organic layer revealed the presence of 100% 2-methylcyclohexanol containing 98.5% of the cis isomer. The results are summarized in Table IV.

Product Isolation from a Preparative Run. In a larger-scale reaction, carried out to test the isolation procedure, 5.6 g of 2-methylcyclohexanone (50 mmol) was added dropwise as a neat liquid to 60 mL of the reagent solution in THF (55 mmol) at 0 °C. The reaction was complete in 1 h. The reaction mixture was then hydrolyzed with 2.5 mL of water for 0.5 h at room temperature. All THF was then pumped off by using an aspirator. Pentane (50 mL) was added to the residue. A white solid precipitated as the mixture was stirred. Fractional distillation of the solution following filtration gave 4.8 g (84% yield) of essentially pure 2-methylcyclohexanol, bp 166-168 °C (753 mm). GC examination revealed the presence of 98.5% cis- and 1.5% trans-2-methylcyclohexanol.

Acknowledgment. The support of this investigation by the United States Army Research Office (Grant ARO DAAG-29-82-K-0047) is gratefully acknowledged.

Synthesis of 4-, 5-, 11-, and 12-(Chloromethyl)benzo[*a*]pyrene[1]

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Received October 21, 1983

The previously unknown title compounds have been synthesized in excellent yields from the ethyl arylacetates **3a-d**. Formylation of **3a-d** allowed the isolation of formyl esters **4a-d** that were cyclized by a novel procedure utilizing dilute solutions (5-10%) of methanesulfonic acid in methylene chloride. The resulting benzo[*a*]pyrene ethyl esters were transformed to the target chloromethyl compound by reduction (LAH) followed by reaction with thionyl chloride. The overall yields obtained from esters **3a-d** ranged from 44% to 66%. These compounds can be used as immediate precursors of benzo[*a*]pyrenylmethyl carbocations which are believed to be relevant in certain carcinogenesis mechanisms.

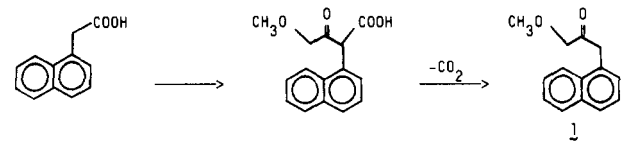
The synthesis of (chloromethyl)benzo[*a*]pyrenes has been an area of interest in our laboratories for several years since they can be used as arylmethyl carbocation precursors.[2-4] In some cases, these ionic species have been considered as possible "ultimate carcinogens".[5-7] These theories are a consequence of the consistent appearance of hydroxymethyl derivatives among the metabolites of many carcinogenic methylated polycyclic aromatic hydrocarbons (PAH).[8,9] For instance, the appearance of 6-(hydroxymethyl)benzo[*a*]pyrene as a metabolite of the potent carcinogens benzo[*a*]pyrene (B[*a*]P) and 6-methyl-B[*a*]P[10] and its role in the promotion of malignant tumors remains to be explained.

Assuming that arylmethyl carbocations are indeed ultimate carcinogens their immediate precursors should show significant tumorigenic activity, as has been shown to be the case in some specific cases.[11] It has also been shown by Dipple and co-workers that the carcinogenicity of a series of bromomethyl PAH's increased along with the stability of their corresponding carbocations.[12]

Since Cl^- has been found to be a good leaving group in the generation of B[*a*]P methyl carbocations and after considering all the findings mentioned above, the synthesis of (chloromethyl)-B[*a*]P in different regions of the B[*a*]P moiety was undertaken. The availability of these compounds, plus the 1-, 6-, and 10-(chloromethyl)-B[*a*]P (also synthesized in our laboratories)[2-4] would make possible a comprehensive study of the kinetics of B[*a*]P methyl carbocation formation. The values obtained can then be compared with both mutagenicity[13] and carcinogenicity data.

In the past, several research groups have shown interest in labeled (^{13}C and ^{14}C)[2,14] functionalized B[*a*]P's. We

Scheme I



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hoped to develop sequences that could be successfully adapted to the production of B[*a*]P's labeled with C-13 at the methylene carbon from available ^{13}C-labeled starting materials such as K*CN and CH_3*COOEt. These labeled compounds can be used to study the selectivity of B[*a*]P methyl carbocations in their reactions with different nucleophiles.[15]

Results and Discussion

Efforts to correlate the electronic density and reactivity of the K region (positions 4, 5 and 11, 12) and the bay

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‡This paper is dedicated to the memory of Prof. Guido Daub who passed away June 4, 1984.

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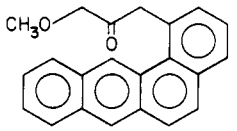
region (positions 10 and 11) of B[a]P with its carcinogenic and mutagenic activity have been of primary concern to some research groups for many years.[16,17] We have developed a single sequence that allows us to functionalize the 4-, 5-, 11-, and 12-positions of B[a]P. Initially a sequence was attempted that involved the conversion of an arylacetic acid to a β-keto acid by generation of the dilithium salt of the starting acid followed by condensation with an appropriate electrophile. When 1-naphthaleneacetic acid was used as a model substrate and methoxyacetyl chloride as the electrophile, the desired β-keto acid was obtained. After decarboxylation, 1-(3-methoxy-2-oxopropanoyl)naphthalene (1) was isolated (Scheme I).

It was then envisioned that if the same sequence were successful using the available benz[a]anthracene-1-acetic acid[18] as the starting material, the obtained 1-(3-methoxy-2-oxopropanoyl)benz[a]anthracene (2) could be cyclized to afford a 11-position functionalized B[a]P that could conceivably be a precursor of 11-(chloromethyl)-B[a]P. Attempts to synthesize 2 failed.



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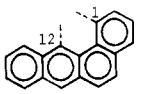
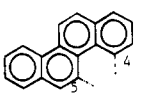
The investigation of another possible sequence was then undertaken. The formylation reaction of synthetically available aryl esters **3a–d** was conceived as an alternative



Series a: Ar = 1-benz[a]anthracenyl



Series b: Ar = 4-chrysenyl

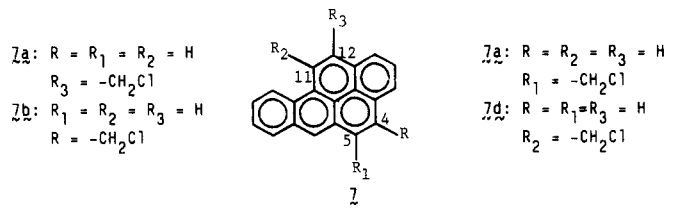
Series d: Ar = 12-benz[a]anthracenyl

Series c: Ar = 5-chrysenyl

because it would provide formyl esters that could be cyclized to provide functionalized B[a]P's. This approach proved successful, allowing the isolation of formyl esters **4a–d**. At this point, a mild cyclizing agent was necessary because when **4a–d** were allowed to react under standard acidic cyclization conditions (polyphosphoric acid, sulphuric acid, HF, etc.) low yields of product and large amounts of polymeric material were observed.

We found that very clean cyclization products **5a–d** could be obtained in high yields if the crude formyl esters **4a–d** were treated with a 5–10% (v/v) solution of methanesulfonic acid (MSA) in CH_2Cl_2 at room temperature for 24 h. The scope of this reagent has been extended to some ketones and epoxy esters.[19]

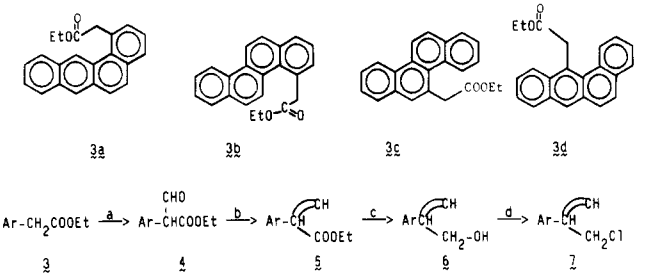
Reduction of esters **5a–d** was accomplished by treatment with lithium aluminum hydride (LAH) in ether. The resulting alcohols **6a–d** were then treated with thionyl chloride in benzene affording the target compounds **7a–d**



7a: R = R_1 = R_2 = H, R_3 = $-CH_2Cl$
7b: R_1 = R_2 = R_3 = H, R = $-CH_2Cl$
7c: R = R_2 = R_3 = H, R_1 = $-CH_2Cl$
7d: R = R_1 = R_3 = H, R_2 = $-CH_2Cl$

7

Scheme II[a]



3a 3b 3c 3d

Ar-CH_2COOEt (3) —a→ Ar-CH(CHO)COOEt (4) —b→ Ar-CH(COOEt) (5) —c→ Ar-CH(CH_2-OH) (6) —d→ Ar-CH(CH_2Cl) (7)

[a] (a) HCOOEt, NaH, benzene, trace EtOH; (b) $MeSO_3H$, CH_2Cl_2; (c) LAH, EtOEt; (d) $SOCl_2$, benzene.

in overall yields that ranged from 44% to 66% from esters **3a–d** (Scheme II).

Experimental Section

Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Ruby Ju of the Department of Chemistry, University of New Mexico.

Both ^1H and ^{13}C NMR spectra were determined on a Varian FT-80A spectrometer. The ^1H and ^{13}C chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si). The ^{13}C chemical shifts were referenced to the solvent peaks: $CDCl_3$ (76.9 ppm), acetone-d_6 (29.8 ppm), or Me_2SO-d_6 (39.6 ppm). Infrared spectra were taken on a Perkin-Elmer 337 grating infrared spectrometer. The spectra were referenced with the 1601 and 1030 cm^{-1} bands of polystyrene. Mass spectra were obtained on a Finnigan 4500 EI CI mass spectrometer, using the solid probe. Medium-pressure chromatography separations were performed by using a Fluid-FMI pump and an Eldex universal fraction collector. Silica Woelm 32-63 (Woelm Pharma) was used as an adsorbent. The following adsorbents were used for column chromatography: silica gel, "Baker Analyzed", reagent (60–200 mesh), aluminum oxide Woelm neutral (activity grade 1). R_f values were measured in Baker Si250F TLC plates.

Ethyl 2-(1-Benz[*a*]anthracenyl)-2-formylacetate (4a). To a mixture of 0.27 g (11.27 mmol) of NaH in 5 mL of dry benzene, 0.89 g (12.03 mmol) of ethyl formate, and one drop of dry ethanol was added a solution of 0.59 g (1.88 mmol) of (**3a**)[17] in 10 mL of dry benzene dropwise over a 35-min period. The resulting greenish mixture was then allowed to stir at room temperature for 24 h after which the color had changed to a light brown. Workup was accomplished by adding 25 mL of 5% aqueous HCl, separating the layers, washing the organic layer with water (3×25 mL), and drying ($MgSO_4$). The solvent was removed under reduced pressure to afford a light brown oil, which was triturated with 95% ethanol to give 0.44 g (68% yield) of light orange solid, mp 122–125 °C. An analytical sample, mp 126–128 °C, was obtained as beige crystals by recrystallization from 95% ethanol: $FeCl_3$ test positive (dark blue); TLC R_f 0.55 (toluene); IR (Nujol) 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 12.17 (d, 1 H, =CHO*H*, *J* = 12.5 Hz), 9.31–7.42, (m, 12H Ar *H* + =C*H*OH), 3.43 (q, 2 H, *J* = 7.1 Hz), 0.40 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.46, 161.34, 131.70, 131.13, 128.72, 128.49, 127.47, 127.32, 126.87, 126.19, 126.10, 125.87, 125.50, 125.34, 125.22, 125.11, 112.41, 60.30, 12.97. Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.49; H, 5.45.

Ethyl Benzo[*a*]pyrene-12-carboxylate (5a). A solution of 0.46 g (1.34 mmol) of **4a** in 44 mL of 10% MSA in CH_2Cl_2 (v/v) was allowed to stir for 45 min at room temperature under a N_2 atmosphere. The resulting deep red solution was then added to 20 mL of ice water, affording a two-phase mixture that was extracted with CH_2Cl_2 (2 × 25 mL), 5% aqueous $NaHCO_3$ (2 × 15 mL), and water (1 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent removed under reduced pressure to give a brown oil that was passed through a short column of neutral alumina affording 0.4 g of oily solid that was triturated with 95% ethanol to afford 0.34 g (77% yield) of bright yellow crystals, mp 109–110 °C. An analytical sample, mp 111–112.5 °C, was obtained by recrystallization from 95% ethanol: TLC R_f 0.50 (toluene); IR (KBr) 1715 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 9.53–7.16 (m, 11 H), 4.38 (q, 2 H, *J* = 7.1 Hz), 1.24

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(t, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.16; H, 5.16.

12-(Hydroxymethyl)benzo[a]pyrene (6a). To a suspension of 47 mg (1.24 mmol) of LAH in 35 mL of dry ether was added a solution of 0.20 g (0.62 mmol) of **5a**, in 35 mL of dry ether, dropwise, over a 1-h period. The reaction mixture was then allowed to react while refluxing for 3.5 h. After allowing the mixture to cool to room temperature, 5 mL of 95% ethanol was slowly added followed by 25 mL of 5% HCl solution. This two-phase mixture was separated, and the organic phase was washed with water (1×25 mL), 5% HCl solution (1×25 mL), and saturated NaCl solution (1×25 mL). After drying ($MgSO_4$), filtering, and evaporating the solvent under reduced pressure, 0.165 g (100% yield) of yellow crystals was obtained, mp 184–185 °C. An analytical sample, mp 186–187 °C, was obtained by recrystallization from benzene: TLC R_f 0.08 (toluene), 0.35 (20% ethyl acetate in toluene); IR (KBr) 3500–3150 cm^{-1} (COH); ^1H NMR (Me_2SO-d_6) δ 9.13–7.88 (m, 11 H), 5.59 (s, 1 H), 5.23 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 137.56, 131.35, 131.03, 129.16, 128.65, 127.94, 127.76, 126.42, 126.29, 125.03, 124.81, 124.39, 121.91, 119.93, 62.05. Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.47; H, 5.10.

12-(Chloromethyl)benzo[a]pyrene (7a). A mixture of 50 mg (0.18 mmol) of **6a** and 50 mg (0.42 mmol) of thionyl chloride in 5 mL of dry benzene was refluxed for 30 min. The resulting golden solution was allowed to cool down to room temperature. The solvent and excess $SOCl_2$ were evaporated under reduced pressure. Benzene (2.5 mL) was added to the resulting solid and then removed under reduced pressure. This process was repeated once more affording 49 mg (91% yield) of bright yellow solid, mp 189–191 °C dec. An analytical sample, mp 193–195 °C, was obtained by recrystallization from benzene: TLC R_f 0.56 (30% cyclohexane in benzene), 0.79 (10% ethyl acetate in toluene). Anal. Calcd for $C_{21}H_{13}Cl$: C, 83.86; H, 4.36. Found: C, 83.57; H, 4.66. MS, m/e (relative intensity) 302 (M^+ + 2, 16.63), 301 (M^+ + 1, 10.74), 300 (M^+, 50.67), 265 (100).

Ethyl Benzo[a]pyrene-4-carboxylate (5b). As described for the synthesis of **4a**, 0.35 g (1.11 mmol) of ethyl 4-chrysene acetate (**3b**)[18] in 6 mL of dry benzene was allowed to react with a benzene suspension of NaH (6.67 mmol), ethyl formate (7.10 mmol), and a drop of dry ethanol. Usual workup afforded 0.40 g of orange oil that was crystallized upon trituration with 95% ethanol to give after filtering and drying 0.28 g (74% yield) of ethyl 2-(4-chrysenyl)-2-formylacetate (**4b**), as an unstable light orange powder, mp 123–127 °C, which was directly carried on to the next step: $FeCl_3$ test, + (dark blue); TLC of **4b** R_f 0.54 (toluene); ^{13}C NMR of **4b** ($CDCl_3$) δ 171.71, 161.26, 131.88, 131.50, 129.10, 128.17, 128.03, 127.79, 127.50, 126.51, 126.28, 126.04, 125.78, 125.66, 125.54, 124.35, 123.17, 121.28, 112.10, 60.42, 13.10.

As described for the synthesis of **5a**, 0.21 g (0.61 mmol) of **4b** in 20 mL of 5% MSA solution in CH_2Cl_2 (v/v) was allowed to react for 24 h. Workup provided a light brown solid that was purified by recrystallization from 95% ethanol to afford 0.16 g (66% overall yield from **3b**) of **5b** as a light yellow solid, mp 102–105 °C. An analytical sample, mp 105–106 °C, was obtained by recrystallizing twice from 95% ethanol: TLC R_f 0.52 (toluene); IR (KBr) 1701 cm^{-1} (C=O); ^1H NMR (acetone-d_6) δ 8.93–7.76 (m, 11 H), 4.54 (q, 2 H, J = 7.2 Hz), 1.51 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (acetone-d_6) δ 167.04, 134.10, 129.44, 128.44, 128.35, 127.57, 127.39, 126.57, 124.34, 123.40, 121.95, 61.12, 14.12. Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 84.98; H, 5.20.

4-(Hydroxymethyl)benzo[a]pyrene (6b). As described for the synthesis of **6a**, 80 mg (0.25 mmol) of **5b** was allowed to react with an ether suspension of LAH at room temperature for 3 h. Workup provided 70 mg (100% yield) of bright yellow crystals, mp 213–215 °C. An analytical sample, mp 214–215 °C, was obtained by recrystallization from benzene: TLC R_f 0.08 (toluene), 0.50 (25% ethyl acetate in toluene); IR (KBr) 3400–3120 cm^{-1} (COH); ^1H NMR (Me_2SO-d_6) δ 9.20–7.69 (m, 11 H), 5.45 (t, 1 H, J = 5.6 Hz), 5.10 (d, 2 H, J = 5.6 Hz); ^{13}C NMR (Me_2SO-d_6) δ 137.28, 130.73, 129.58, 129.01, 218.24, 127.25, 126.81, 126.41, 126.31, 125.27, 124.84, 122.89, 121.99, 120.80, 61.50. Anal. Calcd for $C_{21}H_{14}O$ C, 89.34; H, 5.00. Found: C, 89.09; H, 5.29.

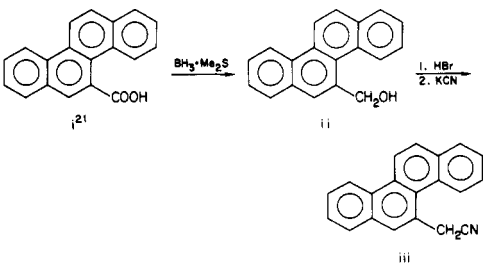
4-(Chloromethyl)benzo[a]pyrene (7b). As described for the synthesis of **7a**, 46 mg (0.16 mmol) of **6b** in 5 mL of dry benzene was allowed to react with 46 mg (0.38 mmol) of thionyl chloride. Workup afforded 49 mg (100% yield) of **7b**, mp 195–198 °C dec. An analytical sample, mp 197–198 °C dec, was prepared by recrystallization from benzene: TLC R_f 0.43 (30% cyclohexane in benzene), 0.78 (10% ethyl acetate in toluene). Anal. Calcd for $C_{21}H_{13}Cl$: C, 83.86; H, 4.36. Found: C, 83.94, H, 4.42. MS, m/e (relative intensity) 302 (M^+ + 2, 21.54), 301 (M^+ + 1, 14.32), 300 (M^+, 61.58), 265 (100).

Ethyl 5-Chryseneacetate (3c). A suspension of 0.286 g (1.07 mmol) of 5-(cyanomethyl)chrysene[20] in a solution of KOH (0.50 g) in ethylene glycol (35 mL) and water (20 mL) was refluxed for 72 h in a 125-mL Teflon Erlenmeyer flask. The reaction mixture was cooled to room temperature, and the resulting precipitate was filtered. Acidification of the filtrate by slow addition of concentrated HCl precipitated a light yellow solid, which was filtered, washed with water, and dried under reduced pressure to afford 0.262 g of the corresponding carboxylic acid as a yellow solid. A solution of this crude material in 20 mL of dry benzene, 4 mL of absolute ethanol, and 0.8 mL of concentrated H_2SO_4 was refluxed overnight in a ground-glass Erlemeyer flask equipped with a Dean-Stark trap and a condenser. The resulting yellow solution was allowed to cool to room temperature and diluted by addition of 25 mL of ether. This solution was then washed with water (1 × 25 mL), 5% NaOH solution (2 × 25 mL), and water (1 × 25 mL). The organic layer was then dried ($MgSO_4$) and filtered, and the solvent was evaporated under reduced pressure to afford a beige solid that recrystallized from 95% ethanol to afford 0.22 g (70% yield over two steps) of beige plates, mp 133–135 °C: TLC R_f 0.58 (10% ethyl acetate in toluene); IR (Nujol) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 872–751 (m, 11 H), 4.48 (s, 2 H), 4.18 (q, 2 H, J = 7.1 Hz), 1.16 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.86, 131.66, 128.56, 127.78, 127.55, 126.69, 126.51, 125.78, 125.64, 125.48, 125.34, 123.01, 122.90, 121.49, 121.36, 60.91, 44.20, 14.00. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.89; H, 5.66.

Ethyl Benzo[a]pyrene-5-carboxylate (5c). As described for the synthesis of **5a**, 0.42 g (134 mmol) of **3c**, in dry benzene, was allowed to react with a benzene suspension of sodium hydride (0.26 g, 10.83 mmol), ethyl formate (0.69 g, 9.32 mmol), and a drop of ethanol. Workup provided an orange oil that was crystallized upon trituration with 95% ethanol to afford 0.42 g of **4c** as an unstable light orange solid, mp 142–146 °C, that was taken directly to the next step: TLC R_f 0.50 (toluene), ^1H NMR of **4c** ($CDCl_3$) δ 12.08 (d, 1 H, J = 12.6 Hz), 8.86–7.30 (m, 11 H), 3.73 (q, 2 H, J = 7.1 Hz), 0.38 (t, 3 H, J = 7.1 Hz); ^{13}C NMR of **4c** ($CDCl_3$) δ 171.34, 160.79, 131.50, 131.35, 128.31, 128.15, 128.00, 127.87, 127.62, 127.49, 126.70, 126.43, 126.31, 126.06, 125.64, 125.51, 122.98, 121.17, 113.35, 60.25, 12.94.

As described for the synthesis of **5a**, 0.35 g (1.08 mmol) of ethyl 5-chrysene-2-formylacetate (**4c**) in 20 mL of a 5% MSA in CH_2Cl_2 (v/v) was allowed to react for 24 h. Workup provided a yellow semisolid that was purified by means of a short alumina column using toluene as elutant. Recrystallization of the resulting yellow solid using 95% ethanol afforded 0.23 (59% yield) of bright yellow solid, mp 104–106 °C. An analytical sample, mp 105–106 °C, was obtained by an additional recrystallization from 95% ethanol: TLC R_f 0.50 (toluene); IR (KBr) 1710 cm^{-1} (C=O). ^1H NMR (acetone-d_6) δ 9.57–7.20 (m, 11 H), 4.57 (q, 2 H, J = 7.0 Hz), 1.54

(20) Obtained by the following sequence:



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(21) Obtained in 78% yield from 2-(1-naphthyl)-3-(2-aminophenyl)-propionic acid[22] by a modification of Foldeak's[23] procedure.

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(t, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.10; H, 5.18.

5-(Hydroxymethyl)benzo[*a*]pyrene (6c). As described for the synthesis of **6a**, 0.19 g (0.59 mmol) of **5c** was allowed to react with an ethereal suspension of LAH. Workup provided 0.17 g (100% yield) of light yellow solid, mp 196–199 °C. An analytical sample, mp 203–204.5 °C, was obtained by recrystallization from benzene: TLC R_f 0.21 (10% ethyl acetate in toluene); IR (KBr) 3400–3050 cm^{-1} (COH); ^{13}C NMR (Me_2SO-d_6) 137.34, 130.87, 129.35, 128.46, 127.86, 127.73, 127.62, 127.28, 126.60, 125.59, 125.31, 124.93, 123.32, 123.19, 122.56, 121.23, 61.68. ^1H NMR (Me_2SO-d_6) δ 9.09–7.23 (m, 11 H), 5.52 (s, 1 H), 5.14 (s, 2 H). Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.09; H, 5.19.

5-(Chloromethyl)benzo[*a*]pyrene (7c). As described for the synthesis of **7a**, 47 mg (.17 mmol) of **6c**, in 5 mL of dry benzene, was allowed to react with 47 mg (0.39 mmol) of $SOCl_2$. Workup afforded 48 mg (100% yield) of bright yellow solid, mp 182–184 °C dec. An analytical sample, mp 184–185 °C dec, was obtained by recrystallization from benzene: TLC R_f 0.45 (30% cyclohexane in benzene), 0.77 (10% ethyl acetate in toluene). Anal. Calcd for $C_{21}H_{13}Cl$: C, 83.83; H, 4.36. Found: C, 83.68; H, 4.61. MS, m/e (relative intensity) 302 (M^+ + 2, 19.83), 301 (M^+ + 1, 13.17), 300 (M^+, 57.08), 265 (100).

Ethyl Benz[*a*]anthracen-12-ylacetate (3d). As described for the synthesis of **3c** 0.520 g (1.95 mmol) of 12-cyanomethylbenz[a]anthracene[24] was allowed to react with a solution of KOH (0.88g) in ethylene glycol (70 mL) and water (11 mL). After workup and subsequent hydrolysis of the collected amide, 0.36 g of carboxylic acid was obtained. Esterification of the crude acid was accomplished as described for the synthesis of **3c**. After workup, a brown oil was obtained. Purification was possible by passing the sample through an MPLC system, using an analytical column (0.9 × 100 cm) and using 10% hexanes in toluene as elutant. After the proper fractions were collected and the solvent evaporated, 0.30 g (58% yield over two steps) of light yellow oil was obtained: TLC R_f 0.57 (10% ethyl acetate in toluene); IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.63–7.35 (m, 11 H), 4.84 (s, 2 H), 4.35 (q, 2 H, J = 7.1 Hz), 1.42 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.29, 133.62, 132.43, 131.34, 131.00, 130.00, 128.28, 128.17, 127.99, 127.59, 127.00, 126.69, 126.44, 126.21, 125.23, 125.10, 124.11, 60.92, 38.94, 14.02. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.16, H, 5.83.

Ethyl Benzo[*a*]pyrene-11-carboxylate (5d). A solution of 0.14 g (0.44 mmol) of **4d** in 3 mL of dry benzene was added dropwise to a mixture of 81 mg (3.37 mmol) of NaH, 0.21 g (2.83 mmol) of ethyl formate, and one drop of dry ethanol in 3 mL of dry benzene. The resulting suspension was allowed to stir at room temperature until the bubbling ceased (18 h). The residual starting material detected by TLC was allowed to react by warming the mixture to ~40 °C and stirring at that temperature for 6 h. Workup as described for previous formylations provided 0.16 g of brown oil that was cyclized by allowing it to react with 15 mL of 5% MSA in CH_2Cl_2 as described for the synthesis of **7a**. Workup gave a brown oil that was purified by means of a silica gel column (2 × 8 in) using 10% hexanes in toluene as the eluant, providing 70 mg (59% yield over two steps) of yellow solid, mp 122–125 °C. An analytical sample, mp 128–130 °C, was obtained by recrystallization from 95% ethanol: TLC R_f 0.51 (toluene); IR (Nujol) 1703 cm^{-1} (C=O); ^1H NMR δ 8.71–7.85 (m, 11 H), 4.57 (q, 2 H, J = 7.1 Hz), 1.38 (t, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 84.93; H, 5.23.

11-(Hydroxymethyl)benzo[*a*]pyrene (6d). As described for the synthesis of **6a**, 40 mg (0.12 mmol) of **5d** was allowed to react with an ethereal suspension of LAH. Workup provided 35 mg (100% yield) of bright yellow crystals, mp 191–194 °C. An analytical sample, mp 193–195 °C, was obtained by recrystallization from benzene: TLC R_f 0.48 (25% ethyl acetate in toluene); ^1H NMR (Me_2SO-d_6) δ 9.47–8.03 (m, 11 H), 5.85 (t, 1 H, J = 5.5 Hz), 5.34 (d, 2 H, J = 5.5 Hz); ^{13}C NMR (Me_2SO-d_6) δ 137.91, 131.73, 131.01, 130.32, 129.69, 129.44, 129.44, 128.85, 128.38, 127.91, 127.28, 126.50, 126.01, 125.82, 125.66, 125.27, 124.81, 65.27. Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found: C, 89.10; H, 5.13.

11-(Chloromethyl)benzo[*a*]pyrene (7d). As described for the synthesis of **7a**, 25 mg (0.09 mmol) of **6d** in 2.5 mL of dry benzene was allowed to react with 25 mg (0.21 mmol) of $SOCl_2$. Workup afforded 20 mg (75% yield) of bright yellow solid, mp 180–182 °C dec. An analytical sample, mp 183–185 °C dec, was obtained by recrystallization from benzene: TLC R_f 0.47 (30% cyclohexane in benzene), 0.74 (10% ethyl acetate in toluene). Anal. Calcd for $C_{21}H_{13}Cl$: C, 83.86; H, 4.36. Found: C, 83.60; H, 4.36. MS, m/e (relative intensity) 302 (M^+ + 2, 29.04), 301 (M^+ + 1, 19.04), 300 (M^+, 84.66), 265 (95.30).

Registry No. **3a**, 67194-44-9; **3b**, 67194-43-8; **3c**, 94500-47-7; **3d**, 94500-50-2; **4a**, 94500-41-1; **4b**, 94500-45-5; **4c**, 94500-48-8; **4d**, 94500-52-4; **5a**, 94500-42-2; **5b**, 94500-55-7; **5c**, 94500-49-9; **5d**, 94500-51-3; **6a**, 94500-43-3; **6b**, 86073-01-0; **6c**, 29852-45-7; **6d**, 94500-53-5; **7a**, 94500-44-4; **7b**, 94500-46-6; **7c**, 29852-26-4; **7d**, 94500-54-6; i, 68723-48-8; ii, 67411-86-3; 5-(cyanomethyl)chrysene, 85083-62-1; 12-(cyanomethyl)benz[a]anthracene, 78533-31-0; ethyl formate, 109-94-4.

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Selective Cathodic Birch Reductions

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The electroreduction of some difficult to reduce substrates was investigated by using aqueous tetrahydrofuran, tetrabutylammonium (TBA^+) electrolyte, and mercury cathodes. The reduction products formed in high yields and the current efficiencies were good. Benzene, anisole, 1,2,3,4-tetrahydro-6-methoxynaphthalene and β-estradiol 3-methyl ether reactions were carried out with constant current at room temperature and were found to be more selective than the corresponding alkali metal–ammonia reductions. Selective reduction of the carbonyl function of estrone methyl ether was achieved while the aromatic ring remained intact. The aqueous THF medium did not affect base-sensitive molecules and a reduction product from 17-α-ethynylestradiol 3-methyl ether could be obtained without loss of the ethynyl group. Most of the compounds studied did not exhibit polarographic waves. A reduction product of TBA^+ was observed by cyclic voltammetry and it is proposed that TBA "amalgam" may participate as a mediator in the reduction of the organic substrates.

In spite of of the recognized utility of Birch reductions,[1-3] the techniques have remained basically unchanged since the early investigations. Alkali-metal reductants, liquid ammonia or simple amine solvents, and some proton source

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