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Supplementary Material Available: Details of purification and characterization of hydroxy silanes, alkenes, and other products shown in Table I (8 pages). Ordering information given on any current masthead page.

Synthesis of Cholanthrene and 6-Methylcholanthrene, Biologically Active Analogues of the Potent Carcinogen 3-Methylcholanthrene

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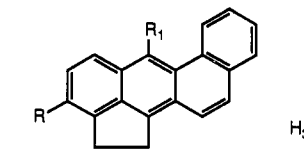
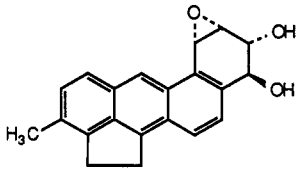
Although the biogenetic origin of 3-methylcholanthrene (3-MC) (**1a**) from steroids postulated by early investigators[1,2] has not been supported by subsequent studies,[3] 3-MC retains an important role in carcinogenesis research because of its exceptional carcinogenic potency.



1a: R = CH_3; R_1 = H. **b**: R = H; R_1 = CH_3. **c**: R = R_1 = H. **d**: R = R_1 = CH_3.

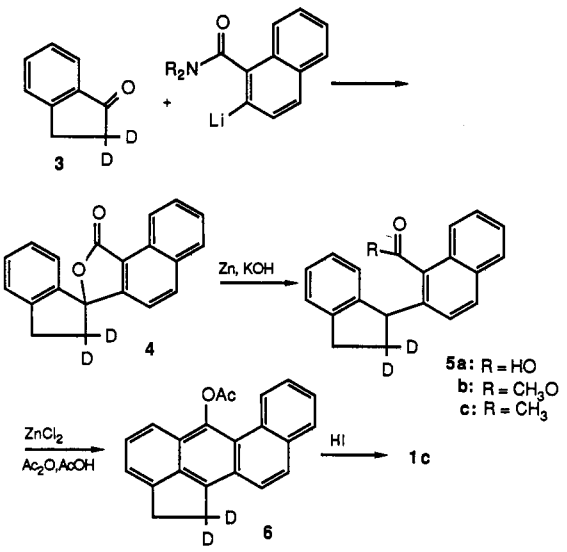


2

Bay region diol epoxide metabolites have been implicated recently as the active forms of other carcinogenic PAHs.[4,5] These intermediates bind covalently to DNA, leading to mutation, and ultimately to tumor induction. Investigations of the metabolic activation of 3-MC indicate that the bay region diol epoxide derivative, **2**,[6] accounts for only a small percentage of the oxidized metabolites of 3-MC which bind to nucleic acids in cells.[7] The majority of the 3-MC–DNA adducts arise from triol epoxides containing a third hydroxyl group in the 1-, 2-, and/or 3-positions.[7-9] In view of the complexity of the metabolism of 3-MC, we have initiated investigations on the parent hydrocarbon, cholanthrene (**1c**), which lacks a methyl group.

We now report convenient syntheses of **1c** and 6-methylcholanthrene (**1b**). The latter is predicted to be a more potent carcinogen than **1a** or **1c** because of the presence of a methyl group in the bay region.[10]

Scheme I



Results and Discussion

Synthesis of cholanthrene (**1c**) was accomplished via the reaction sequence in Scheme I which is based on the general method for the annelation of polycyclic ring systems previously reported.[11] This synthetic approach takes advantage of the availability of *o*-lithioarylamides from the ortho-metalation of *N,N*-diethylarylamides with alkyllithium–amine reagents by the method of Beak.[12] Condensation of 2,2-dideuterioindan-1-one (**3**) with 2-lithio-*N,N*-diethyl-1-naphthamide in ether at −78 °C furnished the addition product which on treatment with *p*-toluenesulfonic acid in refluxing benzene yielded the lactone **4**. The dideuterio analogue of indanone was employed to inhibit enolization of the carbonyl function, known to be a significant competing pathway in reactions of this type.[13] Reduction of **4** with zinc and alkali by the usual method[11] furnished the free acid **5a** in 70% yield. Reduction of **4** with zinc and acetic acid was more satisfactory, affording **5a** in essentially quantitative yield. Treatment of **5a** with $ZnCl_2$ in acetic acid–acetic anhydride yielded 6-acetoxycholanthrene (**6**). Removal of the 6-acetoxy group of **6** took place smoothly on reduction with hydriodic acid in the presence of hypophosphorus acid in refluxing acetic acid to yield cholanthrene.[11,14] Reaction time was short (90 s) to avoid further reduction of **1c** in the meso ring 6,12b-positions.[14] The deuterium isotope is lost in this step through HI-catalyzed exchange of the benzylic hydrogens.

6-Methylcholanthrene was readily synthesized by appropriate modification of the reaction sequence in Scheme I. For this purpose the carboxylic acid intermediate **5a** was esterified by treatment with KOH in hexamethylphosphoramide and methyl iodide to yield the methyl ester **5b**. The latter was converted to the corresponding methyl ketone **5c** by reaction with methyllithium in hexamethylphosphoramide and cyclized in liquid HF to yield the 1,1-dideuterio derivative of **1b**. Exchange of the deuterium atoms for hydrogen was effected by heating **1b** with *p*-toluenesulfonic acid in refluxing benzene.

The syntheses of **1b** and **1c** provide convenient methods for the preparation of these hydrocarbons on any desired

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scale. Several syntheses of cholanthrene were reported in the older literature.[15,16] However, the method now reported requires fewer synthetic steps and provides a higher overall yield. It, therefore, can be recommended as the method of choice. Synthesis of 6-methylcholanthrene has not previously been described.

Biological Activity. Preliminary investigations of the tumorigenicity of **1b** and **1c** confirm that both hydrocarbons are potent carcinogens on mouse skin. Cholanthrene exhibited activity approximately equivalent to that of 3-MC. This finding agrees with an early report which employed a different system.[17] 6-Methylcholanthrene exhibited higher activity at similar dosage in agreement with the previously proposed generalization that methyl groups in nonbenzo bay region positions enhance carcinogenicity.[10] Full details of the biologial studies will be reported in due course.

Experimental Section

Materials and Methods. The NMR spectra were recorded on a Varian EM-360 and/or The University of Chicago 500-MHz spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. Melting points are uncorrected. All new compounds gave satisfactory analyses for C and H within ±0.3% and/or mass spectra consistent with the assigned structures. *N,N*-Diethyl-1-naphthamide was prepared as previously described.[11] THF was distilled from $LiAlH_4$ immediately before use, and the *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was distilled from KOH. 1-Indanone and *sec*-butyllithium solution in hexane were purchased from the Aldrich Chemical Company.

2,2-Dideuterio-1-indanone (3). A mixture of 1-indanone (5 g) and K_2CO_3 (0.5 g) in 50 mL of benzene at reflux was heated to reflux; then CH_3OD (5 mL) was added and heating was continued for 1 h. The benzene–methanol azeotrope was then distilled out until the vapor temperature reached 78 °C. A fresh 5-mL portion of CH_3OD was added, and the procedure was repeated twice more. Conventional workup gave **3**, the proton NMR spectrum of which differed from that of 1-indanone by the absence of the methylene protons at δ 2.5–3.2 and the presence of a broad singlet at δ 8.30 assigned to the benzylic protons.

Synthesis of Lactone 4. A solution of *sec*-butyllithium (44 mmol) was added to a solution of *N,N*-diethyl-1-naphthalamide (4.0 g, 17.6 mmol) and TMEDA (5.1 g, 44 mmol) in diethyl ether (150 mL) under argon at −78 °C. After 1 h, to this solution was added a solution of **3** (5.9 g, 44 mmol) in THF (50 mL). The solution was stirred at ambient temperature overnight. The usual workup gave the crude product which was dissolved in benzene along with 10% by weight of *p*-toluenesulfonic acid. The solution was heated at reflux overnight and then passed through a column of silica gel to afford the lactone **4**: 2.55 g (50%); mp 167–168 °C (benzene–hexane); NMR δ 3.3 (d of d, 2, CH_2, J_{gem} = 16 Hz), 6.7–9.1 (m, 10, Ar); mass spectrum, *m/e* 288 (M^+), 244 ($M^+ - CO_2$).

Reduction of 4 to the Acid 5a. (1) Zn and KOH. A solution of the lactone **4** (1.35 g, 4.7 mmol) in pyridine (20 mL) was added to 15.3 g of zinc dust (activated by treatment with 1.5 g of $CuSO_4 \cdot 5H_2O$ in 15 mL of water) suspended in a solution of 10% KOH (200 mL). The mixture was stirred at reflux overnight, then cooled, and filtered, and the filtrate was worked up to afford the free acid **5a**: 0.95 g (70%) mp 107–109 °C; NMR δ 3.07 (d of d, 2, CH_2, J_{gem} = 16 Hz), 4.81 (s, 1, methine), 6.9–8.0 (m, 10, Ar); mass spectrum, *m/e* 290 (M^+), 272 ($M^+ - H_2O$), 244.

(2) Zn and AcOH. A solution of **4** (780 mg) in acetic acid (100 mL) was heated at reflux with 7.8 g of zinc dust (activated by treatment with dilute HCl and washed with water and CH_3OH) for 24 h. The product was poured on ice and worked up in the usual way to afford **5a** quantitatively; the NMR spectrum matched closely that obtained from alkaline reduction.

Cyclization of 5a to 6. To a solution of **5a** (400 mg, 1.4 mmol) in glacial acetic acid (20 mL) was added $ZnCl_2$ (40 mg), and the mixture was heated at reflux for 2 h. The product was precipitated by addition of water, removed by filtration, and dried. The crude product was taken up in benzene and passed through a column of Florisil eluted with benzene. Recrystallization of the product from benzene–hexane gave **6**: 270 mg (62%); mp 214.5–215.5 °C; NMR δ 2.62 (s, 3, OAc), 3.56 (s, 2, H_2), 7.3–7.8 (m, 8, Ar), 9.21 (d, 1, H_7, $J_{7,8}$ = 8.1 Hz); mass spectrum, *m/e* 314 (M^+), 272 ($M^+ - CH_2CO$).

Cholanthrene (1c). A solution of 57% HI (550 mg) and 50% hypophosphorus acid (300 mg) and acetic acid (15 mL) was brought to reflux and added to a suspension of **6** (200 mg, 0.64 mmol) in acetic acid (15 mL) at 100 °C. Heating was continued for 90 s; then the mixture was poured into ice water. The precipitate was collected by filtration, dried, dissolved in benzene, and adsorbed on a short column of silica gel. Elution with benzene–hexane gave **1c**: 130 mg (80%); mp 173–174 °C (benzene–hexane) (lit.[16] mp 173–173.5 °C); NMR (500 MHz) δ 3.57 (t, 2, H_2), 3.76 (t, 2, H_1), 7.29 (d, 1, H_3, $J_{3,4}$ = 6.6 Hz), 7.49 (t, 1, H_4) 7.6–7.8 (m, 6, Ar), 8.81 (d, 1, H_7, $J_{1,2}$ = 8.2 Hz), 8.95 (s, 1, H_6).

Conversion of the Carboxylic Acid 5a to the Methyl Ketone 5c. To a solution of KOH (400 mg) in H_2O (2 mL) was added a solution of **5a** (1.0 g, 3.4 mmol) in hexamethylphosphoramide (15 mL) and 4 mL of CH_3I. The reaction mixture was stirred overnight and worked up to afford the crude methyl ester **5b**. The latter was purified by chromatography on a short column of Florisil to yield pure **5b**: 870 mg (83%); NMR δ 3.15 (d of d, 2, H_2), 4.01 (s, 3, OCH_3), 4.53 (s, 1, methine), 6.9–7.8 (m, 10, Ar); mass spectrum, *m/e* 304 (M^+), 272 ($M^+ - CH_3OH$), 244.

To a solution of **5b** (680 mg, 2.24 mmol) in diethyl ether (150 mL) was added hexamethylphosphoramide (5 mL) and excess CH_3Li (15 mL of a 1.3 M solution). The resulting purple solution was stirred at room temperature for 3 h. A few drops of methanol was added and the product was worked up conventionally to provide the methyl ketone **5c**: 620 mg (96%) as a colorless residue; NMR (500 MHz) δ 2.70 (s, 3, CH_3), 3.03 (d of d, 1, CH_2, H_2, J_{gem} = 16 Hz), 4.40 (s, 1, methine), 6.8–7.8 (m, 10, Ar); mass spectrum, *m/e* 288 (M^+), 273, 255, 245.

6-Methylcholanthrene (1b). A solution of **5c** (620 mg, 2.2 mmol) in liquid HF (sufficient to dissolve) was stirred overnight in a hood. The HF was evaporated in a stream of N_2, and the solid product was washed with aqueous $NaHCO_3$ solution, then with water, and dried. The crude 1,1-dideuterio-**1b** was further purified by chromatography on a column of Florisil to yield the pure sample of 1,1-dideuterio-**1b**: 530 mg (91%), mp 143–144 °C; NMR (500 MHz) δ 3.33 (s, 3, CH_3), 3.54 (s, 2, CH_2), 7.33 (d, 1, H_3, $J_{3,4}$ = 6.6 Hz), 7.5–7.8 (m, 6, Ar), 7.97 (d, 1, H_5, $J_{4,5}$ = 8.6 Hz), 8.66 (d, 1, H_7); mass spectrum, *m/e* 270 (M^+), 254.

The 1,1-dideuterio-**1b** (60 mg) was converted to **1b** on heating with *p*-toluenesulfonic acid (6 mg) in refluxing benzene (30 mL) for 24 h. The NMR spectrum of **1b** resembled that of its deuterated analogue except for the presence of the H_1 protons at δ 3.72.

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Nucleoside *H*-Phosphonates. 8.[1] Activation of Hydrogen Phosphonate Monoesters by Chlorophosphates and Arenesulfonyl Derivatives

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Recently we have reported on an efficient method for oligonucleotide synthesis[2,3] which involves the reaction of

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