

## Reaction of Styrene 3,4-Oxide with Ethanethiol and Dehydration to Ethylthiostyrenes

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Styrene 3,4-oxide reacts with the nucleophile ethanethiol, and the product is dehydrated to give three isomeric ethylthiostyrenes *via* the corresponding ethylthiovinylcyclohexadienols without formation of thiiranium ions as intermediates.

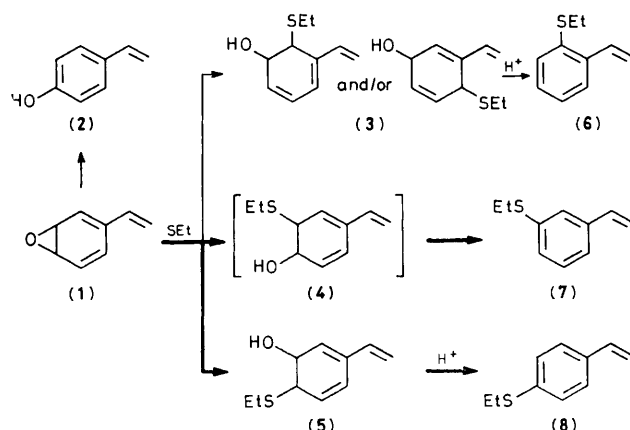
Styrene 3,4-oxide (1),<sup>1</sup> a recently proposed obligatory intermediate in the metabolism of styrene to 4-vinylphenol (2) in man<sup>2</sup> as well as in the rat,<sup>3-5</sup> has potent mutagenicity and cytotoxicity.<sup>5</sup> The only rearrangement product of (1) in protic solvents is (2).<sup>1</sup> Despite its importance for understanding the molecular basis for toxicity mechanisms, information is not available on the reaction with nucleophiles of this new type of

benzene oxide having a conjugated ethylenic group. The present investigation was undertaken to study the mode of reaction of (1) with ethanethiol, a model nucleophile.

The deep yellow liquid epoxide (1) (5 mmol) was dissolved in chilled EtOH (40 ml) containing EtSK (5.5 mmol) and left at 0 °C. After 1 h, the colourless solution obtained was diluted with Et<sub>2</sub>O and shaken with H<sub>2</sub>O in the presence of a

saturating amount of NaCl. From the aqueous phase, separated and acidified, 4-vinylphenol (2) was isolated in 18% yield. An aliquot of the residual organic phase containing non-phenolic materials was treated with 5 M-H<sub>2</sub>SO<sub>4</sub> (0.1 vol.) at room temperature for 30 min and then with powdered NaHCO<sub>3</sub>. G.l.c.-mass spectrometry indicated that the solution contained 2-, 3-, and 4-ethylthiostyrenes† (6), (7), and (8), respectively, in the ratio 1:9:7 in a total yield of 79%.‡

H.p.l.c. of the remaining non-phenolic fraction on a silica column showed two u.v.-absorbing peaks at 2.5 (sharp) and 9.0 (broad) min in the chromatogram.§ The less polar material eluted from the column was found by g.l.c.-mass spectrometry to be identical with 3-ethylthiostyrene (7) and the more polar material yielded 2- and 4-ethylthiostyrene (6) and (8) on treatment with sulphuric acid.‡ These ethylthiostyrenes were present in the same ratio as that observed in the acid treatment of the non-phenolic fraction before h.p.l.c. This strongly suggests that (7) is specifically formed from the highly unstable intermediate (4) by spontaneous dehydration even under alkaline conditions and also that (6) and (8) are specifically



**Scheme 1.** Reaction of styrene 3,4-oxide with ethanethiol and dehydration of the resulting ethylthiovinylcyclohexadienols to ethylthiostyrenes.

derived from the stable intermediates (3) and (5),¶ respectively, only on acid treatment (Scheme 1). From the h.p.l.c. fraction containing (3) and (5), (5) was isolated as needles (m.p. ca. 1 °C) by several recrystallisations from Et<sub>2</sub>O and n-pentane at -10 °C and characterized by g.l.c.-mass spectrometry following formation of the Me<sub>3</sub>Si ether by treatment with hexamethyldisilazane in the presence of trimethylsilyl chloride in dry pyridine. G.l.c. after the acid treatment indicated the crystals to consist only of the precursor of (8) and the mother liquid to contain precursors of (6) and (8).

Thus, the present investigation provides the first direct evidence for dehydration of alkanethiolate adducts of a mono-substituted benzene oxide to alkyl sulphides without formation of alkyl-thiiranium ions as intermediates.

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† Authentic samples of 2-, 3-, and 4-ethylthiobenzaldehydes were synthesized by the reaction of *N,N*-dimethylformamide (2 mol/l) in tetrahydrofuran at 50 °C for 2 h with the Grignard reagents (2 mmol/l) prepared from the appropriate ethyl 2-bromo-, 3-bromo-, and 4-iodo-phenyl sulphide [see J. Renz, J. P. Bourquin, C. Brueschweiler, and G. Schward, *Chem. Abstr.*, 1968, **68**, 95691s; R. Fusco and R. Trave, *Ann. Chim. (Rome)*, 1951, **41**, 139; G. W. Monier-Williams, *J. Chem. Soc.*, 1906, **89**, 279]. For convenience, 2- and 4-ethylthiobenzaldehydes could also be directly synthesized as a 1:10 mixture from ethylthiobenzene by the method of W. E. Smith (*J. Org. Chem.*, 1972, **37**, 3972) and were readily separated by silica column chromatography with benzene-n-hexane (20:1) as eluant. 2-, 3-, and 4-Ethylthiobenzaldehydes (0.5 mol/l each in anhydrous benzene) were treated with powdered methyltriphenylphosphonium bromide (see G. Wittig and G. Geisser, *Liebigs Ann. Chem.*, 1953, **44**, 580; 0.75 mmol/l) at room temperature for 1 h to yield (6), (7), and (8), respectively, in almost quantitative yields (h.p.l.c.). Fractionation to remove solvent followed by distillation *in vacuo* gave the pure compounds as colourless liquids: (6), b.p. 64–67 °C at 8 mmHg, <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, Me<sub>4</sub>Si) δ 7.47–6.87 (m, 4H, ArH), 7.16 (dd, *J* 11.7 and 17.7 Hz, 1H, -CH=CH<sub>2</sub>), 5.50 (dd, *J* 17.7 and 1.7 Hz, 1H, -CH=CHH *cis* to Ar), 5.20 (dd, *J* 11.7 and 1.7 Hz, 1H, -CH=CHH *trans* to Ar), 2.73 (q, 2H), and 1.17 (t, 3H); (7), b.p. 87–89 °C at 8 mmHg; (8), b.p. 92–95 °C at 6 mmHg.

‡ A Hewlett-Packard model 5995A gas-chromatograph-mass spectrometer was used. Retention times of (6), (7), and (8) were 5.2, 6.7, and 7.2 min, respectively, on Silar 10CP (2%, 4 mm × 2 m on Chromosorb W, 60–80 mesh) at a flow rate of 30 ml/min helium (130 °C): *m/z* for (6): 164 (*M*<sup>+</sup>) (12.2%), 136 (11.2), 135 (*M*<sup>+</sup>-CH<sub>2</sub>CH<sub>3</sub>) (100), 134 (25.5), and 91 (36.4).

§ H.p.l.c. was carried out on an Atto Constameric II liquid chromatograph equipped with a Shimadzu SPD-1 stop and flow u.v. spectrometer; column: Spherisorb silica (4 mm × 25 cm, 5 μm particle size, Phase Separation Ltd., New York); solvent: n-hexane containing 5% (v/v) of tetrahydrofuran, 2 ml/min; column temperature: 20 °C.

¶ The mixture was also inseparable by reverse-phase partition h.p.l.c. on a μ-Bondapak C<sub>18</sub> column (3.9 mm × 30 cm, 10 μm particle size, Waters Associates Inc., Milford, Mass.) in aqueous methanol as solvent.