Tetrahedron Letters,Vol.23,No.11,pp 1185-1188,1982 0040-4039/82/111185-04$03.00/0
Printed in Great Britain

1-VINYLBENZENE 1,2- AND 3,4-OXIDES

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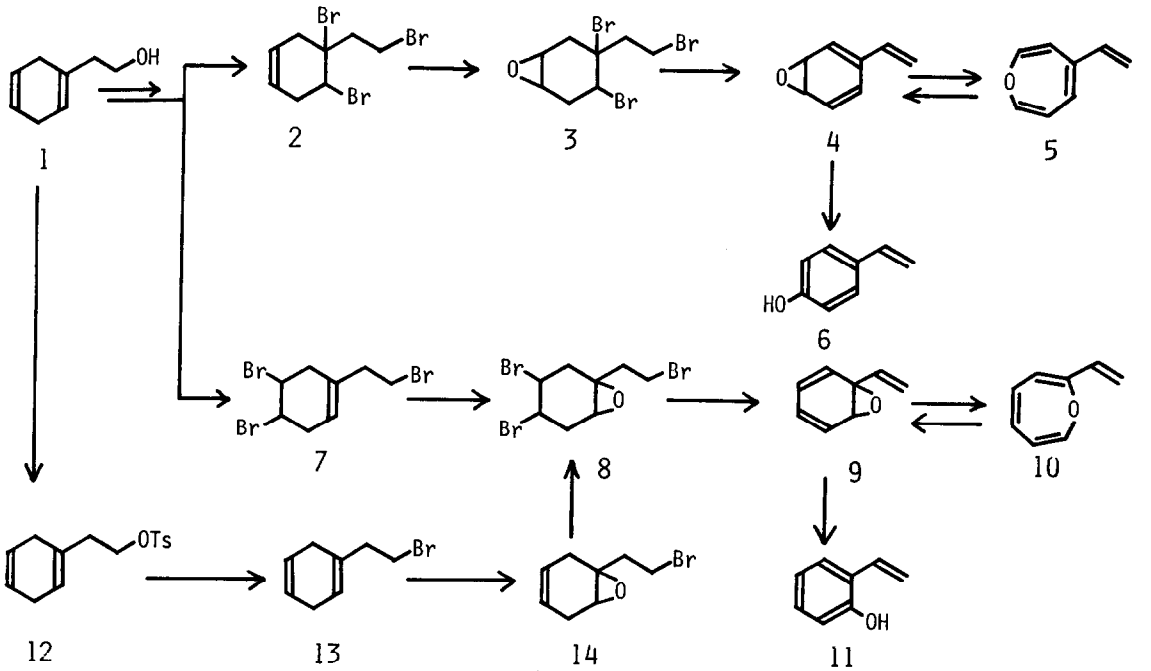
Summary: Synthesis of highly unstable vinyl-substituted benzene oxides has been established.

The recent demonstration that phenyloxirane as the major metabolite of styrene in liver microsomes plays a minor role in the styrene-induced reverse mutation of bacteria[1] raised a question whether 1-vinylbenzene 3,4-oxide, a putative precursor of previously isolated 4-vinylphenol as the urinary metabolite of the plastic monomer,[2] was an ultimate mutagen. However, little predictable information is available as yet on the synthesis and the nature of the vinyl-substituted benzene oxide despite of recent fruitful works on the synthesis of highly reactive epoxides of non-fused benzenes having electron-releasing groups, such as toluene oxides,[3] xylene oxides,[4,5] mesitylene oxides.[5] It could be presumable from previously reported data that the conjugation of a vinyl group with benzene oxide would decrease its stability to a more extreme extent than the case of 3,4-toluene oxide, the most unstable non-fused benzene oxide that has ever been known.[3] In the present communication, we wish to report the synthesis of 1-vinylbenzene 3,4-oxide 4 and its isomer 1-vinylbenzene 1,2-oxide 9.

To a cold solution (-15°C) of 1-(2'-hydroxyethyl)-1,4-cyclohexadiene 1 (bp 92-93°C/3 mmHg; 0.67 M),[6] obtained from 2-phenylethane-1-ol by Birch reduction,[7] in CCl_4 containing 10% (v/v) MeOH[8] was dropwisely added a solution of equimolar bromine (4 M) in the same solvent. The quantitatively yielded dibromoalcohols (0.35 M) in CCl_4 was dropwisely treated at 0°C with a solution of phosphorus tribromide (1.05 M) in CCl_4. The mixture was left stand overnight at room temperature and washed with 5% $NaHCO_3$. The residue obtained on the evaporation of the solvent from the solution was chromatographed on a silica gel column in *n*-hexane to give tribromoethylcyclohexenes 2 and 7 in 12 and 18% yields from 1, respectively.[9] The less polar tribromide 2 (mp 56°C)[10] was epoxidized in chloroform with perbenzoic acid (PBA, 0.36 M) to give a mixture of diastereoisomers of tribromoethylcyclohexene oxide 3 (mp ∿ 97°C),[11] quantitatively. The arene oxide, 1-vinylbenzene 3,4-oxide 4 was obtained in 75% yield as a deep yellow liquid[12] by the portionwise treatment of 3 (0.1 M) in absolute ether with finely powdered potassium *t*-butoxide (0.38 M as a final concentration) at -20°C for 30 min, followed by the removal of the solvent *in vacuo* from the solution which was diluted with *n*-pentane, washed with cold water and dried over anhydrous $MgSO_4$.

The isomeric arene oxide, 1-vinylbenzene 1,2-oxide 9, was synthesized as a deep yellow liquid[13] in 75% yield from the tribromide 7 (mp 40°C)[14] through a mixture of diastereoisomers of tribromoethylcyclohexene oxide 8 (mp ∿ 66°C)[11] by the same method as used for the synthesis of 4.



The oxide 8 was also synthesized in almost quantitative yield specifically from 1 through an alternative pathway involving the highly selective epoxidation of the alkyl-substituted double bond of the 1,4-cyclohexadiene ring. The alcohol 1 (0.41 M) was *p*-toluenesulfonated at 0°C in dry pyridine containing *p*-toluenesulfonyl chloride (0.44 M) to give an ester 12 (mp 38°C).[15] The ester 12 (0.35 M) was then converted to a liquid bromide 13[16] (bp 64°C/2 mmHg) by the treatment with lithium bromide (0.70 M) in boiling anhydrous acetone. The bromoethylcyclohexadiene 13 (0.54 M) dissolved in chloroform was titrated with an equimolar solution of PBA (0.54 M) in chloroform to yield 14 (liquid)[17] which was dibrominated with equimolar bromine at -20°C in CCl_4 to give 8.

The 3,4-oxide 4 was extremely unstable in water or MeOH, so that its deep yellow color faded immediately in these solvents to give colorless solutions which contained quantitatively yielded 4-vinylphenol 6 as the sole rearrangement product.[18] In aprotic solvents such as *n*-hexane and CCl_4, however, it was stable enough to remain unchanged over 24 hr at 20°C in the dark.[19] Uv spectra of 4 in isooctane (λ_{max} nm (ε): 300 (2720), 226 (17900)), in dioxane (λ_{max} nm (ε): 292 (2860)), and in ethanol (λ_{max} nm (ε): 290 (2860), 225 (19500))[20] strongly suggested that the arene oxide existed as valence isomers of 4 and the vinyl-substituted oxepin 5, the latter of which played a larger part in less polar solvents.[21]

The 1,2-oxide 9 was more stable than 4, so that it remained unchanged over a week at 20°C in *n*-hexane or CCl_4 in the dark. However, its deep yellow color faded rapidly in water or MeOH to give colorless solutions which contained quantitatively yielded 2-vinylphenol 11.[18]

Uv spectra of 9 in isooctane (λ_{max} nm (ε): 320 (3930). 221 (32000)), in dioxane (λ_{max} nm (ε) 319.5 (3940)), and in ethanol (λ_{max} nm (ε): 318 (3840), 223 (27100)) also strongly suggested that the arene oxide 9 existed in most part as 2-vinyloxepin 10.[22]

Half-lives of 4 and 9 which were determined by measuring the decrease in their absorbancy at 340 nm were 4.3 sec and 1.6 min, respectively, in dioxane-0.1 M phosphate buffer, pH 7.4 (1:4).[23] Both arene oxides 4 and 9 were highly mutagenic toward *Salmonella typhimurium* TA 100.[24]

References and Notes

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5. (a) D. M. Jerina, N. Kaubisch, and J. W. Daly, *Proc. Natl. Acad. Sci. U. S. A.*, 68, 2545 (1971). (b) E. A. Fehnel, *J. Amer. Chem. Soc.*, 94, 3961 (1972).
6. The ^{1}H NMR spectra in this investigation were recorded in CCl_4 containing tetramethylsilane as an internal standard on a JEOL Model PS-101 100 MHz NMR spectrometer otherwise noted. ^{1}H NMR data for 1: δ 2.15 (t, $J_{1',2'}$ = 7 Hz, 2 H) for H (1'), 2.61 (s, 4 H) for H (3) and H (6), 3.61 (t, $J_{2',1'}$ = 7 Hz, 2 H) for H (2'), 4.28 (broad s, 1 H) for H (-OH), 5.45 (broad s, 1 H) for H (2), 5.65 (broad s, 2 H) for H (4) and H (5); IR (cm^{-1}, neat) ν_{max} 3500-2800 (OH), 1680 (CH=CH-), 1650 (-CH=CH-).
7. L. A. Paquette and J. H. Barrett, *Org. Syn.* 49, 62 (1969).
8. The ratio of 1,2- to 3,4-dibromoalcohols (3:1) was checked by HPLC after *p*-toluenesulfonation: retention times on a μBondapak column (3.9 mm x 15 cm) in MeOH-H_2O (7:3) were 13.4 min and 11.8 min for the tosylates of the 1,2- and 3,4-dibromoalcohols, respectively.
9. Retention times (HPLC data obtained on silica gel (μPorasil, 3.9 mm x 30 cm) in 1.5 ml *n*-hexane/min by refractometry) for 2 and 7 were 9.6 min and 14.9 min, respectively.
10. ^{1}H NMR data for 2 : δ 2.51 (t, $J_{2',1'}$ = 8.2 Hz, 2 H) for H (1'), 3.55 (t, $J_{2',1'}$ = 8.2 Hz, 2 H) for H (2'), 4.37 (broad s, 1 H) for H (5), 5.60 (broad d, J = 3.0 Hz, 2 H) for H (1) and H (2); IR (cm^{-1}, KBr) ν_{max} 1660 (-CH=CH-); MS *m/e* parent-Br 269, 267, 265 (1:2:1), parent-Br-HBr 187, 185 (1:1), base 105.
11. The tribromoepoxides were stable enough to be stored without any change over one month in a refrigerator. Retention times (HPLC data obtained in 1.5 ml *n*-hexane-THF (30:1)/min, see note 9 with the other conditions) for 3 and 8 were 7.1 and 6.1 min, respectively. MS data for 3 : *m/e* parent-Br 285, 283, 281 (1:2:1), parent-Br-Br 204, 202 (1:1), parent-Br-HBr 203, 201 (1:1), base 175; MS data for 8 : *m/e* parent 366, 364, 362, 360 (1:3:3:1), parent-Br 285, 283, 281 (1:2:1), parent-Br-Br 204, 202 (1:1), parent-Br-HBr 203, 201 (1:1), base 283.
12. ^{1}H NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane as an internal standard on a JEOL-FX 200S 200 MHz NMR spectrometer. ^{1}H NMR data for 4 : δ 4.96 (dd, $J_{1',2'\text{-}cis}$ = 11.4 Hz, $J_{2'\text{-}gem}$ = 1.5 Hz, 1 H) for H (2'), 5.18 (dd, $J_{1',2'\text{-}trans}$ = 17.1 Hz, $J_{2'\text{-}gem}$ = 1.5 Hz, 1 H) for H (2'), 5.32 (d, $J_{3,2}$ = 5.7 Hz, 1 H) for H (3), 5.37 (d, $J_{4,5}$ = 5.7 Hz, 1 H) for H (4), 5.62 (t, $J_{5,4} = J_{5,6}$ = 5.7 Hz, 1 H) for H (5), 5.70 (d, $J_{3,2}$ = 5.7 Hz, 1 H) for H (2),

6.04 (d, $J_{5,6}$ = 5.7 Hz, 1 H) for H (6), 6.21 (dd, $J_{1',2'\text{-}cis}$ = 11.4 Hz, $J_{1',2'\text{-}trans}$ = 17.1 Hz, 1 H) for H (1'). The arene oxide could not be purified by distillation because of its facile polymerization accompanied with change in color to dark blue at 30°C.

13. The debromination method used in this investigation was a slight modification of the previous study (see note 3: D. M. Jerina, *et al.*). The ^{1}H NMR spectra were recorded on the same conditions as note 12. ^{1}H NMR data for 9 : δ 5.14 (dd, $J_{1',2'\text{-}cis}$ = 11.4 Hz, $J_{2'\text{-}gem}$ = 1.5 Hz 1 H) for H (2'), 5.61 (t, $J_{2,3} = J_{3,4}$ = 5.7 Hz, 1 H) for H (3), 5.70 (dd, $J_{1',2'\text{-}trans}$ = 17.5 Hz, $J_{2'\text{-}gem}$ = 1.5 Hz, 1 H) for H (2'), 5.92 (d, $J_{2,3}$ = 5.7 Hz, 1 H) for H (2), 6.22 (dd, $J_{1',2'\text{-}cis}$ = 11.4 Hz, $J_{1',2'\text{-}trans}$ = 17.5 Hz, 1 H) for H (1'), 6.26 (dd, $J_{4,5}$ = 10.8 Hz, $J_{5,6}$ = 5.8 Hz, 1 H) for H (5), 6.38 (dd, $J_{3,4}$ = 5.7 Hz, $J_{4,5}$ = 10.8 Hz, 1 H) for H (4), 6.46 (d, $J_{5,6}$ = 5.8 Hz, 1 H) for H (6).
14. ^{1}H NMR data for 7 : δ 2.40 (t, $J_{1',2'}$ = 7.5 Hz, 2 H) for H (1'), 3.35 (t, $J_{2',1'}$ = 7.5 Hz, 2 H) for H (2'), 4.43 (broad s, 2 H) for H (4) and H (5), 5.38 (broad s, 1 H) for H (2); IR (cm^{-1}, KBr) ν_{max} 1670 (C=CH-): MS *m/e* parent 350, 348, 346, 344 (1:3:3:1), parent-Br 269, 267, 265 (1:2:1), parent-Br-HBr 187, 185 (1:1), base 105.
15. At higher temperatures, 2'-chloroethyl-1,4-cyclohexadiene was yielded instead of 12.
16. ^{1}H NMR data for 13 : δ 2.69 (s, 4 H) for H (3) and H (6), 3.38 (t, $J_{2',1'}$ = 7.5 Hz, 2 H) for H (2'), 5.47 (broad s, 1 H) for H (2), 5.63 (broad s, 2 H) for H (4) and H (5).
17. ^{1}H NMR data for 14 : δ 2.15 (t, $J_{1',2'}$ = 7 Hz, 2 H) for H (1'), 2.43 (s, 4 H) for H (3) and H (6), 3.05 (broad s, 1 H) for H (2), 3.40 (t, $J_{2',1'}$ = 7 Hz, 2 H) for H (2'), 5.38 (broad s, 2 H) for H (4) and H (5).
18. Identification of phenols 6 and 11 with respective authentic specimens was carried by GLC on a 15% DEGS column (coated on 60-80 mesh Chromosorb W, 3 mm x 2 m) in 36 ml N_2/min at a column temperature of 160°C: retention times of 6 and 11 were 19.7 and 9.7 min, respectively, and of 3-vinylphenol 17.7 min. The authentic phenols were synthesized by the previously reported methods (see W. J. Dale, H. E. Hennis, *J. Amer. Chem. Soc.*, 80, 3645 (1958)). Specific rearrangement of monosubstituted 1,2- and 3,4-benzene oxides to the corresponding *o*- and *p*-substituted phenols have also been demonstrated with toluene oxides (see note 5: D. M. Jerina, *et al.*, and see H. S.-I. Chao and G. A. Berchtold, *J. Org. Chem.*, 46, 1948 (1981)), and 2'-aminoethylbenzene oxides (see W. H. Rastetter, L. J. Nummy, *J. Org. Chem.*, 45, 3149 (1980)). Similarity in the mode of specific rearrangement of 4 and 9 to in that of these alkyl-substituted benzene oxides, therefore, appears to indicate their vinyl group to have an electron-releasing effect on the benzene oxide.
19. Approximately 5% of 4 was rearranged to 6 in dry *n*-hexane or CCl_4, after 5 days under these conditions.
20. The arene oxide 4 had a half-life longer than at least 30 min in EtOH at room temperature. The spectrum was repeatedly recorded within 2 min from the longer wavelength region as well as from the shorter one.
21. The bathochromic shift of the absorption maximum located at longer wavelength in nonpolar solvents has already been demonstrated with the valence tautomerism between benzene oxide and oxepin (see note: E. Vogel and H. Günther).
22. No change in the spectra recorded in both polar and nonpolar solvents has been demonstrated with 2,7-dimethyl oxepin whose valence isomer, 1,2-dimethylbenzene 1,2-oxide, is recognized not to exist (see note 4: E. Vogel and H. Günther).
23. Phenols 6 and 11 had no absorption at this wavelength in the aqueous solution used.
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(Received in Japan 5 December 1981)