[Contribution from the Department of Chemistry, Colorado A. and M. College]

THE REACTIONS OF *m*- AND *o*-NITROSTYRENE OXIDE WITH PHENOL[1]

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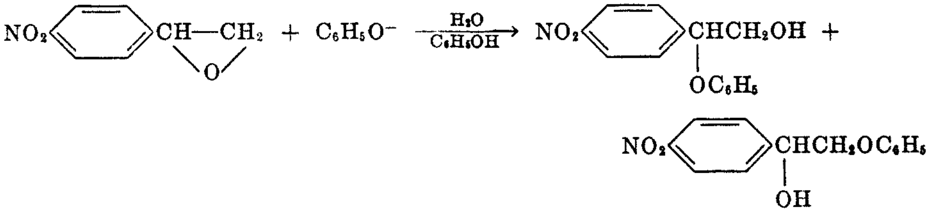
It has been shown (1) that *p*-nitrostyrene oxide interacts with phenoxide ion in water and excess phenol to form about one part of primary alcohol for each two parts of secondary alcohol. Styrene oxide, under identical conditions (2), produces about one part of secondary alcohol for each three parts of primary alcohol. Since a further study of the effect of substituents on the phenyl group of styrene oxide might be helpful in a diagnosis of the mechanism of ring opening, an investigation of the behavior of *m*- and *o*-nitrostyrene oxides was undertaken.



The *m*- and *o*-nitrostyrene oxides were both prepared by the same reaction sequence used with the *p*-isomer (1), namely, bromination of the substituted acetophenone, reduction of the phenacyl bromide with aluminum isopropoxide, and ring closure of the resulting bromohydrin with dilute sodium hydroxide. These oxides were then treated with phenoxide ion in the presence of excess phenol and water in a manner exactly like that used with styrene oxide and *p*-nitrostyrene oxide.

The reaction of *m*-nitrostyrene oxide and phenoxide ion gave an excellent yield of the mixture of isomeric ether-alcohols. Both of the crystalline isomers were isolated by means of the difference in their rates of esterification with phthalic anhydride (2). Proof of structure consisted in catalytic reduction and subsequent deamination to known compounds (2). The secondary alcohol was thus found to be present in the greater amount. A more accurate determination of the composition of the mixture resulted from conversion of the mixture of isomers, by catalytic reduction and deamination, to a mixture whose composition was determined by use of a phase diagram (1, 2). Such a procedure showed that the mixture was 67% secondary alcohol.

The acid-catalyzed reaction of *m*-nitrostyrene oxide with phenol produced a 37% yield of alkali-insoluble material, behaving in this respect like *p*-nitrostyrene oxide. Reduction and deamination proved the presence of the ether-primary alcohol in this fraction. The alkali-soluble portion was presumed to contain prod-

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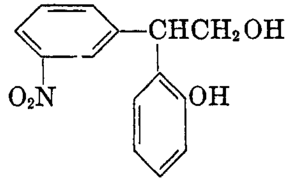
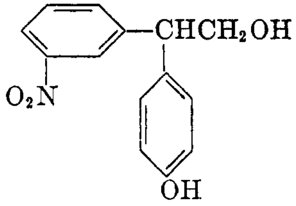
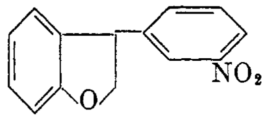
ucts resulting from nuclear alkylation, the oxide ring opening at the *alpha* carbon atom to attack the phenol ring at the *ortho*- and *para*- positions (3).



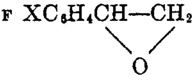




The *ortho*-substituted phenol-alcohol, 2-(2-hydroxyphenyl)-2-(3-nitrophenyl)ethanol, if present, should be capable of being cyclized to 3-(3-nitrophenyl)-2,3-dihydrobenzofuran. A compound corresponding to this furan in chemical behavior and analysis for carbon and hydrogen was isolated, leaving unchanged the isomeric *para*-substituted phenol-alcohol, still somewhat impure as obtained here.

TABLE I

THE REACTION OF $XC_6H_4CH—CH_2$ WITH PHENOXIDE ION



X	COMPOSITION OF MIXTURE OF ALCOHOLS, Secondaryalcohol, %
H	24
p-NO_2	64
m-NO_2	67
o-NO_2	72

o-Nitrostyrene oxide and phenoxide ion also gave a nearly quantitative yield of a mixture whose composition was found to be 72% secondary alcohol. The methods used with the *m*-isomers were again applied here to determine the composition and structure. In the present instance, however, the primary alcohol could not be isolated in a pure state.

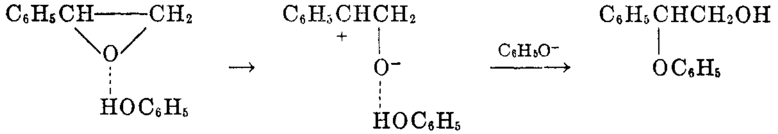
The acid-catalyzed reaction of *o*-nitrostyrene oxide with phenol was followed only to an extent sufficient to verify its anomolous behavior (4). In this oxide the proximity of the nitro group could permit, or favor, an intramolecular interaction with the oxide ring, probably by way of a cyclic intermediate.

Under the same conditions of temperature and concentration of components, styrene oxide (2) and the nitrostyrene oxides (1) react with phenoxide ion in the presence of water and excess phenol as summarized in Table I.

The position of the nitro group in the nitrostyrene oxides has very little effect on the direction of ring opening except in the acid-catalyzed reaction. This behavior is compatible with the concept of a unimolecular route to the primary alcohol when a comparison with the nitrobenzyl chlorides, which have been studied rather extensively, is a criterion. The bimolecular reaction of benzyl chloride with potassium iodide in acetone is increased in rate by substitution of a nitro group in the ring (5, 6), the relative increase being in the order $o > p > m$. Although the accelerating effect of a nitro group on the rate of the bimolecular reactions of benzyl chloride is not always observed, as in the reaction with pyridine (7), it is reasonable to expect that the acceleration would persist when the nucleophilic species is an ion and not a neutral molecule (7). When the β-phenethyl chlorides are considered, the nitro group is again found to accelerate the reaction with potassium iodide (8). These considerations lead to the conclusion that, if the opening of the oxide ring of styrene oxide with phenoxide ion in excess phenol to form the primary alcohol is bimolecular, the nitro group in the nitrostyrene oxides ought to favor the formation of the primary alcohol and to different degrees, depending on the position of the nitro group. This is not observed.

The rate of solvolysis of the benzyl chlorides, on the other hand, is retarded by a nitro group in the ring (6, 9). Furthermore, the degree of retardation is nearly independent of the position of the nitro group, especially when the temperature is increased. This is the type of behavior shown by the nitrostyrene oxides; it is cited in support of the postulate of a unimolecular route to the primary alcohol.

If the reaction of styrene oxide with phenoxide ion in excess phenol is considered to proceed from a hydrogen-bonded complex to a resonance-stabilized and solvated carbonium ion (10), then the nitro group in the nitrostyrene oxides might be expected to decrease the formation and stability of the hydrogen-bonded complex, because of the decreased electron density on the oxide oxygen, and to act against resonance stabilization of the carbonium ion. This would, in either case, be unfavorable to the formation of the primary alcohol. The nitro group might well accelerate a bimolecular attack leading to the secondary alcohol (8). Hence, with the nitrostyrene oxides, the secondary alcohol could be expected to be formed predominantly. A bimolecular route to the primary alcohol is believed to be sterically hindered.



EXPERIMENTAL[2]

m-Nitrostryene oxide. To *m*-nitroacetophenone (11) in chloroform was added a chloroform solution of bromine (12). This *m*-nitrophenacyl bromide (40 g., 0.164 mole, m.p. 94–96°) in isopropyl alcohol (250 cc.) and a 1 *molar* solution (164 cc.) of aluminum isopropoxide in isopropyl alcohol were refluxed with continuous removal of isopropyl alcohol-acetone (250 cc.) during a period of one hour. A test for acetone in the distillate being negative, the yellow reaction mixture was poured into iced hydrochloric acid. The oil that separated soon solidified. Filtration and a water wash, followed by desiccation over calcium chloride, gave 33.3 g. (82.4%) of the light tan *m-nitrostyrene bromohydrin*, m.p. 41–43°. Purifying recrystallizations from benzene-heptane raised the melting point to 42–43°, cream-colored needles.

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[2] All temperature measurements are uncorrected.

Anal. Calc'd for $C_8H_8BrNO_3$: C, 39.04; H, 3.28.
Found: C, 39.15; H, 3.45.

An aqueous solution (150 cc.) of sodium hydroxide (6.0 g., 0.15 mole) was added to *m*-nitrostyrene bromohydrin (33.3 g., 0.135 mole), and the mixture was stirred at 50–60° for 15 minutes. After an additional 30 minutes without heating, the organic layer was taken up in ether and dried over sodium sulfate. Evaporation of the ether under reduced pressure left 21.8 g. (97.7%) of the oxide as a reddish oil, n_D^{20} 1.5670. Distillation of this oil in a modified Claisen flask having two inches of $\frac{1}{8}$″-glass helices gave 19.45 g. (87.3%) of *m-nitrostyrene oxide* as a light yellow oil, b.p. 140–141°/4 mm., n_D^{20} 1.5698.

Anal. Calc'd for $C_8H_7NO_3$: C, 58.18; H, 4.27.
Found: C, 57.99; H, 4.40.

o-Nitrostyrene oxide. The condensation of *o*-nitrobenzoyl chloride with diethyl malonate, followed by hydrolysis and decarboxylation according to the procedures of Reynolds and Hauser (13), gave *o*-nitroacetophenone. Bromination in acetic acid produced *o*-nitrophenacyl bromide, m.p. 55–56° (14).

A solution of *o*-nitrophenacyl bromide (53.7 g., 0.22 mole) in isopropyl alcohol (300 cc.) and a 1 *molar* solution (225 cc.) of aluminum isopropoxide in isopropyl alcohol were refluxed together for one hour while the isopropyl alcohol-acetone mixture (300 cc.) was distilled off. Decomposition of the nearly black reaction mixture gave an oil that solidified. The brown solid was filtered, washed, and dried; 47.8 g. (88.5%), m.p. 57–60°. Recrystallization from benzene-heptane gave the pure *o-nitrostyrene bromohydrin*, m.p. 62–63.5°, as cream-colored needles.

Anal. Calc'd for $C_8H_8BrNO_3$: C, 39.04; H, 3.28.
Found: C, 39.30; H, 3.49.

o-Nitrostyrene bromohydrin (32.8 g., 0.133 mole) was stirred with an aqueous solution (150 cc.) of sodium hydroxide (6.0 g., 0.15 mole) at 40–45° for 15 minutes. When cooled, the oil solidified to a tan solid, which was filtered and dried; 21.6 g. (98.6%). One recrystallization from ethanol-water (Nuchar) raised the melting point of the cream-colored leaves to 64–65°. *o*-Nitrostyrene oxide has been prepared by an alternate method and found to melt at 65° (4).

The reaction of m-nitrostyrene oxide with phenoxide ion. A solution of phenol (7.0 g., 0.075 mole) and sodium hydroxide (1.0 g., 0.025 mole) in water (4 cc.) was brought to the temperature of a boiling water-bath, and *m*-nitrostyrene oxide (4.1 g., 0.025 mole) was added in one minute with stirring. The one-phase mixture immediately turned red and remained that color during the one-hour reaction period. This mixture was added to sodium hydroxide (4 g.) in iced water; the oil that separated was taken up in ether, dried over sodium sulfate, and the ether evaporated under reduced pressure to yield 6.1 g. (94.1%) of a light cream-colored solid, m.p. 65–80°, presumed to be a mixture of the primary and secondary alcohols.

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05.
Found: C, 64.65; H, 5.19.

When the separation of these isomers by fractional crystallization from ethanol-water failed, the mixture was treated with phthalic anhydride and the isolation of both alcohols accomplished (2). Thus, the mixture of isomers (6.0 g., 0.023 mole), phthalic anhydride (7.4 g., 0.05 mole), pyridine (5 cc.), and dioxane (25 cc.) was allowed to stand in solution for five hours at room temperature. The solution was then dissolved in ether (100 cc.), shaken with hydrochloric acid (10 cc.) in water (90 cc.) to remove pyridine, and then extracted with three 50-cc. portions of 7.5% sodium bicarbonate. The combined bicarbonate extract, with added sodium hydroxide (4 g.), was then refluxed for one hour. Extraction of the cooled mixture with ether, followed by drying of the ether solution over sodium sulfate and evaporation of the ether, left 2.55 g. (43.6% of recovered material), m.p. 60–67°. This was reserved. The ether solution from the bicarbonate extraction, presumed to contain the more difficultly esterified secondary alcohol, was freed of ether and the residue refluxed with sodium hydroxide (4 g.) in water (150 cc.) for 20 minutes. A solid that separated was taken up in ether, dried over sodium sulfate, and the ether evaporated to leave 3.3 g. (56.4%

of recovered material), m.p. 77–85°. Two recrystallizations from ethanol-water gave a crystalline material, nearly white, m.p. 89–90°. This was the secondary alcohol, *2-phenoxy-1-(3-nitrophenyl)ethanol.*

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05.
Found: C, 64.77; H, 5.25.

The pale yellow *p-nitrobenzoate* (15) melted at 92–93°, from ethanol.

Anal. Calc'd for $C_{21}H_{16}N_2O_7$: C, 61.76; H, 3.95.
Found: C, 61.62; H, 4.10.

The more easily esterified fraction from the mixture of isomers, obtained as previously described and reserved, was again treated with phthalic anhydride in pyridine and dioxane but for only four hours at room temperature. The more easily esterified material was extracted and hydrolyzed to obtain, from a 1.7-g. charge, 0.8 g. of amber oil which slowly solidified. Two recrystallizations from ethanol-water gave nearly white needles, m.p. 85.5–86.5°. This was the primary alcohol, *2-phenoxy-2-(3-nitrophenyl)ethanol.*

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05.
Found: C, 64.69; H, 5.33.

A mixture melting point of the two pure isomers was 68–80°.

The *p-nitrobenzoate* (15) of the primary alcohol, light yellow crystals from ethanol, melted at 105–106.5°.

Anal. Calc'd for $C_{21}H_{16}N_2O_7$: C, 61.76; H, 3.95.
Found: C, 62.02; H, 4.20.

The composition of the mixture of isomers from the reaction of *m*-nitrostyrene oxide and phenoxide ion was determined by reduction and deamination to a mixture whose composition was found from a phase diagram (1, 2). When the mixture of isomers (6.1 g.) in ethanol (50 cc.) was reduced with hydrogen and Raney nickel at 38 p.s.i., an amber oil (5.0 g.) was obtained. This oil was dissolved in 50% hypophosphorous acid (50 g.) and water (40 cc.) was then added. Diazotization in the cold with a solution (9 cc.) of sodium nitrite (1.5 g. in 10 cc. water) and decomposition of the diazonium salt gave 4.2 g. of a solid. This was distilled under reduced pressure to obtain 3.0 g. of a nearly white solid. Recrystallization from heptane gave the pure mixture, m.p. 48° by the previous technique, and therefore 67% secondary alcohol (1, 2).

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.
Found: C, 78.69; H, 6.83.

The identity of the pure nitrophenylethanols, isolated as described, was proved by reduction and deamination by the same procedure. The isomer melting at 89–90° (1 g.) gave 2-phenoxy-1-phenylethanol (0.65 g. crude, 0.4 g. pure), m.p. 61–63° alone and m.p. 61–64° when mixed with the pure compound (2). Reduction and deamination of the isomer melting at 85.5–86.5° gave a material which was not depressed in melting point when mixed with pure 2-phenoxy-2-phenylethanol.

The acid-catalyzed reaction of m-nitrostyrene oxide with phenol. Phenol (9.4 g., 0.1 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) were melted together and allowed to cool to 40–43°. Then *m*-nitrostyrene oxide (4.1 g., 0.025 mole) was added at a rate (25 minutes) that maintained this temperature. The amber-colored reaction mixture, after ten minutes, was poured into a solution of water (150 cc.) and sodium hydroxide (5 g.). The oil that separated was extracted with ether, which was dried over sodium sulfate. Evaporation of the ether under reduced pressure left 2.3 g. (37%) of a light yellow semi-solid, assumed to be the ether-alcohols. By treatment of the aqueous layer with Dry Ice and extraction with ether it was possible to isolate 7.5 g. of alkali-soluble material, undoubtedly containing some phenol.

The alkali-insoluble material (2.3 g.) was reduced and deaminated by the same procedures used in other portions of this study. Two recrystallizations of the crude product from heptane left 0.5 g., m.p. 76–80°. Admixture with pure 2-phenoxy-2-phenylethanol did not change this melting point; hence, it was concluded that the secondary alcohol was not present in any substantial amount, if at all.

The alkali-soluble fraction (7.5 g.) was dissolved in dioxane (25 cc.) containing phthalic anhydride (9 g.) and pyridine (5 cc.). After about five days at room temperature this solution was dissolved in ether (100 cc.), shaken with hydrochloric acid (5 cc.) in water (50 cc.), then washed with water (50 cc.), and finally extracted with two 50-cc. portions of 5% sodium bicarbonate. A solution of sodium hydroxide (1 g.) in water (20 cc.) was added to the combined bicarbonate extracts, the procedure being patterned after that previously used (16) to effect the intramolecular displacement of carboxylate ion. This solution was refluxed for 30 minutes, cooled, extracted with ether, and the ether solution dried over sodium sulfate. Distillation effected the isolation of 1.2 g. of a viscous, yellow oil, b.p. 210–220°/6 mm., which solidified on standing. The pale yellow crystals from ethanol-water melted at 67–68°. This is presumed to be *3-(3-nitrophenyl)-2,3-dihydrobenzofuran.*

Anal. Calc'd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60.

Found: C, 69.91; H, 4.81.

The alkaline solution from the cyclization reaction was treated with Dry Ice and worked up to give 0.7 g. of a solid, m.p. 146–152° after two recrystallizations from ethanol-water. This is thought to be a mixture of 2-(4-hydroxyphenyl)-2-(3-nitrophenyl)ethanol and 2-(2-hydroxyphenyl)-2-(3-nitrophenyl)ethanol, assuming that the cyclization of the ester of the latter had been accompanied by some hydrolysis (16). Other isomeric products are not excluded, however (3).

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05.

Found: C, 64.75; H, 5.20.

The reaction of o-nitrostyrene oxide with phenoxide ion. Over a period of one minute, *o*-nitrostyrene oxide (4.1 g., 0.025 mole) was added to a solution of phenol (7.0 g., 0.075 mole), sodium hydroxide (1.0 g., 0.025 mole), and water (4 cc.) at the temperature of a boiling water-bath. The color of the one-phase mixture was dark red during the hour of heating and stirring. Addition to sodium hydroxide (4 g.) in iced water and extraction with ether gave a light yellow solution, which was dried over potassium carbonate. Evaporation of the ether left a reddish oil, 6.2 g. (96%).

In order to find out whether this oil was a mixture of primary and secondary alcohols, an attempt was made to prepare the *p*-nitrobenzoate (15). The product obtained, after two recrystallizations from ethanol-water, increased in melting point to 128–132°.

Anal. Calc'd for $C_{21}H_{16}N_2O_7$: C, 61.76; H, 3.95.

Found: C, 61.71; H, 4.23.

Assuming, then, that a mixture of the primary and secondary alcohols was at hand, the composition was determined in order to plan better a separation technique. When the oil (5.7 g.) was reduced with hydrogen and Raney nickel and the resulting oil (4.75 g.) deaminated by the previously described procedure, the product, after distillation, weighed 2.4 g. Two recrystallizations from heptane gave the analytically pure material which melted at 51° (2), indicating 72% secondary alcohol as read from the phase diagram (2).

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.

Found: C, 78.56; H, 6.87.

In the procedure for the separation of the isomers formed in the reaction of *o*-nitrostyrene oxide with phenoxide ion, the reddish oil (5.8 g.), phthalic anhydride (7.4 g., 0.05 mole), pyridine (5 cc.), and dioxane (25 cc.) were allowed to stand at room temperature for five hours, then dissolved in ether and washed with a solution of hydrochloric acid in water. Extraction with three 50-cc. portions of 7.5% sodium bicarbonate removed the half-ester, which was then hydrolyzed by warming after the addition of sodium hydroxide (4 g.). This gave 2.0 g. oil (36.4% of recovered material). The ether solution of the unesterified oil was freed of ether, warmed with 4% sodium hydroxide (100 cc.), and then extracted with ether to recover 3.5 g. of a reddish oil (63.6% of recovered material).

The latter fraction gave a *p-nitrobenzoate*, which was readily purified to m.p. 132–133° from ethanol-water. This was derived from *2-phenoxy-1-(2-nitrophenyl)ethanol.*

Anal. Calc'd for $C_{21}H_{16}N_2O_7$: C, 61.76; H, 3.95.

Found: C, 62.06; H, 4.25.

The oil from which this *p*-nitrobenzoate was made was analytically pure although possibly contaminated by the isomeric primary alcohol.

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05.

Found: C, 64.92; H, 5.17.

When the oil was reduced and deaminated, the product, after two recrystallizations from heptane, melted at 62–64° alone and when mixed with authentic 2-phenoxy-1-phenylethanol (2). This indicated that the oil was largely, if not entirely, the secondary alcohol.

However, the more easily esterified portion of the mixture, the 2.0 g. of oil aforementioned, did not give a pure *p*-nitrobenzoate. Another esterification by phthalic anhydride in dioxane and pyridine, this time for four hours, also failed to produce a fraction capable of yielding a pure *p*-nitrobenzoate.

The acid-catalyzed reaction of o-nitrostyrene oxide with phenol. To a melt of phenol (9.4 g., 0.1 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) at 40–45° was slowly added *o*-nitrostyrene oxide (4.1 g., 0.025 mole). Unlike the mixtures from the *p*- and *m*-isomers, which discolored mildly under these conditions, the very first portion of *o*-nitrostyrene oxide caused the reaction mixture to turn black. Furthermore, during the addition of about the first 25% of the oxide, in 25 minutes, the reaction was strongly exothermic, while the addition of the remainder of the oxide caused little temperature rise. All of the oxide was added in 50 minutes and the mixture was allowed to stand one hour before adding it to water (150 cc.) and sodium hydroxide (5 g.). By filtration a brown solid was isolated, 1.6 g., m.p. 52–60°. This was purified and identified as *o*-nitrostyrene oxide.

Since it became apparent that the acid-catalyzed reaction took a course unlike that encountered with the *p*- and *m*-isomers, an observation not unexpected (4), no serious attempt was made to isolate and to identify products.

SUMMARY

The reactions of *m*-nitrostyrene oxide and *o*-nitrostyrene oxide with phenoxide ion parallel the behavior of the *p*-isomer under the same conditions, giving mixtures containing 67% and 72%, respectively, of the secondary alcohols. This result is presented to support the postulate of a unimolecular route to the primary alcohols. While the acid-catalyzed reaction of *m*-nitrostyrene oxide with phenol is like that for the *p*-isomer, *o*-nitrostyrene oxide shows a marked deviation.

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