Synthesis of Hydroquinone Diacetates from Polycyclic Aromatic Quinones

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A convenient general synthesis of hydroquinone diacetates from polycyclic aromatic quinones through reduction with sodium borohydride in dimethylformamide is described. Improved methods for the synthesis and chromatographic separation of the 1,6-, 3,6-, and 6,12-diones of benzo[*a*]pyrene are also described. 270 MHz N.m.r. spectroscopy is employed to confirm the structural assignments of the latter and the use of this technique is proposed for the characterization of carcinogen metabolites.

POLYCYCLIC aromatic hydrocarbons, the most potent class of carcinogenic molecules, are metabolized to give arene oxides, phenols, dihydro-diols, quinones, and other oxidized derivatives,[1] relative significance of which for the induction of tumours is incompletely understood. Although hydroquinones have not been detected among the products of metabolism, conjugates of 1,6- and 3,6-

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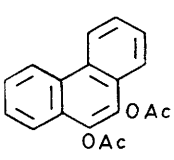
dihydroxybenzo[*a*]pyrene have been identified as major metabolites of benzo[*a*]pyrene in the biliary system of rats.[2] Since the free hydroquinones are generally air-sensitive, it is likely they would be oxidized to quinones and other products during conventional isolation procedures. Indeed, few hydroquinone derivatives of polycyclic hydrocarbons have ever been synthesized, probably also owing to their susceptibility to atmospheric oxidation.

We report here a convenient general synthesis of hydroquinone diacetates from polycyclic aromatic quinones *via* reduction with sodium borohydride in dimethylformamide ($NaBH_4$–DMF). Although reduction of various quinones with metal hydride reagents has been described,[3-7] the products include hydroquinones, diols, quinols, phenols, and hydrocarbons, and no generally satisfactory method for effecting reduction to the hydroquinone stage has been devised.

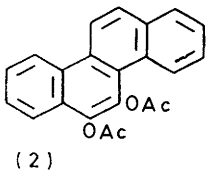
Preliminary studies were conducted with phenanthraquinone, and the products were trapped through diacetylation. Four reagents, sodium bis-(2-methoxyethoxy)aluminium hydride,[8] lithium tri-t-butoxyaluminium hydride,[9] $NaBH_4$ in ' aged ' bis-(2-methoxyethyl) ether,[4] and $NaBH_4$–DMF, afforded 9,10-diacetoxyphenanthrene as essentially the sole product. However, only $NaBH_4$–DMF transformed chrysene-5,6-dione, benzo[*a*]pyrene-1,6-dione, and pyrene-4,5-dione cleanly into the corresponding hydroquinones.

Accordingly, $NaBH_4$–DMF was utilized in a broader study and was found to be highly efficient for selective transformation of polycyclic quinones of all types to the corresponding hydroquinones. Compounds (1)—(6) were synthesized by this means. The only exception encountered was anthraquinone, which underwent conversion in low yield. However, $Li(Bu^tO)_3AlH$ efficiently reduced anthraquinone to the hydroquinone, isolated as 9,10-diacetoxyanthracene (7). This reagent also transformed chrysene-5,6-dione, pyrene-4,5-dione, and benz[*a*]anthracene-7,12-dione into the corresponding hydroquinones, but yields were generally lower than with $NaBH_4$–DMF. In view of the greater cost and lower effectiveness of $Li(Bu^tO)_3AlH$, $NaBH_4$–DMF appears to be the reagent of choice for the selective reduction of quinones of all types to hydroquinones.

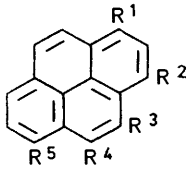
Since the free hydroquinones were sought for biological experiments, their stability in solution under an inert atmosphere was also investigated. For this purpose phenanthrene-9,10-dione, benzo[*a*]pyrene-1,6-dione, and benz[*a*]anthracene-7,12-dione were reduced with $NaBH_4$–DMF, and the products were extracted into benzene or ether under nitrogen. Diacetylation within a short time (*e.g.* 1 h) furnished the corresponding hydroquinone diacetates virtually quantitatively. After longer periods some decline in the percentage of hydroquinone in the benzene solutions became evident, but no decrease was detected in the ether solutions even after 24 h.



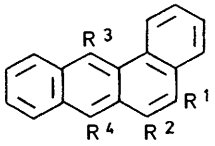
(1)



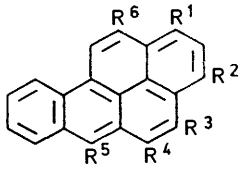
(2)



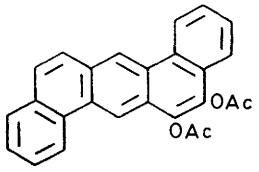
(3) a; $R^1 = R^2 = R^5 = H, R^3 = R^4 = OAc$
b; $R^1 = R^5 = OAc, R^2 = R^3 = R^4 = H$
c; $R^1 = R^3 = R^4 = H, R^2 = R^5 = OAc$



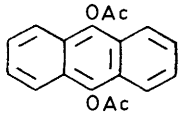
(4) a; $R^1 = R^2 = OAc, R^3 = R^4 = H$
b; $R^1 = R^2 = H, R^3 = R^4 = OAc$



(5) a; $R^1 = R^5 = OAc, R^2 = R^3 = R^4 = R^6 = H$
b; $R^2 = R^5 = OAc, R^1 = R^3 = R^4 = R^6 = H$
c; $R^3 = R^4 = OAc, R^1 = R^2 = R^5 = R^6 = H$
d; $R^1 = R^2 = R^3 = R^4 = H, R^5 = R^6 = OAc$



(6)



(7)

The particular effectiveness of $NaBH_4$–DMF is most probably a consequence of the fact that dissociation of intermediates such as (8) is strongly favoured in this polar medium. The dissociated structure is free to either (*a*) undergo enolization to the thermodynamically more favoured phenol tautomer (9) which, having a

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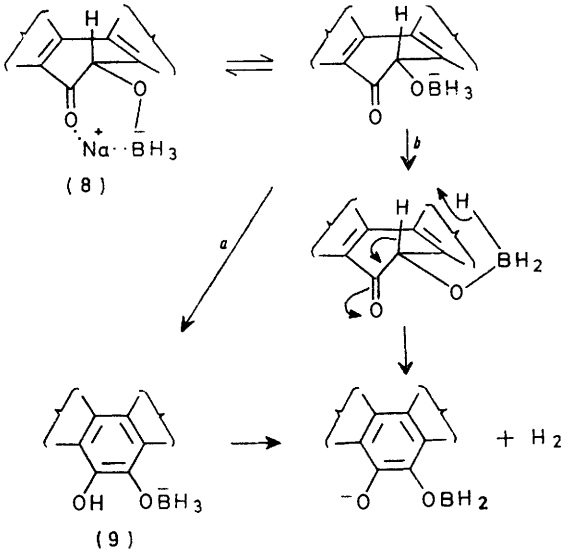
relatively acidic proton, reacts rapidly with hydride to provide the hydroquinone salt with evolution of hydrogen,[3] or (*b*) lose hydrogen directly as illustrated.[6] The two pathways afford the same products and cannot at present be distinguished. For $Li[Bu^tO]_3AlH$ only the enolization path is available.



The quinones of pyrene and benzo[*a*]pyrene required for this study were obtained through direct oxidation of the parent hydrocarbons with sodium dichromate in acetic anhydride–acetic acid. Although oxidation with aqueous chromic acid of both hydrocarbons was described by Vollmann *et al.*[10] and repeated by subsequent investigators,[11-15] the wide range of m.p.s reported suggested the presence of still incompletely resolved mixtures of isomeric quinones or quinols.[16] Passage of our crude product through a column of basic alumina, followed by careful chromatography and rechromatography on Florisil, furnished the pure 1,6-, 3,6-, and 6,12-quinones of benzo[*a*]pyrene, which migrated as orange-yellow, bright red, and yellow bands, in overall yields of 40, 20, and 7%, respectively. The m.p.s of the pure quinones were generally higher than those reported previously. The 6,12-dione was not detected in the earlier investigations, but has been described as a product of photochemical oxidation of benzo[*a*]pyrene.[17] Oxidation of pyrene with sodium dichromate in acetic anhydride–acetic acid followed by similar chromatographic separation furnished the pure pyrene-1,6- and -1,8-diones in 32 and 18% yields, respectively. This compares favourably with the reported oxidation of pyrene by the Vollmann method,[14] which gave 10 and 22% yields, respectively, of the same quinones.

The 270 MHz n.m.r. spectra of the quinones and the related hydroquinone acetates of benzo[*a*]pyrene confirmed the assigned structures and the purity of the samples. While overlapping of some peaks and other ambiguities prevented complete interpretation in all cases, assignment of the majority of proton chemical shifts and coupling constants was possible. The assignments were aided through comparison with the 100 and 220 MHz ^1H n.m.r. spectra of the parent hydrocarbon, previously analysed in detail.[18,19] The highly distinctive n.m.r. spectral patterns exhibited by the individual isomers suggests the potential utility of this technique for the identification of carcinogen metabolites.

EXPERIMENTAL

^1H N.m.r. spectra were taken with Varian T-60 and Brucker 270 MHz spectrometers, with Me_4Si as standard and $CDCl_3$ as solvent unless otherwise indicated. I.r. spectra were obtained with a Perkin-Elmer 137 Infracord spectrometer. Microanalyses for C and H correct to ±0.3% were obtained for all new compounds (from Atlantic Microlabs, Inc.).

Dimethylformamide (DMF) was dried over molecular sieves. The metal hydride reagents were obtained from Ventron, Alfa Products. Chrysene-5,6-dione was synthesized from chrysene by oxidation with chromic acid,[20] purified by passage through a column of basic alumina, and recrystallized from chloroform–ethanol to give red needles, m.p. 244—244.5° (lit.,[20] 240°). Phenanthrene-9,10-dione (Aldrich) was similarly purified. Florisil (100—200 mesh) was activated by heating at 100 °C in a vacuum oven for 5 h prior to use. Benz[*a*]anthracene-5,6-dione, pyrene-4,5-dione, benzo[*a*]pyrene-4,5-dione, and dibenz[*a,h*]anthracene-5,6-dione were synthesized according to methods previously described.[6]

Reductive Acetylation.—In a typical procedure, $NaBH_4$ (100 mg) was added to a solution of the quinone (1 mmol) in DMF (10 ml). The resulting solution, which generally changed colour within a few min, was stirred at ambient temperature for 1 h. Then pyridine (2 ml) in acetic anhydride (18 ml) was added, stirring was continued for an additional 5 h, and the solution was poured into water. The precipitate was collected, washed with water, taken up in a small volume of chloroform, and adsorbed on a short column of Florisil. Elution with benzene and recrystallization from chloroform–ethanol or other appropriate solvent furnished the pure hydroquinone diacetate (Table). The n.m.r. spectra of compounds (1)—(7) showed characteristic OAc peaks in the region δ 2.43—2.68.

Oxidation of Pyrene.—To a solution of pyrene (2.02 g, 10 mmol) in acetic anhydride (100 ml) at 0 °C was added a solution of sodium dichromate dihydrate (8 g) in glacial acetic acid (100 ml). The resulting solution was stirred at room temperature for 1 day, then poured into water (1 l).

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The precipitate was collected, washed with water, dissolved in chloroform, and passed through a column of basic alumina (30 g). Evaporation gave the pyrene-1,6- and -1,8-diones (1.20 g) (2 : 1 by n.m.r.). A solution of the latter in chloroform (120 ml) was introduced onto a column of Florisil (100 g) in benzene. Elution with 2% ethyl acetate–benzene (6.5 l) removed initially a minor contaminant, followed by pyrene-1,6-dione (570 mg) (a yellow-orange band). Further elution with 10% ethyl acetate–chloroform (1 l) removed a red band containing the 1,8-dione and residual 1,6-dione. Rechromatography of the latter twice on Florisil gave the 1,6-dione (170 mg) and the 1,8-dione (420 mg). Recrystallization of the latter from benzene–chloroform provided the pure 1,8-dione as red needles, m.p. 269—270° (sealed capillary) (lit.,[10] 270°; lit.,[14] 272—273°; lit.,[15] 270—272°); δ 6.62 (2 H, d, *J* 10 Hz, H-2 and -7), 7.62 (2 H, s, H-4 and -5), 7.63 (2 H, d, *J* 10 Hz, H-3 and -6), and 8.60 (2 H, s, H-9 and -10). Recrystallization of the 1,6-dione from benzene–chloroform afforded orange needles, m.p. 320—321° (sealed capillary) (lit.,[10] 309°; lit.,[14] 324—326°; lit.,[15] 310—312°); δ 6.65 (2 H, d, *J* 10 Hz, H-2 and -7), 7.63 (2 H, d, *J* 10 Hz, H-3 and -8), 7.79 (2 H, d, *J* 7·5 Hz, H-4 and -9), and 8.45 (2 H, d, *J* 7.5 Hz, H-5 and -10).

Products of reductive acetylation of polycyclic aromatic quinones

Product	Reagent [a]	Yield [b] (%)	M.p. (°C)
(1)	$NaBH_4$	95	203—203.5 [c]
(1)	$Li(Bu^tO)_3AlH$	92	203—203.5 [c]
(2)	$NaBH_4$	78	195—196
(3a)	$NaBH_4$	90	239—240 (decomp.)
(3a)	$Li(Bu^tO)_3AlH$	78	239—40
(3b)	$NaBH_4$	88	225—226 [f]
(3c)	$NaBH_4$	90 [e]	193—194 [g]
(4a)	$NaBH_4$	90 [d]	219.5—220
(4a)	$Li(Bu^tO)_3AlH$	80 [d]	219.5—220
(4b)	$NaBH_4$	90	199—200
(5a)	$NaBH_4$	90	245—247 (decomp.) [h]
(5b)	$NaBH_4$	90	229—230 [i]
(5c)	$NaBH_4$	89 [e]	255—256 [j]
(5d)	$NaBH_4$	96	297—298 [k]
(6)	$NaBH_4$	61 [d]	225—226
(7)	$Li(Bu^tO)_3AlH$	75	264—266

[a] All reactions with $NaBH_4$ and $Li(Bu^tO)_3AlH$, conducted in DMF and in bis-(2-methoxyethyl) ether, respectively, were followed by acetylation with acetic anhydride–pyridine as described in the Experimental section. [b] Yields are for products obtained following chromatography on Florisil and recrystallization from chloroform–ethanol or other solvent as specified. [c] From chloroform–benzene. [d] From benzene. [e] Lit., m.p. 202.5—203.5° (V. O. Lukashevich and E. N. Dokunikhina, *Doklady Akad. Nauk S.S.S.R.*, 1966, **167**, 357). [f] Lit.,[10] m.p. 224°. [g] Lit.,[10] m.p. 190°. [h] Lit.,[10] m.p. 245—246°; lit.,[11] m.p. 243—244°. [i] Lit.,[11] m.p. 215—216°. [j] Lit.,[6] m.p. 268—269°; lit.,[13] m.p. 258—260°. [k] Lit.,[21] m.p. 245—250°.

Oxidation of Benzo[a]*pyrene.*—Similar oxidation of benzo[*a*]pyrene (2.52 g, 10 mmol) with dichromate afforded a product (2.5 g) which was dissolved in chloroform (300 ml), passed through a column of basic alumina, taken up again in chloroform (150 ml), and chromatographed on Florisil (100 g). Elution with 2% ethyl acetate–benzene (1.5 l) gave the 6,12-dione (200 mg), followed by (4 l) the 1,6-dione and some 6,12-dione (1.11 g). Elution with 10% ethyl acetate–chloroform (8 l) furnished the 3,6-dione and the remaining 1,6-dione (670 mg). Rechromatography (twice) of the last fraction gave the 1,6-dione (70 mg) and the 3,6-dione (580 mg). Recrystallization of the latter from benzene–chloroform yielded pure benzo[*a*]pyrene-3,6-dione as red needles, m.p. 295—296° (decomp.; sealed capillary) (lit.,[11] 288—289°; lit.,[12] 291; lit.,[13] 292—293°). The combined fractions of the 1,6-dione were rechromatographed to remove a trace (20 mg) of 6,12-dione, then recrystallized from benzene–chloroform to afford pure benzo[*a*]pyrene-1,6-dione as orange needles (1.15 g), m.p. 326—327° (sealed capillary) (lit.,[11] 290—291°; lit., [12] 292—293°; lit., [13] 291°). Recrystallization of the fractions containing the 6,12-dione from chloroform gave orange needles, m.p. 338—339° (sealed capillary) (lit., [13] 327°; lit.,[21] 316—318°; lit.,[22] 324—326°). R_F Values (t.l.c.) on silica gel with 1 : 1 ethyl acetate–benzene were 0.60, 0.53, and 0.50 for the 6,12-, 1,6-, and 3,6-diones respectively.

The 270 MHz n.m.r. spectra were taken with $F_3C{\cdot}CO_2D$ as solvent (peak assignments in italics are tentative): 1,6-dione, δ 6.84 (1 H, d, *J* 10 Hz, H-2), 7.56 (1 H, t, *J* 7.5 Hz, H-9), 7.64—7.78 (3 H, m, H-3, -4, and -8), 7.97 (1 H, d, *J* 7.5 Hz, H-5), 8.03—8.16 (2 H, m, H-7 and -12), 8.26 (1 H, d, *J* 7.5 Hz, H-10), and 8.36 (1 H, d, *J* 7.5 Hz, H-11); 3,6-dione δ 6.74 (1 H, d, *J* 10 Hz, H-2), 7.50 (1 H, t, *J* 7.5 Hz, H-9), 7.61 (1 H, d, *J* 7.5 Hz, H-12), 7.69 (1 H, t, *J* 7.5 Hz, H-8), 7.72 (1 H, d, *J* 10 Hz, H-1), 7.91 (1 H, d, *J* 7.5 Hz, H-4), 7.96 (1 H, d, *J* 7.5 Hz, H-7), 8.04 (1 H, d, *J* 7.5 Hz, H-5), 8.23 (1 H, d, *J* 7.5 Hz, H-10), and 8.35 (1 H, d, *J* 7.5 Hz, H-11); 6,12-dione δ 7.07 (1 H, s, H-11), 7.48—7.70 (4 H, m, H-2, -3, and -8), 7.85 (2 H, q, *J* 9 Hz, H-4 and -5), 7.91 (1 H, d, *J* 7.5 Hz, H-1), 8.04 (1 H, d, *J* 7.5 Hz, H-7), and 8.27 (1 H, d, *J* 7.5 Hz, H-10); the 4,5-dione gave a complex multiplet.

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