perature for 45 min, during which time a yellow precipitate was observed. The reaction was quenched by the addition of 10 mL of dilute HCl, and the solution was extracted with ethyl acetate. The organic layer was washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and recrystallization of the crude product from ethyl acetate-hexane afforded 228 mg (70% yield) of **20** as a yellow solid: mp 169–170 °C; IR (KBr) 3320, 1720, 1705, 1600, 1570, 1530, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (3 H, s), 4.02 (3 H, s), 4.03 (3 H, s), 4.08 (3 H, s), 4.26 (5 H, s), 7.2 (5 H, m), 8.46 (1 H, s), 9.49 (1 H, s); mass spectrum, *m/e* (relative intensity) 540 (1.0), 494 (7.6), 462 (20.7), 435 (76.8), 105 (38.8), 92 (43.1), 77 (100); exact mass calcd for $C_{25}H_{24}N_4O_{10}$ – NO_2 523.1465, found 523.1451; calcd for $C_{25}H_{24}N_4O_{10}$ – NO_2 – CH_3O 463.1380, found 463.1376; calcd for $C_{25}H_{24}N_4O_{10}$ – PhN_2 435.1039, found 435.1028.

Trimethyl 4,5-Dimethoxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (21). A solution of 38.9 mg (0.0720 mmol) of hydrazone **20** in 35 mL of distilled methanol containing 0.2 mL of 5% HCl and 60 mg of 5% Pd/C was stirred at room temperature under an atmosphere of H_2. The theoretical uptake of hydrogen was complete after 2 h, and the catalyst was removed by filtration. The solution was brought to neutrality with $NaHCO_3$ and was extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo yielded 19.0 mg (66%) of triester **21** of sufficient purity for use in the next step. A sample purified by preparative TLC, eluting with ethyl acetate/hexane (1:1), had the following: mp 220 °C; IR (KBr) 1710, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (3 H, s), 4.09 (3 H, s), 4.13 (3 H, s), 4.17 (3 H, s), 4.33 (3 H, s), 7.51 (1 H, d, J = 2.4 Hz), 8.83 (1 H, s), 12.44 (1 H, br s); mass spectrum, *m/e* (relative intensity) 402 (23.7), 387 (90.1), 355 (100), 327 (33.7), 295 (27.9); exact mass calcd for $C_{19}H_{18}N_2O_8$ 402.1036, found 402.1064.

4,5-Dimethoxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic Acid (22). A solution of 32 mg (0.080 mmol) of triester **21** in 10 mL of methanol containing 1 mL of 5% aqueous KOH was refluxed for 15 h. The mixture was cooled, and a fine yellow solid precipitate formed. The solvent was removed in vacuo, and the solid residue was dissolved in a minimum amount of water and acidified with dilute HCl. An orange solid formed which was collected and purified by reverse-phase chromatography on a Waters Seppak C_{18} cartridge, yielding triacid **22**: IR (KBr) 3500–2500, 1710 cm^{-1}; ^1H NMR (D_2O, pH 7) δ 3.85 (3 H, s), 4.02 (3 H, s), 7.09 (1 H, s), 7.94 (1 H, s).

Trimethyl 4,5-Dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (23). To a suspension of 13 mg (0.032 mmol) of **21** in 1 mL of distilled THF were added 23.6 mg (0.191 mmol) of freshly prepared AgO and 10 drops of 6 N HNO_3.[23] After 10 min complete solution had occurred. The reaction was quenched by the addition of water, and the solution was extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the crude orange solid residue was purified by preparative TLC with chloroform–ethanol (95:5), yielding 8 mg (66%) of **23** as a bright orange solid: mp 220 °C dec; IR (KBr) 1725, 1718, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (3 H, s), 4.07 (3 H, s), 4.18 (3 H, s), 7.47 (1 H, s), 8.89 (1 H, s); mass spectrum, *m/e* (relative intensity) 374 (40.7), 372 (7.3), 344 (33.1), 342 (59.6), 314 (41.9), 286 (72.5), 282 (53), 254 (100); UV (MeOH) λ_{max} 372, 250 nm; exact mass calcd for $C_{17}H_{12}N_2O_8$ 372.0594, found 372.0576.

4,5-Dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (Methoxatin, 1). To a solution of 6.1 mg (0.016 mmol) of triester **23** in 15 mL of THF/water (85:15) was added 19.2 mg (0.802 mmol) of LiOH. After 5.5 h the reaction was quenched by the addition of dilute HCl until acidic, causing precipitation of a dark red solid. The solvent was removed in vacuo, and the solid residue was purified by reverse-phase chromatography on a Waters Seppak C_{18} cartridge with water followed by 30% aqueous methanol as the eluant, affording 4.1 mg (75%) of methoxatin (**1**) as a dark red solid: ^1H NMR (D_2O, pH 7) δ 7.15 (1 H, br s), 8.21 (1 H, vbr s); UV (H_2O, pH 7) λ_{max} 332, 268 (sh), 250 nm.

4,5-Dihydro-5-hydroxy-4-oxo-5-(2-oxopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic Acid (2). A solution of 5 mg (0.015 mmol) of methoxatin (**1**) in 4.0 mL of acetone containing 1 mL of 1% aqueous NH_3 was stirred at room temperature for 0.5 h. The reaction was quenched by the addition of dilute HCl, and the mixture was filtered. The solvent was removed in vacuo, yielding 4.0 mg (70%) of aldol product **2** which was homogeneous by TLC and was identical with an authentic sample:[24] ^1H NMR (Me_2SO-d_6) δ 2.01 (3 H, s), 3.59 (1 H, d, J = 17.3 Hz), 4.00 (1 H, d, J = 17.3 Hz), 7.13 (1 H, d, J = 2.2 Hz), 8.41 (1 H, s), 13.40 (1 H, br); UV (H_2O) λ_{max} 360, 318, 252 nm.

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Registry No. **1**, 72909-34-3; **2**, 73030-04-3; **3**, 4463-33-6; **4**, 77869-39-7; **6**, 78891-29-9; **7**, 78891-30-2; **8**, 78891-31-3; **10**, 78891-33-5; **13**, 78891-34-6; **15**, 78891-36-8; **16**, 78891-35-7; **19**, 78891-37-9; **20**, 78891-38-0; **21**, 78891-39-1; **22**, 81770-66-3; **23**, 74447-88-4; pyruvic acid, 127-17-3; sodiomethylacetoacetate, 34284-28-1.

(24) We greatly appreciate the cooperation of Drs. S. A. Salisbury and H. S. Forrest and thank them for a sample and spectra of **2**.

Synthesis of Nuclear Monobromobenz[*a*]anthracenes[1]

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The syntheses of 2-bromo-, 5-bromo-, 10-bromo-, and 11-bromo-7-methylbenz[*a*]anthracenes, of 5-bromo- and 7-bromo-12-methylbenz[*a*]anthracenes, and of 4-bromo- and 9-bromo-7,12-dimethylbenz[*a*]anthracenes are described. Bromination of 12-methylbenz[*a*]anthracene with tetramethylammonium chlorodibromide was superior to bromine in producing pure 7-bromo-12-methylbenz[*a*]anthracene.

The objective of the research to be described is to synthesize all of the nuclear monobromo derivatives of 7-methylbenz[*a*]anthracene (7-MBA, **1**), 12-methylbenz[*a*]anthracene (12-MBA, **2**), and 7,12-dimethylbenz[*a*]anthracene (DMBA, **3**). The hydrocarbons **1**–**3** represent a planar compound, **1**, of high carcinogenic activity,[3] a nonplanar[4] analogue, **2**, of low carcinogenic activity,[3] and a nonplanar[4] compound, **3**, of the highest carcinogenic

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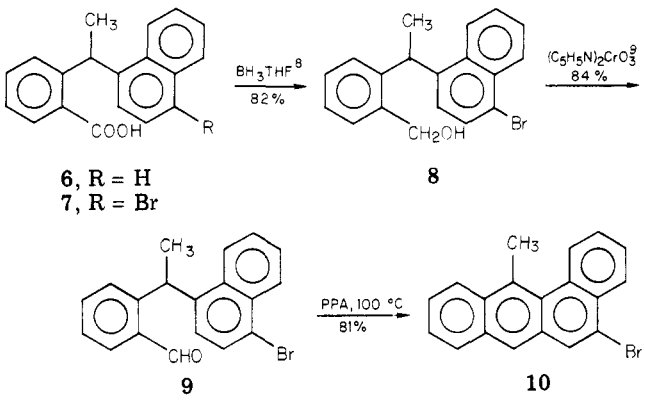
Scheme I



activity[3] of any polycyclic aromatic hydrocarbon so far tested.

The bromo compounds may be converted into the corresponding tritio analogues which will be useful in measuring the rate of electrophilic aromatic substitution at the position involved.[5] This information will be theoretically interesting because the reactivities at each position of a planar hydrocarbon,[3] **1**, and of two nonplanar models, **2**[3] and **3**,[4] will become known. Also, since **1–3** have widely differing carcinogenic activities, clues may be obtained which will help in understanding metabolic changes leading to cancer.

Synthetic Methods

(1) Direct Bromination. The bromination of **1** and **2** with bromine in CS_2[6] and PBR_5[7] has been reported. However, **1** yields 7-(bromomethyl)benz[*a*]anthracene (**4**), and the yield of pure 7-bromo-12-methylbenz[*a*]anthracene (**5**) was not given.[6] We have found that tetramethylammonium chlorodibromide[7] in acetic acid is the preferred reagent with **2** as pure **5** was easily obtained in 80% yield.

(2) Bromination of Intermediates. *o*-[α-(4-Bromo-1-naphthyl)ethyl]benzoic acid[3] (**7**) was converted into 4-bromo-12-methylbenz[*a*]anthracene (**10**) as shown in Scheme I.

In a similar way *o*-[(1-naphthyl)methyl]benzoic acid[25] (**12**) was brominated as described[3] for **7** to yield *o*-[(4-bromo-1-naphthyl)methyl]benzoic acid (**13**), the acid chloride of which reacted with lithium–dimethylcopper reagent[10] to yield *o*-[α-(4-bromo-1-naphthyl)methyl]-acetophenone (**14**). On being heated with PPA,[11] **14** afforded pure 5-bromo-7-methylbenz[*a*]anthracene (**15**) in 80% yield.

4-Bromo-7,12-benz[*a*]anthraquinone[12] was reacted with methyllithium to yield 71% of pure 4-bromo-7,12-dihydroxy-7,12-dimethylbenz[*a*]anthracene[13] (**16**). Reduction of **16** with HCl and $SnCl_2$[14] yielded 71% of pure 4-bromo-7,12-dimethylbenz[*a*]anthracene (**17**).

(3) Replacement of Diazonium Salts. Reaction of 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline[15] with 1-naphthaldehyde followed by hydrolysis yielded 5-methoxy-3-(1-naphthyl)phthalide (**18**, 53% pure) which was reduced in 79% yield to pure 4-methoxy-2-[(1-naphthyl)methyl]benzoic acid (**19**). By reaction with methyllithium in ether, **19** was converted in 79% yield to pure 4-methoxy-2-[(1-naphthyl)methyl]acetophenone (**20**), and this was converted into pure 10-methoxy-7-methylbenz[*a*]anthracene (**21**) in 77% yield by heating with PPA. Demethylation of **21** by sodium ethyl mercaptide essentially as described[17] yielded 89% of 10-hydroxy-7-methylbenz[*a*]anthracene (**22**), which was converted into 10-amino-7-methylbenz[*a*]anthracene (**23**) in 70% yield by heating with $NaHSO_3$ and NH_4OH in dioxane at 180–190 °C in a bomb.[18] By means of a diazotization procedure[19] **23** was converted into pure 10-bromo-7-methylbenz[*a*]-anthracene (**24**) in 30% yield. Because of this low yield and lower yields in the conversion of 11-amino-7-methylbenz[*a*]anthracene (**36**) to 13% of 11-bromo-7-methylbenz[*a*]anthracene (**25**) and of 9-amino-7,12-dimethylbenz[*a*]antrhacene (**37**) to 13% of 9-bromo-7,12-dimethylbenz[*a*]anthracene (**26**), the route via methoxy derivatives was abandoned.

(4) Route via Bromonaphthaldehyde. Bromination of 7-bromo-1-methylnaphthalene[20] followed by treatment with hexamethylenetetramine[21] yielded 85% of 7-bromo-1-naphthaldehyde (**27**). The lithio derivative of 2-phenyl-4,4-dimethyl-2-oxazoline[22] was reacted[16] with **27** to yield 77% of 3-(7-bromo-1-naphthyl)phthalide (**28**). When reduction of **28** with zinc and either KOH or HCOOH media was tried, the bromine was lost. However, use of HI/P in acetic acid[23] afforded pure *o*-[(7-bromo-1-naphthyl)methyl]benzoic acid (**29**) in 83% yield. Reaction of **29** with methyllithium yielded *o*-[(7-bromo-1-naphthyl)methyl]acetophenone (**30**, 76% which was converted[11] into 2-bromo-7-methylbenz[*a*]anthracene (**31**) in 75% yield.

Experimental Section[24]

7-Bromo-12-methylbenz[*a*]anthracene (5). To a solution at 60–70 °C of 1.21 g of **2**[25] in 20 mL of freshly distilled acetic acid was added 1.60 g of powdered tetramethylammonium

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(15) H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975).
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(22) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
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(24) All melting points are uncorrected. All temperatures are in degrees Celsius. The terms "worked up in the usual way" means that an ether–benzene solution of the products was washed with acid and/or alkali, water, and saturated NaCl and filtered through a cone of anhydrous $MgSO_4$. The solvents were either distilled or removed on a rotary evaporator. Most chromatography was done with benzene–hexane mixtures. All new compounds marked with an asterisk gave analyses (Galbraith Laboratories, Knoxville, TN 37921) within ±0.3% of theory and IR, NMR, and mass spectrographic analysis (performed by Mr. Richard Weisenberger, whom we thank) consistent with the assigned structures.
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chlorodibromide[7] during 10 min. After the mixture cooled, 1.55 g of crude product was isolated by usual methods. Recrystallization from benzene–EtOH afforded 1.29 g (80%) of **5**,[26] mp 123–124 °C.[8]

o-[α-(4-Bromo-1-naphthyl)ethyl]benzyl Alcohol (8)*. A stirred solution of 3.55 g of **7**$_3$ in 40 mL of THF at 0 °C was treated with 13 mL of 1 M BH_3/THF solution[8] for 1 h and stirred 1 h at room temperature. After the usual workup the crude product was crystallized from EtOH to yield 2.80 g (82%) of pure **8**, mp 103–104 °C.

o-[α-(4-Bromo-1-naphthyl)ethyl]benzaldehyde (9)*. To a stirred suspension at room temperature of 15 g of bis(pyridine)chromium(VI) oxide[9] in 50 mL of dry CH_2Cl_2 was slowly added a solution of 3.41 g of **8** in 30 mL of CH_2Cl_2. After 1 h the solvent layer was decanted from a black solid which was washed with CH_2Cl_2. The CH_2Cl_2 was removed, and after the usual workup the crude aldehyde was crystallized from EtOH to give 2.85 g (84%) of pure **9**, mp 100–101 °C.

5-Bromo-12-methylbenz[a]anthracene (10)*. After 1.70 g of **9** was worked into 100 g of polyphosphoric acid[11] (approximately $H_6P_4O_{13}$, PPA) for 2 h at about 100 °C, the viscous (at near room temperature) brown mass was stirred into 0.5 L of ice–water. This mixture was extracted with benzene–ether, and the product obtained as usual was chromatographed over neutral alumina by using benzene–hexane (1:3). A picrate (mp 111–112 °C) was prepared, and the picric acid removed by washing with aqueous diethanolamine (picric acid is more soluble in this aqueous basic solution than in NaOH). Recrystallization yielded 1.30 g (81%) of pure pale yellow **10**, mp 105–106 °C.

o-[α-(4-Bromo-1-naphthyl)methyl]benzoic Acid (13)*. A solution of 3.2 g of bromine in 50 mL of $CHCl_3$ was added during 2 h to a refluxing solution of 5.22 g of *o*-[(1-naphthyl)methyl]-benzoic acid, prepared by reduction of 3-(1-naphthyl)phthalide,[27] in 100 mL of $CHCl_3$ in the dark. After 12 h at reflux, the cooled solution was filtered and the solid recrystallized from alcohol to yield 5.20 g (76%) of **13**, mp 185–186 °C.

o-[α-(4-Bromo-1-naphthyl)methyl]acetophenone (14)*. Since the reaction of **13** with methyllithium gave poor yields of **14**, the acid chloride of **13** was prepared from excess $SOCl_2$ in benzene at reflux for 2 h. A solution of the acid chloride in dry ether was added to $(CH_3)_2CuLi$,[10] prepared from 60 mL of 1.1 M CH_3Li and 5.7 g of CuI in ether, at −78 °C. After 15 min at −78 °C the reaction mixture was treated with methanol and worked up as usual to yield 2.50 g (74%) of colorless **14**, mp 104.5–106.0 °C.

5-Bromo-7-methylbenz[a]anthracene (15)*. To 50 g of PPA was added 1.00 g of **14** and the mixture held at 125 °C for 4 h. The brown viscous mixture was added to cold water. After a conventional workup, including chromatography over alumina and picrate recrystallization, there was obtained 0.76 g (80%) of pure colorless **15**, mp 147.5–148.5 °C.

4-Bromo-7,12-dihydro-7,12-dihydroxy-7,12-dimethylbenz-[a]anthracene (16)*. To a stirred solution of 3.37 g of 4-bromo-7,12-benz[a]anthraquinone[12] in 100 mL of benzene and 50 mL of ether was added 20 mL of 1.2 M CH_3Li during 1 h. After being stirred at room temperature for 4 h and at reflux for 6 h, the mixture was worked up as usual, with chromatography of the crude product over alumina, to yield 3.0 g of colorless solid which on crystallization from benzene gave 2.6 g (71%) of **16**,[13] mp 175–176.5 °C.

4-Bromo-7,12-dimethylbenz[a]anthracene (17). To the clear solution obtained by slowly adding 3 mL of concentrated HCl to a suspension of 5.0 g of $SnCl_2$ in 60 mL of ether was added 1.0 g of **16** in portions. After 10 min water was added, and the product was isolated as usual. After chromatography over basic alumina, there was obtained 0.65 g (71%) of pure **17**, mp 150–151 °C (after two crystallizations from benzene–EtOH).

5-Methoxy-3-(1-naphthyl)phthalide (18)*. The reaction of 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline[15] with 1-naphthaldehyde followed by acid hydrolysis[16] of the product afforded in 53% overall yield pure **18**, mp 142.0–143.5 °C (on crystallization from EtOH).

4-Methoxy-2-[(1-naphthyl)methyl]benzoic Acid (19)*. Since the Zn–HCOOH reduction[28] often used[29] here gave poor yield of **19**, the lactone **18** was reduced by refluxing a mixture of 11.6 g of **18**, 45 g of Cu-activated Zn, 250 mL of 20% KOH, and 200 mL of ethylene glycol for 12 h. The usual workup afforded 9.2 g (79%) of **19**, mp 172–173 °C (from EtOH).

4-Methoxy-2-[(1-naphthyl)methyl]acetophenone (20)*. When a stirred solution of 5.84 g of **19** in 150 mL of ether was treated with 30 mL of 1.6 M CH_3Li at 0 °C and then at room temperature for 4 h followed by refluxing for 1 h, there was obtained 5.25 g of colorless solid which was recrystallized from benzene–petroleum ether to yield 4.6 g (79%) of pure **20**, mp 72–73 °C.

10-Methoxy-7-methylbenz[a]anthracene (21)*. Heating a mixture of 5.8 g of **20** and 100 g of PPA on a steam bath followed by a conventional workup yielded 4.95 g of crude **21**, mp 165–169 °C. Recrystallization from benzene–alcohol yielded 4.2 g (77%) of pure **21**, mp 168–169 °C.

10-Hydroxy-7-methylbenz[a]anthracene (22)*. Demethylation of **21** essentially as described[17] yielded 89% of **22**, mp 224.5–226.0 °C (on crystallization from benzene–EtOH).

10-Amino-7-methylbenz[a]anthracene (23)*. A mixture of 1.29 g of **22**, 10 g of $NaHSO_3$, 25 mL of NH_4OH, 15 mL of water, and 25 mL of dioxane was heated in a rocking bomb[18] at 180–190 °C for 12 h. The cooled bomb was opened, and after a conventional workup 1.03 g of yellow solid was obtained. Recrystallization from benzene–petroleum ether yielded 0.90 g (70%) of **23**, mp 156–157 °C.

10-Bromo-7-methylbenz[a]anthracene (24)*. To a stirred suspension at 0–5 °C of 0.51 g of **23** in 30 mL of 20% HCl was added 0.5 g of powdered $NaNO_2$. After 15 min, 1 g of $HgBr_2$ was slowly added.[19] The reddish brown solid was collected, washed with water, and dried in a vacuum desiccator. After the dried complex (1.54 g) was mixed with 0.5 g of powdered NaBr, pyrolysis at 170–180 °C for 30 min and cooling yielded a solid which was crushed and extracted with hot benzene. The crude compound (usual workup) was chromatographed over silica gel to yield 193 mg (30%) pure pale yellow **24**, mp 160–161 °C.

3-Methoxy-2-[(1-naphthyl)methyl]benzoic Acid (32). As in the case of **19**, 11.6 g of 4-methoxy-3-(1-naphthyl)phthalide[30] was reduced to pure **32**: mp 193–194 °C; 80% yield.

3-Methoxy-2-[(1-naphthyl)methyl]acetophenone (33)*. Pure **34** (mp 126–127 °C) was prepared from **32** essentially as described for **20** in 73% yield.

11-Methoxy-7-methylbenz[a]anthracene (34)*. Treatment of 5.0 g of **33** with 100 g of PPA essentially as described for **21** yielded 4.1 g (76%) of pure **34**, mp 154–155 °C (from benzene–EtOH).

11-Hydroxy-7-methylbenz[a]anthracene (35)*. Treatment of 2.72 g of **34** in 25 mL of hot DMF with the sodium ethyl mercaptide[17] from 2 g of ethyl mercaptan and NaH in DMF yielded, after a 2 h reflux, 2.5 g of crude **35**. Recrystallization from benzene–EtOH afforded 2.35 g (91%) of pure colorless **35**, mp 183–184 °C.

11-Amino-7-methylbenz[a]anthracene (36)*. Treatment of 1.29 g of **35** as described[18] for **22** yielded 0.60 g (47%) of yellow **36**, mp 226–227.5 °C (from benzene–petroleum ether).

11-Bromo-7-methylbenz[a]anthracene (25)*. As described above for **24**, 0.514 g of **36** gave 1.42 g of mercuric bromide complex[19] which was heated at 170–180 °C to yield 80 mg (12%) of pure colorless **25**, mp 133–134 °C (from benzene–EtOH).

9-Amino-7,12-dimethylbenz[a]anthracene (37)*. From 1.36 g of 9-hydroxy-7,12-dimethylbenz[a]anthracene[31] was prepared 0.685 g (51%) of pure **37** (mp 163–164.5 °C) as described above for **22**.

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9-Bromo-7,12-dimethylbenz[a]anthracene (26)*. Replacement of the amino group in **37** by bromine essentially as described for **24** gave only 85 mg of **26** (mp 173–175 °C) from 542 mg of **37**.

7-Bromo-1-bromomethylnaphthalene (38)*. Treatment of 11.05 g of 7-bromo-1-methylnaphthalene[20] with 10 g of NBS and 0.5 g of recrystallized benzoyl peroxide in 300 mL of CCl_4 at reflux for 6 h yielded 14.0 g (93%) of pure **38**, mp 108–109 °C (on recrystallization from benzene).

7-Bromo-1-naphthaldehyde (27)*. A suspension of 40 g of hexamethylenetetramine in 50 mL of alcohol and 25 mL of water and 6.0 g of **38** was held at reflux for 6 h. After the mixture cooled, 15 mL of concentrated HCl was added and refluxing continued for 1 h. After the usual workup there was obtained 4.0 g of pure **27**, mp 111–112 °C (on recrystallization from EtOH).

3-(7-Bromo-1-naphthyl)phthalide (28)*. To a stirred solution of 3.5 g of 4,4-dimethyl-2-phenyl-2-oxazoline[22] in 50 mL of dry THF at −20 °C was added 20 mL of *n*-butyllithium (1.2 M) during 15 min. After 0.5 h at −20 °C a solution of 4.7 g of **27** in 20 mL of THF was added in 15 min. After 1 h at −20 °C and 6 h at room temperature, the isolated reaction product was refluxed in 100 mL of EtOH and 5 mL of concentrated H_2SO_4 for 1 h to yield 5.2 g (77%) of **28** (mp 198–200 °C) pure enough for the next step. The analytical sample melted at 200–201 °C. Attempts to use the diethylamide[32] instead of **22** gave very poor results.

***o*-[(7-Bromo-1-napthyl)methyl]benzoic Acid (29)*.** A mixture of 1.5 g of **28**, 2 g of red phosphorus, 50 mL of acetic acid, and 3 mL of hydriodic acid[23] was refluxed for 4 h. The crude brown acid obtained yielded 1.25 g (83%) of colorless **29**, mp 206–707 °C (on crystallization from EtOH). Attempted reductions of **28** with zinc and formic acid or KOH removed bromine to a large degree.

***o*-[(7-Bromo-1-naphthyl)methyl]acetophenone (30)*.** Treatment of a solution of 1.7 g of **29** in ether–benzene with a small excess of 1.2 M CH_3Li at room temperature for 4 h and at reflux for 4 h yielded 1.6 g of crude product after the usual workup. Chromatography over silica gel and recrystallization from benzene–alcohol yielded 1.3 g (76%) of pure **30**, mp 133–134.5 °C.

2-Bromo-7-methylbenz[a]anthracene (31)*. Treatment of 680 mg of **30** with 20 mL of PPA at 110 °C for 2 h yielded crude product which was chromatographed over neutral alumina and recrystallized from benzene–alcohol to yield 480 mg (75%) of pure colorless **31**, mp 130–140 °C.

Registry No. **2**, 2422-79-9; **5**, 81830-40-2; **6**, 35670-68-9; **7**, 35670-69-0; **8**, 81830-41-3; **9**, 81830-42-4; **10**, 81830-43-5; **10** picrate, 81830-44-6; **12**, 69238-67-1; **13**, 81830-45-7; **13** acid chloride, 81830-46-8; **14**, 81830-47-9; **15**, 81830-48-0; **16**, 81830-49-1; **17**, 34698-71-0; **18**, 81830-50-4; **19**, 81830-51-5; **20**, 81830-52-6; **21**, 81830-53-7; **22**, 81830-54-8; **23**, 81830-55-9; **24**, 81830-56-0; **25**, 81830-57-1; **26**, 81830-58-2; **27**, 81830-59-3; **28**, 81830-60-6; **29**, 81846-82-4; **30**, 81830-61-7; **31**, 81830-62-8; **32**, 73453-83-5; **33**, 81830-63-9; **34**, 81830-64-0; **35**, 81830-65-1; **36**, 81830-66-2; **37**, 81830-67-3; **38**, 81830-68-4; 3-(1-naphthyl)phthalide, 81830-69-5; 4-bromo-7,12-benz[a]anthraquinone, 63715-52-6; 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline, 65335-64-0; 1-naphthaldehyde, 66-77-3; 4-methoxy-3-(1-naphthyl)phthalide, 81830-70-8; 9-hydroxy-7,12-dimethylbenz[a]anthracene, 66240-06-0; 7-bromo-1-methylnaphthalene, 33295-35-1; 4,4-dimethyl-2-phenyl-2-oxazoline, 19312-06-2.

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Stereochemistry of 1,4-Addition of Nucleophiles to Ethyl Cyclohexylidenecyanoacetates[1]

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The stereochemistry of 1,4-addition of several nucleophiles such as cyanide, sodium borohydride, and methylmagnesium iodide to three substituted ethyl cyclohexylidenecyanoacetates (**1–3**) has been determined. A higher preference for equatorial attack is observed in these compounds than in related cyclohexanones, which is considerably diminished by the use of aprotic polar solvents. The results do not show any appreciable contribution of product stability control, recently shown to be important for hydride reduction of cyclohexanones, and have been rationalized on the basis of a six-center cyclic transition state in which steric factors play a dominant role. These compounds have also been reduced by catalytic hydrogenation (Pd/C), and, interestingly, with unhindered systems (**1**, **2**), hydrogenation takes place more from the axial side (40–60%) as compared to cyclohexanones.

The stereochemical outcome of reactions of cyclic ketones with metal hydrides and metal alkyls has been intensively investigated and interpreted[2-4] during the last 25 years. A number of concepts[4] such as steric strain control (SSC), product stability control (PSC), torsional strain, and orbital interaction have been advanced to explain the results. Of these, SSC is universally accepted, PSC is severely criticized, and the rest are alternatives to PSC to explain the inherent preference for axial attack on unhindered cyclohexanones. The importance of PSC has, however, been recently revived. Wigfield[4] has rationalized $NaBH_4$ reduction of cyclohexanones by the "steric interactions involved in the product-like transition state" (a concept akin to PSC), and Rei[5] has claimed that the stereochemistry of $LiAlH_4$ reduction of cyclic ketones is "dictated simultaneously and linearly by both SSC and PSC". The C=C bond in ethyl cyclohexylidenecyanoacetates (such as **1**, Chart I) is similar in reactivity to C=O and undergoes comparable 1,4-additions with nucleophiles (including $NaBH_4$), giving products with a $CH(CN)CO_2Et$ side chain of high conformational free energy. If PSC plays a role in these reactions in the manner suggested for cy-

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