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SYNTHESIS OF THE PHENOLIC ESTERS OF 1-HYDROXY- AND 3-HYDROXY-7,8-DIOL-9,10-EPOXIDES OF BENZO[a]PYRENE

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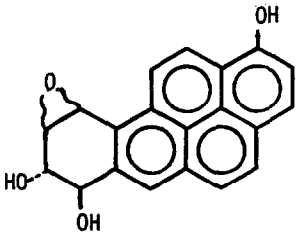
Abstract: A chemical synthesis of the phenolic ester of the triol epoxide derivatives of carcinogenic benzo[a]pyrene is described.

The chemical synthesis of the various reactive metabolites has been an essential factor in elucidating the molecular mechanism that is responsible for polycyclic aromatic hydrocarbon (PAH)-induced carcinogenicity. These reactive metabolites are not isolable as products of metabolism due to their exceptional chemical reactivity. In a recent report[2,3], we have described the total synthesis of regiomeric triols, namely 1-hydroxy-trans-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene (4) and 3-hydroxy-trans-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene (5) latter of which is a known metabolite of 3-hydroxybenzo[a]pyrene[4] (a major metabolite of benzo[a]pyrene). The 9,10-epoxides of these triols (triol epoxides 1 and 2) are of substantial



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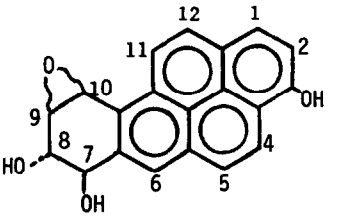

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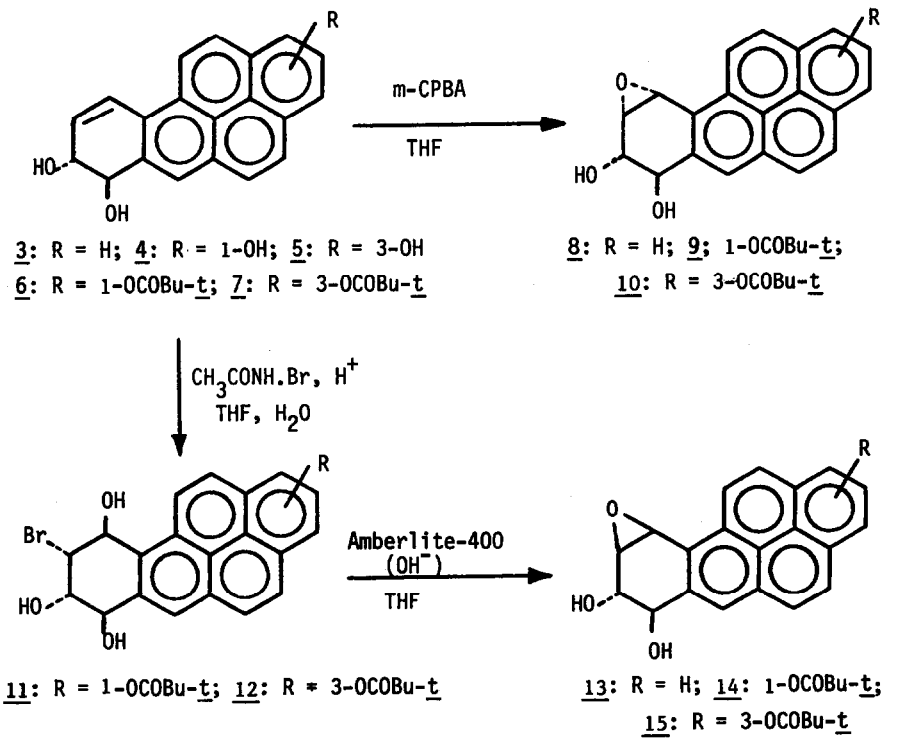
chemical and biological interest because some of these triol epoxides are tentatively identified as the metabolites of 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (8)[5,6] (a putative ultimate carcinogen of benzo[a]pyrene) as well as their triol precursors[7]. In order to understand the role of the triol-epoxides 1 and 2 in the carcinogenesis of benzo[a]-pyrene, these compounds are urgently needed. We report herein the synthesis and spectral properties of the four racemic triol-epoxide diastereomers 9, 10, 14, and 15 in which the phenolic group is esterified. These phenolic esters of the desired triol epoxides are useful precursors for the synthesis of the various 1-hydroxy- and 3-hydroxy-7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene isomers, and the specific deoxyribonucleoside, ribonucleoside, and aminoacid adducts required as markers for understanding the molecular mechanism of benzo[a]pyrene carcinogenesis.

The methodology which was developed by Yagi et al.[8,9] for the synthesis of 9,10-epoxides (8, 13) of trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene (3), failed to produce any signifi-

cant amount of 9,10-epoxides of the triols 4 and 5. Although starting triol disappeared each time from the reaction mixture (as judged by tlc and UV spectrum), the isolated product was always a complex mixture, and did not show any evidence for the presence of the desired triol epoxides 1 or 2 (NMR). Conceivably, the ability of the phenolic group to donate the lone-pair of electrons and thereby stabilizing the carbonium ion at the benzylic carbon (C-10) of the oxirane ring enhances the electrophilicity of the triol epoxide produced in the reaction mixture. As a result, unlike 9,10-epoxides of the dihydrodiol 3 , 9,10-epoxides of the triols 4 and 5 have strong affinity toward the reagents normally used to generate epoxide moiety.

In order to circumvent the problem associated with the high reactivity of the triol epoxides, we preferred to acylate the phenolic group of these triols with the hope that such acylation should diminish the ability of the phenolic group to donate electrons and, consequently, impede the reactivity of the epoxides generated in the reaction mixture. Therefore, these triols (4 and 5) were selectively acylated with trimethylacetyl chloride in dry acetone in the presence of anhydrous potassium carbonate to produce 6 and 7, respectively in 85-95% yields (see Scheme). Trimethylacetyl chloride was the reagent of choice because it is known to acylate phenols[10], but shows resistance to secondary alcohol[11]. The proof that the vicinal diols of 6 and 7 were not acylated came from their NMR studies. Both 6 and 7 showed chemical shifts (δ) and coupling (J value) for non-aromatic protons H_7, H_8, H_9 and H_{10} nearly identical to those of the analogous protons of the triols 4 and 5[2,3]. Furthermore, the observation that

Scheme



3: R = H; 4: R = 1-OH; 5: R = 3-OH
6: R = 1-OCOBu-t; 7: R = 3-OCOBu-t

8: R = H; 9; 1-OCOBu-t;
10: R = 3-OCOBu-t

11: R = 1-OCOBu-t; 12: R = 3-OCOBu-t

13: R = H; 14: 1-OCOBu-t;
15: R = 3-OCOBu-t

Table

NMR SPECTRA (270 MHz)[a,b]

Compound (m.p., °C)	
6 (220-24,dec)	δ 1.57 (6 H, s), 4.66 (1 H, m, H_8), 5.14 (1 H, d, H_7), 6.30 (1 H, dd, H_9), 7.42 (1 H, dd, H_{10}), 7.70 (1 H, d, H_2), 7.95-8.38 (5 H, m), 8.50 (1 H, s, H_6), $J_{2,3}$ = 8.2, $J_{7,8}$ = 11.5, $J_{8,9}$ = 2.0, $J_{8,10}$ = 2.7, $J_{9,10}$ = 10.0 Hz.
7 (189-91, dec)	δ 1.57 (6 H, s), 4.68 (1 H, m, H_8), 5.14 (1 H, d, H_7), 6.30 (1 H, dd, H_9), 7.45 (1 H, dd, H_{10}), 7.69 (1 H, d, H_2), 7.96-8.34 (5 H, m), 8.48 (1 H, s, H_6), $J_{1,2}$ = 8, $J_{7,8}$ = 11, $J_{8,9}$ = 1.3, $J_{8,10}$ = 1.7, $J_{9,10}$ = 8.5 Hz.
9 (c)	δ 1.52 (6 H, s), 3.87 (1 H, d, H_9), 3.95 (1 H, d, H_8), 4.74 (1 H, d, H_7), 5.20 (1 H, d, H_{10}), 7.87 (1 H, d, H_2), 8.04-8.40 (4 H, m), 8.59 (1 H, s, H_6), 8.82 (1 H, d, H_{11}), $J_{2,3}$ = 8.5, $J_{7,8}$ = 9, $J_{8,9}$ = 0, $J_{9,10}$ = 4.5, $J_{11,12}$ = 9.5 Hz.
10 (c)	δ 1.52 (6 H, s), 3.85 (1 H, d, H_9), 3.95 (1 H, d, H_8), 4.74 (1 H, d, H_7), 5.25 (1 H, d, H_{10}), 7.86 (1 H, d, H_2), 8.00-8.44 (4 H, m), 8.57 (1 H, s, H_6), 8.77 (1 H, d, H_{11}), $J_{1,2}$ = 8.3, $J_{7,8}$ = 8.6, $J_{8,9}$ = 0, $J_{9,10}$ = 4.6, $J_{11,12}$ = 9 Hz.
11 (225-30, dec)	δ 1.57 (6 H, s), 4.36 (1 H, dd, H_8), 4.86 (1 H, m, H_9), 5.14 (1 H, d, H_7), 5.96 (1 H, d, H_{10}), 7.73 (1 H, d, H_2), 8.00-8.60 (6 H, m), $J_{2,3}$ = 8.3, $J_{7,8}$ =8.5, $J_{8,9}$ = 2.0, $J_{9,10}$ = 2.7 Hz.
12 (180-90, dec)	δ 1.57 (6 H, s), 4.44 (1 H, dd, H_8), 4.90 (1 H, m, H_9), 5.19 (1 H, d, H_7), 5.99 (1 H, d, H_{10}), 7.74 (1 H, d, H_2), 7.96-8.52 (6 H, m), $J_{1,2}$ = $J_{7,8}$ = 8.2, $J_{8,9}$ = 2.0, $J_{9,10}$ = 2.7 Hz.
14 (173-76, dec)	δ 1.53 (6 H, s), 3.86 (1 H, d, H_9), 3.96 (1 H, m, H_8), 4.92 (1 H, m, H_7), 4.95 (1 H, d, H_{10}), 5.34 (1 H, d, OH_8), 5.44 (1 H, d, OH_7), 7.88 (1 H, d, H_2), 8.05-8.50 (4 H, m), 8.44 (1 H, s, H_6), 8.72 (1 H, d, H_{11}), $J_{2,3}$ = 8.4, $J_{7,8}$ = 6.5, $J_{8,9}$ = 1.6, $J_{9,10}$ = 3.2, $J_{11,12}$ = 9.5, $J_{7,OH}$ = 7.0, $J_{8,OH}$ = 5.0 Hz.
15 (c)	δ 1.52 (6 H, s), 3.85 (1 H, d, H_9), 3.93 (1 H, m, H_8), 4.92 (1 H, m, H_7), 4.98 (1 H, d, H_{10}), 5.37 (1 H, d, OH_7), 5.76 (1 H, d, OH_8), 7.88 (1 H, d, H_2), 8.00-8.46 (5 H, m), 8.65 (1 H, d, H_{11}), $J_{1,2}$ = 8.2, $J_{7,8}$ = 6.5, $J_{8,9}$ = 1.5, $J_{9,10}$ = 4.2, $J_{11,12}$ = 9.6, $J_{7,OH}$ = 6.5, $J_{8,OH}$ = 4.3 Hz.

[a]Spectra were recorded in $(CD_3)_2SO$ and/or $(CD_3)_2SO$-CD_3OD, with Me_4Si as an ineternal standard.

[b]The compound listed gave M^+ and/or M^+-H_2O peaks in the mass spectrum.

[c]These compounds exhibited undefined mp.

the UV spectrum of 6 and 7 was identical to that of the authentic trans-7,8-dihydro-7,8-dihydroxybenzo[a]pyrene (3)[12] also supports the structures given to 6 and 7. The treatment of the appropriate trimethylacetoxy dihydrodiols 6 and 7 with a ten-fold excess of purified m-chloroperoxybenzoic acid (m-CPBA) in freshly distilled THF ($LiAlH_4$) for 2-3 hrs at 0°C under argon atmosphere gave 7β,8α-diol-9α,10α-epoxide diastereomers 9 and 10, respectively, in 85-90% yields. For the synthesis of the corresponding 7β,8α-diol-9β,10β-diol epoxide diastereomers 14 and 15, trimethylacetoxybromo-triols 11 and 12, which were obtained from 6 and 7, respectively, in 75-85% yields under normal conditions[8,9], were cyclized with amberlite-400 (OH^-) in argon atmosphere. Cyclization was monitored by tlc and usually over in 7 hrs.

The structure and the relative stereochemistry of the synthetic 1-(trimethylacetoxy)- and 3-(trimethylacetoxy)benzo[a]pyrene-7,8-diol-9,10-epoxides 9, 10, 14, and 15 have been confirmed by comparing their proton NMR spectra with those of 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (8)[9] and 7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[a]-pyrene (13)[9]. As expected, vicinal diols of 7β,8α-diol-9α,10α-epoxides 9 and 10 ($J_{7,8}$ = 8.6 Hz) are relatively more in quasi diequatorial conformation than those of 7β,8α-diol-9β,10β-epoxides 14 and 15 ($J_{7,8}$ = 6.6 Hz), presumably due to the intramolecular hydrogen bonding between C_7-OH and the oxirane ring. Relative 0.27 ppm down field shift of H_{10} signal in 7β,8α-diol-9α,10α-epoxide diastereomers 9 and 10 than in 7β,8α-diol-9β,10β-epoxide diastereomers 14 and 15 due to "edge deshielding"[13] is also notable and analogous to the earlier observation with the NMR spectrum of diol epoxides 8 and 13. The UV spectrum of all the acyloxydiol epoxides 9, 10, 14 and 15 were identical to that of authentic 8 or 13[14].

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