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DIHYDRODIOLS OF DIBENZ(a,c)ANTHRACENE

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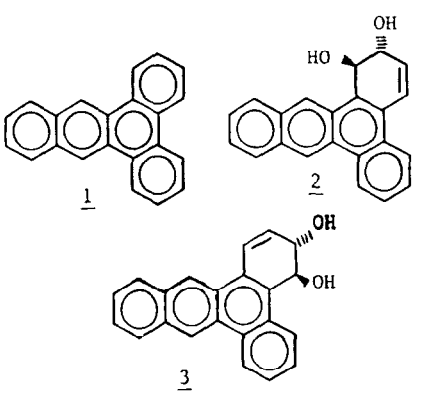
Abstract: An unequivocal synthesis of dihydrodiols of the mutagenic polycyclic aromatic hydrocarbon, dibenz(a,c)anthracene is described

An important aspect of polynuclear aromatic hydrocarbon (PAH)-induced carcinogenesis concerns the mechanism by which these relatively inert molecules are metabolically activated to highly reactive intermediates (ultimate mutagens and carcinogens). The present report is concerned with the PAH, dibenz(a,c)anthracene DBA **1**. Although the carcinogenic activity of DBA is disputed[1], it has been shown to possess tumor initiating activity similar to that of benz(a)-anthracene and chrysene[2,3], and displays mutagenic activity higher than that of carcinogenic dibenz(a,h)anthracene[4,5]. Like other PAHs, DBA binds covalently to nucleic acid in mouse skin[6] and rodent embryo cells in culture[7] *via* reactive metabolites[8], however, the structure of these reactive metabolites has not so far been elucidated. We believe that the bay-region diol epoxides and their precursor dihydrodiols which are implicated in the activation of several mutagenic and carcinogenic PAHs[9], are not likely to be involved in the metabolic activation of DBA, presumably because the diol group which also forms a part of the bay-region of the molecule adopts *quasi* diaxial conformation. The bay-region diol epoxides and their precursor diols with such a conformation are expected to exhibit attenuated mutagenic and carcinogenic activities[10-12]. Therefore, the dihydrodiols **2** and **3** which are the metabolic precursor of the bay-region diol epoxides and tentatively identified as minor metabolites of DBA[13] may not be involved in its



1 **2** **3**

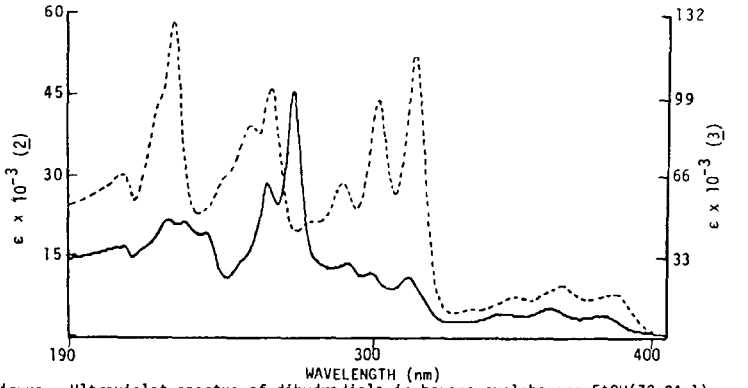
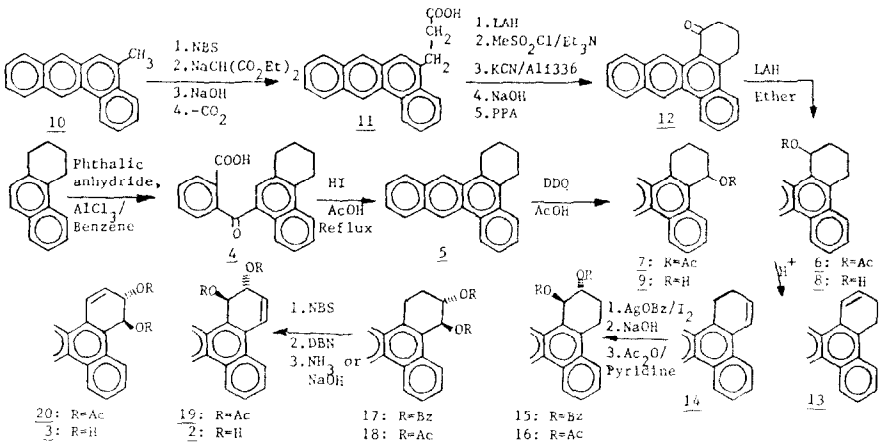


Figure. Ultraviolet spectra of dihydrodiols in hexane-cyclohexane-EtOH(72:24:1): **2** (-------, ε 52,900 at 315 nm; ε 44,400 at 302 nm; ε 46,400 at 263 nm), **3** (———, ε 99,700 at 272 nm; ε 62,100 at 262 nm).

Scheme



metabolic activation. In order to elucidate the mechanism by which DBA expresses its mutagenic and possibly carcinogenic activities, DBA derivatives which are potential metabolites of this PAH are needed. The present communication describes an unambiguous synthesis of DBA-1,2-dihydrodiol **2** and DBA-3,4-dihydrodiol **3**.

The dihydrodiols **2** and **3** are prepared from a common intermediate 1,2,3,4-tetrahydroDBA **5**. In the present study, **5** was conveniently prepared with an overall yield of 95% via oxidative cyclization (HI/AcOH)[14] of the keto-acid **4**, which was obtained in an almost quantitative yield by the Friedel-Crafts acylation of 1,2,3,4-tetrahydrophenanthrene with phthalic anhydride (see scheme). The structure of **5** was confirmed by its dehydrogenation DDQ/benzene which produced DBA **1** identical (NMR, UV, mp and mixed mp) to the authentic DBA prepared according to the published procedures[14a].

Oxidation of **5** with DDQ/AcOH[15] at room temperature afforded nearly 1:1 mixture of 1-acetoxy-1,2,3,4,-tetrahydroDBA **6** and 4-acetoxy-1,2,3,4-tetrahydroDBA **7** in 78% yield. This mixture was best separated by hydrolyzing (NaOH) it to a mixture of hydroxy derivatives **8** and **9** which were then separated by chromatography over dry column grade silica gel (E. Merck) using 5% EtOAc-C_6H_6 as the solvent system. The relatively less polar compound was identified as **8** by comparing its ^{1}H-NMR with that of **9** and **5**. The relatively downfield shift in the H_{14} proton of **8** compared to **9** and **5** clearly suggest that the hydroxy group is substituted at position 1 of **8**. The structure of **8** was further confirmed by its unequivocal synthesis[16] from known 5-methylbenz(a)-anthracene **10**[17] as shown in scheme. Conversion of alcohols **8** and **9** to the corresponding dihydrodiols **2** and **3** was accomplished by identical routes, with similar yields resulting in each series (see scheme), following the procedure analogous to that reported in the literature[18]. Physical and ^{1}H-NMR properties of **2** and **3** as well as their synthetic intermediates are shown in table.

Sims *et al.*[13] have reported the synthesis of two dihydrodiols, namely, diol A and diol B in <.05% yields by the chemical oxidation of DBA with absorbic acid-ferrous sulfate and EDTA system. These authors tentatively identified diol A and diol B as DBA-3,4-dihydrodiol **3** and DBA-1,2-dihydrodiol **2**, respectively, by comparing the chemical shifts of the benzylic carbinol proton and benzylic vinyl proton in the ^{1}H-NMR spectra of these compounds. However, a compari-

TABLE

COMPOUND (mp)	NMR SPECTRUM (270 MHz)[a]
1-Oxo-1,2,3,4-tetrahydro-DBA (182-183)[b] **12**	2.32(m,H_3); 2.87(t,H_2); 3.41(t,H_4); 7.50-8.20(m,7H); 8.84(d,H_8); 9.11(s,H_9); 9.84(s,H_{14}); $J_{2,3}$=6.9; $J_{3,4}$=6.2; $J_{7,8}$=8.2
9-(2-carboxybenzoyl)-1,2,3,4-tetrahydrophenanthrene (207-208)[b] **4**	$CDCl_3$+D_2O: 1.6-2.0(m,4H); 2.71(m,2H); 3.11(m,2H); 7.30-8.10 (m,8H); 8.90(m,1H)
1,2,3,4-TetrahydroDBA (135-136)[b] **5**	2.00(m,4H,H_2 and H_3); 3.10(m,H_4); 3.22(m,H_1); 7.45-8.30(m,7H); 8.48(s,H_{14}); 8.81(m,H_8); 9.12(s,H_9)
1-Hydroxy-1,2,3,4-tetrahydroDBA (163-165)[b] **8**	1.87-2.40(m,H_2 and H_3); 2.10(bs, exchangeable with D_2O,OH); 2.95 (m,H_4); 3.26(dd,$H_{4'}$); 5.56(m,H_1); 7.40-8.10(m,7H); 8.78(s,H_{14}); 8.80(m,H_8); 9.09(s,H_9); $J_{4,4'}$=20; $J_{3,4}$=4
4-Hydroxy-1,2,3,4-tetrahydroDBA (150-151)[b] **9**	1.77-2.40(m,$H_{2,3}$ and OH); 3.04(m,H_3); 3.44(m,$H_{3'}$); 5.42(bs,H_4); 7.50-8.35(m,7H); 8.51(s,H_{14}); 8.78(m,H_8); 9.10(s,H_9)
3,4-DihydroDBA (145-146)[b] **13**	2.50(m,H_3); 3.20(m,H_4); 6.35-6.48(m,H_2); 7.45(d,H_1); 7.50-8.20 (m,7H); 8.66(s,H_{14}); 8.87(m,H_8); 9.20(s,H_9); $J_{1,2}$=10
1,2-DihydroDBA (121-122)[b] **14**	2.40-2.76(m,H_2); 3.34(t,H_1); 6.38(m,H_3); 7.27(m,H_4); 7.37-8.34 (m,7H); 8.58(s,H_{14}); 8.85(m,H_8); 9.16(s,H_9); $J_{2,3}$=$J_{2',3}$=4.5; $J_{2,4}$=$J_{2',4}$=1.7; $J_{3,4}$=10
trans-1,2-Dibenzoyloxy-1,2,3,4-tetrahydroDBA (255-256)[b] **15**	2.42-2.76(m,H_3); 3.22-3.57(m,H_4); 5,82(m,H_2); 7.10(d,H_1); 7.22-8.27(m,17H); 8.50(s,H_{14}); 8.92(m,H_8); 9.20(s,H_9); $J_{1,2}$=3.1
trans-3,4-Dibenzoyloxy-1,2,3,4-tetrahydroDBA (200-201) **17**	2.43-2.74(m,H_2); 3.32-3.70(m,H_1); 5.80(m,H_3); 6.92(d,H_4); 7.25-8.18(m,17H); 8.69(s,H_{14}); 8.89(m,H_8); 9.24(s,H_9); $J_{3,4}$=3
trans-1,2-Diacetoxy-1,2,3,4-tetrahydroDBA (235-236)[b] **16**	2.00(s,3H); 2.11(s,3H); 2.20-2.52(m,H_3); 3.10-3.44(m,H_4); 5.43 (m,H_2);6.70(d,H_1); 7.50-8.20(m,7H); 8.35(s,H_{14}); 8.91(d,H_8); 9.20(s,H_9); $J_{1,2}$=2.6; $J_{7,8}$=8
trans-3,4-Diacetoxy-1,2,3,4-tetrahydroDBA (229-230)[b] **18**	2.00(s,3H); 2.13(s,3H); 2.21-2.58(m,H_2); 3.17-3.57(m,H_1); 5.40 (m,H_3); 6.53(d,H_4); 7.52-8.21(m,7H); 8.62(s,H_{14}); 8.87(m,H_8); 9.20(s,H_9); $J_{3,4}$=2.7
trans-1,2-Diacetoxy-1,2-dihydroDBA (179-180)[b] **19**	2.00(s,3H); 2.07(s,3H); 5.47(dd,H_2); 6.52(dd,H_3); 6.96(bs,H_1); 7.50-8.18(m,7H and H_4); 8.28(d,H_5); 8.58(s,H_{14}); 8.92(d,H_8); 9.22(s,H_9); $J_{1,2}$=1.6; $J_{1,3}$=0.7; $J_{2,3}$=5.5; $J_{3,4}$=9.5; $J_{5,6}$=8.6; $J_{7,8}$=8.2
trans-3,4-Diacetoxy-3,4-dihydroDBA (196-198)[b] **20**	1.99(s,3H); 2.08(s,3H); 5.46(dd,H_3); 6.55(dd,H_2); 6.79(bs,H_4); 7.50-8.23(m,7H and H_1); 8.78(s,H_{14}); 8.89(m,H_8); 9.23(s,H_9); $J_{1,2}$=10; $J_{2,3}$=5.5; $J_{3,4}$=1.5
trans-1,2-Dihydroxy-1,2-dihydroDBA (219-220d) **2**	Acetone d_6: 4.50(d,H_2); 5.55(s,H_1); 6.52(dd,H_3); 7.54(d,H_4); 7.44-8.44(m,7H); 8.99(s,H_{14}); 9.05(m,H_8); 9.43(s,H_9); $J_{1,2}$=0; $J_{2,3}$=5.7; $J_{3,4}$=10

trans-3,4-Dihydroxy-3,4-dihydroDBA (232-234d) **3**	Acetone d_6: 4.46(d,H_3); 5.38(s,H_4); 6.54(dd,H_2); 7.72(d,H_1); 7.50-8.50(m,7H); 9.01(s,H_{14}); 9.02(m,H_8); 9.46(s,H_9); $J_{1,2}$=10; $J_{2,3}$=5; $J_{3,4}$=0

[a]Reported in delta units; unless otherwise noted, spectra were recorded in $CDCl_3$, with TMS as internal standard.

[b]Correct microanalysis was obtained for these compounds, other listed compounds molecular gave corrections in the mass spectrum.

son of the ^{1}H-NMR and UV spectra (Figure) of the authentic DBA-3,4-dihydrodiol **3** and DBA-1,2-dihydrodiol **2** with those of diol A and diol B strongly suggests that, in contrary to what was reported by Sims *et al.*[13], the diol A and diol B are best identified as DBA-1,2-dihydrodiol **2** and DBA-3,4-dihydrodiol **3**, respectively. Since Sims *et al.*[4,9,19] used diol A and diol B for understanding the mechanism of carcinogenesis of DBA, the subsequent biological studies reported by these authors with the tentatively identified dihydrodiols should be interpreted with caution.

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