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SYNTHESIS OF BENZO[c]PHENANTHRENE DIHYDRODIOLS

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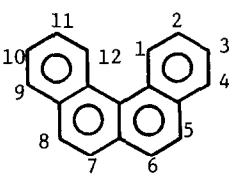
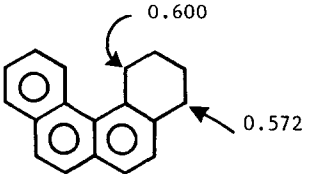
Abstract: Unlike most other alternant polycyclic aromatic hydrocarbons which are carcinogenic, benzo[c]phenanthrene has a "fjord region" instead of a "bay region". For this reason, we have synthesized the three metabolically possible trans 1,2-, 3,4-, and 5,6-dihydrodiols to test them for carcinogenic activity.

The "bay-region" theory[1] proposes that diol epoxides on benzo-rings of polycyclic aromatic hydrocarbons will have the highest chemical reactivity and presumably biological activity when the epoxide group forms part of a bay-region of the hydrocarbon. Predictions of the theory have proved to be quite correct for all hydrocarbons which have been adequately tested thus far;[2] these include benzo[a]pyrene, benzo[a]anthracene as well as its 7-methyl and 7,12-dimethyl derivatives and 3-methylcholanthrene, chrysene and 5-methylchrysene, and dibenzo[a,h]anthracene. In each of the above cases, a clear choice as to which isomeric diol epoxide of a given hydrocarbon would be most reactive was possible based on our application[1] of Dewar's[3] parameter $\Delta E_{deloc}/\beta$. The larger the value of this parameter, the greater the predicted ease of carbonium ion formation at the designated position. The present report is concerned with the hydrocarbon benzo[c]phenanthrene (B[c]Ph) which is unique in several ways; (i) formally, the hydrocarbon has no "bay-region" but has instead a related region referred to as a "fjord" between positions-1 and-12, [4] ii) the calculated ease of carbonium ion formation ($\Delta E_{deloc}/\beta$) at positions-1 versus-4 on 1,2,3,4-tetrahydro B[c]Ph is rather similar



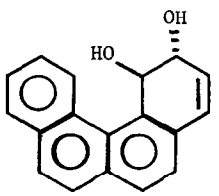
B[c]Ph

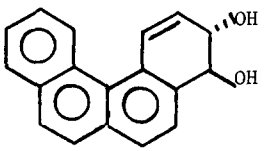


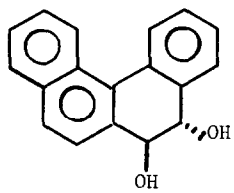
in contrast to related calculations for the above hydrocarbons[1], and iii) the carcinogenic activity of B[c]Ph[5] is somewhat higher than might have been anticipated in that its activity is similar to that of benzo[a]anthracene ($\Delta E_{deloc}/\beta$ = 0.766 at C-1). In order to pursue the mechanism by which B[c]Ph expresses its carcinogenicity, we have synthesized the three metabolically possible trans dihydrodiols of this hydrocarbon.

B[c]Ph is conveniently prepared by photocyclization of β-napth-2-ylstyrene.[6] The hydrocarbon is readily oxidized to its K-region 5,6-quinone by dichromate in acetic acid.[7] Reduction of the quinone (130 mg) in 2-propanol with excess KBH_4 for 16 hr conveniently

provided the trans 5,6-dihydrodiol;[8] 50% yield, mp 178° from benzene, nmr (100 MHz, CD_3OD)







1,2-dihydrodiol 3,4-dihydrodiol 5,6-dihydrodiol

H_5 and H_6 at 5.52 and 5.62 δ with $J_{5,6}$ = 5.3 Hz. Although attempts to directly oxidize B[c]Ph to its K-region oxide with either m-chloroperoxybenzoic acid[9] or sodium hypochlorite[10] were unsuccessful, a modest yield (8%) of the 5,6-oxide was isolated after treatment of the 5,6-diol with tosyl chloride and NaH[11] followed by chromatography on basic alumina (ICN, activity IV) eluted with 5% dioxane in cyclohexane; nmr (100 MHz, $CDCl_3$), H_5 and H_6 at 4.66 and 4.79 δ with $J_{5,6}$ = 4 Hz.

The synthetic approach most generally successful in the preparation of benzo-ring dihydrodiols has consisted of transformation of a tetrahydro benzylic ketone into a tetrahydro trans diol, followed by introduction of the double bond.[12] Thus, synthesis of the 3,4-dihydrodiol requires the known[13] 4-keto-1,2,3,4-tetrahydro B[c]Ph. For the present study, this ketone was synthesized from 4-keto-1,2,3,4-tetrahydrophenanthrene via Reformatsky reaction with methyl bromocrotonate [12] in 28% overall yield. Reduction of the ketone to the alcohol (mp 171°, benzene) with $NaBH_4$ in methanol followed by subsequent dehydration (HCl-acetic acid, 1 hr at 90°) provided 1,2-dihydro B[c]Ph (colorless needles mp 93°, methanol) in 85% overall yield. Prevost reaction (2.5 eq. of silver acetate and 1.25 eq. of I_2) afforded the trans 3,4-diacetate (mp 116°, ethanol) with $J_{3,4}$ = 6.5 Hz in 50% yield. Bromination (NBS, CCl_4) followed by dehydrobromination (diazabicyclononane in THF at 4° for 16 hr) provided the desired 3,4-dihydrodiol diacetate (mp 164°, methanol) in 35% overall yield; nmr (100 MHz, $CDCl_3$) H_3 5.78, H_2 6.30 and H_4 6.40 δ with $J_{3,4}$= 6.1, $J_{2,3}$ = 4, $J_{1,3}$ = 0.9, and $J_{1,2}$ = 10 Hz as the diacetate and nmr (220 MHz, CD_3OD) H_3 4.57, H_4 4.68, H_2 6.23, and H_1 7.32 δ with $J_{3,4}$ = 10.8, $J_{2,3}$ = 2.3, $J_{1,3}$ = 2.0, and $J_{1,2}$ = 10.1 Hz as the free dihydrodiol. Both spectra are very similar to the corresponding 3,4-analogs of benzo[a]anthracene[14] with the exception that H_4 in the free diol of B[c]Ph is at 0.3 ppm higher field.

Synthesis of B[c]Ph 1,2-dihydrodiol was hindered by the fact that 1-keto-1,2,3,4-tetrahydro B[c]Ph is unknown. Careful examination of the cyclization products (HPLC) from γ-(3-phenanthryl) butyric acid under a variety of Friedel-Crafts conditions failed to provide any evidence for the formation of this ketone. Ease of cyclization at the 2-position on the phenanthrene nucleus[15], low reactivity of phenanthrene toward electrophilic substitution at C-4, and steric hindrance in the "fjord" region all probably contribute to the lack of formation of the desired 1-ketone. Attempted partial aromatization of 1,2,3,4-tetrahydro B[c]Ph with DDQ[16] gave only B[c]Ph, and reaction of the tetrahydro B[c]Ph with lead tetracetate[17] gave only the undesired 4-acetoxy-1,2,3,4-tetrahydro B[c]Ph (mp 125°). As an alternative

approach, we considered direct oxidation of the hydrocarbon to the 1,2-dihydrodiol[18]. Analytical HPLC indicated that >60% of the total detectable dihydrodiols was the desired 1,2-dihydrodiol along with ~30% of the 3,4-dihydrodiol and only a minor amount of the 5,6-dihydrodiol. In a typical experiment, 250 mg of B[c]Ph in 750 ml of acetone was mixed with 750 ml of distilled water containing 40 g of ascorbic acid, 5 g of $FeSO_4$ and 2.5 g of sodium EDTA, and air was bubbled through the mixture for 6 hr. After evaporation of most of the acetone and saturation of the solution with $NaHCO_3$, the chloroform extractable products were chromatographed on two 2mm silica gel TLC plates (20 x 20 cm) with 10% ethanol in benzene as eluent. The dihydrodiol band (R_f 0.3-0.4) was further purified on a Whatman silica gel column (0.92 x 50 cm) eluted with 5% ethanol in cyclohexane (ret. time 8.5 min at 4.0 ml/min) to provide 2-3 mg of pure 1,2-dihydrodiol which rapidly turns yellow on exposure to air; nmr (100 MHz, $CDCl_3$) H_2 4.53, H_1 5.62 H_3 6.35, and H_4 6.90 δ with $J_{1,2}$ = 2.3, $J_{1,3}$ <1, $J_{2,3}$ = 5.8, and $J_{3,4}$ = 9.6 Hz. This spectrum is nearly identical to that of the benzo[a]anthracene trans 1,2-dihydrodiol which also has its hydroxyl groups predominantly quasi-diaxial due to steric crowding.[14,19] The basis for the high trans specificity in such oxidations is presently unknown.

The uv spectra of all three dihydrodiols are shown in the Figure. Preliminary evaluation of the ability of liver microsomes to activate these dihydrodiols to mutagens toward S. typhimurium TA100 has indicated that the 3,4-dihydrodiol is 3.6-fold as active as B[c]Ph where as the other two dihydrodiols caused <10% as many mutations.[20] A possible explanation for the inactivity of the 1,2-dihydrodiol is that the diaxial hydroxyl groups prevent metabolic formation of the 1,2-diol-3,4-epoxides.[21]

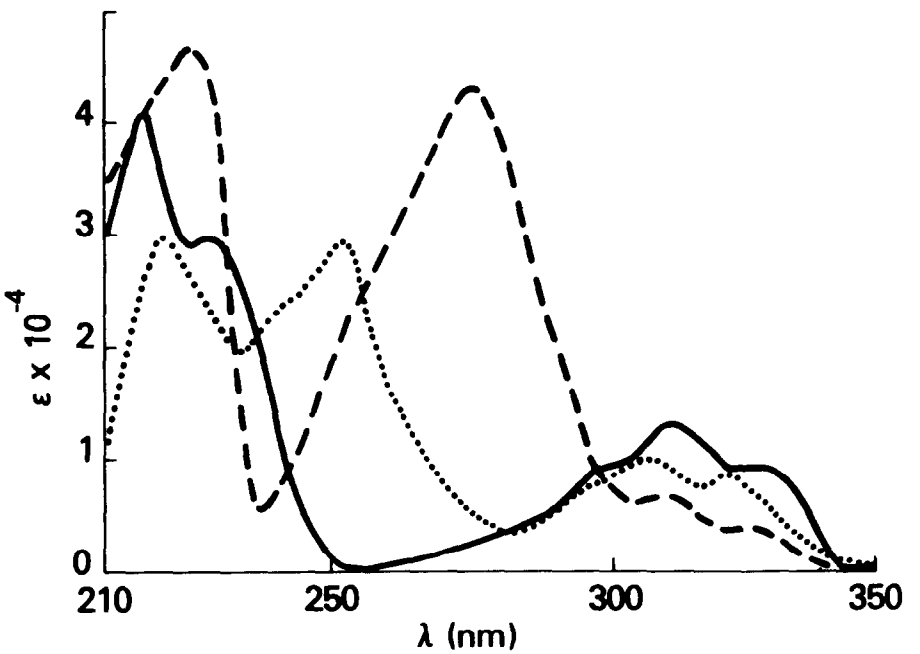


Figure UV spectra (CH_3OH) of B[c]Ph 1,2-(....., ε 27,300 at 253 nm), 3,4-(----, ε 43,300 at 273 nm) and 5,6-(——, ε 13,100 at 310 nm) dihydrodiols.

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