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SYNTHESIS OF THE DIOLS AND DIOLEPOXIDES OF CARCINOGENIC HYDROCARBONS

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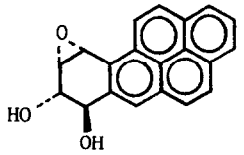
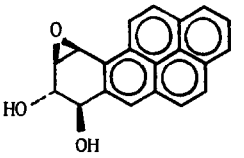
Recent evidence strongly implicates a diolepoxide derivative of benzo[a]pyrene (BP)[1], specifically (+)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydro-BP (*anti*-1d), as the principal active form of this carcinogen. Thus, *anti*-1d has been shown to be the principal metabolite of BP which binds to DNA and RNA *in vivo*.[2] It also exhibits exceptional potency as a mutagen[2d,3] and as an inhibitor of the infectivity of QB RNA and ØX 174 DNA viruses.[4]

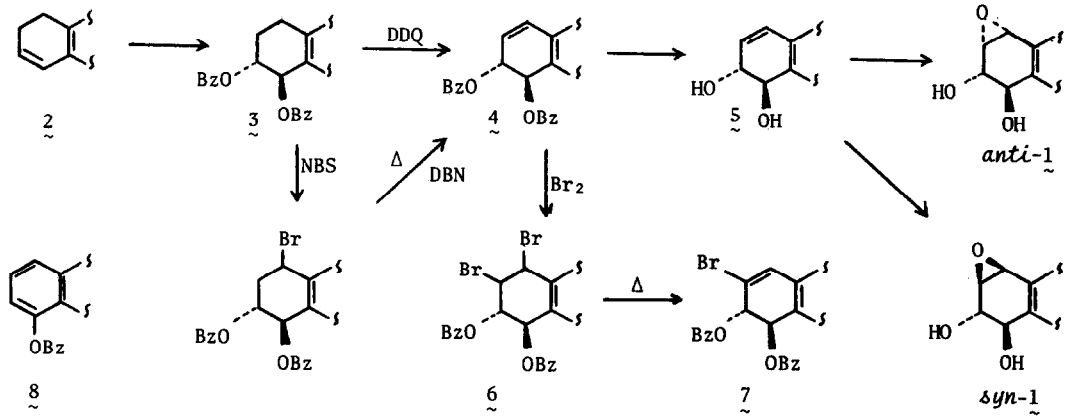


anti-1d

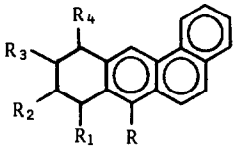


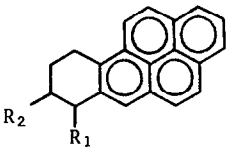
syn-1d

To determine the generality of these findings, other diolepoxide derivatives are urgently required for biological studies. We undertook therefore, the synthesis of a series of diols and the corresponding diolepoxides of carcinogenic hydrocarbons. The synthetic approach employed was based on the method devised earlier[5] for the synthesis of the *syn* and *anti* isomers of 1d. Initial Prévost reaction of the dihydroarenes (2)[6] with silver benzoate and iodine furnished smoothly the corresponding *trans*-dibenzoxy-tetrahydroarenes (3a-d). The related *cis*-7,8-dibenzoxy derivative of 7,8,9,10-tetrahydro BP (3e) was obtained through benzoylation of the corresponding *cis*-diol[7] with benzoyl chloride.



2 3 4 5 *anti*-1 8 6 7 *syn*-1





3a : $R_1 = R_2 =$ *trans*-OBz; $R_3 = R_4 = R = H$

3b : $R_1 = R_2 = R = H$; $R_3 = R_4 =$ *trans*-OBz

3c : $R_1 = R_2 = H$; $R = CH_3$; $R_3 = R_4 =$ *trans*-OBz

3d : $R_1 = R_2 =$ *trans*-OBz

3e : $R_1 = R_2 =$ *cis*-OBz

Attempted introduction of the double bond into 3a-e *via* the standard method involving bromination with NBS followed by thermal or base catalyzed dehydrobromination gave erratic results,[8] poor yields, and products contaminated with variable amounts of secondary products difficult to remove (Table I). The latter include the dibromo compound, 6, the monobromo olefin, 7, and the phenol benzoate, 8. A search for alternative methods has led to the discovery that dehydrogenation of 3 to 4 can be conveniently and efficiently achieved with DDQ. The method appears general, providing excellent yields of the pure dioldibenzoates even in the cases of the *cis* isomer 3e and the 7-methyl-BA derivative 3c which gave 5% of 4e and 0% of 4c, respectively, *via* the bromination route (Table I.) In a typical reaction, a solution of 3b (850 mg, 1.80 mmol) and DDQ (409 mg, 1.80 mmol) in 150 ml freshly distilled dioxane was maintained at reflux for 2 days. The resulting suspension was cooled to ambient temperature and poured onto a column of neutral alumina. Elution with benzene gave 4b (800 mg, 94%) which crystallized from acetone as colorless prisms: mp 180-181°; m/e (70 eV) 470; 270 MHz nmr spectra consistent with structure. Absence of brominated side products greatly facilitated purification of the dioldibenzoates from reaction with DDQ. Small amounts of unreacted starting material, otherwise difficult to remove, could be readily separated by chromatography on 15% silver or cobalt nitrate on Florisil; generally 4 eluted before 3 with benzene-hexane.

Methanolysis of the dioldibenzoates 4a-e with $NaOCH_3$ in CH_3OH-THF (60°, 10 min) furnished the corresponding diols 5a-e. Yields were virtually quantitative from the dioldibenzoates obtained *via* the DDQ route and 70-80% from those synthesized by the NBS approach, a reflection of the higher purity of the former. Recrystallization afforded the analytically pure diols (solvent, mp,[11] crystal form): 5a ($THF-CH_3OH-Et_3N$, 215° dec., plates); 5b (acetone, 202-203°, needles); 5c (acetone, 225°, silky needles); 5d ($THF-CH_3OH-Et_3N$, 217-218°, lit.[10] 216-217°, needles); 5e ($THF-CH_3OH-Et_3N$, 220-221°, needles); mass spectra and nmr analysis (Table II) of all compounds agreed with the assigned structures. During the preparation of this manuscript synthesis of 5a and 5b *via* a bromination-dehydrobromination path was reported by Lehr *et al.*[9] the reported mp were 168-170 dec. and 196-200° dec. respectively, significantly lower than reported herein for the pure diols obtained *via* the DDQ route.

Epoxidation of the *trans*-diols 5a-d with *m*-chloroperbenzoic acid in THF according to the method previously described afforded the corresponding *anti*[12] diolepoxides *anti*-1a-d apparently stereospecifically and in good yield. Similar reaction of the *cis*-diol 5e furnished an equal mixture of *anti*-and *syn*-1e. The isomeric *syn* diolepoxides (*syn*-1a,b,d) were synthesized from the *trans*-diols 5a,b,d through the related bromohydrins followed by cyclization with *t*-BuOK

Table I. Synthesis of Dioldibenzoates[a]

Compound	Time (hr)	Diol-dibenzoate	M.p.[11] (°C)	Avg. Yield, %[b] DDQ	NBS
3a	24	4a	175-176[c]	88(3)	68(5)
3b	48	4b	180-181[d]	90(2)	45(1)
3c	48	4c	197-198	82(1)	0(1)
3d	2	4d	199-200[e]	80(2)	50(10)
3e	16	4e	182-183	93(4)	5(3)

[a]All data, except yields, are for reactions with DDQ. Reactions were conducted in refluxing dioxane (except 3d for which benzene was employed) under a N_2 atmosphere using equimolar ratios of the 3 and DDQ. Mass and nmr spectra data for all compounds agreed with the assigned structures. [b]Yields are the average of the number of repetitions in parentheses. [c]Reported[9] mp 167-168°. [d]Reported[9] mp 170-171°. [e]Reported[10] mp 196-198°.

Table II[a]. 270 MHz Nmr Data on the Diols 4a-e and Diolepoxides *Syn*- and *Anti*-1a-c

Compound	Carbinol	Vinyl or Epoxy	Aromatic[b]
4a	H_8 4.79; h_9 4.39	H_{10} 6.08; H_{11} 6.76	H_1 8.79; H_4 7.98; H_7 8.08; H_{12} 8.57
	($J_{8,9} = J_{10,11} = 10$, $J_{9,10} = J_{9,11} = 2$, $J_{1,2} = J_{3,4} = 8$)		
4b	H_{10} 4.39; H_{11} 4.85	H_8 6.67; H_9 6.08	H_1 8.80; H_4 8.02; H_{12} 8.89
	($J_{8,9} = 9.8$, $J_{8,10} = J_{9,10} = 2.0$, $J_{10,11} = 9.5$, $J_{1,2} = 10$, $J_{3,4} = 9$)		
4c	H_{10} 4.32; H_{11} 4.80	H_8 7.03; H_9 6.14	H_1 8.64; H_{12} 8.69; CH_3 2.70
	($J_{8,9} = J_{1,2} = 10$, $J_{8,11} = J_{9,10} = 4$)		
4d	H_7 4.97; H_8 4.49	H_9 6.25; H_{10} 7.53	H_2 8.04; H_6 8.50; H_{11} 8.49
	($J_{7,8} = J_{9,10} = 10$, $J_{8,9} = J_{8,10} = 2$, $J_{1,2} = J_{2,3} = J_{11,12} = 9$)		
4e	H_7 4.88; H_8 4.35	H_9 6.32; H_{10} 7.60	(8H) 8.00-8.65
	($J_{7,8} = 5$, $J_{8,9} = 4.3$, $J_{9,10} = 10$)		
Anti-1a	H_8 4.59; H_9 3.81	H_{10} 3.76; H_{11} 4.35	(8H) 7.62-9.08
	($J_{8,9} = 9$, $J_{10,11} = 4.5$)		
Syn-1a	H_8 4.65; H_9 4.30	H_{10} 3.86; H_{11} 4.38	(8H) 7.58-9.0
	($J_{8,9} = 3.3$, $J_{9,10} = 2.5$, $J_{10,11} = 4.0$)		
Anti-1b	H_{10} 3.82; H_{11} 4.62	H_8 4.27; H_9 3.75	(8H) 7.6-9.0
	($J_{8,9} = 4.2$, $J_{10,11} = 9.0$)		
Syn-1b	H_{10}^c; H_{11} 4.80	H_8^c; H_9 3.85	(8H) 7.6-9.0
	($J_{8,9} = 4$, $J_{9,10} = 2.5$, $J_{10,11} = 3$, $J_{9,11} = 1.5$)		
Anti-1c	H_{10} 3.75; H_{11} 4.81	H_8 4.59; H_9 3.88	H_1 8.76; H_{12} 8.85; CH_3 2.89
	($J_{8,9} = 4.2$, $J_{9,10} = 1$, $J_{10,11} = 7.7$)		(5H) 7.48-8.07

[a]Spectra taken on a Bruker 270 MHz spectrometer in DMSO-d_6; chemical shifts are in ppm relative to TMS. To aid spectral interpretation, diols were converted to their dideutero derivatives by addition of D_2O. [b]Additional aromatic protons appeared as multiplets not assigned. [c]Overlap made assignment uncertain.

in THF (1 hr, ambient temp.) following the method developed earlier in this laboratory.[5] The assigned structures were confirmed in all cases by mass spectra and nmr analysis.

The synthetic sequence reported herein appears generally applicable to the synthesis of all types of diol and diolepoxide derivatives of carcinogenic hydrocarbons. Particularly notable are the successful syntheses of the diol (5c) and diolepoxides (1c) of 7-methyl-BA utilizing the DDQ approach. 7-Methyl-BA is a powerful carcinogen[13] in contrast to BA which is inactive or borderline. Indeed, many of the most potent carcinogenic hydrocarbons possess methyl or other alkyl substituents in critical molecular regions.[13] The NBS approach appears unsuitable in these cases due to the likelihood of competitive reaction at these sites. Syntheses of the *cis*-diol derivatives 5e and 1e are also significant, since the availability of the *cis*-stereoisomers will permit investigation of their role as carcinogen metabolites.

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REFERENCES AND FOOTNOTES

(1) Abbreviations: BP = benzo[a]pyrene; BA = benz[a]anthracene; NBS = N-bromosuccinimide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

(2) For leading references cf.: (a) I. B. Weinstein, A. M. Jeffrey, K. W. Jennette, S. H. Blobstein, R. G. Harvey, C. Harris, H. Autrup, H. Kasai, and K. Nakanishi, *Science*, 193, 592 (1976); (b) K. Nakanishi, H. Kasai, H. Cho, R. G. Harvey, A. M. Jeffrey, K. W. Jennette, and I. B. Weinstein, *J. Am. Chem. Soc.*, 99, 258 (1977); (c) H. W. S. King, M. R. Osborne, F. A. Beland, R. G. Harvey, and P. Brookes, *Proc. Nat. Acad. Sci. USA*, 73, 2679 (1976); (d) E. Huberman, L. Sachs, S. K. Yang, and H. V. Gelboin, *Ibid*, 601; (e) M. Koreeda, P. D. Moore, H. Yagi, H. Yeh, and D. M. Jerina, *J. Amer. Chem. Soc.*, 98, 6720 (1976).

(3) R. F. Newbold and P. Brookes, *Nature*, 261, 52 (1976).

(4) W. T. Hsu, R. G. Harvey, E. J. Lin, and S. B. Weiss, *Proc. Nat. Acad. Sci. USA*, 262, 1378 (1977).

(5) F. A. Beland and R. G. Harvey, *J. Chem. Soc., Chem. Commun.*, 84 (1976).

(6) Dihydroarenes: 10,11-dihydro-BA (2a); 8,9-dihydro-BA (2b); 7-methyl-8,9-dihydro-BA (2c); and 9,10-dihydro-BP (2d).

(7) P. Sims, *J. Chem. Soc., (C)*, 32 (1968).

(8) The erratic nature of the bromination-dehydrobromination method is indicated by the yields obtained in ten such reactions of 1d: 33,36,40,44,46,47,54,59,71, and 75%.

(9) R. E. Lehr, M. Schaeffer-Ridder, and D. M. Jerina, *J. Org. Chem.*, 42, 737 (1977).

(10) D. J. McCaustland and J. F. Engel, *Tetrahedron Lett.*, 2549 (1975).

(11) Reported mp values are uncorrected, but corrected values differ by less than ± 0.5°.

(12) *Anti* and *syn*, as originally defined[5] for 1a, refer to whether the epoxide oxygen atom and the most distant hydroxyl group (e.g. 7-HO of 1a) are on the opposite or the same faces, respectively, of the molecule.

(13) C. B. Huggins, J. Pataki, and R. G. Harvey, *Proc. Nat. Acad. Sci. USA*, 58, 2253 (1967).