"K-Region" Oxides and Related Oxidized Metabolites of Carcinogenic Aromatic Hydrocarbons[1]

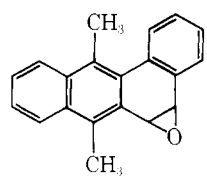
Ronald G. Harvey,* Swee Hock Goh,[2] and Cecilia Cortez

Contribution from the Ben May Laboratory, The University of Chicago, Chicago, Illinois 60637. *Received October 17, 1974*

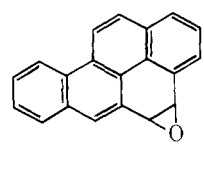
Abstract: A general synthesis of "K-region" oxides from the parent polycyclic hydrocarbons via the corresponding cis dihydrodiols, quinones, and trans dihydrodiols is described. By appropriate adaptation of the general procedure the related K-phenols (both isomers) and the previously unknown K-hydroquinones are also obtained. Thus, all the K-region oxidized metabolites, many of which exhibit carcinogenic, mutagenic, or cell transformation activity, are now synthetically readily accessible. The K-oxidized metabolites of the potent carcinogens benzo[*a*]pyrene, 7,12-dimethylbenz[*a*]anthracene (DMBA), and dibenz[*a,h*]anthracene in addition to those derived from pyrene, phenanthrene, benz[*a*]anthracene, and chrysene were prepared by this means. Several alternative syntheses of the K-oxides are also described, including an osmium tetroxide-catalyzed periodate oxidation of DMBA to the corresponding K-region dialdehyde followed by cyclization. Also, the mechanism and stereochemistry of reduction of the quinones with lithium aluminum hydride are investigated. Acid-catalyzed reaction of the diol diacetates is shown to afford two isomeric phenol acetates providing convenient synthetic access to the K-phenols for which generally only a single isomer has previously been reported. However, 5-acetoxy-DMBA is formed apparently regiospecifically, and 5-hydroxy-DMBA is confirmed to exist preferentially in the keto structure. The K-phenols of other potent carcinogens, namely benzo[*a*]pyrene and dibenz[*a,h*]anthracene, do not exhibit this property. The hypothesis that the K-phenols or their ketonic tautomers may serve as activated carcinogenic intermediates is examined.

The mechanism whereby carcinogenic chemicals trigger the induction of tumors is one of the significant unsolved problems of modern science. Recent evidence increasingly supports the hypothesis that most chemical carcinogens are either strongly electrophilic agents per se or undergo metabolic activation into such in vivo.[3] In the case of the polycyclic aromatic hydrocarbons, arene oxides have been implicated as obligatory primary intermediates[4] which give rise to the quinones, diols, phenols, and their conjugates commonly detected as metabolites.[5] The "K-region" oxides[6] of a number of carcinogenic compounds have been shown to be more active than the parent hydrocarbons in the induction of "malignant transformation" of cells in culture[7] and mutational changes[8] in mammalian cells, bacteriophages, and bacteria, and to bind covalently to the nucleic acids and proteins in vivo and in vitro.[9] Although the K-oxides are currently prominent in attention, some contrary evidence has also begun to emerge,[10,52] and the possible involvement of other intermediates as active (or proximate)[3] carcinogens cannot be excluded at the present time; the mutagenic activity and binding of certain phenolic compounds[12] to DNA, RNA, and proteins is particularly intriguing since the rearrangement of arene oxides to phenols is a facile process, while the reverse is thermodynamically unfavorable.

Major barriers to elucidation of the biomolecular mechanism have been the synthetic inaccessibility of many of the K-oxides and other metabolites of greatest interest and the paucity of knowledge concerning the chemical reactivity, stability, and other properties of the compounds concerned. In preliminary communications, we reported: (1) a new general synthesis of K-oxides[1a] which allowed the synthesis of the previously inaccessible K-oxides (**1a,b**) of the highly



1a



1b

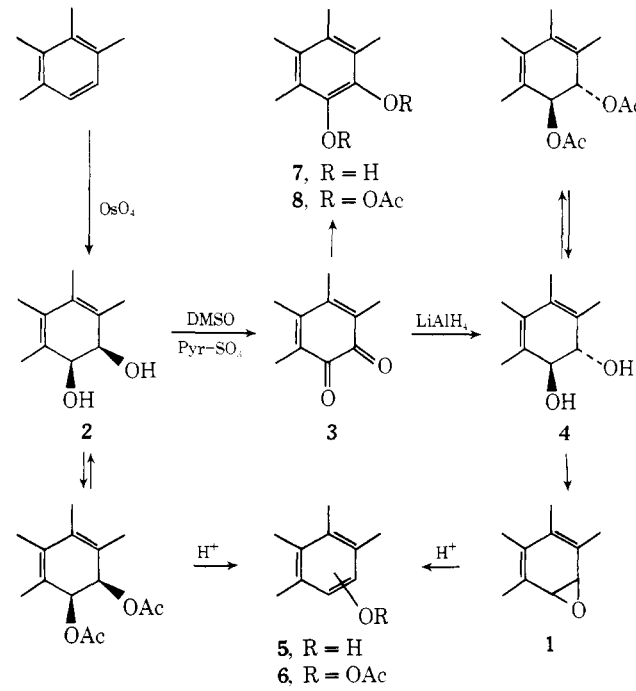
potent[13] carcinogens 7,12-dimethylbenz[*a*]anthracene (DMBA) and benzo[*a*]pyrene (BaP); and (2) a somewhat less general, but simpler, modified procedure[1b] adaptable to larger scale preparations. We now report: (1) full details of the general procedure for synthesis of the K-oxides from the parent hydrocarbons via the corresponding cis diols, quinones, and trans diols; (2) application of the method to other ring systems; (3) modification to permit convenient synthesis of the related K-phenols and hydroquinones; and (4) information on the chemical and physical properties of the various K-oxidized derivatives.

Results

Because of the great interest in K-oxides, such as **1a,b,** which had proved unobtainable via the Newman synthesis,[15] our initial efforts were directed toward development of a more generally applicable synthetic approach, assuming the desired compounds to be sufficiently stable to isolate and characterize.

The general synthetic scheme developed (Chart I) in-

Chart I

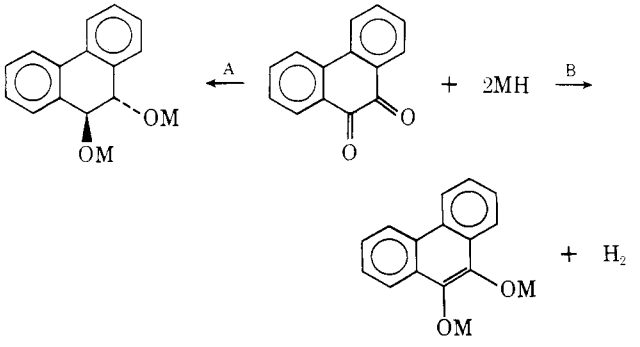


volves the following sequence: (1) generation of the "K-region" cis dihydrodiols (**2**) via interaction of the corresponding hydrocarbons with osmium tetroxide;[16] (2) oxidation with dimethyl sulfoxide and sulfur trioxide–pyridine complex[17] to the quinones (**3**); (3) reduction with lithium aluminum hydride to yield the related trans dihydrodiols[18] (**4**); and finally (4) cyclization of the latter with the dimethyl acetal of dimethylformamide[19] (DMA-DMF) to the desired K-oxides (**1**). *A significant feature of the method is that all the intermediates, the cis and trans diols, as well as the quinones, are themselves K-region oxidized intermediates of interest as potentially biologically active metabolites* Moreover, the remaining K-oxidized derivatives, the K-phenols (**5**) and hydroquinones (**7**), are also conveniently obtainable from these intermediates. Thus, the general sequence provides easy access to all K-region oxidized intermediates.

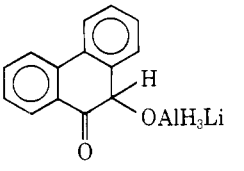
The unique regioselectivity of osmium tetroxide for oxidation of polycyclic hydrocarbons in the K-region was first noted by Cook and Schoental[16] who observed that "the diol from benzo[*a*]pyrene[20] was very sensitive to atmospheric oxidation and all attempts at purification gave a pink amorphous product, mp 200–215° (decomp.)". In our experience, both the intermediate osmate esters and the crude cis diols tend to be susceptible to atmospheric decomposition. This is less serious with phenanthrene, benz[*a*]anthracene, and other noncarcinogen derivatives, but the DMBA and BaP related compounds visibly darken on exposure to air with deleterious effect on yield. Accordingly, all operations and the hydrolyses of the osmate esters were conducted under an inert atmosphere, and the products were separated, where appropriate, by centrifugation rather than by filtration.[21] The crude cis diols, if sufficiently stable, were purified by chromatography on Florisil;[22] otherwise they were converted immediately to the more stable diol diacetates with acetic anhydride–pyridine, chromatographed on Florisil, then regenerated by mild ammonolysis in methanol. The purified cis diols of even DMBA and BaP could be handled in air without significant loss.[23] The cis diol diacetates, in contrast to the cis diols, were generally stable crystalline solids which could be recrystallized and exhibited characteristic sharp, well-defined NMR spectra.

Oxidation of **2** to **3** presented the most serious challenge because of the facility of both dehydration and oxidative cleavage of the benzylic bonds. Of the numerous reagents investigated for this purpose, only the sulfur trioxide–DMSO complex[17] efficiently oxidized all diols to quinones.[24] The related DMSO–acetic anhydride reagent employed by Newman and Davis[25] also afforded **3**, but yields were erratic, and the diol diacetates were a principal by-product. In some cases, the K-quinones are available through direct oxidation of the parent hydrocarbons with chromic acid (e.g., 5,6-chrysenedione and 9,10-phenanthrenedione).

Reduction of **3** with lithium aluminum hydride[18] proceeded smoothly and stereoselectively in refluxing ether to



furnish the expected trans diols. Despite the low solubility of both reactants in this medium, which necessitated relatively long reaction periods and use of a Soxhlet apparatus,[26] this combination proved most generally effective. Substitution of more soluble hydride reagents, such as sodium bis(2-methoxyethoxy)aluminum hydride,[27] lithium tri-*tert*-butoxyaluminum hydride, or aluminum hydride,[28] or more efficient solvents, such as THF, dimethoxyethane, or diisopropyl ether, depressed the yields. In these instances, the solutions exhibited an intense green color, and the crude products became black quickly on exposure to air. Since phenanthrene-9,10-hydroquinone is green in basic solution and undergoes similar facile autoxidation in air, it appears that greater solubilization of the reactants favors reduction to the hydroquinone stage. Reduction of *p*-benzoquinone and anthraquinone reportedly[29] follows these two primary pathways to afford dihydrodiol (path A) and hydroquinone products (path B),[30] the latter with evolution of hydrogen gas. Addition to the conjugated double bonds of *p*-quinones is a further competing process.[31] The factors controlling ratios of these products have not been adequately investigated; however, it is likely that a major factor is competition at the second stage of reaction between nucleophilic attack of hydride on the carbonyl of the initial intermediate and acid–base reaction of hydride with the relatively acidic hydrogen atom α to the carbonyl.



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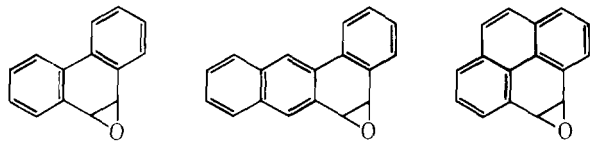
In our more recent studies, sodium borohydride in methanol has also been found to be effective in achieving reduction of certain quinones to the dihydrodiols. The K-quinones of phenanthrene, benz[*a*]anthracene, and 7,12-dimethylbenz[*a*]anthracene were efficiently reduced by this reagent. Yields with the sodium borohydride–methanol reagent, however, have proved more variable and difficult to control than with lithium aluminum hydride.

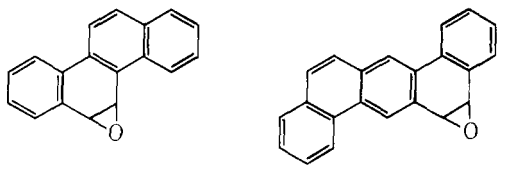
Although high trans stereoselectivity was generally observed in these quinone reductions, particularly with lithium aluminum hydride, the DMBA derivative proved an exception furnishing approximately 45% of the cis isomer[32] with lithium aluminum hydride and 65% with sodium borohydride–methanol. Separation of the cis and trans diols of DMBA was accomplished through (a) selective conversion of the former to its acetonide followed by chromatography and (b) chromatographic separation of the diol diacetates. The trans diols, even more sensitive to decomposition than the cis diols, were also efficiently purified through conversion to their diacetates which were stable crystalline solids showing characteristic NMR spectra. The trans diol diacetates also provide a convenient means to store and preserve the trans diols for prolonged periods.

Finally, conversion of the trans diols to the K-region oxides was effected with the dimethyl acetal of dimethylformamide (DMA-DMF) in dimethylformamide–chloroform (1:3) at reflux. The K-oxides synthesized by this method in addition to **1a** and **1b** include phenanthrene 9,10-oxide (**1c**), benz[*a*]anthracene 5,6-oxide (**1d**), pyrene 4,5-oxide (**1e**), chrysene 5,6-oxide (**1f**), and dibenz[*a,h*]anthracene 5,6-oxide (**1g**).

In the case of **1a**, the cis and trans diol mixture obtained from reduction could be employed directly in this step. While the trans isomer afforded the epoxide, the cis compound was converted by DMA-DMF to the *cis*-6-formyl-

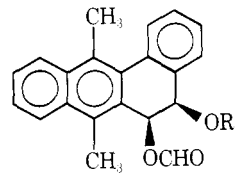


1c 1d 1e



1f 1g

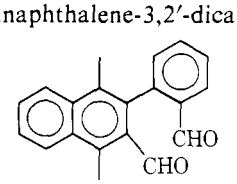
oxy-5-hydroxy derivative **9a.** Acetylation of the latter gave the *cis*-5-acetoxy-6-formyloxy compound **9b,** which in turn



9a, R = H
b, R = Ac

underwent basic hydrolysis and reacetylation to the cis diacetate **4a.** Purification of the crude oxide products was complicated by their sensitivity to decomposition. The most generally effective technique was chromatography on neutral alumina (Brockmann Activity grade IV) and elution with 4% dioxane in cyclohexane. Nitrogen pressure was employed to keep residence time on the column to a minimum. Trituration of the chromatography products with redistilled hexane gave the oxides in sufficient purity for most purposes. If further purification is desired, rechromatography is generally preferable to recrystallization since significant decomposition frequently ensues on heating particularly with the more reactive oxides (**1a,b**). The pure oxides synthesized via the foregoing procedure are reasonably stable and may be stored as solids under refrigeration in the dark for many months without detectable change. Solutions in pure anhydrous solvents, e.g., benzene, are also stable; however, solutions in chloroform darken rapidly.

The observed instability of **1a** suggested that previous failure[15] to synthesize it via interaction of 1,4-dimethyl-2-phenylnaphthalene-3,2′-dicarboxaldehyde (**10**) with tris(di-



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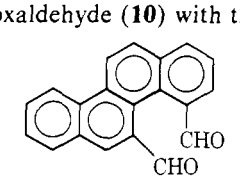

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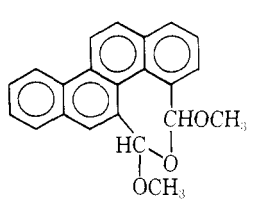

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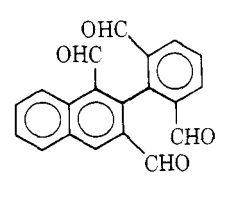

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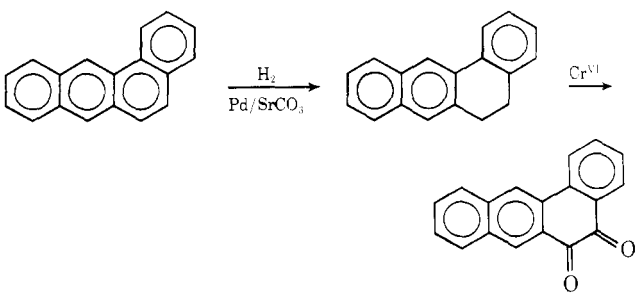
methylamino)phosphine was more due to its facility of decomposition than the inadequacy of the synthetic approach. Reinvestigation confirmed this, and it was found that, with appropriate precautions to minimize decomposition, **1a** was also obtainable through this method.[33] Analogous synthesis of **1b** also proved possible. However, the requisite dialdehyde **11** was furnished in unsatisfactory yield (28%) through the conventional oxidation of the related cis diol with sodium periodate, and it was accompanied by its internal dimethyl acetal (**12**), the tetraaldehyde **13,** and other products.[35] Use of lead tetraacetate in place of sodium periodate afforded a cleaner product mixture and a more satisfactory recovery of **11** (68%). It should be noted, however, the stability of the oxides **1a,b** prepared via the dialdehyde intermediates was observed to be lower than those obtained from the trans diols.

One-step synthesis of the dialdehyde **10** directly from DMBA was effected with osmium tetroxide and sodium periodate in combination. In this procedure, only a catalytic quantity of the expensive and hazardous osmium tetroxide reagent was required since it was continuously regenerated by the excess sodium periodate employed.[34] The most satisfactory procedure employed aqueous dimethylformamide to dissolve both the hydrocarbon and the periodate; the OsO_4 was added as a 1% solution in dioxane, and acetic acid served to catalyze hydrolysis of the intermediate osmate ester. Under these conditions, the yield of the dialdehyde **10,** recovered after chromatography of the crude product, was 70–75% and of suitable purity for conversion to the epoxide **1a.** Similar reactions of benz[*a*]anthracene (BA) and phenanthrene afforded 30–50% of the corresponding dialdehydes; no attempt was made to optimize these yields.[34] The dialdehyde derived from benz[*a*]anthracene (2-phenylnaphthalene-3,2′-dicarboxaldehyde) exhibited tendencies toward decomposition during attempted purification.[36] This difficulty was avoided by conversion to the diacetal with ethylene glycol; chromatography followed by mild acid hydrolysis regenerated the pure dialdehyde.

Variations of the general synthetic method were explored in certain cases (a) where a modified procedure offered a convenient shortcut or (b) to develop procedures adaptable to the preparation of specifically labeled tritiated molecules required for biochemical studies. Thus, the fact that certain polycyclic hydrocarbons undergo oxidation by chromic acid[37] in the K-region to afford the corresponding quinones, was utilized to synthesize the K-quinones of chrysene,[38] phenanthrene,[39] and benzo[*c*]phenanthrene.[40] These quinones, in turn, underwent consecutive reduction with lithium aluminum hydride to the trans diols and cyclization to the corresponding K-oxides. Since oxidation of the majority of other hydrocarbons by reagents other than OsO_4 occurs outside the K-region, alternative approaches were necessary. A novel method[1b] which proved successful with benz[*a*]anthracene, pyrene, and BaP was reduction to the K-region dihydro derivatives followed by oxidation in this region with dichromate in acid-acetic anhydride. Oxidation of 1,2-dihydro compounds in this manner constitutes a new *o*-quinone synthesis; the reaction is remarkable in that it occurs at room temperature, while chromate oxidation of



alkyl groups on aromatic rings usually requires elevated temperatures (>275°).[37] The dihydro compounds were prepared by metal-ammonia reduction in the case of pyrene[41] and BaP[42] or hydrogenation over a catalyst, palladium-

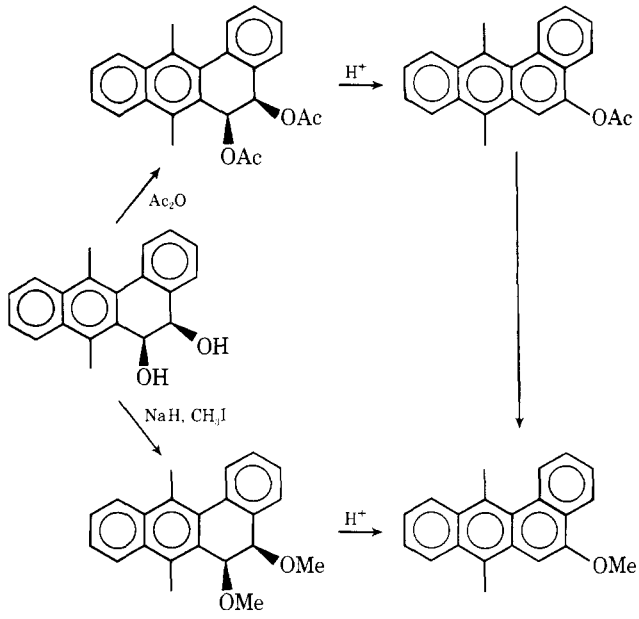
strontium carbonate, which exhibits unique specificity for the K-region.

The K-phenols were found to be most conveniently accessible via acid-catalyzed loss of acetic acid from the related diol diacetates, the principal advantage of this approach being the relative stability and ease of characterization of the resulting phenol acetates. Conversion of the latter to the free phenols was achieved by reductive cleavage with lithium aluminum hydride or through reaction with alkyllithium reagents. Aside from phenanthrene and pyrene, which for reasons of symmetry afford only a single isomer, both possible isomeric K-phenol acetates were generally found as products (detected by the difference in the chemical shift of the acetate peaks in the NMR spectra); specifically 5- and 6-acetoxy-BA, 4- and 5-acetoxy-BaP, and 5- and 6-acetoxydibenz[*a,h*]anthracene were obtained by this means. Reaction of the *cis*-5,6-diol diacetate of DMBA proved an exception, providing only a single isomer shown on the basis of chemical evidence given below to be 5-acetoxy-DMBA. This nonregiospecificity of reaction being contrary to the earlier observations of Cook and Schoental,[16] unquestioned by subsequent investigators,[43] that dehydration of the K-region diols affords a single phenol isomer,[44] dehydration of several of the diols was reinvestigated. However, acetylation of the products furnished similar mixtures of products (demonstrated by NMR) as obtained from the diacetates directly. Although analogous reaction of the *trans*-5,6-diol diacetate of chrysene apparently furnished only 6-acetoxychrysene (single acetoxy peak in the NMR δ 2.50), reaction of the trans diol with methanesulfonyl chloride in pyridine provided both 5- and 6-mesyloxychrysene (1:9). Also, reaction of the diols of both BA and BaP with methanesulfonyl chloride in pyridine provided K-region phenol mesylates which appeared to be a single isomer in the NMR spectrum but were shown to be also a mixture through conversion to the corresponding acetates by treatment with $LiAlH_4$ followed by acetylation.

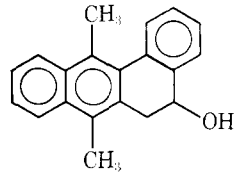
While formation of both K-phenols in these reactions is of some significance both biochemically and chemically, particularly since it provides simple access to the previously unknown and/or less accessible isomers, it introduces problems of separation and structural assignment. These problems are compounded by the observed strong tendency of the acetates, mesylates, and even the methyl ethers to undergo major decomposition during chromatography on all adsorbants. While selective crystallization generally provided the predominant isomers in pure state (except 4-and 5-acetoxy-BaP), considerable sacrifice in yield was necessary to ensure high purity of the isolated isomer, and the minor isomers could not be obtained completely pure. These problems are currently under investigation.

Assignment of the 5-acetoxy-DMBA structure to the compound obtained from the corresponding cis diol diacetate is based on conversion to 5-methoxy-DMBA an authentic sample of which was previously obtained via unequivocal synthesis.[45] Methanolysis with dilute hydrochloric acid in methanol smoothly transformed 5-acetoxy-DMBA to 5-methoxy-DMBA, the NMR spectrum of which was identical with that of the authentic sample. The same isomer was also obtained from analogous acid-catalyzed loss of methanol from 5,6-dimethoxy-5,6-dihydro-DMBA. The ease of methanolysis of 5-acetoxy-DMBA is interesting in that 4- and 5-acetoxy-BaP underwent similar smooth transformation to the methoxy derivative, while 4-acetoxypyrene remained essentially unchanged under similar conditions.

Synthesis of the K-region hydroquinones of all the hydrocarbons treated in this paper has also been accomplished through reduction of the corresponding K-quinones with sodium borohydride in dimethylformamide. The hydroquinones, which proved generally susceptible to atmospheric oxidation, were isolated in the form of their diacetates. The synthetic procedure employed has been extended also to non-K-quinones and found to be quite general. Full details will be reported in the following paper in this series.



Finally, reduction of DMBA 5,6-oxide with lithium aluminum hydride in refluxing ether afforded the monoalcohol 5-hydroxy-5,6-dihydro-DMBA in good yield. Although further examples were not investigated, it is anticipated that this reaction will prove to be general.



Discussion

The foregoing results demonstrate the generality of the reaction sequence outlined in Chart I. The general procedure (along with the modifications described) provides convenient synthetic access to the K-oxides (as well as the K-quinones, cis and trans diols, phenols, and hydroquinones) of polynuclear hydrocarbons, both carcinogenic and noncarcinogenic. Synthesis of K-region arene oxides via dialdehyde intermediates following the method devised by Newman[15] also appears generally applicable. However, this approach is useful only for the preparation of K-oxides and does not provide as intermediates or alternative products any of the other K-region oxidized metabolites, except the cis diols which are common to both approaches. This limitation is serious in our opinion since there is at present no clear proof concerning which metabolite(s) may be the ultimate active form of the carcinogen, and it is, therefore, desirable to have available for studies of metabolism and biological properties a full range of the possible metabolites. Other limitations are the relatively complex mixtures of products sometimes encountered from periodate oxidation of the cis diols, the sensitivity of the dialdehyde intermediates to decomposition during purification, and the greater tendency of the K-oxides prepared by this method toward spontaneous decomposition. In general, therefore, we find synthesis via the dialdehydes less satisfactory, the only exception being the OsO_4-catalyzed reaction of DMBA which

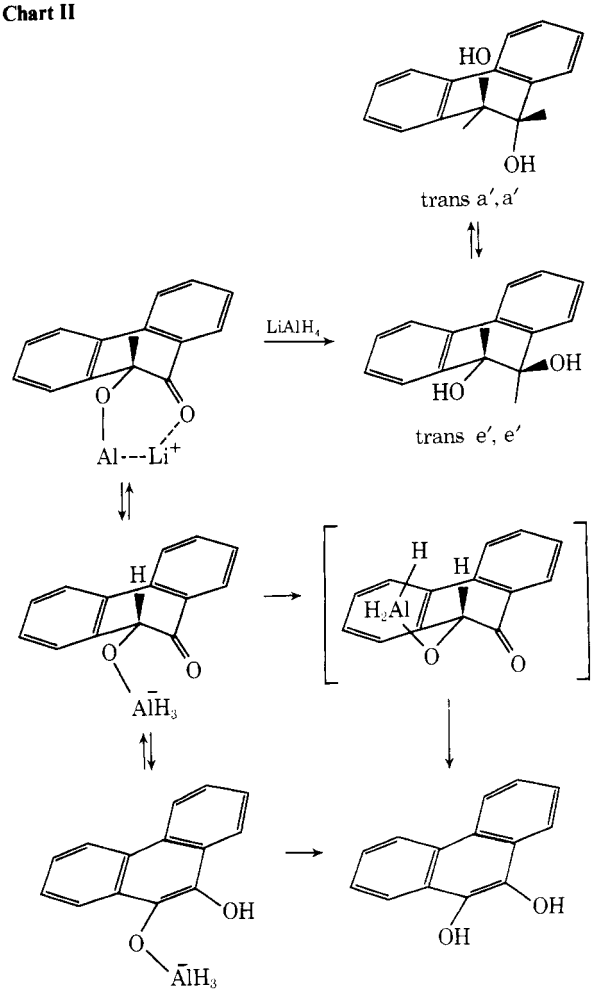
is convenient and adaptable to relatively large scale synthesis. A second alternative synthesis of K-region arene oxides was reported by Dansette and Jerina[46] after completion of this research. The fundamental chemistry upon which the method is based was developed earlier by Newman and Olson[47] and involves transformation of the cis dihydrodiols to 2-alkoxy-1,3-dioxolanes, conversion of the latter into halohydrin esters and cyclization to the oxides with base. Like the route via the dialdehyde intermediates, this approach is useful only for the preparation of the K-oxides, the intermediates being of no intrinsic biological significance. Other limitations are that stereoisomers are obtained at the dioxolane stage, positional isomers are possible at the chloroacetate stage, and phenol acetate by-products (two isomers possible) accompany the oxide products, complicating separation and purification at every stage. In the only case we investigated, we found 5-methoxy-6-acetoxy-5,6-dihydro-DMBA to be an unreported by-product.

The method of choice for synthesis is dependent upon the hydrocarbon concerned and upon whether additional K-oxidized derivatives or only the K-oxides are desired. For hydrocarbons, such as phenanthrene, chrysene, benzo[*c*]phenanthrene, and benzo[*e*]pyrene, direct chromic acid oxidation of which affords the K-quinones, this reaction followed by reduction with $LiAlH_4$ and cyclization with DMA-DMF is most convenient. It requires fewer steps, is readily adaptable to synthesis on any scale, and avoids the use of the hazardous and expensive OsO_4 reagent. For preparation of DMBA 5,6-oxide on any scale, the OsO_4-catalyzed periodate oxidation procedure is recommended since it is operationally quite simple and suffers none of the limitations of the alternate methods. For other compounds, the synthetic routes via the quinones (method A) or the alkoxydioxolane (method B) intermediates would appear operationally and economically insufficiently dissimilar to dictate any preference. Method A requires relatively pure intermediates and careful experimental techniques to ensure high yields, while the requirements for method B appear to be less stringent. The principal difference which may be expected to influence the choice is the purpose for which the products are sought. Since in most cases this is for biological studies in which the quinones, diols, phenols, and other metabolites, as well as the oxides may be of interest, this is likely to dictate the selection of method A.

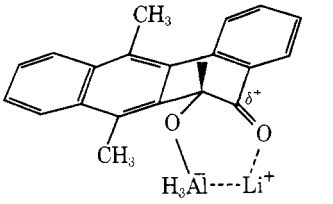
Reduction of the K-quinones with metal hydride reagents afforded dihydrodiols and/or hydroquinones. While the factors controlling the course of these reactions and product stereochemistry are not entirely understood, the observations are explicable in terms of an equilibrium between associated and free forms of an initially formed complex (Chart II). The associated complex may be expected to favor an essentially equatorial structure in order to minimize bond length and ring strain. Hydride transfer from the less crowded face, either intra- or intermolecularly, affords the diequatorial trans diol (e′,e′) after protonation, free to equilibrate with the diaxial conformer (a′,a′) through ring inversion.[48] Variable-temperature NMR studies of the related 9,10-dialkyldihydrophenanthrenes[49] indicate ring inversion to be facile in these systems. The dissociated structure, on the other hand, is free to either (1) enolize to the thermodynamically favored phenol isomer,[50] which having a relatively acidic proton reacts rapidly with the nearby hydride to evolve hydrogen gas and provide the hydroquinone salt, or (2) rotate back upon itself losing hydrogen through a back-biting process. The two pathways afford the same products and cannot at present be distinguished.

Although trans stereoselectivity was generally observed in reduction to the dihydrodiols, significant amounts of the cis isomers were detected in several cases, notably from the

Chart II



DMBA compound. This is explicable as a consequence of the strong steric interaction with the 7-methyl group destabilizing the equatorial associated complex (**14**) relative to its axial counterpart (**15**); hydride transfer to the second



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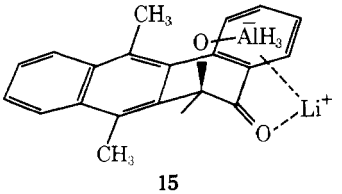


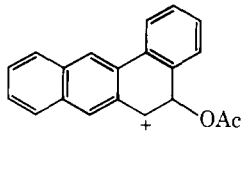
15

carbonyl of the latter from the opposite, more accessible face furnishes the observed cis dihydrodiol.

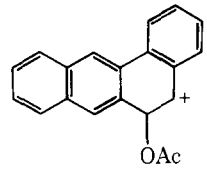
The stability of the K-oxides is dependent upon various factors including structure, purity, mode of preparation, pH, and temperature. The oxides derived from the more potent hydrocarbons (**1a,b**) tend to decompose with greater facility than those from inactive hydrocarbons (**1c–f**) or weak carcinogens (**1g**); however, the number of examples is too few to affirm this generalization with certainty. The purified oxides synthesized via the trans diol route can be

stored as dry solids for many months in the cold (6°); this is less frequently true for impure oxides or those prepared via the dialdehyde route. Solutions in *pure* dry organic solvents (e.g., benzene, cyclohexane, dimethylacetamide) are sufficiently stable at room temperature to permit crystallization and studies of organic reactions;[42] X-ray crystallographic analysis of the K-oxides of DMBA and phenanthrene has been carried out.[51] Solutions of even the more labile K-oxides in aqueous ethanol or acetone at 37° are also sufficiently stable to allow studies of binding to nucleic acids.[52,53]

Although the K-phenols proved to be readily accessible from the cis diol diacetates, the tendency toward formation of both possible isomers raises problems of separation and identification. Also, the assumption of some authors that dehydration of the diols[16,43,44] or rearrangement of the K-oxides affords only a single isomeric phenol must be questioned.[54] We have found, for example, that isomerization of benz[*a*]anthracene 5,6-oxide in acidic methanol furnished 5- and 6-methoxybenz[*a*]anthracene in essentially the same ratio obtained via the cis diol diacetate route. It is rather likely that both phenol isomers are also formed in most other cases but were not distinguishable by the analytical procedure employed (usually TLC and uv spectra), or that one isomer, probably the major one present, was selectively isolated. Since these assignments have been accepted uncritically in experimental studies of the biological activity of these compounds,[7-9] some caution is advised in accepting conclusions based upon these data. Although more detailed studies on the separation (including high-pressure liquid chromatography), characterization, and chemical properties of the K-phenols are in progress, some partial separations have been achieved, and some discussion of preliminary findings is possible. Thus, the major isomeric phenol acetate obtained from acid-catalyzed reaction of the cis diol diacetates of BaP, dibenz[*a,h*]anthracene, and benz[*a*]anthracene were 4-acetoxy-BaP, 5-acetoxydibenz[*a,h*]anthracene, and 5-acetoxybenz[*a*]anthracene, respectively. While only 5-acetoxy-DMBA was isolated from the analogous reaction of the DMBA derivative, it is possible that the 6-acetoxy isomer may be formed in lesser amount; the NMR spectrum of the crude product is inconclusive in this respect. In each case, the structure of the predominant isomer is that bearing the acetoxy group adjacent to the least number of fused aromatic rings; this simple rule is interpreted as a consequence of the relative stability of the two possible intermediate carbonium ions (e.g., **16** > **17**), the ion adjacent



16



17

to the larger number of rings being somewhat more stabilized by resonance.[55] In the case of the analogous DMBA intermediate, steric assistance due to interference between the 7-methyl and 6-acetoxy groups is an additional factor contributing to the regiospecificity observed with this compound.

Since the predominant K-phenol isomer appears predictable as the one bearing the acetoxy substituent adjacent to the fewer aromatic rings, one might expect this feature to be reflected in the NMR spectrum in the chemical shift of the acetate methyl protons. Indeed, this is found to be the case in the examples cited above, the acetate methyl peak of the major isomer appearing at higher field in each case. For the unsubstituted polycyclic aromatic hydrocarbons, at least, it is reasonable to anticipate that this rule may be generally useful.

Conversion of the phenol acetates to the free phenols was achieved through reductive cleavage with lithium aluminum hydride or through displacement with alkyllithium reagents. The phenols, however, proved relatively sensitive to atmospheric oxidation, and completeness of reaction was most conveniently demonstrated through transformation of an aliquot of the phenol in solution into the corresponding methyl ether or tosylate which could be analyzed and identified by NMR spectroscopy. Reductive cleavage was not satisfactory in the case of 5-acetoxy-DMBA which provided a complex mixture of products on treatment with $LiAlH_4$. However, reaction with methyllithium took place smoothly to provide a product shown by NMR (CH_2 protons appear as singlet at δ 3.80) and ir ($\nu^{C=O}$ = 1680 cm^{-1}) to exist predominantly in the keto form. After completion of these studies, the existence of both the 5-hydroxy- and 6-hydroxy-DMBA isomers in the keto form was reported by two groups.[56,57] As Newman and Olson[56] suggest, preference for the keto structure is probably a consequence of the steric inhibition of resonance caused by the strong interaction of the 12-methyl group with the 1-proton. This is not surprising since both DMBA[58] and the 5,6-oxide[51] have been shown by X-ray crystallography to deviate markedly from planarity. The resonance energy advantage of the phenol structure[59] is apparently offset by the more comfortable conformation of the keto form. In contrast, 5-hydroxybenz[*a*]anthracene was shown by NMR to exist in the normal phenolic structure in accord with expectation.

The suggestion by Newman and Olson[56] that the preference of the K-phenols of DMBA for the keto structures may be significant with respect to the carcinogenic activity of DMBA is not supported by the recent finding by Dipple[57] that both compounds "were inactive in tests for tumor initiating activity in mouse skin and tumor production in the subcutaneous tissues of the mouse". Also, the 6-oxo derivative exhibited no significant cell-transforming activity in an in vitro assay system. Moreover, our results do not appear to support any simple correlation between preferential existence of K-phenols in the keto form and carcinogenic activity. Rather, it appears that DMBA (and related 12-alkylbenz[*a*]anthracenes) is relatively unique among carcinogenic hydrocarbons with respect to their internal steric strain and nonplanarity. 3-Methylcholanthrene, dibenz[*a,h*]anthracene, BaP, and other potent carcinogens are not structurally similar in this respect, nor do the NMR spectra of the K-phenols of the latter two compounds prepared by us show any indication of the presence of the keto form. Also, Dipple et al.[57] who investigated the K-phenols of BaP by ultraviolet spectroscopy found no evidence for the keto forms.[60] We would venture to predict that the K-phenols of some noncarcinogenic hydrocarbons, which are structurally related to DMBA such as 1,4-dimethylphenanthrene, probably exhibit similar propensity to exist in the keto form.

Although correlation between preferential existence of K-phenols in the keto form and carcinogenic activity apparently does not exist, it is possible that the ketonic tautomer could function as the proximate carcinogen despite the phenolic tautomer being favored in the keto–phenol equilibrium. Certainly the energy difference between the two forms is likely to be low in most carcinogens because of the high double-bond character of the electron-rich K-region[6] so that preferential reaction of the keto form is quite conceivable. On the other hand, the reported carcinogenic, cell transformation and mutagenic activity of the K-phenolic compounds is usually lower than that of either the parent hydrocarbons or the K-oxides; toxicity is, however, generally higher.[7-9] Although negative findings of biological activi-

ty cannot be considered as entirely conclusive proof that a compound is not a metabolically activated form of a carcinogen, it is the strongest evidence presently available.

In connection with the intercalation theory of hydrocarbon carcinogen action,[61] the central hypothesis of which is insertion of the carcinogen or its active metabolite between the base pairs of the nucleic acids, it is worthwhile to consider the structure of the K-oxides and other metabolites implicated in carcinogenesis. An X-ray crystallography study of the 9,10-oxide of phenanthrene and the 5,6-oxide of DMBA reported elsewhere[51] has revealed the biologically inactive former compound to be essentially planar with the oxide ring projecting ~90° out of the plane, while DMBA 5,6-oxide is severely distorted with the angle between the outer rings close to 35°. This major departure from planarity should markedly restrict both intercalation and donor–acceptor interaction of the latter molecule. Although it is not clearly established whether intercalation is essential for hydrocarbon carcinogenesis, if this is so, it appears highly unlikely that the K-oxides are the active carcinogenic species. The cis and trans dihydrodiols, not being constrained by the cis fusion of the oxide ring, are likely to depart even further from planarity to adopt the usual flattened boat structure of the 9,10-dihydrophenanthrene ring system.[49] The energy barriers for ring inversion of these systems are anticipated to be relatively low,[49] resulting in a dynamic equilibrium of conformers undergoing rapid interconversion at normal temperature. Although the more highly fused ring systems like BaP are somewhat flatter than the less rigid systems such as DMBA and phenanthrene, the effective thickness of the dihydrodiol portion of the molecule renders intercalation unlikely even in these cases. On the other hand, the quinones, phenols, and hydroquinones are all flat and structurally capable of intercalation. Therefore, if intercalation is a crucial step in hydrocarbon carcinogen action, these would appear to be more likely candidates for the active form of the carcinogen than the K-oxide currently favored.

Experimental Section

Physical Data. Proton NMR spectra were obtained on Varian T-60 and Brucker 270 MHz spectrometers; chemical shifts are reported relative to Me_4Si in $CDCl_3$, CCl_4, or DMSO-d_6. Integration was consistent with all assignments. Mass spectra were determined on a Finnigan 1015 mass spectrometer at 70 eV. Infrared and ultraviolet spectra were taken on Perkin-Elmer Infracord 137B and Cary Model 11 spectrometers, respectively. Analyses for C and H for all new compounds were correct to ±0.3%.

Materials. Tetrahydrofuran (THF) and triethylamine were purified by distillation from $LiAlH_4$. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled in vacuo and stored over molecular sieves, type 4A. The dimethyl acetal of dimethylformamide (DMA-DMF) and tris(dimethylamino)phosphine (hexamethylphosphorus triamide) were obtained from Aldrich and redistilled before use. DMBA (Eastman) was purified by chromatography on silica gel. BaP and chrysene were employed as supplied by Koch-Light. Pyridine–sulfur trioxide reagent was purchased from Eastman. Phenanthrene-9,10-quinone (Aldrich) was recrystallized from benzene (charcoal). *trans*-9,10-Dihydroxy-9,10-dihydrophenanthrene was obtained through reduction of the corresponding quinone with $LiAlH_4$;[18] reduction with $NaBH_4$ in methanol also provided the trans diol, but yields were variable and dependent upon precise duplication of experimental conditions.

***cis*-4,5-Dihydroxy-4,5-dihydro-BaP. Method A.** Osmium tetroxide (1.0 g, 3.9 mmol) was added to a solution of BaP (1.0 g, 3.9 mmol) in 80 ml of dry benzene containing 1 ml of anhydrous pyridine in a 250-ml flat-bottomed centrifuge bottle (Kontes). *This reaction and all subsequent operations were conducted under a nitrogen atmosphere.* The reaction mixture was stirred for 4 days, then centrifuged, and the clear benzene solution decanted. The precipitate was washed with benzene, centrifuged, and the solvent decanted. Then the solid was dissolved in methylene chloride (20 ml) and treated with 100 ml of an aqueous solution of 1% KOH and 10% mannitol with stirring for 5 hr. The crude cis diol was separated by centrifugation and decantation (the clear liquid was retained for recovery of osmium) and again washed with the mannitol solution in the same manner. The precipitate was filtered, washed with water, and dried in a vacuum desiccator over P_2O_5 to afford 600 mg of the crude cis diol.

Purification of the latter was accomplished through the diacetate. A solution of pyridine (4 ml) in acetic anhydride (40 ml) was heated at reflux for 15 min, cooled to room temperature, and added to the flask containing the cis diol. The resulting suspension was stirred for 5 hr; complete solution of the cis diol required ca. 30 min and was followed by precipitation of the diacetate. The reaction mixture was cooled, and the product was precipitated by the addition of cold water, isolated by filtration, and dried in vacuo over P_2O_5. The crude product (700 mg) was dissolved in benzene and chromatographed on a column of dry Florisil. Initial fractions eluted with 25–50% benzene in hexane contained minor impurities. Further elution with benzene gave *cis*-4,5-diacetoxy-4,5-dihydro-BaP (590 mg): mp 218–219° (lit.[16] 214–215°); NMR ($CDCl_3$) δ 1.93 (s, 3, CH_3), 2.00 (s, 3, CH_3), 6.43 (s, 2, benzylic), and 7.08–8.67 ppm (m, 10, aromatic).

The cis diacetate (500 mg) was smoothly converted to the pure cis diol on bubbling ammonia gas into a solution in methanol (100 ml) for 5 min at room temperature and 2 hr at 0°. The product which precipitated on addition of water was separated by centrifugation, dried over P_2O_5, then dissolved in dry THF, filtered to remove a minor insoluble component, dried over $MgSO_4$, and evaporated to dryness to afford *cis*-4,5-dihydroxy-4,5-dihydro-BaP (400 mg): mp 175–180° dec; NMR (DMSO-d_6) δ 5.00–5.53 (m, 4, benzylic and OH), and 7.5–9.0 (m, 10, aromatic); on shaking the sample with D_2O, the benzylic peak sharpened to a singlet at δ 5.07 ppm.

Method B. Osmium tetroxide (1.0 g) dissolved in 5 ml of dry pyridine was added to a solution of BaP (1.0 g) in 20 ml of pyridine, and the resulting solution was stirred under nitrogen for 5 days. Then a solution of 2 g of sodium bisulfite in 30 ml of water was added and the mixture stirred for 3 hr. The diol was then precipitated by addition of water, filtered, and washed with water. There was obtained 0.82 g of crude cis diol. Extraction of the filtrate with chloroform afforded an additional 0.20 g of crude cis diol. Acetylation with acetic anhydride and pyridine in the usual manner and chromatography on Florisil provided the pure cis diol diacetate (1.20 g) identical by NMR with that obtained by method A.

BaP-4,5-quinone. (*Scrupulous attention to the exclusion of moisture and the use of pure cis diol are essential to the success of this reaction.*) To 400 mg of the cis diol were added consecutively 4 ml of DMSO, 4 ml of triethylamine, and a solution of pyridine–sulfur trioxide complex (1.8 g) in DMSO (8 ml) prepared 5 min in advance. The resulting suspension of an orange solid was stirred under nitrogen for 30 min. The solid was precipitated by addition of water, filtered, washed with water, and dried in vacuo to afford 340 mg of benzo[*a*]pyrene-4,5-quinone, mp 253–256°. Recrystallization from acetic acid gave small red needles, mp 255–256° (lit.[62] 253–254°).

***trans*-4,5-Dihydroxy-4,5-dihydro-BaP. (a) Reduction of BaP-4,5-quinone in Ether.** The quinone (100 mg, 0.35 mmol) was extracted in a Soxhlet apparatus into a solution of $LiAlH_4$ (100 mg, 2.5 mmol) in refluxing anhydrous ether (100 ml) over a 30-hr period under nitrogen. The reaction mixture was cooled, and water and acetic acid (5 ml) were added. The ether extracts were washed with aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated to afford 100 mg of the crude trans diol.

Purification of the latter was accomplished through the diacetate. A solution of pyridine (0.4 ml) in acetic anhydride (4 ml) was heated at reflux for 15 min, cooled at room temperature, and added to the flask containing the trans diol. The resulting suspension was stirred for 5 hr; complete solution of the trans diol required ca. 30 min and was followed by precipitation of the diacetate. The reaction mixture was cooled and the product precipitated by the addition of cold water, isolated by filtration, and dried in vacuo over P_2O_5. The crude product (100 mg) was dissolved in benzene and chromatographed on a column of dry Florisil. Initial fractions eluted with 25–50% benzene in hexane contained minor

impurities. Further elution with benzene gave *trans*-4,5-diacetoxy-4,5-dihydro-BaP (95 mg), mp 254–255.5°, recrystallization from CH_2Cl_2–petroleum ether gave the analytical sample: mp 259–260.5°; NMR ($CDCl_3$) δ 1.93 (s, 6, CH_3), 6.40 (d, 1, oxirane-H, J = 4.4 Hz), 6.50 (d, 1, oxirane-H, J = 4.4 Hz), and 7.5–8.8 ppm (m, 10, aromatic); mass spectrum *m/e* 370 (parent peak).

The trans diacetate (172 mg) was smoothly converted to the pure trans diol on bubbling ammonia gas into a solution in methanol (100 ml) for 1 hr at 0° and 1 hr at room temperature. The product which precipitated on addition of water was separated by centrifugation, dried over P_2O_5, then dissolved in dry THF, filtered to remove a minor insoluble component, dried over $MgSO_4$, and evaporated to dryness to afford *trans*-4,5-dihydroxy-4,5-dihydro-BaP (123 mg): mp 211.5–213°; NMR (DMSO-d_6) δ 4.98 (m, 2, benzylic, collapsed to an apparent singlet in presence of D_2O), 5.80 (m, 2, OH), and 7.5–9.4 ppm (m, 10, aromatic).

(b) **Reduction in Ether–THF.** Analogous reduction of 100 mg of BaP-4,5-quinone was conducted with $LiAlH_4$ (1 g, 26.4 mmol) in a Soxhlet apparatus with ether (200 ml)–THF (100 ml) for 4 hr. After cautious addition of water (2 g) and acetic acid (5.5 ml), the solvents were distilled off under vacuum. The crude mixture was acetylated with acetic anhydride (15 ml) and pyridine (5 ml) at ambient temperature for 15 hr and worked up in a conventional manner. Chromatography on Florisil gave the trans diol diacetate **4b** (58 mg, mp 254–255.5°, 45%) and 4,5-diacetoxy-BaP (35 mg, mp 268–269°, 27%): NMR ($CDCl_3$) δ 2.57 (s, 3, CH_3), 2.62 (s, 3, CH_3), and 7.6–8.6 ppm (m, 10, aromatic); mass spectrum *m/e* 368 (parent peak).

Benzo[*a*]pyrene 4,5-Oxide. DMA-DMF (102 mg, 0.86 mmol) was added to a solution of the trans diol (122 mg, 0.43 mmol) in dimethylformamide (2 ml) and chloroform (6 ml) and the solution brought to reflux. After 7 hr, the solution was chilled in an ice bath, and cold water was added. The product was extracted as quickly as possible with cold ether, dried, and evaporated to dryness without heating. The crude product was dissolved in benzene and chromatographed on neutral alumina (Bio-Rad), Brockman Activity IV. The first fraction eluted with 4% dioxane in cyclohexane with nitrogen pressure (to minimize decomposition) was benzo[*a*]pyrene 4,5-oxide as a light-yellow solid (100 mg). Trituration with two 5-ml portions of hexane gave the pure oxide (70 mg), the physical data for which were reported earlier.[1a]

Oxidation of *cis*-4,5-Dihydroxy-4,5-dihydro-BaP with Sodium Periodate. The cis diol (1.15 g, 4 mmol) from oxidation of BaP with OsO_4 was treated with sodium periodate (3.5 g, 16 mmol) following the method of Hadler and Kryger,[63] except that the solvents were degassed by boiling under nitrogen. Chromatography on Florisil (100 g) gave **10, 11,** and **12.** Initial elution with benzene provided the internal dimethyl acetal **11** (0.25 g, 20%), isolated as a colorless crystalline solid, the NMR spectrum of which indicated it to be a mixture of cis and trans isomers. The major isomer, presumably *trans*-**11,** separated by fractional crystallization and melted at 165–166°: NMR (CCl_4) δ 3.40 and 3.41 (two s, 6, CH_3), 5.57 (s, 1, benzylic), 5.65 (s, 1, benzylic), and 7.4–8.6 ppm (m, 10, aromatic).

Further elution with 1% ethyl acetate in methylene chloride gave the dicarboxaldehyde **10** (0.31 g, 28%) obtained as yellow crystals from benzene: mp 180.5–181.5°; NMR ($CDCl_3$) δ 7.6–8.8 (m, 10, aromatic), and 10.05, 10.88 ppm (two s, 2, CHO); ir (KBr) 5.95 μ (CHO).

A small amount of 2-phenylnaphthalene-1,2′,3,6′-tetracarboxaldehyde (**12**) was also isolated: mp 191–192°; NMR ($CDCl_3$) δ 7.7–9.2 (m, 8, aromatic), 9.70 (s, 2, 2′,6′-CHO), 9.83 (s, 1, 3-CHO), and 10.16 ppm (s, 1, 1-CHO); ir (KBr) 5.89, 5.99 μ (CHO); mass spectrum *m/e* 316 (parent peak).

Hydrolysis of **11** (0.50 g) in 100 ml of benzene with 2 *M* sulfuric acid (100 ml) for 10 hr at reflux and an additional 12 hr at ambient temperatures followed by conventional work-up procedure and chromatography on Florisil gave 0.30 g of **10.**

Oxidation of *cis*-4,5-Dihydroxy-4,5-dihydro-BaP with $Pb(OAc)_4$. The cis diol (0.58 g, 2 mmol) was stirred with $Pb(OAc)_4$ (1.11 g, 2 mmol) in 160 ml of 1:1 benzene–pyridine at ambient temperatures for 3 hr. The dark-brown color of the solution became lighter after 2 hr. Addition of water (100 ml), followed by extraction with benzene, drying over sodium sulfate, evaporation of the solvent, and chromatography on Florisil (eluted with 1–4% ethyl acetate in benzene), gave the dicarboxaldehyde **10** (0.39 g, 68%).

Synthesis of BaP-4,5-oxide from 10. To a solution of **10** (1.05 g, 3.7 mmol) in 25 ml of dry benzene at 70–72° was added 0.72 ml (4.4 mmol) of $(Me_2N)_3P$. The dialdehyde dissolved completely after 15 min. Stirring was continued for a total of 75 min. The solution was then concentrated by removal of benzene under reduced pressure. Ether (50 ml) was then added and the solution slowly saturated with hexane (~30 ml) to precipitate dark-yellow crystals of BaP-4,5-oxide (0.49 g, 50%). Recrystallization of a sample from hot benzene gave the analytical sample as straw-yellow needles, mp 150° (softens at ~135°), whose physical properties were reported.[1a]

It should be noted that **1b** prepared from the dialdehyde appeared less stable thermally or on storage than the same compound obtained from the trans diol.

4- and 5-Acetoxy-BaP. (a) **From the Cis Diol Diacetate.** A solution of *cis*-**2b** diacetate (200 mg) and *p*-tosic acid (20 mg) in dry benzene (20 ml) was heated at reflux for 3 hr. There was obtained on work-up a mixture of 4- and 5-acetoxy-BaP (190 mg) in 3:2 ratio based on the relative ratio of the acetate peak heights in the NMR spectrum. Tentatively the peak at higher field (δ 2.42) associated with the predominant isomer is assigned to 4-acetoxy-BaP, and the second peak (δ 2.45) is assigned to 5-acetoxy-BaP. While chromatography on Florisil provided samples enriched in one or the other isomer, satisfactory separation could not be achieved. Substantial decomposition was observed to take place on all adsorbants investigated (Florisil, alumina, silica gel) rendering slow, careful chromatographic separation impractical. Total synthesis of isomeric phenol derivatives as well as high-pressure liquid chromatographic methods of separation are currently under investigation.

(b) **From BaP-4,5-oxide.** A sample of **1b** on treatment with 70% aqueous acetic acid at room temperature for 24 hr followed by acetylation with acetic anhydride and pyridine gave a similar mixture of 4- and 5-acetoxy-BaP to that obtained above.

4- and 5-Methoxy-BaP. A solution of 4- and 5-acetoxy-BaP (50 mg) and *p*-tosic acid (10 mg) in methanol (15 ml) and dioxane (5 ml) was heated at reflux overnight. The crude product obtained on work-up (53 mg) showed in the NMR spectrum complete replacement of the acetate peaks by methoxy peaks (δ 4.11, 4.12). Attempted chromatographic separation on Florisil was frustrated by the facility of decomposition.

***cis*-5,6-Dihydroxy-5,6-dihydro-7,12-dimethylbenz[*a*]anthracene (2a).** The modified procedure of Cook and Schoental[16] described above for synthesis of **1b** was employed.[64] Purification by chromatography on Florisil eluted with benzene, followed by recrystallization from benzene–hexane, provided pure *cis*-**2a** identical with that obtained by the procedure of Hadler and Kryger.[63] The diacetate of *cis*-**2a** crystallized from ether–hexane melted at 154–156°.

7,12-Dimethylbenz[*a*]anthracene-5,6-quinone (3a). Method A. Pure dry **2a** (4.83 g, 16.6 mmol) was dissolved in a mixture of dry triethylamine (26.6 ml) and DMSO (90 ml), and pyridine-SO_3 (15.9 g, 100 mmol) was added over 30 min with stirring. After an additional 20 min, the orange-red solution was neutralized with dilute sulfuric acid, whereupon yellow solids precipitated out. Water (180 ml) was added, and the solids were collected and recrystallized from acetone to afford 2.35 g (49%) of **3a** as dark-orange plates: mp 160–162° (lit.[25] 152–153°); NMR ($CDCl_3$) δ 2.85 (s, 3, 7-CH_3), 2.94 (s, 3, 12-CH_3), 7.3–8.4 ppm (m, 8, aromatic). The product was identical with that obtained using DMSO–acetic anhydride.[25]

The following alternative procedure which was quite effective with the cis diols of DMBA, benz[*a*]anthracene, and phenanthrene proved unsatisfactory with the K-region cis diol of BaP.

Method B. To a solution of pyridine-SO_3 (15.9 g, 100 mmol) in DMSO (40 ml), triethylamine (15 ml), and THF (5 ml) at 0° was added the pure dry **2a** (2.90 g, 10 mmol). As the cis diol dissolved, the color of the solution changed from yellow to orange, and the quinone precipitated from solution. After 5 hr, reaction was quenched by addition of water and the precipitate removed by filtration. The cloudy filtrate was extracted with ether and chloroform, and the extracts were combined and dried, and the solvent was removed in vacuo. The solid products were combined to afford 2.80 g (98%) of **3a** satisfactory without further purification for reduction with $LiAlH_4$ or $NaBH_4$.

Reduction of 3a. (a) **$LiAlH_4$.** The DMBA-5,6-quinone (1.01 g, 3.53 mmol) was extracted under nitrogen in a Soxhlet apparatus into a suspension of $LiAlH_4$ (1 g, 26 mmol) in 500 ml of ether over

a 2.5-hr period. The solution was maintained at reflux for an additional 1.5 hr, then 15 ml of water was added, and the mixture was neutralized to pH 4 with dilute sulfuric acid. The ethereal layer was washed with molar sodium hydroxide solution, then with water, dried (K_2CO_3), and evaporated to afford 0.88 g (85%) of *cis*- and *trans*-**4a**; the NMR spectrum of a sample acetylated with acetic anhydride showed that 55% of the diol had trans stereochemistry.

Separation of the isomeric diols was accomplished via selective conversion of the cis diol to its acetonide. An acetone solution of the mixture of diols (0.586 g) was refluxed under nitrogen over 2 g of freshly dried anhydrous copper sulfate for 4 hr. After filtration and removal of the solvent, the mixture was chromatographed through 30 g of Florisil. Elution with methylene chloride afforded 0.28 g of *cis*-**4a** acetonide as almost colorless needles (dry acetone-hexane): mp 132–133°; NMR (CCl_4) δ 1.02 (s, 3, CH_3), 1.50 (s, 3, CH_3), 2.64 (s, 3, 7-CH_3), 2.80 (s, 3, 12-CH_3), 5.09 (d, 1, CH-5, J = 5.2 Hz), 5.29 (s, 1, J = 5.2 Hz, CH-6), and 7.1–8.1 ppm (m, 8, aromatic).

The trans diol was eluted with 1% methanol-methylene chloride and was characterized after acetylation as *trans*-**4a** diacetate: mp 210–211°; NMR ($CDCl_3$) δ 1.84 (s, 3), 1.88 (s, 3), 2.70 (s, 3, 7-CH_3), 2.93 (s, 3, 12-CH_3), 5.96 (d, 1, J = 3.4 Hz, CH-5), 6.49 (d, 1, J = 3.4 Hz, CH-6), and 7.2–8.3 ppm (m, 8, aromatic).

(b) **$NaBH_4$.** To a suspension of DMBA-5,6-quinone (2.84 g, 10 mmol) in methanol (500 ml) at 0° was added $NaBH_4$ (3.0 g, 80 mmol). The reaction mixture was stirred at 0° for 5 hr, then worked up by conventional procedure to afford the crude diol (2.50 g). Acetylation with acetic anhydride–pyridine (5 hr) furnished 2.8 g of the crude diol diacetate, containing 65% cis isomer (based on the relative ratio of the acetate methyl peaks in the NMR spectrum). Chromatography on degassed Florisil eluted with hexane and increasing percentages of benzene gave in order of elution (10–60%) *cis*-**4a** diacetate (1.2 g) (70%), mixed diacetates (0.2 g), and (80–100%) *trans*-**4a** diacetate (0.6 g).

1,4-Dimethyl-2-phenylnaphthalene-3,2′-dicarboxaldehyde (9). (a) From Cis Diol. Oxidation of *cis*-**4a** (3 g) with sodium periodate according to the method of Hadler and Kryger[63] furnished 2.60 g of crystalline **9.**

(b) **One-Step Synthesis from DMBA. Method A.** To a solution of DMBA (1 g) in acetic acid (60 ml) was added a solution of OsO_4 (0.05 g) in 10 ml of benzene, followed by sodium periodate (1 g) in 25 ml of water. The solution was stirred for 1 hr, then allowed to stand for 24 hr, at which time an additional 0.6 g of periodate was added. After another 36 hr, the reaction mixture was worked up in a conventional manner and the crude product chromatographed on Florisil. Elution with benzene and benzene + 1% ethyl acetate furnished **9** (0.60 g) as light-yellow crystals, mp 136–138° (lit.[63] 137–137.5°).

Method B. To a solution of DMBA (5 g) in DMF (100 ml) was added acetic acid (80 ml) and water (20 ml). To the resulting suspension was added a solution of osmium tetroxide (1 g) in dioxane (50 ml), bringing the hydrocarbon back into solution. After 1 hr at room temperature, 5 g of $NaIO_4$ was added over a 5-hr period. A precipitate formed on stirring overnight. An additional 5 g of $NaIO_4$ was added over the following 8 hr, and the reaction was worked up following a second period of stirring overnight. The crude product was purified by passage through a column of Florisil and triturated with ether to afford **9** (3.5 g) identical by NMR with that obtained by method A.

DMBA-5,6-oxide (1a). (a) From the Dialdehyde. To a solution of **9** (2.54 g, 8.8 mmol) in 25 ml of dry benzene under nitrogen at 70–72° was added tris(dimethylamino)phosphine (2.1 ml, 13 mmol). The resulting solution was maintained at 75° for 3 hr, then concentrated in vacuo to a viscous yellow oil. The addition of 45 ml of dry ether followed by 20 ml of hexane and cooling afforded 1.8 g (75%) of **1a** as pale-yellow crystals, recrystallized from benzene-ether-hexane to give pure **1a** as almost colorless crystals: mp ~148° (soften at 139° dec); NMR (CCl_4) δ 2.78 (s, 3, 7-CH_3), 2.93 (s, 12-CH_3), 4.27 (d, 1, J = 4 Hz, CH-5), 4.68 (d, 1, J = 4 Hz, CH-6), 7.2–8.1 ppm (m, 8, aromatic); ir (KBr) 11.3 μ (medium weak); mass spectrum *m/e* 272 (parent peak).

A sample of **1a** on treatment with aqueous acetic acid at room temperature for 15 hr followed by acetylation of the product with acetic anhydride and pyridine gave a mixture containing principally *trans*-**4a** diacetate and 5-acetoxy-DMBA.

(b) **From the Trans Diol.** A solution of the *trans*-**4a** (60 mg, 0.2 mmol) and DMF-DMA (40 mg, 0.3 mmol) in chloroform (0.3 ml) was heated at 50–55° for 26 hr. Removal of the solvent in vacuo gave a yellow oil shown by NMR to contain **1a** (80%). Rapid chromatography on alumina IV with 4% dioxane in dry benzene gave pure **1a** (40 mg).

(c) **From Mixture of Cis and Trans Diols.** The mixture of diols obtained through $LiAlH_4$ reduction of **3a** (0.47 g, 1.6 mmol) was treated with DMA-DMF (0.24 g, 2 mmol) in refluxing chloroform under nitrogen for 24 hr. Removal of the solvent gave an oil which was rapidly chromatographed through 10 g of Florisil eluted with cold methylene chloride. The white solid product (0.1 g) was recrystallized from benzene-cyclohexane and identified as *cis*-5-hydroxy-6-formyloxy-5,6-dihydro-DMBA: mp 186–188°; NMR ($CDCl_3$) δ 2.76 (s, 3, 7-CH_3), 2.90 (s, 3, 12-CH_3), 4.60 (s, 1, OH, disappeared in presence of D_2O), 5.06 (broad d, 1, J = 3 Hz, CH-5), 6.65 (dd, 1, J = 3 Hz, $J \sim 1$ Hz, CH-6), and 7.3–8.2 ppm (m, 8, aromatic); ir (KBr) 3.05 (OH), 5.83 (CHO), 8.5 μ; mass spectrum *m/e* 318 (parent peak).

The oxide **1a** which was the second major product obtained in the foregoing reaction of the diols with DMA-DMF (shown by NMR) was unfortunately lost through decomposition during chromatography on Florisil. However, repetition of this reaction with 194 mg of the diol mixture followed by rapid chromatography on alumina IV furnished **1a** (96 mg).

Acetylation of the formate derivative with acetic anhydride and pyridine gave *cis*-5-acetoxy-6-formyloxy-5,6-dihydro-DMBA: mp 223–225°; NMR ($CDCl_3$) δ 2.27 (s, 3, CH_3CO), 2.70 (s, 3, 7-CH_3), 2.90 (s, 3, 12-CH_3), 6.14 (d, 1, J = 3.0 Hz, CH-5), 6.82 (dd, 1, J = 3.0 Hz, $J \sim 1$ Hz, CH-6), and 7.3–8.2 (m, 8, aromatic); mass spectrum *m/e* 360 (parent peak). Hydrolysis of the compound by brief reflux in aqueous potassium carbonate followed by acetylation furnished *cis*-**2a** diacetate identical with the authentic compound by NMR.

Treatment of the formate derivative with excess *p*-toluenesulfonyl chloride in pyridine at 0–5° afforded smoothly *cis*-5-tosyloxy-6-formyloxy-5,6-dihydro-DMBA: mp 125–126°; NMR (CCl_4) δ 2.50 (s, 3, CH_3), 2.60 (s, 3, 7-CH_3), 2.85 (s, 3, 12-CH_3), 5.70 (broad d, 1, $J \sim 2.8$ Hz, CH-5), 6.50 (d, 1, $J \sim 2.8$ Hz, CH-6), and 7.2–8.3 ppm (m, 2, aromatic); mass spectrum *m/e* 472 (parent peak).

Esterification of *cis*-2a. (a) 5-Acetate. To a solution of *cis*-**2a** (100 mg, 0.35 mmol) in pyridine (1 ml) was added an equimolar amount of acetic anhydride, and the mixture was allowed to stand at ambient temperature for 16 hr. Addition of water, extraction with ether, and conventional work-up gave a mixture of (124 mg) the mono- and diacetates of *cis*-**2a** (2:1 ratio by NMR) free of the diol. Crystallization from benzene-cyclohexane provided *cis*-5-acetoxy-6-hydroxy-5,6-dihydro-DMBA: mp 185–187°; NMR (CCl_4) δ 2.30 (s, 3, CH_3CO), 2.75 (s, 3, 7-CH_3), 2.87 (s, 3, 12-CH_3), 5.92 (broad d, 1, J = 2.8 Hz, CH-5), 5.12 (d, 1, J = 2.8 Hz, CH-6), and 7.2–8.3 ppm (m, 8, aromatic).

(b) **5-Tosylate-6-acetate.** *p*-Toluenesulfonyl chloride (1.1 mmol) was added in three portions to a solution of *cis*-**2a** (1 mmol) in 3 ml of pyridine over a 2-day period. After a total of 3 days, reaction was worked up in a conventional manner by partition between ice-water and ether. Acetylation of the resulting yellow oil with acetic anhydride pyridine for 16 hr at room temperature provided on work-up a crude oily product (480 mg) containing the 5-tosylate-6-acetate of *cis*-**2a** and 5-tosyloxy-DMBA by NMR analysis. Recrystallization from methylene chloride-benzene provided pure *cis*-5-toxyloxy-6-acetoxy-5,6-dihydro-DMBA (70%): mp 134–136°; NMR ($CDCl_3$) δ 1.80 (s, 3, CH_3CO), 2.43 (s, 3, CH_3), 2.57 (s, 3, 7-CH_3), 2.83 (s, 3, 12-CH_3), 5.72 (d, 1, J = 2.8 Hz, CH-5), 6.47 (d, 1, J = 2.8 Hz, CH-6), and 7.2–8.3 ppm (m, 12, aromatic).

The mother liquor was concentrated and recrystallized from benzene-cyclohexane to afford 5-tosyloxy-DMBA (10%): mp 221–222°; NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3), 2.80 (s, 3, 7-CH_3), 3.26 (s, 3, 12-CH_3), and 7.1–8.4 (m, 12, aromatic); mass spectrum *m/e* 426 (parent peak).

Hydrolysis of 1a. A solution of **1a** (20 mg) in 1 ml of 10% aqueous acetone was stirred at room temperature for 3 days. Evaporation in vacuo furnished the trans diol **4a** as a yellow oil; acetylation afforded **4a** diacetate (essentially pure by NMR).

Reduction of 1a. A solution of **1a** (136 mg, 0.5 mmol) in benzene (8 ml) was added dropwise to 37 mg of $LiAlH_4$ in 25 ml of ether.

The solution was heated at reflux for 20 min, then cooled and worked up by consecutive addition of ethanol (1 ml), water (5 ml), acetic acid (10 ml), and water (10 ml). Conventional work-up gave 0.135 g of 5-hydroxy-5,6-dihydro-DMBA containing a trace of the 6-hydroxy isomer. Recrystallization from benzene–hexane gave 5-hydroxy-5,6-dihydro-DMBA as white fluffy needles: mp 156–157°; NMR ($CDCl_3$) δ 2.70 (s, 3, 7-CH_3), 2.95 (s, 3, 12-CH_3), 3.17 (m, 2, CH_2), 4.83 (m, 1, CH), and 7.2–8.3 ppm (m, 8, aromatic); on shaking the sample with D_2O, the broad OH absorption at δ 1.4–2.0 ppm disappeared.

5-Acetoxy-DMBA. A solution of *cis*-**2a** (123 mg, 0.33 mmol) and *p*-tosic acid (10 mg) in dry benzene (10 ml) was maintained at reflux for 3.5 hr. Reaction was quenched with water, extracted with ether, washed with dilute sodium bicarbonate, dried, and evaporated to provide 5-acetoxy-DMBA (95.2 mg) as a pale-yellow oil: NMR ($CDCl_3$) δ 2.43 (s, 3, CH_3CO), 2.90 (s, 3, 7-CH_3), 3.18 (s, 3, 12-CH_3), and 7.2–8.4 ppm (m, 9, aromatic); the assignments and chemical shifts are in agreement with those reported;[56] however, we have been unable to obtain this compound in crystalline form (lit.[56] mp 138–139°). This structural assignment was confirmed by conversion to the known 5-methoxy-DMBA.[65]

5-Methoxy-DMBA. (a) Methanolysis of 5-Acetoxy-DMBA. A solution of 5-acetoxy-DMBA (100 mg, 0.32 mmol) and *p*-tosic acid (10 mg) in methanol was heated at reflux for 8 hr and worked up in a conventional manner. The NMR spectrum of the crude product (90 mg) indicated essentially complete conversion to 5-methoxy-DMBA: NMR δ 2.75 (s, 3, 7-CH_3), 3.10 (s, 3, 12-CH_3), 3.88 (s, 3, CH_3O), 6.92 (s, 1, 6-H), and 7.0–8.3 ppm (m, 8, aromatic); the NMR spectrum matched that of an authentic sample supplied by Dr. James Flesher[45] and agreed with that reported.[56]

It is noteworthy that attempted acid-catalyzed hydrolysis of 5-acetoxy-DMBA in aqueous DMF or acetonitrile resulted in essentially recovery of unreacted starting material.

(b) Loss of Methanol from *cis*-5,6-Dimethoxy-5,6-dihydro-DMBA. ***cis*-2a** (86 mg, 0.3 mmol) was added to a suspension of sodium hydride (1.2 mmol) in dry DMF (5 ml) and the mixture stirred at ambient temperature for 1 hr. Then methyl iodide (1.8 mmol) was added, discharging the pink color of the solution. After another 2 hr, reaction was quenched with water and worked up to furnish an oily solid product. Chromatography on Florisil removed the mineral oil from the NaH dispersion in the initial fractions eluted with hexane followed by the dimethyl ether of *cis*-**2a** (100 mg) eluted with benzene: NMR (CCl_4) δ 2.73 (s, 3, 7-CH_3), 2.85 (s, 3, 12-CH_3), 3.25 (s, 3, 5-CH_3O), 3.65 (s, 3, 6-CH_3O), 4.37 (d, 1, $J \sim 2.5$ Hz, 5-H), 4.92 (d, 1, $J \sim 2.5$ Hz, 6-H), and 7.1–8.2 ppm (m, 8, aromatic).

A solution of *cis*-**2a** dimethyl ether (100 mg) and *p*-tosic acid (10 mg) in dry benzene (10 ml) was heated at reflux for 3 hr. The green color was discharged by addition of water and the product (88 mg) isolated by a conventional procedure. The NMR spectrum indicated essentially complete conversion to 5-methoxy-DMBA.

(c) Reaction of 5-Acetoxy-DMBA with Methyllithium. 5-Acetoxy-DMBA (240 mg, 0.77 mmol) was dissolved in ether (20 ml), and a solution of methyllithium (1.54 mmol) in ether was added, and the resulting suspension was stirred at room temperature under nitrogen for 1 hr. Reaction was quenched with water and worked up by conventional procedure to afford 220 mg of a product which was chromatographed on Florisil. Some decomposition was noted on the column. The major product eluted with benzene–hexane (4:1) was slightly impure 5-oxo-5,6-dihydro-DMBA: ir ($CHCl_3$) 1680 cm^{-1} (lit.[56,57] 1683, 1690 cm^{-1}); NMR (DMSO-d_6) δ 3.80 (lit.[56] 3.62, $CDCl_3$).

Phenanthrene 9,10-Oxide (1c). To a solution of the trans diol (250 mg, 1.17 mmol) in DMF (1 ml)–chloroform (3 ml) was added DMF-DMA (1.76 mmol), and the resulting solution was heated at reflux for 16 hr. The product was isolated following the procedure employed for BaP-4,5-oxide to afford **1c** (240 mg) as a light-yellow solid. It was further purified by trituration with hexane, then taken up in benzene and chromatographed on alumina IV eluted with 4% dioxane in cyclohexane. The NMR spectrum of **1c** showed δ 4.67 (s, 2, oxirane-H), and 7.2–8.3 (m, 8, aromatic). The sample required for X-ray crystallographic analysis[51] was crystallized from methylene chloride–cyclohexane and gave mp 148° (soften at 136°) (lit.[15] 104–105°).

Synthesis of 2,2′-Diformylbiphenyl from Phenanthrene. A suspension of phenanthrene (3.52 g, 20 mmol) and $NaIO_4$ (1 g) in 20% aqueous acetic acid (60 ml) was stirred at room temperature. Additional portions (3 × 1 g) of $NaIO_4$ were added at 1-day intervals, and reaction was quenched and worked up after 5 days. Chromatography of the crude product on Florisil gave recovered phenanthrene (0.8 g) eluted with petroleum ether–benzene followed by 2,2′-diformylbiphenyl (0.95 g, 32%) as yellow crystals: mp 58–61° (lit.[66] 62°); NMR (CCl_4) δ 9.77 (s, 2, CHO) and 7.2–8.4 ppm (m, 8, aromatic).

Reduction of Pyrene-4,5-quinone. Reduction of pyrene-4,5-quinone[1b] (210 mg, 0.91 mmol) according to the procedure employed for BaP (7 hr) gave 4,5-dihydroxy-4,5-dihydropyrene (0.19 g) purified via conversion to the diacetate with acetic anhydride–pyridine and chromatography on a column of dry Florisil. Elution with benzene afforded *trans*-4,5-diacetoxy-4,5-dihydropyrene (222 mg) as white crystals: mp 219–220° (lit.[67] 218°); NMR ($CDCl_3$) δ 1.97 (s, 6, CH_3), 6.43 (s, 2, benzylic), and 7.5–8.0 ppm (m, 8, aromatic).

Ammonolysis of the trans diol diacetate (180 mg) in methanolic ammonia according to the usual procedure furnished pyrene-4,5-*trans*-diol (120 mg) as a pale-yellow solid: mp 220–223° (lit.[67] 222°); NMR (DMSO-d_6) δ 4.97 (m, 2, benzylic, collapsed to singlet in presence of D_2O), 5.60 (m, 2, OH), and 7.4–8.5 ppm (m, 8, aromatic).

Pyrene 4,5-Oxide. Cyclization of pyrene-4,5-*trans*-diol (91 mg, 0.38 mmol) with DMA–DMF by the method employed for BaP gave pyrene 4,5-oxide (90 mg) purified by passage through neutral alumina IV. Elution with 4% dioxane in cyclohexane gave pyrene 4,5-oxide (72 mg) which after trituration with hexane melted at 192–200° dec (lit.[46] 180°); NMR ($CDCl_3$) δ 4.80 (s, 2, oxirane) and 7.2–8.2 ppm (m, 8, aromatic).

***trans*-5,6-Dihydroxy-5,6-dihydrobenz[*a*]anthracene (4d).** Reduction of benz[*a*]anthracene-5,6-quinone[1b] (1.5 g, 5.81 mmol) with $LiAlH_4$ (1.45 g, 38 mmol) in ether according to the method of Boyland and Sims[68] gave **4d** (1.61 g). Acetylation with acetic anhydride and pyridine followed by chromatography on Florisil afforded **4d** diacetate: mp 205–208° (lit.[68] 209°); NMR ($CDCl_3$) δ 1.97 (s, 3, 5-CH_3CO), 2.01 (s, 3, 6-CH_3CO), 6.10 (d, 1, $J \sim 5$ Hz, CH-5), 6.28 (d, 1, $J \sim 5$ Hz, CH-6), and 7.3–8.3 ppm (m, 10, aromatic).

Deacetylation in methanolic ammonia regenerated **4d**, mp 202–205° dec (lit.[68] 210° dec).

Benz[*a*]anthracene 5,6-Oxide (1d). The trans diol (1.05 g, 4 mmol) on treatment with DMA–DMF (8 mmol) according to the procedure described for preparation of **1b** gave the crude product (1.0 g) which was purified by solution in benzene and filtration to remove unreacted trans diol (0.22 g) and trituration with hexane to afford **1d** (0.74 g): mp 130–132° (lit.[15] 119–120°); NMR ($CDCl_3$) δ 4.40 (d, 1, J = 4 Hz, CH-5), 4.55 (d, 1, J = 4 Hz, CH-6), and 7.3–8.6 ppm (m, 10, aromatic).

5- and 6-Acetoxybenz[*a*]anthracene. (a) From Cis Diol Diacetate. A solution of *cis*-**2d** diacetate (130 mg) and *p*-tosic acid (13 mg) in dry benzene (10 ml) was heated at reflux for 22 hr (reaction incomplete in 3 hr). Reaction was quenched with water, extracted with ether, washed with dilute sodium bicarbonate, dried, and evaporated to provide an oil (103 mg) identified as a mixture of 5- and 6-acetoxybenz[*a*]anthracene in 3:1 ratio on the basis of the acetate methyl peak heights at δ 2.03 and 2.07 ppm (CCl_4) in the NMR spectrum. Attempted chromatographic separation on neutral alumina, Florisil, or silica gel led to substantial decomposition. However, careful crystallization afforded a pure sample of the major isomer confirmed by mp 127–128° (lit.[15,16] 128–129°, 126–127°) and the chemical shift of the acetoxy methyl peak (δ 2.03) to be 5-acetoxybenz[*a*]anthracene.

(b) From Cis Diol. Acid-catalyzed dehydration of *cis*-**2d** (50 mg) under similar conditions afforded a similar mixture of the 5- and 6-phenols. Since the NMR spectra of the phenolic derivatives have proved generally less satisfactory (hydrogen bonding and tendency to radical formation are contributing factors), this product was acetylated with acetic anhydride–pyridine to provide a mixture of 5- and 6-acetoxybenz[*a*]anthracene (3:1 by NMR) (54 mg).

5- and 6-Mesyloxybenz[*a*]anthracene. To a solution of *cis*-**2d** (200 mg) in dry pyridine (9 ml) was added methanesulfonyl chloride (1.5 ml). The resulting solution was stirred at ambient temp for 2.5 hr, then worked up in conventional manner to afford 490 mg of a crystalline solid. Despite the appearance of only a single methyl peak (δ 3.18) in the NMR spectrum ($CDCl_3$), this product

was shown through conversion to the corresponding acetate to consist of a mixture of the 5- and 6-mesyloxy derivatives. Attempted chromatography on neutral alumina resulted in extensive decomposition.

Reaction of the 5- and 6-mesylates (156 mg) with $LiAlH_4$ (18 mg) in refluxing ether (75 ml) for 1 hr afforded 5- and 6-hydroxybenz[*a*]anthracene which were in turn acetylated and shown to consist of a mixture of 5- and 6-acetoxybenz[*a*]anthracenes similar to that obtained via the alternative routes.

Acid-Catalyzed Rearrangement of 1d. A solution of **1d** (50 mg) was heated at reflux in methanol (10 ml) containing *p*-tosic acid (5 mg) for 6 hr. Conventional workup furnished a mixture of 5- and 6-methoxybenz[*a*]anthracene in essentially the same ratio (by NMR) as obtained from acid-catalyzed methanolysis of the mixture of 5- and 6-acetoxybenz[*a*]anthracenes from the dioldiacetate; the NMR spectrum of 5- and 6-methoxybenz[*a*]anthracene showed characteristic 5- and 6-methoxy singlets and δ 4.00 and 4.03, respectively; the protons at H_5 and H_6 appeared as broad singlets at higher field (δ 6.72 and 6.87, respectively) than the remainder of the aromatic protons.

Reduction of Chrysene-5,6-quinone. Chrysene-5,6-quinone was reduced with $LiAlH_4$ according to the usual method. The time required for extraction varied with the quantity and purity of the quinone. Typical examples with the pure quinone are 258 mg (3 hr), 1.29 g (19 hr), and 2.58 g (29 hr); unduly prolonged reaction time is not desirable. The crude dihydrodiol was acetylated with acetic anhydride–pyridine in the usual manner (5 hr at room temp) to afford the crude diacetate (15–18% by NMR). Chromatography on Florisil afforded (in order of elution with increasing ratio of benzene in hexane) chrysene (~5%), phenol acetate, cis diol diacetate (15–18%), trans diol diacetate (70–75%), and an additional small quantity of the phenol acetate because of decomposition on the column. Analytical samples of the cis and trans diol diacetates were further purified by a second chromatography. The chrysene-5,6-*cis*-diol diacetate had: mp 165–167° (lit.[16] 164–165°); NMR ($CDCl_3$) δ 1.85 (s, 3, 5-CH_3CO_2), 2.12 (s, 3, 6-CH_3CO_2), 6.33 (d, 1, 5-CH, $J \simeq 4$ Hz), and 7.08 ppm (d, 1, 6-CH, $J \simeq 4$ Hz).

The chrysene 5,6-*trans*-diol diacetate had: mp 223–224.5°; NMR ($CDCl_3$) δ 1.83 (s, 3, 5-CH_3CO_2), 1.93 (s, 3, 6-CH_3CO_2), 6.13 (d, 1, 5-CH, $J \simeq 4$ Hz), and 6.85 ppm (d, 1, 6-CH, $J \simeq 4$ Hz).

Ammonolysis of the trans diol diacetate in methanolic ammonia following the usual procedure furnished the free trans diol, which decomposed on melting and gave a complex NMR spectrum with broad peaks unsatisfactory for characterization; *trans*-**4b** was employed without further purification.

Chrysene 5,6-Oxide (1f). Cyclization of the *trans*-**4f** (212 mg) with DMA-DMF in the usual manner (22 hr) with THF in place of chloroform gave crude **1f** (209 mg), trituration of which with hexane removed impurities. The NMR spectrum of **1f** showed ($CDCl_3$) δ 4.62 (d, 1, 5-oxiranyl, $J \simeq 4$ Hz) and 5.28 ppm (d, 1, 6-oxiranyl).

6-Acetoxy-, 6-Hydroxy-, and 6-Methoxychrysene. (1) 6-Acetoxy. A solution of *trans*-**4f** diacetate (200 mg) and *p*-tosic acid (20 mg) in dry benzene (20 ml) was heated at reflux for 22 hr. There was obtained on work-up 6-acetoxychrysene (185 mg) as a white solid: NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3CO_2).

(2) 6-Hydroxy. The acetoxy compound was heated at reflux in ether (75 ml) with $LiAlH_4$ (25 mg) for 1 hr. Conventional work-up provided 6-hydroxychrysene (170 mg) characterized through the methyl ether.

(3) 6-Methoxy. The 6-hydroxy compound was dissolved in DMF (5 ml), then dimethyl sulfate (1 ml) and BaO (1 g) were added, and the resulting suspension was stirred at ambient temperature for 19 hr. Concentrated NH_4OH (5 ml) was added, and stirring was continued for 30 min. Work-up afforded 6-methoxychrysene (150 mg): NMR ($CDCl_3$) δ 4.10 (s, 3, CH_3O). Rapid chromatography through Florisil and recrystallization from methanol furnished the analytical sample: mp 121–122° (lit.[16] 125–126°).

5- and 6-Mesyloxychrysene. To a solution of *trans*-**4f** (100 mg) in dry pyridine (3 ml) was added mesyl chloride (0.6 ml), and the resulting solution was stirred at room temperature for 2.5 hr. Conventional work-up gave *trans*-**4f** dimesylate, which on chromatography through Florisil was eluted with increasing ratios of benzene in hexane as 5- and 6-mesyloxychrysene (1:9). The major isomer (88 mg), presumed to be the 6-mesyloxy compound, was recrystallized from benzene–hexane and gave: mp 189–191°; NMR δ 3.26 (s, 3, CH_3).

***cis*-5,6-Dihydroxy-5,6-dihydrodibenz[*a,h*]anthracene (*cis*-2g).** Reaction of dibenz[*a,h*]anthracene (DBA) (2 g) with OsO_4 according to method A afforded 1.88 g of the crude *cis*-**2g.** Acetylation with Ac_2O–pyridine in the usual manner gave *cis*-**2g** diacetate (2.54 g) as a beige solid. Decolorization and removal of a trace amount of the trans isomer were accomplished by filtration of a solution in chloroform–benzene through a short column of Florisil (20 g). The *cis*-**2g** diacetate gave: mp 175–177° (lit.[16] 176.5–177.5°); NMR δ 2.07 (s, 3, 5-CH_3CO_2), 2.17 (s, 3, 6-CH_3CO_2), 6.30 (d, 1, 5-CH, $J \simeq 3$ Hz), and 6.48 ppm (d, 1, 6-CH, $J \simeq 3$ Hz). The diacetate was converted to *cis*-**2g** on treatment with methanolic ammonia.

DBA-5,6-quinone (3g). Oxidation of *cis*-**2g** (1.46 g) following the usual procedure gave a product which was dissolved in $CHCl_3$ (3 l.) and passed through a short column of Florisil (20 g) to yield 1.38 g of **3g.** A sample recrystallized from CH_2Cl_2–hexane gave red needles, mp 344° dec. (lit.[69] 349.5–350°).

Reduction of 3g. To a partial suspension of **3g** (1.07 g) in 150 ml of methanol at 0° was added $NaBH_4$ (1 g) in eight portions at 30-min intervals. Conventional work-up afforded 1.21 g of a solid which was acetylated by the usual procedure to yield 1.28 g of crude *trans*-**4g** diacetate. Residual quinone and minor impurities were removed by chromatography on Florisil. The resulting *trans*-**4g** diacetate (1.26 g) had NMR δ 1.93 (s, 3, 5-CH_3CO_2), 2.00 (s, 3, 6-CH_3CO_2), 6.13 (d, 1, 5-CH, $J \simeq 4.5$ Hz), and 6.35 ppm (d, 1, 6-CH, $J \simeq 4.5$ Hz). The diacetate was converted to *trans*-**4g** on treatment with methanolic ammonia: NMR δ 4.67 (m, 2, OH), and 5.67, 5.83 ppm (d of d, 2, benzylic, $J \simeq 4$ Hz).

DBA 5,6-Oxide (1g). Cyclization of the trans diol (312 mg) with DMA-DMF in the usual manner (24 hr) gave crude **1g** (240 mg), (reaction not complete, longer time may be desirable). Trituration with hexane and chromatography on activity IV alumina gave **1g** (140 mg): NMR δ 4.57 (d, 1, 5-CH, $J \simeq 4$ Hz) and 4.77 ppm (d, 1, 6-CH, $J \simeq 4$ Hz).

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