tone–hexanes) to give 91 mg (90%) of furano ketone **20** as a pale yellow oil which solidified upon standing. Recrystallization from Et_2O afforded pale yellow needles of **20**, mp 115–116 °C: R_f 0.45 (3:1 hexanes–acetone); MS m/e 380 (M^+); IR (neat) 2963, 2921, 2834, 1746, 1657, 1644, 1609, 1528, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3 H), 1.93 (m, 1 H), 2.14 (m, 1 H), 2.22 (d, J = 2.0 Hz, 3 H), 2.63–2.79 (m, 4 H), 3.20–3.45 (m, 4 H), 3.33 (s, 3 H), 4.00 (s, 3 H), AB system 4.41, 4.45 (J_{AB} = 11.6 Hz, 2 H). Anal. Calcd for $C_{19}H_{24}O_4S_2$: C, 59.97; H, 6.36. Found: C, 59.75; H, 6.33.

Dithiolane Furano Alcohol 5. A solution of 42 mg (0.11 mmol) of furano ketone **20** in 10 mL of dry MeOH was treated with 23 mg (0.61 mmol) of $NaBH_4$. The reaction mixture was then stirred at rt under an inert atmosphere for 30 min, quenched with 25 mL of pH 7 phosphate buffer, and extracted with 3 × 15 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 39 mg (92%) of **5** as a colorless oil (~3:1 inseparable diastereomeric mixture). Analytical data for the major isomer: R_f 0.46 (3:1 Et_2O–hexanes); MS m/e 382 (M^+); IR (neat) 3430, 2923, 2870, 1730, 1645, 1513, 1455, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3 H), 1.46 (m, 1 H), 1.70 (m, 1 H), 2.04 (m, 2 H), 2.15 (d, J = 2.4 Hz, 3 H), 2.55 (m, 1 H), 2.55 (m, 1 H), 2.76 (dd, J = 6.0, 12.8 Hz, 1 H), 3.15–3.38 (m, 5 H), 3.32 (s, 3 H), 3.95 (s, 3 H), AB system 4.26, 4.33 (J_{AB} = 11.6 Hz, 2 H), 4.66 (m, 1 H).

Dithiolane Furano Acetate 5a. A solution of 36 mg (0.094 mmol) of furano alcohol **5** in 2 mL of dry pyridine was treated with 1 mL of acetic anhydride, and the reaction mixture was stirred at rt for 18 h with protection from moisture. The excess acetic anhydride and pyridine were then evaporated under reduced pressure, and the residue was partitioned between 20 mL of water and 20 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 38 mg (95%) of acetate **5a** as a pale yellow solid (~3:1 inseparable mixture of diastereomers). Recrystallization from Et_2O gave the major isomer as colorless needles, mp 140–141 °C: R_f 0.56 (3:1 Et_2O–hexanes); MS m/e 364 (M^+ – 76 [–CH_3COOH]); IR (neat) 2959, 2923, 2872, 1740, 1645, 1238, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 3 H), 1.63 (m, 1 H), 1.75 (m, 1 H), 2.05 (s, 3 H), 2.09 (m, 2 H), 2.15 (d, J = 2.0 Hz, 3 H), 2.74 (m, 2 H), 3.23 (s, 3 H), 3.17–3.38 (m, 4 H), 3.96 (s, 3 H), AB system 4.08, 4.23 (J_{AB} = 11.6 Hz, 2 H), 5.88 (dd, J = 5.2, 8.4 Hz, 1 H).

Dithiolane Methylene Ester 7. A solution of 35 mg of furanoacetate **5a** in 3 mL of THF was treated with 3 mL of 1 N H_2SO_4, and the resulting solution was stirred at rt for 5 h. The reaction mixture was then diluted with 30 mL of water, neutralized with saturated aqueous $NaHCO_3$, and extracted with 4 × 10 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 1:1 Et_2O–hexanes) to afford 12 mg (43%) of methylene ester **7** as a viscous pale yellow oil that solidified on standing. Recrystallization from Et_2O–hexanes gave **7** as pale yellow needles, mp 107 °C: R_f 0.48 (1:1 Et_2O–hexanes); MS m/e 350 (M^+); IR (KBr) 2953, 2924, 2870, 1725, 1653, 1605, 1435, 1372, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 3 H), 2.08–2.20 (m, 2 H), 2.21 (s, 3 H), 2.39 (dd, J = 6.4, 16.8 Hz, 1 H), 2.47 (m, 1 H), 2.63 (dd, J = 7.6, 16.8 Hz, 2 H), 3.31–3.40 (m, 4 H), 3.69 (s, 3 H), 5.77 (d, J = 1.6 Hz, 1 H), 6.21 (d, J = 1.6 Hz, 1 H), 6.51 (t, J = 6.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{22}O_3S_2$: C, 61.68; H, 6.33. Found: C, 61.64; H, 6.34.

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Supplementary Material Available: ^1H NMR spectra of **5**, **5a**, **7**, **27–37**, **40–43**, **46**, **48**, **18**, and **20** (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering formation.

Synthesis of Ketone and Alcohol Derivatives of Methylene-Bridged Polyarenes, Potentially New Classes of Active Metabolites of Carcinogenic Hydrocabons

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Methods for the syntheses of bridge ketone and alcohol derivatives of methylene-bridged polyarenes from the parent hydrocarbons are described. The polyarenes investigated include 4*H*-cyclopenta[*def*]phenanthrene (**1a**), fluorene (**2a**), 7*H*-benzo[*c*]fluorene (**3a**), 4*H*-cyclopenta[*def*]chrysene (**4a**), 11*H*-Benz[*bc*]aceanthrylene (**5a**), 10*H*-indeno[1,2,7,7a-*bcd*]pyrene (**6a**), 11*H*-dibenzo[*bc*,*l*]aceanthrylene (**7a**), 4*H*-fluoreno[4,4a,4b,5-*abc*]anthracene (**8a**), and 7*H*-dibenzo[*a*,*g*]fluorene (**9a**). The bridge ketone derivatives are most efficiently synthesized via treatment of the parent hydrocarbons with *n*-butyllithium and reaction of the resulting anionic intermediates with molecular oxygen. The direct formation of ketones rather than the expected hydroperoxides from reaction of the bridge anions with O_2 presumably involves intra- or intermolecular abstraction of a proton from the benzylic site of the intermediate by the peroxy anion leading to loss of hydroxide ion with formation of a carbonyl group. Yields are generally high except in the cases of **1a** and **4a**; the former affords as the principal product a dimeric alcohol arising from reaction of the anion of **1a** with the corresponding ketone **1b**. The related bridge alcohols are readily obtained in yields of 75–95% by reduction of the crude products from the preceding oxidations with $NaBH_4$.

Methylene-bridged polycyclic aromatic hydrocarbons (PAHs) are produced by combustion at moderate temperatures of PAHs that bear a bay region methyl group.[1,2] Relatively high ratios of bridged PAHs are present in crude petroleum,[1] and significant levels occur as environmental pollutants. Substantial levels of the ketone derivatives of bridged polyarenes are found in ambient urban air, in carbon black extracts, and in emissions from wood and coal combustion, municipal incineration, and diesel engines.[3,4]

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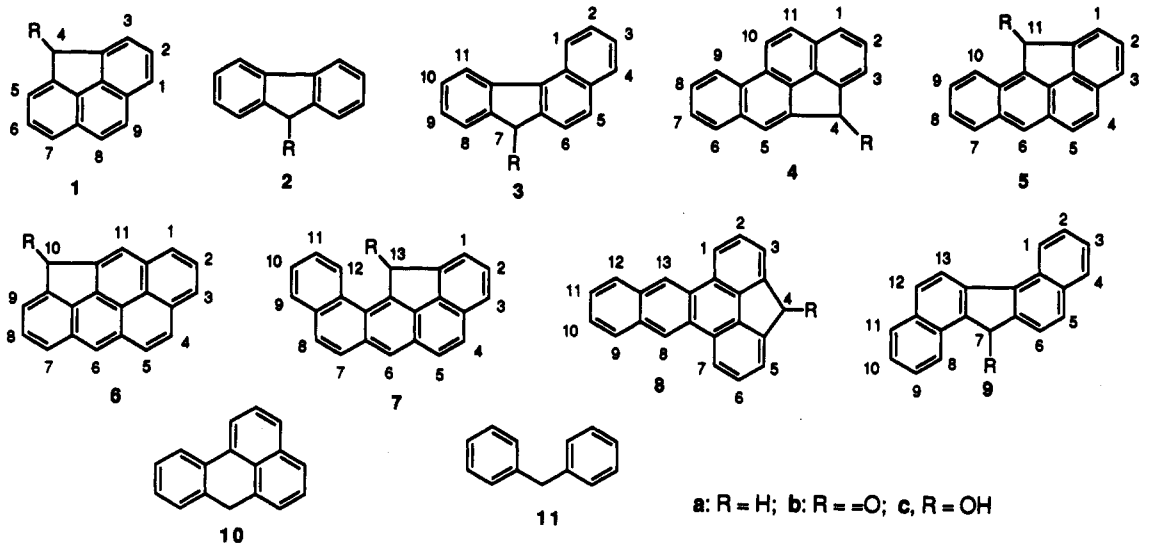
0022-3263/92/1957-6313$03.00/0

Chart I



However, identification of these hydrocarbons and their ketone derivatives in environmental samples has been seriously hampered by the lack of authentic compounds as standards. In most cases, structural assignments are based solely on UV, mass spectra, and other spectroscopic evidence which does not allow unequivocal distinction between possible isomers. The limited available evidence indicates that some bridged PAHs are relatively potent mutagens and carcinogens, and their ketone derivatives tend to show somewhat lower activity.[5] However, investigations of the chemical and biological properties of this unusual class polyarenes have been limited by their relative synthetic inaccessibility.

Recently it was proposed[10] that methylene-bridged polyarenes may undergo metabolic activation to mutagenic and/or carcinogenic metabolites via a mechanism involving enzymatic hydroxylation on the relatively acidic bridge positions followed by conversion to reactive sulfate or other esters.[11-13] It is conceivable that the same hydroxymethylene metabolites may arise via enzymatic reduction of the corresponding bridge ketones.

In order to investigate these hypotheses, we required a method for the efficient synthesis of the bridge ketone and alcohol derivatives of methylene-bridged polyarenes. Since the parent hydrocarbons are now relatively readily available via new synthetic approaches,[10,14-18] it was expedient to utilize them as starting compounds. We now report methods for the facile regiospecific oxidation of methylene-bridged polyarenes (Chart I) to the corresponding alcohols or ketones.

Results and Discussion

Benzylic alcohols are most commonly synthesized from hydrocarbon precursors either by oxidation to ketones followed by reduction or by bromination and displacement of bromide by hydroxide. Methods for the direct oxidation of arylarenes to benzylic alcohols are infrequently employed due to the relative facility of further oxidations and other secondary reactions. The report that oxidation of the prototype methylene-bridged polyarene 4*H*-cyclopenta[*def*]phenanthrene (**1a**) with CrO_3 in AcOH affords a mixture of the 4-keto derivative, and the 8,9-dione[19] indicates that a milder method of oxidation is required.

In our initial studies, several known methods for the oxidation of benzylic sites in hydrocarbons to ketones were investigated. These included *t*-BuOOH with a catalytic amount of CrO_3,[20] pyridinium chlorochromate,[21] and DDQ in aqueous AcOH.[23] Oxidation of **1a** with 70% aqueous *t*-BuOOH and CrO_3 in methylene chloride by the method of Muzart[20] gave in our hands the expected bridged ketone 4*H*-cyclopenta[*def*]phenanthren-4-one (**1b**) in 85% yield. Analogous oxidations of fluorene (**2a**), 7*H*-benzo[*c*]fluorene (**3a**), and 4*H*-cyclopenta[*def*]chrysene (**4a**) with this reagent furnished the corresponding bridge ketones **2b**, **3b**, and **4b** in yields of 85, 76, and 87%, respectively. On the

(5) 4*H*-Cyclopenta[*def*]chrysene is a relatively potent mutagen and a carcinogen comparable in activity to benzo[*a*]pyrene.[6,7] 11*H*-Benz[*bc*]-aceanthrylene is also a potent tumorigen considerably more active than the parent hydrocarbon.[8] 1,11-Methanocyclopenta[*a*]phenanthren-17-one is more carcinogenic than the parent hydrocarbon lacking the bridge and only slightly less active than its 11-methyl analog.[8] 4*H*-Cyclopenta-[*def*]chrysen-4-one exhibits mutagenic and tumorigenic activity at a level lower than that of the parent hydrocarbon.[6,7] 11*H*-Benz[*bc*]aceanthrylen-11-one is essentially inactive as a carcinogen on mouse skin.[6] 7*H*-Benz[*de*]anthracen-7-one has been shown to exhibit high potency in the photodynamic bioassay with *Paramecium caudatum*.[9]

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Table I. Products of Oxidation of Methylene-Bridged Hydrocarbons 1a–11a with (A) *n*-BuLi and O_2 and Reduction with $NaBH_4$, (B) *t*-BuOOH, CrO_3, (C) DDQ, HOAc, H_2O, and (D) Pyridine Chlorochromate

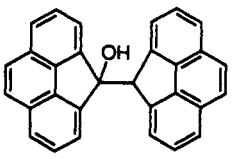
hydrocarbon	A ketone, % yield	A alcohol, % yield	B ketone, % yield	C ketone, % yield	D ketone, % yield
1a	30	96	85	0	
2a	92	83	85		
3a	85	87	76	0	
4a	40	87	87	40	
5a	70	76		45	
6a	68	74			
7a	83	87		0	70
8a	76	82		0	
9a	79	78		59	
10a	0	0		80	
11a	0	0		0	

other hand, similar oxidations of 11*H*-benz[*bc*]aceanthrylene (**5a**), 10*H*-indeno[1,2,7,7a-*bcd*]pyrene (**6a**), 11*H*-dibenz[*bc*,*l*]aceanthrylene (**7a**), 4*H*-fluoreno-[4,4a,4b,5-*abc*]anthracene (**8a**), and 7*H*-dibenzo[*a*,*g*]-fluorene (**9a**) yielded complex mixtures of ketones and ring-oxidized products which were not characterized.

Oxidation of the bridged polyarenes with DDQ in moist acetic acid by the procedure of Lee and Harvey[23] was successful for **4a**, **5a**, **9a**, and **10a**, affording the bridge ketones **4b**, **5b**, **9b**, and **10b** in yields of 40, 45, 59, and 80%, respectively. On the other hand, attempted oxidations of **1a**, **3a**, **7a**, **8a**, and **11a** with this reagent failed to take place, and oxidation of **2a** and **6a** by the same method gave mixtures of products. Oxidation of **7a** with pyridinium chlorochromate[21] furnished the bridged ketone **7b** in 70% yield.

Since all of the foregoing oxidation methods appeared to be limited in their applicability, we sought an alternative method of potentially broader scope. Since the methylene bridge protons are relatively acidic, it seemed likely that oxidation to the alcohol level could be efficiently accomplished by treatment of the bridged hydrocarbon with an alkyllithium reagent, reaction of the resulting anion with O_2, and reduction of the putative hydroperoxide product with $NaBH_4$. In agreement with this expectation, reaction of fluorene with *n*-butyllithium in THF at −78 °C followed by bubbling dry O_2 through the solution of the anion and treatment of the product with $NaBH_4$ furnished smoothly pure 9-fluorenol (83%). Surprisingly, when the borohydride reduction step was omitted, the major product was 9-fluorenone (81%), not the expected hydroperoxide.

Investigation of the oxidation of a larger series of PAHs by these latter procedures showed them to be methods of broad scope for the synthesis of the bridge ketone and alcohol derivatives of methylene-bridged polyarenes. Oxidation of the bridge anion derivatives of **2a**, **3a**, and **5a–9a** with molecular oxygen by the procedure employed for oxidation of the fluorenyl anion took place smoothly to provide good yields of the corresponding ketones (Table I). In the cases of 4*H*-cyclopenta[*def*]phenanthrene and cyclopenta[*def*]chrysene the yields of the corresponding ketones **1b** and **4b** were only moderate (30% and 40%, respectively); in the case of **1a** the major product was identified as the dimeric alcohol 1-hydroxybis(4*H*-cyclopenta[*def*]phenanthrene) (**12**). This structural assignment

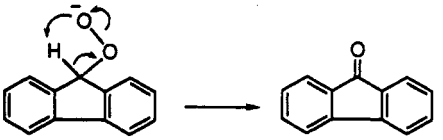


12

was supported by its 300-MHz NMR spectrum which corresponded to that of a 4,4′-dimer of **1a** with all the expected aromatic protons, differing only in the presence of a methylene singlet peak (δ 5.64) shifted upfield from that of **1a** (δ 4.34)[16] and a hydroxyl proton peak which disappeared on addition of D_2O. The corresponding alcohol derivatives of the parent hydrocarbons were not detected as coproducts of any of these reactions. Attempted analogous oxidation of 7*H*-benzanthrene (**10a**) and diphenylmethane (**11a**) by the same method furnished only the recovered starting compounds.

When similar oxidations were conducted with the same series of hydrocarbons but $NaBH_4$ was added to the reaction mixture directly after bubbling O_2 through the solution, the corresponding bridge alcohols were obtained in good yields (Table I). It is notable that the yields of the alcohol products were high even in the cases of hydrocarbons (**1a** and **4a**) for which the yields of ketones were low.

The mechanism for the direct formation of ketone rather than hydroperoxide products from reaction of the bridge anions with molecular oxygen presumably involves intra- or intermolecular abstraction of a proton from the benzylic site of the intermediate by the peroxy anion leading to loss of hydroxide ion and formation of a carbonyl group (eq 1). The remarkable efficiency of this process for the bridge



(1)

methylene anions is probably due to the relative ease of removal of doubly benzylic protons in the intermediates due to their relatively high acidity in comparison with similar intermediates derived from simple benzylic anions. The dimeric alcohol **12** identified as the major product from the reaction of **1a** with *n*-butyllithium and O_2 apparently arises from reaction of the bridge anion with the ketone product **1b**. Analogous dimeric alcohols were not detected as products of other similar syntheses, although small amounts may possibly have gone undetected.

The failure of the attempted oxidation of the benzylic anions derived from compounds **10a** and **11a** is less understandable. Formation of the corresponding anions is evidenced by change of color on addition of the lithium reagent, and other reactions of the 7*H*-benz[*de*]anthracenyl anion have been reported.[24]

In summary, the foregoing synthetic methods provide convenient direct access to the bridge ketone derivatives of methylene-bridged polyarenes through oxidation of the parent hydrocarbons by treatment with an alkyllithium reagent and O_2 and to the related bridge alcohols by reduction of the crude product mixtures with $NaBH_4$. These methods appear to be general in scope, the only exceptions to date being compounds **10a** and **11a**.

Preliminary findings from mutagenesis assays being conducted by Dr. H. R. Glatt, University of Mainz, Germany, indicate that some of the hydroxymethylene-bridged polyarenes synthesized in this investigation may be activated to mutagens by sulfotransferase enzymes.[25] This

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finding supports the hypothesis that hydroxylation on the methylene bridge may play an important role in the mechanism of carcinogenesis of the bridged polyarenes.

Experimental Section

Materials and Methods. Fluorene and diphenylmethane were purchased from the Aldrich Chemical Co. 4*H*-Cyclopenta[*def*]phenanthrene (1) was synthesized by Bachmann's method[28] and by the newer method of Yang and Harvey.[16] 7*H*-Benzo[*c*]fluorene (3), 4*H*-cyclopenta[*def*]chrysene (4), and 7*H*-dibenzo[*a*,*g*]fluorene (9) were synthesized by the enamine alkylation route.[15] 11*H*-Benz[*bc*]aceanthrylene (**5a**),[18] 10*H*-indeno[1,2,7,7a-*bcd*]pyrene (**6a**),[14] 11*H*-dibenz[*bc*,*l*]aceanthrylene (**7a**),[10] and 4*H*-fluoreno[4,4a,4b,5-*abc*]anthracene (**8a**)[10] were synthesized by the methods reported. 7*H*-Benz[*de*]anthracene (**10a**) was prepared from commercially available 7*H*-benzanthrone by reduction with $NaBH_4$ and BF_3-etherate. THF was freshly distilled from Na/benzophenone ketyl, and oxygen was dried over H_2SO_4 and solid KOH.

The ^1H NMR spectra were obtained at 300 MHz in $CDCl_3$. Integrations were consistent with all assignments. The UV spectra were taken on a Perkin-Elmer λ 5 UV/VIS spectrometer, and the IR spectra were obtained as Nujol dispersions.

General Procedure for Oxidation of Hydrocarbons to Ketones. To a solution of fluorene (166 mg, 1.0 mmol) in 5 mL of dry THF at −78 °C under argon was added 0.5 mL of a 2.5 M solution of *n*-BuLi (1.25 mmol) in cyclohexane. The deep yellow colored solution was stirred for 1 h at this temperature, and then dry O_2 was bubbled through the solution for 1 h. The temperature was allowed to rise to rt while O_2 continued to bubble through the solution for an additional 2 h. Reaction was quenched by the addition of water (10 mL) and $CHCl_3$ (10 mL), and stirring was continued for 15 min. The solution was partitioned, and the organic layer was washed with water, dried, and evaporated to dryness. Chromatography of the crude product on a Florisil column on elution with CH_2Cl_2 gave 9*H*-fluoren-9-one (**2b**) (145 mg, 92%), mp 82–84 °C (lit.[29] mp 84–86 °C) identical by NMR analysis with an authentic sample.

4*H*-Cyclopenta[*def*]phenanthren-4-one (1b). Similar oxidation of **1a** (100 mg) gave **1b** (30%), mp 170–71 °C (lit.[19] mp 169.5-70 °C): NMR δ 7.88 (d, 2, $H_{3,5}$; J = 6.5 Hz), 7.83 (d, 2, $H_{1,7}$; J = 8.5 Hz), 7.76 (s, 2, $H_{8,9}$), 7.73 (t, 2, $H_{2,6}$; J = 8.5 Hz). The major product of this reaction was **12** (63 mg, 61%), mp 240–242 °C, which eluted after **1b**: IR (Nujol) 3450 cm^{-1} [OH]; NMR δ 7.65–7.69 (m, 8, $H_{1,3,5,7,1',3',5',7'}$), 7.32 (t, 4, $H_{2,6,2',6'}$; J = 7.5 Hz), 7.10 (br s, 4, $H_{8,9,8',9'}$), 5.64 (s, 1 H_4), 2.93 (s, 1, OH, disappeared with D_2O). Anal. Calcd for $C_{30}H_{18}O$: C, 91.37; H, 4.56. Found: C, 91.18; H, 4.67.

7*H*-Benzo[*c*]fluoren-7-one (3b). Similar oxidation of **3a** gave **3b** (85%), mp 161–62 °C (lit.[22] mp 159–60.5 °C): IR 1730 cm^{-1} [C=O]; NMR δ 8.46 (d, 1, H_1; $J_{1,2}$ = 8.2 Hz), 8.00 (d, 1, H_{11}; $J_{10,11}$ = 7.4 Hz), 7.86 (d, 1, H_8; $J_{8,9}$ = 7.9 Hz), 7.75 (d, 1, H_6; $J_{5,6}$ = 8.1 Hz), 7.71 (d, 1 H_5; $J_{5,6}$ = 8.1 Hz), 7.26–7.06 (m, 5, Ar).

4*H*-Cyclopenta[*def*]chrysen-4-one (4b). Similar oxidation of **4a** gave **4b** (40%), mp 204–05 °C (lit.[17] mp 205–207 °C): IR (Nujol) 1700 cm^{-1} [C=O]; NMR δ 8.54 (d, 1, H_9; $J_{8,9}$ = 8.1 Hz), 8.40 (d, 1, H_{10}; $J_{10,11}$ = 9.0 Hz), 8.20 (s, 1, H_5), 7.60–8.10 (m, 7, Ar); UV λ_{max} (ethanol) 301 nm (ε 15 200), 258 (97 750), 257 (96 100), 227 (86 230), 196 (32 770); MS *m*/*e* 254 (rel. intensity) [M^+ 100].

11*H*-Benz[*bc*]aceanthrylen-11-one (5b). Similar oxidation of **5a** gave **5b** (70%), mp 173–174 °C: IR (Nujol) 1702 cm^{-1} [C=O]; NMR δ 8.80 (d, 1, H_{10}; $J_{9,10}$ = 8.5 Hz), 8.36 (s, 1, H_6), 8.00 (d, 1, H_7; J = 8.5 Hz), 7.48–7.77 (m, 7, Ar); UV λ_{max} (ethanol) 351 nm (ε 6450), 340 (7620), 336 (5790), 260 (62 025), 215 (14 380); HRMS calcd for $C_{19}H_{10}O$ *m*/*z* 254.0732, found *m*/*z* 254.0715.

10*H*-Indeno[1,2,7,7a-*bcd*]pyren-10-one (6b). Similar oxidation of **6a** gave **6b** (68%), mp 230–31 °C: IR (Nujol) 1710 cm^{-1} [C=O]; NMR (DMSO-d_6) δ 8.63 (s, 1, H_{11}), 8.61 (s, 1, H_6), 8.55 (dd, 1, H_7; $J_{7,8}$ = 7.9 Hz, $J_{7,9}$ = 3.1 Hz), 8.50 (d, 1, H_1; $J_{1,2}$ = 8.2 Hz), 8.36 (dd, 1, Ar; J = 7.6, 1.0 Hz), 8.06–8.22 (m, 4, Ar), 7.96 (t, 1, H_2; J = 8.2 Hz); UV λ_{max} (ethanol) 388 nm (ε 3970), 367 (9260), 350 (3970), 250 (39 730); HRMS calcd for $C_{21}H_{10}O$ *m*/*z* 278.0732, found *m*/*z* 278.0750.

11*H*-Dibenzo[*bc*,*l*]aceanthrylen-11-one (7b). Similar oxidation of **7a** gave **7b** (83%), mp 233–34 °C: IR (Nujol) 1700 cm^{-1} [C=O]; NMR δ 10.39 (d, 1, H_{12}; $J_{11,12}$ = 8.5 Hz), 8.35 (s, 1, H_6), 7.63–7.84 (m, 9, Ar), 7.55 (t, 1, H_2; J = 7.2 Hz); UV (ethanol) λ_{max} 288 nm (ε 12580), 243 (3930), 220 (4680), 216 (5355); HRMS calcd for $C_{19}H_{10}O$ *m*/*z* 304.0888, found *m*/*z* 304.0888.

4*H*-Fluoreno[4,4a,4b,5-*abc*]anthracen-4-one (8b). Similar oxidation of **8a** gave **8b** (76%), mp 260–62 °C: IR (Nujol) 1715 cm^{-1} [C=O]; NMR δ 8.87 (s, 2, $H_{8,13}$), 8.40 (d, 1, $H_{1,7}$; J = 8.0 Hz), 8.08 (dd, 2, $H_{3,5}$; $J_{2,3}$ = 8.5 Hz; $J_{1,3}$ = 3.2 Hz), 7.74 (d, 2, $H_{9,12}$; J = 7.0 Hz), 7.59–7.65 (m, 4, $H_{2,6,10,11}$); UV (ethanol) λ_{max} 276 nm (ε 63 690), 268 (43 070), 222 (21 290), 218 (2342); HRMS calcd for $C_{23}H_{12}O$ *m*/*z* 304.0888, found *m*/*z* 304.0900.

7*H*-Dibenzo[*a*,*g*]fluoren-7-one (9b). Similar oxidation of **9a** gave **9b** (79%), mp 162–64 °C (lit.[15] mp 164–05 °C): NMR δ 8.92 (d, 1, H_8; J = 8.5 Hz), 8.41 (d, 1, H_1; J = 8.3 Hz), 8.07 (d, 1, Ar; J = 8.4 Hz), 7.91 (d, 1, Ar; J = 8.4 Hz), 7.78 (d, 1, Ar; J = 7.9 Hz), 7.37–7.76 (m, 7, Ar).

General Procedure for Oxidation of Hydrocarbons to Alcohols. Oxidation of fluorene (166 mg, 1.0 mmol) was carried out as described above except that instead of quenching the reaction by the addition of water, $NaBH_4$ (100 mg) and MeOH (5 mL) were added, and stirring was continued for an additional 1.5 h. The usual workup followed by recrystallization from benzene afforded 9*H*-fluoren-9-ol (**2c**) (151 mg, 83%), mp 157–158 °C (lit.[30] mp 156.5–159 °C): NMR δ 7.63–7.69 (m, 4, $H_{1,4,5,8}$), 7.29–7.45 (m, 4, $H_{2,3,6,7}$), 5.58 (br s, 1, C*H*OH), 2.01 (br s, 1, OH, disappeared with D_2O).

4*H*-Cyclopenta[*def*]phenanthren-4-ol (1c). Similar reaction of **1a** gave **1c** (96%), mp 192.5–193.5 °C ($CHCl_3$–hexane) (lit.[31] mp 190–192 °C): NMR δ 7.79 (d, 2, Ar; J = 8.0 Hz), 7.76 (s, 2, $H_{8,9}$), 7.73 (d, 2, Ar; J = 7.0 Hz), 7.58 (t, 2, $H_{2,6}$; J = 7.5 Hz), 6.20 (d, 1, H_4; J = 8.0 Hz), 2.10 (d, 1, OH; J = 8.0 Hz). Anal. Calcd for $C_{15}H_{10}O$: C, 87.35; H, 4.89. Found: C, 87.25; H, 4.87.

7*H*-Benzo[*c*]fluoren-7-ol (3c). Similar reaction of **3a** gave **3c** (87%), mp 192.5–194.5 °C (benzene): NMR δ 8.61 (d, 1, H_1; $J_{1,2}$ = 8.5 Hz), 8.19 (d, 1, H_{11}; $J_{10,11}$ = 7.8 Hz), 7.90 (d, 1, H_8; $J_{8,9}$ = 9.2 Hz), 7.81 (d, 1, H_6; $J_{5,6}$ = 8.2 Hz), 7.74 (d, 1, H_5; $J_{5,6}$ = 8.2 Hz), 7.68 (d, 1, H_4; $J_{3,4}$ = 8.3 Hz), 7.59 (m, 1 Ar), 7.50 (t, 1, Ar; J = 7.8 Hz), 7.44 (t, 1, Ar; J = 7.3 Hz), 7.32 (t, 1, Ar; J = 7.3 Hz), 5.58 (d, 1, H_7; J = 9.4 Hz), 1.83 (d, 1, OH, disappeared with D_2O; J = 9.4 Hz). Anal. Calcd for $C_{17}H_{12}O$: C, 87.90; H, 5.21. Found: C, 87.62; H, 5.24.

4*H*-Cyclopenta[*def*]chrysen-4-ol (4c). Similar reaction of **4a** gave **4c** (87%), mp 200–201 °C ($CHCl_3$–hexane): NMR δ 8.61 (d, 1, H_9; $J_{8,9}$ = 8.3 Hz), 8.46 (d, 1, H_{10}; $J_{10,11}$ = 8.8 Hz), 8.08 (s, 1, H_5), 8.06 (d, 1, H_{11}; $J_{10,11}$ = 8.8 Hz), 7.98 (d, 1, Ar; J = 7.0 Hz), 7.89 (d, 1, Ar; J = 8.0 Hz), 7.66–7.79 (m, 4, Ar), 6.36 (d, 1, H_4; J = 9.2 Hz), 2.18 (d, 1, OH; J = 9.2 Hz). Anal. Calcd for $C_{19}H_{12}O$: C, 89.03; H, 4.72. Found: C, 88.95; H, 4.76.

11*H*-Benz[*bc*]aceanthrylen-11-ol (5c). Similar reaction of **5a** gave **5c** (76%), mp 187–189 °C (ether–hexane (2:3)): NMR δ 8.51 (d, 1, H_{10}; $J_{9,10}$ = 8.4 Hz), 8.35 (s, 1, H_6), 8.17 (d, 1, H_7; J = 8.4 Hz), 7.54–7.86 (m, 7, Ar), 6.55 (d, 1, H_{11}; J = 8.8 Hz), 2.17 (d, 1, OH, disappeared with D_2O; J = 8.8 Hz). Anal. Calcd for $C_{19}H_{12}O$: C, 89.04; H, 4.72. Found: C, 88.89; H, 4.77.

(25) Mutagenicity was studied in *Salmonella typhimurium* TA98, using external metabolizing systems, and in a genetically-engineered, Chinese hamster V79-derived cell line expressing a rat hydroxysteroid sulfotransferase. The experiments with *Salmonella typhimurium* were carried out following the protocol used previously with 1-hydroxymethylpyrene.[26] The activation of hydroxymethylene-bridged polyarenes required the presence of both cytosol and cofactor for sulfotransferases (3′-phosphoadenosine-5′-phosphosulfate) and was enhanced when Cl^- was present additionally. Mutagenicity in V79-derived cells was studied using previously described protocols.[27] However, instead of cells engineered for the expression of cytochromes P450, analogously constructed lines were used which express rat hydroxysteroid sulfotransferase.

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10*H*-Indeno[1,2,7,7a-*bcd*]pyren-10-ol (6c). Similar reaction of **6a** gave **6c** (74%), mp 240–43 °C (benzene): NMR δ 8.40 (s, 1, H_6), 8.37 (s, 1, H_{11}), 8.34 (dd, 1, H_7; $J_{7,8}$ = 7.8 Hz; $J_{7,9}$ = 3.2 Hz), 8.17 (dd, 1, H_1; $J_{1,2}$ = 8.1 Hz; $J_{1,3}$ = 3.2 Hz), 7.80–8.15 (m, 6, Ar), 6.63 (br s, 1, H_{10}), 2.38 (br s, 1, OH). Anal. Calcd for $C_{21}H_{12}O$: C, 89.98; H, 4.31. Found: C, 89.97; H, 4.34.

11*H*-Dibenz[*bc*,*l*]aceanthrylen-11-ol (7c). Similar reaction of **7a** gave **7c** (87%), mp 276–277 °C ($CHCl_3$): NMR δ 9.51 (d, 1, H_{12}; $J_{11,12}$ = 7.8 Hz), 8.37 (s, 1, H_6), 7.65–7.95 (m, 10, Ar), 6.89 (d, 1, H_{13}; J = 10.5 Hz), 2.26 (d, 1, OH, disappeared with D_2O; J = 10.5 Hz); HRMS calcd for $C_{23}H_{14}O$ m/z 306.1045, found m/z 304.1045.

4*H*-Fluoreno[4,4a,4b,5-*abc*]anthracen-4-ol (8c). Similar reaction of **8a** gave **8c** (82%), mp 270–72 °C: NMR δ 9.03 (s, 2, $H_{8,13}$), 8.34 (dd, 2, $H_{1,7}$; J = 8.0, 3.0 Hz), 8.14 (dd, 2, $H_{7,12}$; J = 9.5, 3.3 Hz), 7.81 (d, 2, $H_{3,5}$; J = 7.0 Hz), 7.59–7.73 (m, 4, Ar), 6.16 (br s, 1, H_4), 2.26 (br s, 1, OH, disappeared with D_2O). Anal. Calcd for $C_{23}H_{14}O$: C, 90.17; H, 4.61. Found: C, 90.09; H, 4.62.

7*H*-Dibenzo[*a*,*g*]fluoren-7-ol (9c). Similar reaction of **9a** gave **9c** (78%), mp 202–04 °C (lit.[32] mp 201–202 °C); NMR δ 8.74 (d, 1, H_8; J = 8.5 Hz), 8.44 (dd, 1, H_1; J = 8.2, 2.0 Hz), 8.40 (d, 1, Ar; J = 8.6 Hz), 7.46–7.98 (m, 9, Ar), 5.91 (d, 1, H_7; J = 10.3 Hz), 1.92 (d, 1, OH, disappeared with D_2O; J = 10.3 Hz).

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Supplementary Material Available: NMR spectral data for compounds **7c** and **5b–8b** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Preparation of Piperidinylpyridines via Selective Reduction of Bipyridines with Nickel–Aluminum Alloy

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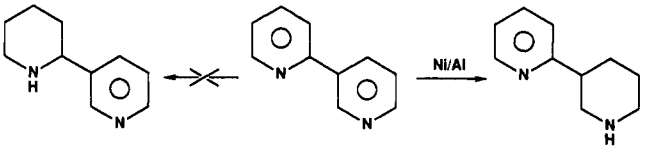
Bipyridines were reduced to piperidinylpyridines in modest yield using nickel–aluminum alloy in potassium hydroxide solution. The reduction was selective, and 3-substituted rings were reduced in preference to 4-substitution in preference to 2-substitution. Thus 2,3-bipyridine gave only 2-(3′-piperidinyl)pyridine, 2,4-bipyridine gave only 2-(4′-piperidinyl)pyridine, and 3,4-bipyridine gave only 4-(3′-piperidinyl)pyridine. The symmetrical 2,2′- and 4,4′-bipyridines also gave the corresponding piperidinylpyridines, but the reduction of 3,3′-bipyridine was too sluggish to be practical. The products were identified using ^{13}C NMR spectroscopy, and the ^{13}C NMR spectra of the starting bipyridines were also recorded.

Substituted piperidines can be prepared using a variety of methods,[1] for example, cyclization reactions[2–4] which include reactions in which the initial product is an unsaturated piperidine (dihydro- or tetrahydropyridine)[5–10] or a piperidone[11–13] which can subsequently be reduced to a piperidine. Other approaches include alkylation of 2-piperideine[14] and reduction of the corresponding pyridines with tin and hydrochloric acid,[15] with sodium in alcohol,[16–19] or electrolytically.[18–20] These methods sometimes produce mixtures of unsaturated piperidines which require further reduction to the piperidine. Piperidinylpyridines have been prepared via cyclization,[10] alkylation of 2-piperideine,[14] reduction with tin and hydrochloric acid,[15] electroreduction,[20] and, in the case of 2-(2-piperidinyl)-pyridine, hydrogenation at high pressure over palladium.[21]

Scheme I



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