ARENE OXIDES-OXEPINS

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I. INTRODUCTION

A. History - Arene oxides are a subclass of aromatic hydrocarbons in which the continuous p-π overlap is interrupted by formation of an epoxide ring between two adjacent carbon atoms. The trivial nomenclature of benzene oxide or dihydrobenzene epoxide for structure 1 and related compounds has found widespread use. More formally, 1 would be named

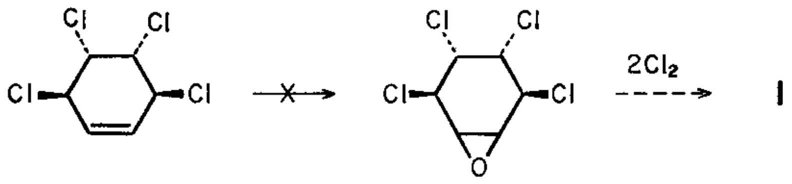
1 2

7-oxabicyclo[4.1.0]hepta-2,4-diene. The term oxepin is widely applied to the 7-membered unsaturated ether 2, the fully reduced hexahydro derivative being oxepane. As will be discussed, the two structures, 1 and 2, are intimately related and co-exist as valence bond tautomers. The relevancy of arene oxides to two widely diverse areas of scientific endeavor, molecular biology and theoretical quantum mechanics, had encouraged synthetic chemists in their attempts to elaborate these structures over a period of more than thirty years. In 1964, the first synthesis of benzene oxide-oxepin, the parent system, was reported by E. Vogel and his colleagues at the University of Köln.[1] In the subsequent ten years, several hundred papers have appeared which either relate to or are directly concerned with the chemistry and biochemistry of the arene oxide-oxepin system.

Much of the theoretical interest in oxepin (2) stemmed from its 8π electron system which, like the analogous unstable cycloheptatrienyl anion and cyclooctatetraene, does not satisfy the (4n + 2) Hückel requirement for aromaticity. Molecular orbital calculations suggested that 2 might possess a certain amount of aromatic character.[2] In addition, it was postulated[3] that 2 might coexist in valence tautomeric equilibrium with benzene oxide (1) by analogy with the suspected norcaradiene-cycloheptatriene equilibrium. This was, at the time, an innovative suggestion since few were willing to believe that 1 could have a finite existence or that facile rupture of the carbon-carbon bond in an oxirane could occur.

Biological interest in arene oxides stemmed, to a great extent, from an observation by Boyland and Levi[2] that anthracene was metabolically converted to *trans*-1,2-dihydroxy-1,2-dihydroanthracene in mammals. Similar results with a number of other polycyclic aromatic hydrocarbons prompted Boyland to suggest in 1950,[5] that arene oxides might be intermediates in aromatic metabolism. Nearly twenty years later this theory was proved correct, and arene oxides were implicated as causative agents in necrosis and carcinogenesis elicited by aromatic compounds.

B. *The First Successful Synthesis* - The first attempts to prepare 1-2, although imaginative, led to discouraging results in that either the desired precursors could not be prepared or, when such compounds were prepared, the final step led only to the isolation of phenol. Attempts to epoxidize "α-benzene tetrachloride" (3) to the tetrachloroepoxide 4 were unsuccessful. Dehalogenation[3] of 4 was expected to generate 1. An analogous



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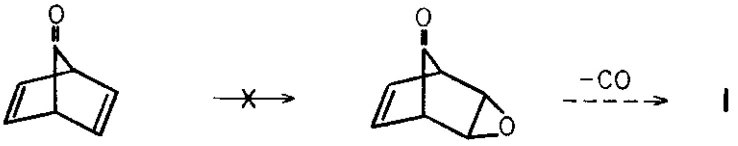
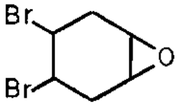
route had, however, been employed in the synthesis of trans-1,2-dihydroxy-1,2-dihydrobenzene.[6] Attempted epoxidation of 7-ketonorbornadiene (5) to 6 also failed.[7]



5 6

Decarbonylation of 6 was hoped to provide a route into 1. Early attempts to dehydrohalogenate 7 with tertiary amine bases[3,8] or 8 with silver oxide in ether[3] yielded phenol. A similar result was obtained on pyrolysis[3] of 9. The persevering efforts of Vogel and co-workers[1] ultimately led to the generation of benzene oxide-oxepin (1-2) through treatment of 7 with the potent dehydrohalogenating agent, diazabicyclononene, and the presence of the valence bond tautomerism was first observed.



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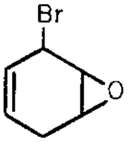

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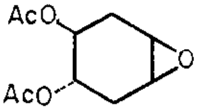

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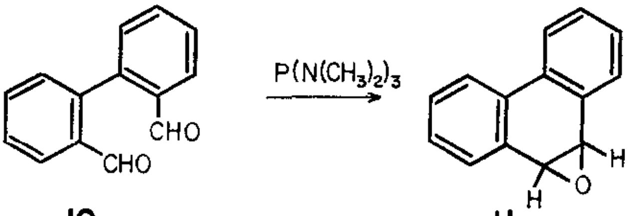
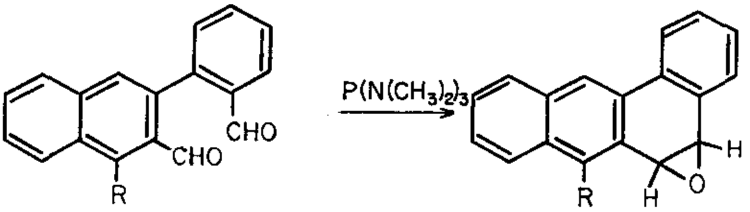
Although the literature contained reports[9,10] that peroxyacid oxidation of polycyclic aromatic hydrocarbons led to the formation of arene oxides at the K-regions of pyrene and dibenzo[a,h]anthracene, the yields in these reactions were diminishingly small, and the products were not pure or definitively characterized. The first unequivocal synthesis of arene oxides at the K-regions of polycyclic aromatic hydrocarbons was that of

Newman and Blum[11] at the Ohio State University in 1964, very shortly after the disclosure of the synthesis of 1-2 by Vogel. Newman elegantly applied Mark's reagent,[12] *tris*-dimethylaminophosphine, to close 2,2'-biphenyldialdehydes (10, 12, 13) to the desired arene oxides.



10 **11**



12 R = H
13 R = CH_3

14 R = H
15 R = CH_3

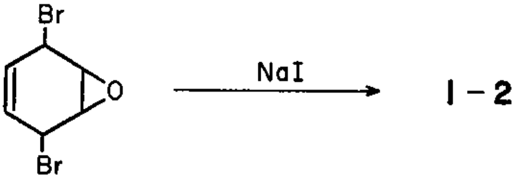
In this manner, phenanthrene 9,10-oxide (11), 1,2-benzanthracene 3,4-oxide (14) and 10-methyl-1,2-benzanthracene 3,4-oxide (15) were obtained as pure crystalline solids in yields in excess of 70%. The starting dialdehydes in these syntheses were readily obtained from the intact hydrocarbons through formation of *cis*-dihydrodiols at the K-regions with OsO_4 and subsequent cleavage. No evidence for oxepin contributors to any of the K-region arene oxides was detected.

C. Nomenclature and Scope of the Review - In order to maintain uniformity and avoid confusion within this review, all derivatives of benzene oxide-oxepin will be named as benzene oxides regardless of where the position of the equilibrium between the two forms lies. For polycyclic hydrocarbons, either the oxide or oxepin nomenclature will be employed since these compounds exist exclusively in one form or the other.

An attempt has been made to provide as comprehensive coverage of the literature as possible through June 1973. Emphasis has been placed on the synthesis of benzene oxides and arene oxides of higher polycyclic hydrocarbons as well as the chemical reactions and biological involvement of these compounds. Since reviews are available on the biological formation and disposition of arene oxides[13] and on the chemical model systems for aryl hydroxylase-catalyzed formation of arene oxides,[14] these areas will be discussed only with the intention of designating the types of studies which have been done. An excellent discussion of the oxide-oxepin valence tautomeric equilibrium as well as many synthetic studies is available.[15] Synthesis of oxepins and hydro-oxepins and their occurrence in sugars, alkaloids, steroids, and terpenes is a broad subject beyond the scope of this article. Fortunately, an excellent and comprehensive review is available.[16] Oxepins will, therefore, be discussed only where appropriate. Brief mention of substitution of other elements for oxygen will be made and leading literature in these areas cited. Substitution of nitrogen for carbon in such compounds has been reviewed.[17]

II. SYNTHESIS

A. Substituted Benzene Oxides - Subsequent to the original report that 1-2 could be prepared by the dehydrohalogenation of 7 with a tertiary amine base, Vogel and co-workers[18] found that dry sodium methoxide in ether was an effective agent for this conversion. In addition, the action of alcoholates on 8 or of NaI on 16, prepared by bromination of 1,4-cyclohexadiene mono-oxide with N-bromosuccinimide have provided useful routes[19]



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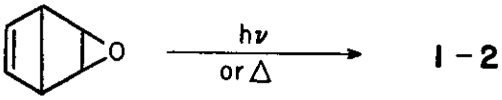
into 1-2. A novel approach to the synthesis of 1-2 has been through the thermolysis or photolysis[10] of 17, prepared by epoxidation of "Dewar benzene."



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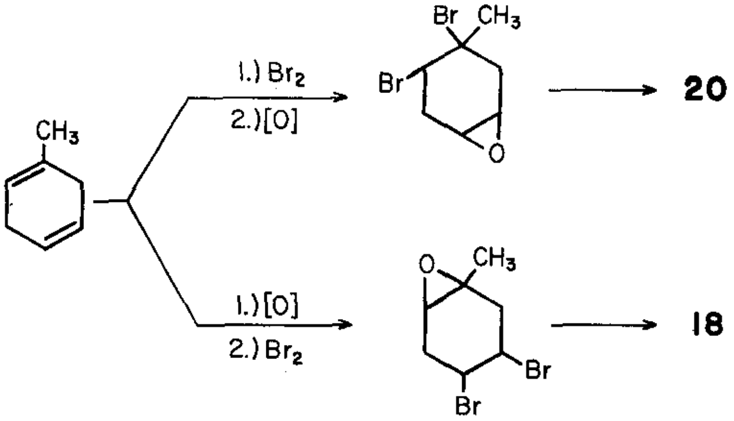
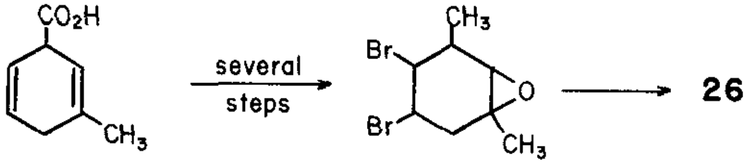
Substantial amounts of phenol are formed as well.

A wide variety of methyl-substituted benzene oxides have been prepared, through application of the Vogel's dehydrohalogenation route. The requisite substituted dibromocyclohexane epoxide precursors have been obtained via an initial Birch reduction of methylbenzenes or benzoic acids. A few typical examples of the general procedure are shown below, and the methylbenzene oxides synthesized to date are given in Table 1.

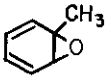
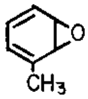
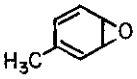
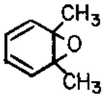
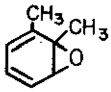
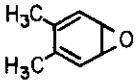
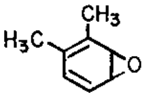
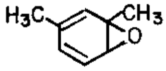
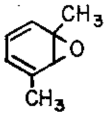
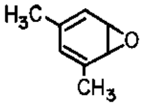
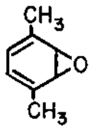
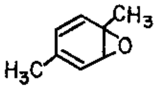
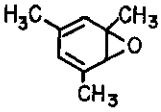


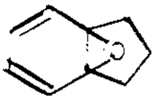


Methyl substitution on the oxirane ring leads to distinctly enhanced stability with regard to isomerization to phenols, while the converse is true for substitution at other ring positions. Because of high instability, several of the compounds in Table 1 have been prepared only in solution or in impure state. A precursor related to <u>8</u> has also been employed[15] in the synthesis of <u>18</u>.

In general, substitution of any group at the 3-position tends to enhance the contribution of the oxide tautomers, while 1-, 4-, or 1,2-substitution favors the oxepin form.[25] Thus, <u>18</u>, <u>20</u>, and <u>21</u> are principally or entirely oxepin, while <u>19</u> exists mainly as the oxide in nonpolar solutions. The effect of 1,2-methylene bridges on the position

TABLE 1. METHYL SUBSTITUTED BENZENE OXIDES

Structure	Name	Reference
	1-Methylbenzene oxide (18)	15
	3-Methylbenzene oxide (19)	21
	4-Methylbenzene oxide (20)	21, 22
	1,2-Dimethylbenzene oxide (21)	1, 15, 23
	1,6-Dimethylbenzene oxide (22)	21
	4,5-Dimethylbenzene oxide (23)	15
	3,4-Dimethylbenzene oxide (24)	21
	1,5-Dimethylbenzene oxide (25)	21
	1,3-Dimethylbenzene oxide (26)	21
	3,5-Dimethylbenzene oxide (27)	21
	3,6-Dimethylbenzene oxide (28)	21
	1,4-Dimethylbenzene oxide (29)	21, 24
	1,3,5-Trimethylbenzene oxide (30)	21



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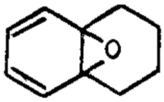

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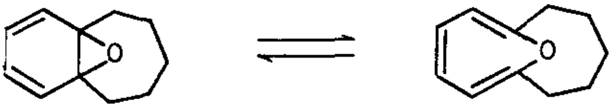

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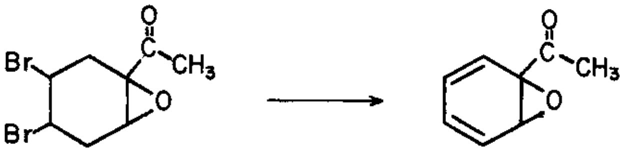
of the oxide-oxepin equilibrium has been examined. While tri- and tetramethylene bridges lock structures 31 and 32 in the oxide form, 33 is sufficiently free of strain to allow the presence of both forms.[15] In the absence of strain considerations, all three of these compounds should exist mainly or entirely as the oxepin forms. In general, low temperature and high dielectric strength media favor the more polar oxide forms when equilibria are present.[15] Preliminary molecular orbital calculations (CNDO/2)[26] are in accord with the spectroscopic studies on the equilibrium.

The dehydrohalogenation route which eliminates two equivalents of bromine (eg 7) has been employed to synthesize benzene oxides with substituents other than methyl. Two examples are 1-acetylbenzene oxide[15] (34) and 3-carbo-*t*-butoxybenzene oxide[27] (35). While 34 exists almost entirely



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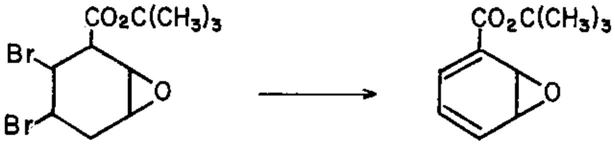
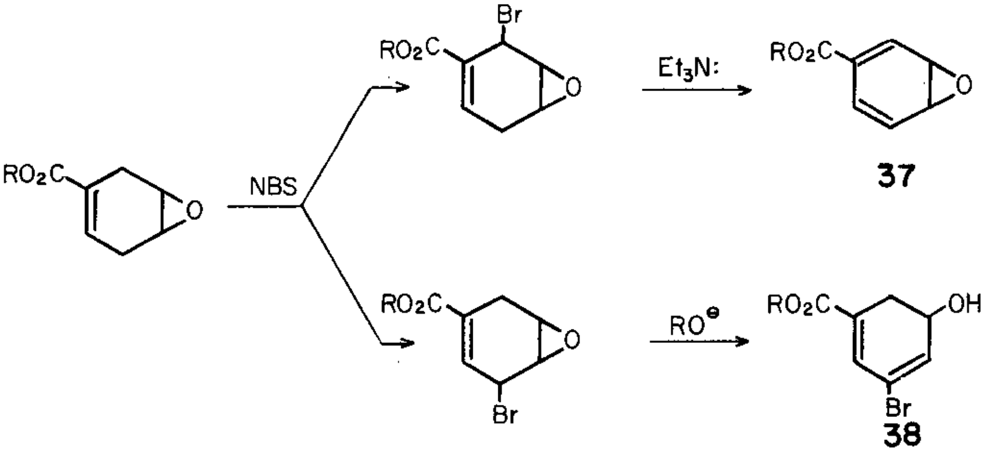


35

in the oxepin form, 35 has a substantial oxide contribution.[25] 3-Chlorobenzene oxide (36) can also be obtained in good yield by this route.[28] As with 35, a large amount of the oxide form is present in the equilibrium.

36

The dehydrohalogenation route which eliminates one equivalent of hydrogen bromide from precursors related to 8 has been successfully employed to prepare 4-carbo-*t*-butoxybenzene oxide[29] (37) and 4-chlorobenzene oxide[27] (39).



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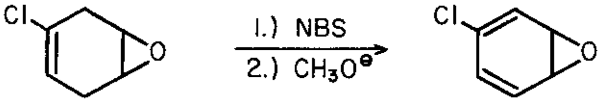
38

R = tertiary butyl



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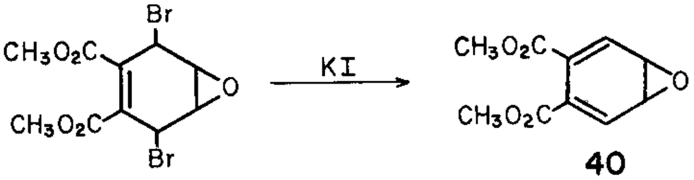
The free acid of 37 has been isolated,[27] and proved to be remarkably stable. One of the bromoisomers enroute to 37 failed to dehydrohalogenate with triethylamine, but could be isomerized to the "benzene hydrate" 38 by the action of potassium *t*-butoxide. The dehalogenation route which employs KI (cf., 16→1-2), has been used to prepare 4,5-dicarbomethoxybenzene oxide[15] (40).



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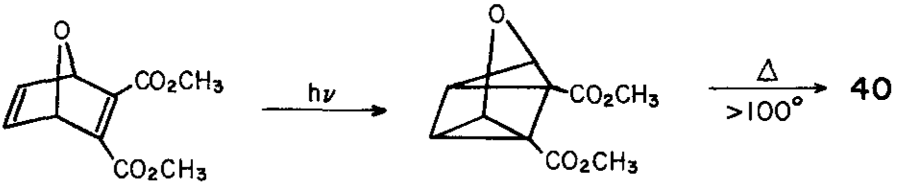
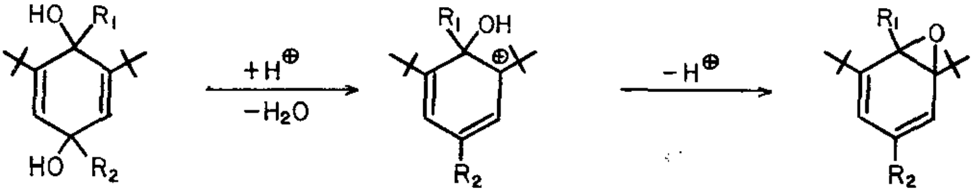
Synthesis of 40 has also been achieved through the elegant thermal route[30] shown below:



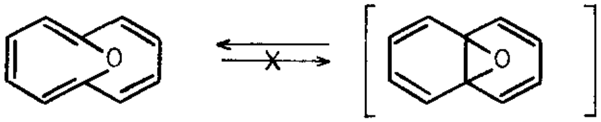
The success of this route rests in the high stability of 40. Another unique entry into highly substituted benzene oxides (41) has been via acid-catalyzed dehydration of 1,4-dihydroxy-1,4-dihydrobenzenes.[31] The



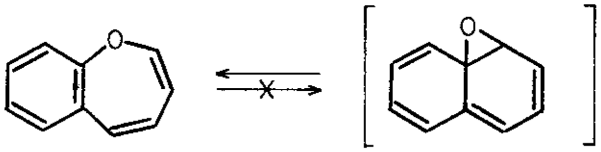
41

required heavy substitution pattern and the by-products limit the synthetic use of the method but do not detract from the mechanistic significance. The compounds (41) exist mainly as oxepins.

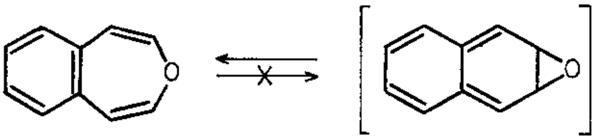
B. Arene Oxides and Oxepins of Naphthalene - The synthesis and chemistry of many substituted and partially reduced oxepins of naphthalene (benzoxepins) has been well reviewed.[16] Our purpose here is to highlight the current studies in the area. Potentially eight compounds (42-49) can be drawn for this system. However, as indicated below, only half of these can exist for any extended period of time because of the gain in resonance energy upon valence bond tautomerism to the indicated stable form. The



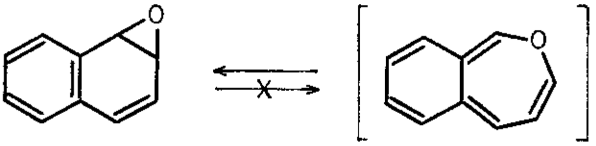
42 43



44 45

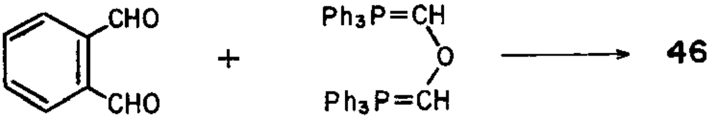


46 47

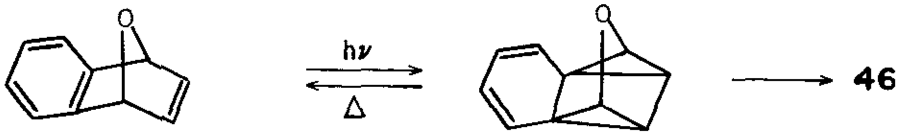


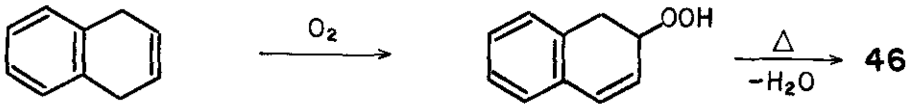
48 49

first member of this series to be described was 3-benzoxepin (46) by Dimroth and Phol[32] in an elegant application of the Wittig reaction on

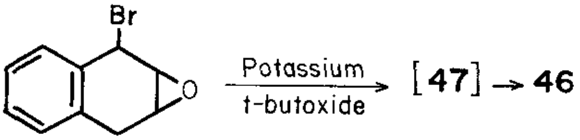


o-phthaldehyde. Subsequently a photochemical route related to the synthesis of 40 was described.[33] A unique hydroperoxide thermolysis

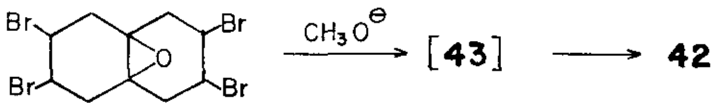




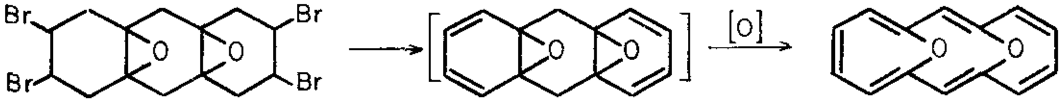
has also been observed to produce 46.[34] A dehydrohalogenation route to 46, presumably *via* transient formation of 47, has also been reported.[15]



Synthesis of 1,6-oxido[10]annulene (42) was achieved simultaneously[15] by two groups from the same tetrabromo precursor. A related dehydrohalogenation



route[15] has provided entry to 1,6; 8,13-bisoxido[14]annulene (50) in which the oxygen bridges are *cis*.



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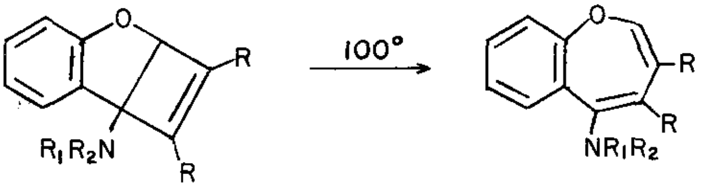
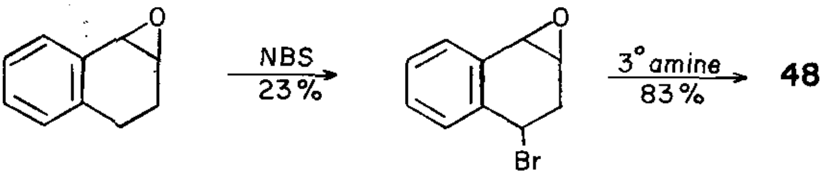
Mild treatment of the annulene 42 results in an "oxygen walk," presumably 43→45, to produce 1-benzoxepin (44).[15] This interesting "oxygen walk" phenomenon will be discussed in detail later. A thermal route to dialkylamino-derivatives (44a) of 44 has recently appeared.[35] The only arene oxide



44a

in the naphthalene series, naphthalene 1,2-oxide (48), was prepared[36] by NBS



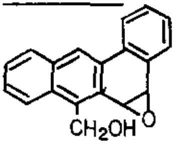
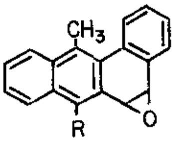
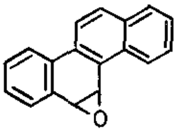
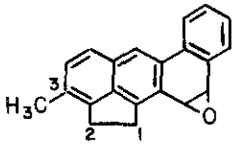
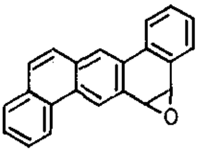
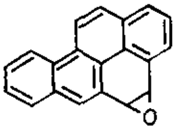
51 **52**

bromination of the tetralin epoxide 51 to provide 52 which smoothly dehydrohalogenated to 48. This general route has been widely applied to the synthesis of non-K-region arene oxides of polycyclic aromatic hydrocarbons. That 48 cannot be in equilibrium with the unstable 49 was proved[37] by the preparation of optically active 48 starting with optically active 51.

C. Arene Oxides of Polycyclic Aromatic Hydrocarbons - As with the previous section, much of the chemistry and synthesis of the oxepins of higher polycyclic hydrocarbons has been well reviewed.[16] Resonance stabilization demands that either the oxide or the oxepin form be the stable species. Valence bond tautomerism between the two forms can, therefore, only occur when sufficient energy is put into the system. All of the polycyclic arene oxides which have been synthesized will be described here. The two routes most commonly employed have been patterned after i) the general procedure developed by Newman[11] for closure of o,o'-biphenyldialdehydes (eg 10, 12, 13), to K-region arene oxides with Mark's reagent[12] or ii) the dehydrohalogenation method by which Vogel[36] synthesized naphthalene 1,2-oxide (48) from a tetralin bromoepoxide (52). The routes compliment each other in that the latter allows synthesis of non-K-region arene oxides via the elaboration of a polycyclic system in which the region of interest in the molecule is saturated and thus isolated, while the former takes advantage of the selectivity of osmium tetroxide for introduction of functionality at the K-region[38,39] of the aromatic system.

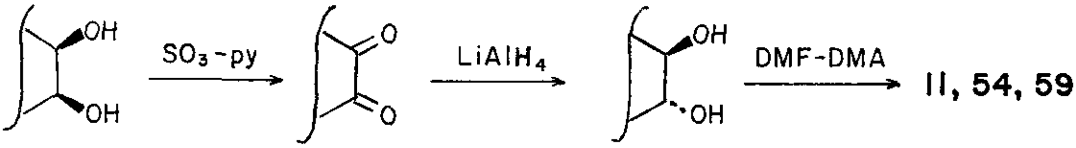
The synthesis of K-region arene oxides is relatively easy due to their considerably higher stability relative to non-K-region oxides. Most non-K-region oxides would not survive the warm to refluxing benzene solution employed for the condensation with tris-(dimethylamino)phosphine. In addition to the three K-region oxides originally prepared (11, 14, and 15),[40] seven other compounds are shown in Table 2. The yields in the reaction are generally high, but occasionally the desired products are accompanied by

TABLE 2. K-REGION ARENE OXIDES PREPARED BY THE NEWMAN METHOD

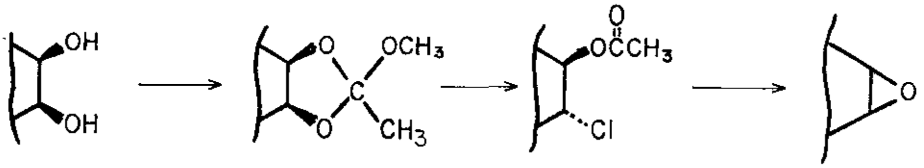
Structure	Reference
	
7-Hydroxymethylbenzo[a]anthracene 5,6-oxide[40] (53)	41
	
R = CH_3, 7,12-Dimethylbenzo[a]anthracene 5,6-oxide (54)	42, 43
R = CH_2OH, 7-Hydroxymethyl-12-methylbenzo[a]anthracene 5,6-oxide (55)	42
	
Chrysene 5,6-oxide (56)	44
	
3-Methylcholanthrene 11,12-oxide (57)	45
	
Dibenzo[a,h]anthracene 5,6-oxide (58)	46
	
Benzo[a]pyrene 4,5-oxide (59)	43
(see in addition structures 11,[43] 14, and 15)	11

polar, phosphorous containing by-products. While the initial attempt to prepare 54 failed,[11] more careful control of the conditions[42,43] for the condensation provided the compound in 75% yield. A controversy exists regarding the actual mechanism of the condensation.[47]

Occasional difficulties with the condensation step have prompted searches for more convenient means of obtaining K-region arene oxides. Thus, the recently described method of H. Neumann[48] for conversion of *trans*-diols to epoxides, with the dimethyl acetal of dimethylformamide (DMA-DMF), has been employed in the synthesis of 11, 54, and 59.[43] By this route, the *cis*-dihydrodiols obtained with osmium tetroxide are oxidized to *o*-quinones by SO_3-pyridine, reduced to *trans*-dihydrodiols with lithium aluminum hydride,[49] and then converted to the desired oxides with DMA-DMF. Although more steps are required and the overall conversions from *cis*-dihydrodiol are often substantially lower compared to the method using Mark's reagent, there are definite practical advantages to the route.[50] In one instance, substantial *cis*-dihydrodiol was formed during the lithium aluminum hydride reduction, and thus the overall yield of 54 was greatly reduced.



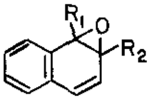
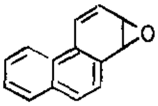
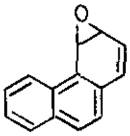
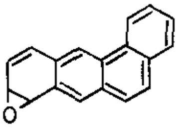
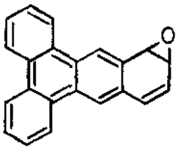
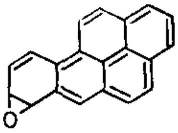
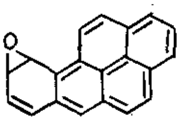
M. S. Newman and C. H. Chen[51] have reported the conversion of ortho esters of 1,2-diols into halohydrin acetates which can then be cyclized to epoxides with base. This procedure has recently proved highly successful



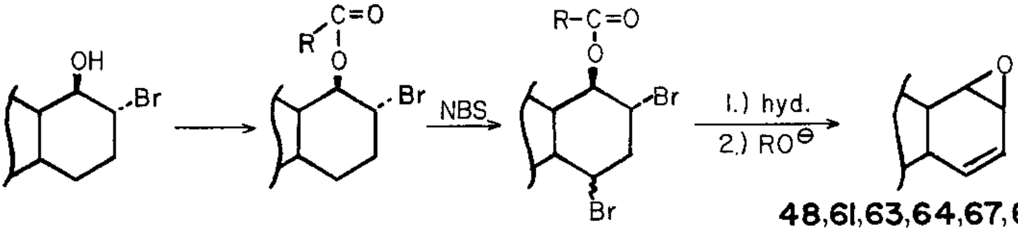
for the preparation of K-region arene oxides of phenanthrene (11), benzo[a]anthracene (14) and pyrene in our hands[52] and may indeed represent the best available procedure for the preparation of such compounds.

Two factors have caused considerable difficulty in the synthesis of non-K-region arene oxides by the general route (51→52→48) developed by Vogel[36] for the synthesis of naphthalene 1,2-oxide (48); i) certain of these oxides have lifetimes as short as a few minutes at room temperature (eg 67), and ii) the precursors analogous to 51 are often very unstable, a factor that severely limits the yields that are attained during the NBS bromination to form analogs of 52. Nonetheless, eight of the ten arene oxides in Table 3 have been generated by this procedure. Our initial interest in establishing an alternate route to non-K-region arene oxides was prompted by our inability[21] to prepare 61 by the original route. Numerous attempts to effect the bromination of 1-methyltetralin 1,2-epoxide with NBS led invariably to ketone and polymer. The same competing reactions have greatly limited the practicality of the syntheses of the designated eight compounds in Table 3. A procedure was sought to introduce functionality which was stable to the conditions of the NBS bromination, but which could be readily converted to the desired oxirane when necessary. Halohydrin

TABLE 3. NON-K-REGION ARENE OXIDES PREPARED BY THE VOGEL ROUTE[a] AND MODIFICATIONS THEREOF[b]

Structure		Reference
	Naphthalene 1,2-oxide (48)	36[a], 53[b]
	2-Methylnaphthalene 1,2-oxide (60)	21[a]
	1-Methylnaphthalene 1,2-oxide (61)	53[b]
	1,2-Dimethylnaphthalene 1,2-oxide (62)	21[a]
	Phenanthrene 1,2-oxide (63)	53[a,b]
	Phenanthrene 3,4-oxide (64)	53[b]
	Benzo[a]anthracene 8,9-oxide (65)	54[a]
	Dibenzo[a,c]anthracene 10,11-oxide (66)	55[a]
	Benzo[a]pyrene 7,8-oxide (67)	53[b], 56[a]
	Benzo[a]pyrene 9,10-oxide (68)	53[b], 56[a]

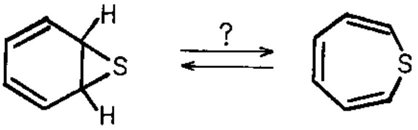
esters proved remarkably useful in this respect.[53] They are completely stable to the bromination conditions and the desired oxides are readily generated as indicated below:



48,61,63,64,67,68

The overall yields of oxide from any given precursor are much higher and all of the reactions are easily carried out.[53]

D. Compounds Related to Arene Oxides and Oxepins – The closest analogs to benzene oxide–oxepin (1–2) are the corresponding thio compounds, benzene sulfide (thianorcaradiene)-thiepin (69–70). Much of the interest

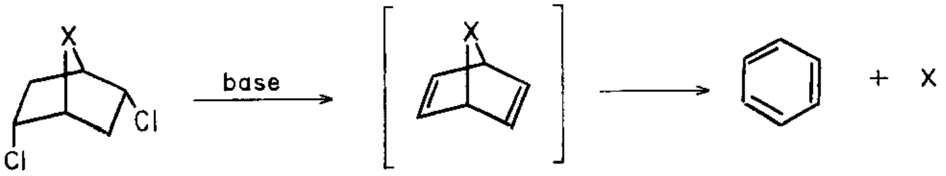


69 **70**

in the system stems from calculations[57] which predict the heterocycle to be slightly antiaromatic. Although a number of substituted derivatives of 70 have been prepared,[16] the parent system is unknown. An approach to the synthesis of 69–70 starting from the thio analog of 7 (71) produced only benzene,[58] presumably by the extrusion of sulfur which could be detected

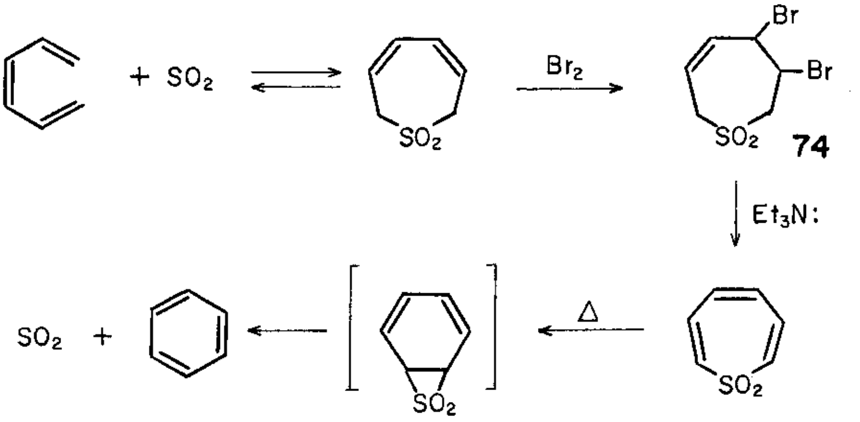
71

as a product. In a like manner, attempts to prepare the thio or thioxide analogs of norbornadiene by dehydrohalogenation of 72 and 73 produced benzene and the corresponding sulfur moiety.[58] Nonetheless, a related route



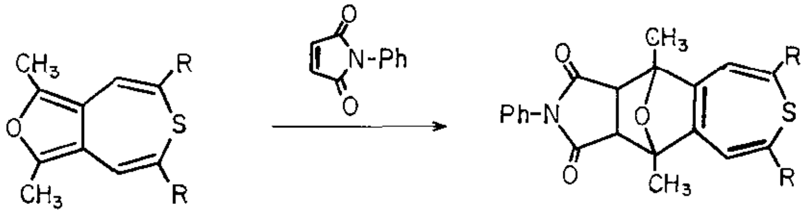
72, X = S
73, X = SO

from the dibromide 74 had provided entry to thiepin 1,1-dioxide (75) which



75

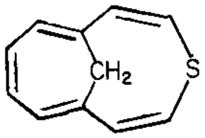
is stable at room temperature, but loses SO_2 on warming.[59] The simplest thiepin (77) known to date was prepared through the Diels-Alder reaction between a furanothiepin (76) and N-phenylmaleimide.[60] The success of the procedure and the stability of the molecule were presumed the result of avoiding the presence of sulfur in a three membered ring, a situation from which sulfur readily extrudes. For this reason, the synthesis of naphthalene 1,2-sulfide and related compounds may not be possible. The abundant literature on the annulated thiepins related to 44 and 46 has been well reviewed.[16] Even bridged annulenes, such as 4,9-methanothia-[11]annulene (78), are known.[61] In general, thiepins contrast oxepins in that thiophenols almost never form by isomerization but instead the sulfur moiety is readily eliminated.



76

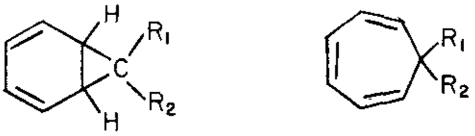
R = $C(CH_3)_2OH$

77



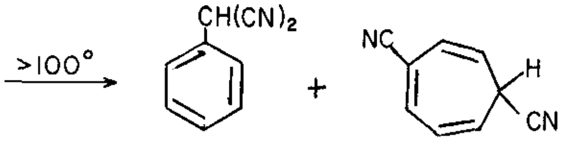
78

Detailed discussion of the analogs of 1-2 in which carbon or nitrogen replace the oxygen atom are beyond the scope of this review. However, the general aspects of the chemistry of these systems as they relate to 1-2 will be briefly discussed. The norcaradiene-cycloheptatriene (79-80) problem has been the subject of an excellent review.[62] When the substituents R_1 and R_2 are hydrogen or trifluoromethyl groups, only the cycloheptatriene



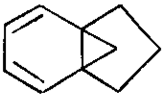
[79]		80	$R_1 = R_2 = H$
[81]		82	$R_1 = R_2 = CF_3$
83		[84]	$R_1 = R_2 = CN$
85	$\rightleftharpoons$	86	$R_1 = CN$, $R_2 = CF_3$

forms (80 and 82) are known. Conversely, when $R_1 = R_2 = CN$ only the norcaradiene structure (83) can be detected. However, substitution of CN and CF_3 at this position allows observation of both forms (85–86) at low temperature, with the cycloheptatriene 86 predominating at all temperatures.[63] In analogy to the conversion of 1 to phenol, 83 is converted[64] to phenylmalononitrile (87) along with the rearranged and ring expanded

83


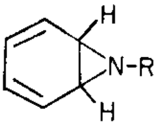
87 88

product 88. In analogy to 31, 89 exists as the norcaradiene form,[65] while compounds with longer methylene bridges exist as cycloheptatrienes [62] (cf. compound 33).

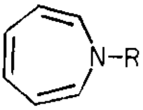


89

The benzene imine (azanorcaradiene)-1*H*-azepin (90-91) system has been recently reviewed.[66] Only compounds with substituents other than hydrogen

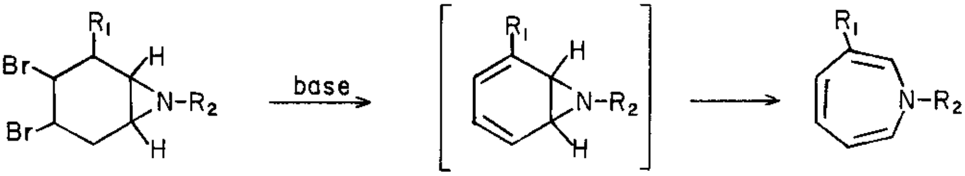


90

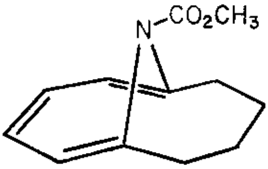


91

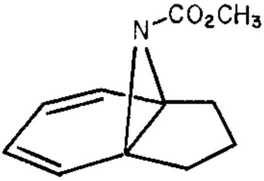
at the 1-position are known. Although aromatic compounds react directly with nitrenes to yield azepins, the best route to substituted azepins is *via* aza analogs[67] of compound 7 as illustrated below:



Only when special structural factors are present, such as constraining methylene bridges, can the imine forms be prepared (eg 92 and 93).[66] Situations where equilibria are present between the generalized forms 90 and 91 are unknown. Furthermore, such interconversions require

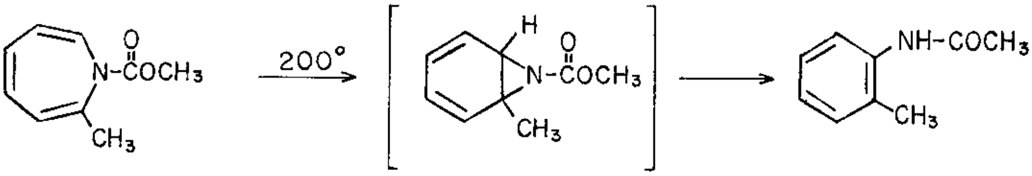


92



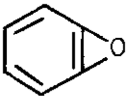
93

considerably more energy than the previous analogs of 1-2 discussed. Nonetheless, isomerizations parallel to the conversion of 1-2 to phenol are known[68] as indicated by the conversion of 94 to the aromatic urethane 95. Surprisingly, synthesis of a simple aziridine at the K-region of a polycyclic aromatic hydrocarbon has not yet been reported.



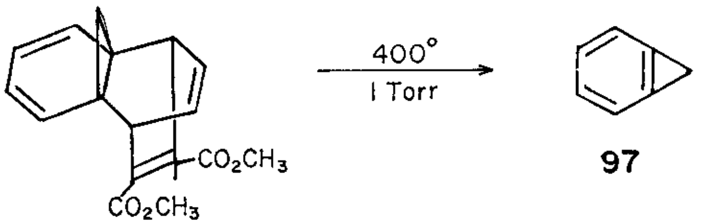
94 **95**

A unique analog of 1 is the unknown "benzyne oxide" (96). On first

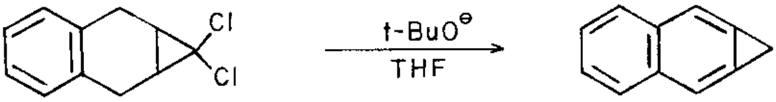


96

consideration, 96 appears too strained to have a finite lifetime, yet there are several instances where oxirenes have been postulated as reaction intermediates.[69] Benzocyclopropene (97)[70,71] and naphtho[b]cyclopropene (98)[72] are known, stable compounds[c]. The only reported attempt[73] to

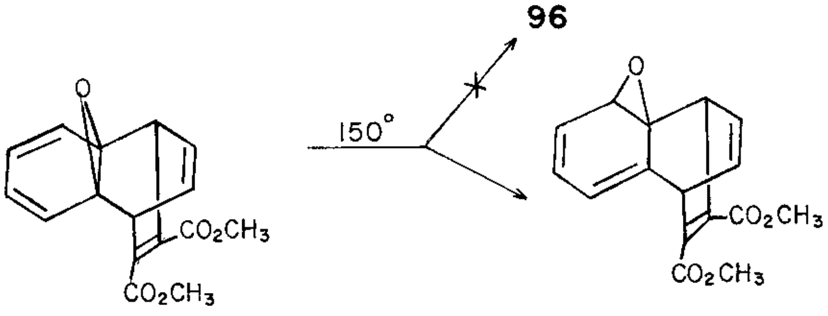


97



98

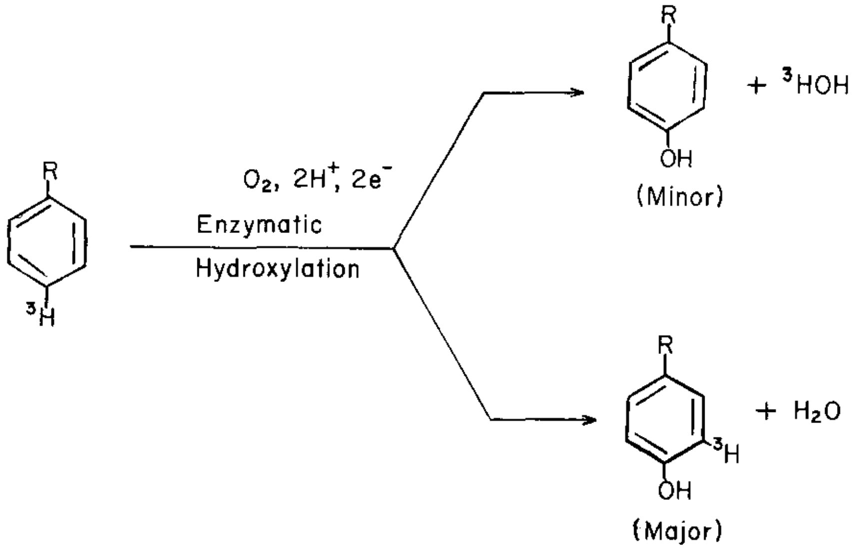
synthesize 96 was patterned after the successful preparation of 97,[70] but resulted instead in the "oxygen walk" product 99.



99

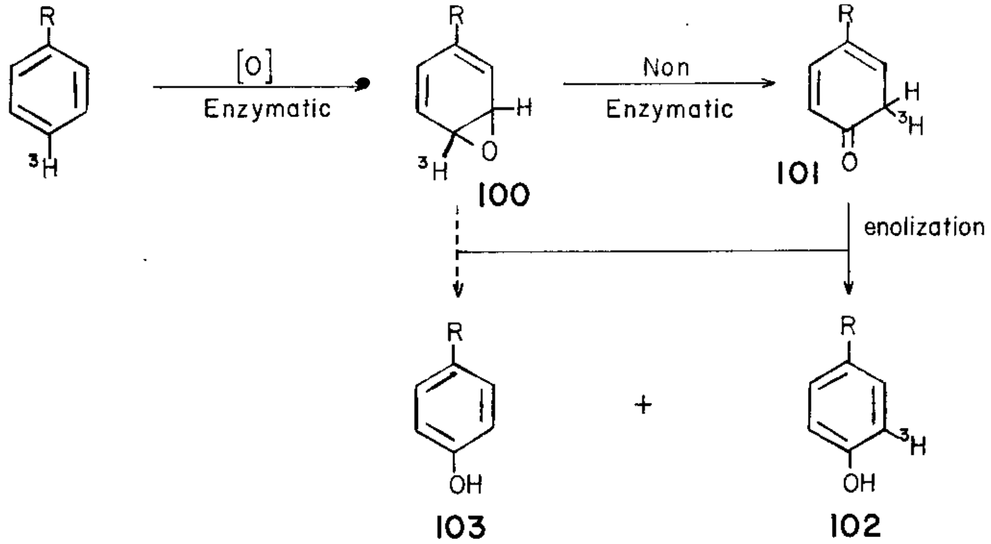
III. THE "NIH SHIFT" — ISOMERIZATION OF ARENE OXIDES TO PHENOLS

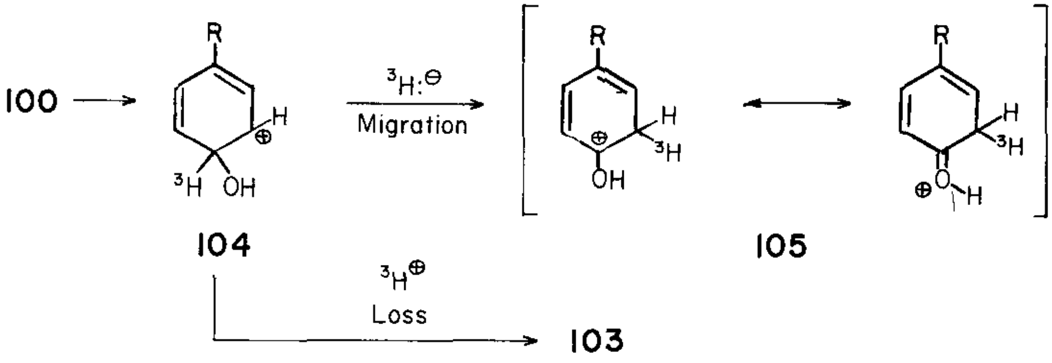
A. Hydroxylation Induced Migrations - Attempts in these laboratories during the mid 1960's to develop simple radiometric assays for the monooxygenase enzymes which hydroxylate aromatic rings were based on the assumption that tritium at the site of hydroxylation in the substrate would be released into the medium. Remarkably, this assumption proved to be incorrect. The majority of the tritium migrated to an adjacent ring position and was retained in the final product as shown:



Retentions of tritium greater than 95% have been observed. In addition to the migration and retention of the heavy isotopes of hydrogen, halogen and alkyl groups have been demonstrated to migrate during these enzyme-catalyzed reactions. The extremely novel nature of these reactions prompted naming them the "NIH Shift" in commemoration of the National Institutes of Health at which the reaction was discovered. A comprehensive review of these studies is available.[13]

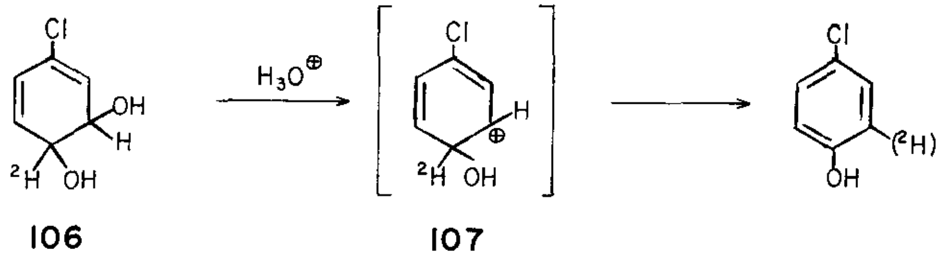
Since the class of enzymes, which catalyze the "NIH Shift" is so important to many of the synthetic and degradative pathways in mammals as well as being responsible for the detoxication of foreign substances, an intimate understanding of the mechanism(s) by which these oxidations occur was essential. As a working hypothesis, arene oxides were assumed to be intermediates in the reaction. The initially formed arene oxide would isomerize to the keto form of the product phenol (100→101) in a pinacol type rearrangement. Enolization of the keto-phenol (101) to either labeled (102) or unlabeled (103) product would determine the degree of migration and retention. Participation of a direct pathway between the arene oxide (100) and unlabeled phenol (103) was also possible. Carbonium ions seemed the most likely species to account for the various steps in the mechanism. The driving force for the "NIH Shift" in the conversion of 104 to 105 is the added stability which results from charge delocalization





104 105 103

onto oxygen. Support for this mechanism came with the finding that 106



106 107

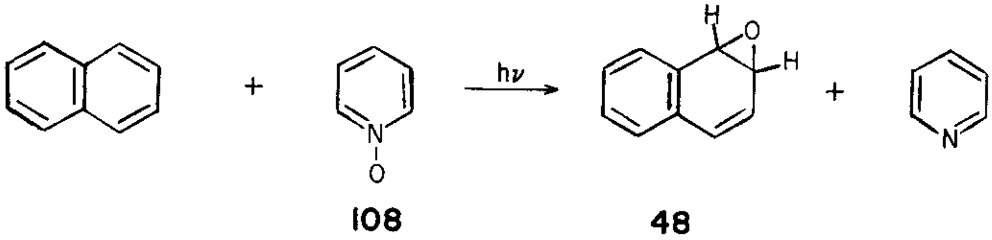
dehydrated to p-chlorophenol via 107 with 25% deuterium retained.[74]

The study of model systems for enzymatic hydroxvlation of the aromatic ring was greatly influenced by the "NIH Shift." Model systems which do not show the "NIH Shift" must operate by mechanisms unrelated to the enzyme-catalyzed reactions. Examination of the most often cited model systems (Fe(II), ascorbate, O_2; Fe(II), H_2O_2; Fe(III), catechol, H_2O_2) showed them not to be relevant, and a search was undertaken for new models which would function as oxygen atom transfer agents, form arene oxides, and cause the "NIH Shift." A number of qualifying systems have been found and are listed in Table 4. One of the most interesting of these systems is the

TABLE 4. OXIDANTS WHICH CAUSE THE "NIH SHIFT"

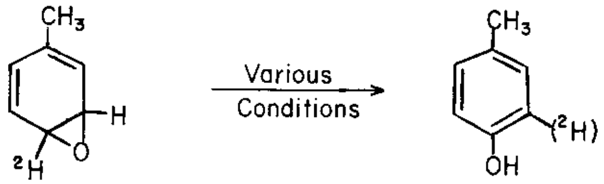
System	Reference
Peroxyacid	75, 76
Sn(II), O_2	77
Pyridine-N-oxide, hν (and related compounds)	78
N_2O, hν	78
t-Butylperoxide, $Mo(CO)_6$	78
Carbene, O_2	78
$CrO_2(OAc)_2$	79

photolysis of aza-aromatic-N-oxides.[78] The conditions are sufficiently mild that naphthalene 1,2-oxide (48) could be isolated when pyridine-N-oxide (108) was irradiated in the presence of naphthalene. The reaction would be of



substantial preparative value for polycyclic arene oxides if conditions were established to obtain high yields. The formal analogy between the reactions of carbenes or nitrenes and the model systems and enzymes which they emulate has prompted these oxygen atom transfer oxidations to be considered as "oxene" or "oxenoid" reactions.[80,81] A detailed discussion of the mono-oxygenase enzymes and the model systems for them is available.[14]

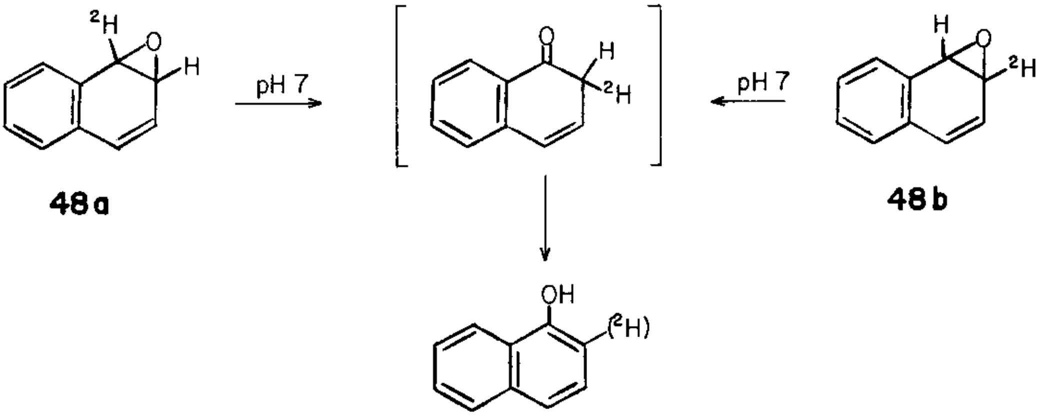
B. Rearrangements Accompanying Isomerization of Arene Oxides - Further evidence that arene oxides mediate the "NIH Shift" was obtained on examination of the deuterated toluene oxide 20a. Rearrangement to *p*-cresol under



40-85% Deuterium retained

20a

a variety of conditions established that as much as 85% of the deuterium migrated and was retained.[22] Rearrangement of the deuterated naphthalene oxides 48a and 48b provided similar information.[82] Since the same retention



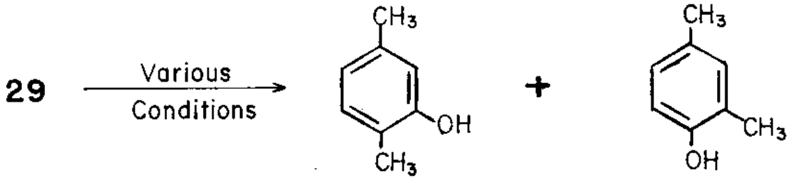
48a

48b

80% Deuterium retained

of deuterium in the 1-naphthol (80%) was observed for either oxide, a common intermediate was required; the keto form of 1-naphthol. The absence of a competing direct loss pathway for the oxides at pH 7 allowed calculation of a value of $k_H/k_D \sim 4$ for the enolization to 1-naphthol. Variation of retention as a function of pH for isomerization of 48a and 48b to 1-naphthol indicated that different mechanisms were operative at the two extremes of pH.[82]

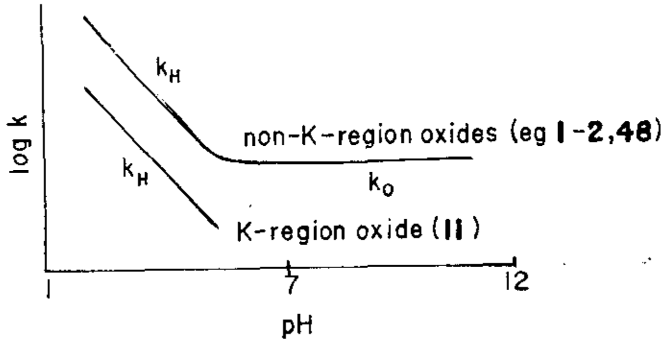
Rearrangements of methyl-substituted arene oxides provided further evidence for a multiplicity of pathways for this reaction. Examination of the ratio of 2,5-dimethylphenol (109) to 2,4-dimethylphenol (110) obtained on isomerization of 1,4-dimethylbenzene oxide (29) as a function of pH[21,24] showed the product resulting from methyl migration to be



109 110

predominant in the neutral to basic region while the reverse was true in acid.

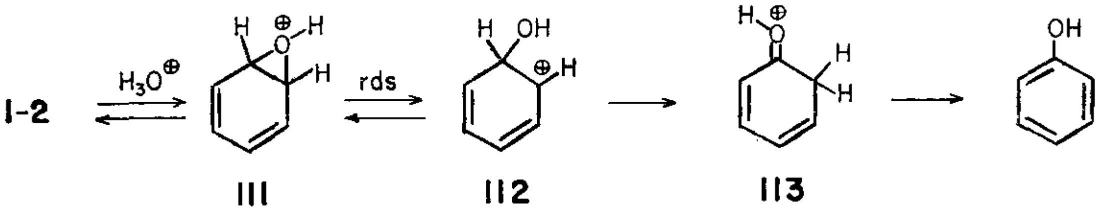
C. Mechanisms of Isomerization - Careful examination of the kinetics of isomerization of benzene oxide (1-2) and naphthalene oxide (48) by Kasperek and Bruice[83] proved the existence of two distinct pathways for aromatization. Plots of log k for the disappearance of arene oxide versus pH showed both acid-catalyzed (k_H) and spontaneous pathways (k_o) were operative. In the case of the relatively stable K-region oxide of



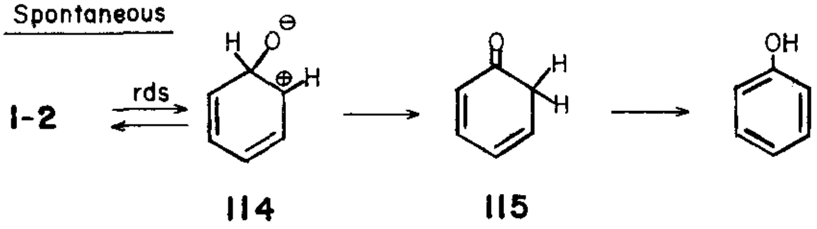
phenanthrene (11), only a k_H pathway could be detected. None of the three substrates showed general acid catalysis at pH 3.77 with acetic acid. Similarly, 48 failed to show general acid catalysis with either imidazole or phosphate at pH 7. Change of solvent from water ($\mu = 1.0$, 30°) to 30% ethanol ($\mu = 0.1$, 30°) decreased the rate of acid-catalyzed isomerization (k_H) of 11 and 48 by a factor of 4.3. For the spontaneous isomerization (k_o) of 48 (0.01M KOH), an $E_{act.} = 14.0 \pm 0.1$ kcal/mole in the temperature range of 20°-50°, a $\Delta S^{\ddagger} = -25.7 \pm 0.3$ eu at 30°, and a solvent kinetic isotope effect of $k_o^{H_2O}/k_o^{^2H_2O} = 1.33$ at 30° were observed. Several possible mechanisms were considered, but a clear choice between stepwise and concerted pathways for the k_o and k_H reactions was not possible from these studies.

Examination of the kinetics of isomerization of a variety of substituted arene oxides did, however, allow assignment of mechanisms for the k_H and k_o pathways.[84] Separate Hammett plots of log k_o or log k_H versus sigma (σ) were linear with rho (ρ) equal to approximately -7 for benzene oxide (1-2), 4-methylbenzene oxide (20), 4,5-dimethylbenzene oxide (23), and 4-chlorobenzene oxide (39). Furthermore, the rates of isomerization (k_o and k_H) of perdeuterobenzene oxide and 1-^{2}H-naphthalene 1,2-oxide (48a), for which all of the deuterium must either migrate or be lost, were essentially identical to those of the normal hydrogen compounds. The lack of a primary kinetic isotope effect and the large negative ρ value observed for the aromatization of the substituted benzene oxides provide strong evidence in favor of a developing positive charge in the transition state without H(^{2}H) transfer for both the spontaneous and acid-catalyzed isomerization of arene oxides to the corresponding phenols. The mechanisms compatible with all the data are shown below for the isomerization of 1-2 (rds = rate determining step);

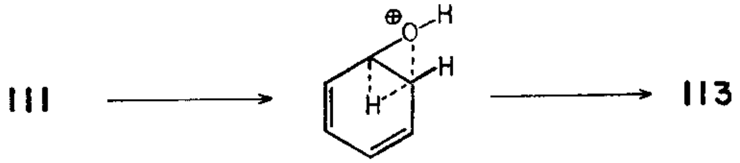
Acid catalyzed



Spontaneous



The only disconcerting piece of data with regard to these mechanisms is the relatively high $\Delta S^{\ddagger}$ of ~ -27 eu measured for 29[85] and 48[83] in the spontaneous region; a value suggestive of a concerted, highly ordered transition states such as 116 and 117.



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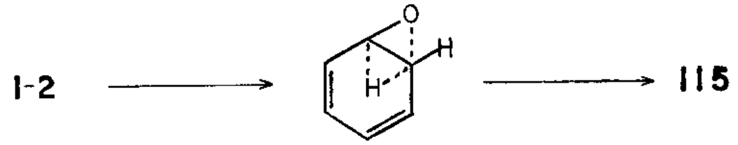


117

However, the differences between 112 and 116 and between 114 and 117 is only a matter of the timing of the migration. The ordering of solvent around 112 and 114 could explain the large negative $\Delta S^{\ddagger}$ as well. Rates of isomerization for the arene oxides measured to date are presented in Table 5.

D. Directed Openings of Arene Oxides - Unsymmetrical arene oxides can undergo isomerization to either of two phenols or to a mixture thereof. Results to date suggest that the energy differences between the alternate cleavages of the oxirane ring are relatively small, and minor environmental or structural changes can cause large shifts in product distribution. Although some quantitative studies are available for individual compounds, the generalities based on them must be, at present, considered qualitative. Unusual solvolysis and isomerization products will be treated in the next section.

TABLE 5. RATES OF ISOMERIZATION OF ARENE OXIDES[a]

Arene Oxide	$k_H (M^{-1} sec^{-1})$	$k_o (sec^{-1})$	Ref.
Benzene oxide (1-2)	3.89	2.74×10^{-5}	83,84
	32^b	1.33×10^{-3b}	
1-Methylbenzene oxide (18)	105	5.20×10^{-4}	84
3-Methylbenzene oxide (19)	96	9.0×10^{-3}	84
4-Methylbenzene oxide (20)	470	1.53×10^{-2}	84
4,5-Dimethylbenzene oxide (23)	4070	5.28×10^{-2}	84
4-Chlorobenzene oxide (39)	0.50	2.9×10^{-5}	84
1,4-Dimethylbenzene oxide (29)	530 & 730^c	4.8×10^{-3}	85
Indane 8,9-oxide (31)	1410^c	1.4×10^{-3}	86
Naphthalene 1,2-oxide (48)	450^b	2.85×10^{-3b}	83,84
	110^d	4.2×10^{-4d}	
Phenanthrene 9,10-oxide (11)	130		83
	30^d		

---

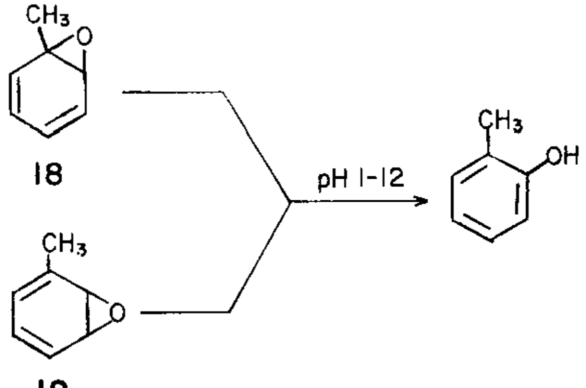
a) Measured in 50% dioxane-water, $\mu = 0.1$ in KCl at 30° unless otherwise noted.

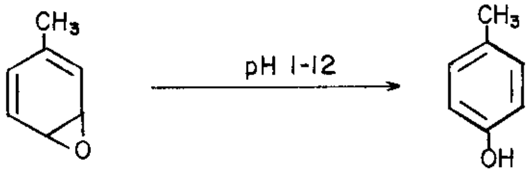
b) Measured in water, $\mu = 1.0$ in KCl at 30°.

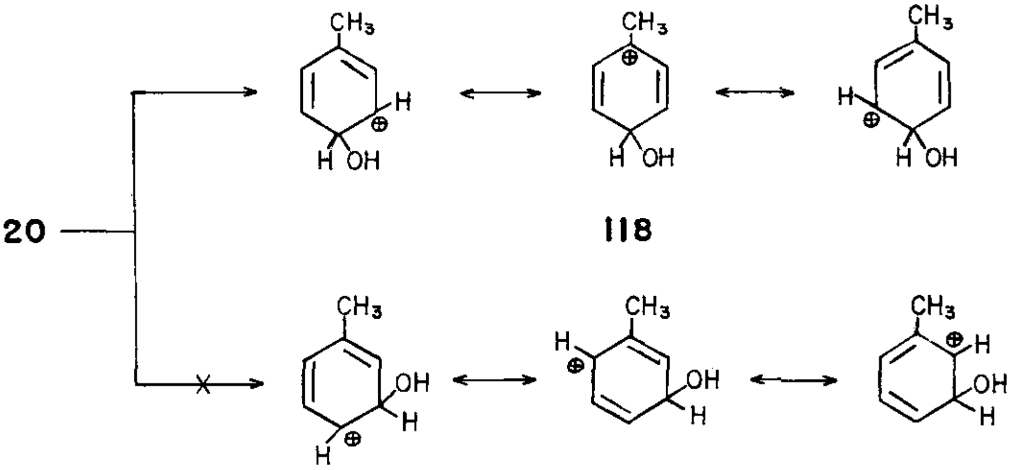
c) Consult section III,E for the significance of these rate constants.

d) Measured in 30% ethanol-water, $\mu = 0.1$ in KCl at 30°.

Consideration of the phenols which result on isomerization of the methyl-substituted benzene oxides in Table 1 has established the fundamental principles which underlie these reactions.[21] The three oxides of toluene (18, 19, and 20), the oxide of mesitylene (30), and 1,3-dimethylbenzene oxide (26) all give rise to only one of the two potentially possible phenols when isomerized at pH 1-12 as illustrated below for the toluene oxides. These highly selective isomerizations are best explained on the basis of carbonium ion stability in the rate determining step. For example, consider the canonical contributors to the two possible sets of ions resulting on acid catalyzed opening of 20. Only the top set, which leads to *p*-cresol, contains a tertiary carbonium ion (118)

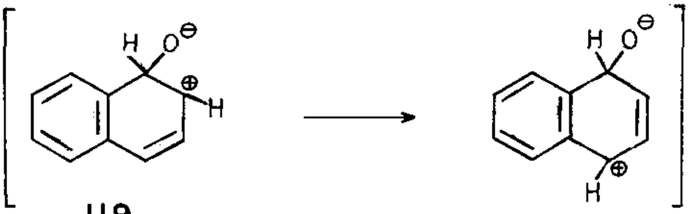






and is thus a more stable set of contributors. The generalization that the ion with the maximum number of tertiary contributors will be determinant in establishing the product distribution applies for all the compounds of Table 1. A similar line of reasoning explains the formation of *p*-chlorophenol from 4-chlorobenzene oxide (**39**),[28] *o*-chlorophenol from 3-chlorobenzene oxide (**36**),[28] and the *meta*-phenol from 4-carbo-*t*-butoxybenzene oxide (**37**).[29]

Isomerization of naphthalene oxide (**48**) should produce only 1-naphthol since opening in this direction leads to two contributors (**119** and **120**)



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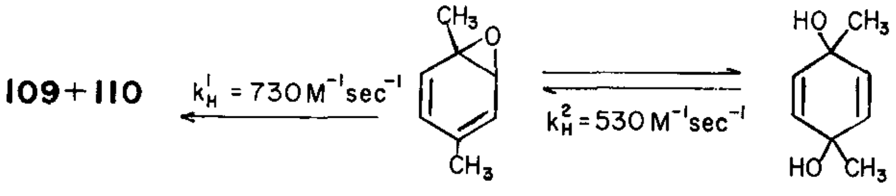
120

which do not disturb the aromaticity of the adjacent ring while only one such contributor is available for opening to 2-naphthol. The product distribution fits these predictions for the k_o reaction, but in acid approximately 10% of 2-naphthol is formed.[86] The basis of this change in product distribution is presently unclear. Careful studies on the distribution of phenols from the arene oxides of other polycyclic hydrocarbons have yet to be done.

Rearrangement of 3,4-dimethylbenzene oxide (24) was expected to produce equal amounts of 2,3- and 3,4-dimethylphenol since the alternate openings of the epoxide ring both produce one tertiary carbonium ion contributor. However, the 2,3-dimethylphenol is only a minor product and varies from 11% to 23% as the pH of the rearrangement medium is increased.[21] As indicated in section IIIB, the ratio of phenols (109 and 110) resulting from direct opening and methyl migration for 1,4-dimethylbenzene oxide (29) was also strongly pH dependent.

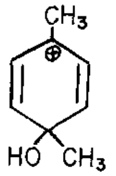
E. *Solvolysis and "Oxygen Walks"* - In contrast to other arene oxides, the K-region oxides of polycyclic hydrocarbons such as 11 and 59 behave like simple epoxides in that they are fairly readily hydrated to *trans*-diols in water.[43,88] Related solvolysis reactions have been recently observed during the study of the mechanism of isomerization of benzene oxide derivatives. When the kinetics for the disappearance of 29 were followed



29

121

in the acid region, phenols continued to form after all the substrate had been consumed.[85] The origin of these phenols, which represented approximately 40% of the total phenols formed, was traced to the extremely unstable *cis*- and *trans*-diols 121 which had accumulated in the medium. Formation of 121 is due to the high stability of carbonium ion 122 and its resonance contributors. Indeed, 121 exchanges its hydroxyl groups with solvent water much faster than it aromatizes. The same remarkable solvolysis was observed during rearrangement of indane 8,9-oxide (31), with the *cis* and *trans*-diols 123 being formed at low pH.[86]



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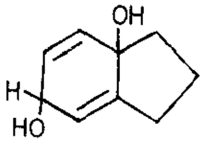

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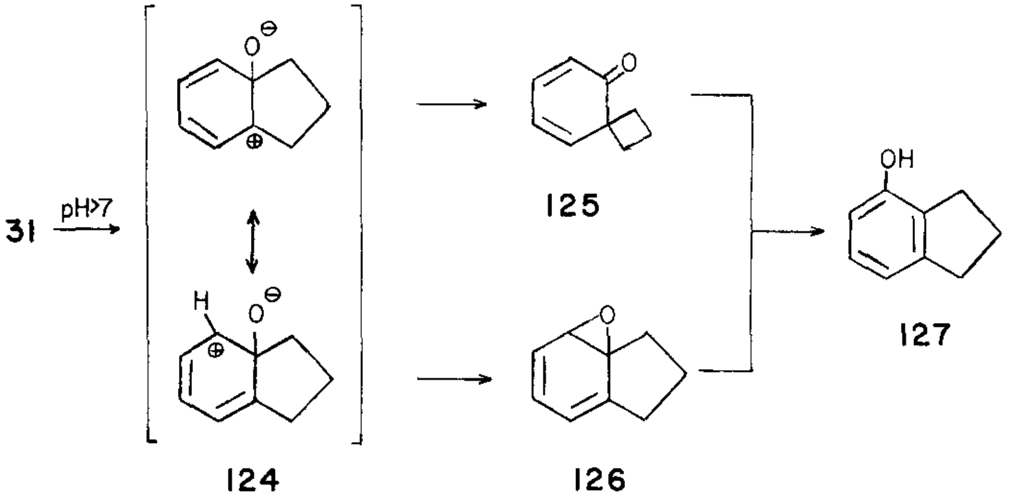
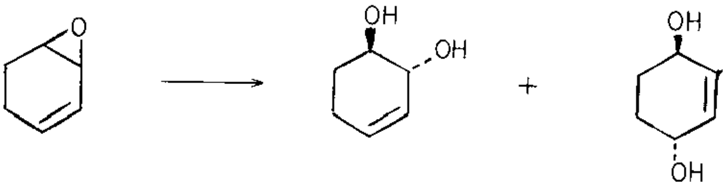
The isomerization of indane 8,9-oxide was even more intriguing, since in order to explain the kinetics, it was necessary to invoke an "oxygen walk" *via* carbonium ion 124 to the new arene oxide 126 which opens selectively



to 127. Only 30% of the 127 was formed in the spontaneous region *via* dienone-phenol rearrangement of the spiroketone 125. The rearrangement products obtained from the methyl-substituted benzene oxides 21, 22, and 27 were also suggestive of "oxygen walks" and diol formations,[21] but studies of mechanism for these rearrangements have yet to be done. Simple allylic epoxides such as 128 are hydrated to diols (129 and 130) in a reaction

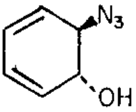


128 129 130

which shows buffer catalysis.[89] Notably, buffer catalysis has not been detectable for any of the arene oxides examined thus far. Thermally induced "walk reactions" have been detected for cycloheptatrienes,[90] azepins,[66] 8,16-oxido-[2.2]metacyclophane-1,9-diene and its N-methyl analog,[91] and the oxido-annulene 42,[15] as well as a photoinduced "walk reaction" for a diazepin.[92]

IV. REACTIONS OF ARENE OXIDES

A. *Addition of Nucleophiles* - Isomerization to phenols and reaction with nucleophiles are two of the most common reactions of arene oxides. Nucleophilic opening reactions were first encountered in the reaction of the thiol group of the cysteine in the tripeptide glutathione (GSH) with benzene oxide (1-2),[93] naphthalene oxide (48),[80] and the K-region oxides of higher polycyclic hydrocarbons.[94] This addition is enzyme-catalyzed and will be discussed later in more detail. The addition of a variety of simple nucleophiles to arene oxides has been studied. Both sulfide and azide readily add to 1-2, while NH_2^- failed to react.[95] The dimer



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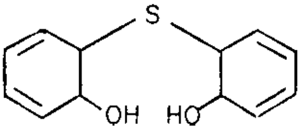
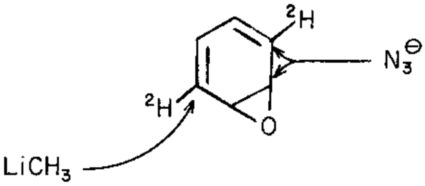


132

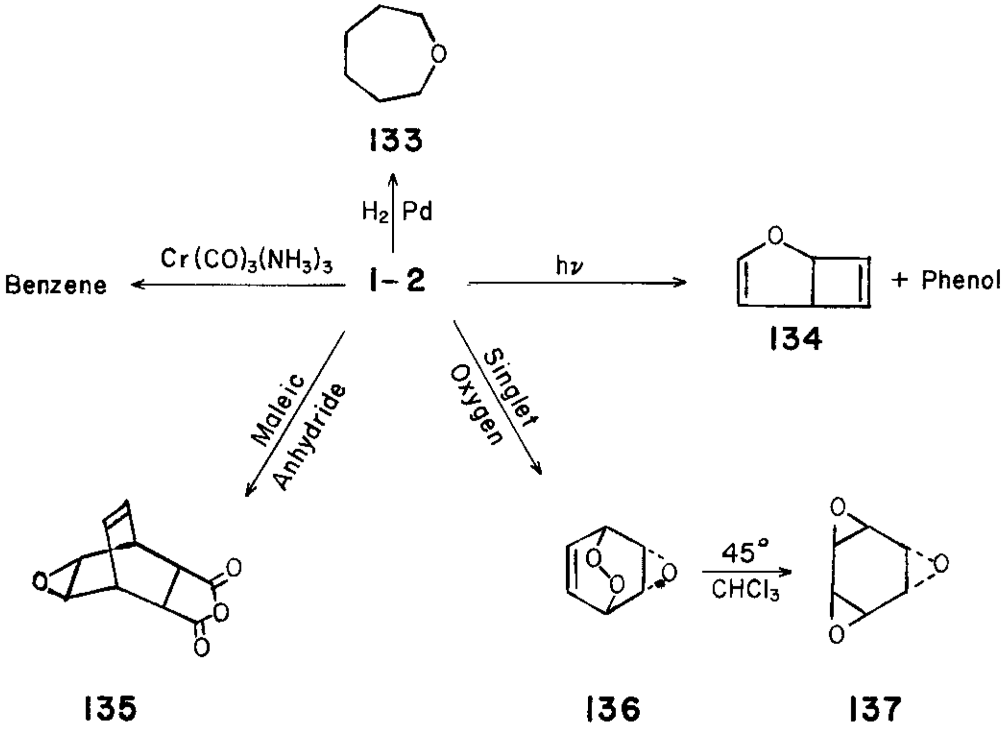
resulting from sulfide addition (132) is a mixture of the two *trans*-*trans*-diastereomers in which direct 1,2-opening has occurred on each molecule of 1-2.[96] Azide addition to yield 131 occurred by both *trans* 1,2-opening and *trans* 1,6-opening as shown with the 3,6-dideuterobenzene oxide (1-2a).[96] Methyl lithium adds *cis*-1,6 [97] while dimethylmagnesium adds both



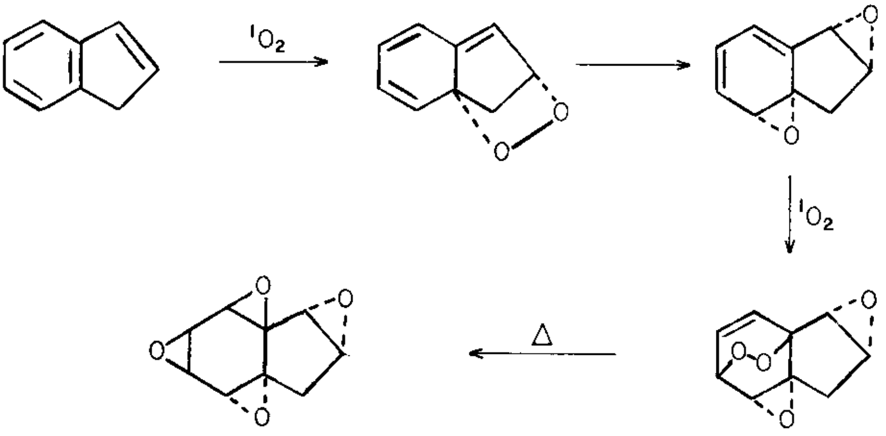
1-2a

cis-1,6 and *trans*-1,2.[96] Attack of thiocyanate[96] on 1-2 produced benzene, presumably *via* 69. Reduction of 1-2 to "benzene hydrate" with lithium hydride[15] and the alkylation of pyridines[98] by K-region arene oxides have been reported. Reactions with soft and polarizable nucleophiles such as thiols and azide are most facile. Phenoxide reacts slowly as an ambident nucleophile in that products resulting from attack both by carbon and by oxygen are produced.[96]

B. Miscellaneous Reactions - Although the principal reactions of arene oxides are isomerization to phenols and attack by nucleophiles, a number of other interesting transformations have been observed. Typical examples of these are illustrated below for benzene oxide-oxepin (1-2), the most studied cogener. Reactions typical of the oxepin tautomer 2



are metal catalyzed reduction to oxepane (133) and photocyclization to the bicyclic compound 134.[15] A related structure is obtained on photolysis of cyclooctatetraene oxide.[99] Alkali metal reduction of 1,2-dimethylbenzene oxide (21), a compound which exists as the oxepin, results in cleavage to 4-octene-2-one.[100] In analogy to the extrusion of sulfur from 69, benzene is formed from 1 on treatment with phosphines or a chromium complex.[15] Tautomer 1 shows typical diene reactions in the formation of Diels-Alder adducts[15] (135) and, quite interestingly, in reaction with singlet oxygen to produce the peroxide 136.[101] Warming the peroxide to 45° results in isomerization to *trans*-benzene trioxide (137). A related series of reactions occur when singlet oxygen reacts with indene[102] to produce 138. *cis*-Benzene trioxide (139) is also known[103,104] and undergoes thermal isomerization to *cis, cis, cis*-1,4,7-trioxacyclononatriene (140) while 137 does not.



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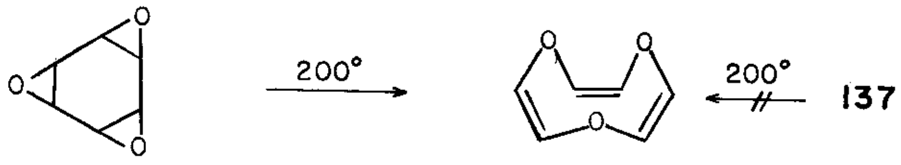

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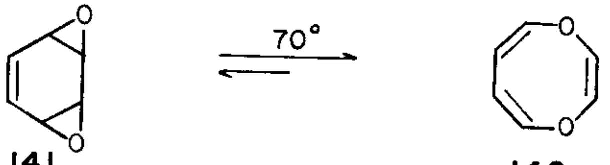

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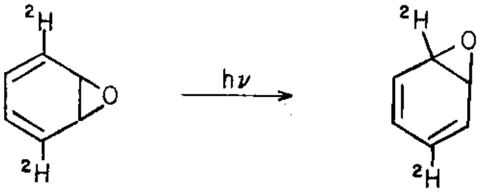
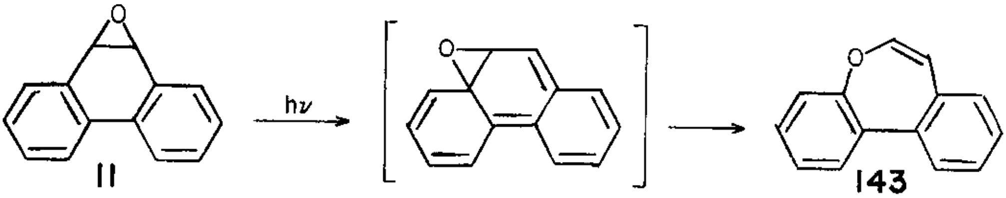
cis-Benzene dioxide (141) exists in equilibrium with dioxocin (142) at elevated temperature.[105,106]

A more detailed examination of the photochemistry of 1-2 has indicated that 1 and 2 isomerize to phenol by a triplet process while the singlet species of 1 deoxygenates and the singlet of 2 cyclizes to 134.[107] Photolysis of 3,6-dideuterobenzene oxide (1-2a) indicates that an "oxygen walk" occurs.[108] Photolysis of benzene oxide (1-2), naphthalene oxide



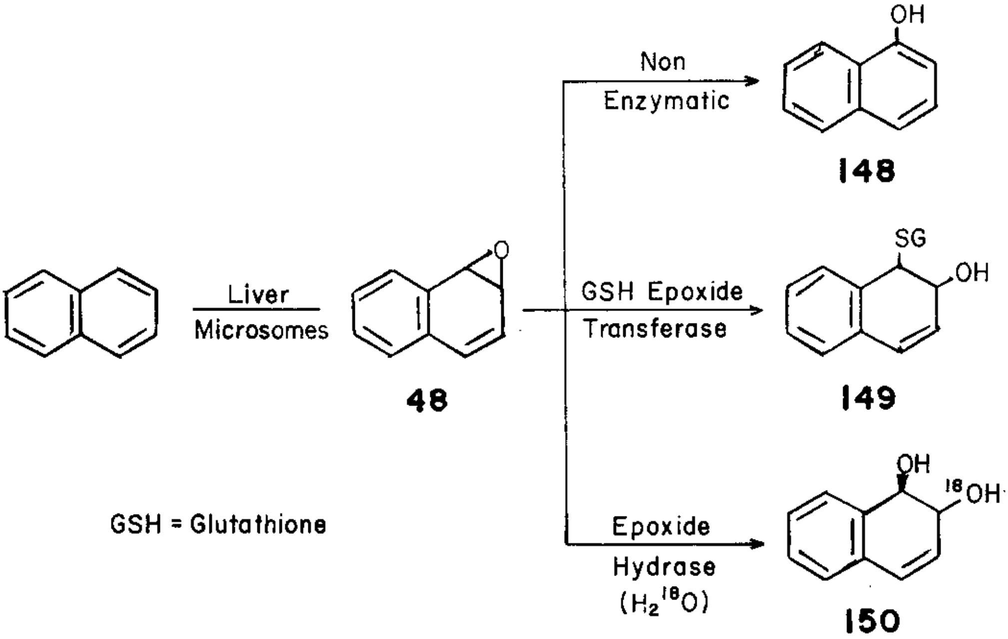
1-2a

(48), and phenanthrene oxide (11) at -196^{0} allowed detection of the keto forms of the corresponding phenols as well as subsequent ketone cleavage products.[108] Phenanthrene oxide (11) also undergoes an "oxygen walk" to the oxepin 143.[108,109]



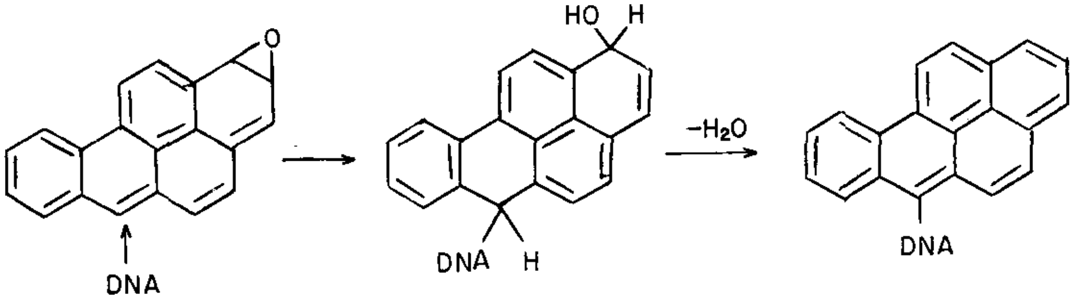
V. BIOCHEMISTRY OF ARENE OXIDES

A. Role in Metabolism - The purpose of the present section and section VB on the biological activity of arene oxides will not be to review the literature, but to indicate the areas of interest since current and comprehensive reviews of the literature are available.[13,110] Nearly 25 years ago, E. Boyland noted that many of the metabolites of aromatic hydrocarbons in mammals could be explained by postulating arene oxides as intermediates in these reactions.[5] In 1968, the first unequivocal demonstration of biological formation of an arene oxide was reported.[93,111] Incubation of naphthalene with the microsomal fraction from rat liver led to the identification of naphthalene 1,2-oxide (48) which was established



as the obligatory intermediate in the formation of 1-naphthol (148), a conjugate (149) with glutathione (GSH) and the dihydrodiol (150). Thus, all of the metabolites of naphthalene could be accounted for by 48. Conjugation with GSH was both non-enzymatic and catalyzed by a soluble enzyme, glutathione-S-epoxide transferase. Hydration to 150 does not occur spontaneously, but requires the microsomal enzyme epoxide hydrase. Enzyme catalysis for the isomerization of 48 to 1-naphthol along with a minor amount of 2-naphthol could not be detected. The half-life of 48 in the incubation medium is on the order of 4 minutes. Subsequently, direct evidence has been presented for the formation of the K-region oxides of several polycyclic aromatic hydrocarbons.[110] The occurrence of the "NIH Shift" during the formation of a phenol or the isolation of metabolites such as *trans*-dihydrodiols, catechols and derivatives thereof, and certain types of conjugates containing cysteine have all been taken as evidence for the biological formation of arene oxides in plants, animals, and microorganisms.[13,110]

B. Toxic Carcinogenic, and Mutagenic Activity - A recent review[112] on the carcinogenicity of organic compounds makes it abundantly clear that these compounds, whether natural or synthetic, share one feature in common — they are either inherently reactive toward or are metabolized to structures which are reactive toward cellular nucleophiles. In all cases, covalent binding to DNA, RNA, and protein occurs.[110,112] Arene oxides with their high reactivity towards nucleophiles are, therefore, prime candidates for the "bioactivated intermediates" responsible for many of the aberrant effects produced by aromatic hydrocarbons in living systems. The initial studies of the carcinogenicity of K-region arene oxides, done by skin painting and subcutaneous injection, showed the oxides less active than the parent hydrocarbons.[110] This may have been the result of the arene oxides never reaching the critical target molecules since recent studies with cells in culture have indicated that arene oxides are highly potent transforming agents.[113] At present, the critical target molecules in the cell are unknown. From the previously described reactions of benzene oxide with simple nucleophiles, it is apparent that the chemistry of the binding of arene oxides will be complex. For example, the 1,2-oxide of benzo/_a_7-pyrene (151) could be attacked at the 6-position after intercalation and then lose water to form 152.[114]



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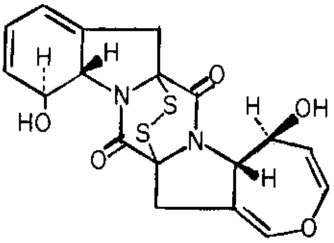
152

Arene oxides of halobenzenes have been proposed as causative agents in liver necrosis[115] based on the observations that radioactive bromobenzene must be metabolically activated and then covalently bind in order to cause necrotic lesions of the liver. Compounds such as toluene which would form relatively short-lived arene oxides[84] are inactive. K-region arene oxides have been shown to act as frameshift mutagens.[116]

C. Involvement in Biosynthesis and Degradation - Exclusive of the wide number of hydroxylations of the aromatic ring by plants, animals, and microorganisms which are accompanied by the "NIH Shift,"[13] a number of compounds have been isolated whose structures suggest an arene oxide may have been involved in their formation. The fungal metabolites aranotin (153) and gliotoxin (154) both originate from phenylalanine and could have been produced *via* the oxide at the 2,3-position on the benzene ring. The seven-membered ring in 153 is suggestive of the intermediate formation of an oxide of the oxepin form of the initial 2,3-oxide.



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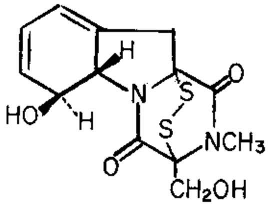

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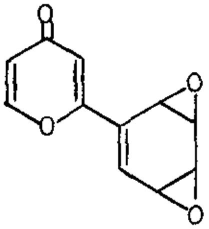
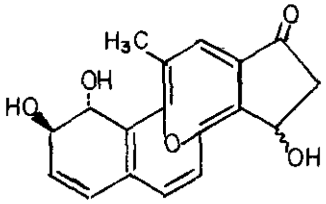
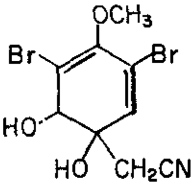
The interesting fungal metabolite LL-Z1220 (155) is a benzene dioxide.[120] The original assignment as trans for the metabolite has been questioned.[106] The only oxido-annulene (156) identified as a metabolite arises from a carcinogenic methylphenanthrene cyclopentanone on incubation with rat liver preparations.[121] Finally, the *Verongia* sponges have provided three metabolites, aeroplysinin-1 (157),[122] aerothionin (158),[123] and homoaerothionin,[123] the latter with an additional methylene group in the central



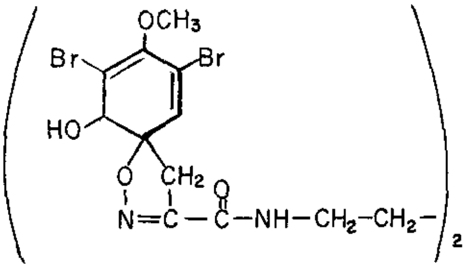
155



156



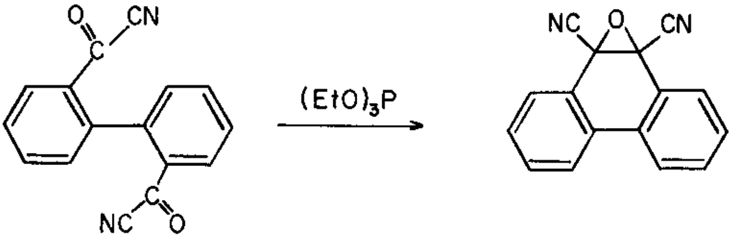
157



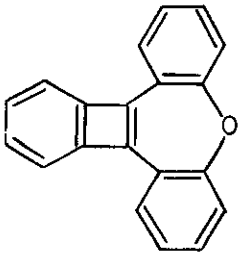
158

carbon chain of 158, which are suggestive of arene oxides as intermediates in their biosynthesis.

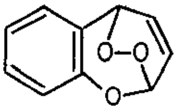
Note Added in Proof. Since the initial writing of this article several additional pieces of information have come to our attention. The synthesis of 9,10-dicyanophenanthrene 9,10-oxide (160) has been achieved by ring-closure of the dialdehyde (159) with triethylphosphite.[124] An interesting new derivative of oxepin (161) which dimerizes at room temperature has been described,[125] and the reaction of 1-benzoxepin (44) to form a novel endoperoxide (162) has been reported.[126] Examination of the early literature on the synthesis of substituted polycyclic hydrocarbons has revealed a report of the preparation of the dimethyl substituted K-region oxide of



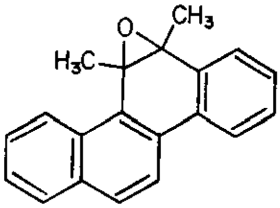
159 **160**



161



162



163

chrysene (163) in 1940.[127] If this report is correct, it predates the synthesis of all other arene oxides by nearly twenty-five years.

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