Synthesis and Characterization of Thermodynamically Unstable Polycyclic Aromatic Hydrocarbon Episulfides and Episulfoxides

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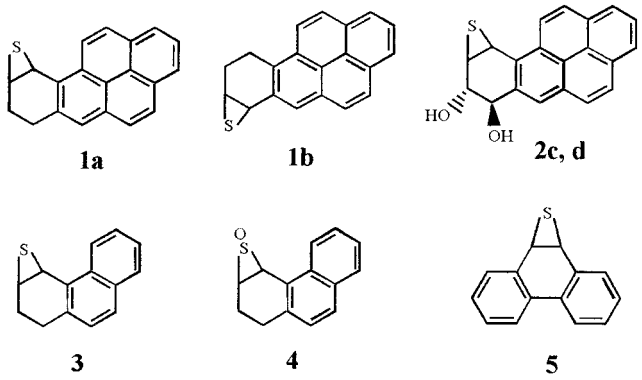
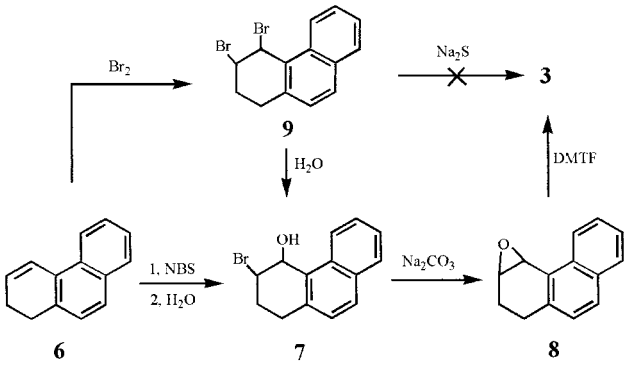
Introduction

Polycyclic arene epoxides have been established as the primary metabolites of the carcinogenic polycyclic aromatic hydrocarbons (PAHs),[1−3] leading, eventually, to the ultimate carcinogenic PAH-diol epoxides (DEs). The first sulfur analogues **1a**,**b** and **2c**,**d** of the parent epoxides and DEs (saturated A-ring) have been just recently prepared,[4,5] while the syntheses of selected polycyclic arene episulfides have been previously attempted[6] and their thermodynamic stability theoretically studied.[6,7] These episulfides were found to be, thermodynamically, significantly less stable than the corresponding epoxides toward elimination of sulfur and oxygen, respectively. Their relative stability can be deduced from the degree of the aromatic character of the rings that do not carry the heteroatom.[7]



Polycyclic aromatic hydrocarbon episulfides are highly interesting. On one hand, they maintain the basic requirement of the PAH carcinogenicity[8] and the particular steric, electronic, and electrophilic requirements in the formation of the corresponding DNA adducts.[9] On the other hand, the higher polarizability of the sulfur atom, the weaker strength of the sulfur−carbon bond compared to the strength of the oxygen−carbon bond, and consequently, the better leaving capacity of the sulfur atom compared to that of the oxygen may make the PAH-episulfides better electrophiles toward the nucleophilic sites of the DNA than their epoxide counterparts.

Scheme 1



We reported previously on a highly efficient method for the conversion of bay-region benzylic PAH epoxides to the corresponding episulfides with *N*,*N*-dimethylthioformamide (DMTF) in the presence of the Lewis acid catalyst $BF_3{\cdot}Et_2O$ at low temperature.[5] We now report the synthesis and characterization of the hitherto unknown polycyclic aromatic hydrocarbon episulfide **3** without the use of the Lewis-type catalyst and the identification/characterization of the first, thus far illusive, corresponding episulfoxide **4**, as well as arene episulfide **5**. In view of the surprising hydrolytic stability of the previously prepared PAH-episulfides,[5] the relatively more electrophilic episulfoxide **4** (compared to sulfide **3**) may result in a hydrolysis rate similar to that of the corresponding epoxide. This has bearing on the formation of the corresponding DNA adducts.

Results and Discussion

Our synthesis of episulfide **3** is given in Scheme 1. The preparation of the key 1,2,3,4-tetrahydrophenanthrene-3,4-oxide (**8**)[10] was first achieved by means of Jerina's procedure (using for the hydrolysis step an ion-exchange resin in a hydroxy anion form).[11] Thus, a 60% yield of **8** was obtained from the racemic 3-bromo-1,2,3,4-tetrahydro-4-hydroxyphenanthrene (**7**). Since benzylic epoxides can undergo both acid- and base-catalyzed solvolysis to the corresponding hydroxy compounds,[5,12,13] various bases, i.e., DBN, sodium methoxide, sodium hydroxide, sodium carbonate, and sodium bicarbonate in different solvent

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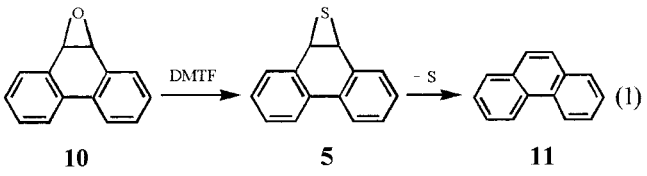
systems, were used to optimize the transformation from **7** to **8**. We have found that sodium carbonate/water/THF was the best system for this purpose, giving the highest yield (83%) of epoxide **8**. Although many polycyclic arene epoxides were prepared via direct epoxidation of the corresponding alkenes with *m*-CPBA,[14−18] the direct epoxidation of **6** with this reagent failed, whereas using methyl (trifluromethyl) dioxirane[19] afforded **8** in too low yield to facilitate purification by recrystallization. The epoxidation of **6** using the DCC/H_2O_2 system[20] also did not afford **8**.

In our hands, the direct preparation of the bromohydrin **7** from **6** using NBS proved to be the method of choice (92% yield), compared to an initial bromination of **6** to give 3,4-dibromo-1,2,3,4-tetrahydrophenanthrene (**9**), followed by the hydrolysis of the latter to afford **7** in 72% yield (i.e., from **6** to **7** via **9**).[21]

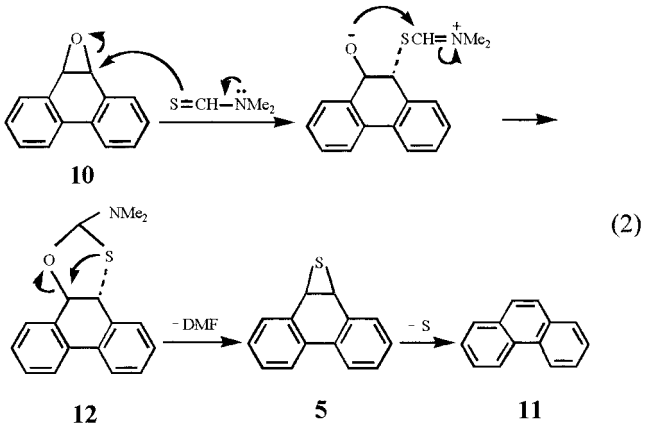
On the basis of our previously developed synthetic methodology for an efficient highly stereoselective conversion of epoxides to the corresponding episulfides in the PAH series,[5] **8** and **10** have been treated with DMTF without any catalyst at −78 to 0 °C to afford the episulfide **3** (in 80% isolated yield) and the decomposition products of episulfide **5**, respectively. Significantly, the ^{1}H NMR ($CDCl_3$) of H_3 and H_4 in **3** (3.77 and 4.64, $J_{3,4}$ = 6.6 Hz) is in full accord with that reported for the corresponding H_3 and H_4 in **1a** (3.92 and 4.98 $J_{3,4}$ = 6.5 Hz).[4] It was previously found experimentally[4,5] and theoretically, via molecular orbital calculations,[6,7] that K-region PAH-episulfides are, thermodynamically, more stable toward sulfur extrusion than their bay-region isomers. This, together with the relatively higher thermodynamic stability of the episulfides with the higher aromatic character of the ring system,[7] is in accord with the instability of **3**. The thus far elusive **5**[4] was previously detected by us via ^{1}H NMR spectroscopy ($CDCl_3$, 3.98, s)[6,7] in accordance with the previously reported data for the corresponding episulfide ring protons in **1b** (3.92 and 4.44).[4] However, it is too unstable to be isolated. Instead, its decomposition products, elemental sulfur (72%) and phenanthrene (**11**) (74%), respectively, were isolated (eq 1).



10 **5** **11** (1)

These results point to a good yield for the transformation of **10** to **5** while the ∼1:1 sulfur:phenanthrene ratio is in accord with the intermediacy of **5**. Traditionally, conversions of oxiranes to the corresponding thiiranes by sulfur transfer agents such as DMTF[22] and 3-methylbenzothiazole-2-thione[23] were achieved only in the presence of an acid or Lewis-type catalyst, e.g., trifluoroacetic acid and BF_3·Et_2O. We have found that excess of DMTF or 3-methylbenzothiazole-2-thione (10 equiv) could transform **8** and **10** into the corresponding episulfides **3** and **5**, respectively, at low temperature in the absence of any catalyst. At these same temperatures, the same transformations can also be achieved using only 2 equiv of DMTF or 3-methylbenzothiazole-2-thione in the presence of catalytic BF_3·Et_2O. In an ^{1}H NMR spectroscopic study of the transformation of **10** to **5** using DMTF as the sulfur transfer agent, neither the resulting DMF nor the starting **10** (4.55 ppm, s) showed any peaks at the 3.4−4.0 ppm range. The new peaks at 3.51 and 3.67 ppm were assigned to the oxothiolane intermediate (**12**).

We propose the following mechanism (eq 2) for the transformation of epoxide **10** to the episulfide **5**, which



10 **12** **5** **11** (2)

is in accord with the accepted mechanism for transformations of epoxides to the corresponding episulfides induced by sulfur transfer agents.[24]

Oxidation of episulfide **3** with *m*-CPBA afforded the corresponding episulfoxide **4**, which lost SO very fast at room temperature to give **6**, so that the isolation of **4** was not possible. However, the IR spectrum of the reaction mixture showed a strong absorption at 1065 cm^{-1}, which is characteristic for the sulfur−oxygen (S=O) stretching frequency of thiirane oxides.[25] The EI-MS of **4** showed a base peak of *m*/*z* 180 (M^+ − SO). Regardless whether the sulfoxide group was eliminated following an initial ionization by the electron impact on **4** or that thermal decomposition is responsible for this elimination,[25] the base peak of *m*/*z* 180 and the expected absence of peak at *m*/*z* 212 strongly suggest that the expected episulfoxide **4** has been formed. The formation of the latter is further corroborated via the low-temperature NMR studies of **4** in which H_4 and C_3 were detected at 6.07 and 53.3 ppm, respectively. To our best knowledge, **4** is the first detected PAH benzylic episulfoxide.

We are currently further exploring the possibilities of preparing both benzylic polycyclic aromatic hydrocarbon episulfide and episulfoxide systems that are more thermodynamically stable than **5** and **4** to facilitate study of their chemistry and biological activity.

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Experimental Section

General. Melting points were recorded on a Buchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.33 MHz, respectively. Mass spectra were determined at an ionization voltage of 70 eV. Column chromatography was performed with silica gel (70−230 mesh). Ether, THF, and toluene were distilled over sodium; **10** was prepared according to the literature procedure.[26] All commercially available reagents were used directly as obtained.

1,2-Dihydrophenanthrene (6). By a modified procedure,[21] a mixture of 1-hydroxy-1,2,3,4-tetrahydrophenanthrene (4.95 g, 25 mmol), *p*-toluenesulfonic acid monohydrate (0.7 g, 3.7 mmol), and benzene (140 mL) was refluxed for 45 min. After cooling to room temperature, the reaction mixture was washed with water, 3% sodium carbonate, and then water again and dried (Na_2SO_4), and the solvent was evaporated to leave **6** (4.53 g, 100%) as a colorless oil that solidified at about 0 °C and had a blue fluorescence.

3-Bromo-1,2,3,4-tetrahydro-4-hydroxyphenanthrene (7). A 50 mL flask was charged with **6** (1.56 g, 8.65 mmol), sodium acetate (0.66 g), water (8 mL), and DMSO (40 mL) and cooled to 0 °C. NBS (3.05 g, 17.1 mmol) was added during 3 min into the above solution with vigorous stirring. Stirring was continued at 0 °C for 1 h. Ethyl acetate (180 mL) was then added followed by water (380 mL). The organic layer was washed several times with water. The solvent was then removed to give a slightly yellow solid. Recrystallization from a mixture of hexane (16 mL)/ethyl acetate (8 mL) afforded **7** (2.2 g, 92%) as a white solid, mp 156−157 °C (lit.[21] mp 157−158 °C).

1,2,3,4-Tetrahydrophenanthrene-3,4-oxide (8). A mixture of **7** (132 mg, 0.476 mmol), sodium carbonate monohydrate (344 mg, 2.77 mmol), water (5 mL), and THF (17 mL) was stirred at room temperature for 2 days under N_2. The THF was removed in vacuo, and the residue was extracted by ether. The organic layer was washed several times with water. The solvent was removed to give a white solid. Recrystallization from hexane gave racemic **8** (77 mg, 83%) as colorless prisms, mp 58−60 °C: ^1H NMR (CD_2Cl_2) δ 1.84 (m, 1H, H_2), 2.48 (m, 1H, $H_{2'}$), 2.76 (m, 2H, H_1), 3.88 (m, 1H, H_3), 4.71 (d, 1H, H_4), 7.29 (d, 1H, H_{10}, $J_{9,10}$ = 8.3 Hz), 7.57 (m, 2H, H_6, H_7), 7.79 (d, 1H, H_9), 7.89 (d, 1H, H_8), 8.33 (d, 1H, H_5, $J_{5,6}$ = 8.4 Hz); ^{13}C NMR (CD_2Cl_2) δ 20.90 (C_2), 24.89 (C_1), 47.05 (C_3), 55.53 (C_4), 121−134.69 (C_5−C_{12}); MS *m*/*z* (EI) 196 (M^+), 180 ($M^+ - O$) (base peak), CI (Isobutane) 197.1 (MH^+), 181.2 ($MH^+ - O$).

1,2,3,4-Tetrahydrophenanthrene-3,4-episulfide (3). Into a solution of **8** (221 mg, 1.12 mmol) in dichloromethane (7 mL) was syringed DMTF (190 μL, 2.23 mmol) at −65 °C followed by a catalytic amount (2 μL) of BF_3·Et_2O. The mixture was stirred until the entire oxide was consumed (4 h, as indicated by TLC on silica gel with a 5:1:0.05 mixture of hexane/ethyl acetate/triethylamine as eluent). The solvent was then evaporated under reduced pressure at −20 °C, and the residue was chromatographed through a short silica gel column with a 10:1:0.05 mixture of hexane/ethyl acetate/triethylamine as quickly as possible. The product obtained, episufide **3**, is a colorless solid (190 mg, 80%). It completely lost elemental sulfur when left to stand at room temperature for a day. It did not deteriorate when stored in the freezer at − 75 °C. IR (CH_2Cl_2) 2963, 1530, 665 cm^{-1}; ^1H NMR (CDCl3, rt) δ 2.24 (m, 1H, H_2), 2.52 (m, 1H, $H_{2'}$), 2.69 (dd, 1H, H_1), 2.91 (m, 1H, $H_{1'}$, $J_{1,2}$ = 5.9 Hz), 3.77 (m, 1H, H_3, $J_{2,3}$ = 3.3 Hz), 4.64 (d, 1H, H_4, $J_{3,4}$ = 6.6 Hz), 7.16 (d, 1H, H_{10}, $J_{9,10}$ = 8.3 Hz), 7.44 (m, 1H, H_7), 7.56 (m, 1H, H_6), 7.65 (d, 1H, H_9), 7.80 (d, 1H, H_8), 8.25 (d, 1H, H_5, $J_{5,6}$ = 8.6 Hz); HRMS calcd for $C_{14}H_{12}S$ 212.0660 (M^+), found 212.0626; calcd for (M^+−S) 180.0939, found 180.0932 (base peak).

Synthesis and Detection of 1,2,3,4-Tetrahydrophenanthrene-3,4-episulfoxide (4). Into a solution of **3** (190 mg, 0.895 mmol) in dichloromethane (7 mL) was added dropwise during 5 min at −65 °C *m*-CPBA (185 mg, 1.07 mmol) in dichloromethane (10 mL). Stirring was continued for 40 min, and the temperature was allowed to rise to − 20 °C. The consumption of the peracid and **4** was checked via a moist iodine-starch paper and TLC (developed with a 10:1:0.05 mixture of hexane/ethyl acetate/triethylamine, R_f for **6** = 0.9, R_f for **3** = 0.5, R_f for **4** = 0.3). The reaction mixture was washed with cold 5% sodium carbonate, and the solvent was removed in vacuo at − 20 °C to give a white solid, the IR and MS of which was immediately taken. IR (CH_2Cl_2) 1065 cm^{-1}; MS *m*/*z* 180 ($M^+ - SO$). The sulfoxide **4** lost SO quickly to give the blue fluorescent **6** at room temperature. It slowly lost SO even when stored in the freezer at −75 °C and could not be detected by IR (1065 cm^{-1}) when stored for more than a month at this temperature.

A solution of epoxide **8** (11 mg, 0.056 mmol) in CD_2Cl_2 (0.5 mL) in an NMR tube was cooled to −40 °C in an NMR instrument. After ^1H and ^{13}C NMR were recorded, the tube was further cooled to −50 °C and DMTF (9.5 μL, 0.11 mmol) followed by BF_3·Et_2O (1 μL) were syringed into it at this temperature. The mixture was then monitored by ^1H NMR at −40 °C. The entire **8** was consumed after 2 h. Episulfide **3**: ^1H NMR δ 4.52 (1H, H_4); ^{13}C NMR δ 21.88 (C_2), 24.02 (C_1), 42.07 (C_3), 69.00 (C_4). *m*-CPBA (29 mg, 0.166 mmol) was then added portionwise at −40 °C ,and the mixture was allowed to warm to −30 °C to avoid solidification of the solution. Mixture: ^1H NMR δ 6.07 (m, H_4 of the episulfoxide **4**); DEPT ^{13}C NMR δ 53.3 (C_3 of the episulfoxide **4**).

Synthesis and ^1H NMR Study of Phenanthrene-9,10-episulfide (5). Epoxide **10** (10 mg, 0.0515 mmol) and $CDCl_3$ (0.4 mL) were loaded into an NMR tube. The solution was monitored by ^1H NMR spectroscopy at −55 °C before and after the addition of DMTF (60 μL, 0.70 mmol).

To a 50 mL flask was added **10** (130 mg, 0.67 mmol) together with dichloromethane (40 mL). The solution was cooled to −78 °C. DMTF (1 mL, 11.7 mmol) was then syringed into the flask, and the stirring was continued for an additional 5 min, allowing the temperature to rise to 0 °C. The solvent was removed in vacuo, and water (8 mL) was added to extract the residue (yellow oil). Removal of the water was followed by further washing of the resulting yellow solid with water. Recrystallization from ethanol (7 mL) afforded 15 mg (0.48 mmol, 72%) of sulfur as a yellow solid, which was identical in its physical and chemical properties with an authentic sample of elemental sulfur. Water (8 mL) was then added into the mother ethanolic solution to deposit the phenanthrene (88 mg, 0.50 mmol, 75%) as an off white solid, which was identical in all respects (mp, mixed mp, IR, TLC) with an authentic sample of phenanthrene.

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