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# DIHYDRODIOLS AND DIOL EPOXIDES OF DIBENZO[a,i]-AND [a,h]PYRENE

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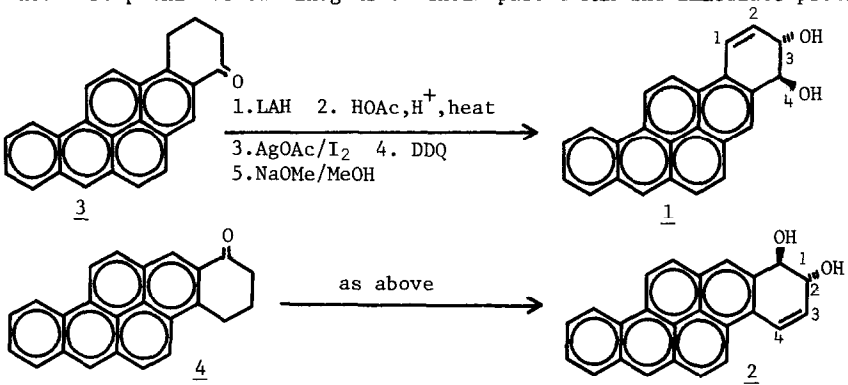
Abstract: Syntheses of dihydrodiols and highly mutagenic diol epoxides of the carcinogenic polycyclic aromatic hydrocarbons dibenzo[a,i]-and[a,h]pyrene are described.

Dibenzo[a,i]-and dibenzo[a,h]pyrene have long been recognized to be two of the most active members of the unsubstituted polycyclic aromatic hydrocarbon (PAH) class of carcinogen.[1] While PAH have been known for some time to require metabolism to reactive intermediates before induction of neoplasia can occur, only recently has strong evidence been obtained that the metabolic route arene → arene oxide → dihydrodiol → diol epoxide is an important pathway in this activation.[2] Furthermore, quantum mechanical calculations predicted and experimental results have confirmed that benzo-ring diol epoxides, in which the oxirane oxygen forms part of a "bay region" are especially biologically active, presumably due to their much greater reactivity.[3]

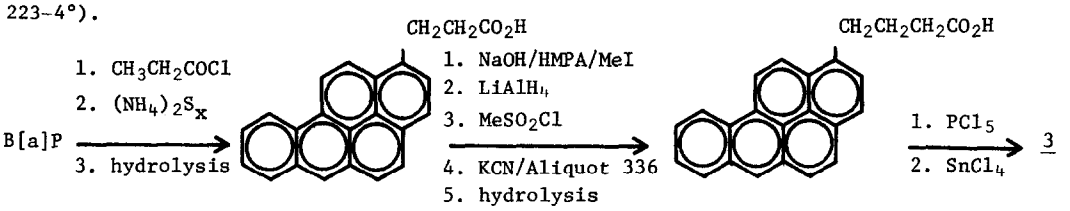
We report herein the preparation of 3,4-dihydroxy-3,4-dihydrodibenzo[a,i]pyrene (1) and 1,2-dihydroxy-1,2-dihydrodibenzo[a,h]pyrene (2). According to the "bay region theory"[3], these dihydrodiols should be proximate carcinogens of their parent PAH and immediate precursors of



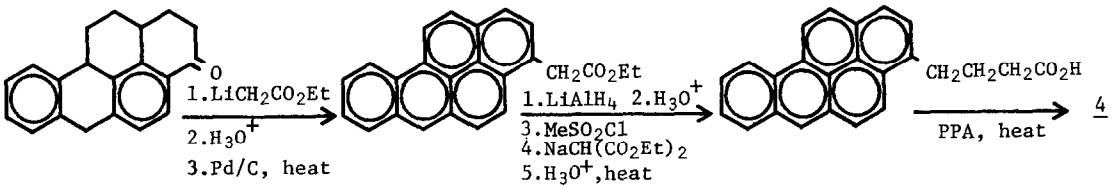

3 1 4 2

highly reactive and carcinogenic bay region diol epoxides. The dihydrodiols were prepared from the corresponding tetrahydroketones, 3 and 4. Of the tetrahydroketones, only 3 has been previously prepared,[4] and the reported yield (5%) was very low. We have devised a new route which enables large quantities of 3 to be prepared (30% overall yield). Acylation of benzo[a]pyrene with propionyl chloride[5] occurs at C-1 in good yield (84%, mp. 123-5°, lit.[5] 125-6°). Treatment of the ketone with ammonium polysulfide at 165° (Willgerodt reaction), followed by hydrolysis of the intermediate amide with ethylene glycol/KOH gave the propionic acid derivative in 73% overall yield. Attempts to introduce a butyric acid side chain directly by analogous reactions was unsatisfactory due to very low yields in the Willgerodt step, and homologation was effected by esterification of the propionic acid with MeI in NaOH/HMPA (90%), reduction of the ester to the alcohol with LAH in THF (98%), conversion to the mesylate with $MeSO_2Cl$(100%), displacement of the

mesylate with cyanide under phase transfer conditions with Aliquot 336 (100%), and hydrolysis of the nitrile to the acid with diethylene glycol/KOH (78%, mp. 227-9°, lit.[4] 234-5°). Cyclization to the ketone was effected *via* treatment of the acid chloride with $SnCl_4$ (75%, mp. 263-5°, lit.[4] 223-4°).




For synthesis of 4, Cook's ketone[6] was converted almost quantitatively to the α-hydroxyester using lithioethyl acetate, and the condensation product was dehydrated and dehydrogenated directly to the substituted ethyl acetate with 5% Pd/C in refluxing p-cymene (70% overall from the ketone, mp. 125-6°). Reduction of the ester with LAH in THF gave the alcohol (96%, mp. 149-152°) which was converted to the mesylate (95%). Condensation with sodiodiethylmalonate in benzene gave the expected diester, which was hydrolyzed to the diacid in aqueous acid. The diacid was




thermally (175-185°) decarboxylated to give the butyric acid derivative (72% based on mesylate, mp. 201-4°), which was characterized as the methyl ester. Cyclization as in the[a,i]-series gave the ketone, 4 (78%). Physical and spectral properties for 3 and 4 as well as intermediates in their preparation are recorded in the Table.

Conversion of ketones 3 and 4 to the corresponding dihydrodiols was accomplished by identical routes, with similar yields being obtained in the two series.[7] The ketones were reduced to the alcohols with LAH/THF and the alcohols were dehydrated with $HOAc/H^+$ to give the alkenes (80-95%, overall). Reaction of the alkenes with $AgOAc/I_2$ gave the trans-tetrahydrodiacetates in modest yield (35-50%). Dehydrogenation with DDQ in refluxing dioxane[8] proceeded rapidly in high yield (70-80%), provided that a two or more molar excess of DDQ was used. Hydrolysis to the dihydrodiols, 1 and 2, was achieved with NaOMe in THF/MeOH (50-60%). Physical and NMR properties of 1, 2 and intermediates for their preparation are recorded in the Table.

Treatment of each dihydrodiol (30 mg) with m-chloroperoxybenzoic acid (300 mg) in THF (30 ml) at 25° for 20-60 min afforded, after the usual workup[9], good yields (70-80%) of the diol epoxides, whose NMR spectra (Table) were very similar to the analogous B[a]P bay region diol epoxide in which the benzylic hydroxyl group is trans to the epoxide oxygen.[9] Preliminary evaluation of the biological activity of these diol epoxides has established that they are about as mutagenic toward S. typhimurium strains TA 98 and TA 100 as is the corresponding B[a]P isomer.[10] Experiments are in progress to establish whether the diol epoxides qualify as ultimate carcinogens of the parent hydrocarbons.

TABLE

| COMPOUND (mp) | NMR SPECTRUM[a] |
|---|---|
| Methyl 3-(1-benzo[a]pyrenyl)-propionate (155-156°)[b] | 2.81(2H,t,J=7.5);3.63(2H,t,J=7.5);3.66(3H,s);7.6-9.1(11H,m) |
| 1-Mesyloxy-3-(1-benzo[a]pyrenyl)propane | 2.0-2.5(2H,m);2.93(3H,s);3.36(2H,t,J=8);4.21(2H,t,J=6);7.5 9.0(11H,m) |
| 3-(1-benzo[a]pyrenyl)-n-butyronitrile (134-135°) | 1.9-2.5(4H,m);3.33(2H,t,J=7);7.5-9.0(11H,m) |
| 4-Oxo-1,2,3,4-tetrahydrodibenzo[a,i]pyrene | 2.1-2.5(2H,m);2.73(2H,t,J=6);3.26(2H,t,J=6);8.2-8.5(7H,m); 8.40(1H,s);8.8-9.1(2H,m) |
| 1,2-Dihydrodibenzo[a,i]pyrene | 2.5-2.7(2H,m);3.5(2H,t);6.25($H_3$,m);6.80($H_4$,m)7.6-9.1(10H,m); $J_{1,2}$=8.5;$J_{2,3}$=4.5;$J_{3,4}$=9;$J_{2,4}$=1.5 |
| trans-3,4-Diacetoxy-1,2,3,4-$H_4$-dibenzo[a,i]pyrene (230-1°) | 1.9-2.5(2H,m);2.03(3H,s);2.16(3H,s);3.31(2$H_1$,t);5.33($H_3$,m); 6.35($H_4$,d);7.5-8.9(10H,m);$J_{1,2}$=$J_{2,3}$=7;$J_{3,4}$=5.5 |
| trans-3,4-Diacetoxy-3,4-dihydrodibenzo[a,i]pyrene (213-5°)[b] | 2.07(3H,s);2.17(3H,s);5.76($H_3$,m);6.31($H_2$,m);6.56($H_4$,d);7.6-8.5(9H,m);8.8-9.6(2H,m);$J_{1,2}$=10;$J_{2,3}$=4;$J_{3,4}$=6 |
| trans-3,4-Dihydroxy-3,4-dihydrodibenzo[a,i]pyrene (>305°,d) | $(CD_3)_2CO$, after exchange:4.50($H_3$,m);5.00($H_4$,d);6.20($H_2$,m); 7.46($H_1$,m);7.6-9.2(2H,m);$J_{1,2}$=10.5;$J_{2,3}$=2;$J_{3,4}$=10.5;$J_{1,3}$=2 |
| (±)-3α,4β-Dihydroxy-1α,2α-epoxy-1,2,3,4-$H_4$-dibenzo[a,i]-pyrene | DMSO-$d_6$:3.7-4.1($H_2$,$H_3$);4.77($H_4$);5.28($H_1$);5.68($OH_3$); 5.92($OH_4$);7.7-9.4(10H,m);$J_{1,2}$=4.5;$J_{3,4}$=8.75;$J_{4,OH}$=7; $J_{3,OH}$=5 |
| Ethyl (3-benzo[a]pyrenyl)acetate (125-6°)[b] | 1.18(3H,t,J=7);4.13(2H,q,J=7);7.5-8.3(9H,m);8.6-8.9(2H,m) |
| Methyl 3-(3-benzo[a]pyrenyl)-butyrate (95-6°)[b] | 1.9-2.6(4H,m);3.25(2H,t,J=7);3.66(3H,s);7.6-8.4(9H,m);8.5-9.1(2H,m) |
| 1-Oxo-1,2,3,4-tetrahydrodibenzo[a,h]pyrene (271-2°)[b] | 2.4-2.6(2H,m);2.92(2H,t,J=6);3.64(2H,t,J=6);7.7-8.6(8H,m); 8.9-9.2(3H,m) |
| 3,4-Dihydrodibenzo[a,h]pyrene | 2.4-2.8(2H,m);3.48(2H,t);6.28($H_2$,m);6.87($H_1$,m);7.6-9.2(10H, m);$J_{1,2}$=9.5;$J_{2,3}$=5;$J_{3,4}$=8 |
| trans-1,2-Diacetoxy-1,2,3,4-$H_4$-dibenzo[a,h]pyrene (241-2°) | 2.0-2.6(2H,m);2.06(3H,s);2.20(3H,s);3.52(2$H_4$,t);5.2-5.5($H_2$, m);5.51($H_1$,m);7.6-9.1(10H,m).$J_{1,2}$=6;$J_{3,4}$=6.5 |
| trans-1,2-Diacetoxy-1,2-dihydrodibenzo[a,h]pyrene (262-4°)[b] | 2.10(3H,s):2.20(3H,s);5.73($H_2$,m);6.30($H_3$,m);6.54($H_1$,d);7.66 $H_4$,d);7.6-9.1(11H,m);$J_{1,2}$=6;$J_{2,3}$=4;$J_{3,4}$=10 |
| trans-1,2-Dihydroxy-1,2-dihydrodibenzo[a,h]pyrene (>330°,d) | $(CD_3)_2CO$, after exchange:4.50($H_2$,m);5.00($H_1$,d);6.22($H_3$,m); 7.44($H_4$,m);7.6-9.2(10H,m);$J_{1,2}$=11;$J_{2,3}$=10.5;$J_{3,4}$=2=$J_{2,4}$ |
| (±)-1β,2α-Dihydroxy-3α,4α-epoxy-1,2,3,4-$H_4$-dibenzo[a,h]-pyrene | DMSO-$d_6$:3.7-4.1($H_2$,$H_3$);4.73($H_1$);5.17($H_4$);5.70($OH_2$); 5.96($OH_1$);7.6-9.4(10H,m);$J_{1,2}$=9.0;$J_{3,4}$=4.5. |

[a]Reported in delta units; unless otherwise noted, spectra were obtained in $CDCl_3$, with internal TMS. [b]Correct microanalysis was obtained for these compounds; other listed compounds gave correct molecular ions in the mass spectrum.

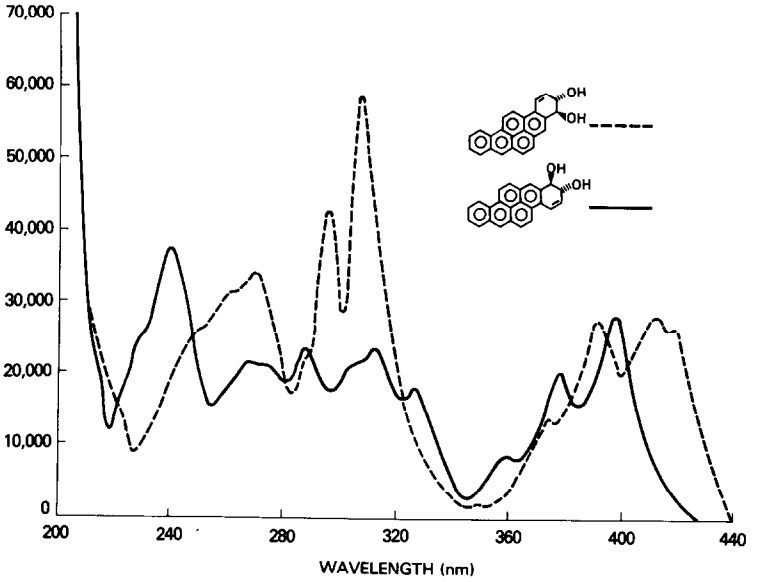



Figure. Ultraviolet spectra of dihydrodiols in THF-EtOH(1:9): 1(----) $\lambda_{max}$ 307 nm, $\varepsilon_{max}$ 58,200; 2(——) $\lambda_{max}$ 240 nm, $\varepsilon_{max}$ 37,400, $\lambda_{max}$ 398 nm, $\varepsilon_{max}$ 27,500.

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