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SYNTHESIS OF 1-HYDROXY- AND 3-HYDROXY-TRANS-7,8-DIHYDRO-7,8-DIHYDROXYBENZO(a)PYRENE

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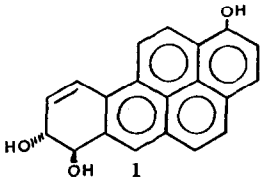
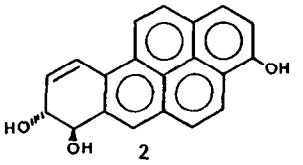
Summary: A facile synthesis and spectral data of 1-hydroxy- and 3-hydroxy-trans-7,8-dihydro-7,8-dihydroxybenzo(a)pyrene the potential carcinogenic metabolites of benzo(a)pyrene, are described.

Previous studies have demonstrated that environmental carcinogen benzo(a)pyrene (BP)[3] is metabolically activated to (+)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydro-BP which has been implicated as the ultimate carcinogen of the parent hydrocarbon[4,5]. More recently, it has been shown that 3-hydroxy-7,8,9,10-tetrahyro-BP-7,8-diol-9,10-epoxide(s)[6] and its precursor 3-hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP (2)[7] are the major metabolites of anti-7,8,9,10-tetrahydro-BP-7,8-diol-9,10-epoxide and 3-hydroxy-BP (a major metabolite of BP), respectively, and might be involved in binding with DNA in vivo[8-10]. However, very little is known about the biological importance of these phenolic dihydro diol and diol epoxide metabolites in the carcinogenicity of BP[11]. In order to understand the role of these metabolites in the carcinogenesis of BP, these and other phenolic dihydro diol and diol epoxides are urgently needed for carcinogenic studies. Therefore, we have undertaken the synthesis of various phenolic dihydro diol and diol epoxide derivatives of BP. The present communication reports a facile synthesis of 1-hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP (1) and 3-hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP (2), and their spectral properties.



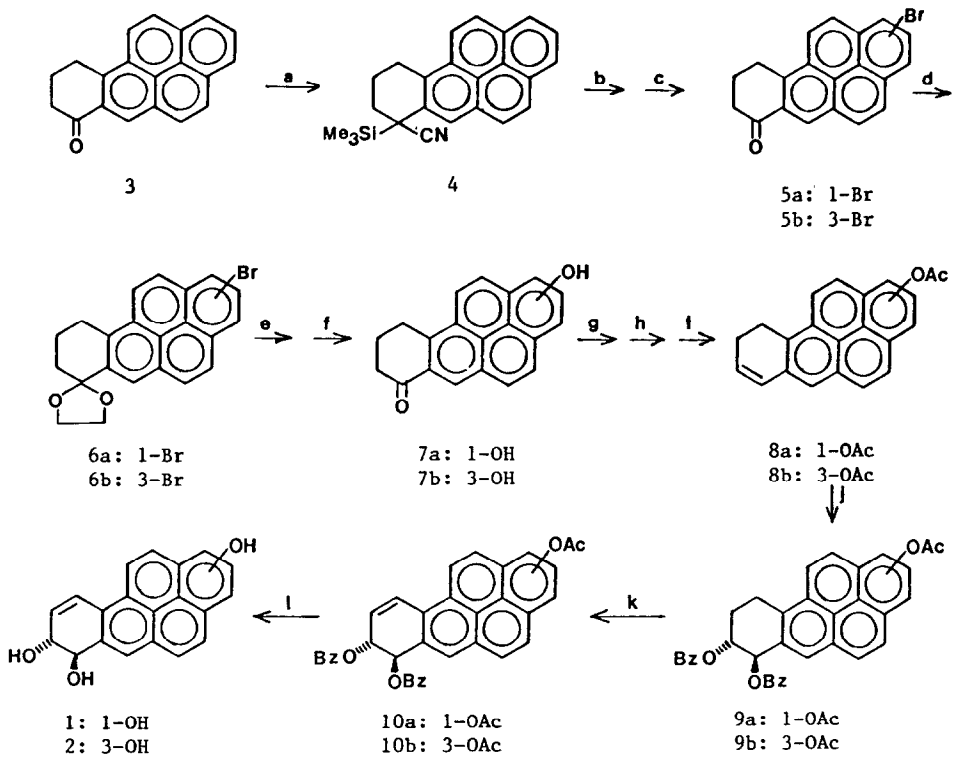
1



2

The phenolic dihydro diols of BP 1 and 2 were prepared from the readily available 7,8,9,10-tetrahydro-BP-7-one (3)[12] (see Scheme). Bromination of the trimethylsilyl cyanide derivative 4 of ketone 3 following the removal of the protecting group was performed according to the procedure of Pataki and Harvey[13]. The column chromatography of the crude product on dry column-grade silica gel (Merck) using benzene as the eluant produced a product which appeared to be a mixture of two bromo-ketones, 5a (major) and 5b (minor) by ^{1}H NMR. These bromo-ketones, which could not be separated by tlc (silica gel, Merck) using benzene as the developing solvent, were resolved using 15% EtOAc-Hexane. The fractional recrystallization (benzene) and/or column chromatography of the mixture of the bromo-ketones on dry column-grade silica gel (Merck) using 10% EtOAc-cyclohexane as the eluant produced pure 5a (∿40%, mp. 212-214°C) and 5b (∿10%, mp. 215-216°C).

Scheme



3 4 5a: 1-Br 5b: 3-Br

6a: 1-Br 6b: 3-Br 7a: 1-OH 7b: 3-OH 8a: 1-OAc 8b: 3-OAc

1: 1-OH 2: 3-OH 10a: 1-OAc 10b: 3-OAc 9a: 1-OAc 9b: 3-OAc

Reagents: a. Me_3SiCN/benzene. b. Br_2/CCl_4. c. AgF. d. Ethylene glycol-H /benzene. e. Mg-B_2H_6/THF. f. H_2O_2/NaOH. g. $NaBH_4$/MeOH. h. H^+/benzene. i. Ac_2O/pyridine j. BzOAg-I_2/benzene. k. DDQ/dioxane. l. NaOMe/THF-MeOH.

The site of the bromine substituent in these bromo-ketones was proven by conversion of individual ketones to the corresponding 1-hydroxy-BP and 3-hydroxy-BP *via* 1-acetoxy- (**8a**) and 3-acetoxy-9,10-dihydro-BP (**8b**), respectively. The relatively non-polar bromo-ketone **5a** was converted to its ketal (**6a**) which was treated with magnesium in dry THF in the presence of diborane to produce a borane complex[14]. The borane complex was oxidized (H_2O_2, NaOH) to 1-hydroxy-7,8,9,10-tetrahydro-BP-7-one (**7a**). The impure hydroxy-ketone (**7a**) was reduced ($NaBH_4$/MeOH), dehydrated (PTSA/benzene) and acetylated (Ac_2O/pyridine) to produce 1-acetoxy-9,10-dihydro-BP **8a** (mp. 194-195°C). Similarly, 3-bromo-7,8,9,10-tetrahydro-7-one (**5b**) was converted to 3-acetoxy-9,10-dihydro-BP **8b** (mp. 166-168°C).

The usual reactions developed previously for synthesizing dihydro diols of unsubstituted polynuclear aromatic hydrocarbons[15,16] were successful in converting alkenes **8a** and **8b** to the phenolic dihydro diols **1** and **2**, respectively (see Scheme). No apparent interference of the aromatic acetoxy substituent on these reactions was observed. However, we noted for the first time that using an excess of reagents (silver benzoate and iodine) in the Prevost reaction of **7a** produced a mixture of tetrahydro diol dibenzoate (**9a**) and dihydro diol dibenzoate (**10a**). The use

of an equivalent amounts of reagents produced **9a** in moderate yield. Furthermore, the dehydrogenation of **9a** and **9b** to the dihydro diol dibenzoates **10a** and **10b** was best carried out by using two to three fold excess of DDQ. The use of an equvalent amount of DDQ resulted in a mixture of tetrahydro and dihydro diol dibenzoates which was difficult to purify. The high resolution ^{1}H NMR spectrum of **1**, **2**, and their intermediates were consistent with their structural assignments (see Table). The H_2 proton of **1** and **2** appeared as a doublet at relatively upfield (δ 7.54) due to the effect of adjacent phenolic group. This finding is consistent with previous observations for the phenolic derivatives of BP[17]. Furthermore, the relatively large values of the coupling constant of the carbinol protons ($J_{7,8}$ = 10.6-11.5 Hz) support the presence of dihydro diol predominantly in the diequatorial conformation. The UV spectra of **1** and **2**, which are valuable for biological studies, are shown in the Figure.

Ribeiro et al.[7] have isolated a phenolic dihydro diol as a bilary metabolite of 3-hydroxy-BP and tentatively identified by its ^{1}H NMR and UV spectra as 3-hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP. Although the UV spectra of **2** shown in figure 1 was nearly identical to that of the reported metabolite, a slight difference between the relative chemical shifts of H_6 in the ^{1}H NMR spectra of the synthetic standard and of the reported metabolite has been noted.

TABLE[18]

COMPOUND (mp. °C)	NMR SPECTRUM (270 MHz)
1-Acetoxy-trans-7,8-dibenzoyloxy-7,8,9,10-tetrahydro-BP (207-209) **9a**	δ 2.38-2.95 (m, $2H_9$); 2.57 (s, 3H); 3.71 (m, $2H_{10}$); 5.78 (m, H_8); 6.96 (d, H_7); 7.19-8.38 (m, 17H); $J_{7,8}$ = 5.9 Hz.
3-Acetoxy-trans-7,8-dibenzoyloxy-7,8,9,10-tetrahydro-BP (242-243) **9b**	δ 2.24-2.84 (m, H_9); 2.55 (s, 3H); 3.73 (m, H_{10}); 5.78 (m, H_8); 6.97 (d, H_7); 7.20-8.48 (m, 17H); $J_{7,8}$ = 5.9 Hz.
1-Acetoxy-trans-7,8-dibenzoyloxy-7,8-dihydro-BP (220-221) **10a**	δ 2.57 (s, 3H); 6.22 (m, H_8); 6.47 (dd, H_9); 7.07 (d, H_7); 7.19-8.45 (m, 18H); $J_{7,8}$ = 7.5; $J_{8,9}$ = 3.6; $J_{8,10}$ = 1.1; $J_{9,10}$ = 10.3 Hz.
3-Acetoxy-trans-7,8-dibenzoyloxy-7,8-dihydro-BP (182-183) **10b**	δ 2.52 (s, 3H); 6.22 (m, H_8); 6.47 (dd, H_9); 7.06 (d, H_7); 7.28-8.42 (m, 18H); $J_{7,8}$ = 7.6; $J_{8,9}$ = 3.5; $J_{8,10}$ = 1.5; $J_{9,10}$ = 10 Hz.
1-Hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP (>360,d) **1**	(DMSO-d_6 + CD_3OD): δ 4.42 (d, H_8); 4.88 (d, H_7); 6.17 (d, H_9); 7.46 (d, H_{10}); 7.55 (d, H_2); 7.88 (d, 1H, J = 9); 7.97 (d, 1H, J = 9); 8.08 (d, 1H, J = 8.6); 8.31 (d, 2H, J = 8.6);8.32 (s, H_6); $J_{2,3}$ = 8.6; $J_{7,8}$ = 11.5; $J_{8,9}$ = 0; $J_{9,10}$ = 10.2 Hz.
3-Hydroxy-trans-7,8-dihydro-7,8-dihydroxy-BP (>360,d) **2**	(DMSO-d_6 + CD_3OD): δ 4.42 (d, H_8); 4.88 (d, H_7); 6.16 (dd, H_9); 7.44 (dd, H_{10}); 7.54(d, H_2); 8.00 (d, 1H, J = 9.2); 8.02 (d, 1H, J = 9.2); 8.07 (d, 1H, J = 8.2); 8.18 (d, 1H, J = 9.6); 8.28 (d, 1H); 8.29 (s, H_6); $J_{1,2}$ = 8.2; $J_{7,8}$ = 10.6; $J_{8,9}$ = 0; $J_{8,10}$ = 1.3; $J_{9,10}$ = 10.2 Hz.

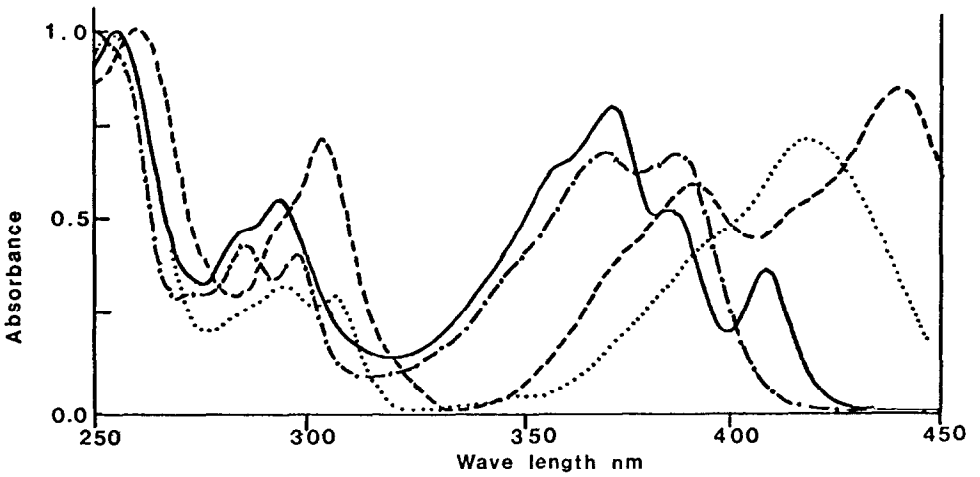


Figure. UV spectra of: **1** in MeOH (———) and in the presence of alkali (-----); **2** in MeOH (—·—·—) and in the presence of alkali (·····).

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REFERENCES AND NOTES

1. Adjunct Associate Research Professor in the Department of Chemistry, SUNY College at Buffalo.
2. Post-doctoral Research Associate
3. Abbreviations: BP = benzo(a)pyrene; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMSO = dimethyl sulfoxide; PTSA = p-toluene sulfonic acid; THF = Tetrahydrofuran.
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18. The compounds with mps. gave correct molecular ion peak in the high resolution mass spectra. Unless otherwise noted, spectra were recorded in $CDCl_3$, with TMS as internal standard.

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