SYNTHESIS AND REACTIONS OF ARENE OXIDE-OXEPIN SYSTEMS

by

Daniel Edward Piccolo

B.S. in Chemistry, Boston College

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August, 1973

Signature of Author _____
Department of Chemistry, August 31, 1973

Certified by _____
Thesis Supervisor

Accepted by _____
Chairman, Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor C. Gardner Swain_____
Chairman

Professor Glenn A. Berchtold_____
Thesis Supervisor

Professor George Büchi_____

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ABSTRACT

Oxepin-benzene oxide (1) undergoes trans 1,2 addition with methoxide ion in methanol to give trans-6-methoxycyclohexa-2,4-dien-1-ol (4). Ethoxide ion in ethanol reacts with 1 in a similar fashion to give the diene 12. Hydroperoxide ion in water undergoes nucleophilic addition to 1 to give, after reduction, trans-1,2-dihydroxy-1,2-dihydrobenzene (2).

Oxepin undergoes electrophilic addition with mercuric acetate to give trans,trans-2,4-hexadien-1,6-dial (18). 2,7-Dimethyloxepin (24) also reacts with mercuric acetate to give trans,trans-3,5-octadien-2,7-dione (26).

The synthesis of 4-chlorooxepin-benzene oxide (29) was accomplished by the following sequence. Bisdecarboxylation of 4-chloro-1,2,3,6-tetrahydrophthalic acid (30) with lead tetraacetate gave 1-chloro-1,4-cyclohexadiene (31). Epoxidation of the diene with peracetic acid gave 1-chloro-4,5-epoxycyclohex-1-ene (33). Allylic bromination of the epoxide with N-bromosuccinimide, followed by treatment with base, gave 29.

4-Chlorooxepin undergoes nucleophilic addition with sodium methiolate in aqueous dioxane to give the dienes 39 and 40 in a ratio of 1:1, respectively. Methoxide ion in methanol undergoes trans addition to 29 to give the dienes 45 and 46 in a ratio of 78:22, respectively. Hydroperoxide ion in water adds to 29 to give, after reduction, 4-chloro-trans-1,2-dihydroxy-1,2-dihydrobenzene (28).

Thesis Supervisor: Glenn A. Berchtold
Title: Professor of Chemistry

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INTRODUCTION

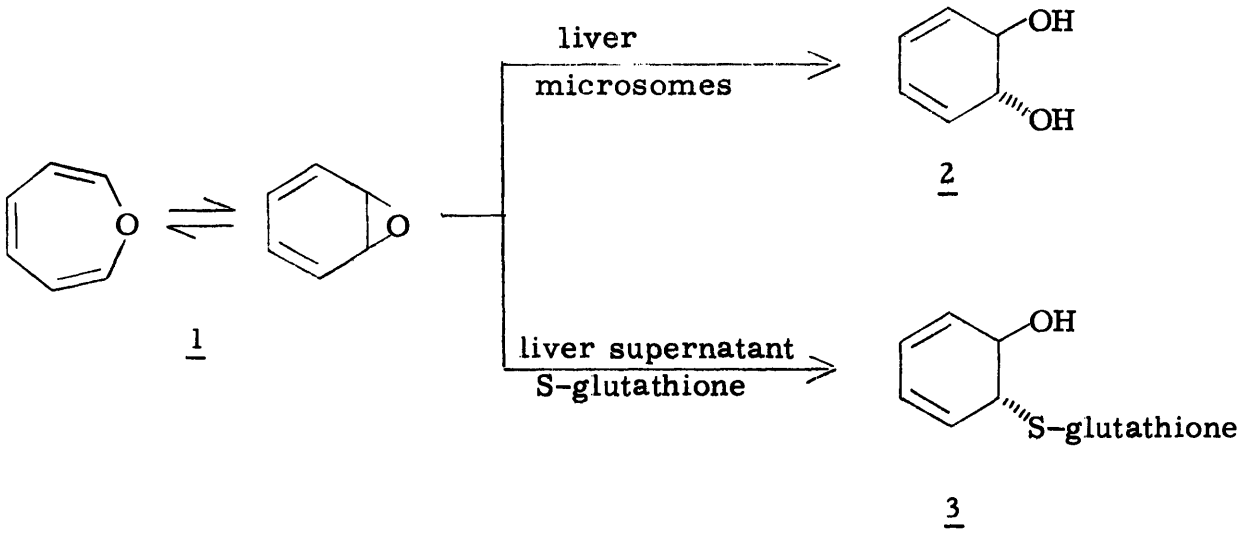
Oxepin-benzene oxide (1) and its derivatives are potential precursors to substituted 1,2-dihydroaromatic substances through nucleophilic additions to the benzene oxide isomer. However, relatively little is known about the susceptibility of arene oxides to such nucleophilic reactions.

Of the nucleophiles which have been examined with benzene oxide, the following has been observed: 1) methyllithium adds cis 1,6;[1] 2) dimethylmagnesium adds cis 1,6 and trans 1,2;[2] 3) sodium sulfide[3] and thiophenoxide[2] add trans 1,2; and 4) azide adds trans.[3]

Arene oxides are now recognized as important biological intermediates. The occurrence of the NIH shift in the enzymatic hydroxylation of aromatic compounds is explained by the intermediacy of arene oxides.[4,5] The metabolism of aromatic substances is known to proceed at least in part through the formation of the arene oxide and subsequent enzyme-catalyzed additions of nucleophiles such as water and glutathione.[5-11] For instance, Jerina et al.[6] have reported the enzyme-catalyzed ring opening of 1 to give the dihydrodiol 2 or the premercapturic acid conjugate 3, as shown in Scheme I.

The carcinogenic activity of arene oxides[12] may be due to similar reactions with macromolecules.

Scheme I



1 2 3

For the above reasons, the reaction of 1 with various oxygen nucleophiles has been investigated in order to determine the reactivity of 1, the site of attack by the nucleophiles, and the stereochemistry of the products formed.

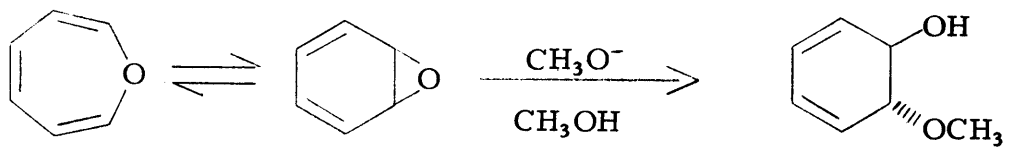
RESULTS AND DISCUSSION

I. Reactions of Oxepin-benzene Oxide

The addition of oxygen nucleophiles to 1, despite being a facile enzymatic reaction[6] (Scheme I), has not been reported in non-enzymatic reactions. In order to determine the utility of 1 as a precursor to 1,2-dihydroaromatic substances, such as 2, the reactions of 1 with various oxygen nucleophiles were investigated.

In neutral methanol 1 undergoes complete rearrangement at room temperature to phenol within two days. However, 1 does react with methoxide ion in methanol to give trans-6-methoxycyclohexa-2,4-dien-1-ol (4) as indicated in Scheme II.

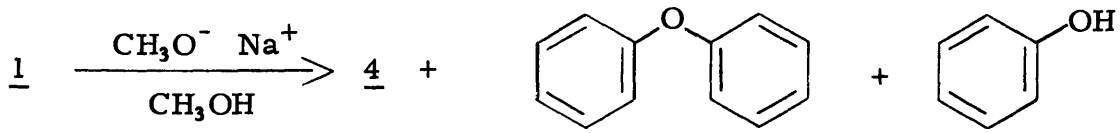
Scheme II



1 4

Initially the reactions of 1 with methoxide ion were carried out in nmr tubes and monitored regularly. The vinyl and allylic protons of 4 could be easily observed in the nmr spectrum of the reaction. With a trace of sodium methoxide in methanol at room temperature, all of the oxepin had reacted after 54 days to give 4 as the major product. In addition to 4 a small amount of aromatic products was observed. Analysis of the crude product by nmr and glpc (see Experimental Section) showed that it consisted of 86% of 4 and 14% of mainly diphenylether (5) and a small amount of phenol (6) (see Scheme III).

Scheme III



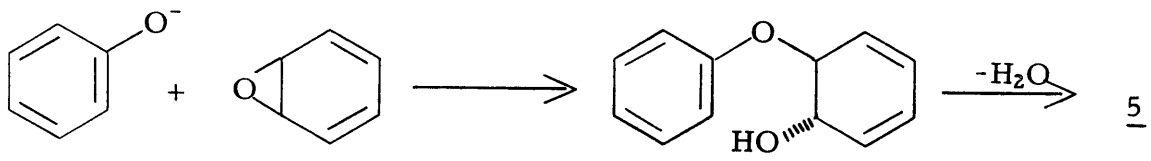
5 6

R.T. (54 d)	86%	14%
48° (7 d)	73%	27%

At 48° the reaction is complete after only 7 days, however the amount of 5 and 6 produced increases (27%).

The phenol is simply the result of rearrangement of 1. The production of 5 is probably the result of nucleophilic attack of phenoxide ion on 1, followed by dehydration as shown in Scheme IV.

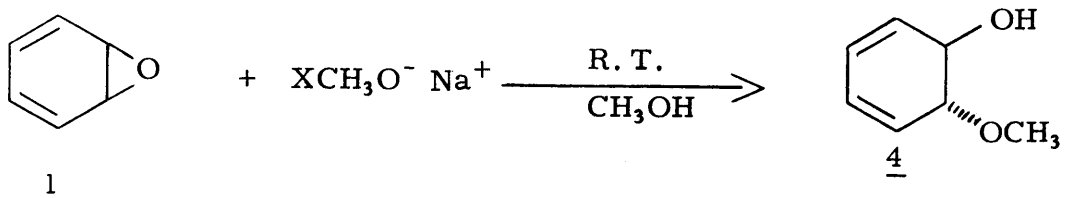
Scheme IV



That the aromatic products are not the result of decomposition of diene 4 was shown by allowing the reactions to continue after all of 1 had reacted. No significant changes in product composition were observed.

In order to avoid the increase in aromatic products associated with increasing the temperature, and to increase the rate so that the reaction becomes synthetically feasible, the following reactions were carried out on a preparative scale and are summarized in Scheme V.

Scheme V



1

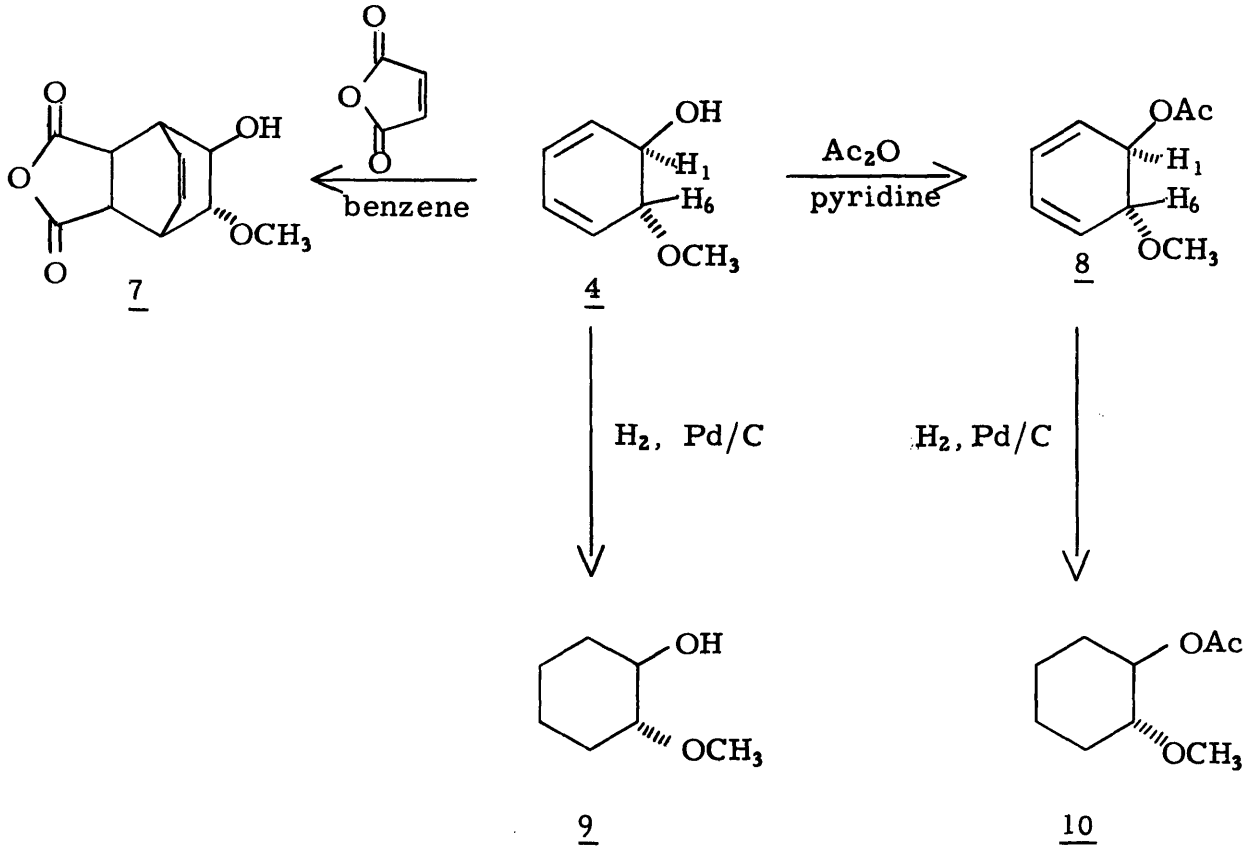
X	Reaction Time	Yield of 4
trace	69 days	78%
2	27 days	65%
4	14 days	64%

In all three cases only a small amount of aromatic products was observed in the nmr spectrum of the reaction.

Thus, the best synthetic procedure to diene 4 is the use of a fourfold excess of sodium methoxide in methanol at room temperature.

Diene 4 forms a 1:1 adduct (7) with maleic anhydride in 40% yield and with acetic anhydride in pyridine it gives a 94% yield of acetate 8, as shown in Scheme VI.

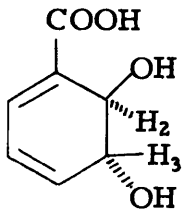
Scheme VI



The assignment of trans stereochemistry in diene 4 and acetate 8 is based on the nmr spectra in which $J_{H_1-H_6}$ in 4 is 10.5 Hz in $CDCl_3$ and 10 Hz in DMSO-d_6; and $J_{H_1-H_6}$ in 8 is 7.5 Hz.

Further confirmation of stereochemistry was obtained by catalytic reduction of 4 and 8 to 9 and 10, respectively, and comparison with authentic samples.[13]

It is interesting to note that $J_{H_1-H_6}$ in the nmr spectrum of 4 does not show the solvent dependence observed for similar systems. Batterham[14] has found that for the diene 11 $J_{H_2-H_3}$ is 8.3 Hz in $CDCl_3$



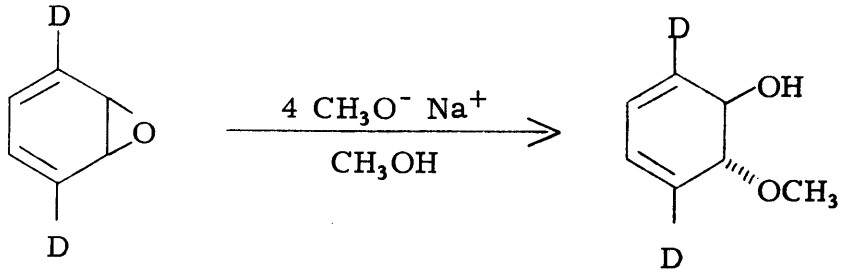
11

and 10% DMSO and is 2.0 Hz in DMSO. The explanation offered is that in $CDCl_3$ and 10% DMSO, the oxygen substituents are held in the quasi-equatorial conformation by intramolecular hydrogen bonding, whereas in pure DMSO these bonds are weakened, allowing the bulky oxygen substituents to more readily assume the less crowded quasi-axial conformation. Apparently, diene 4 adopts the conformation in

which the oxygen substituents are predominantly quasiequatorial in either $CDCl_3$ or DMSO.

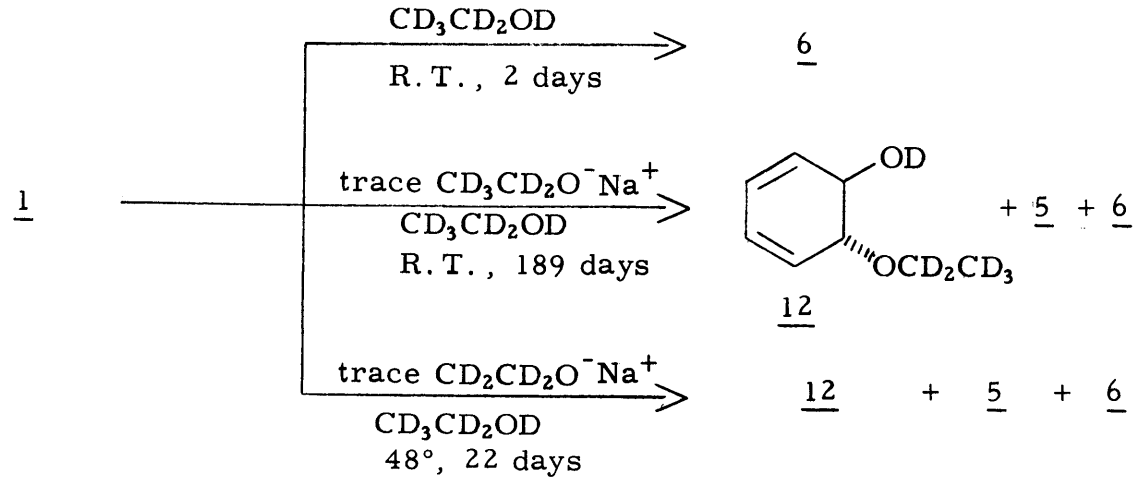
That 4 is formed by a 1, 2 addition of methoxide ion to 1 was established by the reaction of methoxide with labelled oxepin-benzene oxide as indicated in Scheme VII.[2]

Scheme VII



Similar results were obtained with ethoxide ion in ethanol and are summarized in Scheme VIII.

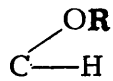
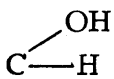
Scheme VIII



The structure of diene 12 was established by comparison of its nmr spectrum with that of diene 4, as shown in Table I.

Table I

NMR ($CDCl_3$) Chemical Shifts (δ, TMS, 60 MHz) of 4 and 12

Compound	Vinyl H		
4	5.95 (m)	4.08, d, J=10.5 Hz	4.55, d, J=10.5 Hz
12	5.92 (m)	4.08, d, J=10.5 Hz	4.52, d, J=10.5 Hz

In 1963, Sato et al.[15] observed trace amounts of trans-1,2-dihydroxy-1,2-dihydrobenzene (2) as an in vivo metabolite (rabbit) of benzene. Nakajima et al.[16] had previously reported the synthesis of the dihydrodiol 2; however, the synthesis involved a difficultly available starting material. In view of the ease of addition of methoxide and ethoxide ions to 1, its ready availability, and the suggested role of 1 in the enzymatic formation of 2 from benzene,[5,6,11] the reaction of 1 with hydroxide ion was examined as a possible entry into the dihydrobenzene diol series.[17a,b]

The reactions were run in nmr tubes in D_2O and a variety of cosolvents and monitored regularly, and in all but one case (D_2O + $CD_3\overset{O}{\overset{\|}{C}}CD_3$) the pH of the solution was adjusted to 10. In each case 1 underwent re-

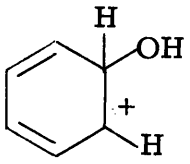
arrangement to phenol; the only difference was in the length of time for the rearrangement to be completed. In no case was the formation of any intermediate products observed. The results are summarized in Table II.

Table II

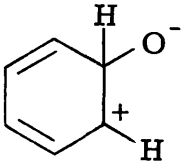
Reaction of Oxepin in D_2O and Cosolvents

Cosolvent	Temp	Time for Disappearance of 1
$CD_3\overset{O}{\overset{\|}{C}}CD_3$	R.T.	instantaneously
CD_3CN	48°	63 days
HMPA	48°	63 days
Dioxane	48°	139 days--still a small amount of oxepin present

These qualitative results are in agreement with kinetic studies by Bruice, which were published at a later date,[18,19] and can be summarized as follows. In aqueous solution under acid, neutral, or basic conditions 1 undergoes rearrangement to phenol. The acid-catalyzed isomerization appears to proceed through initial formation of carbonium ion 13, and the spontaneous isomerization under neutral or basic conditions proceeds via zwitterion 14. Water or simple alcohols are



13

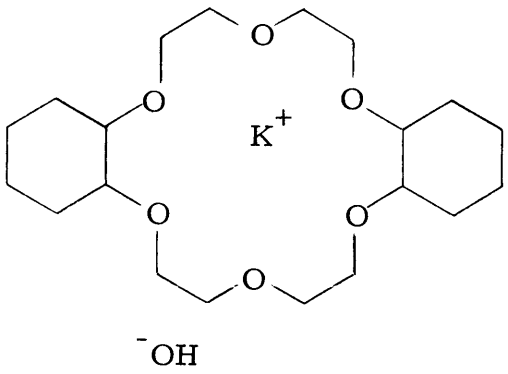


14

not sufficiently nucleophilic in aqueous solution, even at pH 12, to react with 1, 13, or 14 to form dihydrobenzene diol derivatives prior to isomerization.

In light of the smooth addition of ethoxide ion to 1, an alternate entry into the dihydrobenzene diol series seemed to be the addition of 2-cyanoethanol (15) to 1. The $CNCH_2CH_2$- group could then be removed by treatment with base to generate the diol 2. Several attempts to add alcohol 15 to 1 resulted in the formation of phenol exclusively.

Pedersen has reported that toluene solutions of the dicyclohexyl-18-crown-6 ether complex of potassium hydroxide (16) readily saponifies sterically hindered esters which are resistant to saponification by potassium hydroxide in hydroxylic solvents.[20] This was explained by the presence of unsolvated hydroxide ions. This seemed to be a promising method for the addition of hydroxide ion to 1 due to the increased nucleophilicity of the hydroxide ion and the use of a non-aqueous system.



16

Reaction of 1 with the complex 16 in toluene at room temperature gave phenol as the only product.

Nucleophilic addition to 1 is observed in aqueous solution with the more reactive nucleophiles, such as azide and sodium sulfide.[3] Sodium hydroperoxide, although not as nucleophilic as those mentioned above, is a much more reactive nucleophile than sodium hydroxide due to the α effect.[21] Thus, the reaction of 1 with sodium hydroperoxide in water, followed directly by reduction with sodium borohydride (no attempt was made to isolate an organic hydroperoxide, if formed) was investigated.

In the initial attempt to add hydroperoxide anion to 1, one equivalent of 1 was added to an aqueous solution of one equivalent of sodium hydroperoxide (0.2 M). After reduction, the oil isolated from this reaction was mainly phenol; however, there were two small singlets

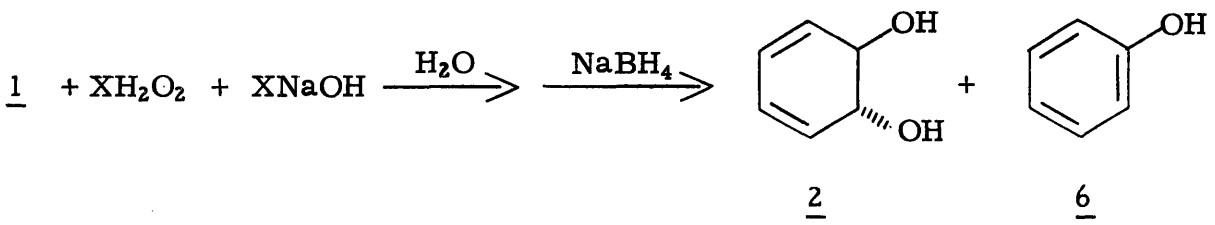
in the nmr spectrum of the reaction mixture at 5.92 and 4.48 ppm indicating the presence of a small amount of the desired dihydrodiol 2. The reaction was repeated with larger excesses of sodium hydroperoxide and at higher concentrations. The results are summarized in Scheme IX.

It is apparent from examination of these results that at low concentrations of hydroperoxide ion, isomerization of 1 in aqueous solution (vide supra) is the major reaction. As the concentration and molar excess of hydroperoxide ion is increased, nucleophilic addition competes favorably with isomerization to phenol. It is also interesting to note that both the concentration and the molar excess are important.

In those cases where water is the solvent, the reaction was heterogeneous due to the low solubility of oxepin in water. It was felt that the use of methanol as a cosolvent would strongly favor the nucleophilic addition reaction for two reasons: 1) The reaction would be homogeneous; and 2) oxepin has been shown to be remarkably stable in basic methanol. As can be seen in Scheme IX, this is not the case. No explanation can be offered.

Diol 2 was obtained in 30% yield as glistening white plates. The nmr spectrum of 2 shows four vinyl H's at 5.92 ppm (singlet), two allylic H's at 4.48 ppm (singlet), and the hydroxyl H's at 2.82 ppm (broad singlet). The ir and uv spectra were in excellent agreement with those of 2 prepared by an alternate route.[16]

Scheme IX



2 6

X	Conc. $Na^+ {}^-OOH$	Time (hr)[a]	Temp (°C)	Solvent	Ratio[b] 2 : 6	Yield of 2[c]
1	0.2 M	2	0-24	H_2O	trace : major	--
4	0.8 M	2	0-15	H_2O	25 : 75	--
15	2.0 M	3	0-20	H_2O	39 : 61	--
30	4.0 M	3	0-15	H_2O	70 : 30	--
30	4.5 M[d]	3.75	0-15	H_2O	56 : 44	30%
6	4.0 M	9	0-23	H_2O	minor : major	--
15	4.0 M	4.5	0-25	H_2O	minor : major	--
4	0.6 M	2.5	0-25	H_2O-CH_3OH	trace : major	--
30	2.7 M[d]	3	18-22	H_2O-CH_3OH	54 : 46	10%

a) Represents the time until the characteristic oxepin color was discharged, before the addition of $NaBH_4$.

b) Determined by integration of the nmr spectrum of the crude product.

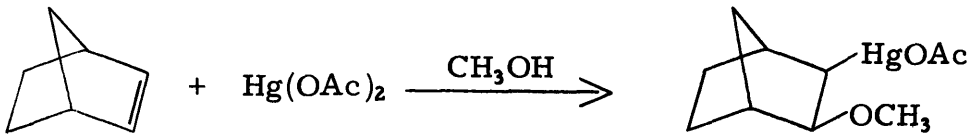
c) Yield of recrystallized diol.

d) Represents a saturated solution.

The preceeding reactions have all involved the addition of an oxygen substituent to 1 by a nucleophilic addition to the epoxide linkage. In order to add an oxygen substituent to 1, and yet leave the epoxide intact, an electrophilic addition to one of the double bonds of the benzene oxide isomer is necessary. Thus, the oxy-mercuration reaction of 1 with mercuric acetate was investigated.

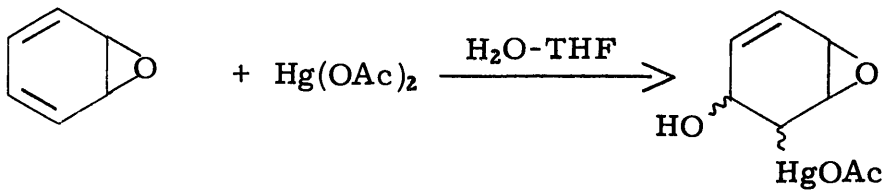
Mercuric acetate is a very powerful electrophilic reagent which reacts with olefins to give cis- and/or trans-addition depending on the strain of the olefin[22] (see Scheme X for an example of the addition with a strained olefin.)

Scheme X



It was hoped that the double bond of the benzene oxide isomer of 1 would also undergo a similar addition with mercuric acetate, as indicated in Scheme XI.

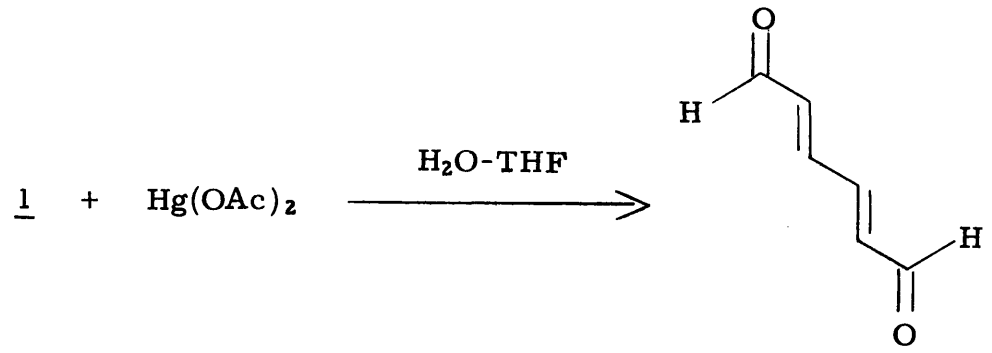
Scheme XI



1 17

When 1 was added to a suspension of mercuric acetate in tetrahydrofuran-water,[23,24] the characteristic yellow color of the mercuric acetate-tetrahydrofuran complex was immediately discharged with the concomitant production of a gray precipitate. The product obtained was not 17 as hoped for, but was instead trans,trans-2,4-hexadien-1,6-dial (18), isolated in 60% yield (Scheme XII).

Scheme XII



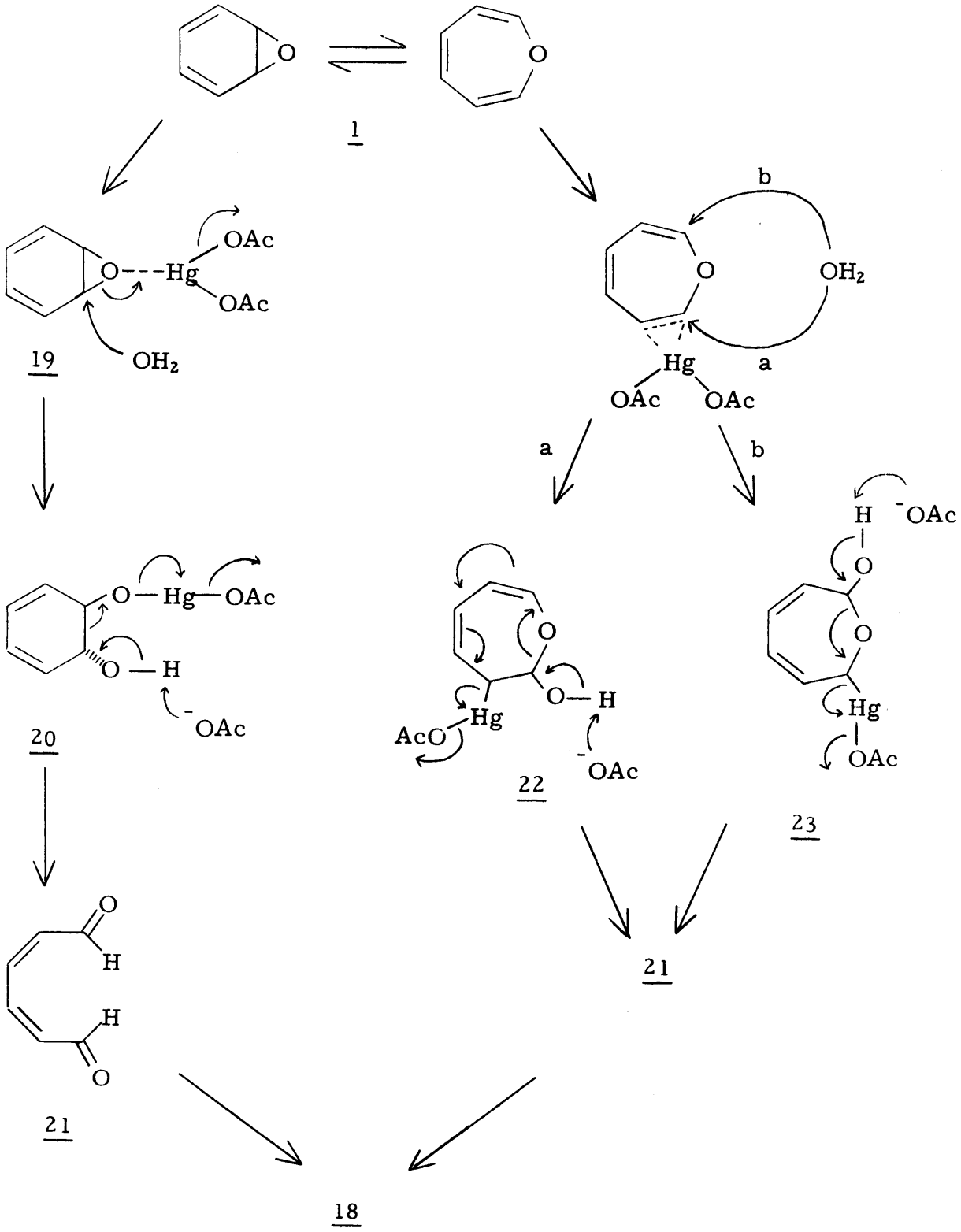
18

Two possible mechanisms for the formation of 18 are shown in Scheme XIII. In the first mechanism mercuric acetate acts as a Lewis acid an complexes with the oxygen of the benzene oxide isomer of 1, enabling water to add nucleophilically to give the intermediate 20. Rearrangement of 20 as shown would then give the cis,cis-isomer 21, which is known to readily isomerize to the trans,trans-isomer 18.[16] In the second mechanism the electron-rich double bond of the oxepin isomer simply undergoes oxy-mercuration to give the hemi-acetals 22 and/or 23 as intermediates. These can then rearrange as shown to give, ultimately, 18.

The first mechanism is considered less likely since 1 is known to undergo rearrangement to phenol with other Lewis acids,[25] and, thus, an intermediate such as 19 would be expected to give some, if not all, phenol. However, no phenol was observed in the nmr spectrum of the crude product. In addition, the following results provided further support for the mechanism involving the oxepin isomer.

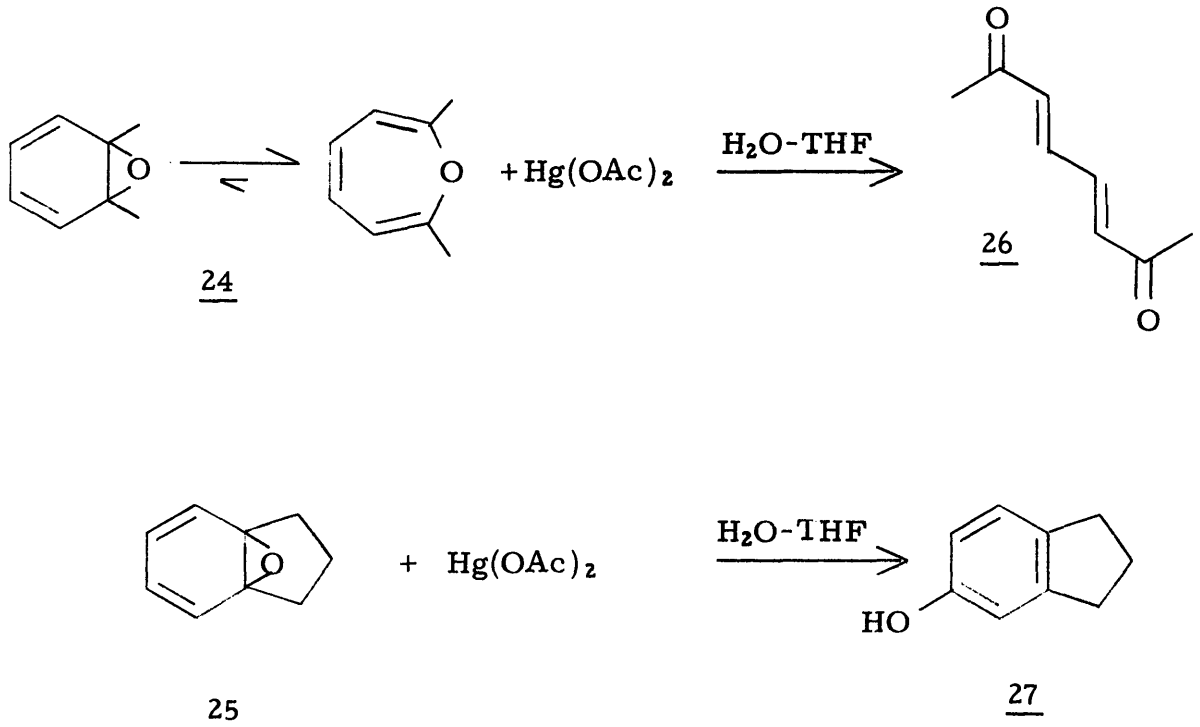
2,7-Dimethyloxepin-benzene oxide (24) exists almost exclusively in the oxepin form, whereas 8,9-indan oxide (25) exists entirely in the oxide form.[25] If the reacting species is the benzene oxide isomer, then both 24 and 25 should react with mercuric acetate in a similar fashion to 1; however, if the reacting species is the oxepin isomer, then only

Scheme XIII


O
O
1
OAc
O---Hg
OAc
OH2
19
b
O
OH2
Hg
a
OAc
OAc
a
b
O—Hg—OAc
O—H
-OAc
20
O
O—H
AcO
Hg
-OAc
22
H
-OAc
O
O
Hg
OAc
23
O
H
H
O
21
21
18

24 should undergo this reaction. The reaction of 24 with mercuric acetate proceeded exactly as in the case of 1 to give a 70% yield of trans,trans-3,5-octadien-2,7-dione (26); however, under identical conditions 25 gave a quantitative yield of 5-indanol (27), which is the rearrangement product of 25 in aqueous media[25] (Scheme XIV).

Scheme XIV



Thus, it seems that the reaction of 1 and 24 with mercuric acetate involves an electrophilic addition to the oxepin isomer.

Of the many reactions of arene oxide-oxepin systems that have been studied, there are only two other examples in which the oxepin isomer is the reacting species: the photolysis of 1[25] and 24[26] to give 2-oxabicyclo[3.2.0]hepta-3,6-dienes; and, the alkali metal reduction of oxepins.[27] Furthermore, this is the first example of an electrophilic reaction with an arene oxide-oxepin system.

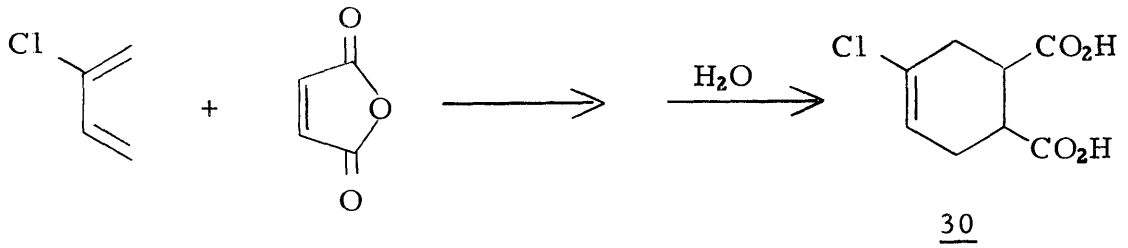
II. Synthesis and Reactions of 4-Chlorooxepin-benzene Oxide.

In 1950 Spencer et al. isolated 4-chloro-trans-1,2-dihydroxy-1,2-dihydrobenzene (28) as one of the minor metabolites of chlorobenzene in mammalian systems.[28] 4-Chlorooxepin-benzene oxide (29) was later proposed as an intermediate.[5] Of the variously substituted oxepin-arene oxide systems which are known, no halogen-substituted oxepins have been prepared. In light of the addition of hydroperoxide anion to oxepin (1) to give 2, 4-chlorooxepin (29) was considered to be the key to the synthesis of the dihydrodiol metabolite 28. For these reasons the synthesis of 4-chlorooxepin (29) was undertaken.

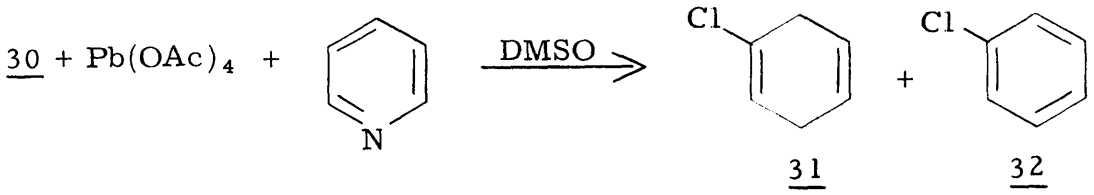
The synthesis of 4-chlorooxepin is outlined in Scheme XV. The diacid 30 was readily prepared in mole quantities by the Diels-Alder reaction of chloroprene and maleic anhydride, followed by recrystallization of the crude product from water.[29] Bisdecarboxylation of the diacid 30 with lead tetraacetate (vide infra) gave, after distillation, a mixture of the chlorodiene 31 and chlorobenzene (32) in a ratio of 1.5:1; the yield of 31 was 18%. It was not necessary to separate 31 and 32 in order to proceed with the synthesis.

Epoxidation of 31 with one equivalent of peracetic acid was very selective, providing an 81% yield of the epoxide 33 as a clear,

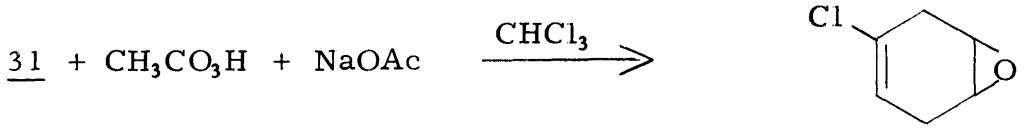
Scheme XV



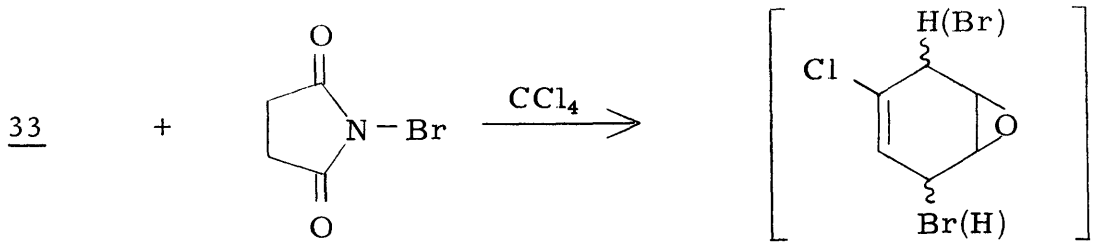
30



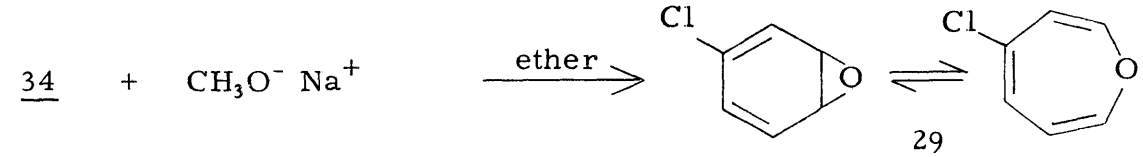
31 32



33



34



29

colorless liquid. Allylic bromination of 33 with N-bromosuccinimide gave a mixture of the bromides 34. Treatment of this crude mixture with an excess of sodium methoxide in refluxing ether gave, after work-up and distillation, 4-chlorooxepin (29) as a gold-colored liquid. The yields were typically in the range of 40-50%, based on 33.

Each of the reactions in the synthesis of oxepin 29 proceeds in excellent yield except for the lead tetraacetate bisdecarboxylation. Initially, many routes were investigated in order to avoid the necessity of this reaction, however they were even less successful (see Appendix).

One of the major factors contributing to the poor yield of the diene 31 was the further oxidation of 31 to chlorobenzene. In almost all of the previously reported bisdecarboxylations, the structures of the 1,2-diacids were such that this could not occur.[30-34] The lead tetraacetate reaction with 30 was investigated under a variety of conditions in an attempt to prevent, or at least minimize, the oxidation of 31 to chlorobenzene. The results are summarized in Table III and need no further explanation.

Table III

Oxidative Bisdecarboxylation of Diacid 30

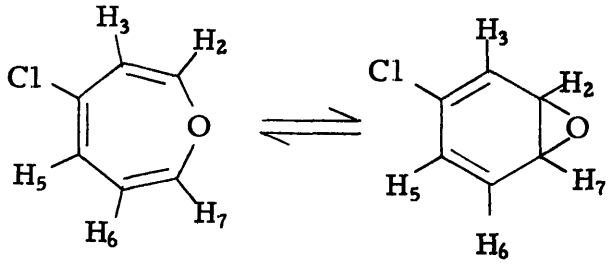
30	$Pb(OAc)_4$[a] (mmoles)	Pyridine[b]	Solvent[b]	Reaction Time	Temp.	Conditions	Ratio[c] 31:32	Yield of 31 + 32
10	11	20	benzene	3 hrs	50-80°	d	25:75	22%
60	60	240	benzene	3 days	r.t.	e	25:75	--
67	70	133	benzene	3 days	r.t.	f[k]	50:50	20%
40	35	80	benzene	10 hrs	r.t.	f[k]	50:50	28%
80	80	160	dimethyl sulfoxide	2.5 hrs	r.t.	g	60:40	33%
80	80	160	"	4 hrs	r.t.	f[k]	65:35	17%
80	80	160	"	4 hrs	r.t.	f[k]	60:40	23%
80	80	80	"	4 hrs	r.t.	f	50:50	19%
80	80	80	"	4 hrs	r.t.	f	60:40	25%
80	80	40	"	4 hrs	r.t.	f	70:30	26%
80	80	40	"	4 hrs	r.t.	f	70:30	26%
80	80	40	"	4 hrs	r.t.	h	40:60	13%
80	80	40	"	4 hrs	r.t.	h	36:64	19%
80	80	160	"	4 hrs	r.t.	h	53:47	16%
20	30	--	pyridine	10 min	65°	i	50:50	33%
	moles		Preparative Scale[j]					Yield of 31
1.0	1.0	0.5	dimethyl sulfoxide	4 hrs	r.t.	f	56:44	18%
1.0	1.0	0.5	"	4 hrs	r.t.	f	60:40	19%
1.0	1.1	0.5	"	4 hrs	r.t.	f	60:40	18%

a) The lead tetraacetate was recrystallized from acetic acid containing a little acetic anhydride and dried in vacuo.
b) Dried over Linde molecular sieves, Type 3A or 4A.
c) Estimated on the basis of peak areas from glpc analysis (6 ft 20% SE30, 70°) of the distilled mixture.
d) The solution of 30 and pyridine was degassed with nitrogen before the lead tetraacetate was added, and nitrogen was bubbled through during the reaction.[30]
e) The solution of 30 and pyridine was degassed with nitrogen before the lead tetraacetate was added.

Table III (Continued)

f) The lead tetraacetate was added in one portion to the solution of 30 and pyridine.
g) The pyridine was added dropwise to the solution of 30 and lead tetraacetate.
h) A solution of lead tetraacetate in dimethylsulfoxide was added to a solution of 30 and pyridine.
i) Oxygen was bubbled through the pyridine.[33]
j) The conditions for the preparative scale reactions were chosen on the basis of the above results; see Experimental Section.
k) Based on the procedure of Chapman et al.[32]

The 220 MHz spectrum of 29 is presented in Table IV.

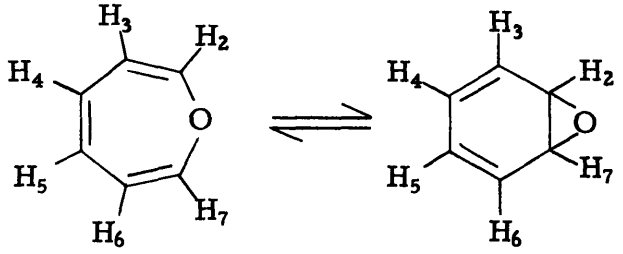


29

Table IV

Proton	Chemical Shift (ppm)	Multiplicity and Coupling Constants
H_2	5.39	d of d of d; J_{23} = 5.4 Hz, J_{25} = 0.4 Hz, J_{27} = 0.4 Hz
H_3	5.57	d of d of d; J_{32} = 5.4 Hz, J_{35} = 1.5 Hz, J_{36} = 0.4 Hz
H_5	6.11	d of d of d of d; J_{56} = 6.8 Hz, J_{53} = 1.5 Hz, J_{52} = 0.4 Hz, J_{57} = 0.4 Hz
H_6	5.52	d of d of d; J_{65} = 6.8 Hz, J_{67} = 5.2 Hz, J_{63} = 0.4 Hz
H_7	5.37	d of d of d; J_{76} = 5.2 Hz, J_{75} = 0.4 Hz, J_{72} = 0.4 Hz

Vogel has demonstrated that for 1 there is a benzene oxide-oxepin valence tautomerism with comparable concentrations of the isomers.[25] Comparison of the chemical shifts of the protons in 1



1

and 29 indicates a similar valence tautomerism for 29 (Table V).

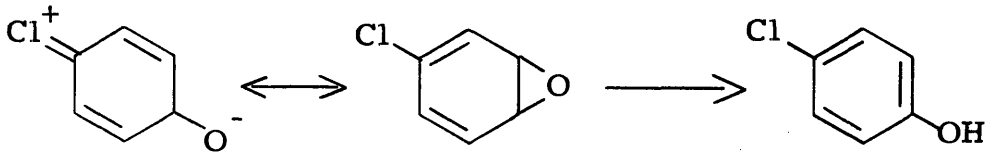
Table V

Chemical Shifts of Protons in 1 and 29

Proton	I[25]	29
H_2 and H_7	5.2	5.39 and 5.37
H_3 and H_6	5.6	5.57 and 5.52
H_4 and H_5	6.1	---- and 6.11

4-Chlorooxepin is much less stable than the parent compound 1, spontaneously rearranging either neat, in protic, or in aprotic solvents to pure 4-chlorophenol (35). The strong orientating influence of the chlorine is probably due to the resonance structure 36 (Scheme XVI).

Scheme XVI



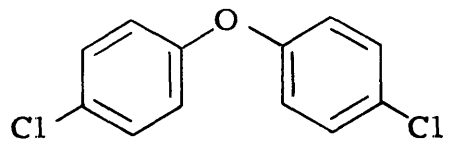
36 29 35

The same instability has also been observed for 4-methyloxepin, which rearranges to pure 4-cresol.[9] This instability relative to 1 could possibly be due to the unsymmetrical nature of the substitution,[36] although 3- and 4-carbo-t-butoxyoxepins are quite stable in relation to 1.[17a,37]

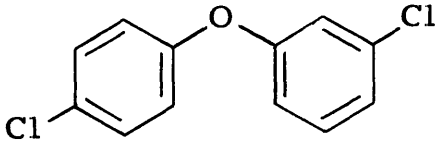
The Diels-Alder reaction of 29 with maleic anhydride gave inconsistent results. In one attempt the 1:1 adduct was isolated; subsequent attempts failed, giving only 4-chlorophenol. Considering the deactivating effect of chlorine on dienes in the Diels-Alder reactions[38,39] and the instability of 29, this is not surprising. 4-Methyl-1,2,4-triazoline-3,5-dione, one of the strongest dienophiles known,[40] forms a 1:1 adduct with 29 in 75% yield within a few minutes.

DeMarinis has reported that 4-carbo-t-butoxyoxepin-benzene oxide undergoes a 1,6-addition with lithium hydroxide in aqueous dioxane to give t-butyl trans-2,3-dihydroxy-2,3-dihydrobenzoate.[17a]

Attempted addition of lithium hydroxide to 29 was unsuccessful. In general, under mild conditions 29 was recovered unchanged; under more forcing conditions only aromatic products were obtained. The spectral evidence indicates that the aromatic products are either 37 and/or 38. In particular, the mass spectrum showed the expected



37

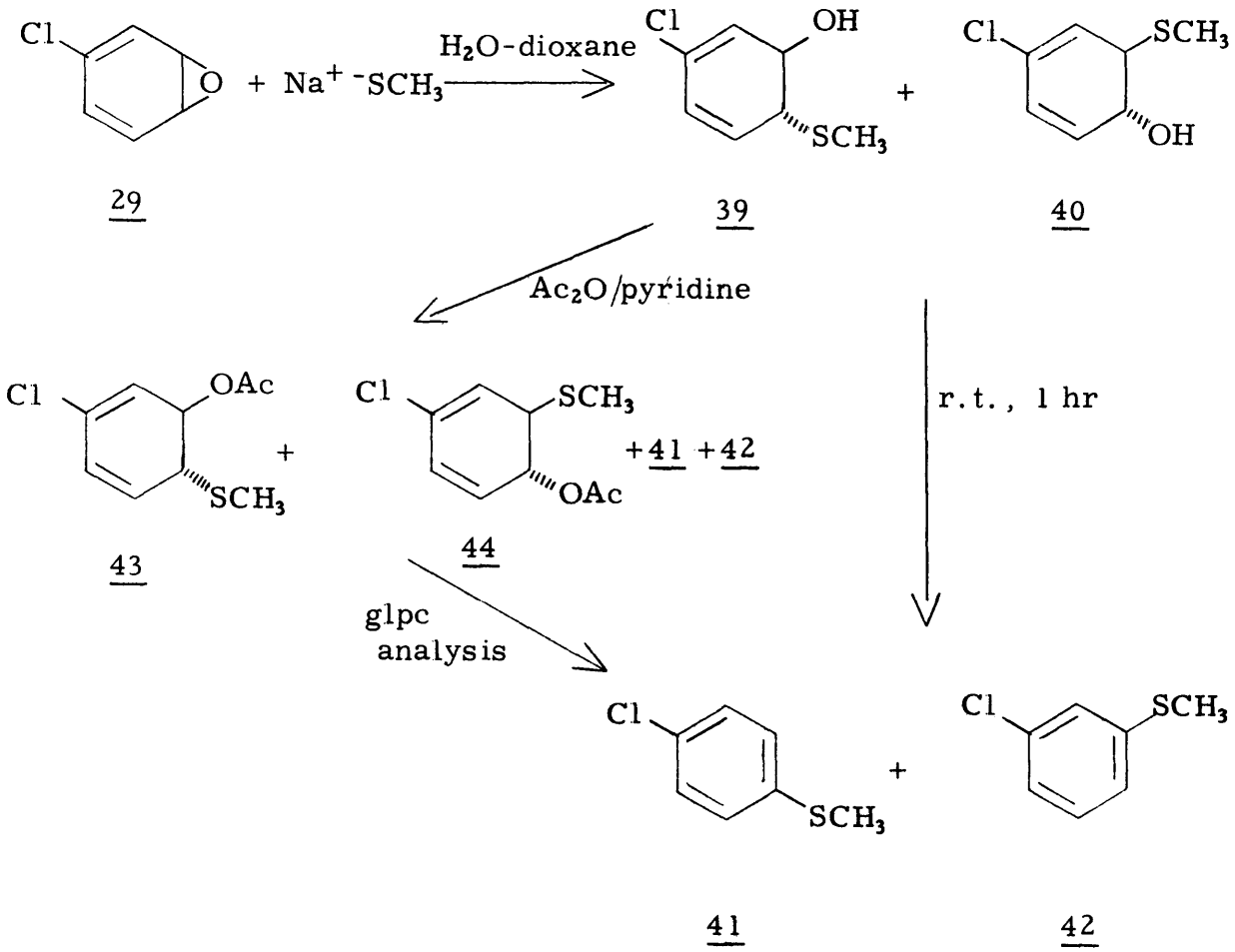


38

3-peak molecular ion cluster at m/e 242, 240, and 238. The formation of the diphenylethers is probably the result of rearrangement of 29 to 35, nucleophilic attack of the anion of 35 on another molecule of 29, followed by dehydration. (If this is the case, then the position of one chlorine is fixed since the only rearrangement product of 29 ever observed under any conditions was 35. The location of the other chlorine is uncertain.) This is reasonable in light of a similar result with 1 (see Scheme IV).

4-Chlorooxepin did undergo nucleophilic addition with the more reactive methiolate ion to give a mixture consisting of 71% of the dienes 39 and 40 in a ratio of 1:1 and 29% of aromatic products, as indicated in Scheme XVII.

Scheme XVII



The nmr spectrum of this mixture is in excellent agreement with the assigned structures–39 and 40: δ 1.92 and 1.93 (3H, two singlets of equal intensity, S-CH_3), 3.05 (1H, broad singlet, hydroxyl H), 3.42 (1H, multiplet, C(SCH3)—H), 4.27 (1H, multiplet, C(OH)—H), and 5.97 ppm (3H, multiplet, vinyl H); aromatic: δ 2.38 (3H, broad singlet,

S-CH_3) and 7.17 ppm (4H, multiplet, aromatic H). The trans stereochemistry is assigned by analogy with the reaction of thiophenoxide ion[2] and azide ion[3] with 1.

After standing for one hour at room temperature the dienes 39 and 40 had completely aromatized to a mixture of 41 and 42 in a ratio of 1:1.

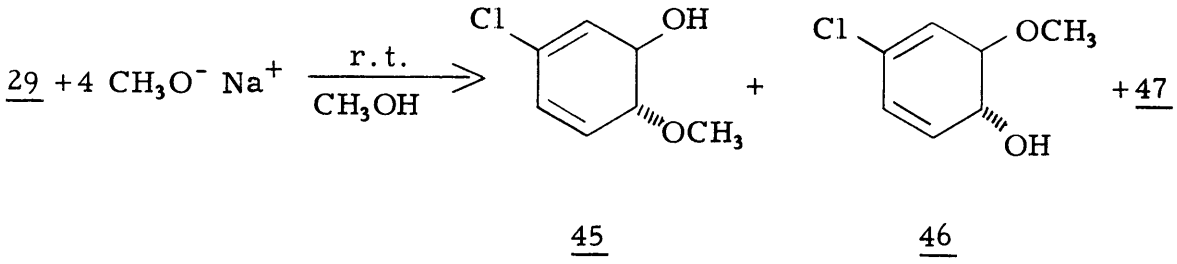
Due to the instability of the dienes 39 and 40, the reaction was repeated and the crude product was immediately acetylated in the hope that the acetates 43 and 44 would be more stable (Scheme XVII). After work-up, distillation gave a mixture consisting of 32% of the acetates 43 and 44 in a ratio of 1:1, and 68% of the thioanisoles 41 and 42 in a ratio of 1:1. The nmr spectrum of this mixture is also in excellent agreement with the assigned structures 43 and 44: δ 1.90 and 1.97 (6H, two singlets of equal intensity, S-CH_3 and $\overset{O}{\overset{\|}{C}}$-$CH_3$), 3.35 (1H, multiplet, $C(SCH_3)-H$), 5.32 (1H, multiplet, $C(OAc)-H$), and 5.87 ppm (3H, multiplet, vinyl H); 41 and 42: δ 2.33 and 2.35 (3H, two singlets of equal intensity, S-CH_3) and 7.10 ppm (4H, multiplet, aromatic H).

Attempted separation of the acetates 43 and 44 by gas chromatography resulted in complete aromatization to thioanisoles 41 and 42.

Due to the success of the addition of methoxide ion to 1, it was decided to carry out this reaction with oxepin 29 to see if it

would also undergo nucleophilic addition. Thus, treatment of 29 with four equivalents of sodium methoxide in methanol at room temperature for 20 days gave, after work-up and distillation, a mixture consisting of a 30% yield of dienes 45 and 46 in a ratio of 78:22, and an 18% yield of 4-chloroanisole (47), as shown in Scheme XVIII.

Scheme XVIII



45 46

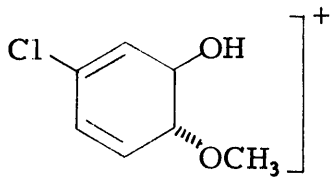
The nmr spectrum of this mixture is in excellent agreement with the assigned structures 45 and 46: δ 2.67 (1H, broad singlet, hydroxyl H), 3.40 and 3.42 (3H, two singlets, O-CH_3), 4.07 (1H, doublet of multiplets, J = 11 Hz, C(OCH$_3$)—H), 4.50 (1H, doublet of multiplets, J = 11 Hz, C(OH)—H), and 5.93 ppm (3H, multiplet, vinyl H); 47: δ 3.77 (3H, singlet, O-CH_3), 6.78 (2H, doublet, J = 9.5 Hz, aromatic H) and 7.22 ppm (2H, doublet, J = 9.5 Hz, aromatic H). The trans stereochemistry of dienes 45 and 46 is assigned on the basis of the

nmr spectrum in which the coupling constant for the allylic protons is 11 Hz in $CDCl_3$, and by analogy with the reaction of methoxide ion with 1.

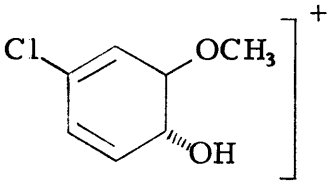
The dienes 45 and 46 were separated by gas chromatography and the isomers were distinguished on the basis of the mass spectral data, as shown in Scheme XIX. One of the major fragments of diene 45 is 48, corresponding to the loss of methanol. However, a major fragment of diene 46 is 50, corresponding to the loss of methanol plus a hydrogen. These observations can be explained by resonance stabilization of the fragment 50 as shown, whereas no similar stabilization of 49 can occur.

It is interesting to note the regioselectivity[41] of the nucleophilic addition of methoxide ion to 29 (78% of 45 and 22% of 46). Apparently the chlorine substituent in 29 effects the electronic distribution such that one C-O bond of the epoxide is weaker. This effect is of such a magnitude that only methoxide, a poor nucleophile, is influenced by it. The

Scheme XIX



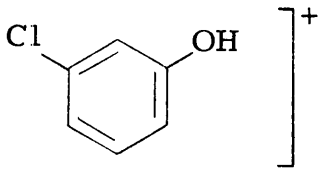
45



46

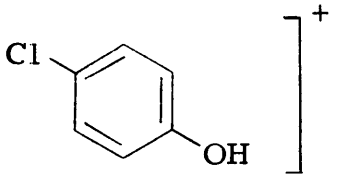
$-CH_3OH$

$-CH_3OH$



48

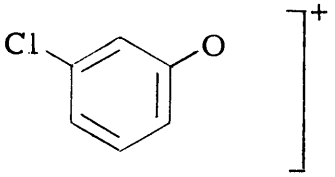
m/e 128(100), 130(32)



m/e 128(12), 130(5)

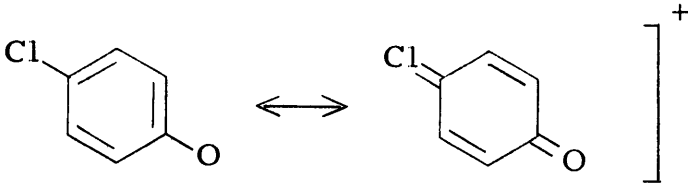
-H

-H



49

m/e 127(6), 129(10)



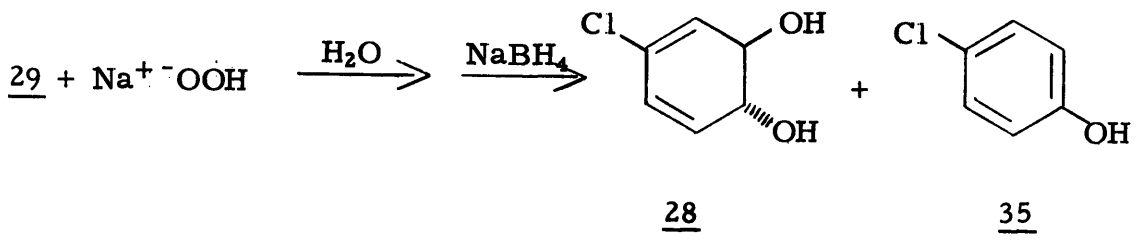
50

m/e 127(55), 129(18)

addition of methiolate ion, a very reactive nucleophile, to 29 was non-regioselective (50% of 39 and 50% of 40). Also, the chlorine seems to have a deactivating effect in 29, as shown by comparison of the reaction times and yields of dienes in the reaction of methoxide ion with 29 (20 days, 30% of 45 and 46) and with 1 (14 days, 64% of 4).

Due to the success of the addition of hydroperoxide ion to 1, it was felt that similar addition to 29 was a feasible route to the dihydrodiol 28, although the yield would be expected to be lower on the basis of the above results. Thus, treatment of oxepin 29 with a large excess of sodium hydroperoxide in water, followed directly by reduction with sodium borohydride, gave a mixture of dihydrodiol 28 and 4-chlorophenol in a ratio of 1:4, as shown in Scheme XX.

Scheme XX



28 35

The yield of crystalline dihydrodiol 28 was 3%. The nmr spectrum of 28 was in excellent agreement with the assigned structure: δ 4.35 (2H, multiplet, C(OH)—H), 5.90 (3H, multiplet, vinyl H), and 8.00 ppm (2H, singlet, hydroxyl H). Comparison of the mass spectra of diols 28 and 2 showed almost identical fragmentation patterns. The uv spectrum of 28 is in excellent agreement with that reported for the dihydrodiol that was obtained from natural sources.[28]

Although a lower yield was expected, a decrease of this extent was not.

In order to avoid the problems associated with an aqueous system, an organic hydroperoxide ion was used. However, attempted addition of t-butylhydroperoxide ion to 29 in methanol failed. Surprisingly, the only cyclohexadiene products observed in this reaction were 45 and 46, the result of addition of methoxide ion.

EXPERIMENTAL SECTION

General. Infrared spectra were taken on a Perkin-Elmer Model 237B spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. The proton nmr spectra were taken on a Varian T-60 or a Perkin-Elmer R-20-B spectrometer, and chemical shift data are reported in parts per million downfield from tetramethylsilane as an internal standard at 0.00. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6D mass spectrometer with an ionizing potential of 70 eV unless otherwise indicated and are expressed in per cent relative intensity to the most intense peak as 100%. Melting points were taken on a Thomas-Hoover "Uni-Melt" and are corrected; boiling points are uncorrected. 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 detectors using 6 ft x 0.25 in stainless steel columns packed with either 20% G. C. grade SE 30 on 100-120 W.H.P. or 20% Carbowax 20M on 80-100 WAW DMCS, or on a Varian Aerograph Series 2100 Chromatograph with a flame ionization detector and glass injection port, glass effluent splitter, and 6 ft x 2 or 3.5 mm I.D. glass columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Mrs. Nancy Alvord, of this department.

Oxepin-benzene Oxide (1). A modified procedure of Vogel[25] was used to prepare 1. Thus, to a stirred solution of 3,4-dibromocyclohexene epoxide (7.00 g, 28 mmol) in 50 ml of ether was added in one portion 4.56 g (84 mmol) of sodium methoxide (commercial). The mixture was stirred at reflux under a nitrogen atmosphere for 1 hr. The mixture was diluted with ether, washed with 2 x 50 ml of water, and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue was distilled (aspirator pressure) to give 1 in 50% yield as identified by nmr.

Due to its instability, 1 was prepared and distilled immediately before use in any reaction.

NMR Scale Reactions of Oxepin with Methanol and Ethanol. General. The following reactions were run in nmr tubes under a nitrogen atmosphere and monitored regularly. The alcohol solvents were made basic to a pH of approximately 10 by the addition of sodium metal. In each case the reactions were worked up in the following manner. The solution was diluted with 50 ml of ether and the ether layer was washed with 2 x 15 ml of 5% aqueous sodium hydroxide, dried (Na_2SO_4), filtered, and concentrated. Glpc analysis was done on a 6 ft 20% Carbowax 20M column at 150°.

The percentage of diene and aromatic products was determined in the following manner. Integration of the nmr spectrum before and after work-up established the amount of phenol present initially. In each case it was a small amount. Glpc analysis of the crude product obtained after work-up in each case showed four peaks, which have been identified (in the case of A) as (in order of increasing retention time) anisole, the diene 4, phenol, and diphenyl ether. The anisole, phenol, and diphenyl ether (5) were identified by comparison of the glpc retention time, ir, and mass spectra with authentic samples. Collection and reinjection of the diene (4) peak showed that decomposition to anisole and phenol was occurring; however, the total amount of decomposition was less than 1%. Comparison of the ratio of the anisole peak to the diene peak from the glpc of the crude product and from the glpc of the collected diene peak established that the anisole observed on the glpc was not present in the crude product, but was the result of decomposition of the diene on the glpc.

A. Oxepin (58 mg) and 0.6 ml of CH_3O^- Na^+/CH_3OD were placed in an nmr tube. After 54 days at room temperature there was no oxepin detectable by nmr. After work-up, nmr and glpc analysis of the crude product showed it to be a mixture of 86% of diene 4 and 14%

of aromatic products. The major aromatic product was identified as diphenyl ether (5).

B. Oxepin (51 mg) and 0.6 ml of $CD_3O^-Na^+/CD_3OD$ were placed in an nmr tube. The solution was heated to 48° and after 7 days there was no oxepin detectable by nmr. After 1 day more no significant change was observed. After work-up, nmr and glpc analysis of the crude product showed it to be a mixture of 73% of 4 and 27% of aromatic products. The major aromatic product was 5.

C. Oxepin (56 mg) and 0.6 ml of $CD_3CD_2O^-Na^+/CD_3CD_2OD$ were placed in an nmr tube. The solution was heated to 48° and after 22 days there was no oxepin detectable by nmr. After 2 days more no significant change was observed. After work-up, nmr and glpc analysis of the crude product showed it to be a mixture of 61% of the diene 12 and 39% of aromatic products. The major aromatic product was 5. The structure of 12 was established on the basis of the following spectral evidence: nmr ($CDCl_3$) δ 1.83 (broad s, 1H), 4.08 (d, J = 10.5 Hz, 1H), 4.52 (d, J = 10.5 Hz, 1H), and 5.92 ppm (m, 4H). Preparative glpc provided an analytical sample of 12: ir ($CHCl_3$) 3580, 3410, 3020, 2990, 2820, 2230, 2200 (sh), 2080, 1730, 1600, 1495, 1400, 1360, 1340, 1305, 1250, 1175, 1120, 1075, 1000, 960 and 885 cm^{-1};

mass spectrum (70 eV) m/e (rel intensity) 128(4), 127(34), 126(2), 97(2), 96(8), 95(100), 94(5), 77(7),67(19), 66(7), 65(10), 63(6), 51(9), 40(6), 39(19), 38(5), 34(8).

Note: In a reaction of oxepin (62 mg) and 0.6 ml of $CD_3CD_2O^-Na^+/CD_3CD_2OD$ at room temperature, after 189 days there was still oxepin present in addition to the diene 12 and aromatic products.

trans-6-Methoxycyclohexa-2,4-dien-1-ol (4). To a stirred solution of oxepin (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 at room temperature under a nitrogen atmosphere. After 14 days, the nmr 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 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was short-path distilled at room temperature (0.03-0.05 mm) to give 0.32 g (64%) of 4 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); nmr ($CDCl_3$)

δ 2.88 (broad s, 1H), 3.47 (s, 3H), 4.08 (d, J = 10.5 Hz, 1H), 4.55 (d, J = 10.5 Hz, 1H), and 5.95 ppm (m, 4H); mass spectrum (70 eV) m/e (rel intensity) 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 hydrogenation of 4 at atmospheric pressure in ethyl acetate using 10% Pd/C catalyst gave trans-2-methoxycyclohexanol (9), the structure of which was established by comparison of the glpc (6 ft 20% Carbowax 20M, 150°) retention time, ir, and mass spectrum with those of an authentic sample prepared as reported previously.[13]

B. In a similar procedure, a solution of 1 (0.50 g, 5.3 mmol) and sodium methoxide (0.57 g, 10.6 mmol) in 10 ml of methanol was stirred at room temperature under a nitrogen atmosphere. After 27 days the nmr spectrum showed that only a trace of 1 remained. Work-up and distillation, as described above, gave a 65% yield of 4.

C. Using the procedure described above, a solution of 1 (0.45 g, 4.7 mmol) in 10 ml of $CH_3O^-Na^+/CH_3OH$, pH ~ 10, was stirred at room temperature under a nitrogen atmosphere. After 69 days, the nmr spectrum showed that no oxepin remained. Work-up and distillation provided a 78% yield of 4.

trans-6-Methoxycyclohexa-2,4-dien-1-yl Acetate (8). To a stirred solution of 4 (0.12 g, 1.0 mmol) in 5 ml of pyridine (predried over Linde molecular sieves, Type 4A) cooled to 0° under a nitrogen atmosphere was added dropwise one ml of acetic anhydride. The solution was allowed to warm to room temperature and was stirred for 22 hr. The solution was added to 20 ml of ice water and the aqueous phase was washed with two 30-ml portions of ether. The combined ether extracts were washed with 2 x 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give a light yellow liquid that, on short-path distillation at room temperature (0.03-0.05 mm), yielded 0.16 g (94%) of 8 as a colorless liquid: ir ($CHCl_3$) 3020, 2980, 2920, 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); nmr ($CDCl_3$) δ 2.13 (s, 3H), 3.47 (s, 3H), 4.17 (d of d, J = 7.5 Hz, 2 Hz, 1H), 5.70 (d, J = 7.5 Hz, 1H), and 6.05 ppm (m, 4H); mass spectrum

(70 eV) m/e (rel intensity) 136(4), 133(3), 109(10), 108(100), 94(21), 93(16), 79(16), 78(56), 77(19), 65(71), 63(13), 60(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 hydrogenation of 8 at atmospheric pressure in ethyl acetate using 10% Pd/C catalyst gave trans-2-methoxycyclohexyl acetate (10), the glpc (6 ft 20% SE 30, 120°) retention time, ir, and mass spectrum of which were identical to those of the product from acetylation of the authentic sample of 9.[13]

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

trans-5-Hydroxy-6-methoxybicyclo[2.2.2]oct-2-ene-7,8-dicarboxylic Acid Anhydride (7). To a stirred solution of 4 (0.14 g, 1.1 mmol) in 8 ml of benzene was added in one portion 0.11 g (1.1 mmol) of maleic anhydride (sublimed). The solution was stirred at room temperature under a nitrogen atmosphere for 12 days. The solution was concentrated under reduced pressure and the residue was recrystallized from benzene yielding 0.10 g (40%) of 7 as a white grannular solid: mp (sealed tube) 122-125° (dec); ir ($CHCl_3$)

3570, 3370, 2920, 2890 (sh), 2820, 1870, 1790, 1615, 1465, 1370, 1340, 1300, 1215, 1110, 1100, 1075 (sh), 1040, 1000, 945, 925, 870 and 830 cm^{-1}; nmr (acetone-d_6) δ 2.87 (broad s, 1H), 3.13 (m, 2H), 3.42 (broad s, 5H), 3.70 (m, 2H), and 6.30 ppm (m, 2H).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.80; H, 5.42.

Attempted Addition of Hydroxide to Oxepin (1). A. Oxepin (139 mg) was placed in an nmr tube with 150 µl of $NaOD/D_2O$, pH 10. CD_3CN was added until a solution was obtained. The solution was heated to 48° under a nitrogen atmosphere and the reaction was monitored by nmr. NMR analysis showed that 1 underwent slow decomposition to phenol. The decomposition took 63 days and no intermediate products were observed.

B. Oxepin (104 mg) was placed in an nmr tube with 150 µl of $NaOD/D_2O$, pH 10. Dioxane was added until a solution was obtained. The solution was heated to 48° under a nitrogen atmosphere and the reaction was monitored by nmr. NMR analysis showed that 1 underwent slow decomposition to phenol. After 139 days there was still a small amount of 1 present. No intermediate products were observed.

C. Oxepin (130 mg) was placed in an nmr tube with 150 μl of $NaOD/D_2O$, pH 10. The mixture was cooled to 0° and 800 μl of hexamethylphosphoramide (distilled) was added. The resulting solution was heated to 48° under a nitrogen atmosphere and the reaction was monitored by nmr. NMR analysis showed that 1 underwent slow decomposition to phenol. The decomposition took 63 days and no intermediate products were observed.

Attempted Addition of 2-Cyanoethanol (15) to Oxepin (1).

General. The following reactions were monitored regularly by nmr.

A. A solution of 1 (60 mg) in 0.6 ml of $CNCH_2CH_2O^-Na^+$/$CNCH_2CH_2OH$, pH ~ 10, in an nmr tube was left at room temperature under a nitrogen atmosphere. After 12 days 1 had undergone complete decomposition to phenol, and no intermediate products were observed.

B. A solution of 1 (55 mg) in 0.6 ml of $CNCH_2CH_2O^-Na^+$/$CNCH_2CH_2OH$, pH ~ 10, in an nmr tube was heated to 48° under a nitrogen atmosphere. After 1 day 1 had undergone complete decomposition to phenol, and no intermediate products were observed.

C. A solution of 1 (43 mg) in 0.6 ml of $CNCH_2CH_2OH$, neutral, in an nmr tube was left at room temperature under a nitrogen atmos-

phere. After 2 days 1 had undergone complete decomposition to phenol, and no intermediate products were observed.

Reaction of Oxepin (1) with Potassium Hydroxide: Dicyclohexyl-18-Crown-6 Ether Complex (16). The procedure of Pedersen[20] was used to prepare a solution of dicyclohexyl-18-crown-6 ether (1.49 g, 4.0 mmol) and potassium hydroxide (0.26 g, 4.0 mmol) in 30 ml of toluene. To this stirred solution of 16 was added in one portion a solution of 0.42 g (4.4 mmol) of oxepin in 5 ml of toluene. The solution was stirred at room temperature under an argon atmosphere for 27 hr, after which time the characteristic oxepin color had faded to brown. The solution was washed with 2 x 10 ml of water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a viscous oil. Glpc analysis on a 6 ft 20% Carbowax 20M column showed only two peaks which had the same retention times as phenol and the crown ether.

trans-1,2-Dihydroxy-1,2-dihydrobenzene (2). To a stirred solution of 20.34 g (180 mmol) of a 30% solution of hydrogen peroxide in 10 ml of water at 10° was added dropwise a solution of 7.20 g (180 mmol) of sodium hydroxide in 15 ml of water. This gives a solution in which the concentration of sodium hydroperoxide is approximately

4.5 M. The solution was then cooled to 0° and 0.50 g (5.3 mmol) of oxepin was added in one portion. The resulting mixture was the characteristic oxepin color. After 3 and 3/4 hr this color was discharged and the mixture had warmed to 15°. The mixture was diluted with 30 ml of water, 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 and 1/2 hr. The solution was allowed to warm to room temperature and was stirred for 15 hr. The aqueous solution was continuously extracted with ether for 72 hr. The ether solution was dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of a pale yellow liquid and a white solid. Analysis of the nmr spectrum of this crude product showed that it was a mixture of 2 and phenol in a ratio of 56:44. Recrystallization from ether gave 176 mg (30%) of 2 as white plates: mp 73-75° (lit.[16] 73-74°); nmr ($CDCl_3$) δ 2.82 (broad s, 2H), 4.48 (s, 2H), and 5.92 ppm (s, 4H). A second recrystallization from ether gave 2 as glistening white plates: mp 74-75°; ir (nujol mull) 3310 (sh), 3220, 1470, 1460, 1375, 1350, 1295, 1260, 1075, 1065, 1015, 830, and 680 cm^{-1}; uv max (95% C_2H_5OH) 261 nm (ϵ 3490); mass spectrum (70 eV), m/e (rel intensity) 113(6), 112(36), 111(5), 110(4), 109(4), 98(4), 97(7), 96(5), 95(9), 94(55), 93(5), 85(6), 84(7), 83(43), 82(7), 81(15), 80(4), 79(6), 78(20), 77(14), 71(7), 70(5), 69(10), 68(27),

67(19), 66(100), 65(36), 64(7), 63(12), 62(6), 58(5), 57(17), 56(10), 55(39), 54(7), 53(20), 52(11), 51(22), 50(14), 47(8), 44(10), 43(14), 42(9), 41(31),40(31), 39(65), 38(17), 37(9), 36(8).

Anal. Calcd for $C_6H_8O_2$: C, 64.26; H, 7.21. Found: C, 64.50; H, 7.23.

The ir and uv spectra are in excellent agreement with those of 2 prepared by an alternate route.[16]

Reaction of Oxepin (1) with Mercuric Acetate. To a solution of mercuric acetate (1.69 g, 5.3 mmol) in 8 ml of water was added 8 ml of tetrahydrofuran.[23,24] This produced a bright yellow mixture. To the stirred mixture at room temperature was added in one portion 0.50 g (5.3 mmol) of oxepin. The yellow color was immediately discharged producing a greenish mixture with a gray precipitate. After stirring for 22 hr at room temperature, 3 ml of saturated aqueous sodium chloride was added and the mixture was stirred for 5 min. The mixture was washed with three 20-ml portions of chloroform, the combined chloroform extracts were filtered, and dried ($MgSO_4$). The solution was concentrated under reduced pressure to give a reddish-orange crystalline solid. Recrystallization from ether-chloroform gave 0.35 g (60%) of trans,trans-2,4-hexadien-1,6-dial (18) as a yellow solid: mp 119-122° (lit.[42] 117°); ir ($CHCl_3$) 3010, 2820, 2730,

1680, 1615, 1585, 1085, 1005, and 985 cm^{-1}; nmr ($CDCl_3$) δ 6.3-6.8 (m, 2H), 7.0-7.3 (m, 2H), and 9.80 ppm (d, J = 7 Hz, 2H).

Reaction of 2,7-Dimethyloxepin (24) with Mercuric Acetate. The procedure was the same as described for oxepin. Thus, 2,7-dimethyloxepin[43] (0.27 g, 2.2 mmol) was added to a stirred mixture of 0.70 g (2.2 mmol) of mercuric acetate in 14 ml of water-tetrahydrofuran (1:1). The yellow color was immediately discharged producing a greenish mixture with a gray precipitate. After stirring for 22 hr at room temperature, the mixture was worked up as described above to give a yellow solid. Recrystallization from ether gave 0.21 g (70%) of trans,trans-3,5-octadien-2,7-dione (26) as a yellow solid; mp 123-125° (sealed tube) (lit.[42] 126-126.5°). The structure was confirmed by comparison of the ir[44] and nmr[45] with those reported in the literature.

Reaction of 8,9-Indan Oxide (25) with Mercuric Acetate. The procedure was the same as described above for 1. Thus, 8,9-indan oxide[46] (0.67 g, 5.0 mmol) was added to a stirred mixture of 1.60 g (5.0 mmol) of mercuric acetate in 16 ml of water-tetrahydrofuran (1:1). After 2 hr there was no change in the appearance of the mixture, and after 36 hr the mixture had lightened in color only slightly. The mixture was worked up as described above (when the saturated aqueous

sodium chloride solution was added it produced a gray precipitate and a colorless solution immediately) to give a quantitative yield of 5-indanol as a pale yellow solid. The structure was established by comparison of the nmr, mass spectrum, and glpc (6 ft, 3% SE 30, glass column) retention time with those of an authentic sample (Aldrich).

4-Chloro-1,2,3,6-tetrahydrophthalic Acid (30). The diacid 30 was prepared in 89% yield according to the procedure of Carothers et al.:[29] mp 173-174° (lit.[29] mp 173-175°); nmr (acetone-d_6) δ 10.60 (s, 2H), 5.80 (m, 1H), 3.3-2.9 (m, 2H), and 2.9-2.4 ppm (m, 4H).

1-Chloro-1,4-cyclohexadiene (31). All glassware used in this reaction was dried in an oven at 125° overnight. The dimethyl sulfoxide and pyridine were predried over Linde molecular sieves, Type 3A.

To a stirred solution of 30 (205 g, 1.0 mol) and 40 g (0.5 mol) of pyridine in 1400 ml of dimethyl sulfoxide was added in one portion 443 g (1 mol) of lead tetraacetate (recrystallized from acetic acid containing acetic anhydride and dried in vacuo). The solution was stirred under a nitrogen atmosphere for 4 hr. The solution was continuously extracted with hexane, and the hexane solution was washed with 100 ml of water, 100 ml of saturated aqueous sodium chloride, and

dried ($MgSO_4$). The hexane was removed by distillation through a 30-cm Vigreux column under a nitrogen atmosphere. The residue was distilled through a 15-cm Vigreux column under a nitrogen atmosphere yielding 35.59 g of a colorless liquid, bp 130-143°. Glpc analysis of this distillate on a 6 ft 20% SE 30 column at 70°, indicated that it was a mixture of chlorobenzene (the structure of which was established by comparison of the ir and nmr with an authentic sample) and 31 in a ratio of 40:60. The yield of 31 is thus 21.35 g (19%). Preparative glpc provided a pure sample of 31: ir ($CHCl_3$) 2880, 2820, 1680, 1640, 1430, 1355, 990 and 960 cm^{-1}; nmr ($CDCl_3$) δ 5.75 (m, 1H), 5.60 (broad s, 2H), and 2.83 ppm (m, 4H); mass spectrum (70 eV) m/e (rel intensity) 116(5), 114(16), 112(8), 80(7), 79(100), 78(20), 77(87), 53(7), 52(10), 51(29), 50(20).

Anal. Calcd for C_6H_7Cl: C, 62.89; H, 6.17; Cl, 30.94. Found: C, 62.59; H, 6.01; Cl, 30.72.

The mixture of 31 and chlorobenzene was used in the subsequent epoxidation reaction without further purification.

1-Chloro-4,5-epoxycyclohex-1-ene (33). To a solution of 31 (16.6 g, 0.14 mol) in 350 ml of chloroform was added 16.6 g of anhydrous sodium acetate. To this stirred mixture at 0° under a nitrogen

atmosphere was added dropwise 32.3 g (0.17 mol) of peracetic acid as a 40% solution in acetic acid over the course of 1 hr. The mixture was stirred for an additional hour at 0° and for 20 hr at room temperature. The chloroform solution was washed with 2 x 100 ml of water, 2 x 100 ml of saturated aqueous sodium bicarbonate, and 100 ml of saturated aqueous sodium chloride and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue was distilled through a 15-cm Vigreux column at reduced pressure to give 14.8 g (81%) of 33 as a colorless liquid: bp 83-87° (14 mm); ir ($CHCl_3$) 2990, 2900, 2820, 1670, 1420, and 1355 cm^{-1}; nmr (CCl_4) δ 5.50 (m, 1H), 3.13 (broad s, 2H), and 2.63 ppm (m, 4H); mass spectrum (70 eV) m/e (rel intensity) 132(27), 130(84), 114(10), 112(25), 102(12), 101(20), 100(10), 95(92), 88(10), 79(10), 77(31), 75(11), 67(79), 66(67), 65(100), 63(12), 51(21), 50(15), 41(38), 40(22), 39(76), 38(17).

Anal. Calcd for C_6H_7ClO: C, 55.18; H, 5.41; Cl, 27.15. Found: C, 54.97; H, 5.50; Cl, 27.01.

4-Chlorooxepin-benzene Oxide (29). To a solution of 33 (1.00 g, 7.64 mmol) in 20 ml of carbon tetrachloride was added 1.78 g (10 mmol) of freshly recrystallized N-bromosuccinimide and approximately 50 mg of azobisisobutyronitrile. The mixture was stirred at reflux under a nitrogen atmosphere and irradiated with an ultra-

violet lamp until the bromination was complete (usually 1-2 hr). The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure to give 2.14 g of allylic bromides 34 as a viscous yellow liquid. The crude bromides were not further purified but were dissolved in 25 ml of ether and 0.81 g (15 mmol) of sodium methoxide was added in one portion. The mixture was stirred at reflux under a nitrogen atmosphere for 1 hr. The mixture was cooled to room temperature, and filtered; the filtrate was diluted with 75 ml of ether, washed with 25 ml of water and 2 x 25 ml of 5% aqueous sodium hydroxide, and dried (K_2CO_3). The solution was concentrated under reduced pressure to give an orange liquid that, on short-path distillation at room temperature (0.25-0.10 mm), yielded 0.49 g (48%) of 29 as a gold liquid: ir ($CHCl_3$) 3010, 1630, 1610, 1575, 1490, 1405, 1385, 1355, 1215, 1085, and 1010 cm^{-1}; uv max (95% C_2H_5OH) 253 nm (ϵ 1440 sh), 275 nm (ϵ 1660), trailing to 400 nm; uv max (iso-octane) 281 nm (ϵ 1450), trailing to 400 nm; 220 MHz nmr[35] (CCl_4) δ 5.37 (d of d of d, J_{76} = 5.2 Hz , J_{75} = 0.4 Hz, J_{72} = 0.4 Hz, H_7), 5.39 (d of d of d, J_{23} = 5.4 Hz, J_{25} = 0.4 Hz, J_{27} = 0.4 Hz, H_2), 5.52 (d of d of d, J_{65} = 6.8 Hz, J_{67} = 5.2 Hz, J_{63} = 0.4 Hz, H_6), 5.57 (d of d of d, J_{32} = 5.4 Hz, J_{35} = 1.5 Hz, J_{36} = 0.4 Hz, H_3), and 6.11 ppm (d of d of d of d, J_{66} = 6.8 Hz, J_{53} = 1.5 Hz, J_{52} = 0.4 Hz, J_{57} = 0.4 Hz, H_5).

Oxepin-benzene oxide 29 was too unstable for an analysis to be obtained, but it did form stable crystalline 1:1 adducts with maleic anhydride and with 4-methyl-1,2,4-triazoline-3,5-dione (see below).

Due to its instability, 29 was prepared and distilled immediately before use in any reaction.

4-Chloro-5,6-epoxybicyclo[2.2.2]oct-2-ene-7,8-dicarboxylic Acid Anhydride. To a solution of 29 (0.41 g, 3.2 mmol) in 20 ml of benzene was added 0.31 g (3.2 mmol) of maleic anhydride (sublimed). The solution was stirred at room temperature under a nitrogen atmosphere for 24 hr, after which time the characteristic oxepin color had been discharged. The benzene was removed under reduced pressure to give a yellow liquid. Trituration with ether gave 0.42 g (58%) of a white crystalline solid, which was recrystallized from benzene to give the adduct as white crystals: mp 179.5-181.0°; ir ($CHCl_3$) 3000, 1870, 1790, 1620, 1085, 1055, and 925 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 229(1), 228(7), 227(3), 226(22), 163(4), 156(3), 155(2), 154(11), 153(4), 152(14), 130(11), 129(3), 128(36), 127(32), 126(9), 125(100), 119(22), 118(14), 102(9), 101(4), 100(20), 99(10), 92(7), 91(79), 90(15), 89(26), 78(20), 77(15), 75(7), 74(4), 73(10), 65(34), 64(9), 63(28), 62(10), 52(6), 51(24), 50(14), 45(6), 39(34), 38(10).

Anal. Calcd for $C_{10}H_7ClO_4$: C, 53.00; H, 3.12. Found: C, 53.27; H, 3.10.

Subsequent attempts to repeat this reaction failed. In each case 29 decomposed to pure 4-chlorophenol as identified by nmr.

4-Methyl-1,2,4-triazoline-3,5-dione Adduct of 4-Chlorooxepin. To a stirred solution of 29 (0.57 g, 4.4 mmol) in 16 ml of acetone (dried over sodium sulfate) at room temperature was added in one portion a solution of 0.50 g (4.4 mmol) of 4-methyl-1,2,4-triazoline-3,5-dione[47] in 16 ml of acetone. This gave a bright red solution. Within 10 min the solution had lightened considerably, and no further color change was observed after an additional 15 hr.

The solution was concentrated under reduced pressure to give a pink solid which was recrystallized from acetone to give 0.75 g (75%) of the adduct as a white crystalline solid: mp 164-166° (with decomposition to a bright red liquid); ir ($CHCl_3$) 3000, 1785, 1715, 1615, 1460, 1395, 1265, 1185, 1065, 1025, 1010, 990, 955, 915, 885, 845, and 815 cm^{-1}; nmr (acetone-d_6) δ 3.02 (s, 3H), 3.90 (m, 2H), 5.38 (m, 2H), and 6.23 ppm (m, 1H).

Anal. Calcd for $C_9H_8ClO_3N$: C, 44.74; H, 3.34; Cl, 14.67; N, 17.39. Found: C, 45.02; H, 3.13; Cl, 14.73; N, 17.58.

Attempted Addition of Lithium Hydroxide to 4-Chlorooxepin (29).

A. To a solution of 29 (0.71 g, 5.5 mmol) in 10 ml of dioxane was added in one portion a solution of 0.27 g (11.0 mmol) of lithium hydroxide in 10 ml of water. The mixture was stirred at 50° under a nitrogen atmosphere for 2 hr. To the mixture was added 60 ml of ether and the ether solution was washed with 2 x 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give an orange liquid which was identified by nmr as 29.

B. To a solution of 29 (0.66 g, 5.1 mmol) in 10 ml of dioxane was added in one portion a solution of 0.27 g (11 mmol) of lithium hydroxide in 10 ml of water. The mixture was stirred at reflux under a nitrogen atmosphere for 2 hr. The reaction was worked up as in A to give a small amount of a brown viscous liquid: nmr ($CDCl_3$) δ 7.6-6.5 (m). . Glpc analysis of this crude product on a 6 ft 20% SE 30 column at 172° showed only one major peak which has been identified as dichlorodiphenyl ethers 37 and/or 38 by collecting the peak as it was eluted from the glpc: ir ($CHCl_3$) 1585, 1485, 1220, 1090, 1010, and 905 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 242(4), 241(3), 240(18), 239(4), 238(27), 212(1), 210(1), 205(1), 204(1), 203(2), 202(3), 178(2), 177(15), 176(6), 175(49), 174(1), 173(3), 169(3), 168 (20), 167(2),

152(1), 151(3), 150(1), 149(9), 141(2), 140(8), 139(20), 138(2), 137(1), 130(3), 129(2), 128(9), 127(5), 115(3), 114(3), 113(10), 112(3), 111(24), 101(13), 100(5), 99(31), 87(6), 86(2), 85(11), 76(21), 75(100), 74(25), 73(30), 65(11), 64(16), 63(46), 62(14), 61(7), 51(31), 50(63), 41(6), 39(27), 38(20), 37(7), 36(28), 35(11).

C. To a solution of 29 (0.47 g, 3.6 mmol) in 10 ml of dioxane was added in one portion a solution of 0.086 g (3.6 mmol) of lithium hydroxide in 8 ml of water. The solution was stirred at 55-60° under a nitrogen atmosphere for 70 hr. The reaction was worked up as in A to give a yellow liquid whose nmr and glpc (6 ft, 20% SE 30) retention time were identical to the product obtained in B.

D. To a solution of 0.394 g (2.2 mmol) of hexamethylphosphoramide (distilled) in 15 ml of benzene (distilled) was added 0.053 g (2.2 mmol) of lithium hydroxide. The mixture was stirred at reflux under a nitrogen atmosphere for one hr, after which time it appeared that only some of the lithium hydroxide had dissolved. To this refluxing benzene mixture was then added in one portion a solution of 0.28 g (2.2 mmol) of 29 in 5 ml of benzene. The mixture was stirred at reflux under a nitrogen atmosphere for 18 hr. The reaction was worked up as in A to give a gold liquid which was identified by nmr as 29.

Reaction of 4-Chlorooxepin (29) with Sodium Methiolate. To a stirred solution of 29 (0.43 g, 3.3 mmol) in 6 ml of dioxane at 0° was added in one portion 3.2 ml (3.3 mmol) of a 1.04 M aqueous solution of sodium methiolate in 15 ml of water. The mixture was stirred at 0° for 45 min and at room temperature for 2 and 1/2 hr under a nitrogen atmosphere, after which time the characteristic oxepin color faded. The mixture was extracted with 30 ml of ether and the ether layer was washed with 10 ml of water, 10 ml of 5% aqueous sodium hydroxide, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give a yellow liquid. Analysis of the nmr spectrum of this crude product indicated it to be a mixture consisting of 71% of a 1:1 mixture of dienes 39 and 40 and 29% of aromatic products: nmr ($CDCl_3$) 39 and 40: δ 1.92 and 1.93 (two s of equal intensity, 3H), 3.05 (broad s, 1H), 3.42 (m, 1H), 4.27 (m, 1H), and 5.97 ppm (m, 3H); aromatic: δ 2.38 (broad s, 3H) and 7.17 ppm (m, 4H).

Attempts to effect further purification resulted in decomposition mainly to a 1:1 mixture of 4- and 3-chlorothioanisoles (41 and 42, respectively) and a small amount of 4-chlorophenol, as identified by ir, nmr, and mass spectral data.

The above reaction was repeated, however the crude product was immediately dissolved in 5 ml of pyridine (predried over Linde

molecular sieves, Type 4A). To this stirred solution at 0° under a nitrogen atmosphere was added dropwise one ml of acetic anhydride. The solution was stirred for 1 hr at 0° and for 12 hr at room temperature. The solution was added to 20 ml of ice water and the aqueous phase was washed with two 30-ml portions of ether. The combined ether extracts were washed with 2 x 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give a liquid that, on distillation (Hickmann still, pot temperature 115°, 0.004 mm), gave a pale yellow liquid. Analysis of the nmr spectrum of the distillate indicated it to be a mixture consisting of 32% of a 1:1 mixture of acetates 43 and 44 and 68% of a 1:1 mixture of 41 and 42: nmr (CCl_4)—43 and 44: δ 1.90 and 1.97 (two s of equal intensity, 6H), 3.35 (m, 1H), 5.32 (m, 1H), and 5.87 ppm (m, 3H); 41 and 42: δ 2.33 and 2.35 (two s of equal intensity, 3H) and 7.10 ppm (m, 4H).

Attempts to effect separation of the diene isomers, 43 and 44, by glpc (6 ft, 20% SE 30) resulted in decomposition to a mixture of 41 and 42.

Reaction of 4-Chlorooxepin (29) with Sodium Methoxide. To a stirred solution of 29 (0.48 g, 3.8 mmol) in 12 ml of methanol at room temperature was added in one portion 0.82 g (15.2 mmol) of sodium

methoxide. The solution was stirred at room temperature under a nitrogen atmosphere. After 20 days the nmr spectrum of the reaction showed thatonly a trace of 29 remained. The yellow methanol solution was diluted with 100 ml of ether, washed with 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was short-path distilled (pot temperature 55°, 0.05-0.04 mm) to give 0.28 g of a yellow liquid. Analysis of the nmr spectrum showed it to be a mixture consisting of an 18% yield of 4-chloroanisole and a 30% yield of a mixture of the diene isomers, 45 and 46: nmr ($CDCl_3$)—45 and 46: δ 2.67 (broad s, 1H), 3.40 and 3.42 (two s, 3H), 4.07 (d of m, J = 11 Hz, 1H), 4.50 (d of m, J = 11Hz, 1H), and 5.93 ppm (m, 3H); 4-chloroanisole: δ 3.77 (s, 3H), 6.78 (d, J = 9.5 Hz, 2H), and 7.22 ppm (d, J = 9.5 Hz, 2H).

Glpc analysis of this distillate on a 6 ft 20% SE 30 column at 120° and on a 6 ft 20% Carbowax 20M column at 150° showed three major peaks (A, B, and C). The shortest retention time peak (A) was identified as 4-chloroanisole by nmr and glpc retention time. Peaks B and C were the diene isomers and were present in a ratio of 78:22. Preparative glpc (6 ft, 20% Carbowax 20M) of peaks B and C provided pure samples of both for spectral analysis (reinjection of each peak showed only one peak).

Peak B: ir ($CHCl_3$) 3580, 3400, 2980 (sh), 2930, 2830, 1635, 1595, 1565, 1490, 1470, 1440, 1375, 1290, 1285, 1215, 1125, 1100, 1080, 1030, 975, 965, 935, and 845 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 162(2), 160(5), 145(2), 144(8), 143(4), 142(21), 141(3), 131(4), 130(32), 129(10), 128(100), 127(6), 126(10), 113(6), 112(12), 111(8), 110(5), 101(8), 100(13), 99(21), 98(7), 97(5), 93(6), 92(5), 77(13), 76(4), 75(17), 74(18), 73(17), 72(7), 65(44), 64(20), 63(56), 62(25), 61(15), 53(8), 51(8), 50(15), 49(6), 44(13), 39(22), 38(16), 37(15).

Peak C: ir ($CHCl_3$) 3570, 3380, 2980 (sh), 2920, 2820, 1635, 1590, 1490, 1460, 1385, 1210, 1100, 1090, 1010, 990, 940, and 860 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 162(1), 160(2), 145(4), 144(34), 143(10), 142(100), 141(1), 132(1), 130(5), 129(18), 128(12), 127(55), 126(2), 113(3), 112(5), 111(6), 101(20), 100(5), 99(58), 77(10), 76(3), 75(15), 74(9), 73(16), 64(9), 63(22), 62(9), 51(8), 50(15), 39(9), 38(10), 37(6).

Peak B was assigned to the diene isomer, 45, and Peak C was assigned to the diene isomer, 46, on the basis of the mass spectral data (see Results and Discussion).

4-Chloro-trans-1,2-dihydroxy-1,2-dihydrobenzene (28). The aqueous solution of sodium hydroperoxide (180 mmol, 4.5 M) was prepared in the same manner as in the preparation of 2. To this stirred

solution at 0° was added in one portion 0.50 g (3.9 mmol) of 29. After 4 hr the characteristic oxepin color was discharged and the temperature was 18°. The mixture was diluted with 30 ml of water, 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 2 and 1/4 hr. The solution was allowed to warm to room temperature and was stirred for 12 hr. The resulting solution was continuously extracted with ether for 73 hr. The ether solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 0.21 g of a colorless liquid and a white solid. Analysis of the nmr spectrum of this crude product showed that it was a mixture of 28 and 4-chlorophenol in a ratio of 1:4. Preparative TLC on a 20 x 20 cm plate of silica gel (2000 microns) gave 41 mg of 28 as a pale yellow crystalline solid: R_f 0.38 (ether); nmr (acetone-d_6) δ 4.35 (m, 2H), 5.90 (m, 3H), and 8.00 ppm (s, 2H). Recrystallization from chloroform-pentane gave 17 mg (3%) of a white powder: mp 96-98°; ir ($CHCl_3$) 3560, 3210, 2800, 1625, 1585, 1370, 1245, 1080, 1060, 1010, 1000, and 860 cm^{-1}; uv max (H_2O) 266 nm (ϵ 3380); mass spectrum (70 eV) m/e (rel intensity) 149(4), 148(27), 147(9), 146(83), 145(5), 131(3), 130(5), 129(6), 128(12), 127(6), 119(18), 118(5), 117(51), 116(4), 115(8), 112(6), 111(15), 110(6), 109(7), 104(7), 103(5), 102(47), 101(14),

100(100), 99(15), 94(5), 93(7), 91(6), 90(3), 89(16), 83(10), 82(9), 81(39), 75(6), 74(5), 73(9), 67(9), 66(8), 65(48), 64(9), 63(16), 62(8), 61(6), 55(22), 54(10), 53(58), 52(8), 51(25), 50(16), 49(7), 48(2), 47(14), 43(8), 42(6), 41(8), 40(11), 39(42), 38(12), 37(7). (This sample contained less than 1%, by glpc analysis on a 6 ft 3% SE 30 glass column, of a higher molecular weight impurity believed to be 1-chloro-3-bromo-4,5-dihydroxycyclohex-1-ene: 228(2), 227(4), 226(3), 192(1), 191(2), 190(2). Comparison of this mass spectrum with one of a less pure sample of 28 showed that the relative intensities of only three peaks below the 149 peak changed: 145(17), 109(21), 99(37).)

The uv spectrum of 28 is in excellent agreement with that reported for the dihydrodiol that was obtained from natural sources:[28] uv max (H_2O) 264 nm (ε 3030).

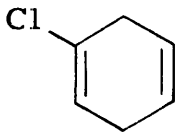
Attempted Addition of t-Butylhydroperoxide Anion to 4-Chlorooxepin 29. Sodium methoxide (0.22 g, 4.0 mmol) and t-butylhydroperoxide (0.36 g, 4.0 mmol) were dissolved in 6 ml of methanol and the solution was stirred at room temperature while a solution of 29 (0.51 g, 4.0 mmol) in 2 ml of methanol was added in one portion. The solution was stirred at room temperature under a nitrogen atmosphere.

After 69 days the nmr spectrum of the reaction showed that only a trace of 29 remained. The methanol solution was diluted with 100 ml of ether, washed with 25 ml of 5% aqueous sodium hydroxide, 25 ml of water, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give 0.55 g of a yellow liquid which was shown by nmr to be mainly a mixture of 45 and 46.

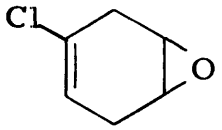
APPENDIX

APPROACHES TO THE SYNTHESIS OF 4-CHLOROOXEPIN-BENZENE OXIDE

Two precursors considered essential for the synthesis of 4-chlorooxepin (29) were either the chlorodiene 31 or the epoxide 33.



31

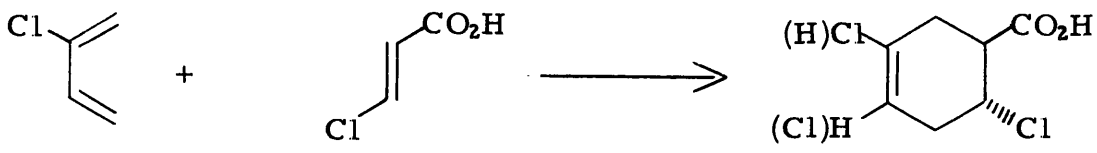


33

These products could then be carried on to oxepin 29, as already demonstrated (see Results and Discussion). Initial attempts to prepare either 31 or 33, or suitable precursors to them, which were unsuccessful are now described.

Norris has reported that the Diels-Alder reaction of butadiene and trans-2-chloroacrylic acid (51) gave a 68% yield of the 1:1 adduct.[48] However, reaction of chloroprene and 51 under similar conditions and a variety of modifications gave the 1:1 adduct as a mixture of isomers 52 in a maximum yield of 15% (Scheme XXI).

Scheme XXI

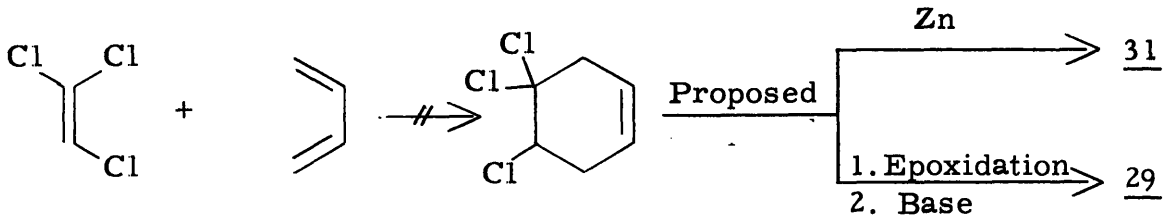


51 52

Although decarboxylative elimination of 52 gave 31 in 52% yield, the procedure was discarded due to the low yield of 52 and the high cost of 51.

Schmerling has reported the preparation of 53 by the Diels-Alder reaction of butadiene and trichloroethylene.[49] Attempted repetition of the reaction under a variety of conditions failed. The proposed transformations of 53 are indicated in Scheme XXII.

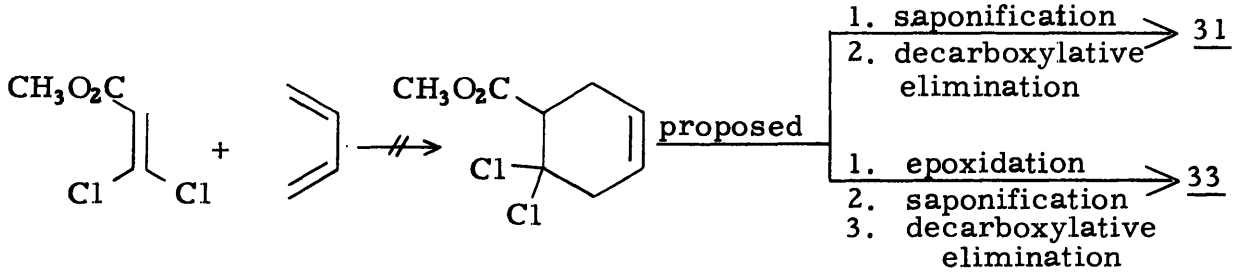
Scheme XXII



53

Repeated attempts of the Diels-Alder reaction of butadiene and methyl 2,2-dichloroacrylate[50] did not give the desired adduct 54. The proposed transformations of 54 are shown in Scheme XXIII.

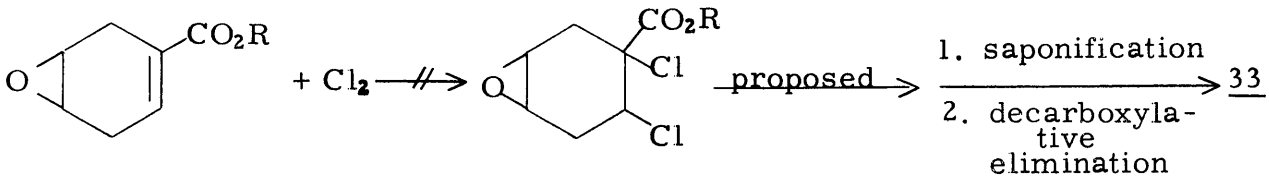
Scheme XXIII



54

Attempted chlorination of 55 or 56 under a variety of conditions did not give 57 or 58 (Scheme XXIV).

Scheme XXIV

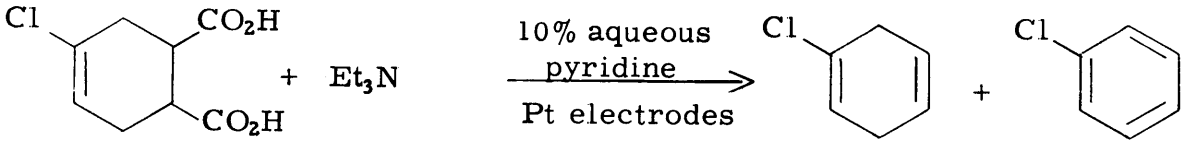


55, R=CH_3 57, R=CH_3

56, R=H 58, R=H

In addition to the use of lead tetraacetate, bisdecarboxylation of 1,2-dicarboxylic acids can be achieved by electrolysis.[51,52] On a millimole scale electrolysis of the diacid 30 under a variety of conditions provided yields of the chlorodiene 31 in the range of 20-28%. Chlorobenzene (32) was also produced, but in every case the ratio of 31 to 32 was 9:1 (Scheme XXV).

Scheme XXV



30 31 32

The lead tetraacetate procedure (see Experimental Section) was finally selected as the method of choice for the synthesis of 31 due to the simplicity of the procedure, the ability to easily scale-up the reaction to mole quantities, and the low cost of the materials involved.

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