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DIMETHYLDIOXIRANE EPOXIDATION OF POLYCYCLIC FLUORANTHENE HYDROCARBONS

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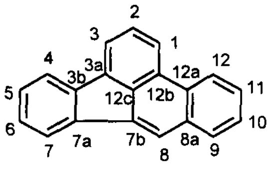
Abstract: Direct epoxidation of polycyclic fluoranthenes with dimethyldioxirane provides several new mono- and di-oxide derivatives.



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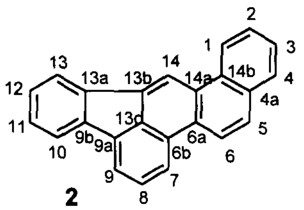

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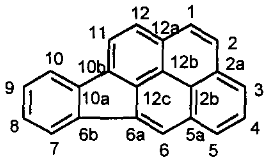

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Polycyclic aromatic hydrocarbons (PAHs) represent an important group of environmental carcinogens. Epoxidation of PAHs to arene oxides is an essential initial step towards their metabolic activation to mutagenic phenols and dihydrodiol epoxides in mammalian cells. Arene oxides have been prepared by several different synthetic routes, some of which require multiple steps.[1] Dimethyldioxirane (DMD) has been shown to be an excellent oxygen transfer agent for oxidation of a wide range of organic molecules,[2] including some common PAHs.[3] Herein we report direct DMD oxidation of three polycyclic fluoranthenes; benz[e]acephenanthrylene (**1**), indeno[1,2,3-hi]chrysene (**2**), and indeno[1,2,3-cd]pyrene (**3**).[4] The resulting epoxides (**4**, **6**, **8**, and **9**) represent a new class of arene oxides, which are structurally distinct from bay- and K-region epoxides in that an epoxide is formed at the highly strained, trisubstituted ring junction.

In a typical run, the arene was treated with DMD, generated in situ by mixing acetone and potassium monoperoxysulfate (Caroate®)[5] and the reaction progress was monitored by HPLC coupled with a photodiode array detector.[6] In general, arene oxide formation was readily recognized by the appearance of a polar peak(s), whose longer wavelength UV absorptions are generally not observed. Structural characterization of the new oxides (**4**, **5**, **6**, **8**, and **9**) and phenols (**8-OH-1**, **14-OH-2**) was accomplished by analyses of UV, ^{1}H NMR (NOE and COSY experiments) and low and high resolution mass spectral data.[7]

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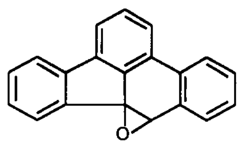

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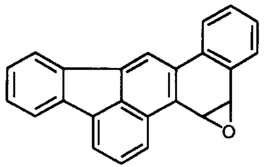

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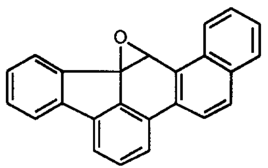

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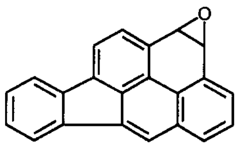

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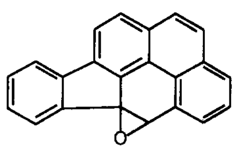

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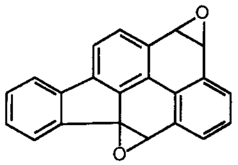

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The DMD epoxidation of **1** was completed in 8 h to furnish a single arene oxide. The major feature in the ^{1}H NMR spectrum was the absence of the characteristic H8 signal of **1** and the appearance of a singlet oxirane proton at 5.52 ppm, while the ^{13}C NMR spectrum exhibited two resonances at 57.3 (quaternary) and 53.0 (methine) ppm. Irradiation of the oxirane H8 resulted in enhancement of intensities of H7 and H9. On the basis of these findings the mono-oxide was assigned the 7b,8-epoxybenz[e]acephenanthrylene structure (**4**). This result is in good agreement with the DEWAR-PI molecular orbital calculations, which predict C8 to be the most reactive.[8] The nitration of **1** occurred at the 8 position,[9] although bromination took place at 1.[10] It should be noted that the energy difference between the two positions is only 3.8 kcal/mol.[8] The assigned structure was confirmed by its acid-catalyzed conversion to the phenol analog 8-OH-**1**, whose ^{1}H NMR and UV spectral data match with those reported previously.[11]

The epoxidation of **2** proceeded about 60% in 48 h, providing two peaks at 6.8 and 7.3 min. The ^{1}H NMR spectrum of the major product (36%) retained the H14 singlet at 8.6 ppm and two ABMX networks (H10,11,12,13 and H1,2,3,4).[12] Most revealing was the presence of two oxirane protons at 5.50 and 4.85 ppm (J = 4.2 Hz), which after irradiation gave NOE to H4 and H7, respectively. Thus, the major product was assigned as 5,6-epoxyindeno[1,2,3-hi]chrysene (**5**). The minor oxide (5%) showed a singlet oxirane proton at 6.1 ppm and lacked the H14 singlet of **2** in the ^{1}H NMR spectrum, which were in good agreement with the 13b,14-oxide structure (**6**). The observed oxidation pattern for **2** is consistent with the MO calculations, which predict an electrophilic substitution at C5, followed by C14. The minor oxide **6** was readily rearranged in an acidic environment to the corresponding phenol 14-OH-**2**.

The DMD epoxidation of **3** was completed in 12 h, affording three identifiable arene oxides at 4.5, 6.9, and 8.2 min. The ^{1}H NMR data of the major product (33%) matched those of the 1,2-oxide (**7**), which was previously prepared by treatment of **3** with OsO_4 in pyridine.[13] The minor product (4%) at 6.8 min was identified as the 6,6a-oxide (**8**) by the absence of the characteristic H6 singlet of **3** and the appearance of a singlet oxirane proton at 5.9 ppm in its ^1H NMR spectrum in comparison with that of **3**. The mass spectral data indicated the most polar peak at 4.5 min (3%) to be a dioxide, which was assigned to the 1-2,6-6a-diepoxyindeno[1,2,3-cd]pyrene structure (**9**). It was isolated as a diasteromeric mixture (i.e., cis and trans) depending on whether the oxides are located in the same or opposite side of the PAH. The distinctive feature in the ^1H NMR spectrum of **9** was the presence of a 7:3 ratio of two sets (a and b) of oxirane protons: a) two doublets at 4.79 and 4.74 ppm (H1,2, $J_{1,2}$ = 3.8 Hz) and one singlet at 5.59 ppm (H6); and b) two apparent singlets at 5.62 and 4.64 ppm in a 1:2 ratio (H6 and H1,2). The available data did not allow us to make specific diastereomeric assignments. The predicted sites of electrophilic substitution on **3** are the 3- and 5-positions followed by 12, which is only 1.4 kcal/mol higher in energy.[8] Both bromination[10] and nitration[9] are known to occur at the 12-position.[9] The greater double bond character on the 1,2- and 6,6a-bonds appears to be responsible for the preferential epoxidation.

In the three cases examined, epoxidation occurs consistently (although in low yields) at the highly strained, electron-rich junction bond adjacent to the indeno ring (i.e., 7b-8, 13b-14, and 6-6a for **1**, **2**, and **3**, respectively). Dihydrodiol epoxide derivatives of fluoranthene[14] and benz[j]fluoranthene,[15] which contain a similarly rigid oxide, have been detected in mouse skin, and human and rat livers, respectively. This may be significant since DMD has been suspected as an environmental oxidant that can mimic enzymes involved in metabolic activation of PAHs.[16]

References and Notes

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6. In a typical run, the arene (0.1 mmol) and 10 mg of tetra-n-butylammonium hydrogen sulfate were dissolved in acetone (20 mL), dichloromethane (15 mL) and a pH 7.2 phosphate buffer (10 mL). To this was added an aqueous solution of Caroate® (3 g, 4.88 mmol). The reaction mixture was stirred vigorously while maintaining the pH of the solution at 7.3 - 7.5 and the reaction temperature kept at 8 - 12 °C. The reaction was terminated by pouring into a separate funnel containing an equal volume of ice-water. The layers were separated and the organic layer was washed with H_2O, dried over K_2CO_3, and evaporated. The residue was purified by column chromatography on silica, eluting first with hexane and then with a mixture of hexane, ethyl acetate, triethylamine (78:18:4). Triethylamine was added to prevent acid-catalyzed rearrangement to a phenol.

7. The high-resolution mass spectral (HRMS) data were obtained on a Micromass 70-VSE. HPLC data were collected on a Waters Associates system equipped with a Hitachi L-3000 photodiode array detector using a 5μm Ultrasphere ODS analytical column (4.6 x 250 mm) and methanol as an eluent. All NMR spectra were measured in acetone-*d6* on a Bruker AM300 operating at 300 MHz. **4**: (64%); mp 199 - 201°C; HPLC t_R 5.0 min; UV (methanol) 225, 265, 277, 292 nm; ^{1}H NMR δ 8.31 (d, H12, $J_{11,12}$ = 7.7 Hz), 8.04 (d, H1, $J_{1,2}$ = 7.9 Hz), 7.95 (d, H4, $J_{4,5}$ = 7.4 Hz), 7.92 (d, H9, $J_{9,10}$ = 8.9 Hz, $J_{9,11}$ = 1.3 Hz), 7.87 (d, H3, $J_{2,3}$ = 7.4), 7.62 (m, H2), 7.60 (m, H11), 7.55 (m, H7), 7.54 (m, H10), 7.51 (m, H5), 7.41 (m, H6), 5.52 (s, H8); ^{13}C NMR δ 133.0, 131.3, 128.5, 125.2, 123.2, 122.0, 121.6, 120.9, 120.6, 120.3, 119.3, 119.0, 115.4, 114.4, 113.4, 112.43, 111.0, 57.3 (C7b), 53.0 (C8); HRMS, Calcd for $C_{20}H_{12}O$, 268.0888, Found *m/z* 268.0894 (M^+). **5**: (36%); mp 172 - 174°C; HPLC t_R 7.3 min; UV (methanol) 285 nm; ^{1}H NMR δ 9.10 (s, H14), 8.62 (d, H1, $J_{1,2}$ = 8.0 Hz), 8.52 (d, H7, $J_{7,8}$ = 7.8 Hz), 8.22 (m, H13), 8.12 (d, H9, $J_{9,8}$ = 6.6 Hz), 8.05 (m, H10), 7.90 (m, H4), 7.87 (m, H8), 7.62 (m, H2), 7.52 (m, H3), 7.45 (m, H11), 7.43 (m, H12), 5.50 (d, $J_{5,6}$ = 4.2 Hz), 4.85 (d, $J_{5,6}$ = 4.2 Hz); HRMS, Calcd for $C_{24}H_{14}O$, 318.1045, Found *m/z* 318.1039 (M^+). **6**: (5%); UV (methanol) 220, 270 nm; HPLC t_R 6.8 min; ^{1}H NMR δ 8.55 (d, H1, $J_{1,2}$ = 8.5 Hz), 8.20 (d, H6, $J_{5,6}$ = 8.8 Hz), 8.00 - 7.85 (m, 3*H*), 7.80 - 7.30 (m, 8*H*); HRMS, Calcd for $C_{24}H_{14}O$, 318.1045, Found *m/z* 318.1050 (M^+). **7**: (33%); HPLC t_R 8.2 min; UV and ^{1}H NMR match with those reported; ^{1}H NMR δ 8.50 (s, H6), 8.25 - 8.15 (m, H3,5,7,10,11,12), 7.80 (t, H4), 7.55 - 7.45 (m, H8,9), 4.97 (d, H1/H2, $J_{1,2}$ = 3.7 Hz), 4.91 (d, H1/H2). **8**: (4%); HPLC t_R 6.9 min; UV (methanol) 250, 278, 330, 345 nm; ^{1}H NMR δ 8.20 - 8.09 (m), 8.02 (dd, H10, $J_{9,10}$ = 8.4 Hz, $J_{8,9}$ = 1.9 Hz), 7.96 (m) H5, $J_{4,5}$ = 9.0 Hz), 7.80 (t, H4), 7.65 (d, H7, $J_{7,8}$ = 7.0 Hz), 7.56 (m, H9), 7.43 (m, H8), 5.90 (s, H6); HRMS, Calcd for $C_{22}H_{12}O$, 292.0888, Found *m/z* 292.0890 (M^+). **9**: (3%); HPLC t_R 4.5 min; UV (methanol) 220, 290 nm; ^{1}H NMR δ 8.05 - 7.85 (m, 5*H*), 7.65- 7.50 (m, 3*H*), 7.42 (m), 5.62 (s, H6), 5.59 (s, H6), 4.79 (d, $J_{1,2}$ = 3.8 Hz), 4.74 (d, $J_{1,2}$ = 3.8 Hz), 4.64 (s, H1,2), 7.39 - 7.65 (m, 4*H*), 7.86-8.00 (m, 5*H*); HRMS, Calcd for $C_{22}H_{12}O_2$, 308.0837, Found *m/z* 308.0846 (M^+). 8-OH-**1**: UV and mp match to those reported;[11] HPLC t_R 3.8 min; ^{1}H NMR δ 9.52 (s, OH, D_2O exchangeable), 8.82 (dd, H12, $J_{11,12}$ = 8.1 Hz, $J_{10,12}$ = 1.2 Hz), 8.60 (dd, H9, $J_{9,10}$ = 7.2 Hz, $J_{7,9}$ = 1.6 Hz), 8.52 (d, H1, $J_{1,2}$ = 8.5 Hz), 8.38 (d, H7, $J_{6,7}$ = 6.2 Hz, $J_{7,9}$ = 1.6 Hz), 8.12 (d, H3, $J_{2,3}$ = 6.7 Hz), 8.05 (dd, H4, $J_{4,5}$ = 8.1 Hz, $J_{4,6}$ = 1.6 Hz), 7.82 (m, H11), 7.70 (m, H10), 7.68 (m, H2), 7.48 (m, H5), 7.44 (m, H6). 14-OH-**2**: HPLC t_R 5.63 min; UV (methanol) 265, 280, 310 nm; ^{1}H NMR δ 10.10 (d, J = 8.5 Hz), 8.85 (d, J = 6.1 Hz), 8.67 (d, 8.3 Hz), 8.45 (d, 6.9 Hz), 8.20 - 8.05 (m, 4*H*), 7.80 - 7.60 (m). 3*H*, 7.40 (m, 2*H*); HRMS, Calcd for $C_{24}H_{14}O$, 318.1045, Found *m/z* 318.1048 (M^+).

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