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SYNTHESIS OF THE A-RING DIOLS AND DIOLEPOXIDES OF BENZ[a]ANTHRACENE

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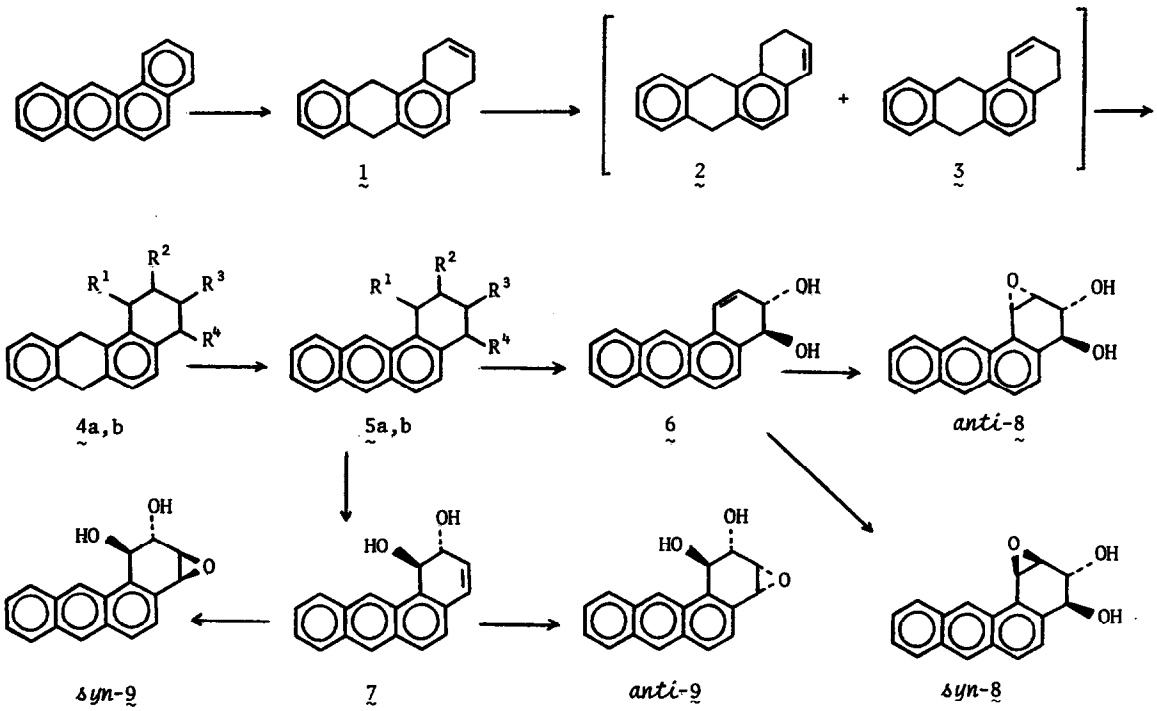
Metabolism of the common environmental carcinogen benzo[a]pyrene (BP) by mammalian cells affords a diolepoxide derivative, (+)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydro-BP, which binds covalently to DNA and RNA *in vivo*.[1] This metabolite exhibits exceptional potency as a mutagen,[2] as a carcinogen,[3] and as an inhibitor of the infectivity of the QB RNA and ØX 174 DNA viruses,[4] and is suggested to be the active form of this carcinogen.[1-3] In view of the intense interest generated by these findings, we wish to report a novel and convenient synthetic approach to diolepoxide derivatives of polycyclic hydrocarbons which requires fewer steps from available starting materials than existing methods.[5]

The procedure can be illustrated by its application to benz[a]anthracene (BA). Stepwise reduction of the latter with lithium in liquid ammonia was shown previously to afford 1,4,7,12-tetrahydro-BA (1) in excellent yield.[6] Isomerization of 1 takes place smoothly on treatment with $NaOCH_3$ or $NaOC_2H_5$ in DMSO in the absence of air[7] to furnish the olefins 2 and 3 in the ratio 55:45.[8] Attempted separation of the latter by conventional techniques or by chromatography on adsorbants impregnated with picric acid or 2,4,7-trinitrofluorenone[9] was not satisfactory. However, the mixture of olefins underwent conversion to the corresponding *trans*-dioldibenzoates (4a,b) *via* the Prévost reaction with silver benzoate and iodine.[5a,b,e] Yields were 70-80% for reactions employing a twofold excess of the reagent for 18 hr; reactions employing less than stoichiometric ratios of the reagent or shorter reaction times (6-8 hr) afforded the unreacted olefins considerably enriched in 3.

Dehydrogenation of 4a,b with *o*-chloranil (or DDQ) in refluxing benzene (3 hr) furnished the related *trans*-dioldibenzoates of tetrahydro-BA (5a,b) virtually quantitatively. The latter were readily separated by fractional crystallization. The less soluble isomer, *trans*-3,4-dibenzoyloxy-1,2,3,4-tetrahydro-BA (5a) crystallized from 30% acetone in ethanol as pale yellow needles, mp 189-191° (lit.[5d] 187-188°), while the second isomer *trans*-1,2-dibenzoyloxy-1,2,3,4-tetrahydro-BA (5b) was obtained from ethanol as needles, mp 164-166° (lit.[5d] 162-163°). The combined overall yield of 5a and 5b from BA in five steps was 60%. Attempted introduction of a double bond into 5a or 5b through further dehydrogenation with DDQ failed, though this reagent recently was found to be superior to others for synthesis of the analogous D-ring dioldibenzoates of BA and BP.[5e] However, bromination of 5a with NBS in refluxing CCl_4 with azobisisobutyronitrile as

initiator gave a mixture of the epimeric 1-bromo-*trans*-3,4-dibenzoyloxy-1,2,3,4-tetrahydro-BA derivatives from which the major isomer (70%) could be separated by virtue of its low solubility in ether. This isomer underwent dehydrobromination with DBN in THF at 0° to furnish the *trans*-dioldibenzoate of dihydro-BA which on treatment with $NaOCH_3$ in THF methanol (reflux, 25 min) using the established procedure[5a,e] provided *trans*-3,4-dihydroxy-3,4-dihydro-BA (6), mp 210-214° (lit.[5d] 215-217°) in 96% yield. Similar bromination-dehydrobromination of 5b followed by methanolysis furnished the isomeric dihydrodiol *trans*-1,2-dihydroxy-1,2-dihydro-BA (7), mp 164-166° (lit.[5d] 167-168°) in 94% yield. It is worthy of note that conversion of the dioldibenzoates to the corresponding dioldiacetates prior to introduction of the double bond as recommended by Lehr *et al.*[5d] was not found necessary; good yields of the dihydrodiols 6 and 7 were obtained *via* the direct route utilizing the dibenzoates.



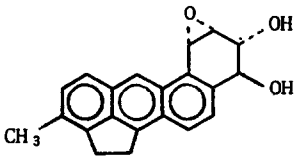
a : $R^1 = R^2 = H$; $R^3 = R^4$ = *trans*-OBz

b : $R^1 = R^2$ = *trans*-OBz; $R^3 = R^4 = H$

Epoxidation of the *trans*-dihydrodiols 6 and 7 with *m*-chloroperbenzoic acid in THF according to the method previously described[5a,b] afforded the corresponding *anti*[10] isomeric diolepoxides 8 and 9, in 40% and 55% yield, respectively. The corresponding *syn* isomers of 8 and 9 were synthesized from 6 and 7 *via* the related bromohydrins which were cyclized with *t*-BuOK in THF following the method devised earlier in this laboratory.[5a,e] The NMR spectra and other physical data for both sets of isomers were consistent with their assignments and in close agreement with those

recently reported by Lehr *et al.*[5d]

The synthetic sequence described offers significant advantages over established methods[5] which require ketonic starting materials, such 1-keto- and 4-keto-1,2,3,4-tetrahydro-BA. The latter must be individually synthesized from smaller polycyclic arenes, usually by Friedel-Crafts succinoylation, Clemmensen reduction of the resulting keto acids to aryl butyric acids, and cyclization. Conversion of the ketones to the olefins (e.g. 2 and 3) requires two additional steps, reduction with $NaBH_4$ and acid-catalyzed elimination. The method reported herein, in addition to its obvious greater simplicity and higher overall yields, is potentially applicable to the synthesis of the dihydrodiols and diolepoxides of many of the most potent carcinogens, such as 3-methylcholanthrene (10) 7,12-dimethylbenz[a]anthracene (11) and dibenz[a,h]anthracene (12) which are at present relatively inaccessible through existing methods. The synthesis of these diolepoxides is currently in progress in our laboratory.



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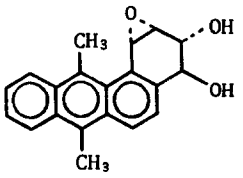

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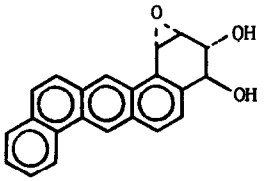

12

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REFERENCES AND FOOTNOTES

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6. R. G. Harvey and K. Urberg, *J. Org. Chem.*, 33, 2206 (1968).

7. Attempted isomerization of 1 catalyzed by acid or by *t*-BuOK in DMSO afforded more complex mixtures of unidentified products. Exclusion of air was necessary to prevent air oxidation of intermediates to BA.
8. Isomeric assignments were initially based on analysis of the 270 MHz NMR spectra. The major isomer 2 exhibited δ 2.24 (*m*,2,H_2), 2.76 (apparent *t*,2,$J_{1,2}$=7.5 Hz,H_1), 3.84 (s,4, $H_{7,12}$), 5.90 (doublet of triplets, 1,$J_{2,3}$=5 Hz,$J_{3,4}$=9.3 Hz,H_3), 6.39 (d,1,$J_{3,4}$=9.3 Hz,H_4) and 6.77-7.22 ppm (*m*,6, aromatic). Isomer 3 had δ 2.16 (*m*,2,H_3), 2.66 (apparent *t*,2,$J_{3,4}$= 7.5 Hz,H_4), 3.83 (s,2,H_7), 3.90 (s,2,H_{12}), 6.40 (doublet of triplets,1,$J_{1,2}$=9 Hz,$J_{2,3}$=5 Hz, H_2) and 7.11-7.55 ppm (*m*,7,H_1 and aromatic). The relatively low field chemical shifts of the H_1 and H_{12} protons of isomer 3 are indicative of steric interaction between them, confirming the structural assignment.
9. R. G. Harvey and M. Halonen, *J. Chromatog.*, 25, 299 (1966).
10. NMR spectra of all compounds were consistent with the structural assignments and in generally good agreement with the data for some of the same compounds reported after completion of this work by Lehr *et al.*[5d]
11. *Anti* and *syn*, as originally defined,[5a] refer to whether the epoxide oxygen atom and the benzylic hydroxyl group are on the opposite or the same faces, respectively, of the molecule.

Note: **Synthesis of the diolepoxides of benz[a]anthracene has recently been reported by R. E. Lehr, M. Schaeffer-Ridder, and D. M. Jerina, *Tetrahedron Lett.*, 539 (1977). The nmr data reported therein confirm the isomeric structural assignments made in this paper.**