Biogenesis of Epidithiadiketopiperazines. Synthesis of the Three Isomeric (β-Aminoethyl)benzene Oxides

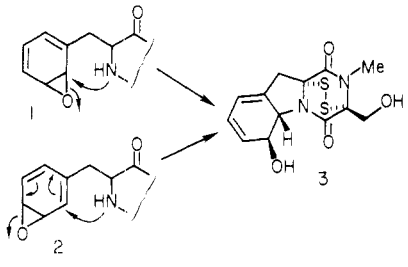
William H. Rastetter* and Larry J. Nummy

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

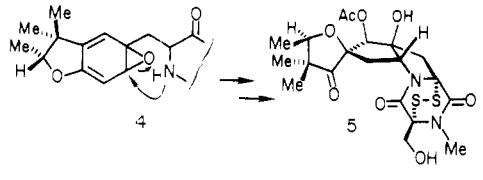
Received March 25, 1980

Three isomeric amine-substituted arene oxides have been synthesized to serve as models for the postulated involvement of amino acid derived arene oxides during the biosyntheses of various epidithiadiketopiperazines. No biogenetic-type reactivity was noted for the arene oxides. In all three cases aromatization rather than amine/epoxide cyclization was observed. The failure to duplicate the presumed in vivo reactivity of aminoarene oxides is discussed in terms of possible enzyme-mediated cyclizations in the natural systems.

Various amine-substituted arene oxides (**1**, **2**, and **4**) have been suggested as biogenetic precursors of fungal metabolites of the epidithiadiketopiperazine class.[1] Labeling studies strongly implicate the intermediacy of an arene oxide such as **1** or **2** in the biosynthesis of gliotoxin (**3**).[2,3] The trans stereochemistry in gliotoxin between the

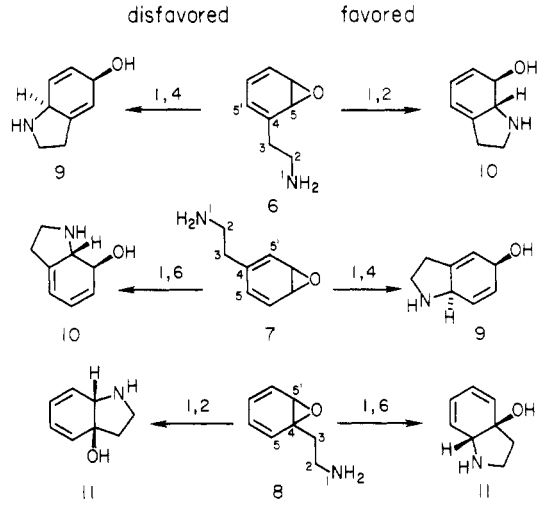


diketopiperazine nitrogen and the vicinal, dihydrobenzene hydroxyl group might arise via 1,2-addition, **1** → **3**, or via 1,6-addition, **2** → **3**. The stereochemistry between the diketopiperazine nitrogen and the vicinal, tertiary hydroxyl group of the sirodesmins similarly has been suggested[4a] to arise via 1,2-addition, **4** → **5**. An enzymatic conversion

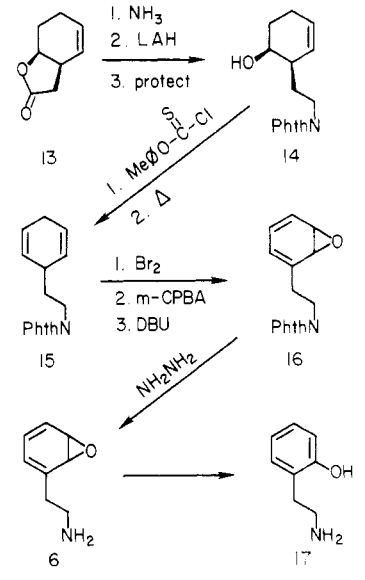


of arene oxide **1** to an oxepin oxide is likely responsible for the biogenesis of the aranotins.[2a,b,5] The epicorazines[6] display gliotoxin-related, modified, dihydroarene ring systems which may also be derived via arene oxides such as **1** or **2**. Herein we report the syntheses of the β-aminoethyl-substituted arene oxides **6**–**8** (Scheme I). Our

Scheme I



Scheme II



(1) For reviews of epidithiadiketopiperazines, see: (a) Kirby, G. W. *Pure Appl. Chem.* **1979**, *51*, 705; (b) Ganem, B. *Tetrahedron* **1978**, *34*, 3353; (c) Leigh, C.; Taylor, A. *Adv. Chem. Ser.* **1976**, *No. 149*, 228; (d) Sammes, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51; (e) Leigh, C.; Taylor, A. In "Mycotoxins"; Purchase, I. F. H., Ed.; Elsevier: Amsterdam, 1974; p 228; (f) Taylor, A. In "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. VII, p 337.

(2) (a) Neuss, N.; Nagarajan, R.; Molloy, B. B.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, 4467. (b) Neuss, N.; Boeck, L. D.; Brannon, D. R.; Cline, J. C.; DeLong, D. C.; Gorman, M.; Huckstep, L. L.; Lively, D. H.; Mabe, J.; Marsh, M. M.; Molloy, B. B.; Nagarajan, R.; Nelson, J. D.; Stark, W. M. *Antimicrob. Agents Chemother.* **1968**, 213. (c) Bu'Lock, J. D.; Ryles, A. P. *Chem. Commun.* **1970**, 1404. (d) Johns, N.; Kirby, G. W. *Ibid.* **1971**, 163. (e) Brannon, D. R.; Mabe, J. A.; Malloy, B. B.; Day, W. A. *Biochem. Biophys. Res. Commun.* **1971**, *43*, 588.

(3) Also see: Kirby, G. W.; Patrick, G. L.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1336 and references cited therein.

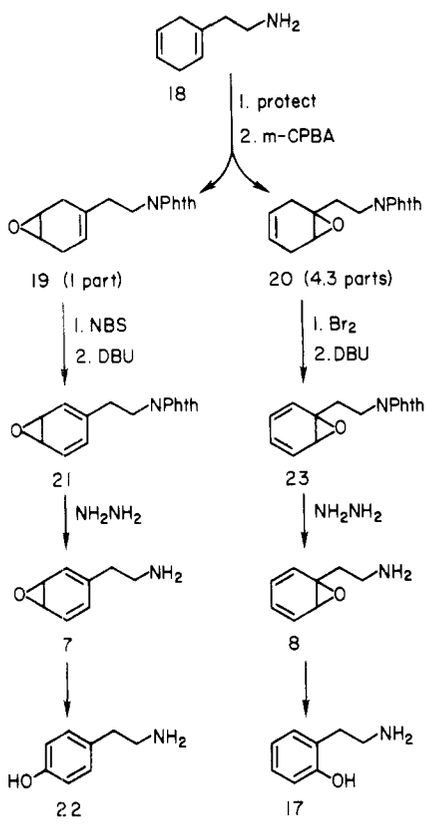
(4) (a) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Cameron, A. F.; Freer, A. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 180. (b) Fêrézou, J.-P.; Riche, C.; Quesneau-Thierry, A.; Pascard-Billy, C.; Barbier, M.; Bousquet, J.-F.; Boudart, G. *Nouv. J. Chim.* **1977**, *1*, 327. (c) Fêrézou, J.-P.; Quesneau-Thierry, A.; Barbier, M.; Kollmann, A.; Bousquet, J.-F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 113.

(5) Rastetter, W. H. *J. Am. Chem. Soc.* **1976**, *98*, 6350.

(6) (a) Baute, R.; Deffieux, G.; Baute, M.-A.; Filleau, M.-J.; Neveu, A. *Tetrahedron Lett.* **1976**, 3943. (b) Deffieux, G.; Gadret, M.; Leger, J. M. *Acta Crystallogr., Sect. B* **1977**, *B33*, 1474. (c) Baute, M.-A.; Deffieux, G.; Baute, R.; Neveu, A. *J. Antibiot.* **1978**, *31*, 1099. (d) Deffieux, G.; Baute, M.-A.; Baute, R.; Filleau, M.-J. *Ibid.* **1978**, *31*, 1102. (e) Deffieux, G.; Filleau, M.-J.; Baute, R. *Ibid.* **1978**, *31*, 1106.

0022-3263/80/1945-3149$01.00/0

Scheme III



inability to cyclize these materials in a biogenetic fashion is discussed in relation to presumed enzyme intervention during epidithiadiketopiperazine biosynthesis.

Syntheses of Model Arene Oxides. As starting material for the synthesis of arene oxide **6**, we utilized the known[7] lactone **13** (Scheme II). Aminolysis, reduction, and protection gave imide alcohol **14** (overall 65–74%). Regiospecific generation of the 1,4-cyclohexadiene **15** was achieved by pyrolytic syn elimination of the *p*-tolyl thiocarbonate derivative[8] of alcohol **14** (overall 65–79%). Bromination, epoxidation, and dehydrobromination produced phthaloyl-protected aminoarene oxide **16** (overall 38–49%). Finally, deprotection of **16** was effected by 4 equiv of NH_2NH_2 in CH_2Cl_2, cleanly giving 3-(β-aminoethyl)benzene oxide (**6**) as a pale yellow oil after high-vacuum transfer (61%).

The Birch reduction product from β-phenylethylamine, amino diene **18**[9] (Scheme III), served as starting material for arene oxides **7** and **8**. Protection and epoxidation of **18** gave **19** (minor isomer) and **20** (major isomer) in a combined yield of 65%[10] after separation on silica gel. Allylic bromination of **19** (47%) followed by dehydrobromination afforded protected aminoarene oxide **21** (58% crude). Deprotection of **21** with hydrazine and high-vacuum transfer gave pure amine **7**, albeit in only 11–12% yield.[11]

Epoxide **20** was converted to arene oxide **8** by the bromination, dehydrobromination, deprotection sequence also depicted in Scheme III. The pure amine **8** was produced after high-vacuum transfer in an overall yield of 36% from **20**.

The spectral data for **6**–**8** (see Experimental Section) can be used to estimate the equilibrium position between each arene oxide and its oxepin valence tautomer. The arene oxide component decreases in the series **6** > **7** > **8**. Though **8** exists largely in the oxepin form, a considerable quantity of the oxide form is present for nucleophilic capture or for competing aromatization[12] to phenol **17** (Scheme III). Both processes must proceed from the oxide valence tautomer.

General Considerations on Reactivity. Several reaction paths can be envisioned for model arene oxides **6**–**8**. A consideration of competing pathways is particularly interesting when the reactivities of **6**–**8** (vide infra) are compared with the apparent reactivities of presumed biogenetic precursors **1**, **2**, and **4**. Aromatization of arene oxides is a generally facile and much studied process.[12] Clearly, the rate of intramolecular amine/arene oxide reactions must compete with aromatization (isomerization to phenols) if biogenetic-type cyclizations are to be observed. Further, more than one cyclization must be considered for each model arene oxide. Scheme I shows possible cyclizations of the arene oxides to give fused-ring systems by closures of five-membered rings. The depicted closures are either anti 1,2-additions, syn 1,4-additions, or anti 1,6-additions. Anti 1,2- and anti 1,6-additions of azide anion to benzene oxide[13] occur at competitive rates. We have shown[14] a 1,4-addition of thiolate anion to an arene oxide, but the stereochemistry of the process is not known. Practically all theoretical treatments of the S_N2' reaction have concluded that there should be a syn relation of entering and leaving groups.[15] Stork and Kreft[15] have shown, however, that the stereochemistry of the S_N2' process may be greatly affected by the nature of the displacing and departing groups.

The relative facility of the alternate modes of ring closure for the model arene oxides **6**–**8** can be evaluated by consideration of the amine approach vectors.[16] For each arene oxide the attack at atom 5 should be favored over attack at atom 5′ (Scheme I). For example, the rules outlined by Baldwin[16] indicate that the gliotoxin-type closure **6** → **10** should be favored over the alternate process **6** → **9**. This prediction is supported by inspection of Drieding models which show a facile approach of the amine (atom 1 in structure **6**) to the backside of the epoxide, placing atoms 1 and 5 and the epoxide oxygen in a linear array. By contrast, the linking chain of atoms 2, 3, and 4 restricts the approach of the amine to atom 5′, and the preferred amine trajectory[16] is unattainable. A similar analysis was suggested by Stork to rationalize results of epoxy nitrile cyclizations.[17]

Approach-vector arguments also predict that formation of the gliotoxin-type ring system **10** from isomer **7** and formation of gliotoxin (**3**) from postulated precursor **2** are disfavored processes (both are 5-Endo-Trig closures).[16] Isomer **8** might serve as a model for the proposed sirodesmin intermediate **4**; its favored product (anti attack at atom 5) and disfavored product (anti attack at atom 5′) are the same. In nature, arene oxide **4** might circumvent

(7) (a) Kondo, K.; Matsumoto, M.; Mori, F. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 103. (b) Corey, E. J.; Ravindranithan, T. *Tetrahedron Lett.* **1971**, 4753.

(8) Gerlach, H.; Huong, T. T.; Müller, W. *J. Chem. Soc., Chem. Commun.* **1972**, 1215.

(9) Sugasua, S.; Tachikawa, R. *Tetrahedron* **1958**, *4*, 205.

(10) Conducting the reaction at lower temperatures gave somewhat greater combined yields but less of the useful, minor isomer **19**.

(11) ^1H NMR shows a significant portion of **7** entrained in the high-vacuum-transfer pot residue.

(12) Review: Bruice, T. C.; Bruice, P. Y. *Acc. Chem. Res.* **1976**, *9*, 378.

(13) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; DeMarinis, R. M.; Foster, C. H.; Piccolo, D. E.; Berchtold, G. A. *J. Am. Chem. Soc.* **1974**, *96*, 6929.

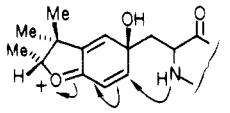
(14) Rastetter, W. H.; Lewis, M. D.; Richard, T. J.; Adams, J. *J. Org. Chem.* **1979**, *44*, 3175.

(15) Stork, G.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1977**, *99*, 3850, 3851.

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(17) (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268. (b) Stork, G.; Cohen, J. F. *Ibid.* **1974**, *96*, 5270.

the disfavored 1,2-addition by a two-stage reaction via stabilized cation **12**. The cation could easily collapse to product in an enzyme-mediated, favored 5-Exo-Trig[16] closure.

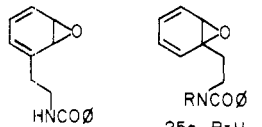


12

Reactivity of Model Systems. We have been unsuccessful in achieving biogenetic-type cyclizations of any of the model arene oxides (**6**–**8**). For example, arene oxide **6** is stable in $CDCl_3$ and CH_2Cl_2 (Al_2O_3 treated); a chloroform-*d* solution of **6** was stored in a freezer for 2 months without cyclization or appreciable rearrangement to phenol **17** (Scheme II). Rearrangement to **17** is more rapid in methanol-d_4 or in alkaline D_2O. Isomerization to **17** rather than cyclization was also effected by Woelm-200 basic alumina in Et_2O[18] or by lithium perchlorate in benzene-d_6 at 60 °C. By contrast, arene oxide **6** was virtually unchanged by heating in benzene-d_6 containing 5% CD_3OD.

Arene oxides **7** and **8** could be stored routinely in $CDCl_3$ (Al_2O_3 treated) solution in a freezer for months without noticeable cyclization or rearrangement (^1H NMR). Isomer **8** displays moderate stability at ambient temperature in CD_3CN/D_2O mixtures containing up to 25% D_2O. In 75/25 CD_3CN/D_2O, **8** rearranges to phenol **17** (Scheme III) over 13 h at 50 °C. Arene oxide **8** rearranges rapidly at 75 °C as a neat liquid or at ambient temperature in neutral aqueous media. Thus, **8** could not be trapped by azide anion[13] in pH 7 buffer; after 45 min a 92% yield of phenol **17** was obtained. Treatment of **8** with $[Rh(CO)_2Cl]_2$, used by Berchtold[19] to add methanol to arene oxides, also failed to cyclize the arene oxide.

Cyclizations were also attempted with the benzamides derived from **6**–**8** (e.g., **24**). Reactions using methanol/



24

25a, R=H
25b, R=Me

potassium methoxide, *tert*-butyl alcohol/potassium *tert*-butoxide, tetrahydrofuran/potassium hydroxide, or *n*-decyl alcohol/sodium *n*-decyloxide to generate equilibrium concentrations of the benzamide anions yielded only the corresponding phenols. Arene oxide **25a** could be recovered after treatment with sodium hydride in tetrahydrofuran or with potassium *tert*-butoxide in acetonitrile. Reaction of **25a** with sodium hydride in *N*,*N*-dimethylformamide was also ineffective in causing cyclization. The anion so generated could be trapped with methyl iodide, giving **25b**.

Discussion

Epoxide structure influences the rate of nucleophilic addition to epoxides as well as the rate of epoxide rearrangement. The balance of the two rates determines the "nucleophilic susceptibility"[12] of an epoxide. High mutual reactivity between epoxide and a nucleophile does not ensure that nucleophilic addition will take place. A more rapid rearrangement may actually predominate under a given set of reaction conditions. Features which determine the relative rates of epoxide rearrangement, hydration, and addition of nucleophiles have been discussed by Bruice[12,20a] and by Harvey.[20b]

Many examples[21a-g] exist of intramolecular additions of nucleophiles to epoxides under both protic and aprotic conditions. Thus, the condition for mutual reactivity of nucleophile and epoxide in the cases of model systems **6**–**8** appears to be fulfilled. Yet the in vitro reactivities of the model systems do not match the assumed reactivities of the proposed biogenetic precursors **1**, **2**, and **4**. The failure to achieve biogenetic-type cyclizations of **6**–**8** or of their derived amides reflects the greater propensity of the arene oxides to aromatize under the conditions of our experiments. Protic conditions which should facilitate nucleophilic opening of the epoxides[22] also accelerate the arene oxide to phenol rearrangement.[12] Closure experiments in aprotic media show reduced rates of aromatization but no perceptible rates for nucleophilic additions. Thus, the "nucleophilic susceptibilities"[12] of **6**–**8** and the derived amides are low; the epoxides are not opened even by intramolecular attack.

The failure to cyclize our model arene oxides should not cast doubt on the involvement of arene oxides during the biosyntheses of epidithiadiketopiperazines. The evidence for an arene oxide intermediate, probably arene oxide **1**,[23] is particularly compelling for gliotoxin.[2,3] Circumstantial evidence for the intermediacy of **1** in the biogenesis of the aranotins[2a,b,5] is provided in the structure of apoaranotin[2a,b] which displays both the gliotoxin dihydroarene ring system and the aranotin dihydrooxepin ring system. More generally, the involvement of arene oxides in the biogenesis of fungal metabolites from aromatic amino acids is particularly reasonable in the light of the extensive evidence which has accumulated on the in vivo formation of arene oxides from aromatic substrates.[24] Our models have failed presumably because we have failed to duplicate suitable cyclization conditions in our in vitro experiments. The arene oxides, if not our cyclization conditions, may remain good models for the natural systems.

A similar dilemma is posed by the enzyme, epoxide hydrolase,[25] which mediates the addition of water to epoxides of low "nucleophilic susceptibility" (e.g., benzene oxide).[24] Similar additions have been achieved without enzyme intervention only recently by use of alumina[18] or transition-metal catalysis,[19] yet these strategies fail in our model systems (vide supra).

Arene oxide structure greatly influences the ability to observe nucleophilic addition to this class of epoxides. For example, addition of water, oxy anions, and amines to K-region arene oxides is common,[12] while simple arene oxides do not add amine nucleophiles intermolecularly[13]

(18) Posner, G. A. and Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208.
(19) Ashworth, R. W.; Berchtold, G. A. *Tetrahedron Lett.* **1977**, 343.
(20) (a) Becker, A. R.; Janusz, J. M.; Rogers, D. Z.; Bruice, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 3244. (b) Fu, P. P.; Harvey, R. G., Beland, F. A. *Tetrahedron* **1978**, *34*, 857.
(21) For example, see: (a) Barton, D. H. R. *J. Chem. Soc.* **1951**, 2988. (b) Hodgsen, G. L.; MacSweeney, D. F.; Money, T. *Tetrahedron Lett.* **1972**, 3683. (c) Henbest, R.; Nicholls, B. *J. Chem. Soc.* **1959**, 221. (d) Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1974**, *39*, 3822. (e) Achini, R.; Oppolzer, W. *Tetrahedron Lett.* **1975**, 369. (f) McMurray, J. E.; Isser, S. J. *J. Am. Chem. Soc.* **1972**, *94*, 7132. (g) Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *Ibid.* **1964**, *86*, 3162.
(22) See for example: (a) Enikolopiyan, N. S. *Pure Appl. Chem.* **1976**, *48*, 317. (b) Parker, R. E.; Rockett, B. W. *J. Chem. Soc.* **1965**, 2569. (c) Burfield, D. R.; Gan, S.; Smithers, R. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 666.
(23) See the approach-vector argument earlier in text.
(24) Reviews: (a) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science (Washington, DC)* **1967**, *157*, 1524. (b) Daly, J. W.; Jerina, D. M.; Witkop, B. *Experientia* **1972**, *28*, 1129. (c) Jerina, D. M.; Daly, J. W. *Science (Washington, DC)* **1974**, *185*, 573.
(25) See: (a) DuBois, G. C.; Appella, F.; Levin, W.; Lu, A. Y. H.; Jerina, D. M. *J. Biol. Chem.* **1978**, *253*, 2932; (b) Hanzlik, R. P.; Edelman, M.; Michaely, W. J.; Scott, G. *J. Am. Chem. Soc.* **1976**, *98*, 1952 and references therein.

or intramolecularly (vide supra).

Kishi's elegant synthesis of gliotoxin (3)[26] utilizes an arene oxide intermediate [4-(carbo-*tert*-butoxy)benzene oxide] in the formation of the required dihydroarene–diketopiperazine, carbon–nitrogen bond. The facile amide anion condensation observed with the arene oxide (formally a 1,6-addition) undoubtedly is a two-step process involving Michael addition to the unsaturated ester and subsequent *intramolecular* epoxide opening. The reaction of 4-(carbo-*tert*-butoxy)benzene oxide with an amine nucleophile is analogous.[12]

The present results strongly suggest that biogenetic cyclizations such as 1 → 3, 2 → 3, or 4 → 5 may occur in vivo only through enzyme intervention. The nature of the presumed enzyme catalysis remains, however, an intriguing and unanswered question. It is appealing to speculate that an enzyme "catalyzes" cyclization by *retarding the competing NIH shift*[24] required for aromatization while providing *unexceptional* conditions for cyclization, e.g., proximate binding of epoxide and amine plus a hydrogen bonding source for the epoxide. A strategically placed ammonium (or imidazolium) cation could retard the rate-determining cation formation required for the NIH shift while providing stabilization of the developing negative charge on oxygen during amine nucleophilic opening of the epoxide. Epoxide hydrolase may function by an analogous mechanism. A histidine residue has been implicated at the active site of epoxide hydrolase.[25a]

Experimental Section

^{1}H NMR spectra were obtained on a Perkin-Elmer R-24B (60 MHz), a Varian T-60 (60 MHz), a JEOL FX-60 Q (60 MHz), or a JEOL FX-90 Q-2 (90 MHz) spectrometer. High-resolution ^{1}H NMR spectra were determined on a Bruker HFX-270 spectrometer. ^{13}C NMR spectra were measured by using a JEOL FX-60 Q spectrometer (at 15 MHz). Chemical shifts downfield from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 567 grating infrared spectrophotometer. Mass spectra were determined on a CEC 110B Mattauch-Herzog (Du Pont instruments) high-resolution mass spectrometer. Melting points were measured in open capillary tubes with a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed either by Robertson Laboratory or by Midwest Microlab. Ultraviolet spectra were obtained by using a Perkin-Elmer 554 spectrophotometer.

Conventional chromatography was carried out with E. Merck silica gel 60 (70–230 mesh) and "flash" chromatography with E. Merck Silica Gel 60 (230–400 mesh) by the method of Still et al.[27]

All glassware used in the preparation and handling of compounds containing the benzene oxide moiety was base treated prior to use as follows: one rinse with 1 N KOH, followed by two rinses with concentrated ammonium hydroxide and oven or flame drying. All solvents used in the preparation and handling of benzene oxides were filtered through Alfa-Ventron, activity 1, basic alumina with the exception of tetrahydrofuran (THF) and ether. THF from a Na/benzophenone ketyl still was used directly, and Mallinkrodt anhydrous ethyl ether was used directly. Solvents for other reactions and manipulations were reagent grade unless otherwise indicated.

Model Arene Oxide 6. Synthesis of Imide Alcohol 14. Bicyclic lactone 13 (39.1 g, 283.0 mmol) was cleaved by reaction with an equal volume of liquid ammonia in a sealed tube at ambient temperature for 5 days. The crude product was recrystallized from MeOH, yielding 35.0 g of pure amide alcohol. An additional 2.7 g of product was obtained by chromatography (10% MeOH/Et_2O) of the mother liquors: combined yield 86%; mp 129.5–130.5 °C; ^{1}H NMR (acetone-d_6/D_2O, 60 MHz) 1.58–2.80 (7 H, m), 4.05 (1 H, m), 4.20 (3 H, exchangeable), 5.65 (2 H, m); IR (KBr) 3320 (br), 3155, 2940, 2895, 2858, 1650 (br), 1450, 1290, 1183, 1083, 1073, 986, 953, 778, 720 cm^{-1}; exact mass calcd for $C_8H_{13}NO_2$ 155.094 62, found 155.094 53. Anal. Calcd: C, 61.91; H, 8.44; N, 9.02; O, 20.61. Found: C, 61.71; H, 8.50; N, 8.92; O, 20.32.

The amide alcohol (15.52 g, 100 mmol) was added portionwise to $LiAlH_4$ (19.0 g, 501 mmol) in THF (300 mL) with ice-bath cooling. The resulting mixture was warmed to ambient temperature, mechanically stirred for 18 h, and then heated at 45–50 °C for 2 h. The reaction was quenched by cautious addition of $Na_2SO_4 \cdot 10H_2O$ (102 g, 316.6 mmol) to the ice-bath-cooled mixture. After the mixture was stirred overnight, the precipitated white salts were filtered and washed with hot THF. The combined filtrates were concentrated in vacuo, and the residue was short-path distilled, providing the amino alcohol (10.64 g, 75%) as a viscous colorless liquid which crystallized upon being allowed to stand: bp 72–74 °C (0.03 mmHg); mp 48.5–50.0 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) 1.41–2.92 (12 H, m), 3.95 (1 H, m), 5.51 (2 H, br AB q, J = 10 Hz); IR (neat) 3500–3040 (br), 3010, 2920 (br), 2850 (br), 1595, 1430, 1355, 1195, 1170, 1070, 950, 732 cm^{-1}; exact mass calcd for $C_8H_{15}NO$ 141.115 36, found 141.116 72.

Protection of the amino alcohol (25.71 g, 182.1 mmol) was achieved in 1,1,2-trichloroethane (400 mL) by the action of *N*-(carboethoxy)phthalimide[28] (39.52 g, 180.3 mmol) for 1 h at ambient temperature and 1 h at reflux. Extractive purification (CH_2Cl_2/H_2O) gave imide alcohol 14 as an oil: 49.12 g (100%); ^{1}H NMR ($CDCl_3$, 60 MHz) 1.5–2.5 (8 H, m), 3.82 (2 H, half an A_2B_2 pattern, J = 7 Hz), 4.07 (1 H, br s), 5.60 (2 H, m), 7.73 (4 H, m); IR ($CHCl_3$) 3500, 3030, 3010, 2940, 1770, 1703, 1615, 1470, 1440, 1400, 1335, 1070, 720 cm^{-1}; exact mass calcd for $C_{16}H_{17}NO_3$ 271.120 84, found 271.122 19.

Conversion of 14 into Diene 15. Imide alcohol 14 (52.03 g, 191.8 mmol) was azeotropically dried with benzene and then dissolved in dry pyridine (750 mL, distilled from CaH_2 and stored over 3-Å sieves). The resulting solution was cooled (ice bath) and stirred while *p*-tolyl chlorothioformate[8] (39.89 g, 213.71 mmol) was added dropwise via syringe over a period of 1 h and 15 min. The dark mixture was warmed to ambient temperature and stirred for 21 h. Pyridine was removed at room temperature under reduced pressure, the residue taken up in Et_2O, and the ethereal suspension washed with 5% HCl(aq). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. Crystallization (Et_2O/CH_2Cl_2) together with flash chromatography of mother liquors provided pure thionocarbonate (64.70 g, 80%) as a white solid: mp 115.5 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) 1.7–2.8 (7 H, m), 2.40 (3 H, s), 3.85 (2 H, half an A_2B_2 pattern, J = 7.5 Hz), 5.75 (3 H, m), 7.15 (4 H, m), 7.80 (4 H, m); IR ($CHCl_3$) 3038, 3005, 2955, 2935, 2875, 1770, 1708, 1504, 1440, 1398, 1372, 1290, 1185, 720 cm^{-1}; exact mass calcd for $C_{16}H_{16}NO_2$ (M^+ – *p*-$MeC_6H_4OC(S)O$) 254.118 10, found 254.117 11; calcd for $C_8H_8O_2S$ (*p*-$MeC_6H_4OC(S)OH^+\cdot$) 168.024 50, found 168.025 70. Anal. Calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32; O, 15.18; S, 7.61. Found: C, 68.25; H, 5.24; N, 3.37; O, 15.38; S, 7.34.

Pyrolysis of the thiocarbonate (64.70 g, 153.49 mmol) was effected in diglyme (300 mL) at reflux over 8 h. Removal of the solvent in vacuo, extractive purification, and flash chromatography gave diene 15 (38.7 g, 99%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 60 MHz) 1.81 (2 H, m), 2.68 (3 H, m), 3.73 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.74 (4 H, AB q), 7.76 (4 H, m); IR ($CHCl_3$) 3030, 2940, 2870, 2825, 1770, 1710, 1615, 1470, 1440, 1399, 1370, 1352, 1230, 1188, 1172, 1055, 1005, 940, 720 cm^{-1}; exact mass calcd for $C_{16}H_{15}NO_2$ 253.110 27, found 253.110 98.

Synthesis of Protected Arene Oxide 16. A solution of diene 15 (38.7 g, 152.7 mmol) in dry CH_2Cl_2 (250 mL, passed through activity 1, basic alumina) was cooled in a CO_2(s)/acetone bath. A solution of bromine (7.8 mL, 152.7 mmol) in dry CH_2Cl_2 (200 mL) was added dropwise over 5.5 h with vigorous stirring. After the addition was complete, the solvent was removed at reduced pressure below 0 °C. The dibromide (63.5 g, 100%), produced as an oily mixture of diastereomers, was sufficiently pure to use directly: ^{1}H NMR ($CDCl_3$, 60 MHz) 1.91 (2 H, m), 2.25–3.22 (3 H, m), 3.80 (2 H, half an A_2B_2 pattern, J = 6.5 Hz), 4.20–4.90 (2 H, m), 5.58 (2 H, m), 7.80 (4 H, m); IR ($CHCl_3$) 3040, 3015, 2950,

(26) Fukuyama, T. F.; Kishi, Y. *J. Am. Chem. Soc.* **1976**, *98*, 6723.
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Nefkens, G. H. L. *Nature (London)* **1960**, *185*, 309.

1772, 1710, 1615, 1470, 1440, 1400, 1377, 1360, 1190, 1060, 1010, 720, 650, 595 cm^{-1}; exact mass calcd for $C_{16}H_{15}{}^{79}BrNO_2$ (M^+ - Br) 332.028 61, found 332.030 54.

The mixture of dibromo olefins (63.1 g, 152.7 mmol) was epoxidized with 85% *m*-chloroperoxybenzoic acid (36.7 g, 180.8 mmol of active oxygen) in refluxing dry chloroform (300 mL, passed through activity 1, basic alumina) over a 5-h period. Extractive purification yielded the dibromo epoxide (70.1 g, 107% of the theoretical weight) as a mixture of diastereomers. Flash silica gel chromatography (30% hexane/Et_2O) separated the mixture into two components with R_f ~0.5 and ~0.3 in a weight ratio of 3:1, respectively. Only the faster eluting fraction could be transformed efficiently into arene oxide **16**.[29] In a typical chromatographic separation, the dibromo epoxides (21.85 g) were separated into the desired component (R_f ~0.5; 10.68 g, 49%), the undesired component (R_f ~0.3; 3.47 g, 16%), and an overlapping band (4.10 g, 19%) after two successive passes on silica gel. Data for the R_f ~0.5 component: mp 131–132 °C (raised to 146.5–147.5 °C by fractional recrystallization from Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$, 60 MHz) 2.20 (2 H, m), 2.45–3.00 (3 H, m), 3.24 (2 H, br s), 3.82 (2 H, half an A_2B_2 pattern, J = 6 Hz), 4.60 (2 H, br s), 7.80 (4 H, m); IR (KBr) 3010, 2955, 1770, 1710, 1618, 1470, 1448, 1402, 1360, 1192, 1175, 1080, 1010, 978, 871, 830, 770, 720, 572, 538 cm^{-1}; exact mass calcd for $C_{16}H_{15}{}^{81}BrNO_3$ (M^+ - Br) 350.021 48, found 350.022 42. Anal. Calcd for $C_{16}H_{15}Br_2NO_3$: C, 44.79; H, 3.52; Br, 37.24; N, 3.26; O, 11.19. Found: C, 44.57; H, 3.33; Br, 37.15; N, 3.15; O, 11.02. Data for the R_f ~0.3 component: mp 137.5–140 °C; ^1H NMR ($CDCl_3$, 60 MHz) 1.90–3.00 (5 H, m), 3.00–3.67 (2 H, m), 3.67–4.50 (2 H, m), 7.86 (4 H, m); IR (KBr) 3000, 2980, 2945, 1770, 1705, 1610, 1468, 1437, 1402, 1359, 1332, 1189, 1072, 1003, 935, 868, 830, 719, 600, 535 cm^{-1}; exact mass calcd for $C_{16}H_{15}{}^{81}BrNO_3$ (M^+ - Br) 350.021 48, found 350.021 55. Anal. Calcd for $C_{16}H_{15}Br_2NO_3$: C, 44.79; H, 3.52; Br, 37.24; N, 3.26; O, 11.19. Found: C, 44.63; H, 3.59; Br, 37.15; N, 3.19; O, 11.51.

Dehydrobromination of the faster eluting dibromo epoxide (R_f ~0.5;[29] 0.334 g, 0.778 mmol) was achieved with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU; 0.304 mL, 2.02 mmol). DBU was added dropwise to a THF (1.5 mL) solution of the dibromo epoxide cooled in an ice bath; the reaction temperature was allowed to rise as the ice bath melted, and the mixture was stirred for a total of 24 h. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed three times with pH 7.2 phosphate buffer. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, giving arene oxide **16** (0.214 g, 103% of the theoretical weight) as a waxy yellow solid: ^1H NMR ($CDCl_3$, 60 MHz) 2.78 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.95 (2 H, half an A_2B_2 pattern, J = 7 Hz), 4.55 (2 H, br s), 6.20 (3 H, br s), 7.78 (4 H, m); IR (KBr) 3105, 3055, 3030, 2950, 2900, 1778, 1710, 1640, 1575, 1470, 1440, 1396, 1371, 1340, 1112, 1010, 890, 870, 843, 775, 725, 539 cm^{-1}.

3-(β-Aminoethyl)benzene Oxide (6). To a stirred solution of arene oxide **16** (0.245 g, 0.916 mmol) in CH_2Cl_2 (2 mL) was added anhydrous hydrazine (0.117 mL, 3.66 mmol) at ambient temperature. After 24 h the mixture was filtered and the filtrate concentrated in vacuo at or below 25 °C. The residue was transferred bulb to bulb under high vacuum to afford the pure amine **6** as a pale yellow liquid: 0.077 g (61%);[30] ^1H NMR (benzene-d_6, 60 MHz) 1.09 (2 H, br s), 2.28 (2 H, half an A_2B_2 pattern, J = 6 Hz), 2.88 (2 H, half an A_2B_2 pattern, J = 6 Hz), 4.47 (2 H, m), 6.11 (3 H, m); ^1H NMR ($CDCl_3$, 270 MHz) 1.31 (2 H, br s), 2.46 (2 H, half an A_2B_2 pattern, J = 6 Hz), 2.95 (2 H, half an A_2B_2 pattern, J = 6 Hz), 4.35 (1 H, br s), 4.48 (1 H, br s), 6.16 (2 H, m), 6.31 (1 H, m); ^{13}C NMR ($CDCl_3$, 15 MHz) 38.75, 40.83, 73.56, 74.08, 122.72, 125.45, 128.56, 136.36; IR (neat) 3375, 3300, 3050, 3020, 2935, 2860, 1638, 1607, 1570, 1420, 1220, 1070, 1030, 943, 845, 825, 771, 750, 703 cm^{-1}; exact mass calcd for $C_8H_{11}NO$ (M^+) 137.084 06, found 137.084 18; UV (*n*-BuOH) λ_{max} 271 nm (ϵ 3.0 × 10^3). Arene oxide **6** was derivatized by a Diels–Alder reaction with bis(trichloroethyl) azodicarboxylate;[5] the crystalline adduct melts at 136.5–137.5 °C. Anal. Calcd for $C_{22}H_{17}Cl_6N_3O_7$: C, 40.76; H, 2.64; Cl, 32.82; N, 6.48; O, 17.28. Found: C, 41.01; H, 2.75; Cl, 32.53; N, 6.38; O, 17.47. We were unable to epoxidize the Diels–Alder adduct as described in ref 5 for the unsubstituted system.

The ^{13}C NMR, ^1H NMR, and UV data for **6** indicate a predominance of the oxide valence tautomer in its arene oxide ⇄ oxepin equilibrium. The epoxide ^{13}C absorptions (δ 73.56 and 74.08), the epoxide ^1H absorptions (δ 4.35 and 4.48), and the position and extinction coefficient of the UV absorbance unambiguously support this assignment when compared to literature data on related systems.[31a-c] The ^1H NMR for **6** closely resembles that reported[32a] for toluene 2,3-oxide, with the exception of the alkyl substituent absorptions.

Model Arene Oxide 7. Syntheses of Imide Epoxides 19 and 20. To a stirred solution of amino diene **18**[9] (57.11 g, 463.6 mmol) in toluene (1.0 L) was added *N*-(carboethoxy)phthalimide[28] (100.59 g, 458.9 mmol) in portions at ambient temperature. The mixture was stirred 1 h and then refluxed 1 h. Extractive purification and removal of toluene in vacuo gave the phthaloyl-protected amine (117.2 g, 100%) as an off-white solid. The material was sufficiently pure for further use but could be recrystallized from EtOAc/hexanes: mp 100–101 °C; ^1H NMR ($CDCl_3$, 60 MHz) 2.30 (2 H, half an A_2B_2 pattern, J = 7 Hz), 2.60 (4 H, br s), 3.72 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.38 (1 H, br s), 5.61 (2 H, br s), 7.65 (4 H, m); IR (KBr) 3015, 2935, 2860, 2820, 1775, 1705, 1450, 1430, 1400, 1355, 1310, 1170, 1095, 1015, 965, 930, 725 cm^{-1}; exact mass calcd for $C_{16}H_{15}NO_2$ (M^+) 253.110 27, found 253.112 14.

Epoxides **19** and **20** were obtained by addition of 85% *m*-chloroperoxybenzoic acid (1.05 g, 5.17 mmol of active oxygen) in one portion to a refluxing CH_2Cl_2 (12 mL) solution of phthaloyl-protected amino diene (1.19 g, 4.70 mmol). Extractive purification and chromatographic separation on silica gel (5% EtOAc/CH_2Cl_2) yielded, in order of elution, epoxide **20** (0.673 g, 53%), epoxide **19** (0.157 g, 12%), and 0.100 g of material which appears to be a diepoxide as evidenced by ^1H NMR characterization. Full characterization was obtained for the monoepoxides. Data for **20**: mp 91–93 °C; ^1H NMR ($CDCl_3$, 60 MHz) 2.02 (2 H, half an A_2B_2 pattern, J = 7 Hz), 2.50 (4 H, m), 3.05 (1 H, br s), 3.85 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.48 (2 H, br s), 7.80 (4 H, m); IR (KBr) 3060, 3030, 2940, 2885, 1767, 1710, 1615, 1448, 1429, 1400, 1360, 1320, 1195, 1171, 1120, 1028, 935, 892, 872, 722, 669, 539 cm^{-1}; exact mass calcd for $C_{16}H_{15}NO_3$ (M^+) 269.105 19, found 269.104 40. Anal. Calcd: C, 71.36; H, 5.61; N, 5.20; O, 17.82. Found: C, 71.29; H, 5.62; N, 5.07; O, 18.04. Data for **19**: mp 140–141.5 °C; ^1H NMR ($CDCl_3$, 60 MHz) 2.10–2.80 (6 H, br m), 3.35 (2 H, br s), 3.87 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.25 (1 H, br s), 7.80 (4 H, m); IR (KBr) 3060, 3000, 2900, 1768, 1710, 1606, 1450, 1395, 1375, 1310, 1115, 1055, 880, 821, 730, 720 cm^{-1}; exact mass calcd for $C_{16}H_{15}NO_3$ (M^+) 269.105 19, found 269.106 18. Anal. Calcd: C, 71.36; H, 5.61; N, 5.20; O, 17.82. Found: C, 71.12; H, 5.75; N, 5.01; O, 18.07.

Conversion of Epoxide 19 into Arene Oxide 21. Allylic bromination of **19** (2.25 g, 8.36 mmol) was effected by *N*-bromosuccinimide (1.49 g, 8.36 mmol) in refluxing CCl_4 (35 mL). Radical initiation was provided by dibenzoyl peroxide added in two portions (0.082 g, 0.34 mmol, added initially plus 0.070 g, 0.29 mmol, added after 30 min at reflux). After a total reflux time of 60 min the mixture was refrigerated overnight. Filtration of the mixture and concentration of the filtrate in vacuo gave the crude product of epimeric monobromides (3.7 g) as an oil. The unstable monobromides were chromatographed rapidly[27] over a 20 × 4 cm column of Merck silica gel 60 (230–400 mesh), eluting

(29) The faster eluting component is probably composed of diastereomers having a cis relationship between the β-phthalimidoethyl group and the vicinal bromine atom. Only these diastereomers will be subject to two antiperiplanar dehydrobrominations.

(30) This was the highest yield obtained for this reaction. Over many runs, yields were typically about 47%.

(31) (a) For ^{13}C NMR data see: Günther, H.; Jikeli, G. *Chem. Ber.* **1973**, *106*, 1863. (b) Benzene oxide/oxepin exists with comparable concentrations of both valence tautomers in rapid equilibrium. The epoxide protons and the corresponding protons in the oxepin form appear as a single absorption (rapid exchange) at δ 5.20 (CS_2): Vogel. E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385. In $CHCl_3$ the absorption appears at δ 5.10 (data from our laboratory). (c) For UV data, see ref 31b.

(32) (a) Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizami, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483. (b) Jerina, D. M., Daly, J. W.; Witkop, B. *Ibid.* **1968**, *90*, 6523. (c) Günther, H.; Schubart, R.; Vogel, E. *Z. Naturforsch, B: Anorg. Chem., Org. Chem.* **1967**, *22B*, 25. Also see ref 31b.

with 5% Et_2O/CH_2Cl_2, yielding the epimeric mixture (1.36 g, 47%). The mixture of monobromides generally was used without separation for conversion into arene oxide **21**. An analytical sample (mp 116.5–119 °C dec) was prepared by two recrystallizations from CH_2Cl_2/Et_2O: ^1H NMR ($CDCl_3$, 60 MHz) 2.40 (2 H, half an A_2B_2 pattern, J = 7 Hz), 2.69 (2 H, br s), 3.75 (2 H, m), 3.93 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.05 (1 H, br s), 5.60 (1 H, br s), 7.95 (4 H, m); IR (KBr) 3020, 2905, 1772, 1715, 1615, 1475, 1455, 1419, 1397, 1345, 1260, 1195, 1177, 1115, 1022, 881, 747, 727, 540 cm^{-1}; exact mass calcd for $C_{16}H_{13}{}^{81}BrNO_2$ (M^+ – OH) 332.01092, found 332.01348. Anal. Calcd for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; Br, 22.95; N, 4.02; O, 13.78. Found: C, 55.15; H, 4.10; Br, 23.21; N, 4.01; O, 14.02.

Dehydrobromination of the allylic bromide mixture (1.28 g, 3.68 mmol) in THF (12 mL) was achieved with 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU; 0.067 mL, 4.05 mmol) which was added dropwise to the stirred reaction mixture cooled with a CO_2(s)/CCl_4 bath. Stirring was continued over 24 h while the cooling bath was allowed to rise to ambient temperature. Removal of solvent in vacuo and extractive purification (CH_2Cl_2/pH 7.2 phosphate buffer) gave an organic layer which was dried (Na_2SO_4) and evaporated to yield impure phthaloyl-protected aminoarene oxide **21** (0.576 g, 58% crude) as a foam. The material was used directly in the subsequent hydrazine deprotection step: ^1H NMR ($CDCl_3$, 60 MHz) 2.47 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.78 (2 H, half an A_2B_2 pattern, J = 7 Hz), 4.87 (2 H, m), 5.95 (3 H, m), 7.78 (4 H, m).

4-(β-Aminoethyl)benzene Oxide (7). Anhydrous hydrazine (0.276 mL, 8.60 mmol) was added to a stirred solution of crude imide **21** (0.576 g, 2.15 mmol) in CH_2Cl_2 (4 mL) at ambient temperature. After 24 h the solution was filtered and concentrated at reduced pressure, at or below ambient temperature, to afford a yellow liquid. Bulb-to-bulb transfer under high vacuum yielded the pure amine **7**: 0.034 g (11.6%); yellow liquid; ^1H NMR ($CDCl_3$, 270 MHz) 1.17 (2 H, br s), 2.32 (2 H, half an A_2B_2 pattern, J = 7 Hz), 2.83 (2 H, half an A_2B_2 pattern, J = 7 Hz), 4.90 (2 H, m), 5.83 (1 H, d, J = 4 Hz), 6.02 (1 H, dd, J = 4, 7.5 Hz), 6.13 (1 H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 15 MHz) 40.50, 40.96, 95.12, 95.90, 121.10, 122.26, 128.95, 139.60; IR (neat) 3370, 3040, 2940, 2865, 1640, 1619, 1585, 1465, 1440, 1380, 1320, 1250, 1085, 1035, 970, 945, 805, 760 cm^{-1}; exact mass calcd for $C_8H_{11}NO$ (M^+) 137.08406, found 137.08334; UV (*n*-BuOH) λ_{max} 272.5 nm (ϵ 1.8 × 10^3).

The ^{13}C NMR, ^1H NMR, and UV data for **7** show that both arene oxide and oxepin valence tautomers are present in comparable concentrations. This assignment is supported by the ^{13}C epoxide absorptions (δ 95.12 and 95.90), the epoxide ^1H absorptions (δ 4.90), and the UV data.[31a–c] The ^1H NMR for **7** closely resembles that reported[32b] for toluene 3,4-oxide with the exception of the alkyl substituent absorptions.

Model Arene Oxide 8. Conversion of Epoxide 20 into Arene Oxide 23. Bromination of **20** (8.618 g, 32.0 mmol) was performed in CH_2Cl_2 (60 mL) solution at –78 °C (CO_2(s)/acetone bath). Bromine (1.60 mL, 31.06 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 2–2.5 h to the vigorously stirred olefin at a rate which maintained a pale yellow reaction mixture. The dibromide was isolated by warming the mixture to ambient temperature, removing the solvent in vacuo, and triturating the resulting syrup with Et_2O. The product was obtained as a white microcrystalline solid (10.12 g, 76% yield); no attempt was made to purify the dibromide which remained in the mother liquor. Data for the dibromide: mp 121–122 °C; ^1H NMR ($CDCl_3$, 60 MHz) 1.96 (2 H, half an A_2B_2 pattern, J = 7 Hz), 2.15–3.25 (5 H, m), 3.84 (2 H, half an A_2B_2 pattern, 7 Hz), 4.24 (2 H, m), 7.85 (4 H, m); IR (KBr) 3020, 2960, 2930, 1768, 1708, 1615, 1469, 1450, 1412, 1389, 1197, 1135, 1025, 877, 731, 721 cm^{-1}; exact mass calcd for $C_{16}H_{15}{}^{81}BrNO_3$ (M^+ – Br) 350.02148, found 350.02056. Anal. Calcd for $C_{16}H_{15}Br_2NO_3$: C, 44.78; H, 3.52; Br, 37.24; N, 3.26; O, 11.19. Found: C, 44.66; H, 3.70; Br, 37.10; N, 3.15; O, 11.39.

Dehydrobromination of the dibromide (6.44 g, 15.0 mmol) in THF (30 mL) was effected by 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU; 5.85 mL, 39.1 mmol) which was added dropwise to the stirred, cooled (ice bath) reaction mixture. The reaction temperature was allowed to rise to ambient temperature over 24 h. The mixture was filtered and concentrated to a yellow oil in vacuo. Extractive purification (CH_2Cl_2/pH 7.2 phosphate buffer), drying of the organic layer (Na_2SO_4), and evaporation of solvent gave imide **23** (3.80 g, 94%) sufficiently pure for subsequent use: ^1H NMR ($CDCl_3$, 60 MHz) 2.57 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.90 (2 H, half an A_2B_2 pattern, J = 7 Hz), 5.60 (3 H, m), 6.10 (2 H, m), 7.78 (4 H, m).

1-(β-Aminoethyl)benzene Oxide (8). Imide **23** (3.80 g, 14.1 mmol) in CH_2Cl_2 (30 mL) was treated with anhydrous hydrazine (4.8 mL, 150 mmol) at ambient temperature for 24 h. The resulting mixture was filtered and the filtrate washed with 1 N KOH. Drying (Na_2SO_4), concentration in vacuo, and bulb-to-bulb transfer under high vacuum of the organic layer gave pure amine **8**: 0.981 g (51%); ^1H NMR ($CDCl_3$, 270 MHz) 1.42 (2 H, br s), 2.18 (2 H, half an A_2B_2 pattern, J = 6 Hz), 2.86 (2 H, half an A_2B_2 pattern, J = 6 Hz), 5.56 (1 H, br s), 5.65 (2 H, br s), 6.10 (2 H, m); ^{13}C NMR ($CDCl_3$, 15 MHz) 38.29, 39.33, 113.82, 117.46, 127.00, 128.82, 132.59, 144.80; IR (neat) 3500–3100 (br), 3030, 2940, 2870, 1645, 1620, 1575, 1465, 1425, 1375, 1310, 1222, 1150, 1060, 820, 740 cm^{-1}; exact mass calcd for $C_8H_{11}NO$ (M^+) 137.08406, found 137.08475; UV (*n*-BuOH) λ_{max} 290 nm (ϵ 1.5 × 10^3).

The ^{13}C NMR, ^1H NMR, and UV data for **8** show that the arene oxide exists primarily as the oxepin valence tautomer. This is clearly indicated by the downfield shift for the ^{13}C epoxide absorptions (δ 132.59 and 144.80) and for the epoxide ^1H absorptions (δ 5.56) as compared to isomers **6** and **7** and to other model compounds.[31a,b] Unlike isomers **6** and **7**, **8** shows a single 60-MHz ^1H NMR absorption for the protons on C_2, C_3, and C_6 of the oxide tautomer (on C_7, C_3, and C_6, respectively, of the oxepin tautomer). The spectrum thus closely resembles that reported for toluene 1,2-oxide[32c] which exists predominantly as 2-methyloxepin (2-methyloxepin/toluene 1,2-oxide ratio of 7:3 at –119 °C in CF_3Br). The UV data for **8** also indicates an appreciable concentration of the oxepin valence tautomer.[32c]

Cyclization Attempts with Arene Oxide 6. Characterization of Phenol 17. The stability of arene oxide **6** in nonpolar solvents was shown by storage of a $CDCl_3$ solution in a freezer for 2 months. The ^1H NMR showed no appreciable rearrangement to phenol **17** and no absorptions attributable to cyclized product. The stability of **6** in CH_2Cl_2 over 24 h is shown by the deprotection of **16**; arene oxide **6** is inert to NH_2NH_2 and to intramolecular amine attack. Rearrangement of **6** to **17** in CD_3OD at ambient temperature is complete after 16 h. The arene oxide **6** is virtually unchanged, however, in benzene-d_6 containing ~5% CD_3OD at 41 °C for 13 h or at 62 °C for 1 h (^1H NMR).

Arene oxide **6** (48.1 mg, 0.351 mmol) was mixed with a $NaOD/D_2O$ solution, prepared from oil-free NaH (21 mg, 0.54 mmol) and D_2O (400 μL). CD_3OD (100 μL) was added to the cloudy mixture and the ^1H NMR spectrum recorded. Only absorptions attributable to aromatized material (anion of **17**) were discernible.

Arene oxide **6** (42.0 mg, 0.306 mmol) was dissolved in Et_2O (1.5 mL) and the resulting solution stirred with Woelm 200B alumina at ambient temperature for 1 h. MeOH (20 mL) was added and stirring continued for 4 h. Filtration and evaporation gave **17** (32 mg) as a colorless glass.

Arene oxide **6** (66.1 mg, 0.482 mmol) was dissolved in benzene-d_6 (400 μL) and a small portion of $LiClO_4$ added. The mixture was shaken well (some $LiClO_4$ remained undissolved) and heated for 15 min at 55 °C with periodic shaking. A small, second portion of finely ground $LiClO_4$ was added and the heterogeneous mixture again heated. After 30 min the ^1H NMR showed complete rearrangement to phenol **17**: mp 112.5–114 °C [lit. mp 113–115 °C (Beilstein)]; ^1H NMR (CD_3OD, 60 MHz) 2.66 (4 H, A_2B_2), 4.66 (3 H, s), 6.60 (4 H, m); IR (KBr) 3200–2300 (br), 2200 (br), 1588, 1554, 1480, 1443, 1260, 1152, 1098, 1048, 938, 831, 760, 750, 742 cm^{-1}; exact mass calcd for $C_8H_{11}NO$ (M^+) 137.08406, found 137.08605.

Stability of Arene Oxide 7. Characterization of Phenol 22. Arene oxide **7** was stored in a $CDCl_3$ (Al_2O_3 treated) solution for 43 days in a freezer. No change in the ^1H NMR spectrum was discernible. The pot residue from vacuum transfer of **7** upon dissolution in CD_3OD shows ^1H NMR absorptions attributable to phenol **22** plus residual **7**. Complete characterization of **22** was obtained as the *N*-benzoyl derivative (vide infra) and as the *N*-phthaloyl derivative. The latter, obtained by passage of protected arene oxide **21** over silica gel, displayed the following: mp 231.5–232.5 °C; ^1H NMR (dimethyl-d_6 sulfoxide, 60 MHz) 2.77

(2 H, half an A_2B_2 pattern, J = 7.5 Hz), 3.31 (1 H, br s), 3.74 (2 H, half an A_2B_2 pattern, J = 7.5 Hz), 6.59 (2 H, half an AA'BB' pattern, J = 8.4 Hz), 6.95 (2 H, half an AA'BB' pattern, J = 8.4 Hz), 7.80 (4 H, s); IR (KBr) 3290 (br), 2950, 2920, 1765, 1680, 1612, 1599, 1515, 1403, 1350, 1270, 1234, 1175, 1010, 945, 818, 722 cm^{-1}; exact mass calcd for $C_{16}H_{13}NO_3$ (M^+) 267.089 54, found 267.089 05.

Cyclization Attempts with Arene Oxide 8. An NMR sample of **8** in CD_3CN (ca. 300 μL) plus D_2O (2 drops, adjusted to "pH" 7.6 with Na_2CO_3) was stable at ambient temperature and at 47–49 °C for 1.5 h. Additional untreated D_2O was added (total D_2O ca. 25%) and the solution heated at 50 °C for 13 h. The ^1H NMR shows rearrangement of **8** to phenol **17** (data reported above).

Heating of **8** at 75 °C (0.2 mmHg) as a neat liquid yields a distillate containing **8** and roughly 30% of phenol **17**.

Arene oxide **8** (137.1 mg, 1.0 mmol) was dissolved in pH 7.2 phosphate buffer (1.5 mL) and NaN_3 (80.0 mg, 1.23 mmol) rapidly added. After 30 min the mixture showed a copious white precipitate. Stirring was continued for an additional 15 min and CH_2Cl_2 added to dissolve the white solid. Drying (Na_2SO_4) and evaporation of the organic phase yielded **17** (126 mg, 92%).

A sample of arene oxide **8** (67 mg, 0.49 mmol) containing ~30% phenol **17** (from distillation of **8**, vide supra) in $CDCl_3$ (ca. 400 μL, Al_2O_3 treated) was treated with $[Rh(CO)_2Cl]_2$ (38.8 mg, 0.10 mmol). The deep red mixture was monitored by ^1H NMR which showed after 10 min an increase in aromatic absorptions at the expense of the vinyl absorptions of **8**. After 24 h, **8** had been completely aromatized. GLC analysis (SE-30) showed the presence of 2-phenylethylamine as the only volatile component other than solvent (under conditions where polar aminophenol **17** was not eluted).

Syntheses of Benzamide Derivatives (e.g., 24). Cyclization Attempts. Arene oxides **6–8** were converted to the corresponding benzamide derivatives. The procedure for **6** is illustrative of the general method. A solution of **6** (0.058 g, 0.42 mmol) and Et_3N (0.117 mL, 0.85 mmol) in CH_2Cl_2 (1.0 mL) was stirred and ice bath cooled. Benzoyl chloride (0.044 mL, 0.38 mmol) was added dropwise via syringe. After 10 min the mixture was warmed to ambient temperature for 25 min and then extracted three times with pH 7.2 phosphate buffer. Drying (Na_2SO_4) and evaporation of the organic phase provided amide **24** (0.095 g) in quantitative yield: ^1H NMR ($CDCl_3$, 60 MHz) 2.58 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.63 (2 H, q, J = 7 Hz), 4.37 (2 H, m), 6.20 (3 H, m), 6.90 (1 H, br m), 7.40 (3 H, m), 7.80 (2 H, m); IR ($CHCl_3$) 3450, 3330, 3010, 2930, 2855, 1638, 1602, 1580, 1525, 1487, 1310, 1290, 1175, 1100, 1076, 1033, 1018, 993, 942 cm^{-1}; exact mass calcd for $C_{15}H_{15}NO_2$ (M^+) 241.110 27, found 241.110 84.

The benzamide derived from **7** displayed the following: ^1H NMR ($CDCl_3$, 60 MHz) 2.39 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3 47 (2 H, q, J = 7 Hz), 4.86 (2 H, m), 5.90 (3 H, m), 6.55 (1 H, br m), 7.39 (3 H, m), 7.70 (2 H, m); exact mass calcd for $C_{15}H_{15}NO_2$ (M^+) 241.110 27, found 241.109 45.

The benzamide derived from **8** (**25a**) displayed the following: ^1H NMR ($CDCl_3$, 60 MHz) 2.40 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.57 (2 H, q, J = 7 Hz), 5.51 (3 H, m), 6.04 (2 H, m), 6.95 (1 H, br m), 7.35 (3 H, m), 7.70 (2 H, m); IR ($CHCl_3$) 3445, 3340, 3010, 1645, 1602, 1580, 1522, 1488, 1300, 1290, 1220, 1148, 1060 cm^{-1}; exact mass calcd for $C_{15}H_{15}NO_2$ (M^+) 241.110 27, found 241.109 29.

Cyclizations of benzamide **24** were attempted with CD_3OK/CD_3OD, t-BuOK/t-BuOH, n-$C_{10}H_{21}ONa$/n-$C_{10}H_{21}OH$, and CD_3ONa/CD_3OD. In each case ^1H NMR and TLC revealed formation of the phenol as the predominant product. No products resulting from cyclization could be isolated from reaction mixtures. Data for the amide phenol (benzamide derivative of **17**) are as follows: mp 140.5–141.5 °C; ^1H NMR (acetone-d_6, 60 MHz) 2.95 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.74 (2 H, half an A_2B_2 pattern J = 7 Hz), 6.98 (5 H, m), 7.45 (3 H, m), 7.90 (2 H, m); IR (KBr) 3350, 3030, 2930, 2860, 1624, 1605, 1572, 1542, 1460, 1355, 1320, 1265, 1230, 1202, 872, 750, 725 cm^{-1}; exact mass calcd for $C_{15}H_{15}NO_2$ (M^+) 241.110 27, found 241.111 84.

A cyclization was attempted with the benzamide derivative of arene oxide **7** by dissolution of the amide in CH_3ONa/CH_3OH. ^1H NMR and TLC revealed the predominant product after 31 h to be the phenol. No cyclized product could be isolated from the reaction mixture. Data for the amide phenol (benzamide derivative of phenol **22**) are as follows: mp 164.5–165.5 °C (lit.[33] mp 161–162 °C); ^1H NMR (acetone-d_6, 90 MHz) 2.90 (2 H, half an A_2B_2 pattern, J = 7 Hz), 3.56 (2 H, q, J = 7 Hz), 6.76 (2 H, half an AA'BB' pattern, J = 8.4 Hz), 7.08 (2 H, half an AA'BB' pattern, J = 8.4 Hz), 7.48 (3 H, m), 7.84 (2 H, m); IR (KBr) 3370, 3320, 3050, 3020, 2930, 2855, 1635, 1600, 1542, 1509, 1443, 1310, 1234, 816, 685 cm^{-1}; exact mass calcd for $C_{15}H_{15}NO_2$ (M^+) 241.110 27, found 241.108 38.

Cyclizations of benzamide **25a** were attempted with $CH_3ONa/CH_3OH/THF$, 1 N KOH/THF, t-BuOK/t-BuOH, t-BuOK/CH_3CN, and CD_3OK/CD_3OD. All showed starting arene oxide with varying amounts of phenol rearrangement product (^1H NMR and TLC). For example, after 188 h at ambient temperature the CD_3OK/CD_3OD reaction showed by ^1H NMR a ratio of ~ 60:40 of the phenol/arene oxide. No product corresponding to nucleophilic opening of the epoxide (e.g., cyclization) could be isolated from any of the reaction mixtures. The data for the amide phenol (benzamide derivative of **17**) are reported above.

Amide arene oxide **25a** (73.6 mg, 0.305 mmol) in *N,N*-dimethylformamide (DMF, 0.75 mL) at −23 °C (CO_2(s), CCl_4) was added to NaH (15.9 mg, 0.331 mmol) in DMF (0.25 mL) also maintained at −23 °C. After 1 h the stirred mixture was warmed to 0 °C for an additional 1 h, CH_3I (62 μL, 1.0 mmol) was added, and stirring was continued at ambient temperature for 2 h. The solvent was removed in vacuo and the residue partitioned between Et_2O and pH 7.2 phosphate buffer. Drying (Na_2SO_4) and evaporation of the organic phase gave (^1H NMR) the N-methylated amide arene oxide **25b** (69.3 mg, 89%). Full characterization was obtained after aromatizing the arene oxide on a preparative silica TLC plate. The data for the *N*-methylbenzamide are as follows: mp 115–116 °C; ^1H NMR ($CDCl_3$, 60 MHz) 2.95 (5 H, br s), 3.55 (2 H, br m), 6.85 (4 H, br m), 7.29 (6 H, br s); IR (KBr) 3600–3000 (br), 2940, 2880, 2735, 1609, 1590, 1570, 1460, 1412, 1310, 1270, 1075, 787, 753, 718, 700 cm^{-1}; exact mass calcd for $C_{16}H_{17}NO_2$ (M^+) 255.125 92, found 255.126 46.

Acknowledgment is made to the National Institutes of Health (Grant No. RO1 CA 20574 and T32 CA 09112) for support of this work. We also thank Dr. C. Costello for mass spectra and Philip Fiore for preparation of starting materials.

(33) Kinel, F. A.; Romo, J.; Rosenkranz, G.; Sondheimer, F. *J. Chem. Soc.* **1956**, 4163.