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ACETOXYLATION AT BENZYLIC POSITIONS OF TETRAHYDROBENZO RINGS WITH DDQ IN ACETIC ACID

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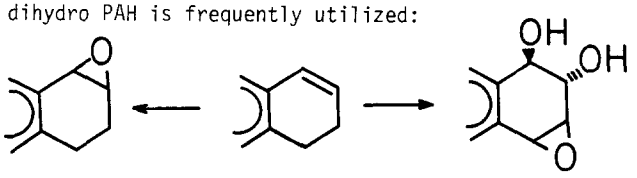
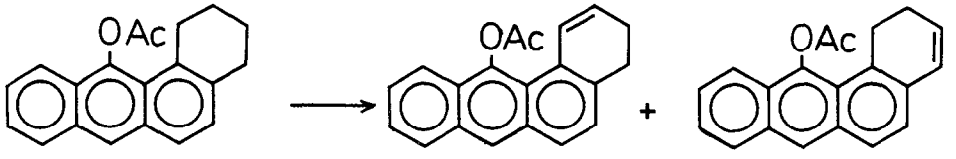
Abstract: Good-excellent yields of monoacetoxy derivatives at benzylic positions are obtained upon reaction of polycyclic aromatic hydrocarbons (PAH) containing an angular tetrahydrobenzo ring with DDQ in acetic acid.

Bay-region diol epoxides are now generally recognized as ultimate carcinogenic forms of PAH[1]. Though a variety of synthetic approaches to diol epoxides and the related tetrahydroepoxides exist[2], a dihydro PAH is frequently utilized:



In the course of studies directed toward the preparation of the 1,2- and 3,4-epoxide derivatives of 1,2,3,4-tetrahydro-12-methylbenz[a]anthracene, we had need of pure samples of 1,2- and 3,4-dihydro-12-acetoxybenz[a]anthracene. Although a variety of methods exist



for substitution at benzylic positions on tetrahydrobenzo rings, the need to separate the products of substitution at C-1 and C-4 chromatographically suggested that a polar substituent be introduced, so that advantage could be taken of the different steric environments at the bay (C-1) and non-bay (C-4) positions on the ring.

We have found that, at moderate temperatures, a variety of tetrahydrobenzo ring derivatives of PAH react with DDQ in HOAc to produce good-excellent yields of the benzylic acetoxy compounds. The results for several compounds are cited in Table 1. Except for 1,2,3,4-tetrahydrobenz[a]anthracene, the yields cited are for purified compounds. In that case, the isolated yield of the mixture of monoacetates was 75 % and NMR integration was used to estimate the relative percentages of the isomers. For the benz[a]anthracene derivatives, the product mixtures were separated by chromatography on silica gel, using 0-10 % EtOAc in petroleum ether or benzene. For all cases except the unsubstituted 1,2,3,4-tetrahydrobenz-

[a]anthracene, reactions proceeded at acceptable rates at temperatures between 25-30°. For the unsubstituted compound, a temperature of 55° was needed to complete the reaction in one day. Generally, 1.1-1.2 moles of DDQ per mole of hydrocarbon were used. This slight stoich-

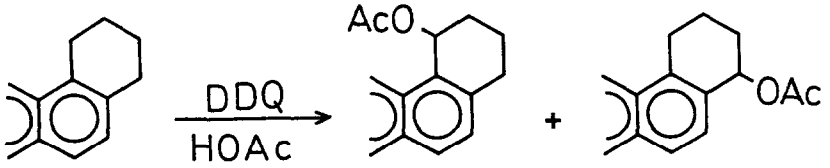
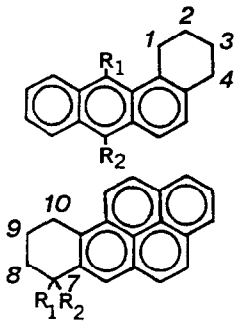


TABLE 1. Product distribution for the formation of tetrahydrobenzo ring acetates from several tetrahydro PAH



R_1	R_2	% OAc derivative at C-1	C-4	C-10	% aromatic product
H	H	40	35	-	9
OAc	H	33	39	-	8
H	OAc	32	39	-	5
H	H	-	-	82	5
CH_3	CH_3	-	-	95	0

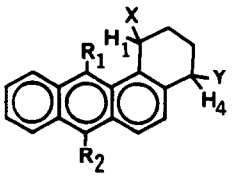
iometric excess compensates for the relatively small amount of aromatization, which should consume two moles of DDQ per mole of substrate. For reactions of the benzo[a]pyrene derivatives, an immediate formation of a blue-green precipitate is observed, which is presumed to be a charge-transfer complex between the hydrocarbon and DDQ. A similar precipitate is formed when DDQ is added to a solution of pyrene in HOAc. Despite the formation of precipitate, the reaction of the benzo[a]pyrene derivatives is complete within 24 hours.

The NMR absorptions of the acetoxy and meso hydrogens and of the hydrogen atoms at the acetoxy-substituted carbon atoms at C-1 and C-4 for the products of reaction of the 1,2,3,4-tetrahydrobenz[a]anthracene compounds are compared in Table 2. As expected, the bay-region hydrogen atoms (H_1) are significantly downfield (0.48-0.65 delta) compared to the corresponding hydrogen atoms (H_4) at the non-bay benzylic positions (cf. compounds 1-3 vs. 4-6)[3]. Also, H_1 is shifted upfield by 0.2 delta due to the presence of the acetoxy group at C-12 (cf. compound 3 vs. compounds 1 and 2).

In a typical experiment, 7,8,9,10-tetrahydrobenzo[a]pyrene (200 mg, 0.00078 mole) was stirred magnetically in glacial HOAc (8.8 mL). DDQ (192 mg, 0.00085 mole) was added, all at once, and the dark mixture was stirred magnetically at room temperature (20-25°). After 22 hours, the HOAc was removed at room temperature under vacuum on a rotary evaporator, and the residue was treated with equal volumes of benzene and 10 % aq. KOH. The aqueous phases were combined and extracted with benzene. The benzene phases were combined, washed with water,

dried (Na_2SO_4), filtered and evaporated. Trituration of the white, solid residue with ether gave 201 mg (82 %) of 10-acetoxy-7,8,9,10-tetrahydrobenzo[a]pyrene, mp 175-178 (lit. 174-175[4]).

TABLE 2. Chemical shifts of selected protons in the products of DDQ/HOAc reaction of the tetrahydrobenz[a]anthracene derivatives in Table 1.[a]



Compound[b]	H_1	H_4	C_1-OAc	C_4-OAc	H_7	H_{12}	C_7-OAc	C_{12}-OAc
1 R_1=R_2=Y=H X=OAc	6.79	-	2.08	-	8.38 or 8.35		-	-
2 R_1=Y=H R_2=X=OAc	6.79	-	2.08	-	-	8.31	2.63	-
3 R_1=X=OAc R_2=Y=H	6.58	-	2.03	-	8.31	-	-	2.60
4 R_1=R_2=X=H Y=OAc	-	6.16	-	2.14	8.39 or 8.57		-	-
5 R_1=X=H R_2=Y=OAc	-	6.14	-	2.12	-	8.51	2.63	-
6 R_1=Y=OAc R_2=X=H	-	6.10	-	2.13	8.30	-	-	2.58

[a]300 MHz, in $CDCl_3$ with TMS as internal standard [b]Satisfactory combustion analyses were obtained on new compounds 2 (mp 156-157), 3 (mp 201-205, dec.), 5 (mp 160-162) and 6 (mp 121-124) as well as for 10-acetoxy-7,7-dimethyl-7,8,9,10-tetrahydrobenzo[a]pyrene (mp 186-187, dec.).

Some clear advantages to the DDQ/HOAc procedure are evident by comparison with literature results. First, 10-acetoxy-7,8,9,10-tetrahydrobenzo[a]pyrene has previously been prepared by reaction of 7,8,9,10-tetrahydrobenzo[a]pyrene with lead tetraacetate[4]. However, extensive purification was needed to produce the pure product, and the best yield (70 %) was lower than that obtained here (82 %). Second, the DDQ/HOAc procedure appears to minimize unwanted aromatization. For example, treatment of tetrahydrobenzo ring PAH with an equivalent of DDQ in benzene has proven a successful approach for the preparation of several dihydro PAH[5]. However, in some cases, including 1,2,3,4-tetrahydrobenz[a]anthracene, only the fully aromatic derivative was detected[6]. In contrast, less than 10 per cent aromatization is observed in the reaction of 1,2,3,4-tetrahydrobenz[a]anthracene with DDQ/HOAc.

The regioselectivity shown by the data in Table 1 is interesting. 7,8,9,10-Tetrahydrobenzo[a]pyrene reacts highly selectively at C-10, and this corresponds to the position at

which the more stable carbocation is predicted to be formed ($\Delta E_{deloc}/\beta$ [7] at C-10 = 0.794; at C-7, $\Delta E_{deloc}/\beta$ = 0.488). However, nearly equal amounts of products are formed at C-1 and C-4 of the benz[a]anthracene derivatives. Calculations indicate a greater stability for the carbocation at C-1 ($\Delta E_{deloc}/\beta$ = 0.766 at C-1 vs. 0.622 at C-4) for the unsubstituted hydrocarbon. The very similar yields of products at C-1 and C-4 for the three tetrahydrobenz[a]anthracene derivatives indicates an insensitivity to electronic and steric effects of the acetoxy substituent. Previous results for the production of the dihydro derivatives of 7- and 12-methyl-8,9,10,11-tetrahydrobenz[a]anthracene with DDQ in benzene were consistent with a predominating steric effect of the methyl groups upon the position of incorporation of the double bond[5].

Benzylic acetates 2, 3, 5 and 6 have proven to be suitable precursors for the 1,2- and 3,4-epoxide derivatives of 7- and 12-methyl-1,2,3,4-tetrahydrobenz[a]anthracene. Details of these conversions will be presented in a full paper.

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REFERENCES AND NOTES

1. For recent reviews of PAH carcinogenesis, see R.E.Lehr, S.Kumar, W.Levin, A.W.Wood, R.L. Chang, A.H.Conney, H.Yagi, J.M.Sayer and D.M.Jerina, in "Polycyclic Hydrocarbons and Carcinogenesis", R.G.Harvey, Ed., ACS Symposium Series No. 283, 1985, pp. 63-84; A.H. Conney, Cancer Research, 1982, 42, 4875-4917; D.H.Phillips, Nature, 1983, 303, 468-472; R.G.Harvey, American Scientist, 1982, 70, 386-393; A. Dipple, Cancer Research, 1983, 43, 2422s-2425s.
2. For a recent review, see R.G.Harvey, in "Polycyclic Hydrocarbons and Carcinogenesis", R.G. Harvey, Ed., ACS Symposium Series No. 283, 1985, pp. 35-63.
3. This has been a general observation in the PAH field; see, for example, R.E.Lehr, M. Schaefer-Ridder and D.M.Jerina, J. Org. Chem., 1977, 42, 736-744.
4. G.A.R.Kon and E.M.F.Roe, J. Chem. Soc., 1945, 143-146.
5. P.P.Fu, H.M.Lee and R.G.Harvey, Tetrahedron Lett., 1978, 551-554.
6. P.P.Fu and R.G.Harvey, Chem. Rev., 1978, 78, 317-361. This article contains numerous references to reactions of PAH with DDQ.
7. M.J.S.Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, pp. 214-217 and 304-306 (1969).

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