Synthesis of a Series of Novel Polycyclic Aromatic Systems: Isomers of Benz[a]anthracene Containing a Cyclopenta-Fused Ring

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The four possible isomers of benz[a]anthracene containing a cyclopenta-fused ring have been synthesized and characterized. These systems are of interest for structure–activity studies in bioactivation because of their predicted high level of activity. Formation of fused five-membered rings by intramolecular cyclodehydration, often difficult to accomplish, was found to be smoothly effected in anhydrous HF, provided the reactivity index (N_t) for the appropriate electrophilic addition was favorable. The dihydro polycyclic aromatic alcohols obtained from reduction of the corresponding keto cyclodehydration products were best dehydrated to the desired PAH by activity grade I neutral alumina in refluxing benzene. This dehydration proceeds in high yield without the formation of isomeric or polymeric side products that occurred even under such mild acid catalysis as *p*-toluenesulfonic acid.

Recent confirmation of the mutagenicity and carcinogenicity of cyclopenta[*cd*]pyrene[1] (CPP, 1) and development of screening systems based on structure–activity considerations have evoked considerable interest in polycyclic aromatic hydrocarbons (PAH) containing a fused cyclopenta ring.[2,3] These compounds are nonalternant, and metabolism of this class of PAH has not been systematically investigated. Analysis of metabolite profiles may contribute insights into mechanism of bioactivation and structure–activity correlations.

Among the largest stabilization energies calculated for carbocations derived from possible PAH metabolites are those of carbocations generated from ring-opening of epoxides on the cyclopenta ring of the benzaceanthrylenes.[3] Since this large delocalization energy is a predictor of biological activity,[4] we wished to investigate the metabolism of these compounds and to assess their predicted biological activity. Four isomers are possible, with cyclopentene rings fused at positions 4-5, 6-7, 7-8, and 11-12. It is interesting to note that the compounds of this series are isomeric to benzo[a]pyrene, a potent mutagenic and carcinogenic PAH. We report herein simple, efficient and high-yield syntheses of all four isomers.

The fused five-membered ring of the compounds of interest can be generated by two routes. The first involves preparation of the appropriate (benzanthryl)acetic acids, cyclodehydration to the polycyclic ketones having the correct carbon frameworks, and conversion of the ketones to the desired PAH's by reduction to alchols and dehydration. The second route utilizes a starting compound containing the cyclopenta-fused ring and involves construction of the benz[a]anthracene (2) skeleton.

Results

Benz[*j*]aceanthrylene (11). Benz[*j*]aceanthrylene has been synthesized by two routes, both involving cyclization of (benzanthryl)acetic acids. The route outlined in Scheme I was designed to take advantage of Friedel–Crafts acylations at preferred positions in obtaining the intermediates 3(3-phenanthryl)butanoic acid (3) and 1-oxo-1,2-dihydrobenz[*j*]aceanthrylene (9). Reformatsky reaction of ketone 4, from the polyphosphoric acid (PPA) catalyzed cyclization[6] of 3, yielded hydroxy ester 5, which was dehydrated to the mixture of exo- and endocyclic olefins 6. Mixture 6 was smoothly aromatized to (benzanthryl)-acetate 7 by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and the corresponding (benzanthryl)acetic acid (8) obtained by basic hydrolysis.[7] Although intramolecular cyclodehydration of 8 should be highly favored (reactivity index N_t = 1.35),[8,9] a variety of Friedel–Crafts catalysts have surprisingly failed to effect cyclization of 8 or its acid chloride.[7] However, catalysis by anhydrous hydrofluoric acid (HF) produced ketone 9 cleanly in high yield. Reduction of ketone 9 with sodium borohydride and dehydration of the resulting alcohol (10) with *p*-toluenesulfonic acid gave benz[*j*]aceanthrylene (11).

Although the overall yield of 11 was acceptable (12%), Scheme I involves a large number of steps. Scheme II provides a shorter route to 11 and a simultaneous pathway to benz[*e*]aceanthrylene (19). Benz[a]anthracene (from reduction of benzanthracene-7,12-quinone[10]) was chloromethylated at C_7 by paraformaldehyde and HCl, the methyl substituent homologated by addition of cyanide,[11] and the resulting nitrile (13) hydrolyzed to (7-benzanthryl)acetic acid (14).[11]

Interestingly, cyclization of acid 14 has not been reported. The expected products, ketones 15 and 16, are precursors for the j and e isomers, respectively of benzaceanthrylene. Attempted cyclizations of related acids **14a**[12] and **14b**[13] were reportedly unsuccessful, although reactivity indexes suggest that cyclization to both C_8 (N_t = 1.63) and C_6 (N_t = 1.66) positions should proceed in good yield and in approximately equal proportion. In anhydrous HF, 14 did indeed cyclize smoothly to a mixture of the

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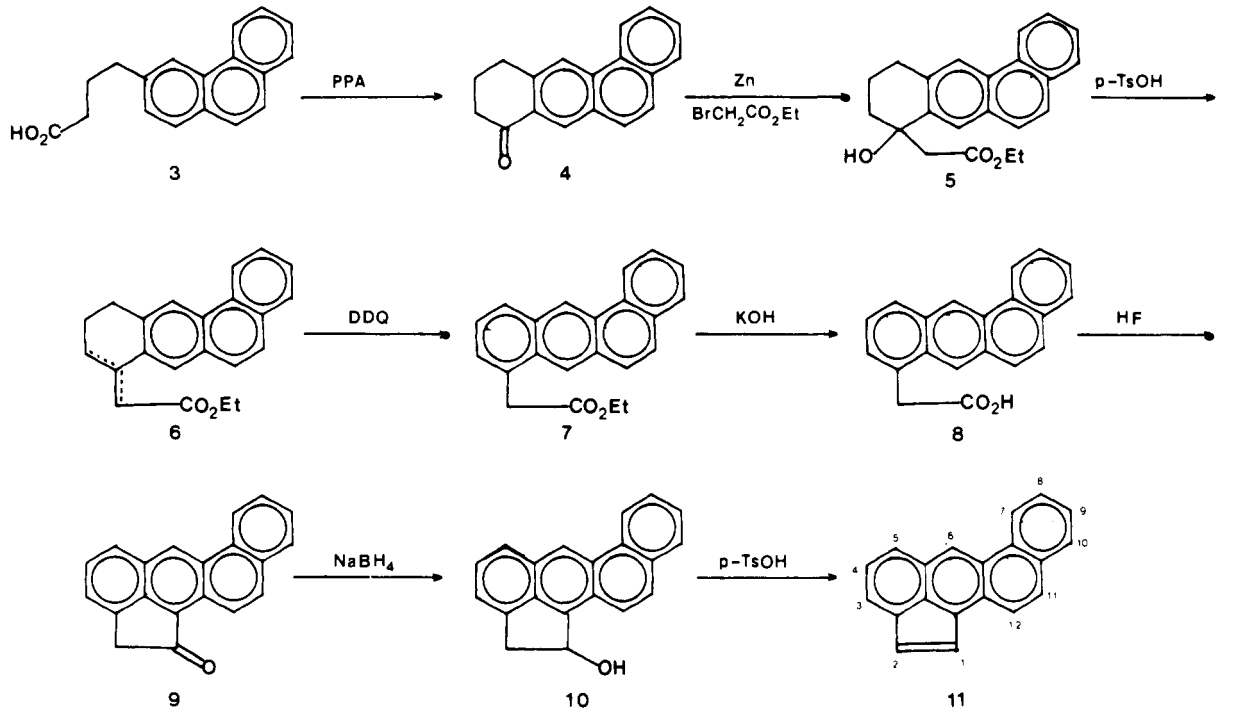
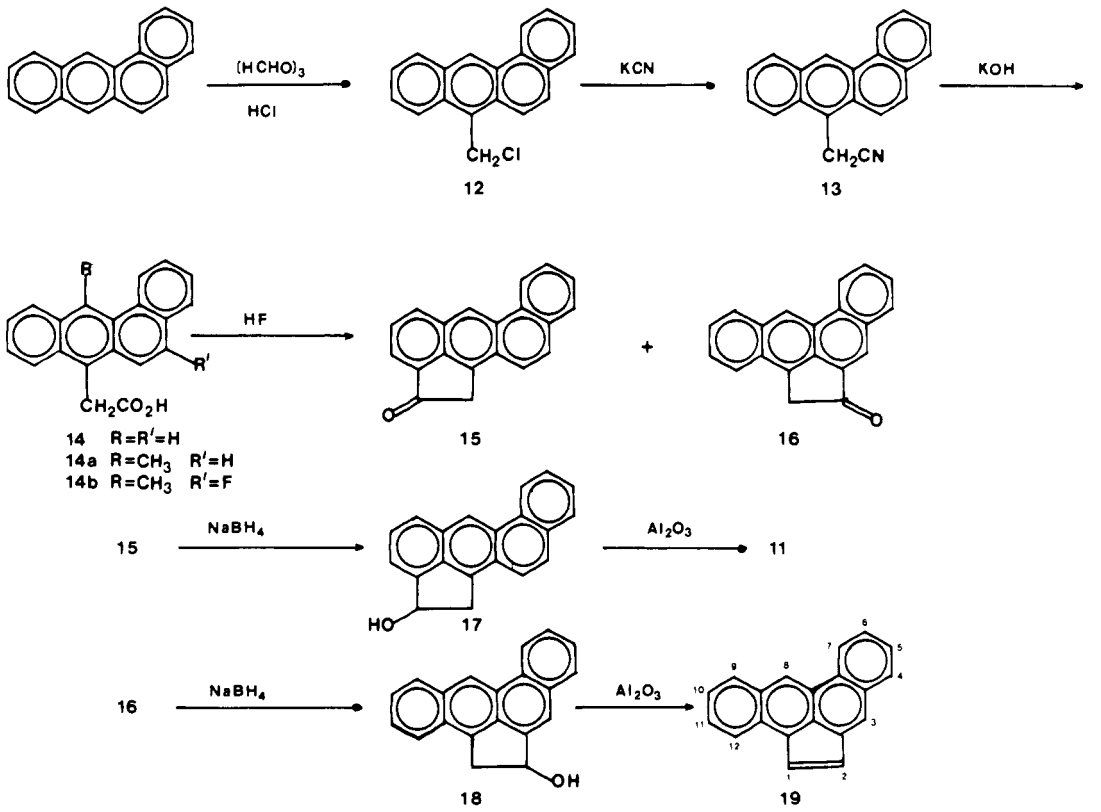
Scheme I



Scheme II



expected ketones with **15** predominating approximately 3-fold over **16**. The structures of the regioisomers were established by ^{1}H NMR, the crucial distinction being the presence of a second one-proton aromatic singlet for **16** from the single K-region proton at C_3.

Reduction of ketone **15** to alcohol **17** and dehydration of **17** by treatment with activity I neutral alumina in refluxing benzene[14] yielding compound **11** and confirmed the structural assignments **15** and **16**.

Benz[*e*]aceanthrylene (19). Published synthetic routes to the benz[*e*]aceanthrylene skeleton[15-17] do not provide a convenient basis for synthesis of this PAH. The availability of ketone **16**, however, enabled the synthesis of **19** in high yield and purity by the application of the

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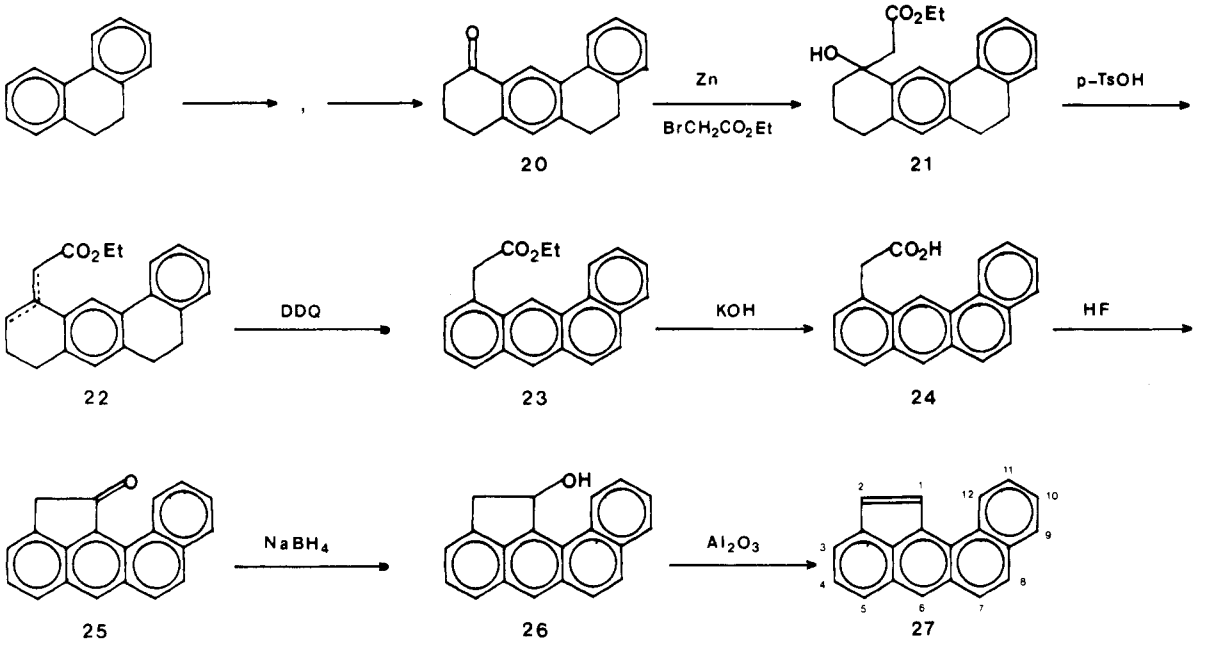
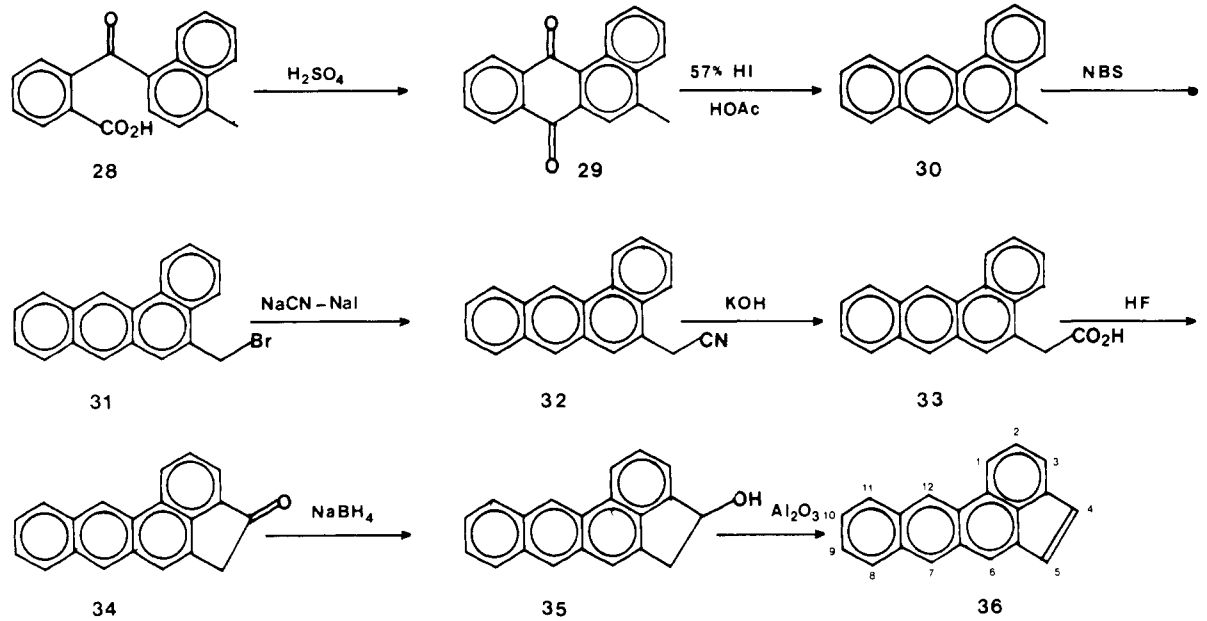
Scheme III



Scheme IV



same reduction–dehydration sequence by which **11** was obtained from ketone **15**.

Benz[*l*]aceanthrylene (27). Synthesis of **27**[18] and its 1,2-dihydro derivative has been described;[19] however, the yield is low, the sequence of reactions lengthly, and the 4-bromoindane starting material difficult to prepare. The straightforward synthetic approach in Scheme III is based on readily available 9,10-dihydrophenanthrene. Clemmensen reduction of the succinoylation product[20] followed by cyclodehydration yielded ketone **20**, which was carried forward to the PAH by the same reaction sequence applied in the synthesis of **11** from ketone **4**. Reduction by sodium borohydride in tetrahydrofuran–methanol and dehydration by netural aluminum oxide were utilized in the final two steps. The presence of extra bands in the published electronic spectrum[18] of benz[*l*]aceanthrylene suggests that the product obtained from the previously reported synthesis was impure.

Benz[*k*]acephenanthrylene (36). Syntheses of the benz[*k*]acephenanthrylene carbon framework have been reported[21,22] based on starting materials containing the fused cyclopenta-ring but involve low overall yields and a large number of steps. In Scheme IV the desired carbon framework is generated by cyclodehydration of (5-benzanthryl)acetic acid (**33**). The starting compound 2(4-methylnaphthoyl)benzoic acid (**28**) is easily obtained[23] and yielded 5-methylbenzanthracenequinone **29** on heating for a short time[24] with sulfuric acid (H_2SO_4). (The same

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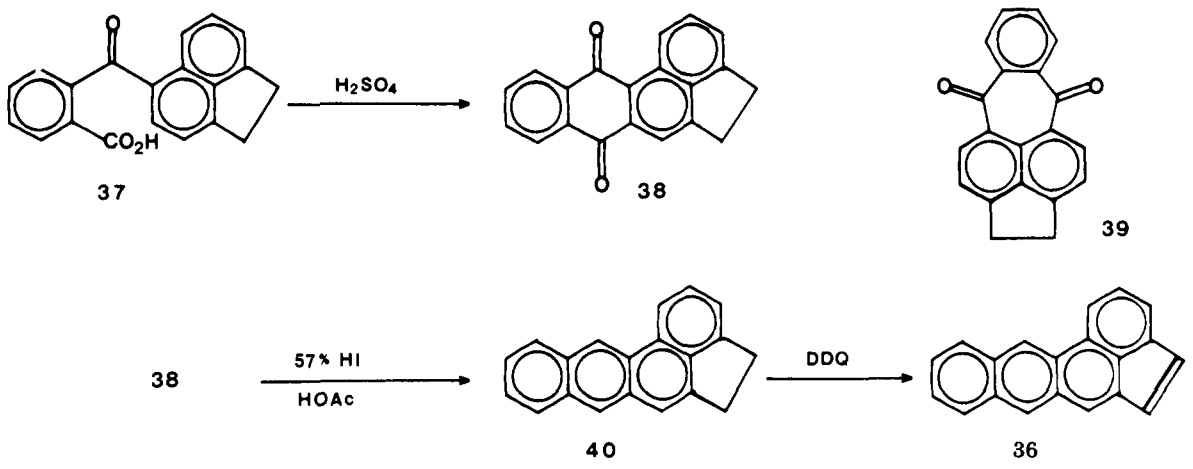
Scheme V



condensation has recently been effected[25] at room temperature over 5 days.) Reduction of the quinone with hydriodic acid (HI) and acetic acid[25] afforded 5-methylbenzanthracene, which was converted to (5-benzanthryl)acetic acid (**33**) by methods reported for the synthesis of 4-pyrenylacetic acid from 4-methylpyrene.[26] Homologation of the bromomethyl compound **31** was best achieved with sodium cyanide–sodium iodide in dry acetone.[27] Attempts to accomplish the conversion with potassium cyanide in Me_2SO at a variety of temperatures invariably yielded a tarry side product.

The cyclodehydration of **33** in HF resulted in a disappointingly low yield of ketone **34** (21%). Nevertheless, PAH **36** was obtained from the ketone by reduction with sodium borohydride and dehydration with alumina. The reactivity index for the cyclization to C_4 of benz[a]anthracene (N_t = 1.84) suggests that this cyclodehydration is not favorable. The condensation of phthalic anhydride with acenaphthene, as indicated in Scheme V, would yield a quinone having the desired carbon framework while avoiding the unfavorable intramolecular cyclization. The naphthoylbenzoic acid **37** was readily afforded by a published procedure.[28] H_2SO_4 is known to be a suitable medium for cyclization of various derivatives of **37** to benzanthracene quinones[29] and for rearrangement of phthaloylnaphthalenes to benzanthracene quinones.[30] Therefore, despite reported difficulty[31,32] in the cyclization of **37** to quinone **38** by a variety of other catalysts, treatment of **37** with H_2SO_4 was attempted in hopes of obtaining **38** either directly or via rearrangement of **39**. The product, obtained in acceptable yield (50%), was identified as **38**[33] by the appearance in the ^1H NMR spectrum of a broadened four-proton doublet of doublets at δ 3.38 arising from the nonequivalent positions on the saturated cyclopenta ring. Structural assignment **38** was confirmed by reduction to **40**, unequivocally identified by the similarity of its electronic spectrum with that of benz[a]anthracene and the appearance of the characteristically highly deshielded singlet and doublet of the bay-region protons in the ^1H NMR spectrum. Dehydrogenation of **40** with DDQ afforded **36**, identical with the product obtained by Scheme IV.

Discussion

Synthetic Schemes II, III, and V provide convenient methods for the preparation of the complete set of isomeric cyclopenta-fused benz[a]anthracenes. Reduction of the penultimate ketone intermediates (**15**, **16**, **25**, **34**) with sodium borohydride in THF–methanol leads to alcohols conveniently isolable for dehydration. The reduction can be monitored readily by the change in color of the reaction solution (yellow to colorless) or by UV spectra of aliquots taken at intervals. The appearance of the alcohols is readily observed through development of the extrememly sharp, intense bands characteristic of the benzanthracene system at ~295, 280, and 270 nm. Dehydration with activity grade I alumina in refluxing benzene is advantageous because the PAH are so acid-labile that even *p*-toluenesulfonic acid catalyzed dehydration leads to some polymerization. Dehydration was monitored by UV spectrophotometry since the disappearance of the characteristic alcohol bands can be conveniently followed.

Like other cyclopenta-PAH,[34,35] the final products do not fluoresce under long-wavelength UV light and are highly colored. Compounds **27**, **19**, and **11** are bright orange, while **36** is orange-yellow.

Elemental composition of the PAH's was established by accurate mass determination on the molecular ion of material that appeared homogeneous by reverse-phase HPLC. Mass spectrometric fragmentation patterns (in an electron impact source) were typical of PAH,[36] with the molecular ions ($M^{+\cdot}$) as base peaks and fragments corresponding to $(M - H_2)^+$, M^{2+}, and $(M - H_2)^{2+}$.

Chemical shifts and coupling patterns in the 250-MHz ^1H NMR spectra of the PAH's are consistent with the assigned structures. The AX quartets of the protons on the etheno bridges are readily apparent from upfield shifts and small coupling constants in accord with the highly olefinic character and cis configuration of the double

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bonds. Assignments of the AX signals were verified by spin decoupling. Absence of interring coupling (characteristic of PAH[38]) results in singlet resonances for all isolated protons and was helpful in analyzing NMR spectra. Features critical in confirming the structures of the isomers are summarized as follows (refer to structural formulas of the respective compounds for numbering conventions).

The lowest field proton resonance of compounds **11**, **19**, and **36** is the singlet of the highly deshielded peri proton in the bay region. As expected, this is the only singlet resonance in the spectrum of **11**. For **19**, an additional singlet at higher field from K-region H_3 is observed, and for **36**, two additional higher field singlets result form peri-proton H_7 and K-region H_6. The lone singlet in the spectrum of **27** arises from peri H_6 and appears well upfield from the doublet resonance of highly deshielded H_{12} on the benzo ring of the "fjord". The H_1 protion of the etheno AX quartet also exhibits the expected strong deshielding and is observed at lower field than all aromatic resonances except H_6 and H_{10}. (See paragraph at conclusion of this paper concerning NMR spectra obtainable as supplementary material).

Preliminary biological testing has been carried out on the benzaceanthrylene isomers (**11**, **19**, **27**). The dose–response curves on the Ames tester strain TA98 have been determined and compared to curves obtained with benzo[*a*]pyrene and 3-methylcholanthrene. Relative activities based on the slopes of the linear protions of the dose–response curves are ordered: 3-methylcholanthrene $\ll$ benzo[*a*]pyrene $\sim$ benz[*j*]aceanthrylene $<$ benz[*l*]aceanthrylene $<$ benz[*e*]aceanthrylene. Hence the three isomers tested are highly active bacterial mutagens. Like other active PAH's, the benzaceanthrylenes require metabolic activation and induce frameshift mutations. Of interest in future studies will be the ability of these compounds to cause malignant cell transformation in eukaryotic test systems and the relative importance of the cyclopenta-ring and bay-region features in mediating biological activity.

Experimental Section

^{1}H NMR spectra were obtained at 250 MHz, room temperature, on a Bruker WM250. Mass spectra were obtained on a VG7070 Micromass mass spectrometer with an electron impact source at 70 eV and melting points (uncorrected) on a Fisher-Johns melting point apparatus.

8-Oxo-8,9,10,11-tetrahydrobenz[*a*]anthracene (4). Acid **3**, (10 g) prepared in two steps from phenanthrene by a previously reported method,[5] was heated in polyphosphoric acid (350 g) with mechanical stirring for 3 h at 80 °C. The reaction mixture was poured into a large excess of ice water and extracted with ether (2 × 300 mL). The ether extract was washed sequentially with aqueous $NaHCO_3$ (5%, 200 mL) and water (100 mL), dried (Na_2SO_4), and evaporated to yield the desired ketone **4**: 6.5 g (70%); mp 178–179 °C (from ethanol) (lit.[6] mp 179–180 °C); ^{1}H NMR ($CDCl_3$) δ 2.30 (br quintet, 2 H, J = 6 Hz, $ArCH_2CH_2$), 2.85 (br, 2 H, J = 6 Hz, $ArCH_2$), 3.30 (br t, 2 H, J = 6 Hz, $ArCOCH_2$), 7.55–8.00 (m, 6 H, Ar H), 8.50 (s, 1 H, Ar H_7 or Ar H_{12}), 8.60 (s, 1 H, Ar H_{12} or Ar H_7).

(8-Benzanthryl)acetic Acid (8). To a suspension of activated zinc dust (5 g) and iodine (0.2 g) in dry benzene (30 mL) and dry ether (30 mL) under refulx was added ethyl bromoacetate (2 mL) with stirring. After the addition was complete, the reaction mixture was stirred and refluxed for 15 min and then ketone **4** (2.4 g) was added in one portion. The reaction mixture, cooled after an additional 2 h of reflux, was diluted with methanol (30 mL) and filtered. The filtrate was hydrolyzed with cold dilute HCl. The benzene–ether solution was separated, and the aqueous phase was extracted once with ether (100 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (5%, 100 mL) followed by water (100 mL), dried (Na_2SO_4), and evaporated to afford 2.7 g (83%) of hydroxy ester **5**.

A solution of ester **5** (2.7 g) and *p*-toluenesulfonic acid (100 mg) in benzene (300 mL) was refluxed for 2 h. After washing with brine (2 × 100 mL), the benzene was evaporated to give a mixture of exo- and endocyclic (as determined from ^{1}H NMR) dehydration products **6** (2.4 g), which were utilized directly in the following step.

The mixture of esters **6** (2.4 g) and DDQ (2.0 g) in dry benzene (400 mL) was refluxed for 4 h. The precipitated hydroquinone was filtered off and the filtrate chromatographed [neutral alumina, 1:1 benzene–petroleum ether (30–60 °C)] to yield the aromatized ester **7**: 2.1 g (88%).

Ester **7** (2 g) was heated with a mixture of aqueous KOH (45%, 10 mL) and methanol (40 mL) for 1 h on a steam bath. The methanol was boiled off, and the residue, dissolved in hot water (500 mL), was acidified with concentrated HCl to give acid **8**: 1.6 g (88%); mp 232 °C (from acetone–benzene)(lit.[7] mp 233–234 °C).

1-Oxo-1,2-dihydrobenzo[*j*]aceanthrylene (9). Acid **8** (1.6 g) was stirred in anhydrous HF (100 mL) for 15 h at ambient temperature. After evaporation of the HF under a stream of N_2, the solid residue was dissolved in benzene–ether (1:1, 300 mL), washed with aqueous NaOH (5%, 100 mL) and water (100 mL), and dried (Na_2SO_4). Evaporation of the solvent yielded crude ketone **9**, which was purified by chromatography on silica with benzene eluant: 1.25 g (88%); yellow needles (from benzene) mp 230 °C (lit.[7] mp 230 °C).

1-Hydroxy-1,2-dihydrobenz[*j*]aceanthrylene (10). Sodium borohydride (~1 g) was added to a solution of the ketone **9** (1 g) in dimethyl formamide (300 mL) and stirred at ambient temperature for 6 h. Addition of the reaction mixture to brine (500 mL) followed by extraction with ether (2 × 100 mL), washing with water (100 mL), drying over Na_2SO_4, and evaporation of solvent furnished alcohol **10**, 0.95 g (95%), which was used directly in the next step.

Benz[*j*]aceanthrylene (11). A solution of the alcohol **10** (0.95 g) and *p*-toluenesulfonic acid (10 mg) in dry benzene (400 mL) was refluxed for 45 min, washed with water (2 × 100 mL), dryed (Na_2SO_4), and evaporated to give the crude PAH. Purification of the crude sample was accomplished by chromatography on silica with hexane eluent to yield benz[*j*]aceanthrylene (**11**) : 0.55 g (62%); orange plates (from hexane) mp 170–171 °C; UV (hexane) λ_{max} ($\epsilon \times 10^4$) 414 (0.92), 392 (0.86), 379 (0.71), 360 (0.53), 313 (2.38), 302 (2.42), 278 (2.70), 261 (3.64), 259 (3.62), 221 (3.66) nm; accurate mass of molecular ion, 252.0947 (calcd for $C_{20}H_{12}$, 252.0939); major fragments at m/z 252 ($M^{+\cdot}$), 250 ($(M - H_2)^{+\cdot}$), 126 M^{2+}, 125 ($(M - H_2)^{2+}$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.10 (d, 1 H, J = 4.9 Hz, etheno H_2), 7.52 (d, 1 H, J = 4.9 Hz, etheno H_1), 8.03 (d, 1 H, J = 8.0 Hz, bay region H_8), 9.14 (s, 1 H, bay region peri H_6), 7.52–8.03 (m, 8 H, remaining Ar H).

7-(Cyanomethyl)benz[*a*]anthracene (13). A solution of the chlormethylated compound **12**[10] (2.4 g) in Me_2SO (40 mL) was added over 5 min to a rapidly stirred suspension of KCN (1.3 g) in Me_2SO (40 mL) at 70 °C. The reaction mixture was stirred at 70 °C for an additional 2 h and then poured into water (500 mL). After saturation with NaCl, the solution was extracted with ether (3 × 100 mL) and the extract was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated to give crude nitrile **13**: 2.05 g (88%); mp 177 °C (lit.[11] mp 177–178 °C); ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2 H, Ar CH_2), 7.10–8.50 (m, 11 H, Ar H).

(7-Benzanthryl)acetic Acid (14). A solution of the nitrile **13** (2.2 g) and KOH (3.0 g) in ethylene glycol (90 mL) and water 60 mL) was heated at reflux for 24 h and then poured into ice water and filtered. The filtrate was washed once with ether (100 mL) and acidified with concentrated HCl. The precipitate was washed with water and dried to give acid **14**: 2.0 g (85%); mp 280–281 °C (lit.[11] mp 281–282 °C). Recrystallization from dilute acetic acid furnished pure **14**: mp 281 °C; ^{1}H NMR (acetone-d_6) δ 4.70 (s, 2 H, Ar CH_2), 7.20–9.10 (m, 12 H, Ar H, CO_2H).

Cyclization of Acid 14. A solution of acid **14** (2.0 g) in anhydrous HF (100 mL) was stirred for 24 h at room temperature. The solid residue, after evaporation of HF under a stream of N_2, was dissolved in ether–benzene (1:1, 300 mL) and the solution washed with aqueous NaOH (10%, 100 mL) followed by water

(38) K. D. Bartle, D. W. Jones, and J. E. Pearson, *J. Mol. Spectrosc.*, **24**, 330 (1967).

(100 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a yellow solid. The crude product was purified by chromatography on alumina with benzene to give a crystalline yellow solid (1.65 g, 88%), which was found to be a mixture by analytical HPLC.

A portion of the mixture (0.5 g) was separated by preparative HPLC on silica with toluene eluant. Collected peaks were further subjected to flash chromatography on silica with benzene eluant.

The earlier eluting ketone **16** (104 mg) was obtained as yellow needles (from methanol): mp 238–239 °C; UV (MeOH) λ_{max} ($\epsilon \times 10^4$) 411 (sh, 0.37), 381 (0.85), 263 (0.75), 245 (sh, 0.36), 322 (1.84), 308 (1.96), 294 (0.78), 272 (sh, 5.21), 268 (6.49), 251 (sh, 5.07), 229 (6.12) nm. Ketone **16** was identified as the e isomer by its 250-MHz ^1H NMR.

The later eluting ketone **15** (284 mg) was obtained as yellow needles from methanol: mp 186–188 °C; UV (MeOH) λ_{max} ($\epsilon \times 10^4$) 412 (0.74), 385 (0.54), 306 (sh, 4.10), 299 (4.40), 294 (sh, 4.15), 273 (3.52), 240 (sh, 3.11), 234 (3.06), 212 (4.51) nm.

Ketone **15** was identified as the oxobenz[*j*]aceanthrylene isomer by its 250-MHz ^1H NMR and subsequent reduction and dehydration to **11**.

Reduction–Dehydration of Ketones to PAH. The following sequence was employed with reagents in the same proportions for conversions of ketones **15**, **16**, **25**, and **34** to the corresponding PAH.

In a typical reaction, 100 mg of ketone was dissolved in 10 mL of THF and then 5 mL of MeOH added.

Sodium borohydride (40 mg) was added in several portions to the stirred reaction and the course of the reduction followed by UV (see Discussion). Upon complete reduction, 25 mL of distilled H_2O was added and the organic solvents were removed by briefly evacuating the mixture on a rotary evaporator. The alcohol was extracted into CH_2Cl_2 (25 mL), dried over Na_2SO_4, and the solvent evaporated, leaving the colorless solid alcohol that was used directly in the next step.

The alcohol was dissolved in 30 mL of benzene by refluxing, and 1 g (10-fold excess by weight) neutral activity grade I alumina was added. (Use of activity grade I is crucial.) The reaction was refluxed with stirring until the dehydration was complete (see Discussion), generally 45 min. The reaction mixture was filtered and evaporated dryness. The PAH was separated from traces of alcohol by flash chromatography over silica with hexane eluant and recrystallized from methanol or hexane.

Benz[*e*]aceanthrylene (19). Treatment of **16** by the sequence described above yielded benz[*e*]aceanthrylene (60%) as orange needles (from methanol): mp 138 °C; UV (hexane) λ_{max} ($\epsilon \times 10^4$) 394 (1.13), 375 (1.26), 360 (sh, 0.99), 331 (1.26), 316 (1.39), 292 (sh, 3.65), 265 (5.13), 258 (4.87), 231 (3.91) nm; accurate mass of the molecular ion 252.0947 (calcd for $C_{20}H_{12}$, 252.0939); major fragments of *m/z* 252 ($M^{+\cdot}$), 250 ($(M - H_2)^{+}$), 126 (M^{2+}), 125 ($(M - H_2)^{2+}$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.10 (d, 1 H, J = 4.9 Hz, etheno H_2), 7.67 (d, 1 H, J = 4.9 Hz, etheno H_1), 8.02 (s, 1 H, K region H_3), 8.76 (d, 1 H, J = 8 Hz, bay region H_7), 8.90 (s, 1 H, bay region peri H_8), 7.41–8.3 (m, 7 H, remaining Ar H).

Ethyl (11-Benzanthryl)acetate (23). To a suspension of activated zinc dust (5 g) and iodine (0.2 g) in dry benzene (30 mL) and dry ether (30 mL) was added a solution of ethyl bromoacetate (2 mL) and ketone **20** (2.2 g) (prepared in three steps from 9,10-dihydrophenanthrene, as described by Fieser and Johnson[20]) in benzene–ether (1:1, 40 mL) with stirring and refluxing. After completion of the addition, the reaction mixture was stirred and refluxed for an additional 2 h and then cooled and treated with cold dilute HCl. The organic layer was separated, and the aqueous layer extracted once with ether (100 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (5%, 100 mL) and water (100 mL) and dried (Na_2SO_4). Evaporation of solvent afforded crude β-hydroxy ester **21** (2.5 g, 84%), which was used directly in the next step.

A solution of ester **21** (2.5 g) and *p*-toluenesulfonic acid (100 mg) in dry benzene (300 mL) was heated under reflux for 2 h. The benzene solution was washed with brine (2 × 100 mL), dried (Na_2SO_4), and evaporated to give a mixture of exo- and endocyclic dehydration products **22** (2.3 g).

Mixture **22** (2.3 g) and DDQ (4.0 g) were reacted in dry benzene (400 mL) at reflux for 6 h, cooled to room temperature, and filtered. The filtrate was chromatographed on neutral alumina with benzene eluant to yield ester **23**: 1.95 g (86%).

(11-Benzanthryl)acetic acid (24). Ester **23** (1.5 g) was heated with methanolic KOH (2.0 g of KOH, 10 mL of H_2O, 40 mL of methanol) for 1 h on a steam bath. The methanol was boiled off and the alkaline solution acidified with concentrated HCl to give the acid **24**: 1.25 g (91%); mp 210–212 °C dec.

1-Oxo-1,2-dihydrobenz[*l*]aceanthrylene (25). Cyclodehydration of acid **24** (1.2 g) in anhydrous HF (100 mL) by the procedure described for ketone **9** yielded ketone **25**, which was purified by chromatography on alumina by using benzene as eluant: 950 mg (84%); yellow needles (from benzene) mp 189–190 °C; UV (MeOH) λ_{max} ($\epsilon \times 10^4$) 422 (0.56), 396 (0.66), 380 (0.63), 298 (5.29), 271 (2.48), 250 (3.06), 228 (3.34) nm.

Benz[*l*]aceanthrylene (27). The reduction–dehydration as described for **19** yielded benz[*l*]aceanthrylene (62%): mp 157–158 °C; UV (hexane) λ_{max} ($\epsilon \times 10^4$) 411 (0.33), 396 (0.83), 375 (0.79), 358 (0.46), 321 (1.61), 309 (4.57), 296 (3.20), 284 (3.20), 254 (2.69), 233 (2.42), 222 (3.22) nm; accurate mass of molecular ion, 252.0947 (calcd for $C_{20}H_{12}$, 232.0939); major fragments at *m/z* 252 ($M^{+\cdot}$), 250 ($(M - H_2)^{+}$), 126 (M^{2+}), 125 ($(M - H_2)^{2+}$; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.26 (d, 1 H, J = 5.4 Hz, etheno H_2), 8.12 (d, 1 H, J = 5.4 Hz, etheno H_1), 8.40 (s, 1 H, peri H_6), 9.20 (d, 1 H, J = 8 Hz, bay region H_{12}), 7.5–8.0 (m, 8 H, remaining Ar H).

5-Methylbenz[*a*]anthracene-7,12-quinone (29). 2-(4-Methylnaphthoyl)benzoic acid[23] (**28**, 5 g) was heated with H_2SO_4 (95.6%, 50 mL) for 1 h at 60 °C. The dark-violet reaction complex was poured into crushed ice, and the greenish yellow precipitate was filtered. Flash chromatography on silica with CH_2Cl_2 eluant yielded pure quinone **29**: 2.55 g (54%); yellow needles (methanol); mp 178–179 °C (lit.[24] mp 178.5–179.5 °C); UV ($CHCl_3$) λ_{max} 285 nm.

5-Methylbenzanthracene (30). Quinone **29** (2.7 g) was reduced to 5-methylbenzanthracene (**30**) by using HI (57%, 10 mL) and glacial acetic acid (120 mL) by the procedure of Fu and co-workers.[25] The crude product was purified by flash chromatography on alumina with benzene–hexane (1:1) eluant to afford pure **30**: 2.32 g (96%); mp 156–157 °C (lit.[23] mp 155.9–156.9 °C).

5-(Bromomethyl)benz[*a*]anthracene (31). To a solution of **30** (2.24 g) in CCl_4 (300 mL) was added *N*-bromosuccinimide (2.0 g) and benzoyl peroxide (10 mg). The reaction mixture was refluxed for 3 h under N_2 and then cooled. Ether (300 mL) was added, and the organic phase was washed with water (300 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the bromomethyl compound **31**.

5-(Cyanomethyl)benz[*a*]anthracene (32). To a solution of **31** in dry acetone (50 mL) were added NaCN (1.5 g) and NaI (200 mg), and the reaction mixture was refluxed with vigorous stirring for 20 h. The reaction mixture was cooled, filtered, and washed with acetone. The residue obtained after evaporation of acetone was dissolved in benzene (200 mL), washed with hot water (3 × 100 mL), dried (Na_2SO_4), and evaporated to give crude **32**. Chromatography on silica with benzene eluant furnished **32**; 2.10 g (85% based on **30**).

(5-Benzanthryl)acetic acid (33). Hydrolysis of **32** (1.8 g) by KOH (3 g) in ethylene glycol (80 mL) and water (50 mL) was carried out as described for compound **13**, and the product obtained was recrystallized to yield acid **33**: 1.68 g (87%); mp 172–175 °C.

4-Oxo-4,5-dihydrobenz[*k*]acephenanthrylene (34). Treatment of acid **33** (1.3 g) with anhydrous HF (100 mL) yielded **34**, which was purified by flash chromatography on silica with benzene eluant. The yellow band (fluorescent in UV light) was collected and on evaporation of solvent gave **34**; 250 mg (21%).

4,5-Dihydrobenz[*k*]acephenanthrylenequinone (38). Cyclodehydration of 2-(4-acenaphthoyl)benzoic acid[22] (**37**, 5 g) with H_2SO_4 (95.6%, 50 mL) was carried out following the procedure described for the keto acid **28**. The dark-violet reaction complex was poured onto ice, and the resulting solution (with some solid residue) was extracted with CH_2Cl_2 (4 × 200 mL). The CH_2Cl_2 extract was dried (Na_2SO_4) and evaporated to give crude product, which was purified by flash chromatography on silica. Elution with CH_2Cl_2 gave **38**: 2.35 g (50%); mp 219–220 °C (lit.[33] mp 221–222 °C); ^1H NMR ($CDCl_3$, resonance of ethano protons) δ 3.38 (dd, 4 H, J = 15, 5 Hz).

4,5-Dihydrobenz[*k*]acephenanthrylene (40). Quinone **38** (1.42 g) was heated at reflux with HI (57%, 5 mL) and glacial

HOAc (60 mL) for 6 h. The reaction was poured into $Na_2S_2O_5$ solution, and the precipitate collected by filtration was purified by chromatography on silica with benzene as eluant to give **40**: 1.23 g (97%); pale yellow leaflets (ligroin), mp 192–193 °C (lit.[21] mp 192.5–193.5 °C); ^1H NMR ($CDCl_3$) δ 3.40 (br s, 4 H, ethano), 8.44 (d, 1 H, H_1), 9.06 (s, 1 H, H_{12}).

Benz[*k*]acephenanthrylene (36). A mixture of compound **40** (1.0 g) and DDQ (1.0 g) in dry xylene (80 mL) was heated at reflux for 20 h. The cooled solution was filtered and the filtrate passed through a column of alumina. Elution by benzene–hexane (1:1) and collection of the yellow non-fluorescent band afforded benz[*k*]acephenanthrylene (**36**): 685 mg (69%); yellowish orange plates (hexane), mp 233–234 °C; UV (hexane) λ_{max} ($\epsilon \times 10^4$) 416 (0.80), 395 (0.12), 352 (1.01), 340 (1.18), 310 (3.60), 297 (1.98), 265 (sh, 4.10), 257 (5.04) nm; accurate mass of molecular ion, 252.0951 (calcd for $C_{20}H_{12}$, 252.0939); major fragments at m/z 252 ($M^{+\cdot}$), 250 ($(M - H_2)^{+}$), 126 (M^{2+}), 125 ($(M - H2)^{2+}$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.11 (d, 1 H, J = 4.5 Hz, etheno H), 7.26 (d, 1 H, J = 4.5 Hz, etheno H), 8.11 (s, 1 H, K- region H_6), 8.49 (dd, 1 H, J = 8 Hz, 2.5 Hz, bay regionm H_1), 8.54 (s, 1 H, peri H_7), 9.14 (s, 1 H, bay region peri H_{12}), 7.6–8.3 (m, 6 H, remaining Ar H).

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Supplementary Material Available: NMR spectra of compounds **11**, **19**, **27**, and **36** (4 pages). Ordering information is given on any current masthead page.

Regioselective Catalytic Transfer Hydrogenation of Dimethyl Bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, Dimethyl Bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate, and Related Compounds over Palladium on Carbon

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The catalytic transfer hydrogenation (CTH) of dimethyl bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**) on palladium on carbon is highly regioselective, giving predominant reduction at the least-substituted olefinic site. The CTH of dimethyl bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate also occurs with exclusive suprafacial exo addition of hydrogen to afford the endo isomer. An increase in the relative concentration of palladium on carbon (ca. 40–45 wt/wt % based on the acceptor) accelerates the rate of CTH while the substituted cyclohexenes undergo CTH faster than cyclohexene with dimethyl bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate.

The catalytic transfer hydrogenation (CTH) process[1] utilizes organic molecules of relatively low oxidation potential as hydrogen donors, DH_n, in the presence of solubilized catalysts (e.g., Ru,[2] Rh,[3] Pd[3b,c]) and heterogeneous metal catalysts (e.g., Pd,[4] Ni[5]) to effect hydrogen transfer to an organic substrate or "acceptor" (A, eq 1).

$$DH_n + A \xrightarrow[\text{solvent}]{\text{catalyst}} AH_2 + DH_{n-2} \quad (1)$$

The CTH process has received considerable recent attention as a useful synthetic method for the reduction of carbonyl compounds[6] and highly substituted olefins[7] as well as hydrogenolysis of "protected" peptides[8] and carbohydrates.[9] While there exists a variety of donor molecules capable of transferring hydrogen atoms to acceptor molecules with varying degrees of efficiency, cyclohexene (**1**), 1,3-cyclohexadiene (**2**), and their alkylated derivatives exhibit a relatively high propensity for hydrogen transfer in the presence of palladium black and palladium on

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