquors from ether gave the second isomer: ^1H NMR (60 MHz) δ 8.0–8.6 (8 H, m), 7.06 (H_9, d), 6.0–6.4 (2 H, m), 2.6–3.6 (2 H, m), 2.16 (3 H, s), 2.08 (3 H, s). Both isomers were slightly cross-contaminated, and were not purified further.

***trans*-9,10-Diacetoxy-9,10-dihydrobenzo[*e*]pyrene (14a).** To a solution of **13** (250 mg, isomeric mixture) in freshly distilled THF (15 mL) at 0 °C, under N_2, was added 1,5-diazabicyclo[4.3.0]non-5-ene (70 drops). The mixture was stirred at 0 °C for 2.5 h. EtOAc (50 mL) was added and the organic phase was extracted with H_2O (2 × 40 mL), 0.1 N HCl (2 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and H_2O (40 mL), dried, filtered, and concentrated to give **14a** as an off-white solid (192 mg, 94%) that was pure by NMR. Recrystallization of **14a** from EtOAc gave material of mp 146–147 °C; ^1H NMR (100 MHz) δ 7.9–8.6 (8 H, m), 7.81 (H_{12}, d), 7.05 (H_9, br s), 6.57 (H_{11}, m), 5.47 (H_{10}, dd), 2.05 (3 H, s), 1.97 (3 H, s), $J_{10,11}$ = 5.6, $J_{11,12}$ = 10.5, $J_{9,10}$ = 2.2 Hz; M^+ 370.

***trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*e*]pyrene (14b).** Diacetate **14a** (106 mg) was dissolved in THF (30 mL) and MeOH (30 mL) and NH_3 was bubbled through the cooled (0 °C) solution for 15 min. The solution was stirred for 28 h at room temperature, then concentrated, and the residue was chromatographed on Florisil with CH_2Cl_2 as the first solvent, which removed minor, highly colored impurities, then with EtOAc/CH_2Cl_2 = 1:1, which eluted **14b** (75 mg, 91%). Although TLC (silica gel, 1:1 = EtOAc/hexane) showed only one spot, **14b** was further purified by recrystallization from CH_2Cl_2, which gave **14b** as an off-white solid: mp 185–186 °C dec; ^1H NMR (100 MHz, acetone-d_6 after exchange with MeOH-d_4) δ 8.6–8.8 (2 H, m), 8.0–8.4 (6 H, m), 7.72 (H_{12}, d), 6.58 (H_{11}, dd), 5.64 (H_9 br s), 4.54 (H_{10}, m), $J_{11,12}$ = 10.0, $J_{10,11}$ = 5.4, $J_{9,11}$ = 1.1 Hz; UV (EtOH) λ_{max} (ϵ) 230 (39 600), 242 (47 300), 275 (24 200), 283 (29 700), 295 (sh, 13 500), 337 (13 200), 347 (14 600), 361 (13 600). The fluorescence spectrum (MeOH, excitation at 242 or 280 nm) exhibited a broad emission, with maxima at 397 and 406 nm, and a shallow minimum at 402 nm. Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.83; H, 5.13.

***trans*-9,10-Dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (12b).** Tetrahydrodiacetate **12a** (182 mg) was dissolved in THF (30 mL) and MeOH (60 mL) and NH_3 was bubbled through the cooled (0 °C) solution for 15 min. The solution was stirred for 24 h at 25 °C and concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL). The usual workup gave a residue from which **12b** (110 mg, 78%) was obtained by crystallization from CH_2Cl_2 as an off-white solid: ^1H NMR (100 MHz, acetone-d_6, after exchange with MeOH-d_4) δ 7.9–8.8 (8 H, m), 5.40 (H_9, br s), 4.42 (H_{10}, m), 3.3–3.6 (2 H, m), 2.1–2.8 (2 H, m).

***cis*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (15a).** To benzo[*e*]pyrene (1 g) in pyridine (12 mL) was added a solution of OsO_4 (1 g) in pyridine (2 mL). The solution was stored at room temperature for 6 weeks in the dark. The desired osmate ester, which had separated as a dark precipitate, was decomposed with $NaHSO_3$ in aqueous pyridine[22] followed by extraction of the dihydrodiol into EtOAc. Conventional workup gave the crude product, which was acetylated with Ac_2O/pyridine at room temperature for 16 h. The *cis*-diacetate **15b** (730 mg, 50%) was isolated by preparative layer chromatography on silica gel, using $CHCl_3/CH_3OH$ = 90:5 as solvent, as a solid: mp 192–194 °C; M^+ 370; ^1H NMR (100 MHz) δ 8.4–8.7 (4 H, m), 7.5–7.7 (6 H, m), 6.50 (2 H, s), 2.06 (6 H, s). Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.89. Found: C, 77.71; H, 5.05. The *cis*-diacetate (600 mg) was dissolved in THF (10 mL) and MeOH (70 mL) and the solution was saturated with NH_3. The reaction was worked up after 24 h at room temperature to give the crude product, which upon recrystallization from EtOAc gave **15a** (450 mg, 97%) as a solid: mp 208–214 °C dec; M^+ 286.

Benzo[*e*]pyrene-4,5-dione (16). A solution of *cis*-dihydrodiol **15a** (50 mg) and DDQ (300 mg) in dioxane (25 mL) was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in $CHCl_3$. The organic phase was washed with saturated Na_2CO_3, dried, and concentrated to give **16** (47 mg, 95%), which upon recrystallization from $CHCl_3$ had mp >320 °C. Anal. Calcd for $C_{20}H_{10}O_2$: C, 85.09; H, 3.57. Found: C, 84.83; H, 3.32.

***trans*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (17a).** A mixture of quinone **16** (149 mg) and KBH_4 (120 mg) in freshly distilled THF (100 mL) and *i*-PrOH (30 mL) was refluxed for 3 days. The reaction was worked up to give the crude *trans*-dihydrodiol, which was converted to the *trans*-diacetate in pyridine (2 mL) and Ac_2O (3 mL) at room temperature for 16 h. The reaction mixture was concentrated to dryness and the *trans*-diacetate **17b** (120 mg, 61%) was isolated by preparative layer chromatography on silica gel using benzene/EtOAc = 95:5 as developing solvent. Recrystallization from MeOH/EtOAc gave **17b** as a solid; mp 201–205 °C; ^1H NMR (100 MHz) δ 8.4–8.8 (4 H, m), 7.5–7.9 (6 H, m), 6.38 (2 H, s), 1.94 (6 H, s); M^+ 370. Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.89. Found: C, 77.76; H, 4.86. The *trans*-diacetate **17b** was converted to the *trans*-diol **17a** under conditions that were used to convert **15b** to **15a**, except that the reaction was run under N_2 in order to avoid oxidation of the air-sensitive *trans*-dihydrodiol. The *trans*-dihydrodiol **17a** was obtained in quantitative yield: mp >185 °C dec; UV (MeOH) λ_{max} (ϵ) 254 (59 700), 261 (77 950), 287 (14 900); M^+ 286 (base peak). No quinone could be detected by analytical LC.

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Registry No.—5, 66787-94-8; **5** methyl ester, 66787-95-9; **6,** 66787-96-0; **7,** 66787-97-1; **8,** 66787-98-2; **9,** 66787-99-3; **10,** 66788-00-9; **11,** 66788-01-0; **12a,** 66788-02-1; **12b,** 66788-03-2; **13** isomer 1, 66808-48-8; **13** isomer 2, 66788-04-3; **14a,** 66788-05-4; **14b,** 66788-06-5; **15a,** 24909-10-2; **15b,** 66788-07-6; **16,** 66788-08-7; **17a,** 66788-09-8; **17b,** 66788-10-1; 8-hydroxy-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene, 66793-68-8; 9,10-epoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene, 66788-11-2; benzo[*e*]pyrene, 192-97-2.

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Syntheses of Dihydropyrenes and Triple-Layered [2.2]Metacyclophanes

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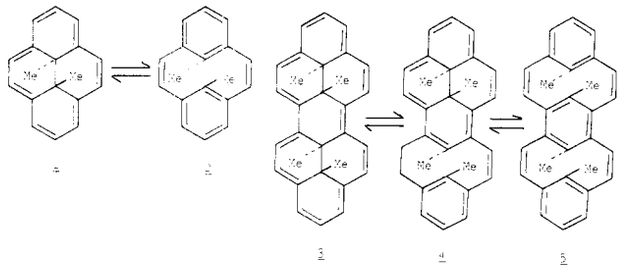
Two synthetic routes have been explored for the possible synthesis of a bridged [22]annulene (**3**) of the peropyrene type. Although the synthesis of **3** was not achieved, a number of *cis*- and *trans*-1,2,3-trisubstituted-15,16-dimethyldihydropyrenes were prepared. Also the triple-layered [2.2]metacyclophane derivative **24** has been synthesized and shown to have a staircase-type geometry.

One of the important outstanding problems in Hückel molecular orbital theory is the experimental definition of whether, and at what ring size, the larger [4*n* + 2]annulenes will lose aromaticity and simply show polyene character. As has been discussed elsewhere,[1] bridged [4*n* + 2]annulenes are probably the best experimental models for testing this upper limit. In Haddon's system for empirically evaluating aromaticity by measuring effective ring currents, *trans*-15,16-dimethyldihydropyrene (**1**) is an exceptionally good example



of aromaticity in annulenes and was selected as the reference standard for comparing other molecules.[2] It seemed, therefore, that, in trying to assess the aromaticity of a bridged [22]annulene, a peropyrene structure such as **3**, having a double *trans*-15,16-dimethyldihydropyrene moiety, would be particularly appropriate. Aside from having the desirable features of the dihydropyrenes, structure **3** offers some intriguing possibilities for valence tautomerization. It is well known that the dihydropyrenes readily undergo valence tautomerization (**1** ⇌ **2**) both thermally and photochemically.[3] A similar valence tautomerization of **3** could yield both **4** and **5**, molecules whose relative thermodymamic stability would be of some interest.

The first approach we investigated for the synthesis of **3** is outlined in Scheme I and is based on methods previously developed for the synthesis of *trans*-dihydropyrene derivatives.[4] The steps in the conversion of 2,5-dimethylaniline (**6**) to **8** proceeded in good yield and require no comment. The coupling reaction of **8** with 2,6-bis(mercaptomethyl)toluene gave a mixture of the syn and anti isomers (**9a** and **9b**) of 2,11-dithia-5,7-dibromo-6,8,18-trimethyl[3.3]metacyclophane in an overall yield of 84%, but with a ratio of syn to anti isomers of 1.3:1.0. This is in sharp contrast to the parent example, where the ratio of syn to anti isomers is 1.0:7.0.[4] As has been discussed elsewhere,[5] the relative ratios of syn to anti isomers formed in these coupling reactions is very dependent on what substituents are present. Electron-withdrawing substituents, such as the bromine atoms present in **8**, greatly increase the relative amount of syn isomer formed, presumably due to charge-transfer stabilization of the transition state leading to the syn isomer. The formation of such a large fraction of the syn isomer was unfortunate, both because the anti isomer is the one needed as precursor for the synthesis of **3** and because of the additional difficulties in separation and purification of **11b** from the mixture.

Scheme I