K-Region *trans*-Dihydrodiols of Polycyclic Arenes; An Efficient and Convenient Preparation from *o*-Quinones or *o*-Diphenols by Reduction with Sodium Borohydride in the Presence of Oxygen

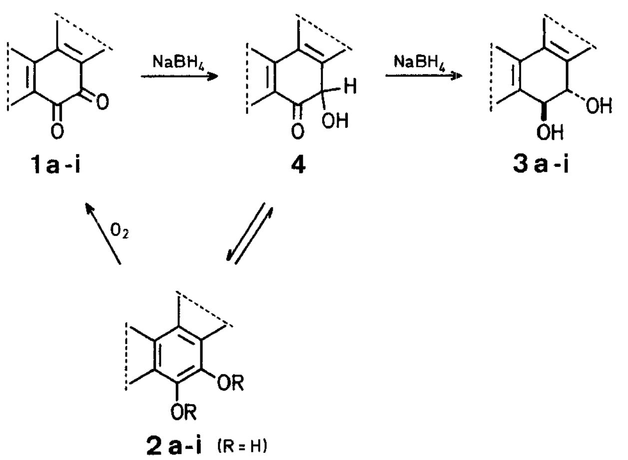
Karl L. PLATT, Franz OESCH*

Institute of Pharmacology, Section on Biochemical Pharmacology, University of Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, Federal Republic of Germany

K-Region[1,2] *trans*-dihydrodiols are important metabolites of polycyclic aromatic hydrocarbons. They are produced by epoxide hydrolase-mediated hydration of the primarily formed arene oxides[3]. The formation of K-region dihydrodiols is usually regarded as inactivation of the electrophilically reactive arene oxides but further activation of K-region dihydrodiols to mutagenic products has also been reported[4,5]. Moreover, K-region *trans*-dihydrodiols can be used as precursors of arene oxides[6]. For all these reasons there exists a continued interest in their efficient preparation.

K-region *trans*-dihydrodiols are usually synthesized by stereoselective reduction of the corresponding *o*-quinones with complex metal hydrides such as lithium aluminum hydride[6-16], the reduction is being performed by continuously extracting the *o*-quinone with refluxing ether from the thimble of a Soxhlet apparatus into a solution of lithium aluminum hydride in ether. Phenanthrene-9,10-quinone can be successfully reduced by this procedure[6,8,13] whereas in other cases of K-region *o*-quinones the yield of the dihydrodiol is low[10,13,15] or has not even been reported[9,12,14]. The low yields are caused by the poor solubility in diethyl ether of most K-region *o*-quinones derived from polycyclic arenes; thus, long reduction times are required and this leads to oxidative degradation of the sensitive dihydrodiols. The use of more soluble hydride reagents, such as sodium bis[2-methoxyethoxy]-aluminum hydride, lithium tri-*t*-butoxyaluminum hydride, or aluminum hydride, or of other solvents such as tetrahydrofuran, 1,2-dimethoxyethane, or diisopropyl ether lowered the yields even more[16]. Other complex metal hydrides like sodium borohydride[16] and potassium borohydride[15,17,18,19] have less frequently been used for the reduction of K-region *o*-quinones, the reported yields not exceeding 61%.

Our first attempts to use sodium or potassium borohydride in methanol or ethanol for the reduction of K-region *o*-quinones were little encouraging[6,20,21] although we used the conditions described in the literature[15]. When phenanthrene-9,10-quinone (**1b**) was reduced in standard laboratory equipment (round bottom flask, drying tube) with an excess of the borohydrides an air-sensitive product was obtained in 90% yield; it was found to be 9,10-dihydroxyphenanthrene (**2b**, R = H)[6]. 9,10-*trans*-Dihydroxy-9,10-dihydrophenanthrene (**3b**) was obtained only in a yield of a few percent under these conditions. The use of different reaction times and temperatures, different ratios of the reactants, different solvents (such as mixtures of tetrahydrofuran/2-propanol as described in Ref.[18]) did not improve the results substantially. We finally found that polycyclic *o*-quinones (**1**) can be conveniently reduced to the corresponding *trans*-dihydrodiols (**3**) by carrying out the reduction with borohydrides in the presence of oxygen. The essential fact that oxygen has to be present has hitherto not been mentioned in the literature[22]. The role of oxygen in the reduction may be rationalized by the following mechanism.



The initially formed reaction product is probably the ketol[16,23] **4** which either isomerizes to the fully aromatic diphenol[23] **2** (R = H) or is further reduced to the *trans*-dihydrodiol[16] **3**. In the case of **1b**, aromatization prevails leading to a mixture of **2b** (R = H) and only little **3b**. Since the *o*-diphenol **2b** (R = H) is much more prone to autoxidation to the starting quinone **1b** than the *trans*-dihydrodiol **3b**, only **2b** is oxidized by the oxygen present giving **1b** which is then again reduced. As a result of this reduction-oxidation cycle, the pure *trans*-dihydrodiol **3b** accumulates so that it can be isolated in high yield. The proposed mechanism is supported by the observation that not only *o*-quinones but also *o*-diphenols and their acetates are reduced to the dihydrodiols in high yields under the same conditions.

trans-Stereospecificity was observed in most cases (**3a–3g**). The presence of the *cis*-diol could be excluded by T.L.C. on silica gel under which conditions the *cis*-dihydrodiols[24] always show a distinctly higher mobility than the *trans*-isomers. However, a mixture of *cis*- and *trans*-dihydrodiols was obtained by reduction of 7,12-dimethylbenz[*a*]anthraquinone (**1h**) and of 3-methylcholanthrenequinone (**1i**). The poor stereoselectivity of reductions with metal hydrides has been reported in the case of **1h**[11,13,16] as a consequence of the steric interaction with the alkyl substituent in the immediate proximity of the K-region[16].

As already mentioned, the presence of oxygen is essential for the reduction **1**→**3** to proceed satisfactorily. Although it is not necessary to pass oxygen through the reaction mixture, free access of air has to be secured. Sodium and potassium borohydride are equally effective as reducing agents; they are best used in a 10 molar excess with respect to the *o*-quinone. Suitable solvents are the lower aliphatic alcohols such as methanol, ethanol, and 2-propanol in pure form or with 10–20% water content. In cases in which the maximum conversion of the borohydride is desired, e.g., when using tritiated borohydride to synthesize tritium-labeled K-region *trans*-dihydrodiols, 2-propanol is the best solvent[6]. The amount of borohydride can then be reduced to less than 2 mmol per mmol *o*-quinone. The reaction is best performed at room temperature since both higher (reflux) and lower (0-5 °C) temperatures lead to lower yields and/or less pure product.

Our method of reducing K-region *o*-quinones (and also the corresponding *o*-diphenols and their acetates) derived from polycyclic arenes represents a significant improvement of the synthesis of K-region *trans*-dihydrodiols. In all cases investigated, the dihydrodiols were obtained in high yield and in a high state of purity. Our procedure has the additional advantage of simple performance and work-up and thus compares

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favorably with the laborious preparation using lithium alanate.

The K-region *o*-quinones **1c**–**1g**, **1i** were conveniently prepared in 70–90% yield by oxidation of the corresponding *cis*-dihydrodiols[24] with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[18]. Compound **1h** was prepared in 43% yield by oxidation of the corresponding *cis*-dihydrodiol[24] with sulfur trioxide/dimethyl sulfoxide[16].

K-Region *trans*-Dihydrodiols 3; General Procedure:

The K-region *o*-quinone **1** (1 mmol) is added in small portions to the stirred suspension of sodium borohydride (380 mg, 10 mmol) in ethanol (26 ml) and water (4 ml). The deep orange color of the quinone disappears immediately and an almost colorless solution results. The mixture is stirred at room temperature for 24 h; then, ice-water (100 ml) is added to the white suspension followed with 2 normal hydrochloric acid for acidification. In most cases, the *trans*-dihydrodiol (**3c**–**g**, **3i**) can be isolated by filtration; if this is not possible the product (**3a**, **b**, **h**) is extracted with dichloromethane (3 x 80 ml). The organic phase is washed neutral, dried with magnesium sulfate, evaporated to dryness, and the product is recrystallized from a suitable solvent (see Table).

Table. Synthesis of K-Region *trans*-Dihydrodiols

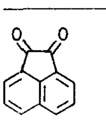
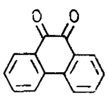
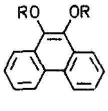
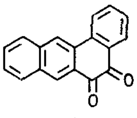
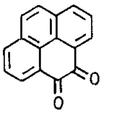
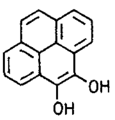
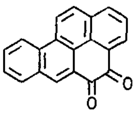
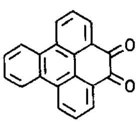
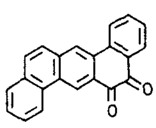
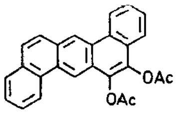
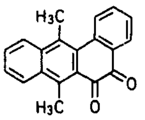
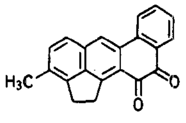
Educt		Product[a]	Yield [%]	m.p. [°C] (solvent)	Lit. m.p. [°C]
	**1a**	**3a**	62	159° (methanol)	160–163°[25]
	**1b**	**3b**	77	189° (benzene/methanol)	185°[8]
	**2b** (R = H)[6]	**3b**	84	188° (benzene/methanol)	185°[8]
	2b (R = Ac)[6,26]	**3b**	88	188° (benzene/methanol)	185°[8]
	**1c**	**3c**	91	205° ($CHCl_3$)	202–205°[16]
	**1d**	**3d**	85	218° ($CHCl_3$/hexane)	220–223°[16]
	**2d** (R = H)[27]	**3d**	88	217° ($CHCl_3$/hexane)	220–223°[16]
	**1e**	**3e**	78	210° ($CHCl_3$)	211.5–213°[16]
	**1f**	**3f**	90	221° ($CHCl_3$)	> 185° (dec)[18]
	**1g**	**3g**	80	228° ($CHCl_3$)	227°[9]
	**2g** (R = Ac)[28]	**3g**	78	228° ($CHCl_3$)	227°[9]

Table. (continued)

Educt		Product[a]	Yield [%]	m.p. [°C] (solvent)	Lit. m.p. [°C]
	**1h**	**3h**	29[b] (60)	159–161°	—[c]
	**1i**	**3i**	57[b,d] (33)	190–192°	193°[10]

[a] The mass and N.M.R. spectra of all compounds were in accordance with the proposed structure; the microanalyses were in satisfactory agreement with the calculated values: C, ±0.3; H, ±0.2.

[b] The crude reaction product consisted of a mixture of *cis*- and *trans*-dihydrodiol as the sole components. The *trans*-isomer was isolated by preparative T.L.C. on silica gel with chloroform/methanol (95:5 v/v) as the mobile phase. The number in brackets refers to the isolated yield of the *cis*-dihydrodiol.

[c] ^1H-N.M.R. (90 MHz, acetone-d_6):
cis-**3h**: δ = 2.80 (s, 3 H, CH_3); 2.91 (s, 3 H, CH_3); 4.66–4.86 (m, 1 H, H-5); 5.07–5.18 (m, 1 H, H-6); 7.20–8.18 (m, 8 H_{arom})
trans-**3h**: δ = 2.80 (s, 3 H, CH_3); 2.90 (s, 3 H, CH_3); 4.78 (d, 1 H, H-5, $J_{5,6}$ = 3.8 Hz); 5.20 (d, 1 H, H-6); 7.16–7.60 (m, 6 H_{arom}); 7.89–8.18 (m, 2 H_{arom})

[d] ^1H-N.M.R. (90 MHz, acetone-d_6):
cis-**3i**: δ = 2.38 (s, 3 H, CH_3); 3.21–3.41 (m, 2 H, CH_2); 3.43–3.61 (m, 2 H, CH_2); 4.71–4.88 (m, 1 H, H-5); 4.93–5.04 (m, 1 H, H-6); 7.13–8.06 (m, 7 H_{arom})
trans-**3i**: δ = 2.39 (s, 3 H, CH_3); 3.17–3.38 (m, 2 H, CH_2); 3.48–3.70 (m, 2 H, CH_2); 4.71 (d, 1 H, H-5, $J_{5,6}$ = 5.8 Hz), 4.93 (d, 1 H, H-6), 7.11–7.64 (m, 5 H_{arom}); 7.84–8.09 (m, 2 H_{arom})

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* Address for correspondence.

[1] The K-region in a polycyclic aromatic hydrocarbon is structurally equivalent to the 9,10-bond in phenanthrene which is the bond with the highest electron density.

[2] A. Pullmann, B. Pullmann, *Adv. Cancer Res.* **3**, 117 (1955).

[3] F. Oesch, *Xenobiotica* **3**, 305 (1973).

[4] A. W. Wood et al., *Cancer Res.* **38**, 1967 (1978).

[5] K. L. Platt, M. Bücker, M. Golan, F. Oesch, *Mutation Res.*, in press.

[6] F. Oesch, A. J. Sparrow, K. L. Platt, *J. Lab. Comp. Radiopharm.* **17**, 93 (1980).

[7] L. W. Trevoy, W. G. Brown, *J. Am. Chem. Soc.* **71**, 1675 (1949).

[8] J. Booth, E. Boyland, E. E. Turner, *J. Chem. Soc.* **1950**, 1188.

[9] E. Boyland, P. Sims, *Biochem. J.* **97**, 7 (1965).

[10] P. Sims, *Biochem. J.* **98**, 215 (1966).

[11] E. Boyland, P. Sims, *Biochem. J.* **104**, 394 (1967).

[12] P. Sims, *Biochem. J.* **105**, 591 (1967).

[13] S. H. Goh, R. G. Harvey, *J. Am. Chem. Soc.* **95**, 242 (1973).

[14] H. Cho, R. G. Harvey, *Tetrahedron Lett.* **1974**, 1491.

[15] A. S. Dey, J. L. Neumeyer, *J. Med. Chem.* **17**, 1095 (1974).

[16] R. G. Harvey, S. H. Goh, C. Cortez, *J. Am. Chem. Soc.* **97**, 3468 (1975).

[17] R. M. Moriarty, P. Dansette, D. M. Jerina, *Tetrahedron Lett.* **1975**, 2557.

[18] R. E. Lehr et al., *J. Org. Chem.* **43**, 3462 (1978).

[19] M. Croisy-Delcey, Y. Ittah, D. M. Jerina, *Tetrahedron Lett.* **1979**, 2849.

[20] M. D. Golan, *Dissertation*, Universität Mainz, 1979.

[21] A. J. Sparrow, Universität Mainz, unpublished results.

[22] Dr. P. Dansette, C.N.R.S., Paris, France, had also observed that oxygen was essential (personal communication after completion of our experimental work).

[23] H. Cho, R. G. Harvey, *J. Chem. Soc. Perkin Trans. 1* **1976,** 836.

[24] J. W. Cook, R. Schoental, *J. Chem. Soc.* **1948,** 170.

[25] L. D. Hayward, I. G. Csizmadia, *Tetrahedron* **19,** 2111 (1963).

[26] G. Rio, J. Berthelot, *Bull. Soc. Chim. Fr.* **1972,** 822.

[27] H. Vollmann, H. Becker, M. Corell, H. Streek, *Justus Liebigs Ann. Chem.* **531,** 1 (1937).

[28] H. Cho, R. G. Harvey, *J. Chem. Soc. Perkin Trans. 1* **1976,** 836.

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