Benzo[c]phenanthrene and Its Oxidized Metabolites

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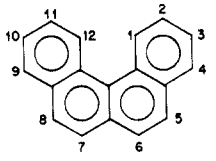
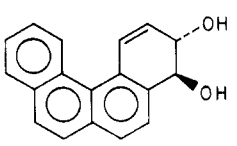
A novel synthesis of benzo[c]phenanthrene (BcP) and its 3- and 4-phenolic derivatives via the key intermediate 4-oxo-1,2,3,4-tetrahydrobenzo[c]phenanthrene (8) is described. Compound 8 is also a synthetic precursor of the 3,4-dihydrodiol of BcP and its diol epoxide derivative, implicated as proximate and ultimate carcinogenic metabolites, respectively, of BcP. Reaction of the potassium and thallium salts of 1,3-cyclohexanedione with 2-(2-naphthyl)ethyl iodide under a variety of conditions affords predominantly the product of O-alkylation. However, reaction of the potassium salt of 1,5-dimethoxycyclohexa-1,4-diene with this alkyl halide in liquid ammonia takes place regioselectively in the 6-position to provide the 2-alkyl diketone 6. The latter undergoes cyclization in polyphosphoric acid and dehydrogenation with DDQ to afford 8. Reduction of 8 with $NaBH_4$ followed by dehydration and dehydrogenation provides BcP in superior yield and fewer steps than previous methods. The overall synthetic approach represents a potentially general method for the preparation of polycyclic hydrocarbons and their substituted derivatives.

Benzo[c]phenanthrene (BcP) is a relatively weak carcinogen[1] present in the atmosphere[2] at levels comparable to those of the more potent and better known carcinogen benzo[a]pyrene. The 3,4-dihydrodiol (1) and the corresponding diol epoxide (2) derivatives of BcP have been implicated as proximate and ultimate carcinogenic metabolites, respectively.[3]



BcP



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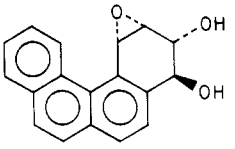
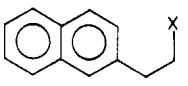


2

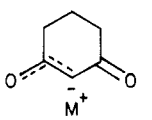
We now report a novel synthesis of 4-oxo-1,2,3,4-tetrahydro-BcP (8), a key intermediate in the synthesis of 1 and 2.[4] Compound 8 is also utilized as an intermediate in the synthesis of BcP as well as 3- and 4-hydroxy-BcP, possible phenolic metabolites of BcP. The synthetic approach employed represents a potentially general method for the synthesis of polycyclic aromatic ring systems.

Results and Discussion

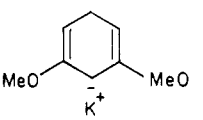
1,3-Cyclohexanedione represents an attractive potential building block for the construction of polycyclic ring systems. However, alkylation of the metallic salts of 1,3-cyclohexanedione is complicated by the relatively greater facility of alkylation of the ambident anion on oxygen than carbon. However, monoalkylation on carbon of the thallium salts of β-dicarbonyl compounds by alkyl iodides has been reported by Taylor et al.[5]



3a, X = OH
b, X = I



4a, M = Tl
b, M = K



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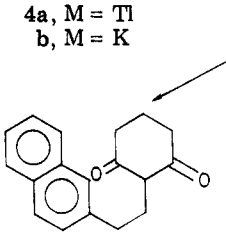

6

Our initial studies were directed, therefore, to the investigation of the reaction between 2-(2-naphthyl)ethyl iodide (**3b**) and the thallium salt of 1,3-cyclohexanedione (**4a**). Synthesis of **3b** was readily accomplished through reaction of 2-(2-naphthyl)ethanol (**3a**) with P_2I_4 by the method of Lauwers et al.[6] Reaction of **4a** with **3b** did indeed furnish the alkylated diketone **6**, albeit in low yield, ~10%. A limited study of experimental conditions failed to effect any significant improvement.[7] Analogous reaction of the potassium salt of 1,3-cyclohexanedione (**4b**) with **3b** provided **6** in 13% yield (18% based on **3b** consumed). The principal product was the O-alkylated enol ether which on hydrolysis with HCl in methanol gave recovered 2-(2-naphthyl)ethanol (51%). However, an alternative method involving alkylation of the potassium salt of 1,5-dimethoxycyclohexa-1,4-diene (**5**) with **3b** in liquid ammonia proved more satisfactory, affording the desired diketone **6** in 70% yield.

Cyclization of **6** took place smoothly in polyphosphoric acid to afford the cyclic ketone **7**. Dehydrogenation of **7** with DDQ gave **8**. Synthesis of BcP was achieved from **8** through reduction of the carbonyl function with $NaBH_4$, acid-catalyzed dehydration to 1,2-dihydro-BcP (**9a**), and dehydrogenation with DDQ. Subsequently, a more efficient synthesis of BcP entailing fewer steps was devised. This involved reduction of the intermediate ketone **7** with $NaBH_4$ to the corresponding alcohol **10** which underwent

(1) Stevenson, J. L.; von Haam, E. *Am. Ind. Hyg. Assoc. J.* **1965**, *26*, 475.
(2) Lunde G.; Bjorseth, A. *Nature (London)* **1977**, *268*, 518.
(3) Wood, A. W.; Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Croisy-Delcey, M.; Ittah, Y.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 2876. Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218.
(4) Croisy-Delcey, M.; Ittah, Y.; Jerina, D. M. *Tetrahedron Lett.* **1979**, 2849.
(5) Taylor, E. C.; Hawks, C., III; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421.
(6) Lauwers, M.; Regnier, B.; von Eenoo, M.; Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1979**, 1801.
(7) Analogous reaction of **4a** with methyl iodide under various conditions gave 2-methyl-1,3-cyclohexanedione in yields of 38–49%. In accord with the present findings, predominant O-alkylation of **4a** with a series of alkyl halides has been reported by McIntosh, J. M.; Beaumier, P. M. *Can. J. Chem.* **1973**, *51*, 843.

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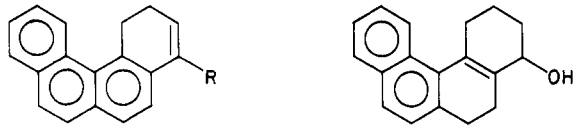
simultaneous dehydration and dehydrogenation over a 10% Pd/charcoal catalyst directly to BcP, mp 66–67 °C (85%).

7 8

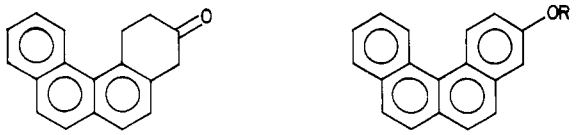


9a, R = H
b, R = OAc 10

Conversion of 8 to 4-hydroxy-BcP (**11b**) was effected through reaction with isopropenyl acetate to generate the enol acetate **9b**, which was dehydrogenated with DDQ to 4-hydroxybenzo[c]phenanthrene acetate (**11a**). Acidic methanolysis of **11a** gave **11b**.

11a, R = Ac
b, R = H

Synthesis of 3-hydroxy-BcP (**13b**) was accomplished from 1,2-dihydro-BcP through epoxidation with *m*-chloroperbenzoic acid, acid-catalyzed rearrangement to 3-oxo-1,2,3,4-tetrahydro-BcP (**12**), formation of the enol acetate, dehydrogenation with DDQ to **13a**, and acidic methanolysis.



12 13a, R = Ac
b, R = H

The novel syntheses described herein offer the advantages of fewer steps and superior yield over previous methods. Thus synthesis of 8 in five steps (28% yield) was previously reported by Croisy-Delcey et al.[4] from 4-oxo-1,2,3,4-tetrahydrophenanthrene, which was itself synthesized from tetralin by the method of Newman[8] in another five steps (15% overall yield). The present method entails only four steps from 2-naphthaleneethanol and provides 8 in 35% overall yield. This method also represents a potentially general synthetic approach to angular polyarenes. Application of this method to the synthesis of the potent carcinogen 5-methylchrysene is currently under investigation.

Experimental Section

2-(2-Naphthyl)ethyl Iodide (3b). To a solution of 5.94 g (10.4 mmol) of P_2I_4 in 300 mL of dry CS_2 was added at once 6.89 g (40 mmol) of 2-naphthaleneethanol. The dark-brown solution was stirred for 48 h at room temperature under Ar, when the color faded to light orange. After addition of 50 mL of saturated K_2CO_3 solution, stirring was continued for 20 min more. Conventional workup gave crude **3b** (9.85 g), which was recrystallized from methanol to provide pure **3b** (8.93 g, 79%): mp 81.5–83 °C: NMR δ 3.37 (br s, 4), 7.38–7.87 (m, 7, aromatic).[9]

2-[2-(2-Naphthyl)ethyl]cyclohexane-1,3-dione (6). Alkylation of 5 in Ammonia. To a solution of metallic potassium (21.5 mmol) in liquid ammonia (100 mL) under argon was added 1,5-dimethoxycyclohexa-1,4-diene[10] (7.0 g, 50 mmol). The resulting reddish brown solution was stirred for 8 min and then a solution of **3b** (2.8 g, 10 mmol) in ether (50 mL) was added over 8 min. The solution was stirred for 2 min and then poured on ice and worked up conventionally to afford **6** (1.87 g, 70%), mp 169–176 °C. Recrystallization from ethyl acetate gave 1.76 g of **6**, mp 182–183 °C. The analytical sample melted at 183.5–184.5 °C.

Alkylation of 4b. A solution of potassium ethoxide was prepared from 782 mg (20 mmol) of metallic potassium and 12 mL of anhydrous ethanol under argon. To this solution was added 2.24 g (20 mmol) of freshly recrystallized cyclohexane-1,3-dione. After the solution was gently warmed, the K salt of the dione separated. To this mixture were added 5.64 g (20 mmol) of **3b** and 30 mL of anhydrous alcohol, and the solution was heated at reflux for 20 h. Some crystalline KI separated. The mixture was poured on ice and extracted twice with CH_2Cl_2. The combined extracts were washed with water and dried, and the solvent was evaporated. The oily residue (5.1 g) was chromatographed on 150 g of Florisil. Hexane eluted **3b** (1.68 g, 30%); elution with benzene–10% and 20% ether gave the oily enol ether of 1,3-cyclohexanedione (2.81 g) which, on hydrolysis with HCl in methanol, gave 1.77 g (51.4%) of 2-naphthaleneethanol: mp 63–67 °C; NMR δ 1.91 (s, 1, OH), 2.93 (t, 2, CH_2, J = 7 Hz), 3.83 (t, 2, CH_2, J = 7 Hz). Further elution with benzene–30% and 40% ether furnished crude **6**. Recrystallization from methanol gave 670 mg (13%) of pure **6**, mp 183.5–184.5 °C. Similar results were obtained when the reaction was performed in aqueous ethanol, using KOH instead of ethoxide.

Alkylation of 4a. Analogous reaction of **3b** with **4a** in acetone or dimethylformamide gave **6** in ~10% yield; the major product was the enol ether (28–43%). Under similar conditions reaction of **4a** with methyl iodide afforded 2-methylcyclohexane-1,3-dione in 38–47% yield.

4-Oxo-1,2,3,4,5,6-hexahydrobenzo[c]phenanthrene (7). Compound **6** (2.39 g, 9 mmol) was heated with 60 g of polyphosphoric acid for 1 h at 115 °C. The product was poured into ice–water and then extracted twice with CH_2Cl_2. The combined extracts were dried and evaporated, and the residue (2.27 g) was chromatographed on 70 g of Florisil. Benzene and benzene–10% ether mixture eluted crude **7** (2.03 g). Recrystallization from methanol gave pure **7** (1.71 g, 76.6%): mp 120–121 °C; NMR δ 1.68–3.17 (m, 10, $H_{1,2,3,5,6}$), 7.28–8.24 (m, 6, aromatic). From the mother liquors an additional 0.11 g (4.9%), mp 119–121 °C, was obtained.

4-Oxo-1,2,3,4-tetrahydrobenzo[c]phenanthrene (8). A solution of **7** (1.98 g, 8 mmol) and DDQ (1.82 g, 8 mmol) in 60 mL of dry benzene was treated at reflux for 20 min. The mixture was cooled, and the hydroquinone (1.71 g) was filtered and washed with benzene. The filtrate was evaporated to dryness and the residue (1.82 g) chromatographed on Florisil. Hexane–benzene (1:1) eluted **8** (1.70 g), which on recrystallization from methanol gave pure **8** (1.61 g, 81.8%): mp 126.5–128.5 °C (lit.[8] mp 126–127 °C); NMR δ 2.11 (q, 2, H_2), 2.81 (t, 2, H_3), 3.73 (t, 2, H_1), 7.41–8.76 (m, 8, aromatic).

1,2-Dihydrobenzo[c]phenanthrene (9a). To a stirred solution of **8** (862 mg, 3.5 mmol) in methanol (86 mL) was added $NaBH_4$ (266 mg, 7 mmol) in portions over 30 min. The solution was stirred for 30 more min, then water was added, and the precipitate was filtered off and washed with 50% methanol to afford pure 4-hydroxy-1,2,3,4-tetrahydrobenzo[c]phenanthrene (609 mg), mp 184–185 °C (lit.[4] mp 171 °C); a second crop (241 mg), mp 174–179 °C, was obtained from the mother liquors. A solution of the alcohol (850 mg) in 100 mL of benzene was heated at reflux with *p*-tosic acid (100 mg) for 1 h. The usual workup afforded **9a** (790 mg). Recrystallization from methanol gave pure **9a** (437 mg, 54.3%), mp 92.5–94 °C (lit.[4] mp 93 °C). The mother liquors were evaporated to dryness, dissolved in minimal hexane,

(8) Newman M. S.; Blum, J. *J. Am. Chem. Soc.* **1964**, *86*, 503.

(9) All new compounds gave satisfactory microanalytical data for C and H within ±0.3%.

(10) Birch, A. J. *J. Chem. Soc.* **1947**, 102.

and adsorbed on a short column of Florisil. Elution with hexane–benzene (1:1) gave an additional crop of **9a** (318 mg) recrystallized from methanol to provide **9a** (224 mg), mp 91–92 °C (27.8%).

Benzo[*c*]phenanthrene. (a) From 1,2-dihydro-BcP. Dehydrogenation of **9a** (230 mg, 1 mmol) was carried out with DDQ (227 mg, 1 mmol) in refluxing benzene (10 mL). Separation of the hydroquinone was almost instantaneous. After 10 min, the mixture was cooled, the hydroquinone was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in hexane–benzene (1:1) and filtered through a short column of Florisil eluted with the same solvent mixture. The product was crystallized from hexane–ethanol to provide BcP (139 mg, 61%): mp 66.5–67.5 °C (lit.[11] mp 68 °C); second crop 33 mg (14.5%), mp 64–66 °C.

(b) From 7. To a stirred solution of **7** (497 mg, 2 mmol) in methanol (50 ml) was added $NaBH_4$ (152 mg, 4 mmol) in portions over 25 min. The usual workup gave 4-hydroxy-1,2,3,4,5,6-hexahydrobenzo[c]phenanthrene (**10**) (497 mg, mp 139.5–140 °C). A mixture of **10** (250 mg) and 10% Pd–C catalyst was heated in an oil bath at 285 °C for 1 h. The usual workup and filtration through a short column of Florisil gave an oil (200 mg) which crystallized from hexane–ethanol to afford pure BcP (129 mg): mp 67–67.5 °C; second crop (29 mg), mp 66–67 °C (69% yield).

4-Hydroxybenzo[*c*]phenanthrene Acetate (11a). A solution of **8** (246 mg, 1 mmol), *p*-tosic acid (20 mg) in 12.5 mL of isopropenyl acetate, and 2.5 mL of acetic anhydride was heated at reflux for 16 h. The solution was cooled and stirred with ice–water for 30 min, and the mixture was extracted twice with ether. Conventional workup gave a residue which was dissolved in minimal benzene, adsorbed on 6 g of Florisil, and eluted with benzene to afford the enol acetate **9b** (228 mg, 100%) as yellow crystals.

The enol acetate was heated at reflux with DDQ (227 mg, 1 mmol) in 10 mL of anhydrous benzene for 15 min. The mixture was cooled, and the hydroquinone was filtered and washed with benzene. The filtrate was concentrated and chromatographed on a column of 6 g of Florisil. Elution with benzene afforded a crystalline residue of **11a** (208 mg). Recrystallization from methanol gave pure **11a** (137 mg, 47.9%), mp 126–127 °C, and a second crop of 49 mg (17%), mp 124–126.5 °C: NMR δ 9.18 and 9.02 (apparent d, 2, H_1 and H_{12}), 7.20–8.07 (m, 9, aryl), 2.48 (s, 3, CH_3).

(11) Cook, J. W. *J. Chem. Soc.* **1931**, 2524.

4-Hydroxybenzo[*c*]phenanthrene (11b). A solution of **11a** (100 mg) in 20 mL of methanol and 0.4 mL of concentrated HCl was allowed to stand for 24 h at room temperature under argon. The usual workup gave a tan, crystalline residue which was dissolved in a small amount of benzene and passed through a short column of Florisil eluted with benzene. The crystalline product (87 mg) was recrystallized from hexane to afford **11b** (71 mg, 82.7%), mp 112.5–113 °C (lit.[8] mp 110–111 °C); a second crop (5 mg, 5.8%) melted at 111–112 °C.

3-Oxo-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (12). To a solution of **9a** (430 mg, 1.87 mmol) in CH_2Cl_2 (43 mL) were added *m*-chloroperoxybenzoic acid (430 mg, 2.39 mmol) and a solution of 430 mg of $NaHCO_3$ in 20 mL of water. The mixture was stirred for 4 h, and then the organic layer was separated, washed with 5% Na_2CO_3 solution, and dried. Evaporation of the solvent under reduced pressure, avoiding heating, gave the crude epoxide which was dissolved in anhydrous tetrahydrofuran (40 mL) and diluted with 20 mL of anhydrous ether. To this solution was added 0.8 mL of BF_3 etherate. After 2 min, the reaction was quenched and worked up in the usual manner to furnish an oily residue. Crystallization from ether gave **12** (343 mg), mp 106–112 °C. Recrystallization from methanol afforded pure **12** (212 mg, 46%): mp 115–117 °C; NMR δ 7.28–8.54 (m, 8, aryl), 3.91 (t, 2, H_1), 3.8 (s, 2, H_4), 2.48 (t, 2, H_2).

3-Hydroxybenzo[*c*]phenanthrene Acetate (13a). Reaction of **12** (209 mg, 0.85 mmol) with isopropenyl acetate (10 mL), acetic anhydride (2 mL), and *p*-tosic acid (20 mg) was carried out by the procedure for the analogous reaction of **8** to afford the corresponding enol acetate. The latter (241 mg, 0.84 mmol) was dissolved in 10 mL of dry benzene, DDQ (191 mg, 0.84 mmol) was added, and the solution was heated to reflux for 15 min under argon. The usual workup gave 236 mg of an oil which crystallized from ether–hexane to give **13a** (178 mg, 73%), mp 126.5–127.5 °C, and 8 mg (3.3%), mp 124–125 °C; recrystallization from methanol raised the melting point to 127–128 °C: NMR δ 7.31–9.20 (m, 11), 2.37 (s, 3, CH_3).

3-Hydroxybenzo[*c*]phenanthrene (13b). Treatment of **13a** (100 mg) in 20 mL of methanol with 0.4 mL of concentrated HCl for 24 h, following the usual workup, gave **13b** (86 mg). Recrystallization from ether–hexane furnished **13b** (66 mg, 77%), mp 113–114 °C, and 12 mg (14%), mp 112–114 °C (lit.[8] mp 112–113 °C).

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Regioselective Alkylation of Anthrahydroquinone and Anthrone in Water with Quinonemethides and Other Alkylating Agents

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Anthrahydroquinone (AHQ) and anthrone are alkylated in the C_{10} position by quinonemethides, generated in situ from *p*-acetoxybenzyl chlorides, to give adducts **13–15, 24, 25, 28, 29,** and **32.** Aqueous alkylations of AHQ with methyl vinyl ketone, cinnamaldehyde, and benzyl chloride also produces C_{10}-substituted 10-hydroxyanthrones. Simple ketones and aldehydes do not, however, alkylate AHQ in aqueous alkali.

A critical step in the making of paper from wood by an alkaline pulping process is the efficient removal of one wood component, lignin, without destroying too much of the valuable component, cellulose.[1] Addition of catalytic amounts of anthraquinone (AQ) to alkaline pulping systems causes an acceleration in the rate at which lignin is removed, while increasing the yield of pulp.[2] Considerable interest has developed in the mechanism of how AQ achieves this desirable selectivity.

(1) J. P. Casey, "Pulp and Paper Chemistry and Chemical Technology", 3rd ed., Vol. I, Wiley-Interscience, New York, 1980.

(2) H. H. Holton, *Pulp Paper Can.*, **78**, T218 (1977).

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