Stereochemical Course in Reactions between Nucleophiles and Arene Oxides[1]

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Abstract: Reactivity and site of attack for a variety of carbon, nitrogen, oxygen, and sulfur nucleophiles have been examined with representative members of the arene oxide–oxepin system. In most instances, 1,2-dihydroaromatic products result, providing a convenient synthetic entry into such systems. Examples of cis and trans 1,6 additions, as well as the expected trans 1,2 additions, were found for benzene oxide–oxepin, while naphthalene 1,2-oxide underwent exclusive trans 1,2 addition, and 3-benzoxepin suffered ring cleavage.

Since the demonstration that arene oxides are formed from aromatic hydrocarbons by the microsomal enzyme fraction from mammalian liver[3] and that arene oxides subsequently lead to phenols, by nonenzymatic rearrangement, and to dihydrodiols and cysteine conjugates, by enzyme catalysis,[4] substantial interest has developed in the chemistry and biochemistry of the reactive molecules. The most intriguing of the biochemical studies are those which have implicated arene oxides as causative agents in mutagenesis, carcinogenesis, and tissue necrosis.[5] These aberrant side effects of aromatic metabolism are thought to be the result of reaction and subsequent covalent binding of arene oxides at nucleophilic sites on cellular constituents, such as proteins and nucleic acids. Since relatively little is known about the susceptibility of arene oxides to attack by nucleophiles, the present investigation explores the reactivity of benzene oxide–oxepin (**1**) and naphthalene 1,2-oxide (**2**); site of attack, stereochemistry of addition, and methods for preparing substituted 1,2-dihydroaromatic substances, obtainable only with difficulty by other methods, are described. Simple nucleophiles, in which the available electron pair resides on carbon, nitrogen, oxygen, or sulfur, have been employed.

Reaction of **1** and **2** with the strong carbon nucleophiles methyllithium and dimethylmagnesium has been examined in ether solution. Vogel[6] has reported previously that **1** reacts with methyllithium to give a mixture of *cis*- and *trans*-6-methylcyclohexa-2,4-dienols (*cis*-**3** and *trans*-**3**) in which the cis:trans ratio is higher than 9 and with lithium aluminum hydride to give benzene, presumably from dehydration of the intermediate 1,2-dihydrophenol.[7] Formation of the cis isomer as the major product in the reaction of **1** with methyllithium suggests that the reaction occurs by a cis 1,6 addition, particularly in view of the observed conjugative addition of organometallic reagents to 3,4-epoxy-1-butene[8,9] and 3,4-epoxycyclohexene,[7,10,11,12] where the position of attack of the organometallic reagent has been explained in terms of hard and soft acid–base principles.[11] In our hands, the reaction of **1** with methyllithium gave only *cis*-6-methylcyclohexa-2,4-dien-1-ol (*cis*-**3**) in 67% yield (see Scheme I). Reaction with dimethylmagnesium, however, gave a 26% yield of alcohols consisting of 37% of *cis*-**3** and 63% of *trans*-**3**. The stereochemistry was established by catalytic reduction to *cis*- and *trans*-2-methylcyclohexanol, respectively, and comparison with authentic samples.[13]

The site of attack by the organometallic reagents on **1** was established from the corresponding reactions of benzene oxide–oxepin-*3,6-d*$_2$.[14] Methyllithium produced *cis*-**4** by exclusive 1,6 addition,[15] as deduced from the pmr spectrum of the product. The signal for the methyl group (1.15 ppm) appears as a triplet (J = 1.0

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(3) (a) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, 90, 6525 (1968); *Biochemistry*, 9, 147 (1970); (b) for a review of the subject, see J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 28, 1129 (1972).

(4) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *Arch. Biochem. Biophys.*, 123, 176 (1968).

(5) For leading references, see (a) "World Symposium on Model Studies in Chemical Carcinogenesis" Baltimore, Nov 1972, Marcel Dekker, New York, N. Y., and (b) D. M. Jerina and J. W. Daly, *Science*, 185, 573 (1974).

(6) E. Vogel and G. Günther, *Angew. Chem.*, 79, 429 (1967); *Angew. Chem., Int. Ed. Engl.*, 6, 385 (1967).

(7) A synthesis of 1,2-dihydrophenol has been reported: J. Stavascik and B. Rickborn, *J. Amer. Chem. Soc.*, 93, 3046 (1971).

(8) R. J. Anderson, *J. Amer. Chem. Soc.*, 92, 4978 (1970).

(9) R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, 92, 4979 (1970).

(10) D. M. Wieland and C. R. Johnson, *J. Amer. Chem. Soc.*, 93, 3047 (1971).

(11) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, 38, 4263 (1973).

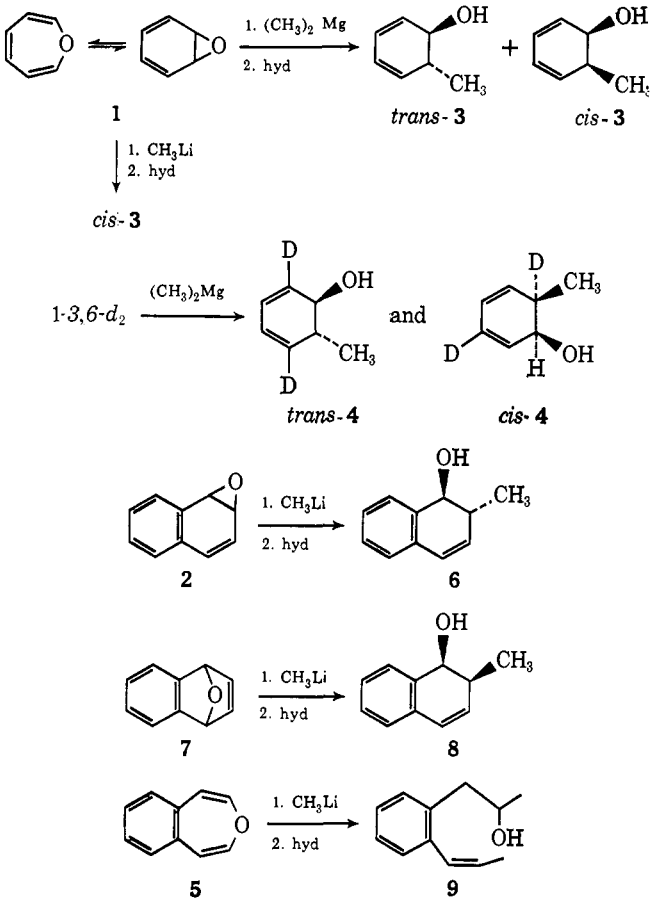
(12) See ref 6 and 9 for relative yields of cis and trans products from 1,2 and 1,4 addition. The trans product is formed predominantly or entirely in the 1,4 addition of methyl- or phenyllithium and lithium dialkyl- or diphenylcuprate.

(13) E. L. Eliel and C. A. Lukach, *J., Amer. Chem. Soc.*, 79, 5986 (1957).

(14) G. R. Ziegler and G. S. Hammond, *J. Amer. Chem. Soc.*, 90, 513 (1968), have questioned the assignment[6] of the pmr spectrum of **1** which exists mainly as oxepin at room temperature. The spectrum of **1** in acetone-d_6 shows complex signals at δ 5.28, 5.8, and 6.2 ppm corresponding to the α, β, and γ hydrogens, respectively. The spectrum of **1**-*3,6-d*$_2$ shows two sharp singlets at δ 5.28 and 6.18 ppm, thus unequivocally confirming the original assignment.[6]

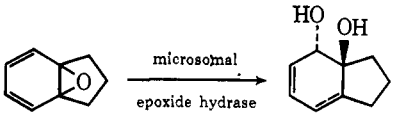
(15) Reported in preliminary form, C. H. Foster and G. A. Berchtold, *J. Amer. Chem. Soc.*, 93, 3831 (1971).

Scheme I. Organometallic Reagents



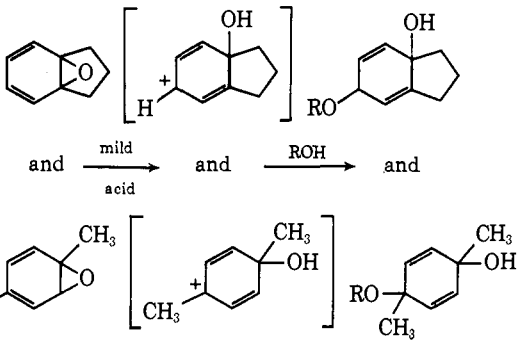
Hz) coupled only to deuterium; the vinyl region integrates for three hydrogens, and the multiplet at 2.28 ppm (CH_3–C*H*) in *cis*-**3** is absent. Analysis of the cis alcohol from the reaction with dimethylmagnesium showed it also to be *cis*-**4** resulting from cis 1,6 addition, whereas the trans alcohol (*trans*-**4**) is formed exclusively by trans 1,2 addition. To explore the possibility that the cis 1,6 addition of methyllithium results from attack on the oxepin form of **1**, reactions of **2** and 3-benzoxepin (**5**) which appear to exist exclusively in the oxide[16] and oxepin[17] forms, respectively, were examined. Although reaction of **2** could occur either by direct opening resulting from attack at C-1 or C-2 or by conjugative addition resulting from attack at C-4, a single product (**6**) arising by trans opening from attack at C-2 is produced. The trans stereochemistry in **6** was confirmed by preparing the cis isomer (**8**) through conjugative addition of methyllithium to 1,4-dihydronaphthalene 1,4-*endo*-oxide (**7**), presumably by a concerted addition.[18] Reactions of **1** and **2** with methyllithium are thus in direct contrast. No further insight to this problem was gained by examining the reaction of the oxepin **5** with methyllithium. Reaction was much slower, 2 mol of the organometallic reagent was consumed, and ring cleavage occurred to produce 1-[2-(1-*cis*-propenyl)phenyl]-2-propanol (**9**). The mechanism of this remarkably stereospecific reaction was not pursued. A related ring-opening reaction has been observed in the alkali metal reduction of **5** and 2,7-dimethyloxepin.[19]

Study of oxygen nucleophiles is of particular interest because of the direct analogy with the biological reaction in which the enzyme "epoxide hydrase" adds water to arene oxides to form the so-called dihydrodiols. The initial demonstration of this microsomal enzyme activity[4] established that **1** was converted to *trans*-1,2-dihydroxy-1,2-dihydrobenzene. Subsequently, the enzymatic hydration of **2** was shown to occur exclusively by attack of solvent water at C-2.[3] Although enzyme-catalyzed conjugative addition does not occur with **1**, this may be the case for indan 8,9-oxide as shown below.[20,21]



As yet, evidence has not been forthcoming to indicate whether these enzymatic reactions were acid catalyzed, base catalyzed, or both.

Most chemical additions of oxygen nucleophiles, reported to date, have been under neutral to mildly acidic conditions. Thus, water or alcohol can trap the highly stabilized carbonium ions generated from indan 8,9-oxide[21] and 1,4-dimethylbenzene oxide[22] as shown below. Similarly, treatment of K-region arene

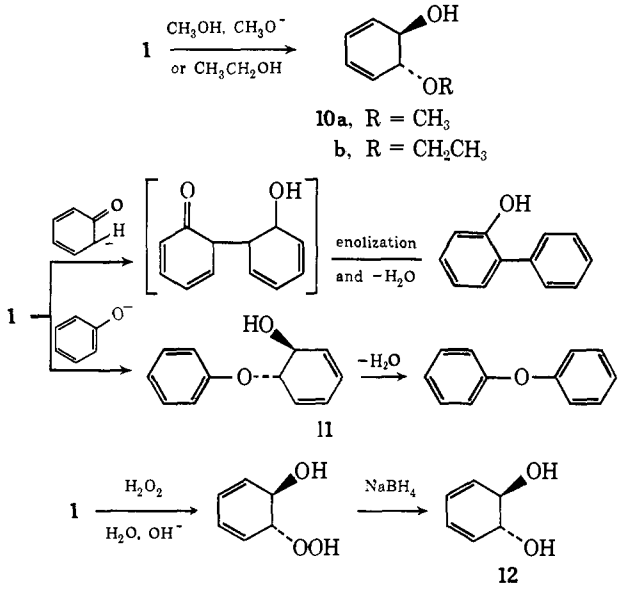


oxides of polycyclic hydrocarbons under mild conditions with aqueous organic solvents leads to trans dihydrodiols.[23] Notably, these additions of oxygen nucleophiles have only been detected for arene oxides which have alkyl substitution on the oxirane ring or are K region; both are examples of highly stable arene oxides which do not rapidly rearrange to phenols. In addition, *endo*-1,4-oxides undergo solvolysis in acidic methanol to produce monomethyl ethers of trans 1,2-diols.[24] Prior to this study, only one report of the nucleophilic addition of oxygen nucleophiles has been described. Both hydroxide and methoxide undergo trans 1,6 addition to 4-carbo-*tert*-butoxybenzene oxide to form the free and methylated 1,2-diol.[25]

(16) See citations 4 and 84 in ref 6 and discussion therein.
(17) D. R. Boyd, D. M. Jerina, and J. W. Daly, *J. Org. Chem.*, **35**, 3170 (1970).
(18) R. Caple, G. M. S. Chen, and J. D. Nelson, *J. Org. Chem.*, **36**, 2874 (1971).
(19) L. A. Paquette and T. McCreadie, *J. Org. Chem.*, **36**, 1402 (1971).
(20) J. W. Daly, D. M. Jerina, H. Ziffer, B. Witkop, F. G. Klarner, and E. Vogel, *J. Amer. Chem. Soc.*, **92**, 702 (1970).
(21) For an equally plausible alternate explanation, see G. J. Kasperek, P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Amer. Chem. Soc.*, **95**, 6041 (1973).
(22) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kaubisch, and D. M. Jerina, *J. Amer. Chem. Soc.*, **94**, 7876 (1972).
(23) For a review of the chemistry and synthesis of arene oxides, see D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973).
(24) K. Reiff, U. Schumacher, G. Stubenrauch, and W. Tochtermann, *Tetrahedron Lett.*, 1553 (1973).
(25) R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz, and G. A. Berchtold, *J. Amer. Chem. Soc.*, **96**, 1193 (1974).

In the present study, a variety of oxygen nucleophiles have been examined with **1** (Scheme II). Generally,

Scheme II. Oxygen Nucleophiles

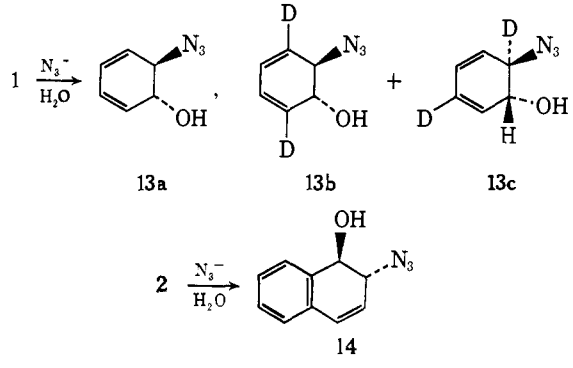


reactivity of **1** and **2** with alkoxides is slow, as these reagents are used in the final stage of their preparation. However, reaction of **1** with a trace of methoxide ion in methanol (Scheme II) yields 78% of *trans*-6-methoxycyclohexa-2,4-dien-1-ol (**10a**) after 69 days. The yield was 64% after 14 days with 4 equiv of methoxide ion. The trans stereochemistry in **10a** was established from the large coupling between the hydrogens at sp^3 carbon ($J_{1,6}$ = 10.5 Hz in $CDCl_3$ and 10.0 Hz in DMSO-d_6) and by reduction of **10a** and its acetate to the known trans cyclohexane derivatives. That the reaction proceeded by 1,2 addition was established from the pmr spectrum of the product, when **1**-*3,6*-d_2 was employed as starting material. While attempts to add ethoxide in ethanol to **1** led mainly to phenol and no detectable ether products, storage of **1** in ethanol for 2 months at room temperature provided a small amount of the ethanol addition product **10b**, whose stereochemistry was assumed trans from the large coupling between the hydrogens at sp^3 carbon ($J_{1,6}$ = 11.2 Hz, $CDCl_3$).

Initial attempts to add hydroxide or the much more nucleophilic hydroperoxide anion[26] to **1** in aqueous solution were without success. Failure of HOO^- to add was thought to be due to base-catalyzed decomposition of the peroxide rather than lack of reactivity of the nucleophile. Thus, the more stable *tert*-butyl hydroperoxide was employed in the presence of *tert*-butyl alcohol and potassium *tert*-butoxide. Surprisingly, the only detectable products were phenol and diphenyl ether; presumably the phenolate anion generated *in situ* from **1** had proved to be the better nucleophile. Reaction of **1** in *tert*-butoxide–*tert*-butyl alcohol at room temperature for 3 weeks provided *trans*-6-phenoxycyclohexa-2,4-dien-1-ol (**11**) in 5% yield, while at reflux for 16 hr, diphenyl ether, by dehydration of **11**, and *o*-hydroxydiphenyl ether, by enolization and dehydration of the dihydroaromatic produced when phenol acts as an ambident nucleophile, were obtained in low yield in a ratio of 3:1. The stereochemistry of **11** was assumed trans from the large coupling between the hydrogens on the adjacent sp^3 carbons ($J_{1,6}$ = 11.2 Hz, $CDCl_3$). Finally, reaction of **1**, with a large excess of hydrogen peroxide in aqueous base followed by borohydride reduction of the resulting hydroperoxide produced the desired *trans*-1,2-dihydroxy-1,2-dihydrobenzene (**12**) in 30% yield. This last reaction represents the most convenient synthesis of this material presently available.[27]

Nitrogen nucleophiles, unless fairly polarizable, are quite unreactive toward **1**. Failure of NH_3 and NH_2^- to add to **1**, while N_3^- adds readily, has been reported.[28] The azide addition product, *trans*-6-azidocyclohexa-2,4-dien-1-ol (**13a**), was assigned trans stereochemistry based on reduction and subsequent acetylation of either the crude or purified amino alcohol to the known *trans*-2-acetamidocyclohexadienyl acetate.[29] Further confirmation that the crude oil (**13a**) consists of essentially a single isomer was found by complete analysis of the 220-MHz pmr spectrum for which the vinyl region is quite complex (Figure 1, $J_{1,6}$ = 3.8 Hz). The necessity for clearly establishing this point lies in the fact that **13a** is generated by two distinct pathways; both trans 1,2 and trans 1,6 addition occur to form **13b** and **13c**, respectively, from **1**-*3,6*-d_2 in a ratio of 3:2 (Scheme III, see Experimental Section for discussion of the pmr

Scheme III. Nitrogen Nucleophiles



spectra). The ratio of the two types of addition products is most easily measured when **1**-*1,2,3,4,5*-d_5 is used as substrate since the hydrogen on the carbon bearing the azide group (1,6 addition) stands apart in the pmr spectrum (interchange hydrogen and deuterium in structures **13b** and **13c** for these products). Reduction of the azido alcohols obtained from either di- or pentadeuterio **1** to the corresponding deuterated aminocyclohexanols further establishes the two modes of addition. The rates of dehydration of **13b** and **13c**, catalyzed by a trace of trifluoroacetic acid in $CDCl_3$, were found identical, and thus a single stereochemistry (trans) for all molecules is suggested. The exclusive trans nature for the 1,6 addition of azide to **1** is in direct contrast to the cis 1,6 additions of organometallic reagents previously described. Reaction of **2** with azide resulted in attack at C-2 to produce **14**. The

(26) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 84, 16 (1962).

(27) M. Nakajima, *et al.*, *Chem. Ber.*, 89, 2224 (1956).

(28) R. M. DeMarinis and G. A. Berchtold, *J. Amer. Chem. Soc.*, 91, 6525 (1969).

(29) N. Kurihara *Agr. Biol. Chem.*, 33, 1186 (1969).

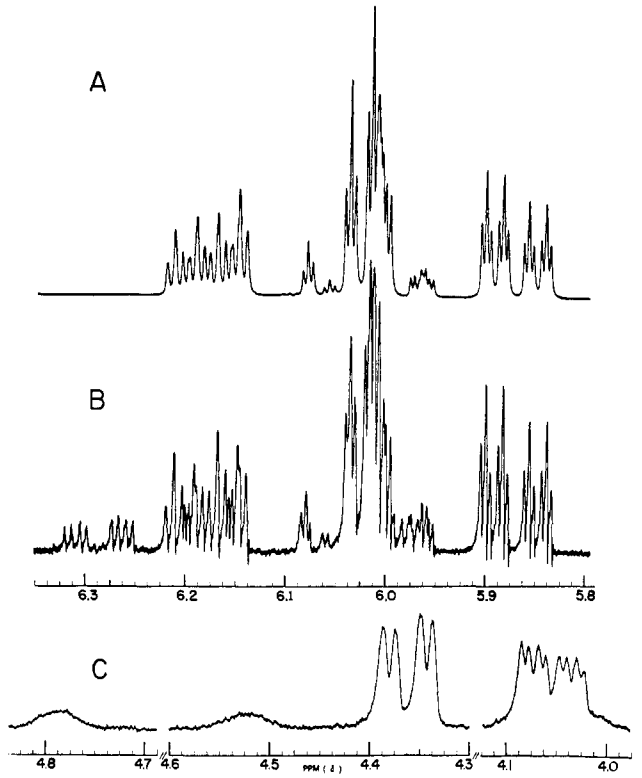


Figure 1. The 220-MHz spectrum of *trans*-6-azidocyclohexa-2,4-dien-1-ol (**13a**). Values of chemical shifts and coupling constants were estimated from spectrum B (vinyl hydrogens), spectrum C (allylic hydrogens), and comparison of spectra from the deuterated analogs. By a process of iteration, these values were adjusted to generate the first-order computer-derived spectrum [N. Sharpless, NIAMDD, National Institutes of Health, NMRIT Program on IBM 360] shown in trace A for the vinyl hydrogens of **13a**. The final constants used were: (H_1) δ 4.39, (H_2) 5.99, (H_3) 6.04, (H_4) 6.17, (H_5) 5.87, (H_6) 4.09 ppm, J_{1-2} = 2.6, J_{1-3} = 0.9, J_{1-4} = 0.3, J_{1-6} = 8,3; J_{2-3} = 9.5, J_{2-4} = 1.2, J_{2-5} = 0.9, J_{3-4} = 5.3, J_{3-5} = 1.05, J_{4-5} = 9.5, J_{3-6} = 1.55, J_{5-6} = 3.8 Hz. With the exception of the minor signals at 4.52, 4.78, 6.26, and 6.32 ppm and in the region of H_2 and H_4, good comparison was obtained between the computed and observed spectra, which strongly suggests that the major component is a single isomer. The minor signals appear at chemical shifts which are compatible with 1,4 addition.

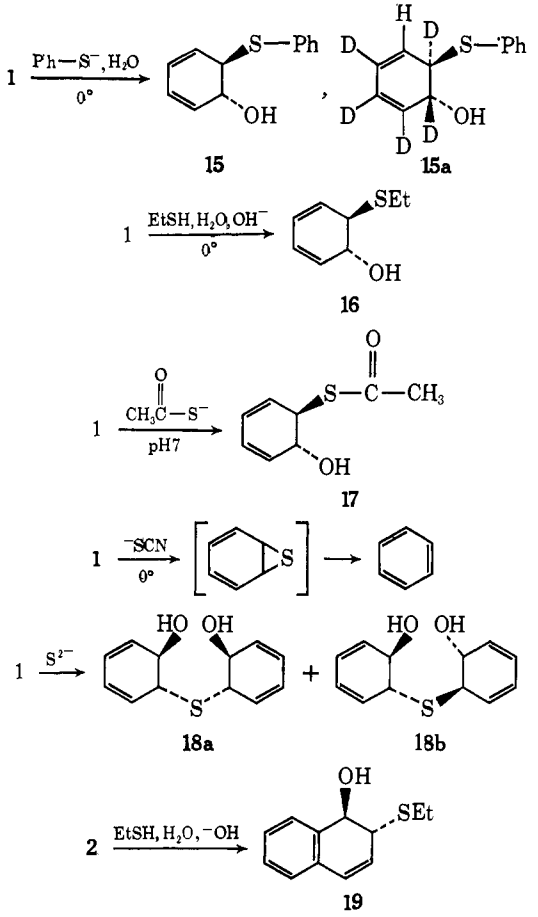
stereochemistry of **14** was assumed, but not proved, as trans.

In mammals, the enzyme-catalyzed addition of glutathione to arene oxides[4] appears to be one of the principal means of protection against the cytotoxic effects elicited by metabolically formed arene oxides.[30a,b] The glutathione conjugates emerge as *N*-acetylcysteine derivatives (mercapturic acids) in urine. The enzyme-catalyzed additions have been assumed, but not proved, to occur by trans 1,2 addition. The kinetics of addition of a series of thiols, including glutathione, to **1** have been examined.[30b]

A number of sulfur nucleophiles have been examined both with **1** and **2** (Scheme IV). Addition of sodium thiophenoxide to **1** in aqueous medium readily produces *trans*-6-phenylthiocyclohexa-2,4-dienol (**15**) in 64% yield at 0°. Although the stereochemistry of **15** could not be deduced directly (see Experimental Section), the pmr spectrum of the acetate derivative of the

(30) (a) W. D. Reid and G. Krishna, *Exp. Mol. Pathol.*, **18**, 80 (1973); (b) D. M. E. Reuben and T. C. Bruice, *J. Chem. Soc., Chem. Commun.*, 113 (1974).

Scheme IV. Sulfur Nucleophiles



Diels–Alder adduct between maleic anhydride and **15** established the addition as trans. To establish whether the nucleophilic addition had occurred 1,2 or 1,6, the reaction was repeated with **1**-*1,2,3,4,5-d*$_5$. The pmr spectrum of the product (**15a**) showed signals for vinyl hydrogen only and thus established that addition of thiophenoxide had proceeded by direct trans 1,2 opening. In similar experiments, the addition of thioethanol and thioacetate to **1** to produce *trans*-6-ethylthiocyclohexa-2,4-dienol (**16**) and *trans*-6-thioacetoxycyclohexa-2,4-dienol (**17**), respectively, were established as the result of direct 1,2 opening. The trans stereochemistry was assumed from the preceding experiment. Reaction of **1** with thiocyanate was hoped to provide a synthesis of the elusive benzene sulfide–thiepin. As in the previous attempt,[31] only benzene could be detected, arising possibly by the extrusion of sulfur from the desired compound. Similarly, **2** was converted preponderantly to naphthalene, and only traces of thionaphthols could be detected.

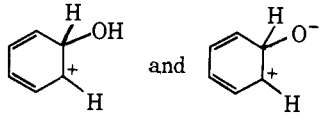
Previously, bis(6-*trans*-1-hydroxycyclohexa-2,4-dienyl) sulfide was reported[28] from the reaction of **1** with sulfide. Reexamination of this reaction with the intention of establishing whether the sulfide results from 1,2 addition has now led to the conclusion that both the meso (**18a**) and *d,l* (**18b**) diastereomers of this material are produced. The pmr spectrum of the crude product from the reaction of either **1**-*3,6-d*$_2$ or **1**-*1,2,3,4,5-d*$_5$ with sulfide indicates that all addition has oc-

(31) T. J. Barton, M. D. Martz, and R. G. Zika, *J. Org. Chem.*, **37**, 552 (1972).

curred 1,2 regardless of what stereochemistries may be present in the molecules; equal numbers of protons appear in the vinyl and allylic regions, or only vinyl protons are seen, respectively. Attempts to completely analyze the 100-MHz pmr spectrum of the crude product from **1**-*3,6-d*$_2$ directly or of the crude product from **1** by double resonance indicated more than a single geometry was present. Consideration of all stereochemical possibilities indicates that a cis,cis meso compound, meso and racemic trans,trans compounds, and two racemic cis,trans compounds could be produced. As previously described,[28] the crude product from **1** provides a single pure isomer on crystallization from ether. However, careful chromatography of the mother liquor has now provided a different pure isomer. The ^{13}C nmr of each of these materials indicates a single relative stereochemistry is present in both rings for each molecule. Both of the racemic cis,trans molecules are thus eliminated. Mild acid treatment of either isomer provides **15**, the trans addition product of thiophenoxide. Thus the cis,cis meso compound is eliminated. Assignment of which trans,trans isomer is meso *vs.* racemic has not been possible.

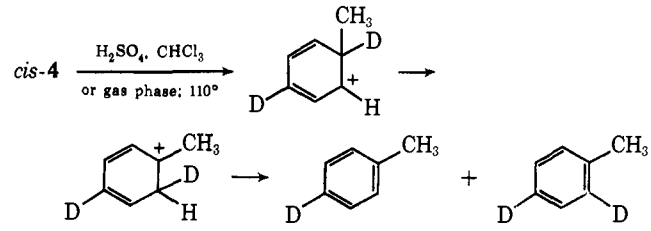
Reaction between **2** and thioethanol provided *trans*-1-hydroxy-2-ethylthio-1,2-dihydronaphthalene. Only a trace of what may have been attack at the 1 position could be detected. Relative stereochemistry of the major product was established trans by a determination of the sign for $J_{2,4}$, which must be negative in the trans isomer (see Experimental Section). Interestingly, all reactions of **2** described in this report as well as the enzyme-catalyzed addition of water[3] occur at C-2. Yet the glutathione addition product has been suggested to result from attack at C-1.[3,32] This latter reaction should be the subject of further scrutiny.

Arene oxides readily rearrange to phenols in aqueous media throughout the normal pH range. In acid, the rate-controlling step is formation of a carbonium ion, while under neutral to basic conditions, a zwitterion is formed.[33,34] Thus, for **1**, the species below are indicated. Further, migration of the hydrogen (or other



substituents) on the carbon bearing oxygen to the carbon bearing the positive charge (a keto form of the phenol) can result in a net migration and retention (the NIH shift[3]) of this hydrogen. Thus, dehydration of *cis*-**4** (Scheme V) with sulfuric acid in chloroform or by thermal means produced toluene-d_1 and toluene-d_2 in a ratio of approximately 2:1. The initially formed cation must undergo a 1,2 shift of deuteride ion to the more stable cation, which suffers preferential loss of H^+ owing to an isotope effect. The observed migration emphasizes the significant difference in stability of secondary *vs.* tertiary allylic carbonium ions,[35] which was suggested as a dominant factor in controlling the

Scheme V. Dehydration of *cis*-**4**



direction of rearrangement to phenols for a number of methyl substituted analogs of **1**. A similar deuterium migration has been noted in the acid-catalyzed dehydration of a deuterium-labeled dihydrodiol.[36]

In summary, it is quite clear that arene oxides are susceptible to attack by nucleophiles, and that binding of these reactive molecules to cellular nucleophiles under mild conditions is plausible. Of particular import is the fact that soft and polarizable nucleophiles (azide, thiol anions, and phenoxide) seem to add readily, while harder anions (carbanions and hydroperoxide anion) must be strongly nucleophilic in order to react. Alcohols add only with difficulty, and ammonia and NH_2^- are unreactive. The high stereospecificity for the reactions in aqueous media, reported here, are indicative more of nucleophilic opening rather than of trapping of carbonium ions formed in route to phenols. Alternatively, some of this high stereospecificity might be explained in terms of trapping of carbonium ions which are involved in tight ion pairs. The mixed stereochemistry of solvolytic products formed under acid conditions may be more representative of this latter type of mechanism.[21,22] The binding of K-region arene oxides, as well as phenols, dihydrodiols, and the parent polycyclic hydrocarbons, to DNA, RNA, and protein has been studied extensively.[37-41] As is the case for other alkylating agents,[42,43] the oxides were found to be more reactive toward the purine bases, especially guanine. Information on the chemical nature of this binding has yet to be reported. The present studies make it abundantly clear that a wide variety of structural types could readily be produced during binding of arene oxides to cellular macromolecules.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. The proton nmr spectra were taken in $CDCl_3$, except where otherwise indicated with Varian 60-, 100-, or 220-MHz instruments or a Perkin-Elmer R-20 spectrometer, and chemical shift data are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (J) in Hz. Unless otherwise designated, spectra were measured at 60 MHz. Carbon-13 nmr spectra were taken on a Brucker HFX-90 spectrometer interfaced with a Digilab FTS/NMR-3 Data System at 22.6326 MHz. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6D mass spectrometer with an ionizing potential of 80 eV, unless otherwise indicated, and are expressed

(32) J. Booth, E. Boyland, and P. Sims, *Biochem. J.*, **74**, 117 (1960).
(33) G. P. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Chem. Soc. D*, 784 (1972).
(34) G. J. Kasperek and T. C. Bruice, *J. Amer. Chem. Soc.*, **94**, 198 (1972).
(35) N. Kaubisch, J. W. Daly, and D. M. Jerina, *Biochemistry*, **11**, 3080 (1972).
(36) D. M. Jerina, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, **89**, 5488 (1067).
(37) I. Y. Wang, R. E. Rasmussen, and T. T. Crocker, *Biochem. Biophys. Res. Commun.*, **49**, 1142 (1972).
(38) A. Borgen, H. Darvey, N. Castagnoli, T. T. Crocker, R. E. Rasmussen, and I. Y. Wang, *J. Med. Chem.*, **16**, 502 (1973).
(39) P. L. Grover and P. Sims, *Biochem. Pharmacol.*, **19**, 2251 (1970).
(40) P. L. Grover and P. Sims, *Biochem. Pharmacol.*, **22**, 661 (1973).
(41) P. Brooks in ref 5a.
(42) P. Sims, *Biochem. J.*, **125**, 159 (1971).
(43) E. C. Miller and J. A. Miller, *Pharmacol. Rev.*, **18**, 805 (1966).

in per cent relative to the most intense peak. Gas chromatographic analyses and isolations were carried out with either an F and M Model 810 research gas chromatograph or a Hewlett-Packard Model 5750 gas chromatograph with thermal conductivity or flame ionization detectors using 4–6 ft × 0.25 in. columns with the specified liquid phase on 60–80 mesh Chromosorb P. A LKB 9000 combined gas chromatograph–mass spectrometer was used with 6 ft × 0.25-in. columns and operated at 70 eV. When compounds were separated by thin layer chromatography on fluorescent silica gel with solvents as indicated, products were isolated from the gel by elution with ether containing 10% methanol. Melting points were taken on a Thomas-Hoover Uni Melt and are corrected.

Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark; Galbraith Laboratories, Knoxville, Tenn.; or Mrs. Nancy Alvord, Massachusetts Institute of Technology.

Preparation of Arene Oxides. Benzene oxide–oxepin (**1**) was prepared by a modification[4] of the original procedure.[6] By an analogous method, **1-*3,6-d*$_2$** was prepared from cyclohexa-1,4-diene-*3,3,6,6-d*$_4$[44] obtained from butadiene-*1,1,4,4-d*$_4$[45] (96.2% d_4 and 3.8% d_3). The pmr spectra of **1-*3,6-d*$_2$** (neat) showed two broadened singlets at 6.3 and 5.3. Birch reduction of perdeuteriobenzene provided cyclohexa-1,4-diene-*1,2,3,4,5,6-d*$_6$, which was converted to **1-*1,2,3,4,5-d*$_5$** as above. The mass spectrum of the maleic anhydride adduct of this material showed the isotope content to be H_2–D_4 (18.3%), H–D_5 (50.0%), and D_6 (31.7%). Naphthalene 1,2-oxide (**2**) and 3-benzoxepin were prepared as described.[6]

Reaction of 1 with Methyllithium. *cis*-6-Methylcyclohexa-2,4-dien-1-ol (*cis*-3). To a solution of 550 mg (5.85 mmol) of **1** in 20 ml of anhydrous ether maintained under N_2 at 0° was added slowly 8 ml (8.0 mmol) of 1 *M* methyllithium in ether. The solution was stirred at 0° for 1 hr, after which time the bright yellow color had disappeared, and the solution was cloudy. One milliliter of methanol was added carefully while the mixture was kept at 0°. After addition was complete, 20 ml of water was added, and the ether layer was brought to about 50 ml. The ether layer was separated, washed with 20 ml of water, and dried (Na_2SO_4). Evaporation of the ether gave a slightly yellow oil that was distilled at room temperature under high vacuum to give 433 mg (67% of *cis*-**3**) as a colorless oil: ir (neat) 3350, 3030, 2980, 2930, 2865, 2805, 1455, 1410, 1180, 1120, 1080, 1040, 1020, 955, 930, 890, 745, and 700 cm^{-1}; uv max (95% C_2H_5OH) 258 nm (ε 4942); pmr (CH_3) 1.22, (OH) 2.34, (H_6) 2.58, (H_1) 3.95, (H_{2-5}) 5.5–6.1 with J_{CH_3-6} = 7, J_{1-6} = 2; mass spectrum M$^+$ 110 (34), 95 (67), 92 (62), 91 (100).

Anal. Calcd for $C_7H_{10}O$: C, 76.36; H, 9.09. Found: C, 76.10, H, 9.27.

Catalytic hydrogenation of *cis*-**3** at atmospheric pressure in ethyl acetate using 10% Pd on carbon catalyst gave *cis*-2-methylcyclohexanol, the structure of which was established by comparison of the ir spectrum with that of an authentic sample prepared by literature methods.[13]

Compound **1-*3,6-d*$_2$** (260 mg, 2.7 mmol) was treated with methyllithium as described above for the reaction of **1** to give *cis*-**4** in 33% yield: ir ($CHCl_3$) 3580, 3440, 3000, 2970, 2880, 2260, 2085, 1460, 1405, 1380, 1220, 1100, 1060, 1010, 970, 945, 910 and 880 cm^{-1}; pmr (CH_3) 1.19, (OH) 2.25, (H_1) 3.95, (H_2) 6.02, (H_4 and H_5) 5.64 and 5.98 with J_{CH_3-D} = 1.0.

Acid-catalyzed dehydration of *cis*-**4** was effected by dissolving the alcohol in $CHCl_3$ and adding one drop of H_2SO_4. Glpc analysis (10% Carbowax 20M column) showed complete conversion to toluene: mass spectrum 95 (3.8), 94 (40.7), 93 (100), 92 (2.8).

Reaction of 1 with Dimethylmagnesium. *cis*- and *trans*-3. Thirty-two milliliters of a 0.5 *M* ethereal solution of dimethylmagnesium (used as obtained from Org Met Chemical Co.) was added at 0° to a solution of **1** (0.5 g, 5.3 mmol) in 5 ml of anhydrous ether. After stirring 50 min at 0°, the reaction was quenched by addition of 8 ml of NH_4Cl solution (3.5 g in 25 ml of H_2O). The ether layer was separated from the viscous aqueous layer. The aqueous phase was washed with 15 ml of ether; the combined ether phases were washed with 20 ml of 5% NaOH, followed by 20 ml of water. The ether phase was dried over Na_2SO_4 and the solvent evaporated to give a yellow oil which was distilled under aspirator pressure (pot temperature 55–65°) to give a colorless liquid (148 mg, 26% yield): pmr (H_{2-5}) 5.6–6.1, (H_1) 4.0, (H_6 and OH) 2.2–2.6, (CH_3) 1.1 and 1.2 (2 doublets, J = 7). The larger doublet (63%) at 1.1 was assigned to the *trans*-**3**, and the smaller doublet (37%) at 1.2 was assigned to the *cis*-**3** on the basis of comparison with the CH_3Li reaction product and hydrogenation to the known saturated alcohol as described below. Gas chromatography of the product mixture on a 6-ft, 10% Carbowax 20M column at 95° showed two major peaks in a ratio of 36.5:63.5. The first peak had the same retention time (49 min) as *cis*-**3** obtained from reaction of CH_3Li with **1**. The second component (retention time, 56 min) was isolated by preparative glpc: ir ($CHCl_3$) 3570, 2950, 2920, 2860, 1500, 1450, 1380, 1015, 985, 970, 898 cm^{-1}. It was identified as *trans*-**3** by catalytic hydrogenation at atmospheric pressure in ethyl acetate using 10% Pd/C catalyst to give *trans*-2-methylcyclohexanol, the structure of which was established by comparison of the ir spectrum with that of an authentic sample prepared by literature methods.[13]

Reaction of **1-*3,6-d*$_2$** (214 mg) with dimethylmagnesium as described above for the reaction of **1** gave, after distillation, a 21% yield of *cis*- and *trans*-**4**. The pmr data for the cis isomer (37% of mixture) were identical with those of *cis*-**4** obtained from reaction with CH_3Li. The trans isomer (63% of mixture) had the following pmr: (CH_3) 1.02, (OH) 1.62, (H_6) 2.2–2.6, (H_1) 3.92, (H_{2-5}) 5.7–6.1 with J_{CH_3-6} = 7, J_{1-6} = 6.5.

Reaction of 2 with Methyllithium. *trans*-1-Hydroxy-2-methyl-1,2-dihydronaphthalene (6). To an ether solution of **2** (30 mg) at −15° was added an excess of methyllithium in pentane. After storage at 0° for 6 hr, the excess reagent was destroyed with 2-propanol, water was added, and the products were extracted into ether. The product (**6**) was isolated (15 mg) by tlc (R_f 0.15, benzene); pmr (CH_3) 1.08, (H_1) 4.47, (H_2) 2.64, (H_3) 5.92, (H_4) 6.48, (aromatic) 7.0–7.5 with J_{CH_3-2} 7.2, J_{1-2} = 6.0. J_{2-3} = 4.4, J_{2-4} = 1.5, J_{3-4} = 9.6. A sample of **6** (50 μg) was dehydrated in 1 *M* HCl–methanol (1:4) for 0.5 hr, and the methylnaphthalenes were separated by gplc on 15% SE-30 at 136°, which showed the major isomer to be 2-methyl- (13 min) and the minor (<5%) to be 1-methylnaphthalene (14 min). The presence of the 1-methyl isomer is presumed to arise *via* a minor attack of methyllithium at C-1 in **2**. In the presence of 10% Pd/C in ethanol solution, **6** took up 1 mol of hydrogen to produce the known *trans*-1-hydroxy-2-methyltetralin by comparison of nmr spectra; J_{1-2} = 6.0 obsd (6.0 lit.).[46] These data from the pmr spectra, dehydration, and reduction allow assignment of **6** as *trans*-1-hydroxy-2-methyl-1,2-dihydronaphthalene.

The corresponding cis isomer (**8**) was obtained by reacting 100 mg of 1,4-dihydronaphthalene 1,4-*endo*-oxide[47] (**7**) with methyllithium as above and was isolated by tlc (68 mg, R_f 0.15, benzene): pmr (CH_3) 1.18, (H_1) 4.57, (H_2) 2.58, (H_3) 5.78, (H_4) 6.49, (aromatic) 6.9–7.5 with J_{CH_3-2} = 7.4, J_{1-2} = 5.0, J_{2-3} = 3.2, J_{2-4} = 2.3, J_{3-4} = 9.4. On reduction as above, 1 mol of hydrogen was consumed to produce *cis*-1-hydroxy-2-methyltetralin; J_{1-2} = 2.6 obsd (3.0 lit.).[46]

Reaction of 3-Benzoxepin (5) with Methyllithium. 1-[2-(1-*cis*-propenyl)phenyl]-2-propanol (9). 3-Benzoxepin (**5**) (1 mmol) was reacted in ether with 5 mmol of methyllithium at room temperature for 24 hr. The products were separated by tlc with benzene. The major uv absorbing compound (R_f 0.17, 36 mg) was eluted and repurified by tlc with benzene:ethyl acetate, 9:1 (R_f 0.5, 12.5 mg); mass spectrum showed M$^+$ 176 (8), 158 (8), 147 (10), 143 (16), 133 (40), 132 (37), 131 (41), 117 (100), 115 (35), 91 (42). The compound was not completely pure at this stage. Acetylation with acetyl chloride in pyridine at 0° and separation of the product by tlc (R_f 0.47, benzene) gave acetate, which was judged essentially pure from its nmr spectrum: (CH_3–C(=O)–) 1.90, (H_3) 1.20, (H_2) 5.09, (H_1) 2.73 and 2.91, (H_1') 6.58, (H_2') 5.87, (H_3') 1.71, (aromatic) 7.20 with J_{1-1} = 13.6, J_{1-2} = 6.7 (both), J_{2-3} = 6.3, $J_{1'-2'}$ = 12.0, $J_{1'-3'}$ = 1.5, $J_{2'-3'}$ = 6.8 which compares well with 1-phenylpropan-2-ol and *cis*-β-methylstyrene (Chemical Samples Co.). The mass spectrum of **9** showed a molecular ion at 218 (2%) with other ions at 158 (54), 143 (100), 131 (55), 129 (50), 128 (52), 91 (36); M$^+$ calcd 218.1307, found 218.1314.

Reaction of 1 with Sodium Methoxide. *trans*-6-Methoxycyclohexa-2,4-dien-1-ol (10a). To a stirred solution of **1** (0.38 g, 4.0 mmol) in 10 ml of methanol was added in one portion 0.93 g (17.2 mmol) of sodium methoxide. The solution was stirred under a nitrogen atmosphere at room temperature. After 14 days, the pmr spectrum of the reaction showed that only a trace of **1** remained, and no aromatic products were formed. After 5 days more, no significant change was observed. The yellow methanol solution was diluted with 100 ml of ether, washed with 5% aqueous sodium hydroxide and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was short-path

(44) W. T. Norris, *J. Org. Chem.*, **33**, 4540 (1968).
(45) A. C. Cope, G. A. Berchtold, and D. L. Ross, *J. Amer. Chem. Soc.*, **83**, 3859 (1961).
(46) S. Mitsui, A. Kasahara, and K. Hanaya, *Bull. Chem. Soc. Jap.*, 41, 2526 (1968).
(47) L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965).

distilled at room temperature (0.03–0.05 mm) to give 0.32 g (64%) of **10a** as a colorless liquid: ir ($CHCl_3$) 3580, 3440, 3040, 2990, 2930, 2820, 1605, 1500, 1460, 1405, 1360, 1340, 1310, 1230, 1190, 1110, 1080, 1020, 995, and 945 cm^{-1}; uv max (95% C_2H_5OH) 262 nm (ϵ 3645); pmr (CH_3) 3.47, (OH) 2.88, (H_1 and H_6) 4.08 and 4.55, (H_{2-5}) 5.95 (broad s) with J_{1-6} = 10.5; mass spectrum 127 (1), 126 (6), 109 (10), 108 (100), 95 (6), 94 (64), 93 (17), 79 (14), 78 (55), 77 (20), 68 (9), 67 (6), 66 (29), 65 (84), 64 (7), 63 (15), 62 (7), 61 (6), 55 (10), 51 (24), 50 (16), 41 (7), 40 (11), 39 (56), 38 (15), 37 (7).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.60; H, 7.85.

Catalytic reduction of **10a** at atmospheric pressure with 10% Pd/C catalyst gave *trans*-2-methoxycyclohexanol, the structure of which was established by comparison of the ir and mass spectrum with that of an authentic sample prepared as reported previously.[48]

trans-6-Methoxycyclohexa-2,4-dien-1-yl acetate was prepared as a colorless liquid in 94% yield (short-path distillation) from reaction of **10a** with acetic anhydride in pyridine: ir ($CHCl_3$) 3020, 2980, 2810, 1735, 1455, 1410, 1370, 1295, 1225, 1100, 1080, 1020, 995, 945 and 900 cm^{-1}; uv max (95% C_2H_5OH) 259 nm (ϵ 4470); pmr ($CH_3C(=O)$–) 2.13, (CH_3O) 3.47, (H_6) 4.17, (H_1) 5.70, (H_{2-5}) 6.05 with J_{1-6} = 7; mass spectrum 136 (4), 133 (3), 109 (10), 108 (100), 94 (21), 93 (16), 79 (16), 78 (56), 77 (19), 65 (71), 63 (13), 51 (21), 50 (13), 45 (22), 44 (34), 43 (28), 39 (38), 38 (10).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.18. Found: C, 64.05; H, 7.35.

Catalytic reduction of the acetate at atmospheric pressure using 10% Pd/C catalyst gave *trans*-2-methoxycyclohexyl acetate, the ir and mass spectrum of which were identical with those of the product from acetylation of the authentic sample.[48]

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.89; H, 9.45.

The procedure used to prepare **10a** was used for the reaction of **1-*3,6-d*$_2$** (230 mg) with 556 mg of NaOMe in 6 ml of methanol for 21 days at room temperature. Short-path distillation of the product at room temperature (0.05 mm) gave **10a-*2,5-d*$_2$** in 31% yield: pmr (CH_3O) 3.5, (OH) 2.8, (H_1 and H_6) 4.1 and 4.6, (H_{2-5}) 6.0 with J_{1-6} = 12; the ir and mass spectrum were also consistent with the assigned structure.

Reaction of 1 with Ethanol. *trans*-6-Ethoxycyclohexa-2,4-dien-1-ol (10b). A solution of **1** (250 mg) was stored in 10 ml of ethanol for 2 months at room temperature. After evaporation of the solvent under reduced pressure, the residue was separated by tlc (benzene–chloroform–ethyl acetate, 1:1:1) to provide 50 mg of **10b** (R_f 0.6): pmr (vinyl) 5.73–6.0, (OH, broad) 2.28, (CH_3) 1.21, (CH_2) 3.62 and 3.53, (H_1 and H_6) 4.15 and 4.53 with $J_{CH_3-CH_2}$ = 7.0, J_{1-6} = 11.2, and J_{1-2} and J_{5-6} < 0.5. The compound (λ max 260 nm) is unaffected by warming with 1 *N* NaOH but when heated to 100° in 1 *N* HCl, the λ max changed to 270 nm.

Decomposition of 1 in the Presence of *tert*-Butoxide. A solution of 50 mg of **1** and 100 mg of potassium *tert*-butoxide was stored in 1 ml of *tert*-butyl alcohol at room temperature for 3 weeks. Most of the butanol was removed under reduced pressure before addition of 1 ml of 10% sodium carbonate and extraction of the products into ether. Evaporation of the ether and separation of the residual oil by tlc ($CHCl_3$) provided 5 mg of **11** which migrated slightly faster than phenol: pmr (H_1 and H_6) 4.75 and 5.12, (vinyl) 5.98, (aromatic) 6.8–7.6 with J_{1-6} = 11.0; λ max 264 nm (CH_3OH); mass spectrum, M^+ 188 (3%), 170 (42%), 160 (13%), 159 (28%), 95 (66%) and 94 (100%); M^+ calcd 188.0837, found 188.0822. In 50% aqueous methanol, 3 *M* in HCl, **11** decomposes to a mixture of phenol and diphenyl ether, identified by gplc. A comparable yield of **11** was obtained when **1** was reacted with sodium phenoxide for 12 hr in water.

A solution of 500 mg of **1** and a molar excess of potassium *tert*-butoxide was heated at reflux in 5 ml of *tert*-butyl alcohol for 12 hr at which time most of the starting oxide had been consumed. The solution was concentrated, 1 ml of water was added, the pH was adjusted to 7 with acetic acid, and the products were extracted with 2 × 5 ml of ether. The ether was removed under vacuum, and the residue was acetylated with acetic anhydride–pyridine. Analysis of the solution by gplc–mass spectrometry (15% SE-30, 190°) showed the presence of diphenyl ether (3.0% yield, 4.2 min) and *o*-acetoxybiphenyl (0.8% yield, 8.5 min) in addition to a large amount of phenyl acetate. A trace component corresponding to *p*-acetoxybiphenyl (16 min), as well as two other minor unidentified compounds, were detected.

(48) S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, **65**, 2196 (1943).

Reaction of 1 with Hydrogen Peroxide. *trans*-Cyclohexa-3,5-diene-1,2-diol (12). A solution prepared from 20.3 g of 30% hydrogen peroxide, 7.2 g (180 mmol) of NaOH, and 25 ml of water was cooled to 0°, and 0.50 g (5.3 mmol) of **1** was added in one portion. After 3.75 hr, the characteristic color of **1** was discharged. The mixture was diluted with 30 ml of water and cooled to 0°, and a solution of 7.60 g (200 mmol) of sodium borohydride in 80 ml of water was added dropwise with stirring over the course of 1.5 hr. The solution was allowed to warm to room temperature, was stirred for 15 hr, and was continuously extracted with ether for 72 hr. The ether solution was dried (Na_2SO_4) and concentrated under reduced pressure to give a product mixture that consisted of 56% **12** and 44% phenol. Recrystallization from ether gave 176 mg (30%) of **12**: mp 74–75° (lit.[27] mp 73–74°). The ir and uv spectra of **12** were identical with those reported previously.[27]

Reaction of 1 with Azide. *trans*-6-Azidocyclohexa-2,4-dien-1-ol (13a). A mixture of 1.90 g (20 mmol) of **1** and 1.40 g (22 mmol) of sodium azide in 50 ml of water was stirred at room temperature for 3 hr. The organic layer gradually dissolved, and all the characteristic yellow of **1** faded to brown. The solution was extracted with two 50-ml portions of ether. The ether layer was separated, washed with 5% aqueous NaOH, and dried. Evaporation gave 1.5 g (55%) of a very pale yellow liquid, **13a**, that could be distilled as a colorless oil: bp 60–65° (3–4 mm); ir (CCl_4) 3600, 3400, 3050, 2840, 2130, 1420, 1315, 1290, 1260, 1230, 1085, 1030, 890, and 790 cm^{-1}; uv max (95% C_2H_5OH) 262 nm (ϵ 3163); pmr (see Figure 1); mass spectrum 95 (7), 94 (100), 79 (42), 77 (12), 66 (30), 65 (20), 51 (10), 43 (53).

Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.12. Found: C, 52.49; H, 5.25.

A solution of **13a**, as prepared above (1.30 g, 9.5 mmol) in 25 ml of ether, was added dropwise to a slurry of lithium aluminum hydride (2.0 g, 52.5 mmol) in 75 ml of ether at 0°. The mixture was stirred for 1 hr and hydrolyzed by adding carefully at 10-min intervals: 2.0 ml of water, 1.5 ml of 20% aqueous NaOH, and 7.0 ml of water. The solution was stirred for several hours, until all the hydride had formed a granular precipitate. The solution was filtered, and the precipitate was washed with six portions of ether. The filtrate and combined washes were dried, filtered, and evaporated to give a yellow oil that was distilled under high vacuum (0.05 mm, pot temp 60°) to yield 631 mg (60%) of a colorless oil that crystallized in the receiver. Recrystallization from ether–pentane gave *trans*-2-amino-3,5-cyclohexadien-1-ol as glistening white needles: mp 62.0–63.5°; ir ($CHCl_3$) 3580, 3460, 2980, 2910, 2840, 1580, 1410, 1080, 1015, and 890 cm^{-1}; λ max (CH_3OH) 260 nm (ϵ 2731); pmr (NH_2 and OH) 2.80 (exchangeable), (H_2) 3.50, (H_1) 4.18, (H_{3-6}) 5.85 with J_{1-2} = 12; mass spectrum 112 (2), 111 (36), 94 (17), 93 (38), 82 (45), 80 (12), 69 (14), 68 (13), 67 (19), 66 (42), 65 (27), 59 (31), 56 (14), 55 (14), 54 (13), 44 (14), 43 (100), 42 (14), 41 (22), 40 (11), 39 (38); M^+ calcd 111.06841, found 111.06818.

Anal. Calcd for C_6H_9NO: C, 64.87; H, 8.19; N, 12.61. Found: C, 65.09; H, 8.43; N, 12.53.

Acetic anhydride in pyridine at 0° converted the amino alcohol to the diacetate derivative (59%), the spectral data of which were identical with those reported in the literature.[29]

Deuterated analogs of **13a** were prepared with either **1-*3,6-d*$_2$** or **1-*1,2,3,4,5-d*$_5$** in a manner similar to that described above, with the exception that the product was isolated by tlc ($CHCl_3$ at 0°, R_f 0.35) in order to avoid potential and selective destruction of less stable isomers which might have been present. The yields were similar to that obtained for **1**. The pmr spectrum (100 MHz) of the tlc isolated product from **1-*1,2,3,4,5-d*$_5$** showed (H_1) absent, (H_2) 6.0, (H_3) 6.04, (H_4) absent, (H_5) 5.86, and (H_6) 4.08 as broad singlets after D_2O exchange. An additional signal at 6.3 was also present. The signal at 4.08 can only be attributed to 1,6 addition. A corresponding signal of equal intensity for this molecule, present at 6.04, is required. Signals at 6.0 and 5.86 correspond to 1,2 addition. The signal at 6.3, which appears more complex at 220 MHz (see Figure 1) in the sample of **13a**, was attributed to the vinyl hydrogens resulting from 1,4 addition. Integration of the 100 MHz spectrum indicated the percentages of each as 55% for 1,2, 40% for 1,6, and 5% for 1,4 addition. Since the amount of apparent 1,4 addition was very small, no attempt was made to isolate or further characterize this product. Reduction and acetylation of **13a** (see above) were demonstrated to produce only the trans acetamidoacetate. Thus the pentadeuterio products were reduced to the amino alcohols to ensure that none of the products resulting from the three modes of addition was selectively lost. After hydrolysis as above and tlc purification (R_f 0.55, 1% concd NH_4OH in

methanol, 4°), integration of the pmr spectrum, with signals at 3.52, 5.76, 5.89, and 5.96, indicated that this was the case. The pmr spectrum of **13b** and **13c** was entirely consistent with these arguments and Figure 1.

Reaction of 2 with Azide. *trans*-**1-Hydroxy-2-azido-1,2-dihydronaphthalene (14).** A mixture of 25 mg of **1**, 20 mg of sodium azide, and 4 ml of water was stirred for 5 hr at 0° at which time all the **2** had been consumed. The organic products were extracted into ether, and the ether was washed with dilute NaOH, dried with sodium sulfate, and concentrated to yield 20 mg of white crystalline solid, mp 72–73° from benzene–petroleum ether. The pmr spectrum of the crude product indicated a 10:1 mixture of two isomeric components. The major component (**14**) showed (H_1) 4.83, (H_2) 4.20, (H_3) 5.92, (H_4) 6.65, (aromatic) 7.0–7.6 with J_{1-2} = 8.0, J_{2-3} = 3.5, J_{2-4} = 1.6, and J_{3-4} = 9.6. The signal for H_2 shows line broadening owing to quadrupole relaxation and confirms this assignment based on line position when compared to the corresponding diol.[49] The minor component presumably arising by attack of azide at C-1, showed (H_1) 4.69 and (H_2) 4.47. The remaining hydrogens were obscured by the major component. In comparison with *trans*-1,2-dihydroxy-1,2-dihydronaphthalene,[49] the upfield shift from >CHOH to >CHN$_3$ was 0.27 in the major isomer **14** and 0.24 in the minor isomer, while the carbinol hydrogens in these components corresponded exactly. The mass spectrum for **14** showed 188 (M + 1, 23), 187 (M^+, 2), 159 (19), 183 (70), 127 (100), and 94 (83); M^+ calcd 187.074, found 187.072.

Reaction of 1 with Thiophenol. *trans*-**6-Phenylthiocyclohexa-2,4-dienol (15).** Thiophenol (7.8 g, 71 mmol) and NaOH (2.84 g, 71 mmol) were dissolved in 65 ml of water, and the solution was stirred, while **1** (1.33 g, 14.2 mmol) was added. After 45 min, the white solid that formed was isolated by filtration. The solid was washed with cold water and cold petroleum ether and was recrystallized from hexane to give 1.87 g (64%) of **15**, as white crystals: mp 35–36.5°; ir (CCl_4) 3580, 3050, 3000, 1580, 1480, 1438, 1410, 1380, 1200, 1080, 1060, 1020, 990, and 950 cm^{-1}; pmr (100 MHz in $CDCl_3$) (H_1) 4.33, (H_6) 4.10, (H_{2-5}) 5.7–6.1, (aromatic) 7.1–7.4 with J_{1-6} = 3.0 (D_2O washed); mass spectrum, M^+ 204 (16), 186 (5), 185 (4), 110 (100), 95 (67), 94 (42); M^+ calcd 204.0609, found 204.0605.

Sulfide **15** reacted with maleic anhydride in ether at 0° over a period of 36 hr to form a Diels–Alder adduct (33%) that was acetylated with acetic anhydride in pyridine to form *trans*-6-acetoxy-5-phenylthiobicyclo[2.2.2]oct-2-ene-7,8-dicarboxylic anhydride. The acetate was purified by recrystallization from THF–pentane; pmr (100 MHz, acetone-d_6) (CH_3) 2.0, ($H_{1,4,6,7,8}$) 3.3–3.9, (H_5) 4.7, ($H_{2,3}$) 6.3–6.5, (aromatic) 7.3–7.6 with J_{5-6} = 3. The observed coupling of 3 between the hydrogens on the carbons bearing the acetoxy and phenylthio groups is consistent only with the trans isomer.[50]

Reaction of thiophenol with **1-*1,2,3,4,5-d*$_5$** in a manner analogous to that described above followed by acetylation with acetic anhydride–pyridine provided the deuterated acetate, the pmr spectrum of which showed only vinyl hydrogens at 5.85 and 5.93, in addition to the acetate signal at 1.9 and aromatic protons at 7.1–7.6. The integration of the vinyl region indicated ~0.5 hydrogens were present relative to the aromatic and acetate signals, in good agreement with the deuterium content determined from the mass spectrum of the maleic anhydride adduct of the starting oxide.

Reaction of 1 with Thioethanol. *trans*-**6-Ethylthiocyclohexa-2,4-dien-1-ol (16).** A mixture of 50 mg of **1**, 100 mg of thioethanol, and 2 ml of 1 *M* NaOH was stirred at 0° for 1 hr at which time all **1** had been consumed. The product was extracted into ether which was dried ($NaSO_4$) and concentrated to 60 mg of an oil (R_f 0.27, $CHCl_3$); mass spectrum, M^+ 156 (83), 138 (9), 127 (39), 109 (19), 95 (100), 94 (91); M^+ calcd 156.0608, found 156.0573; pmr spectrum (100 MHz), (H_1) 4.26, ($H_{2,5}$) 5.86, ($H_{3,4}$) 5.96 and 6.1, and (H_6) 3.50 with J_{1-6} = 3.5, J_{1-2} = 4.5, J_{4-6} = 0.7, and J_{5-6} = 4.5 (D_2O washed), in addition to the signals from the ethyl group. The coupling of J_{1-6} = 3.5 in **16** compares well with the value of 3.0 in **15**, which was proved to have trans stereochemistry. In the monoacetate of **16**, the signal for H_1 appears at 5.50, while H_6 remains nearly unchanged at 3.60, confirming the assignment for these two positions with J_{1-6} = 2.0. When the reaction with thioethanol was repeated with **1-*1,2,3,4,5-d*$_5$**, the pmr spectrum of the product showed a signal at 5.86 for $H_{2,5}$, while no signal could be detected for H_1 or H_6, indicating exclusive 1,2 addition.

Reaction of 1 with Thiolacetate. *trans*-**6-Thiolacetoxycyclohexa-2,4-dien-1-ol (17).** A mixture of 50 mg of **1**, 100 mg of thiolacetic acid, and 2 ml of phosphate buffer (pH 7.0, 0.1 *M*) was stirred at 0° until **1** was consumed (4 hr). The solution was extracted with ether, and the ether was dried and concentrated to provide 70 mg of colorless oil. The infrared spectrum as a thin film showed a strong band at 1690 cm^{-1} indicative of a thiol ester,[51] while the pmr spectrum showed (H_1) 4.22, (H_{2-5}) 5.8–6.2, (H_6) 4.50, and ($CH_3C(=O)$–) 2.37 with J_{1-2} = 5.0, J_{1-6} = 3.0, J_{5-6} = 5.5. The electron-impact mass spectrum does not show a molecular ion. However, chemical ionization (isobutane) shows M + 1 (171, <1%) and loss of water (153, 100%); (M + 1)$^+$ calcd 171.0480, found 171.0450. Treatment with 1% trifluoroacetic acid in $CHCl_3$ gave, upon separation by gplc (15% SE-30, 130°), phenol (15%, 4.2 min) and thiophenyl acetate (85%, 17.8 min). Based on this information, the structure was assigned as **17**; the value of J_{1-6} = 3.0 is similar to **15** and **16**, and the trans stereochemistry is assumed. When reaction with thiolacetic acid was repeated with **1-*3,6-d*$_2$**, integration of the pmr spectrum of the product indicated one hydrogen at positions 1 and 6, relative to the methyl group, which established 1,2 addition had occurred.

Reaction of 1 and 2 with Thiocyanate. A mixture of 50 mg of **1**, 200 mg of KSCN, and 2 ml of water was stirred at 0° for 4 hr, at which time most of the starting oxide had been consumed. The pmr spectrum of a $CDCl_3$ extract of the aqueous solution after D_2O exchange showed the presence of benzene and phenol in a ratio of 1:10, as well as some residual benzene oxide. The benzene was further characterized by gplc–mass spectrometry. A solution of 30 mg of **2**, 30 mg of NaSCN, and 0.4 ml of methanol-d_4 was monitored by pmr at room temperature for 3 hr. Within 24 hr, all the starting **2** had been consumed. Only fully aromatic products could be detected during the course of the reaction. After acetylation with an excess of acetic anhydride, combined gplc–mass spectrometry with a 1% OV-17 column programmed up from 80° at 5°/min established the presence of naphthalene (90%) and acetoxynaphthalenes (10%), along with trace amounts of several other materials.

Reaction of 2 with Thioethanol. *trans*-**1-Hydroxy-2-ethylthio-1,2-dihydronaphthalene (19).** A mixture of 28 mg of **2**, 100 mg of thioethanol, and 5 ml of 1% aqueous NaOH was agitated under nitrogen for 5 hr. The products were extracted into ether which was then dried (Na_2SO_4) and concentrated to yield 30 mg of colorless oil: pmr spectrum (100 MHz) (H_1) 4.76, (H_2) 3.68, (H_3) 5.98, (H_4) 6.55, (CH_2) 2.46, (CH_3) 1.18, and (aromatic) 7.0–7.75 with J_{1-2} = 4.2, J_{2-3} = 4.6, J_{3-4} = 9.2, $J_{CH_2-CH_3}$ = 8.0. A minor contaminant (<15%) showed absorptions at 4.07, 4.36, and the vinyl region. A major component was assigned as **19** by arguments similar to those used in assignment of **14**. The mass spectrum of the mixture showed M^+ 206 (15), 188 (25), 160 (20), 145 (54), 144 (35), 128 (100), 115 (54); M^+ calcd 206.0765, found 206.0771; λ max 260 nm (methanol). When the pmr spectrum of **19** was measured in dimethyl-d_6 sulfoxide, an additional coupling (J_{2-4}) was observable; thus J_{1-2} = 2.8, J_{1-3} = 1.0, J_{2-3} = 5.4, J_{2-4} = 1.0, J_{3-4} = 9.4. Observation of J_{2-4} in this solvent provides an unequivocal means of assigning relative stereochemistry to the molecule. Bond angles between all four hydrogens were estimated by inspection of Dreiding models of the cis and trans isomers in each of their extreme conformations. The Karplus relationship[52] for the expected sign and magnitude of these coupling constants requires the absolute sign of only one coupling, the four bond J_{2-4} in the trans isomer, to have a negative absolute sign. The sign of J_{2-4} was demonstrated to be opposite from that of J_{2-3}, which is necessarily positive[52] by the standard spin-tickling experiment.[53] Thus, the major isomer, arising from attack by sulfur at C-2, has the trans stereochemistry. The minor contaminant is assumed to arise from attack at C-1 from the observed line positions.

Reaction of 1 with Sodium Sulfide. Bis(6-*trans*-1-hydroxycyclohexa-2,4-dienyl) Sulfide (18a,b). A mixture of **1** (2.5 g, 26.6 mmol) and $Na_2S \cdot 9H_2O$ (32 g, 133 mmol) in 25 ml of water was stirred at 0° for 45 min. The mixture was washed with 6 × 60-ml portions of ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a crystalline product that was washed with pentane and dried: 1.6 g (54%); mp 75–79°; ir ($CHCl_3$) 3580, 3400, 3040, 3000, 1415, 1385, 1220, 990, and 950 cm^{-1}; λ max (95% C_2H_5OH) 258 nm (ε 7930); mass spectrum (20 eV) M^+

(49) D. M. Jerina, J. W. Daly, A. M. Jeffrey, and D. T. Gibson, *Arch. Biochem. Biophys.*, 142, 394 (1971).

(50) D. T. Gibson, *et al.*, *Biochemistry*, **9**, 1626 (1970).

(51) R. A. Nyquist and W. J. Potts, *Spectrochim. Acta*, 7, 514 (1959).

(52) E. D. Becker, "High Resolution NMR," Academic Press, New York, N. Y., 1969, p 104.

(53) See, for example, R. Freeman and W. A. Anderson, *J. Chem. Phys.*, **37**, 2053 (1962).

222 (13), 204 (12), 186 (100), 128 (29), 126 (28), 110 (100), 95 (92), 94 (90), 78 (80).

Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.86; H, 6.31. Found: C, 64.62; H, 6.29. The ^{13}C nmr spectrum of this material, however, suggested the presence of a major and minor isomer; ^{13}C nmr (acetone) in parts per million upfield from ^{13}C = 0 of solvent (major isomer) δ 78.4 (4 C, olefinic), 81.3 (2 C, olefinic), 82.5 (2 C, olefinic), 137.1 (2 C, C–O), and 160.5 ppm (2 C, C–S); (minor isomer) δ 78.8 (2 C, olefinic), 79.1 (2 C, olefinic), 81.5 (2 C, olefinic), 82.2 (2 C, olefinic), 137.3 (2 C, C–O), and 160.7 ppm (2 C, C–S).

The major product could be converted to a pure, crystalline diacetate in 67% yield from reaction of the mixture with acetic anhydride in pyridine: mp 115.5–116.5°; ir ($CHCl_3$) 3045, 3000, 2940, 1730, 1375, 1225, 1020, 995, and 915 cm^{-1}; λ max (95% C_2H_5OH) 258 nm (ϵ 6760), 283 nm (ϵ 3570 sh); pmr ($CDCl_3$) ($CH_{3'8}$) 2.08, ($H_{1'8}$) 5.60, ($H_{6'8}$) 3.85, ($H_{2-5'8}$) 5.7–6.5 with J_{1-2}, $J_{1-6} < 1$, and $J_{5-6} = 4.5$;[54] ^{13}C nmr ($CHCl_3$) relative to $^{13}CHCl_3$ δ 92.9 (2 C, C=O), −50.1 (2 C, olefinic), −48.3 (2 C, olefinic), −46.7 (2 C, olefinic), −43.5 (2 C, olefinic), 7.7 (2 C, *C*–OAc), 35.5 (2 C, C–S), and 56.1 ppm (2 C, CH_3–); mass spectrum 188 (4), 187 (12), 186 (72), 185 (37), 184 (15), 171 (6), 152 (6), 109 (7), 78 (16), 77 (17), 69 (10), 65 (12), 60 (37), 52 (8), 51 (37), 50 (15), 45 (89), 43 (100), 42 (17), and 39 (17).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.80; H, 5.88. Found: C, 62.68; H, 5.69.

The above reaction was repeated on 100 mg of **1** but without the pentane wash to provide a 72% yield of crude products. The ^{13}C nmr spectrum of this sample showed the above two isomers to be present in approximately equal amounts. In addition, about one-third of the sample had dehydrated to **15**, which was identified from its tlc properties and pmr spectrum. Neither ^{13}C nmr nor pmr gave any indication that this sample of **15** was a mixture of stereoisomers. An approximately 1:1 mixture of the bis sulfides above was stored in chloroform at room temperature until more than 50% decomposition had occurred (R_f 0.35 for bis sulfides, 0.60 for **15**, and 0.90 for diphenyl sulfide; chloroform–ethyl acetate, 1:2). The pmr (100 MHz) spectra of the starting bis sulfide mixture and the recovered bis sulfide mixture were identical but could not be assigned since two superimposed spectra were clearly present. Irradiation of the vinyl protons or substitution by deuterium (see below) enables this to be seen more clearly. At 4° the two isomers are separable by tlc (solvent above), provided small amounts of material are applied to the plates. The compound at high R_f (0.38) was crystalline; pmr spectrum, (H_1) 4.32, (H_{2-5}) 5.8–6.2, (H_6) 3.62 with J_{1-2} = 4.5, J_{1-6} = 4.5, J_{5-6} = 4.6. The lower R_f (0.32) isomer remained an oil; pmr spectrum (H_1) 4.27, (H_{2-5}) 5.7–6.2, (H_6) 3.59 with J_{1-2} = 4.8, J_{1-6} = 2.9, J_{5-6} = 5.2. These spectra were measured at 220 MHz after exchange with D_2O. The crystalline and oily isomers show identical mass spectra at 20 eV.

In summary, the ^{13}C nmr spectrum of the crystalline isomer requires that the same stereochemistry be present in both rings. Similarly, the pmr spectra of the separated isomers indicate the same stereochemistry is present in both rings of each molecule. In addition, both isomers dehydrate at about the same rate and give only **15**, which eliminates the possibility that either is cis,cis. The only remaining possibility is that the two isomers are the meso and racemic trans,trans structures **18a** and **18b**, bis(6-*trans*-1-hydroxycyclohexadien-2,4-yl) sulfide.

Through the use of **1**-*3,6*-d_2 and **1**-*1,2,3,4,5*-d_5, it was established that the additions for both rings in both isomers occurs exclusively by 1,2 opening; *cf.* reactions of azide and thiophenoxide with deuterated **1** for method of analysis.

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(54) The previous assignment of J_{1-6} = 4.5 Hz is incorrect.[28] Note also the change in numbering system used here.

Stereochemical Aspects of the Reaction of 2-Phenyl-Substituted Alkenylidenecyclopropanes with Chlorosulfonyl Isocyanate[1]

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Abstract: The stereochemical aspects of the reactions of alkenylidenecyclopropanes with CSI to produce bisalkylidenecyclopentane derivatives have been studied using (−)-(*R*)-2-phenylisobutenylidenecyclopropane ((−)-(*R*)-**5**) and a mixture of (*E*)- and (*Z*)-2-phenyl-1-(2,4-dimethyl-1-pentenylidene)cyclopropane (**13**). At 0° and below (−)-(*R*)-**5** reacts to form **6** in a highly stereoselective manner with inversion of configuration. The diene **7** is also formed optically active, the right-handed helicity of the diene being assigned on the basis of stereochemical interrelations and mechanistic arguments. At +30° the reaction proceeds with partial loss of optical activity, while at 61.2° complete loss of optical activity is observed. The observations are discussed in terms of the relative rates of bond rotation (leading to loss of optical activity) *vs.* collapse of the dipolar intermediate formed in the reaction. The results derived with **13** show that the facial selectivity of attack by CSI on the alkenylidenecyclopropane is sensitive to the steric features of groups attached to the terminal allene carbon and on the three-membered ring indicating that the CSI must attack the perpendicular (to the ring) p orbital on C_4 of the C_1–C_4 double bond.

Alkenylidenecyclopropanes (**1**) react with chlorosulfonyl isocyanate (CSI) to produce, in part depending on the nature of the functions attached to the three-membered ring, cycloaddition adducts of structure **2** and **3**.[2] The mechanism for the formation of **2** and **3** was visualized as proceeding *via* electrophilic attack on the perpendicular (with respect to the plane of the three-membered ring) p orbital on C_4 resulting in the formation of a cyclopropyl cation which underwent disrotatory ring opening to produce a dipolar intermediate (**4**). Collapse of **4** by nucleophilic attack by nitrogen or oxygen on either end of the allyl cation portion of **4**

(1) Part VII of a series Cycloaddition Reactions of Cyclopropane-Containing Compounds. For part VI see D. J. Pasto and J. K. Borchardt, *J. Amer. Chem. Soc.*, **96**, 6220 (1974).

(2) D. J. Pasto, A. F.-T. Chen, G. Ciurdaru, and L. A. Paquette, *J. Org. Chem.*, **38**, 1015 (1973).