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NOVEL SYNTHESIS OF THE DIHYDROARENE PRECURSORS OF CARCINOGENIC ARENE DIHYDRODIOLS AND DIOLEPOXIDES

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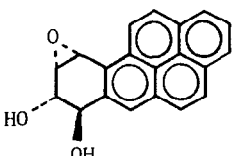
Identification of the diolepoxide derivative 1 as the probable biologically active form in humans[1] and other species[2] of the common environmental carcinogen benzo[a]pyrene (BP) has stimulated strong research interest in the analogous derivatives of other polycyclic arenes. Although general synthetic approaches to the isomeric *syn* and *anti* arene diolepoxides have been developed[3,4], the quantities of these compounds available for biological studies are inadequate to meet the rapidly expanding need. A key problem is the unavailability of the dihydroarenes required as starting materials (e.g. 9,10-dihydro-BP 2 is the synthetic precursor of 1), except through multistep synthesis from polycyclic arenes having one less ring[5].



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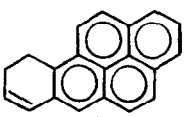

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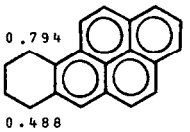
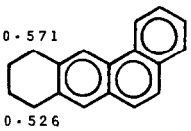
We now wish to report a simple and convenient two step synthesis of the requisite dihydroarenes directly from the parent hydrocarbons. The method involves regioselective hydrogenation over a Pt/C catalyst to the tetrahydroarene, followed by dehydrogenation with DDQ[6] to the conjugated dihydroarene. Hydrogenation of benz[a]anthracene (BA) over a Pt catalyst at low pressure was shown previously[7] to take place regioselectivity in the terminal ring to furnish 8,9,10,11-tetrahydro-BA (3)(95%). Similar regioselectivity of hydrogenation over Pt/C under mild conditions has now been confirmed for a larger series of polycyclic arenes (Table I). Dibenz[a,c]anthracene and benzo[e]pyrene undergo regiospecific hydrogen addition in this region, while similar reaction of BP and the 7-methyl- and 12-methyl derivatives of BA occurred with high regioselectivity in the analogous molecular region. These results contrast with the previous observation of regiospecific hydrogenation of polycyclic arenes in the K-region over a palladium catalyst[7].

Reaction of the tetrahydroarenes with an equimolar portion of DDQ in refluxing benzene furnished the corresponding polycyclic dihydroarenes[8]. Surprisingly good yields of the dihydro compounds were obtained in most cases, despite the fact that further dehydrogenation to fully aromatic products might have been anticipated to be thermodynamically favorable[9]. Two isomeric dihydroarenes are possible in cases where the tetrahydroarene is not symmetrical. The

important influence of steric effects on product isomer ratios is shown clearly by dehydrogenation of the 7- and 12-methyl derivatives of 8,9,10,11-tetrahydro-BA (3) which are found to occur regiospecifically in the bond most distant from the methyl groups. Dehydrogenation of 7,12-dimethyl-3[3d] fails to take place under similar conditions. Treatment of 3 itself with DDQ in refluxing benzene gave 8,9- and 10,11-dihydro-BA (4 and 5) in the ratio of 4:1. On the other hand, reaction of 7,8,9,10-tetrahydro-BP (8) furnished only a single isomeric dihydroarene, 7,8-dihydro-BP. The major isomer is expected, in the absence of overriding steric considerations, to be a function of the relative ease of hydride abstraction from the respective benzylic positions. This is theoretically predictable through MO theoretical calculation of the stability of the respective benzylic carbocations[10]. The experimental findings are in agreement with prediction made on the basis of the perturbational MO method of Dewar[10,11]. Thus, the delocalization energies (expressed in β units) of the carbocations derived from 3 and 8 are highest in the 11- and 10-positions, respectively, the regions of observed preferential dehydrogenation. Further experimental study will be required to establish the general validity of these observations.



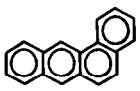
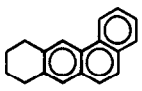
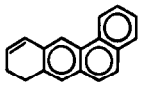
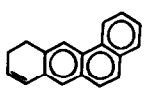
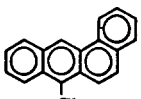
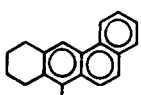
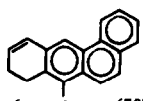
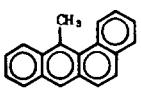
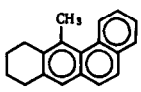
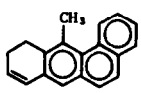
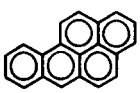
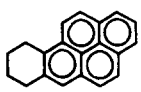
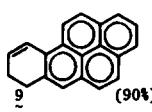
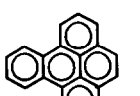
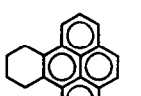
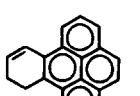
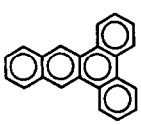
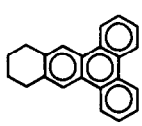
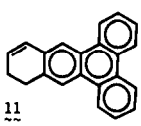


Hydrogenations were conducted in ethyl acetate over a 10% Pt on charcoal catalyst at ambient temperature and 40-50 psig. Reactions were generally complete in 16-18 hr (BA required ~ 44 hr); the extent of hydrogenation is conveniently monitored by tlc on TNF impregnated silica gel[12]. Reactions with DDQ were carried out in refluxing benzene (5-15 min) with equimolar amounts of DDQ and the hydrocarbon and worked up by conventional procedures. The dihydroarenes may be freed of residual tetrahydroarene and arene by chromatography on TNF impregnated silica gel[12]. It is more convenient where the ultimate goal is synthesis of the dihydrodiols to treat the reaction mixture directly with silver benzoate and iodine[3,4]. The resulting *trans*-dioldibenzoates are readily separable by chromatography, and the recovered tetrahydroarene and arene can be recyclized.

The DDQ route to dihydroarenes offers certain advantages in addition to its relative simplicity. In particlular, compounds or isomers relatively inaccessible *via* total synthesis (e.g. 4,6,7,11) are readily obtainable by this method. Although the tetrahydroarenes employed in this study were synthesized *via* hydrogenation of the corresponding arenes, these compounds may, of course, be synthesized by any convenient alternative route. For example, Wolff-Kishner reduction of the commercially available 7(8H)-oxo-9,10-dihydro-BP has been employed in this laboratory to synthesize 8.

All of the dihydroarenes reported herein, with the exception of 11, have subsequently been converted to the corresponding dihydrodiols and diolepoxides. Preliminary experiments indicate that several of these compounds exhibit significant activity as inhibitors of ØX 174 DNA viral replication[13]. Full details will be reported when these studies are completed.

Table I. Synthesis of Dihydroarenes *via* (a) Low Pressure Hydrogenation over Pt/C and (b) Dehydrogenation with DDQ[a]

Arene	Tetrahydroarene[b] (Yield)	Dihydroarenes (Yield)[i]	
	 3 (95%)[c]	 4 (52%)	 5 (13%)
	 (90%)[d]	 6 (70%)	
	 (65%)[e]	 7 (65%)	
	 8 (86%)[f]	 9 (90%)	
	 (80%)[g]	 10 (56%)[j]	
	 (100%)[h]	 11 (50%)	

[a]Experimental conditions are described in the body of the paper. [b]NMR spectra were consistent in all cases with the assigned structures. [c]Mp 88-89° (lit.[14] 88.5-89.5°); 7,12-dihydro-BA (5%) was a coproduct. [d]Mp 72-74° (lit.[14] 73.5-74.4°); 7,12-dihydro-7-methyl-BA (10%) was a coproduct. [e]Mp 103-104°; 7,12-dihydro-12-methyl-BA (10%) and 5,6,8,9,10,11-hexahydro-BA (25%) were coproducts. [f]Mp 113-114° (lit.[15] 113°); synthesis of 8 (40% yield) by hydrogenation of BP over a Pt catalyst in acetic acid-cyclohexane has been described[16]; compound 8 employed herein was obtained in 86% yield *via* Wolff-Kishner reduction of 7(8H)-oxo-9,10-dihydro-BP. [g]Mp 124-126°. [h]Mp 201-203° (lit.[17] 198-198.5°; lit.[18] 202°). [i]Yields are based on percentage conversion. [j]Mp 124-126°.

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4. R. G. Harvey and P. P. Fu in "Polycyclic Hydrocarbons and Cancer: Chemistry, Molecular Biology and Environment," H. V. Gelboin and P.O.P. Ts'o, Eds., Academic Press, in press.
5. The dihydroarenes are conventionally synthesized *via* the standard sequence of Friedel-Crafts succinoylation of the corresponding arene (or its bromomagnesium derivative, where appropriate) having one less ring, Clemmensen or Wolff Kishner reduction of the resulting keto acid to an aryl butyric acid, acid-catalyzed cyclization to the cyclic ketone, and reduction with $LiAlH_4$ or $NaBH_4$ followed by acid-catalyzed dehydration of the resulting alcohol[4].
6. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) was purchased from the Arapahoe Chemical Co.
7. P. P. Fu and R. G. Harvey, *Tetrahedron Lett.*, 415 (1977).
8. Nmr spectra of the dihydroarenes were consistent in all cases with the assigned structures; the latter were also supported by microanalysis and/or mass spectra and nmr spectra of the corresponding dioldibenzoates obtained by Prévost reaction[3,4].
9. Dehydrogenation of the vicinal dioldiesters of tetrahydroarenes with DDQ was recently described[3a]; the diester functions efficiently block further dehydrogenation to fully aromatic products.
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