Aromatization of Arene 1,2-Oxides. Comparison of the Aromatization Pathways of 1-Carboxy-, 1-Carbomethoxy-, 1-Formyl-, 1-(Hydroxymethyl)-, and 1-(2-Hydroxy-2-propyl)benzene Oxide

Herbert S.-I. Chao and Glenn A. Berchtold*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received July 21, 1980*

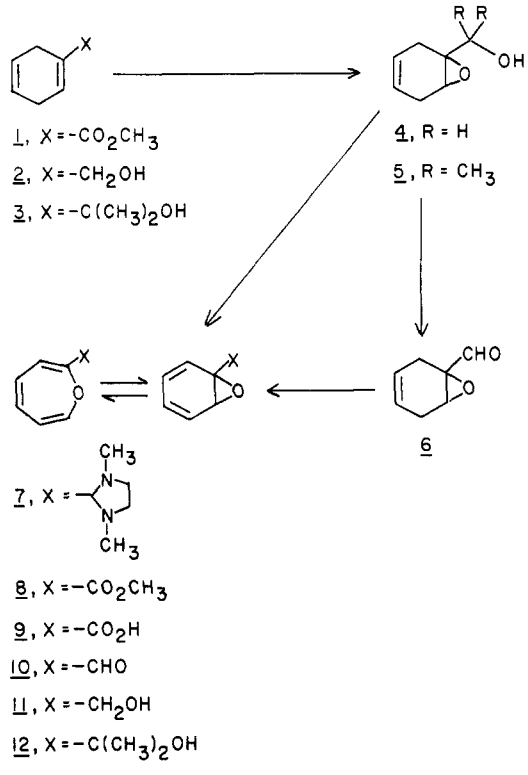
Abstract: The mechanisms for aromatization of the title compounds in 1:1 tetrahydrofuran/water at various pHs have been investigated through product studies and studies with the deuterium-labeled arene oxides. Arene oxide **8** isomerizes to methyl salicylate; the extent of carbomethoxy migration during product formation is 70% at pH 0.1 and 83% at pH 7. Arene oxide **9** affords salicylic acid (40% at pH 1, 20% at pH 7) and phenol (60% at pH 1; 80% at pH 7); salicylic acid is formed without migration of the carboxyl group. Aromatization of **10** (pH 0.1–10) gives phenol (88–94%) and salicylaldehyde (6–12%) without migration of the formyl group. Aromatization of **11** (pH 1.1–10) gives phenol (8–17%) and *o*-hydroxybenzyl alcohol (83–92%) without migration of the side chain. Phenol (40–45%) and *o*-(2-hydroxy-2-propyl)phenol (55–60%) are formed from **12** during aromatization at pH 1.1–10.

Ortho hydroxylation of monosubstituted benzenes without substituent migration by a metabolic pathway involving initially the arene oxide could proceed via the 1,2- or the 2,3-oxide. Hydroxylations involving arene oxide intermediates that occur with loss of the substituent at the site of hydroxylation or with migration of the substituent to an adjacent ortho position must proceed via the 1,2-oxide. Whether substituent loss or substituent migration occurs is determined by the direction of oxirane ring opening in the acid- or water-catalyzed aromatization by the NIH shift pathway.[1,2] If biological hydroxylation of a benzene derivative occurs by monooxygenase-catalyzed addition of HO^+ or HO· with subsequent oxidation to a cationic intermediate, then ortho hydroxylation without substituent migration involves the cationic intermediate obtained from oxirane cleavage of the arene 1,2-oxide at C_1, and hydroxylation at the carbon atom bearing the substituent with substiuent loss or migration involves the cationic intermediate obtained from oxirane cleavage of the arene 1,2-oxide at C_2.

Numerous examples of biological hydroxylation reactions of benzene derivatives in which the arene 1,2-oxide may be the initial metabolic intermediate are reported in the literature. Because of their importance in understanding the biological hydroxylation reactions in addition to a general interest in understanding the effect of 1-substituents, we are involved in a general study of the course of aromatization of arene 1,2-oxides. Detailed studies of the aromatization of arene 1,2-oxides where the substituent is CH_3,[3] $Si(CH_3)_3$,[4] CO_2CH_3,[2] and CO_2H[2] have been reported previously. Reported herein are additional data for CO_2Me and CO_2H and studies of aromatization for CHO, CH_2OH, and $C(CH_3)_2OH$ substituents.

The preparation of arene oxides **8** and **9** has been reported previously.[2] Arene oxides **10–12** were prepared as outlined in Scheme I. Reduction of **1** ($LiAlH_4/Et_2O$) afforded **2** that was oxidized regioselectively by the Sharpless procedure[5] [$VO(acac)_2$, *t*-$BuOOH/C_6H_6$] to afford **4**. Oxidation of **4** [Me_2SO, $(CF_3CO)_2O/CH_2Cl_2$][6] gave epoxy aldehyde **6**. It was not possible to convert **6** directly to arene oxide **10** by a bromination–elimination procedure. Protection of the formyl group was necessary prior to elimination. After addition of Br_2 to the olefinic moiety of **6**, the formyl group was protected as the imidazolidine derivative by reaction with *N,N'*-dimethylethylenediamine. Subsequent elimination of HBr (DBN/Et_2O) afforded **7**. Removal of the imidazolidine protecting group of **7** in a biphasic solvent mixture ($CHCl_3$/aqueous phosphate buffer, pH 6) gave arene oxide **10**.

Scheme I



Silylation of **4** (Me_3SiCl, Et_3N/THF) followed by bromination of the double bond and subsequent elimination of HBr (DBN/Et_2O) afforded the trimethylsilyl derivative of **11** that was converted to arene oxide **11** by cleavage of the silyl ether with KF in methanol. The silyl derivative of **4** could also be converted to the silyl derivative of **11** by allylic bromination (NBS/CCl_4) and subsequent elimination of HBr (KO-*t*-Bu/Et_2O). Yields (40–45%) were the same for either sequence.

Arene oxide **12** was prepared by a similar sequence. Reaction of **1** with 2.1 equiv of methyllithium afforded **3** that was oxidized (*m*CPBA/CH_2Cl_2) to **5**. Conversion of **5** to the trimethylsilyl

(1) Daly, J. W.; Jerina, D. M.; Witkop, B. *Experientia* **1972**, *28*, 1129–1149.
(2) Boyd, D. R.; Berchtold, G. A. *J. Am. Chem. Soc.* **1979**, *101*, 2470–2474.
(3) Chao, H. S.-I.; Boyd, D. R.; Berchtold, G. A.; Jerina, D. M.; Yagi, H.; Dynak, J., manuscript in preparation.
(4) Van Epp, J. E.; Boyd, D. R.; Berchtold, G. A.; submitted for publication.
(5) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63–74.
(6) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3330.

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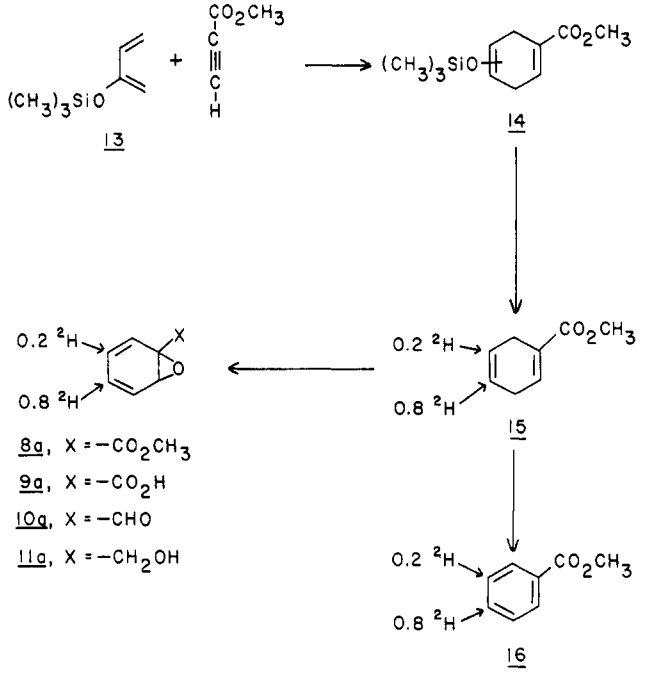
Scheme II



ether derivative, bromination of the double bond, elimination of HBr (DBN/Et_2O), and removal of the silyl protecting group with KF in methanol gave **12**.

To determine the extent of oxirane ring opening at C_1 vs. C_2 during aromatization of **8–12** without loss of the X substituent and consequently the extent of migration of the substituent, it was necessary to label the arene oxides at C_4 or C_5. The method selected for deuterium labeling was not regiospecific, but it was sufficiently regioselective for accurate measurements of the degree of substituent migration. The sequence is outlined in Scheme II. Reaction of **13** with methyl propiolate afforded isomers **14** that, on treatment with diborane-d_6 followed by aqueous acid, gave deuterium-labeled methyl 2,5-dihydrobenzoate (**15**). The deuterium distribution in **15** was established by two independent procedures. Bromination of **15** occurred selectively at the C_3–C_4 double bond, and the dibromide underwent base-catalyzed elimination of HBr to afford deuterium-labeled methyl benzoate (**16**) with no loss of total deuterium content. The distribution of deuterium at C_3 and C_4 of **16** was measured by integration of the ^1H NMR spectrum. Alternatively, since **15** serves as the precursor for **8–12** and since the chemical shifts of the ring protons of **8** are well separated (250 MHz) and have been assigned,[2] **15** was converted to **8a**, and the deuterium content at C_4 and C_5 of each was measured by integration of the ^1H NMR spectrum. The two procedures gave consistent results with values of 80 ± 3% and 20 ± 3% deuterium distribution as indicated in Scheme II. These results provide assignment of the deuterium distribution in **15** as indicated, and **14** must be an 80:20 mixture of the 4- and 3-trimethylsiloxy derivatives, respectively.[7] Diene **15** was used to prepare deuterated arene oxides **8a–11a** by the procedures indicated above for the unlabeled substances. The ^1H NMR spectra were consistent with the deuterium distribution as indicated.

The pathways for acid- or water-catalyzed aromatization of arene oxides **8–12** are outlined in Scheme III. Formation of ortho-substituted phenol without substituent migration, i.e., **17a**, occurs by cleavage of the C_1–O oxirane bond to afford cation A that is aromatized to **17A** by direct loss of H^+ or by NIH shift of hydrogen to form the cyclohexadienones indicated in the scheme and subsequent enolization. Formation of ortho-substituted phenol with substituent migration, i.e., **17B**, occurs by cleavage of the C_2–O oxirane bond to afford cation B. Aromatization via cation B involves migration of X to either of the equivalent ortho positions

(7) Reaction of **13** with methyl acrylate is reported to be regiospecific.[8]
(8) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935–2938.

Scheme III

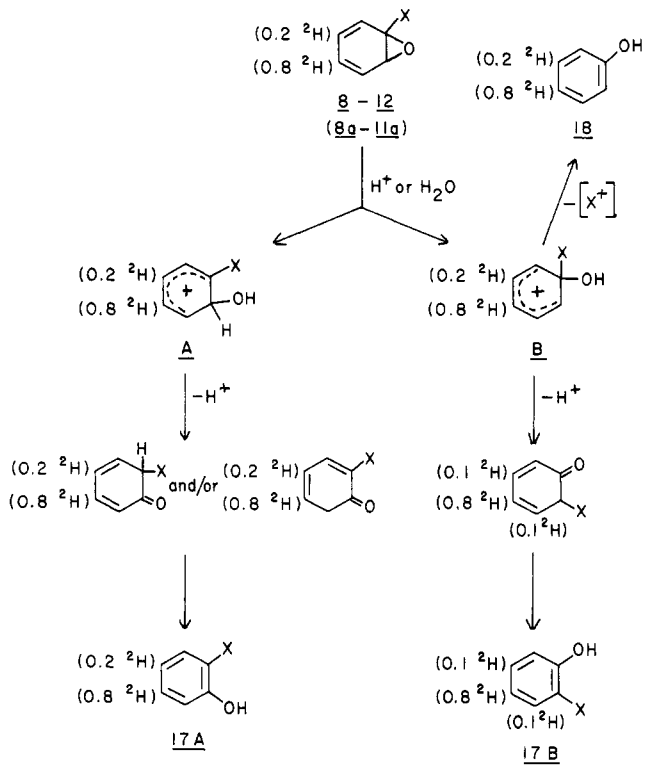


Table I. Summary of Aromatization Reactions

arene oxide	conditions[a]	% yield of *o*-XC_6H_4OH: total	via cation A[b]	via cation B[c]	% yield of phenol[d]
8, X = CO_2CH_3	CF_3CO_2H	100	36	64	
	pH 0.1	100	30	70	
	pH 1.1	100	33	67	
	pH 7.0	100	17	83	
9, X = CO_2H	pH 1.0	40	40	0	60
	pH 7.0	20	20	0	80
10, X = CHO	CF_3CO_2H/Et_2O	22			78
	pH 0.1	11			89
	pH 1.1	11	11	0	89
	pH 4.0	6			94
	pH 7.0	7			93
	pH 10.0	12			88
11, X = CH_2OH	pH 1.1	89	89	0	11
	pH 4.0	91			9
	pH 7.0	92	92	0	8
	pH 10.0	83			17
12, X = $C(CH_3)_2OH$	pH 1.1	60			40
	pH 4.0	57			43
	pH 7.0	58			42
	pH 10.0	55			45

[a] Reactions in which the pH is indicated were run in 1:1 tetrahydrofuran/water with the pH of the aqueous portion as indicated. [b] No migration of X. [c] Migration of X. [d] Via cation B.

and enolization of the resulting cyclohexadienone to **17B**. Aromatization with loss of the substituent occurs by fragmentation of X^+ (H^+ + neutral molecule) from cation B to afford phenol (**18**). The distribution of deuterium in phenolic products from aromatization of **8a–11a** via cations A and B would be that indicated in Scheme III. Integration of the aromatic hydrogen absorptions in the ^1H NMR spectra of the ortho-substituted phenols provides a measurement of the deuterium distribution in these products and thus establishes the extent of ortho-substituted phenol formation with and without substituent migration during aromatization of the arene oxides.

The arene oxides were aromatized under the conditions indicated in Table I. The yields of ortho-substituted phenols and phenol from loss of substituent were determined from aromatization of the unlabeled arene oxides. The extent of substituent migration (reaction via cation A vs. cation B) was determined from ^{1}H NMR analysis of ortho-substituted phenol from aromatization of the deuterium-labeled arene oxides. Results are summarized in Table I. All reactions were run in duplicate.

1-(Carbomethoxy)benzene oxide–oxepin (**8**) undergoes aromatization to methyl salicylate in quantitative yield.[2] Previous results indicated that the reaction occurs via cation B (X = CO_2CH_3) with migration of the carbomethoxy substituent but did not exclude the possibility that a significant amount of the product was formed via cation A (X = CO_2CH_3) without substituent migration. That the latter situation is indeed the case was established from analysis of the deuterium distribution in methyl salicylate from aromatization of **8a**. Under the acidic conditions investigated (Table I), approximately one-third of the product is formed without substituent migration. Considerably less product (17%) is formed without substituent migration under neutral conditions. Thus, regardless of the electron-withdrawing character of the carbomethoxy substituent, a significant fraction of the aromatization reaction occurs by initial cleavage of the C_1–O oxirane bond of **8**, but C_1–O cleavage becomes less favorable in the absence of acid catalysis. If formation of cation B (X = CO_2CH_3) from **8a** is a reversible process, scrambling of deuterium label would occur in **8a** since epoxide formation from cation B (X = CO_2CH_3) could occur at either ortho position, and results would be meaningless. To establish that such was not the case, we carried the aromatization of **8a** at pH 7.0 to partial completion, and **8a** was recovered. The ^{1}H NMR spectrum of recovered **8a** showed no change in the deuterium distribution.

1-Carboxybenzene oxide–oxepin (**9**) undergoes aromatization to a mixture of phenol and salicylic acid, and the ratio of products is pH dependent.[2] Phenol is formed via cation B (X = CO_2H) from oxirane cleavage at C_2. In order to establish unambiguously that salicylic acid is formed exclusively by cleavage of the C_1–O oxirane bond, we investigated the aromatization of **9a** at pH 1.0 and 7.0. Salicylic acid formed in each case had the deuterium distribution indicated by **17A** and, consequently, was formed exclusively by initial oxirane cleavage to cation A (X = CO_2H).

1-Formylbenzene oxide–oxepin (**10**) is a stable orange-red liquid that exists predominantly as the oxepin valence tautomer. It was aromatized under the conditions listed in Table I. The aromatization reaction was rapid (2 min) at pH 0.1, but the rate decreased with increasing pH and it required 20 days for complete aromatization at pH 7.0. Aromatization of **10** affords a mixture of phenol and salicylaldehyde, the ratio of which does not differ significantly as a function of pH in aqueous tetrahydrofuran. Aromatization of **10a** at pH 1.1 resulted in salicylaldehyde with a deuterium distribution corresponding to **17A**, and, consequently, salicylaldehyde is formed exclusively by cleavage of the C_1–O oxirane bond of **10** to afford cation A (X = CHO). No migration of the formyl group is observed; reaction via cation B (X = CHO) results in complete loss of the side chain (H^+ + CO) to afford phenol. The ratio of salicylaldehyde:phenol, i.e., cleavage at C_1 vs. C_2 of **10**, is consistent with the electron-withdrawing character of the formyl group.

Aromatization of 1-(hydroxymethyl)benzene oxide–oxepin (**11**) affords a mixture of *o*-hydroxybenzyl alcohol and phenol due to loss of the side chain during the reaction. The ratio of *o*-hydroxybenzyl alcohol to phenol between pH 1.1 and 7.0, 9:1, within experimental error is independent of pH, but at pH 10 slightly more phenol is formed. Under more acidic conditions, pH 0.1 in 1:1 aqueous tetrahydrofuran or in trifluoroacetic acid, the yield of 2-hydroxybenzyl alcohol and phenol is considerably less than quantitative due to phenol–formaldehyde-type polymerization under the strongly acidic conditions. Deuterated *o*-hydroxybenzyl alcohol from aromatization of **11a** at pH 1.1 and 7.0 showed the deuterium distribution corresponding to **17A** and thus established that all *o*-hydroxybenzyl alcohol arises via cation A (X = CH_2OH) from cleavage of the oxirane C_1–O bond of **11**. Cleavage of the C_2–O bond of **11** leads to cation B (X = CH_2OH) that suffers loss of the side chain (H^+ + H_2CO) to afford phenol. Hamilton has suggested[9] such a pathway for biological dehydroxymethylation reactions catalyzed by monooxygenases if benzene 1,2-oxides are intermediates. Results from the aromatization of **11** demonstrate the validity of the suggestion; but, in the absence of biological catalysis, significant loss of the side chain during aromatization would require the presence of an additional substituent that favors cleavage of the C_2–O bond of the arene oxide. Alternatively, enzyme-catalyzed addition of HO^+ to the aryl carbon atom bearing the hydroxymethyl substituent would result in aromatization with complete loss of substituent.

Alkyl substitution at the side-chain carbon atom of **11** increases the extent of C_2–O oxirane cleavage during aromatization. Thus arene oxide **12** affords 40–45% phenol via cation B (X = C-$(CH_3)_2OH$) in the pH range investigated. It is assumed that the ortho-substituted phenol from **12**, by analogy with the aromatization of **11**, is formed exclusively via cation A (X = C-$(CH_3)_2OH$).

The present work provides examples of arene 1,2-oxide aromatization reactions proceeding by all the possible general routes to ortho-substituted phenols and phenol with substituent loss. The results support literature suggestions that arene 1,2-oxides may be intermediates in hydroxylation reactions of biological systems. The extent of oxirane ring opening at C_1 vs. C_2 of the arene 1,2-oxides investigated appears to be determined primarily by the electron-withdrawing or electron-donating character of the substituent, but other factors may be involved. If reaction occurs by cleavage of the oxirane at C_2 to afford cation B, whether migration or loss of the C_1 substituent is observed depends on the nature of the substituent. If the substituent is CO_2Me, migration is observed since fragmentation of the side chain would require formation of a highly energetic cationic species. On the other hand, if the substituent is CO_2H, CHO, or CR_2OH (R = H, Me), fragmentation of the side chain as H^+ and a stable, neutral molecule becomes the favored process, and substituent migration is not observed.

Experimental Section

Melting points were determined with use of a Thomas-Hoover Unimelt apparatus and are corrected. ^{1}H NMR spectra were obtained at 60 or 250 MHz with Varian T-60, Perkin-Elmer R24B, and Brücker FT spectrometers, respectively. Chemical shift values (δ) are reported in ppm downfield from tetramethylsilane. Infrared spectra were obtained with a Perkin-Elmer Model 283B spectrophotometer. Ultraviolet spectra were obtained with a Perkin-Elmer Model 552 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

α-Hydroxy-2,5-dihydrocumene (3). To a solution of 10.0 g (0.072 mol) of **1**[2,10] in 100 mL of anhydrous diethyl ether at room temperature was added dropwise 110 mL of 1.4 M methyllithium (0.154 mol) in diethyl ether. The solution was stirred for 1 h after addition was complete, and saturated NH_4Cl solution was added dropwise. The organic layer was separated, washed with saturated NH_4Cl solution and with water, and dried (K_2CO_3). The filtrate was concentrated in vacuo and distilled to yield 8.86 g (89%) of *3*: bp 55 °C (0.45 mm); IR (neat) 3360, 1655, 1630 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.70 (s, 3 H), 2.70 (s, 4 H), 1.62 (s, 1 H), 1.33 (s, 6 H).

1-(Hydroxymethyl)-1,2-oxido-4-cyclohexene (4). A solution of anhydrous *tert*-butyl hydroperoxide in benzene was prepared by removing 40 mL of distillate from a solution of 90% *tert*-butyl hydroperoxide (30 g) in 120 mL of benzene,[5] and it was added dropwise over 20 min to a solution of **2**[3] (31.5 g, 0.25 mol) and $VO(acac)_2$ (0.5 g) in 300 mL of benzene under reflux. After addition was complete, the mixture was heated under reflux for an additional 3 h and cooled. Excess oxidizing agent was destroyed by the addition of 30 mL of 10% Na_2SO_3 at 5 °C, and the mixture was stirred until the starch–iodide test was negative (2 h). The organic layer was separated, and the aqueous layer was extracted with 30 mL of ether. The organic layers were combined, dried ($MgSO_4$), concentrated in vacuo, and distilled to give 31.5 (88%) of **4**: bp 68 °C (0.45 mm); IR (neat) 3450, 1665 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ

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(10) Petrov, A. A.; Rall, K. B. *J. Gen. Chem. USSR (Engl. Transl.)* **1956**, *26*, 1779–1783.

5.48 (s, 2 H), 3.69 (s, 2 H), 3.32 (s, 1 H), 2.70 (br s, 1 H), 2.48 (br s, 4 H). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.35; H, 8.06.

1-(2-Hydroxy-2-propyl)-1,2-oxido-4-cyclohexene (5). To a solution of **3** (8.86 g, 64 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added portionwise 85% *m*-chloroperbenzoic acid (13.9 g, 68 mmol), and the solution was stirred at 0–5 °C for 2 h. Precipitated *m*-chlorobenzoic acid was removed by filtration, and the filtrate was washed consecutively with 5% Na_2SO_3, 5% $NaHCO_3$, and saturated NaCl solution. The CH_2Cl_2 solution was dried ($MgSO_4$), concentrated in vacuo, and distilled to give 6.0 g (61%) of **5**: bp 48 °C (0.3 mm); IR (neat) 3460, 1660 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 5.53 (s, 2 H), 3.49 (s, 1 H), 2.49 (s, 4 H), 2.23 (s, 1 H), 1.33 (s, 6 H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.08; H, 9.38.

1-Formyl-1,2-oxido-4-cyclohexene (6). Trifluoroacetic anhydride (37.8 g, 0.18 mol) in 60 mL of CH_2Cl_2 was added to a solution of dry dimethyl sulfoxide (18.7 g, 0.24 mol) in 120 mL of CH_2Cl_2 at −65 °C.[6] The temperature was maintained while a solution of **4** (19.7 g, 0.15 mol) in 80 mL of CH_2Cl_2 was added over a period of 10 min; the mixture was stirred for 30 min, and triethylamine (50 mL) was added dropwise over a period of 10 min. The mixture was warmed to room temperature and extracted with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated, and distilled to give 13.8 g (70%) of **6**, bp 57–60 °C (0.85 mm), that was contaminated with ~5% aromatic impurity. An analytical sample of **6** was obtained by collection from VPC (14% carbowax on 60-100 mesh Choromosorb W, 110 °C): IR (neat) 1730, 1668 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 8.87 (s, 1 H), 5.42 (s, 2 H), 3.45 (s, 1 H), 2.0–3.3 (m, 4 H). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.49. Found: C, 68.06; H, 6.50.

1-Formylbenzene Oxide–Oxepin (10). The 4,5-dibromo derivative of **6** was prepared by dropwise addition of 4.2 mL of Br_2 in 100 mL of $CHCl_3$ to **6** (10.4 g, 84 mmol) in 100 mL of $CHCl_3$ at −65 °C. Removal of solvent in vacuo and short-path distillation (Kugelrohr) gave 10.5 g (44%) of diastereomeric dibromo aldehydes as a viscous oil: IR (neat) 2820, 2720, 1722 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 8.77 and 8.81 (2 s, 1 H), 4.1–4.6 (m, 2 H), 3.4–3.7 (m, 1 H), 2.0–3.4 (m, 4 H).

To a solution of the dibromo aldehyde (4.29 g, 15 mmol) in 20 mL of CCl_4 was added *N,N'*-dimethylethylenediamine (1.5 g, 17 mmol), and the solution was stirred for 1 h. The mixture was diluted with 20 mL of CCl_4, dried ($MgSO_4$), and concentrated to give 5.2 g of crude imidazoline derivative that was dissolved in anhydrous ether. To the ether solution under N_2 at room temperature was added dropwise 2.5 equiv (37 mmol) of DBN, and the mixture was stirred for 10 h. The precipitated salts were removed by filtration. The filtrate was washed with two 20-mL portions of NaCl solution. The aqueous layer was separated and extracted with two 10-mL portions of ether. The combined ether layers were dried (K_2CO_3), filtered, and concentrated. Short-path distillation (Kugelrohr) of the residue gave 0.8 g (29%) of **7** estimated by ^1H NMR to be 90% pure; ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (m, 2 H), 6.17 (m, 1 H), 5.94 (m, 1 H), 4.96 (d, J = 4.8 Hz, 1 H), 3.28 (m, 2 H), 2.65 (s, 1 H), 2.50 (m, 2 H), 2.39 (s, 6 H).

Arene oxide **7** (1.3 g, 6.7 mmol) in 10 mL of $CHCl_3$ was stirred vigorously with 900 mL of pH 6 aqueous phosphate buffer for 4 h. The organic layer was separated, and the aqueous layer was extracted with three 50-mL portions of ether. The ether and $CHCl_3$ fractions were combined, dried ($MgSO_4$), and concentrated in vacuo to afford crude **10**. Column chromatography of the crude product on silica gel (1:9 ether/pentane) gave 0.4 g (49%) of **10** as an orange-red oil: IR 3040, 2820, 2730, 1722, 1680, 1605 cm^{-1}; UV_{max} (pentane) 218 (ϵ 12 700), 320 nm (ϵ 2690); ^1H NMR (250 MHz, $CDCl_3$) δ[11] 9.28 (s, 1 H, CHO), 6.55 (d, 1 H, H_6), 6.48 (d d, 1 H, H_4), 6.35 (d d, 1 H, H_5), 6.01 (d, 1 H, H_2), 5.66 (t, 1 H, H_3) ($J_{2,3}$ = 5.5, $J_{3,4}$ = 5.5, $J_{4,5}$ = 10.8, $J_{5,6}$ = 5.9 Hz).

A crystalline Diels–Alder adduct of **10** was prepared by reaction with maleic anhydride in ether: mp 180–182 °C ($CHCl_3$/pentane); IR (KBr) 1860, 1835, 1770, 1710 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 9.17 (s, 1 H), 6.07 (m, 1 H), 5.98 (m, 1 H), 4.11 (d d, J = 4.8, 0.8 Hz, 1 H), 3.85 (m, 2 H), 3.63 (d d, J = 8.5 and 3.5 Hz, 1 H), 3.54 (dd, J = 8.5 and 3.2 Hz, 1 H). Anal. Calcd for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.88; H, 3.70.

1-(Hydroxymethyl)benzene Oxide–Oxepin (11). A solution of **4** (4.83 g, 38.3 mmol), 15 mL of triethylamine, and 15 mL of chlorotrimethylsilane in 75 mL of dry tetrahydrofuran was stirred at room temperature for 8 h under N_2. The solution was diluted with 150 mL of ether and washed with 250 mL of 5% aqueous NaOH solution. The aqueous phase was separated and extracted with 75 mL of ether. The combined organic layers were washed with 100 mL of saturated NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was distilled to give 6.30 g (83%) of 1-[((trimethylsilyl)oxy)methyl]-1,2-oxido-4-cyclohexene: bp 54 °C (0.3 mm); ^1H NMR (60 MHz, $CDCl_3$) δ 5.48 (s, 2 H), 3.65 (s, 2 H), 3.17 (s, 1 H), 2.49 (s, 4 H), 0.13 (s, 9 H).

Bromination of the double bond was effected by dropwise addition of 0.70 mL of Br_2 in 30 mL of CCl_4 to a solution of 3.0 g (15 mmol) of the *O*-trimethylsilyl derivative of **4** in 40 mL of CCl_4 at 0 °C. Concentration of the solution in vacuo and short-path distillation (Kugelrohr) gave 5.4 g (98%) of a mixture of the diastereomeric dibromides: ^1H NMR (60 MHz, $CDCl_3$) δ 4.30 (m, 2 H), 3.63 (m, 2 H), 3.16 (broad s, 1 H), 3.10–2.20 (m, 4 H), 0.15 (s, 9 H). The dibromides were stirred with 4 mL of DBN in ether at 0 °C for 10 h. The ether solution was decanted, the solvent was removed in vacuo, and the residue was short path distilled to give 1.3 g (44%) of 1-[((trimethylsilyl)oxy)methyl]-1,2-benzene oxide as a pale yellow liquid; ^1H NMR (250 MHz, $CDCl_3$) δ 5.7–6.4 (m, 4 H), 5.13 (d, J = 4.8 Hz, 1 H), 4.01 (s, 2 H), 0.15 (s, 9 H).

Removal of the silyl group was accomplished by stirring 3.6 g (18 mmol) of the silylated arene oxide with 1.5 g of KF in 20 mL of methanol at 0 °C for 2 h. The solvent was removed, and the residue was dissolved in 20 mL of ether. The solution was washed with pH 7 buffer solution, dried (K_2CO_3), and concentrated under high vacuum to give 2.0 g (92%) of **11**: IR (neat) 3360, 1650, 1620, 1590 cm^{-1}; UV_{max} (CH_3OH) 269 nm (ϵ 1500); ^1H NMR (250 MHz, $CDCl_3$) δ 6.27 (m, 2 H), 6.02 (m, 2 H), 5.03 (d, J = 4.4 Hz, 1 H), 4.81 (s, 1 H), 4.01 (s, 2 H).

Arene oxide **11** aromatized on attempted distillation. A crystalline Diels–Alder adduct of **11** was prepared by reaction with 4-phenyl-1,2,4-triazoline-3,5-dione in $CHCl_3$: mp 175–176 °C (CH_3OH); IR (KBr) 3440, 1755, 1690, 1610 cm^{-1}; ^1H NMR (60 MHz, acetone-d_6) δ 7.50 (s, 5 H), 6.28 (m, 2 H), 5.35 (m, 2 H), 4.5–3.6 (m, 4 H). Anal. Calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 59.99; H, 4.46; N, 13.86.

1-(2-Hydroxy-2-propyl)benzene Oxide–Oxepin (12). A mixture of 7.9 g (51 mmol) of **5**, 8.69 g (2.5 equiv) of imidazole, and 6.72 g (1.2 equiv) of chlorotrimethylsilane in 150 mL of anhydrous dimethylformamide was stirred under N_2 at room temperature for 10 h. The solution was diluted with 200 mL of water and extracted with two 150-mL portions of pentane. The combined pentane extracts were washed with water, dried ($MgSO_4$), and concentrated. Distillation of the residue gave 9.87 g (86%) of the *O*-trimethylsilyl derivative of **5**: bp 52–55 °C (0.45 mm); ^1H NMR (60 MHz, $CDCl_3$) δ 5.50 (s, 2 H), 3.27 (s, 1 H), 2.53 (s, 4 H), 1.27 (s, 6 H), 0.16 (s, 9 H).

Bromination of the double bond was accomplished by the same bromination procedure described in the preparation of **11** and gave 12.3 g (81%) of dibromide product: ^1H NMR (60 MHz, $CDCl_3$) δ 4.7–4.0 (m, 2 H), 3.20 (br s, 1 H), 3.1–2.2 (m, 4 H), 1.23 (s, 6 H), 0.17 (s, 9 H). A solution of the dibromide (11.2 g, 29 mmol) and DBN (8.85 g, 73 mmol) in 50 mL of anhydrous ether was stirred at room temperature for 4 h. The solution was decanted, diluted with ether, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated. Short-path distillation (Kugelrohr) gave 2.70 g (41%) of 1-[2-((trimethylsilyl)-oxy)-2-propyl]benzene oxide: ^1H NMR (250 MHz, $CDCl_3$) δ 6.3–6.1 (m, 3 H), 5.9–5.8 (m, 1 H), 5.20 (d, J = 4.4 Hz, 1 H), 1.40 (s, 6 H), 0.14 (s, 9 H).

Removal of the silyl group was accomplished by the same procedure described in the preparation of **11** and gave **12** in 87% yield as a yellow oil: IR (neat) 3440, 1670, 1640, 1620 cm^{-1}; UV_{max} (CH_3OH) 243 (ϵ 2230), sh 269 nm (ϵ 1520); ^1H NMR (250 MHz, $CDCl_3$) δ 6.30 (m, 2 H), 6.16 (m, 1 H), 6.05 (m, 1 H), 5.03 (dd, J = 5.0, 1.0 Hz, 1 H), 2.12 (s, 1 H), 1.40 (s, 6 H).

A crystalline Diels–Alder adduct of **12** was prepared by reaction with 4-phenyl-1,2,4-triazoline-3,5-dione in $CHCl_3$: mp 180–182 °C (CH_3O-H); IR (KBr) 3440, 1765, 1695 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 7.57–7.3 (m, 5 H), 6.33 (m, 1 H), 6.16 (m, 1 H), 5.44 (m, 1 H), 5.33 (m, 1 H), 4.01 (s, 1 H), 3.89 (d, J = 4.8 Hz, 1 H), 1.43 (s, 3 H), 1.30 (s, 3 H). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38 H, 5.23; N, 12.84. Found: C, 62.10; H, 5.14; N, 12.63.

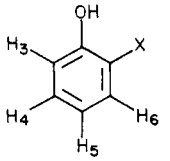
Methyl 3- and 4-[(Trimethylsilyl)oxy]-2,5-dihydrobenzoate (14). A mixture of **13**[8] (4.83 g, 34 mmol) and methyl propiolate (2.8 g, 33 mmol) was refluxed under N_2 at 125 °C for 18 h. Distillation of the product mixture gave 6.25 g (82%) of **14**: bp 76 °C (0.3 mm); ^1H NMR (60 MHz, $CDCl_3$) δ 6.80 (m, 1 H), 4.84 (m, 1 H), 3.70 (s, 3 H), 2.88 (m, 4 H), 0.19 (s, 9 H).

Methyl 2,5-Dihydro[3,4-^{2}H]benzoate (15). To a solution of 66.7 g (0.29 mol) of **14** in 150 mL of dry tetrahydrofuran at 0 °C under N_2 was added dropwise 161 mL (0.145 mol) of 0.9 M borane-d_3-THF in tetrahydrofuran (Alfa Division, Ventron Corp.).[12] The solution was stirred

(11) Assignments are based on the numbering system for the benzene oxide valence tautomer.

(12) Procedure of: Larson, G. L.; Hernandez, D.; Hernandez, A. *J. Organomet. Chem.* **1974**, *76*, 9–16. Larson, G. L.; Hernandez, E.; Alonso, C.; Nieves, I. *Tetrahedron Lett.* **1975**, 4005–4008.

Table II. Chemical Shift Data and Deuterium Distribution in Ortho-Substituted Phenols



arene oxide	chemical shifts of aromatic protons,[a] ppm				^{2}H distribution in ortho-substituted phenol			
	X	H_3 and H_5	H_4	H_6		C_4	C_5	C_6
8a	CO_2CH_3	6.9–7.0	7.53	7.85	CF_3CO_2H	0.36	0.59	0.05
					pH 0.1	0.30	0.62	0.08
					pH 1.1	0.33	0.61	0.06
					pH 7.0	0.21	0.70	0.09
9a	CO_2H	6.8–7.1	7.47	7.88	pH 0.1	0.80	0.80	
					pH 7.0	0.76	0.24	
10a	CHO	6.7–7.1	7.36	7.56	pH 1.1	0.80	0.20	
11a	CH_2OH	6.75–6.85	7.09	7.25	pH 1.1	0.81	0.19	
					pH 7.0	0.80	0.20	

[a] In acetone-d_6.

at 25 °C for 1 h, and a few drops of water was added cautiously to destroy excess hydride. Aqueous 10% HCl (200 mL) was added, and the mixture was heated under reflux for 4 h. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with 5% $NaHCO_3$ and with water, dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residue gave 27.6 g (68%) of **15**: bp 49 °C (0.7 mm); ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.90 (br s, 1 H), 5.74 (br s, 1 H), 3.72 (s, 3 H), 2.87 (s, 4 H).

The deuterium distribution in **15** was established by ^{1}H NMR analysis of the deuterium-labeled methyl benzoate formed from **15** by conversion to the *trans*-4,5-dibromo derivative as described previously for the unlabeled compound[2] and subsequent elimination of HBr with DBN in anhydrous ether with no loss in total deuterium content. For methyl benzoate: ^{1}H NMR (250 MHz, acetone-d_6) δ 7.52 (meta H), 7.65 (para H), 8.01 (ortho H). Integration of the aromatic proton absorption in the ^{1}H NMR spectrum of the labeled methyl benzoate from **15** gave a deuterium distribution of 0.801 para ^{2}H and 0.199 meta ^{2}H and 0.787 para ^{2}H and 0.213 meta ^{2}H in two separate determinations.

Preparation of Deuterium-Labeled Arene Oxides 8a–11a. Arene oxides **8a** and **9a** were prepared from **15** by our literature procedure[2] for the preparation of **8** and **9** from **1**. Arene oxides **10a** and **11a** were prepared from **15** by the procedures described herein for the preparation of **10** and **11** from **1**. On the basis of previously assigned proton chemical shifts for **8**,[2] integration of the 250-MHz ^{1}H NMR spectrum of **8a** established the deuterium distribution to be 0.815 ^{2}H at C_4 and 0.185 ^{2}H at C_5.[11] This result is in good agreement with the deuterium distribution determined in the previous experiment, and an average value of 0.80 ^{2}H at C_4 and 0.20 ^{2}H at C_5[11] was used for **8a–11a**.

Aromatization of Arene Oxides 10–12. Aromization of each arene oxide was studied under the conditions indicated in Table I by using a few drops of trifluoroacetic acid in ether or a 1:1 tetrahydrofuran/water solvent in which the pH of the aqueous portion was 0.1 (HCl), 1.1 (HCl), 4.0 (biphthalate buffer), 7.0 (phosphate buffer), or 10.0 (carbonate/borate buffer).

10. Reaction time for complete aromatization varied from 2 min (pH 0.1) to 31 days (pH 10). Phenol and salicylaldehyde were the only products of the reaction under the conditions studied. Yields (Table I) were dtermined by VPC analysis (3% SE-30 on 80–100 mesh Gas-Chrom Q, 90 °C).

11. Reaction time varied from a few seconds (pH 1.1) to 3 days (pH 10). Phenol and *o*-hydroxybenzyl alcohol were the only products observed under the conditions studied. Reaction at pH 0.1 gave diminished yields of products due to polymerization and was not investigated further. When aromatization of each reaction was complete, the solution was diluted with ether, and the aqueous layer was saturated with NaCl. The organic layer was separated, dried, and concentrated. Yields (Table I) of phenol and *o*-hydroxybenzyl alcohol were determined by silylation [*N*,*O*-bis(trimethylsilyl)trifluoroacetamide] and VPC analysis (3% SE-30 on 80–100 mesh Gas-Chrom Q, temperature programmed 55–110 °C). Analysis of the reaction mixture by 250-MHz ^{1}H, NMR spectroscopy gave similar results.

12. Reaction time varied from a few seconds (pH 1.1) to 3 days (pH 10). Phenol and *o*-(2-hydroxy-2-propyl)phenol were the only products observed. The reactions were worked up immediately after aromatization was complete to avoid dehydration of *o*-(2-hydroxy-2-propyl)phenol. Reaction workup was the same as described for **11**. Yields (Table I) were determined by integration of the 250-MHz ^{1}H NMR spectrum of each product mixture.

Aromatization of 8a–11a. The aromatization procedure for the deuterium-labeled arene oxides was the same as described for the unlabeled materials. Conditions investigated for each were **8a**, CF_3CO_2H pH 0.1, 1.1, and 7.0; **9a**, pH 1.0 and 7.0; **10a**, pH 1.1; **11a**, pH 1.1 and 7.0. The ortho-substituted phenol was isolated from each reaction, and the deuterium distribution was determined by analysis of the ^{1}H NMR spectrum. Chemical shift data and experimentally determined deuterium distribution for the ortho-substituted phenols are listed in Table II. The percent migration of the carbomethoxy group during aromatization of **8a** to methyl salicylate was calculated from

$$\% \text{ migration} = \frac{(\%\ ^1\text{H at } C_4) - 20}{0.7} = \frac{80 - (\%\ ^1\text{H at } C_5)}{0.6}$$

Results are summarized in Table I. Within experimental error substituent migration is not observed in the aromatization of **9a–11a**.

Acknowledgment. We are grateful to the National Institutes of Health, Grant GM 26388, for financial support.