# Reduction of *ortho*-Quinones to Dihydrodiols [1]

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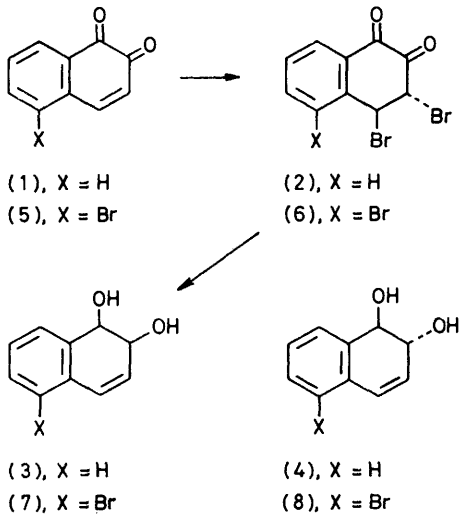
1,2-Naphthaquinone, 5-bromo-1,2-naphthaquinone and dibenz[*a*,*h*]anthracene-3,4-quinone in the form of dibromo-intermediates were reduced to a mixture of *cis*- and *trans*-diols by the action of sodium borohydride in ethanol. An alternative synthesis of *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene is also reported.

POLYCYCLIC aromatic hydrocarbons, which are known to occur in the environment as pollutants, have been shown to have carcinogenic activity.[2] From recent extensive studies,[3] the non-K-region dihydrodiols, derived from polycyclic aromatic hydrocarbons, have been established to be the proximate carcinogens in the carcinogenesis due to benz[*a*]anthracene, dimethylbenz[*a*]anthracene, and benzo[*a*]pyrene. In view of their considerable importance in carcinogenic and mutagenic processes, the syntheses of several of these dihydrodiols have recently been reported.[4] Although the reduction of K-region † *o*-quinones with conventional reducing agents like lithium aluminium hydride gives rise to good yields of K-region dihydrodiols,[5,6] the reduction of non-K-region *o*-quinones with lithium aluminium hydride afforded only very small amounts of the corresponding dihydrodiols.[7]




SCHEME 1

Booth and co-workers [5] have claimed to have obtained a *ca.* 48% yield of 1,2-dihydroxy-1,2-dihydronaphthalene from lithium aluminium hydride reduction of 1,2-naphthaquinone. Our repeated attempts to reproduce the results, however, have only afforded a 1.4% yield of dihydrodiol. Use of other reducing agents, *e.g.* aluminium hydride or sodium borohydride in ethanol, have not improved the yield (see Experimental section). Cho and Harvey [8] have described a convenient method for the reduction of quinones to hydroquinone diacetates. Recently Fujita and Sano [9] have described a method for the reduction of quinones to hydroquinones, but no satisfactory method for the reduction of non-K-region quinones to the corresponding dihydrodiols or their derivatives have yet been described.

In this paper we describe a convenient method for the reduction of non-K-region *o*-quinones to dihydrodiols through a dibromo-intermediate as shown in Scheme 1. 1,2-Naphthaquinone was studied as a model compound.

## RESULTS AND DISCUSSION

When 1,2-naphthaquinone (1) was treated with bromine in benzene, a dibromo-compound (2) was obtained. The formation of the dibromo-derivative was seen from t.l.c.; however, attempts to isolate a pure dibromo-compound failed due to decomposition. Compound (2) on reduction with an excess of sodium borohydride in ethanol yielded a mixture of *cis*- and *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (3) and (4) in good yield, from which the *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (4) was crystallized out. From m.p. and spectral data this sample of dihydrodiol was identical with an authentic sample of *trans*-1,2-dihydroxy-1,2-dihydronaphthalene synthesized by aluminium hydride or lithium aluminium hydride reduction of 1,2-naphthaquinone.

Similarly, 5-bromo-1,2-naphthaquinone (5) yielded a tribromo-compound (6), which on reduction with excess of sodium borohydride in ethanol yielded a mixture of *cis*- and *trans*-5-bromo-1,2-dihydroxy-1,2-dihydronaphthalene (7) and (8). In this case, the *cis*-compound could be crystallized from the mixture as a pure crystalline material. Its structure was established by analytical and spectral data. The n.m.r. spectrum of the compound established its *cis*-stereochemistry as is evident from the coupling constant ($J_{1,2}$ 4.6 Hz) [10,11] (Table).

The yields of the dihydrodiols obtained by this new method from the *o*-quinones are much higher than those usually obtained by the action of conventional hydride reducing agents on the *o*-quinones. It is evident that reduction must proceed through an intermediate (9). Although some evidence for the formation of intermediate (9) was obtained by t.l.c. when (2) was reduced with sodium borohydride (1 equiv.), attempts to isolate (9) were not successful. Reductive elimination probably proceeds through a mechanism as shown in Scheme 2.

When dibenz[*a*,*h*]anthracene-3,4-quinone (11) was

† The 9,10-carbons of phenanthrene constitute a K-region, whereas the 1,2,3,4-region is a non-K-region.

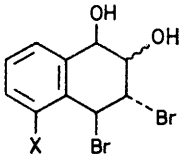
reduced with lithium aluminium hydride, usually the quinol was obtained.

The quinone (11) was, however, easily converted to the dibromo-compound (12) which, due to instability, could not be isolated in a completely pure form. The dibromo-quinone (12) was reduced with an excess of sodium borohydride and the reduced mixture was acetylated to a

$^1$H N.m.r. spectra (δ values) of dihydrodiols

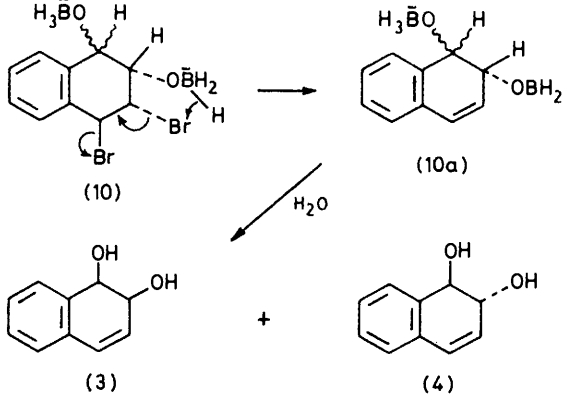
| Compound | Non-aromatic protons | Aromatic protons |
|---|---|---|
| (4) | $H^2$, 4.49 $H^1$, 4.84 $H^3$, 5.94 $H^4$, 6.41 ($J_{1,2}$ 10.5, $J_{2,3}$ 2.2, $J_{2,4}$ 2.0, $J_{3,4}$ 9.9 Hz) | 7.01—7.59 |
| (8) | $H^2$, 4.47 $H^1$, 4.80 $H^3$, 6.08 $H^4$, 6.80 ($J_{1,2}$ 11, $J_{2,3}$ 2.2, $J_{2,4}$ 2.0, $J_{3,4}$ 10 Hz) | 7.02—7.56 |
| (7) | $H^2$, 4.36 $H^1$, 4.66 $H^3$, 6.17 $H^4$, 6.94 ($J_{1,2}$ 4.6, $J_{2,3}$ 4.2, $J_{3,4}$ 10 Hz) | 7.04—7.54 |
| (16) | $H^3$, 4.39 $H^4$, 4.80 $H^2$, 6.24 $H^1$, 7.46 ($J_{1,2}$ 10, $J_{1,3}$ 2, $J_{2,3}$ 2, $J_{3,4}$ 11 Hz) | 7.65—9.40 |

mixture of the acetates (13) and (14). The mixture was purified by column chromatography on neutral deactivated alumina. The different fractions obtained from column chromatography were separately subjected to ammonolysis with methanolic ammonia to yield the dihydrodiols (15) and (16) from which the *trans*-diol



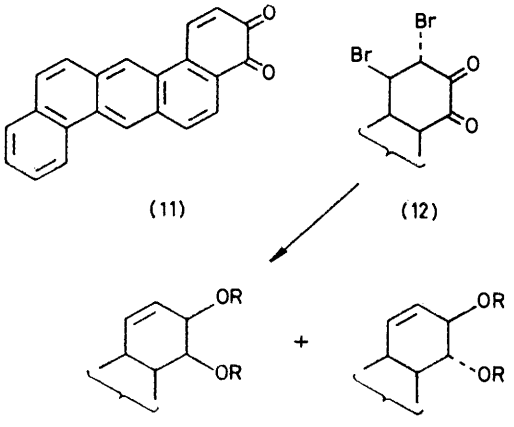

(9), X = H or Br

(16) was isolated as a pure crystalline compound. On t.l.c. the *trans*-isomer of 3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene moves more slowly than the corresponding *cis*-isomer. In the case of *cis*- and *trans*-isomers of 1,2-dihydroxy-1,2-dihydronaphthalene and 5-bromo-1,2-dihydroxy-1,2-dihydronaphthalene also, the *trans*-isomers are slower-moving than the corresponding




SCHEME 2

*cis*-isomers. Boyland and Sims [12] have reported a dihydroxy-dihydro-dibenz[*a*,*h*]anthracene which they identified as 3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene. Karle and his co-workers [13] have also recently reported an alternative synthesis of 3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene. The *trans*-stereochemistry of our compound is evident from the failure of the compound to form an acetonide and from its n.m.r. spectrum (Table). The $C^3$- and $C^4$-hydrogens are coupled with *J* 11 Hz, which is the case with the other *trans*-vincinal-dihydroxy-dihydro-compounds, *e.g. trans*-1,2-dihydroxy-1,2-dihydronaphthalene (4) and 5-bromo-*trans*-1,2-dihydroxy-1,2-dihydronaphthalene (8) (Table).




(13), R = Ac (14), R = Ac

(15), R = H (16), R = H

The bay-region hydrogen $C^1$-H is shifted considerably downfield (δ 7.46) as is expected of such bay-region hydrogens.[14] Each of the $C^1$- and $C^2$-hydrogens is seen as a double doublet. The $C^1$- and $C^2$-hydrogens are coupled with *J* 10 Hz, each of them also being coupled to a small extent with the $C^3$-hydrogen, *J* 2 Hz. Both *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene and the corresponding diacetate have end-absorption in the visible region, whereas absorption in the visible region due to 3,4-diacetoxydibenz[*a*,*h*]anthracene is quite weak. Similar end-absorptions have been observed [14] for 1,2-dihydroxy-1,2-dihydro- and 3,4-dihydroxy-3,4-dihydro-benz[*a*]anthracene, but not in the case of 9,8-dihydroxy-9,8-dihydro- and 10,11-dihydroxy-10,11-dihydro-benz[*a*]anthracene.

## EXPERIMENTAL

T.l.c. was carried on Eastman Chromagram Sheet, 6060 silica gel with fluorescent indicator in the solvents indicated; solvent I, chloroform; solvent II, benzene–ethanol (19 : 1); and solvent III, benzene–ethanol (9 : 1). 1,2-Naphthaquinone was obtained from Aldrich Chemical Co. 5-Bromo-1,2-naphthaquinone and dibenz[*a*,*h*]anthracene-3,4-quinone were synthesized in our laboratory.[15]

trans-1,2-*Dihydroxy*-1,2-*dihydronaphthalene* (4).—*Method A: reduction through a dibromo-intermediate.* Bromine (1.2 g, 7.5 mmol) in benzene (100 ml) was added dropwise during 1 h to a solution of 1,2-naphthaquinone (1 g, 6.4 mmol) in benzene (80 ml) at room temperature. The mixture was stirred for another 1 h at room temperature and then solvent was removed. The brown gummy residue was dissolved in ethanol (50 ml) and then added to a solution of sodium borohydride (2.7 g) in ethanol (100 ml) at room temperature. The mixture was stirred for 4 h and a light yellow solution

was obtained. Excess of sodium borohydride was decomposed with glacial acetic acid and ethanol was removed. The residue was treated with water (50 ml) and extracted with ether. The ether layer was washed with sodium hydroxide (1N), water, dried, and solvent removed to yield a neutral fraction as a brown gum (340 mg, 2.16 mmol, 34%), which was crystallized from ether–light petroleum (b.p. 30—75 °C) to yield *trans*-1,2-dihydroxy-1,2-dihydronaphthalene as small white needles, m.p. 105—106 °C (lit.,[5] m.p. 103 °C) (Found: C, 74.05; H, 6.25. Calc. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21%); $R_F$ 0.07 (solvent I), 0.20 (solvent II); $\nu_{max.}$ (KBr) 3 250 (br, OH), absence of band at 1 670 $cm^{-1}$ (quinone); $\lambda_{max.}$ 212, 218, and 263 nm (ε 24 390, 22 602, and 7 642). From mixed m.p. and i.r. comparisons the above sample of dihydroxydihydronaphthalene was identical with a sample of dihydroxydihydronaphthalene synthesized by aluminium hydride reduction of 1,2-naphthaquinone (see below). The n.m.r. spectra (see the Table) are the same as reported [11] in the literature for *trans*-1,2-dihydroxy-1,2-dihydronaphthalene. The alkaline extract on acidification and ether-extraction yielded a brown gum (450 mg) which was not characterized.

*Method B: reduction with aluminium hydride.* Aluminium hydride reagent was made by stirring lithium aluminium hydride (912 mg) in tetrahydrofuran (20 ml) at 0—5 °C. To the cold solution sulphuric acid (1 g) in tetrahydrofuran (20 ml) was added dropwise and stirred for 1 h. To the cooled solution 1,2-naphthaquinone (948 mg) in tetrahydrofuran (20 ml) was added and the mixture stirred at 5 °C for 16 h. The mixture was decomposed with sulphuric acid (1N) and extracted with ether. The ethereal extract was washed with sodium hydroxide solution (2N) and water, dried, and the solvent removed to yield a slightly dark white solid (75 mg, 7.5%) which was crystallized from ether–light petroleum (b.p. 30—75 °C) into cream needles, m.p. 105—106 °C (lit.,[5] m.p. 103 °C); mass spectrum *m/e* 162 ($M^+$), 144 ($M^+ - H_2O$); $\nu_{max.}$ (KBr) 3 250 (br, OH), absence of band at 1 670 $cm^{-1}$ (quinone).

*Method C: reduction with lithium aluminium hydride.* To an ice-cold suspension of lithium aluminium hydride (800 mg, 21 mmol) in ether (100 ml) the powdered 1,2-naphthaquinone (1 g, 6.3 mmol) was added in the solid state within 5 min. The mixture was stirred at 0—5 °C for 24 h, decomposed with ice-cold sulphuric acid (1N) and extracted with ether. The ethereal layer was washed with sodium hydroxide solution (2N) and water, dried, and the solvent removed to yield a neutral material (15 mg, 0.09 mmol, 1.4%). T.l.c. and mass spectrometry showed it to be identical with *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (4).

*Method D: reduction with sodium borohydride.* To a solution of sodium borohydride (2.7 g, 67.5 mmol) in ethanol (150 ml), 1,2-naphthaquinone (1 g, 6.3 mmol) dissolved in tetrahydrofuran (20 ml) was added at room temperature. The mixture was stirred at room temperature for 2 h, decomposed with acetic acid, and ethanol removed. The residue was treated with water and extracted with ether. The ethereal extract was washed with sodium hydroxide solution (2N) and water, dried, and the solvent removed to yield a neutral residue (12 mg, 0.07 mmol, 1.2%). T.l.c. and m.s. showed it to be identical with *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (4).

5-*Bromo*-cis-1,2-*dihydroxy*-1,2-*dihydronaphthalene* (7).—*Reduction through a dibromo-intermediate.* 5-Bromo-1,2-naphthaquinone (240 mg, 1.0 mmol) was treated with bromine (200 mg) in benzene (30 ml) under the conditions described for 1,2-naphthaquinone. The crude bromo-compound was reduced with sodium borohydride (400 mg) in ethanol (25 ml) as described before. After the usual work-up, a neutral white solid (160 mg, 0.66 mmol, 66%) was obtained. T.l.c. in chloroform showed it to be a mixture of two spots of $R_F$ 0.12 and 0.07, respectively. H.p.l.c. analysis of the mixture in 60—90% methanol–water gradient on a Zorbax-ODS column (0.25 m × 4.6 mm i.d.) showed it to be a 2 : 1 *cis/trans* mixture. On crystallization from ether, colourless plates of the cis-*isomer* (7), m.p. 155—156 °C, were obtained (Found: C, 50.15; H, 4.0; Br, 33.45. $C_{10}H_9BrO_2$ requires C, 49.79; H, 3.73; Br, 33.20%); $R_F$ 0.12 (solvent I), 0.36 (solvent II); $\nu_{max.}$ (95% EtOH) 220, 224, and 265 nm (ε 20 000, 19 848, and 8 133); *m/e* 241, 243 ($M^+$), 223, and 225 ($M^+ - H_2O$); $\nu_{max.}$ (KBr) 3 200 (br, OH), absence of band at 1 670 $cm^{-1}$ (quinone).

5-*Bromo*-trans-1,2-*dihydroxy*-1,2-*dihydronaphthalene* (8).—The 5-bromo-1,2-naphthaquinone (474 mg, 2 mmol) was reduced with aluminium hydride made from lithium aluminium hydride (456 mg) in sulphuric acid (588 mg) in tetrahydrofuran (35 ml) as described under reduction of 1,2-naphthaquinone. After the usual work-up, a neutral material (50 mg, 0.21 mmol, 10.5%) was obtained. This was crystallized from ether–light petroleum (b.p. 30—75 °C) as light cream *needles*, m.p. 152—154 °C (Found: C, 50.1; H, 4.0. $C_{10}H_9BrO_2$ requires C, 49.79; H, 3.73%); $R_F$ 0.07 (solvent I), 0.21 (solvent II); *m/e* 243 and 241 ($M^+$), 225 and 223 ($M^+ - H_2O$); n.m.r. spectrum (Table) established it to be the *trans*-isomer.

3,4-*Dibromodibenz*[a,h]*anthracene*-3,4-*quinone* (12).—Bromine (210 mg) in chloroform (15 ml) was added with stirring to a suspension of dibenz[*a,h*]anthracene-3,4-quinone (300 mg, 0.97 mmol) at room temperature. The mixture was stirred for 30 min and the solvent removed *in vacuo*. The residue was dissolved in bezene (100 ml) and filtered from some insoluble residue. The benzene solution was concentrated to give brown crystals (285 mg, 0.61 mmol, 63%). On further crystallization of the material from cold benzene, red crystals, m.p. 170—172 °C, were obtained. T.l.c. showed it to be a single-spot substance of $R_F$ 0.8 in chloroform–methanol (10 : 1); DBA–3,4-quinone had a $R_F$ 0.00 in the same solvent system; $\nu_{max.}$ (KBr) 1 735, 1 680, 1 675, and 1 605 $cm^{-1}$. Due to decomposition no satisfactory analysis could be obtained.

trans-3,4-*Diacetoxy*-3,4-*dihydrodibenz*[a,h]*anthracene* (14).—Dibenz[*a,h*]anthracene-3,4-quinone (600 mg, 1.9 mmol) was treated with bromine (500 mg) in benzene (600 ml). The mixture was stirred at room temperature for 2 h, at the end of which it was filtered to yield 325 mg of recovered quinone. The filtrate was evaporated to dryness and the residue in tetrahydrofuran (50 ml) was added to sodium borohydride (600 mg) in 95% ethanol (200 ml). The reaction was stirred at room temperature for 4 h, decomposed with acetic acid, and the whole mixture was evaporated to dryness. The dry residue was acetylated with a mixture of acetic anhydride (25 ml) and pyridine (2.5 ml) (which was previously refluxed together and cooled) by stirring at room temperature for 15 h. Pyridine and acetic ahydride were removed *in vacuo* (at < 40 °C) and the residue was chromatographed on a column (24 cm × 2 cm) of neutral alumina (Woelm) deactivated by the addition of 10% water. The column was washed with 500 ml benzene–light petroleum (b.p. 30—75 °C) (1 : 2). Subsequent elution of the column with benzene afforded the 3,4-diacetoxy-3,4-dihydrodibenz[*a,h*]anthracene (200 mg, 66%). On crystallization from

methanol, *trans*-3,4-diacetoxy-3,4-dihydrodibenz[*a*,*h*]-anthracene crystallized as small light yellow plates, m.p. 204 °C (lit.,[13] m.p. 183—185 °C) (Found: 78.8; H, 5.15. Calc. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09%). T.l.c. of the sample gave a single spot in both solvents II and III. On high-pressure liquid chromatography in 1 : 1 (v/v) hexane–dichloromethane–propanol-2-ol–acetic acid, (1 000 : 20 : 0.1), on a Zorbax (silica) column (0.25 × 2.2 mm i.d.), this was seen as a single-peak substance at 8 ml; $\nu_{max.}$ (KBr) 1 740 and 1 240 $cm^{-1}$; δ 2.09 and 2.14; *m/e* 396 ($M^+$), 336 ($M$ — $MeCO_2H$); $\lambda_{max.}$ (95% EtOH) 249, 278, 287, 298, 335, 352, 372, and 400 nm (ε 32 300, 79 200, 97 800, 111 000, 8 730, 9 490, 8 400, and 5 300).

trans-3,4-*Dihydroxy*-3,4-*dihydrodibenz*[a,h]*anthracene* (16). — *trans*-3,4-Diacetoxy-3,4-dihydrodibenz[*a*,*h*]anthracene was quantitatively converted to *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene by stirring with methanol saturated with ammonia at room temperature for 5 h. It was crystallized from methanol as light brown needles, m.p. 274—275 °C (decomp.) (Found: C, 84.5; H, 5.2. $C_{22}H_{16}O_2$ requires C, 84.59; H, 5.16%); $R_F$ 0.13, 0.10 and 0.25 (in solvents I, II, and III respectively); $\lambda_{max.}$ (95% EtOH) 280, 289, 299, 338, 353, 371, 288, and 395 nm (ε 54 311, 72 752, 62 385, 4 761, 6 679, 7 725, 5 440, and 5 294).

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