

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE
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REACTIONS OF HETEROCYCLES WITH PHENOLS. STUDIES IN THE REACTION OF ETHYLENE OXIDE WITH PHENOL

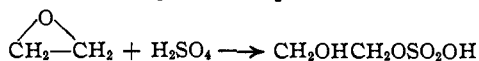
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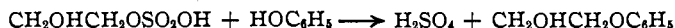
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A survey of the literature to date reveals the following reports of interactions of phenols with heterocyclic compounds: (1) ethylene oxide, the simplest oxygen heterocycle, under the influence of heat combines with phenol to yield (β -hydroxy-ethyl)-phenyl ether. The same phenoxy compound can be obtained from ethylene chlorohydrin and sodium phenoxide.¹ Epichlorohydrin and phenol under the influence of heat yield the analogous phenyl ether.² (2) In the field of nitrogen heterocycles, reactions have been reported with diazomethane,³ isatin⁴ and alloxan.⁵ Ethylene-imine and its homologs, as being structurally related to the ethylene oxide studied in this paper, are under investigation.

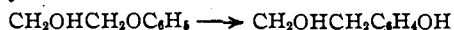
In the following investigation ethylene oxide was caused to react with phenol in the cold and in the presence of sulfuric acid to form, not an ether, as would be indicated by the work cited, but a substituted phenol. This product appears to be *o*-vinylphenol, for which the following proofs of structure are offered. (1) The explanation here given for a reaction mechanism appears to be well justified; it may be assumed that the first step in the reaction is the addition of sulfuric acid to ethylene oxide to form ethanol sulfuric acid according to the equation



The resulting compound then reacts with phenol to form (β -hydroxy-ethyl)-phenyl ether with the elimination of sulfuric acid



Inasmuch as ethylene oxide and phenol under the action of heat and pressure form this compound, it is plausible to assume the formation of it here, as an intermediate, with the sulfuric acid acting in the capacity of a catalyst. Phenolic ethers with a negative group in the side chain, as in the foregoing case, rearrange readily in the presence of mineral acids to form substituted phenols. We assume this to be the case here with the formation of *o*-hydroxyphenylethyl alcohol



¹ Roithner, *Monatsh.*, **15**, 674 (1894).

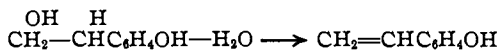
² Lindeman, *Ber.*, **24**, 2146 (1891); E. Fischer and Kramer, *ibid.*, **41**, 2730 (1908).

³ Pechmann, *ibid.*, **28**, 857 (1895).

⁴ Baeyer and Lazarus, *ibid.*, **18**, 2641 (1895); Liebermann and Danaïla, *ibid.*, **40**, 3593 (1907).

⁵ Bohringer, German Patents 107,720 and 115,817.

The presence of concentrated sulfuric acid causes dehydration with the formation of *o*-vinylphenol



As a modification of the foregoing mechanism, dehydration of the phenoxy glycol may precede rearrangement. It has been shown that unsaturated ethers of the type which would thus be formed rearrange very readily to give ortho substituted phenols.⁶ (2) The physical and chemical constants of the compound obtained corresponded with those given in the literature for *o*-vinylphenol. For further identification, two derivatives, the 3,5,1¹,1²-tetrabromo-2-hydroxyethylbenzene and the *o*-vinylphenoxyacetic acid, were prepared; the physical properties of these also agreed with those given in the literature.

In order, however, to substantiate more fully the reaction mechanism offered, the *o*-vinylphenol was synthesized by a different method as follows.

Ethylene chlorohydrin was treated with potassium phenoxide and the corresponding (β -hydroxy-ethyl)-phenyl ether obtained; this same ether can also be obtained by the action of ethylene oxide on phenol. The ether was then treated with concentrated sulfuric acid in a manner analogous to that used in the phenol-ethylene oxide condensation. The product was worked up as before and proved to be *o*-vinylphenol with the same physical constants and yielding the same derivatives. This indicated that the rearrangement and dehydration assumed in the proposed mechanism are allowable. The reaction is also of general interest as it substantiates the explanation offered in the condensation reactions taking place in the cold between unsaturated compounds (hydrocarbons, alcohols, esters, ethers, aldehydes, acetals, ketones, acids, nitriles, amines and halides) with phenols in the presence of concentrated sulfuric acid.⁷

Experimental

(1) **Vinylphenol from Ethylene Oxide and Phenol.**—A fifth mole of concentrated sulfuric acid was slowly added with cooling to a solution of molar quantities of phenol and ethylene oxide. The action during addition was vigorous. The containing flask was then closed with a stopper containing a calcium chloride drying tube and allowed to stand for one week. The product was washed with cold water to remove phenol, ethylene oxide, sulfuric and sulfonic acids and other water-soluble by-products. *o*-Vinylphenol is slightly soluble in water. The resulting liquid was distilled in vacuo. Redistillation yielded pure *o*-vinylphenol in about 65% yield. It was found that hydroquinone was a good inhibitor to polymerization. The rate of reaction as well as the yield of product can be controlled by the amount of sulfuric acid used. Pure *o*-vinylphenol melts at 29–29.5° (corr.) and boils at 56° under a pressure of 4 mm. The boiling point given by Fries and Fickewirth of 108° at 15 mm. is incorrect for the pure product.

⁶ Claisen and Eisleb, *Ann.*, **401**, 21 (1914); *Ber.*, **58**, 275 (1925).

⁷ Niederl and Natelson, *THIS JOURNAL*, **53**, 272 (1931).

which at that pressure boils at 77°. Upon distilling *o*-vinylphenol from the polymerized product a temperature approximating that given by Fries and Fickewirth is noted.⁸

(2) **3,5,1¹,1²-Tetrabromo-2-hydroxy-ethylbenzene.**—*o*-Vinylphenol, as prepared above in a chloroform solution, was treated with an excess of bromine with cooling. After the action had subsided, the hydrogen bromide, excess bromine, and chloroform were driven off with heat and the remaining solid purified by recrystallization from benzene. The final product melted at 105°, which is in agreement with the literature.

(3) ***o*-Vinylphenoxyacetic Acid.**—Molar quantities of *o*-vinylphenol, as prepared above, and bromoacetic acid were allowed to stand at room temperature in an alkaline solution for a few hours. The solution was then acidified and the resulting product purified by recrystallization from benzene or dilute alcohol. Prisms melting at 137° were obtained. This also was in agreement with the literature.

(4) **(β -Hydroxy-ethyl)-phenyl Ether.**—Molar quantities of potassium phenoxide and ethylene chlorohydrin were heated at 150° for six hours, and after cooling and filtering the liquid was distilled in vacuo. The fraction boiling at 163–167° at 80 mm. was retained as being the desired phenoxy glycol.

(5) ***o*-Vinylphenol from (β -Hydroxy-ethyl)-phenyl Ether.**—A molar quantity of the phenoxy glycol was allowed to stand for one week at room temperature with a fifth molar quantity of concentrated sulfuric acid. The product was washed with water and distilled in vacuo. *o*-Vinylphenol with the same boiling point as previously given was obtained; it formed the same bromine and acetic acid derivatives, proving that the compounds prepared by the two different methods were identical.

Summary

1. Ethylene oxide reacts with phenol in the cold in the presence of concentrated sulfuric acid to yield an ortho substituted phenol.
2. A probable mechanism for the above reaction has been advanced and reasons substantiating it have been given.
3. Two new methods for the preparation of *o*-vinylphenol have been discussed.

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NOTES

The Optical Activity of Cystine Preparations Used for Animal Experimentation.—Marston and Robertson¹ have recently expressed the opinion that much of the confusion in the literature dealing with cystine metabolism might have been avoided by determining the optical activity of the preparations used and have severely criticized certain studies on this account.

For several years we have been using cystine, prepared from human hair, in animal feeding experiments. Most of our preparations, as well as a number of student preparations subsequently reprecipitated by the author,

⁸ Fries and Fickewirth, *Ber.*, **41**, 370 (1908).

¹ Marston and Robertson, "The Utilization of Sulfur by Animals," Commonwealth of Australia, Council for Scientific and Industrial Research, Melbourne, 1928, Bulletin No. 39, 51 pp.