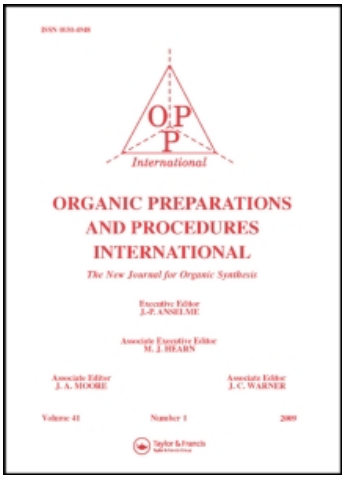

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SYNTHESIS OF 3-HYDROXYDIBENZ[a,c] ANTHRACENE

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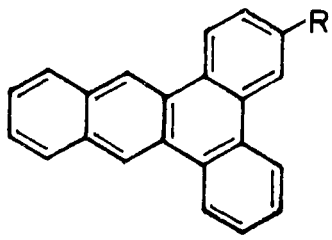
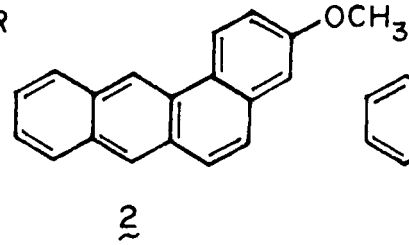
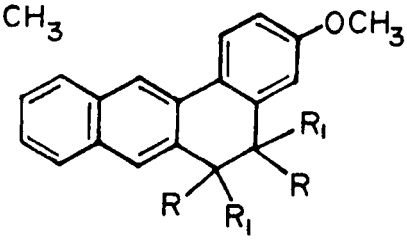
In connection with a program to synthesize the oxidized metabolites of polycyclic aromatic hydrocarbons as authentic standards for carcinogenesis research, we required a practical synthetic route to 3-hydroxydibenz[a,c]anthracene (1b). This phenol, in addition to its possible role as a metabolite of dibenz[a,c]anthracene (1a), was also sought as a potential synthetic precursor[1] of the weakly tumorigenic[2] trans-3,4-dihydroxy-3,4-dihydrodibenz[a,c]anthracene and its presumed biologically active diol epoxide metabolite trans-3,4-dihydroxy-anti-1,2-epoxy-1,2,3,4-tetrahydrodibenz-[a,c]anthracene.[3]



1a: R = H
b: R = OH
c: R = OCH_3



2



3a: R = H; R_1 = cis-OH
b: RR_1 = O
c: R = OH; R_1 = CH=CH_2
d: R = OH; R_1 = C≡CH

Synthesis of 1b was accomplished from 3-methoxybenz[a]anthracene (2) utilizing the method of annelation recently reported.[4] Oxidation of 2 with OsO_4 took place regiospecifically to furnish cis-5,6-dihydroxy-5,6-dihydro-2 (3a) which underwent further oxidation to the corresponding quinone (3b) on treatment with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or pyridine-SO_3 in dimethyl sulfoxide.[5] Excellent yields were obtained with both reagents. Addition of excess vinylmagnesium bromide to 3b gave the divinyl diol 3c in moderate yield (43%). This was doubled by utilization of a two step procedure involving addition of lithium acetylide to 3b followed by reduction of the diethynyl diol adduct (3d) with $LiAlH_4$. On treatment with $POCl_3$, 3c underwent cyclization and dehydration to yield 1c. Demethylation with HBr or sodium ethylmercaptide furnished the free phenol 1b.

Attempts to oxidize 1b to the corresponding 3,4-dione with either $(PhSeO)_2O$ or $[(KSO_3)_2NO]$, the reagents previously employed to synthesize the analogous quinones of other polycyclic hydrocarbons,[1] were unsuccessful. Apparently resistance to oxidation is related to the fact that the desired quinone function is situated in a relatively sterically crowded bay region.[6] The synthetic inaccessibility of this quinone prevents its use as an intermediate for the preparation of the corresponding dihydrodiol and diol epoxide derivatives.[1]

EXPERIMENTAL

Cis-5,6-Dihydroxy-5,6-dihydro-3-methoxybenz[a]anthracene (3a).- A solution of 3-methoxybenz[a]anthracene[7] (5g, 19 mmol) and OsO_4 (5 g, 19 mmol) in 125 ml of pyridine was stirred in the dark under N_2 for 5 days. The mixture was poured into 5% aqueous sodium bisulfite solution (1 L) and stirred at room temperature overnight. The mixture was filtered, washed with H_2O and dried to afford 3a (5.5 g); recrystallization from acetone gave pure 3a (5.1 g, 90%), mp 203°C: NMR (270 MHz) δ ($CDCl_3$ + DMSO-d_6) 3.82 (s,3,OCH_3), 4.64 (br s,1,OH), 4.76 (br s,1,OH), 5.20 (d,1, benzylic, $J_{5,6}$

= 5.2 Hz), 5.28 (d,1, benzylic, $J_{5,6}$ = 5.2 Hz), 6.98 (dd,2, aromatic), 7.09 (s,1, aromatic), 7.45 (m,2, aromatic), 7.87-7.94 (m,2, aromatic), 8.24 (s,2, aromatic).

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.51. Found: C, 78.02; H, 5.53.

3-Methoxybenz[a]anthracene 5,6-dione (3b). DDQ method.- A solution of 3a (2.25 g, 7 mmol) and DDQ (8 g, 35 mmol) in dioxane (250 ml) was stirred under N_2 for 48 h. After removal of the solvent under vacuum, the residue was taken up in CH_2Cl_2, washed several times with 5% aqueous sodium carbonate, H_2O, and dried ($MgSO_4$). Evaporation of the solvent furnished 3b (2.2 g, 99%) as red crystals, employed directly in the next step; recrystallization from $CHCl_3$-THF gave the analytical sample, mp 240°C: NMR (270 MHz, $CDCl_3$) δ 3.90 (s,3,OCH_3), 7.26-7.57 (m,5H), 7.86 (t,1H), 8.01 (t,1H), 8.19 (s,1H), 8.63 (s,1H); MS (70 eV) m/e 288 (M^+), 260 (M^+-CO).

Anal. Calcd for $C_{19}H_{12}O_3$: C, 79.15; H, 4.19. Found: C, 79.11; H, 4.21.

SO_3-DMSO method.- Into a solution of 3a (8.5 g, 29 mmol) in 300 ml of DMSO containing Et_3N (6 ml) was added pyridine · SO_3 complex (11 g, 80 mmol) in small portions during 15 min. The solution was stirred under N_2 for 2 h then poured carefully with stirring into H_2O (2 L). The precipitate was filtered, dried, dissolved in EtOAc/CH_2Cl_2 (1:1) and passed through a short column of Florisil to yield 3b (8.1 g, 97%), mp 214-216°C; recrystallization from CH_2Cl_2 gave pure 3b (7.6 g, 91%) mp 240°C undepressed on admixture with 3b prepared by the DDQ method.

5,6-Diethynyl-5,6-dihydroxy-3-methoxybenz[a]anthracene (5d).- A saturated solution of dry acetylene gas in 20 ml of anhydrous THF at -20°C was diluted with 300 ml of THF and cooled to -78°C. Into this was added dropwise with stirring 80 ml of 1.1 M n-butyllithium (8.8 mmol), followed by a solution of 3b (3 g) in THF (250 ml). The reaction mixture was allowed to warm to room temperature, then diluted with ether (500 ml) and quenched by careful addition of water (20 ml). Partition between ether and water, separation of the organic layer, drying and removal of solvent furnished 5d (3.5 g, 98%); a sample of 5d crystallized from CH_2Cl_2 melted at 213-214°C (dec.):

NMR (60 MHz, $CDCl_3$) δ 2.35 (d,2,C≡CH), 3.3 (br s,2,OH), 3.8 (s,3,OCH_3), 6.9-8.3 (m,9, aromatic).

Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.17; H, 4.70. Found: C, 81.21; H, 4.78.

5,6-Dihydroxy-5,6-divinyl-3-methoxybenz[a]anthracene (3c).- To a solution of 3d (2 g, 6 mmol) in anhydrous ether (400 ml) was added $LiAlH_4$ (1 g). The solution was held at reflux for 30 h, then excess hydride was decomposed by slow, careful addition of H_2O (10 ml) followed by 5% HCl (200 ml). Conventional workup gave a residue which was chromatographed on Florisil to yield 3c (1.8 g, 39%) employed directly in the next step; the analytical sample had mp 169°C (ether): NMR (60 MHz, $CHCl_3$) δ 2.8 (br s,2,OH), 3.9 (s,3,OCH_3), 5.1-6.2 (m,6,vinylic), 7.0-8.0 (m,7, aromatic), 8.2 (s,2,$H_{7,12}$).

Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.23; H, 5.81. Found: C, 80.11; H, 5.79.

Direct preparation of 3c from 3b was carried out by addition of a solution of vinylmagnesium bromide (1.1 mmol) to a solution of 3b (0.2 g, 0.7 mmol) in THF (50 ml) at 0°C dropwise with stirring under N_2. The temperature was allowed to rise to room temperature, and excess reagent was decomposed by the addition of aqueous NH_4Cl solution. Conventional workup followed by chromatography on a Florisil column eluted with benzene - CH_2Cl_2 (1:1) gave 3c (100 mg, 43%), mp 163-165°C which did not depress on admixture with 3c prepared from 3d.

3-Methoxydibenz[a,c]anthracene (1c).- A solution of the divinyl diol 3c (900 mg, 2.6 mmol) in pyridine (20 ml) containing $POCl_3$ (1.1 ml) was heated at reflux for 10 min, then cooled, and decomposed by pouring onto ice. Extraction with CH_2Cl_2 and chromatography on Florisil followed by recrystallization from benzene gave 1c (270 mg, 33%), mp 196-198°C: NMR (60 MHz, $CDCl_3$) δ 3.9 (s,3,OCH_3), 7.1-9.1 (m,13, aromatic); MS (70 eV) m/e 308 (M^+).

Anal. Calcd for $C_{23}H_{16}O$: C, 89.61; H, 5.19. Found: C, 89.71; H, 5.08.

3-Hydroxydibenz[a,c]anthracene (1b). Sodium ethylmercaptide method.- A solution of ethanethiol (0.5 g, 8 mmol) in dry dimethylformamide (5 ml) was added to a suspension

of NaH (100 mg of a 50% oil suspension) in DMF (5 ml) under N_2. After 5 min, a solution of 1c (90 mg, 0.3 mmol) in DMF (2 ml) was added, and the resulting suspension was stirred at reflux for 3 h. The product was acidified with dil. HCl and worked up to afford 1b (60 mg, 70%) as a white solid, mp 247°C (dec.): NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ 7.1-8.1 (m,8, aromatic), 8.5-8.9 (m,3, aromatic), 9.0 (s,1,$H_{9 \text{ or } 14}$), 9.45 (s,1,$H_{9 \text{ or } 14}$).

Anal. Calcd for $C_{22}H_{14}O$: C, 89.77: H, 4.78. Found: C, 89.83; H, 4.84.

HBr Method.- A mixture of 1c (400 mg, 1.3 mmol), HOAc (25 ml) and 48% HBr (15 ml) was heated at reflux for 5 h, then decomposed by pouring into ice-water to yield 1b (300 mg, 78%), identical in all respects with 1b prepared by the alternative method.

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6. It was previously observed[4] that similar oxidation of the structurally related 3-hydroxyphenanthrene also failed to afford a quinone product.

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