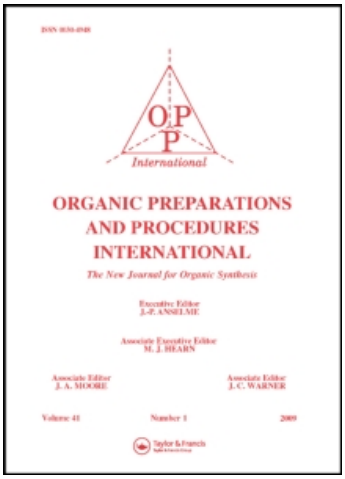

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SYNTHESES OF OXYGENATED DERIVATIVES OF 3-METHYLCHOLANTHRENE

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SYNTHESES OF OXYGENATED DERIVATIVES OF 3-METHYLCHOLANTHRENE

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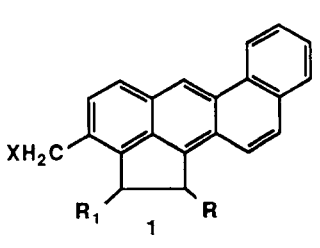
Carcinogenic polycyclic aromatic hydrocarbons are believed to be activated enzymatically to reactive diol epoxide metabolites which bind covalently to DNA.[1-3] The potent carcinogen 3-methylcholanthrene (3-MC) (**1a**) appears exceptional in that its bay region diol epoxide derivative (**2a**)[4] accounts for only a small fraction of the DNA-bound adducts in mammalian cells.[5] Metabolism studies indicate that the principal active species is a triol epoxide containing an additional hydroxyl group in the 1-, 2-, or 3-positions (**2b-d**).[5-9] Further elucidation of the mechanism of metabolic activation of 3-MC is dependent upon the synthetic accessibility of the appropriate oxygenated derivatives of 3-MC. We now report improved syntheses of 1- and 2-hydroxy-3-MC (**1b,1c**) and a convenient synthesis of the methyl ether of 3-hydroxymethylcholanthrene (**1e**).



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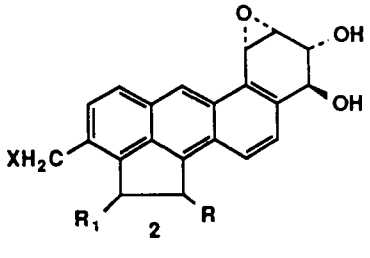

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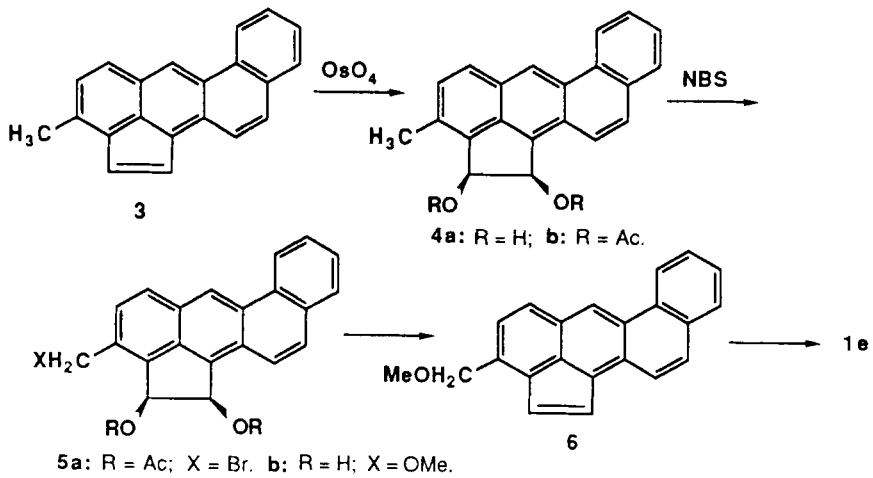
a: R = R_1 = X = H. **b**: R = OH; R_1 = X = H. **c**: R = X = H; R_1 = OH.
d: R = R_1 = H; X = OH. **e**: R = R_1 = H; X = OMe.

Synthesis of **1e** was based on 3-MC[10]. The greater reactivity of the methylene groups of 3-MC in relation to the methyl function necessitated introduction of blocking groups into these positions. This was accomplished by conversion of 3-MC to cis-1,2-diacetoxy-3-MC (**4b**) via dehydrogenation with DDQ



to 3-methylcholanthrylene (**3**), followed by cis-dihydroxylation with OsO_4, and acetylation. Bromination of **4b** with NBS catalyzed by benzoyl peroxide afforded smoothly the 3-bromomethyl diacetate derivative **5a**. Treatment of **5a** with sodium methoxide in methanol resulted in displacement accompanied by concurrent deacetylation to yield cis-1,2-dihydroxy-3-methoxy-methylcholanthrene (**5b**). Deoxygenation of **5b** with triphenyl phosphite, imidazole and iodine[11] furnished 3-methoxymethylcholanthrylene (**6**) which was hydrogenated over a Pd/charcoal catalyst to yield **1e**. Attempted demethylation of **1e** with various reagents (BBr_3, HCl, Ph_3CBF_4) to generate the free alcohol were unsuccessful.[12]

Oxidation of **1a** with lead tetraacetate in benzene at 0°C gave pure **1b** acetate virtually quantitatively, a significant improvement over the yield (46%) obtained from analogous reaction in glacial acetic acid.[13] Treatment of **1b** acetate with KOH in methanol provided pure **1b**. Oxidation of **1a** with DDQ in aqueous acetic acid gave 3-methylcholanthren-1-one (68%) which underwent reduction with $NaBH_4$ in THF-methanol to also yield **1b** (98%).

2-Hydroxy-3-MC (**1c**) was conveniently prepared from 3-methylcholanthren-2-one obtained by acidic dehydration of the dihydrodiol **4a**.[14] Reduction of the ketone with $NaBH_4$ furnished pure **1c** (98%).

The compounds **1b, 1c,** and **1e** were employed in metabolism studies which have led to identification of **2d** as the principal DNA-bound metabolite of 3-MC in mouse cells.[5] Failure to demethylate **1e** was not a problem for the biological studies, since the hydroxylated metabolites could be readily methylated for comparison.

EXPERIMENTAL SECTION

Materials and Methods. 3-Methylcholanthrene was prepared by the method described.[10] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. N-Bromosuccinimide (NBS) was crystallized from water prior to use. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. The NMR spectra were recorded on a Varian EM-360 60 MHz spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. Melting points are uncorrected.

3-Methylcholanthrylene (3).- A solution of **1a** (4.43 g, 16.4 mmol) and DDQ (4.10 g, 18 mmol) in dry benzene (400 ml) was stirred at room temperature for 1 hr. The solution was passed through a column of neutral alumina eluted with benzene to afford **3** (3.46 g, 79%) as a yellow solid: mp 196-197°C (lit.[14] 194°C); NMR δ 2.65 (s, 1, CH_3), 7.1-8.2 (m, 9, Ar and $H_{1,2}$), 8.5 (m, 1, H_7), 9.1 (s, 1, H_6).

cis-1,2-Diacetoxy-3-methylcholanthrene (4b).- To a suspension of **3** (2.12 g, 7.9 mmol) in 10 ml of pyridine was added a solution of OsO_4 (2 g, 7.9 mmol) in 50 ml of pyridine. The mixture was stirred at room temperature for 4 days. A solution of $NaHSO_3$ (3.6 g) in 60 ml of H_2O and 40 ml of pyridine was added. The precipitate of cis-1,2-dihydroxy-3-methylcholanthrene (2.06 g) was filtered and dried. A suspension of the diol in pyridine (50 ml) and acetic anhydride (70 ml) was stirred at ambient temperature for 4 days. The mixture was poured into ice water. The precipitate was dissolved in benzene and chromatographed on a column of Florisil. Elution with EtOAc/CH_2Cl_2 (1:1) afforded **4b** (1.5 g, 50%) as a white solid: mp 210-212°C; NMR δ (s, 6, $COCH_3$), 2.5 (s, 3, CH_3), 6.85 (d, 1, H_1, $J_{1,2}$ = 6 Hz), 7.3 (d, 1, H_2), 7.4-8.1 (m, 7, Ar), 8.6 (m, 1, H_7), 9.1 (s, 1, H_6); MS(EI) calcd for $C_{25}H_{20}O_4$, m/e 384, found 384.

3-Bromomethyl-cis-1,2-diacetoxycholanthrene (5a).- To a solution of **4b** (386 mg, 1 mmol) in CCl_4 (25 ml) were added a few crystals of benzoyl peroxide and NBS (200

mg, 1.1 mmol). The solution under N_2 was refluxed under the irradiation of a sun lamp for 1 hr. The resulting suspension was dissolved in CH_2Cl_2 and washed with H_2O three times. Evaporation of the solvent afforded **5a** (460 mg, 99%) as a white solid virtually pure by NMR : mp > 230°C; NMR δ 2.2 (s, 3, $COCH_3$), 2.3 (s, 3, $COCH_3$), 4.65 (s, 2, CH_2), 7.2 (q, 2, methine), 7.5 -8.2 (m, 7, Ar), 8.8 (d of d, 1, H_7), 9.2 (s, 1, H_6); MS(EI) calcd for $C_{25}H_{19}O_4Br$, m/e 462, found 462, 464 (p+2).

cis-1,2-Dihydroxy-3-methoxymethylcholanthrene (5b).- A solution of **5a** (460 mg, 1 mmol) in THF (20 ml), MeOH (50 ml) and 1 N NaOH (10 ml) was stirred at ambient temperature for 3 hr. The solution was worked up conventionally to afford **5b**(292 mg, 88%) as a yellow solid: mp > 230°C; NMR (acetone-d_6/D_2O) δ 3.4 (s, 3, CH_3), 4.9 (s, 2, CH_2), 5.8 (q, 2, methine), 7.6-8.5 (m, 7, Ar), 8.9 (m, 1, H_7), 9.3 (s, 1, H_6).

3-Methoxymethylcholanthrylene (6).- To a solution of **5b** (76 mg, 0.23 mmol), triphenyl phosphite (572 mg, 1.84 mmol), and imidazole (126 mg, 1.84 mmol) in 20 ml of benzene was added I_2 (250 mg, 1.4 mmol). The solution was stirred for 45 min, then diluted with ether, washed with aqueous $NaHCO_3$ and $NaHSO_3$ solutions, dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed on a Florisil column eluted with ether to yield **6** (44 mg, 65%) as a yellow solid : mp 162-163°C; NMR δ 3.4 (s, 3, CH_3), 4.85 (s, 2, CH_2), 7.2-8.2 (m, 7, Ar), 8.8 (m, 1, H_7), 9.2 (s, 1, H_6); MS(EI) calcd for $C_{22}H_{16}O$, m/e 296, found 296.

3-Methoxymethylcholanthrene (1e).- Compound **6** (47 mg, 0.24 mmol) dissolved in ethyl acetate (120 ml) and benzene (80 ml) was hydrogenated over a 10% Pd/C catalyst (25 mg) at 10 psig at ambient temperature for 20 min. The usual workup followed by chromatography on a column of Florisil afforded **1e** (29 mg, 62%) as a white solid: mp 148-149°C; NMR δ 3.3 (s, 3, CH_3), 3.5 (m, 4, $H_{1,2}$), 4.55 (s, 2, CH_2), 7.2-7.9 (m, 7, Ar), 8.7-9.5 (m, 2, $H_{6,7}$); MS(EI) calcd for $C_{22}H_{18}O$, m/e 298.135, found 298.134.

1-Hydroxy-3-methylcholanthrene (1b).- To a solution of **1a** (135 mg, 0.5 mmol) in 20 ml of benzene was added a suspension of $Pb(OAc)_4$ (244 mg, 0.55 mmol) at 0°

cover 1 hr. The reaction mixture was concentrated to 1/3 the original volume and the residue was diluted with benzene. The organic phase was washed with water, dried and the solvent was evaporated to give **1b** acetate (160 mg, 98%) which was virtually pure by NMR: mp 167.5-168.5°C (benzene) (lit.[13] 177.5-178.5°C); NMR δ 2.2 (s, 3, $COCH_3$), 2.5 (s, 3, CH_3), 3.0-4.2 (m, 2, CH_2), 7.1-9.1 (m, 8, methine and Ar), 8.9 (m, 1, H_7), 9.2 (s, 1, H_6); MS(EI) calcd for $C_{23}H_{18}O_2$, m/e 326, found 326.

A solution of **1b** acetate (200 mg, 0.6 mmol) in 5% KOH in methanol (130 ml) was heated at reflux for 40 min. The solvent was evaporated and ice water was added to the residue. The precipitate which formed was collected and dried to provide **1b** (180 mg, 99%) which was pure by HPLC: mp 215-216°C (dec.) (lit.[13] 214-216°C).

To a solution of **1a** (135 mg, 0.5 mmol) in acetic acid (130 ml) and H_2O (10 ml) was added DDQ (250 mg, 1.1 mmol) at 40°C. The solution was stored at 40°C for 1 hr during which time the dark green color changed to dark red. The solution was cooled, diluted with ether, and extracted with H_2O and aqueous NaOH. The organic phase was dried and the solvent was evaporated to dryness. The crude product was chromatographed on a Florisil column eluted with ether to yield 3-methylcholanthren-1-one (97 mg, 68%) as a yellow solid: mp > 250°C (lit.[13] 262-3°C); NMR δ 2.5 (3, s, CH_3), 3.7 (2, s, CH_2), 7.2-9.2 (8, m, aromatic), 9.3 (1, s, H_6).

A solution of 3-methylcholanthren-1-one (97 mg, 0.34 mmol) and $NaBH_4$ (100 mg) in THF (30 ml) and MeOH (30 ml) was stirred for 1 hr at room temperature. The usual workup gave **1b** (95 mg, 98%) as a white solid which was identical with that prepared via the alternative procedure.

2-Hydroxy-3-methylcholanthrene (1c).- 3-Methylcholanthren-2-one was synthesized according to the procedure of Sims[14] : mp 203-204°C (lit.[14] 205°C); NMR δ 2.85 (s, 3, CH_3), 3.95 (s, 2, CH_2), 7.2-8.2 (m, 6, Ar), 8.7 (m, 1, H_7), 9.05 (s, 1, H_6).

A solution of this ketone (118 mg, 0.42 mmol) and $NaBH_4$ (120 mg) in THF (30 ml) and MeOH (30 ml) was stirred for 1 hr at room temperature. The usual workup

gave **1c** (115 mg, 98%) as a white solid: mp 219-220°C (EtOAc) (lit.[14] 186°C). The alcohol was further characterized by acetylation with acetic anhydride and pyridine at room temperature overnight. After the usual workup, the **1c** acetate was crystallized from benzene-ether to give pure **1c** acetate: mp 173-174°C; NMR δ 2.2 (s, 3, $COCH_3$), 2.5 (s, 3, CH_3), 3.5 and 4.2 (pair of d of d, 2, CH_2), 6.85 (d of d, 1, methine), 7.3-8.1 (m, 7, Ar), 8.8 (m, 1, H_7), 8.95 (s, 1, H_6); MS(EI) calcd for $C_{23}H_{18}O_2$, m/e 326, found 326.

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