[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

THE REACTION OF *p*-NITROSTYRENE OXIDE WITH PHENOL

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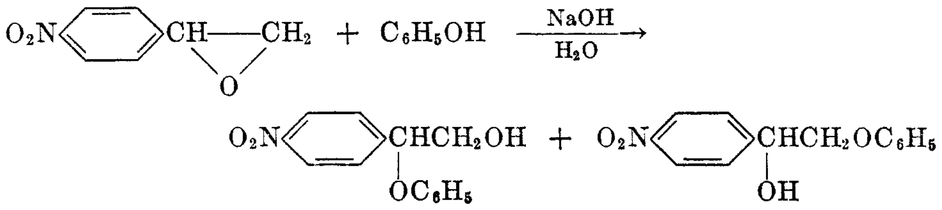
The role of the phenyl group in directing the ring opening reactions of styrene oxide has been discussed in several recent articles (1–8). In particular, the base-catalyzed reactions of styrene oxide have been interpreted in terms of a +I effect (2), a −I effect (3), and a steric effect (5, 8) as exerted by the phenyl group, assuming that a bimolecular substitution (S_N2) reaction obtained. Resonance stabilization of a transitory state has also been cited (4, 8, 9) in explaining experimental results. It now appears (6) that a unimolecular mechanism can predominate in the "base-catalyzed" reaction of styrene oxide with phenol, a circumstance characterized by the preferential formation of the primary alcohol as induced by a resonance-stabilized transitory state.

The present work was undertaken in an attempt to clarify the effect of the phenyl group in directing the ring opening reactions of styrene oxide. It seemed reasonable to expect that *p*-nitrostyrene oxide would be useful for this purpose. The base-catalyzed reaction would presumably take the course shown



I II

to produce I or II or a mixture of I and II. Since the *p*-nitrophenyl group would be expected to show a −I (electron-attracting) effect, one can then speculate that the primary alcohol (I) should be formed predominantly or exclusively. The *p*-nitrophenyl group would not be expected to exhibit +I characteristics, so the secondary alcohol (II) should not be found except possibly in small quantities. Alternatively, if the *p*-nitrophenyl group exerted a steric effect, then II would be expected to be the favored product.

In our work it was found that the base-catalyzed reaction of *p*-nitrostyrene oxide with phenol formed good yields of an alkali-insoluble mixture. This mixture was easily separated into a crystalline fraction and an oil fraction. The crystalline material, comprising about two-thirds of the total, was then catalytically reduced and subsequently deaminated to give 2-phenoxy-1-phenyl-

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ethanol (4), a secondary alcohol, as shown by a mixture melting point determination. When the oil was similarly treated, it formed 1-phenoxy-1-phenylethanol (4), a primary alcohol. Also, when the mixture of alkali-insoluble products from the reaction was reduced and deaminated and the composition then determined by use of a phase diagram (4), concordant results were obtained. This is believed to indicate that the bimolecular nucleophilic substitution occurred at the least substituted carbon in spite of a −I effect operating on the *alpha* carbon. It is apparently the steric effect of the *p*-nitrophenyl group which is dominant in directing the ring opening. It follows that the steric effect of the phenyl group has a similar role in the bimolecular displacement reactions of styrene oxide (6). The formation of the primary alcohol is believed to result, in part at least, from a unimolecular ring opening mechanism (10). That steric effects are important in displacement reactions has previously been deduced by others to explain experimental findings (13, 14, 8). The present data lends substantial support to this prior evidence.

The acid-catalyzed reaction of *p*-nitrostyrene oxide with phenol proceeded to form large amounts of alkali-soluble materials. However, the presence of I in the alkali-insoluble fraction from the reaction was demonstrated. The acid-catalyzed reaction of styrene oxide with 2-naphthol (7) gives a mixture that is relatively less complex, so more promise is held for a study of the acid-catalyzed reaction of *p*-nitrostyrenie oxide with 2-naphthol instead of phenol (10).

The preparat on of *p*-nitrostyrene oxide followed the sequence: *p*-nitroacetophenone → *p*-nitrophenacyl bromide → *p*-nitrostyrene bromohydrin → *p*-nitrostyrene oxide. Each step gave a 90% yield or better.

EXPERIMENTAL[3]

p-Nitrostyrene bromohydrin. *p*-Nitroacetophenone, prepared by the procedure of Long and Troutman (15), was brominated to *p*-nitrophenacyl bromide in the manner reported by Engler and Zielke (16). The *p*-nitrophenacyl bromide (81.3 g., 0.33 mole, m.p. 97–99°) in isopropyl alcohol (500 cc.) was reduced with a 1 *molar* solution (350 cc., 0.35 mole) of aluminum isopropoxide in isopropyl alcohol. After distillation of the isopropyl alcohol-acetone mixture (575 cc.) in two hours, the distillate gave a substantially negative test for acetone. The reaction mixture was poured into ice and hydrochloric acid; the oil which separated soon solidified as an orange-tan solid. This was washed with water and dried under a vacuum over calcium chloride; yield, 74 g. (90%), m.p. 83–86°. Recrystallization from benzene-heptane with Norit treatment gave nearly white needles, m.p. 86–87°.

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

Found: C, 39.25; H, 3.58.

This reduction was also accomplished by the shorter procedure of Winstein, *et al.*, (17) with essentially the same results.

p-Nitrostyrene oxide. The bromohydrin (61.9 g., 0.252 mole, m.p. 85–87°) was stirred with sodium hydroxide (12 g., 0.3 mole) in water (300 cc.) at 50° for 15 minutes and an additional hour without heating. The reaction appeared to be very rapid, the yellow color of the oxide being evident within five minutes. A solid phase was present at all times. The slurry was filtered, the oxide washed well with water, and dried under a vacuum over calcium chloride. This product, 41.3 g. (99.5%) melted at 82–85°. One recrystallization

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[3] All melting points and boiling points are uncorrected. Microanalyses are by the Elek Micro Analytical Laboratories and by Mr. Joseph Pirie of this Department.

from ethanol gave light yellow needles, m.p. 84–86°. The analytical sample melted at 85–86°. Although the bromohydrin and the oxide have nearly identical melting points, they give a large depression when mixed and melted.

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

Found: C, 58.24; H, 4.53.

Base-catalyzed reaction of p-nitrostyrene oxide with phenol. p-Nitrostyrene oxide (4.1 g., 0.025 mole) was added to phenol (7.0 g., 0.075 mole) in sodium hydroxide (1 g., 0.025 mole) and water (4 cc.) at the temperature of a boiling water-bath. The stirred mixture, one phase, was initially dark red but soon darkened and was nearly black at the end of the two-hour reaction period. This mixture was added to sodium hydroxide (4 g.) in water (100 cc.) to remove excess phenol. The insoluble product was a dark oil which solidified and could be isolated by filtration. Usually the solid was taken up in ether and the resulting reddish solution dried over sodium sulfate. Evaporation of the ether under a vacuum left 5.4 g. (83.3%) of a sticky tan solid. Yields of over 90% were often obtained at this point.

The foregoing solid was dissolved in ethanol, treated with Norit, and then allowed to crystallize after the addition of water. Tan needles, 3.4 g. (52.5%), m.p. 88–93° were thus isolated. The filtrate was reserved. Recrystallization of the solid gave very faintly yellow needles, m.p. 90–93°, and further recrystallization did not change this melting point. The melting point indicated that this *2-phenoxy-1-p-nitrophenylethanol* (II) was impure although the analytical values were acceptable.

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

Found: C, 65.11; H, 5.13.

The *p-nitrobenzoate* was prepared (18); m.p. 122–123° after recrystallization from ethanol.

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

Found: C, 61.68; H, 3.89.

To the mother liquor reserved above was added excess water and the separated oil was extracted with ether. After this solution was dried over sodium sulfate, the ether was evaporated to leave 1.7 g. (26.2%) of a red oil. All attempts to induce crystallization of the oil failed. It was distilled unchanged (b.p. 210–215°/1 mm.), as shown by formation of the same *p*-nitrobenzoate before and after distillation. It gave the reactions of *2-phenoxy-2-p-nitrophenylethanol* (I) as shown later. A pure *p-nitrobenzoate* was easily prepared (18) from the oil and recrystallized from ethanol, m.p. 144–145°.

Anal. Calc'd for $C_{21}H_{16}N_2O_7$: C, 61.76; H, 3.95; N, 6.86.

Found: C, 62.16; H, 3.92; N, 7.04.

Assuming the identity of the crystalline product and the oil as indicated, the mixture contained 66.7% of the secondary alcohol.

Structure elucidation. The reactions involved in the determination of the structure of the products mentioned consisted in catalytic reduction to the amine and subsequent deamination to known products.

The crystalline reaction product, heretofore designated as 2-phenoxy-1-*p*-nitrophenylethanol (II), m.p. 90–93°, was reduced with hydrogen and Raney nickel in ethanol at 38 p.s.i. and room temperature. Reduction proceeded rapidly, and at the end of 30 minutes the catalyst was filtered off. Evaporation of the ethanol left a 73.8% yield of the amine which, after one recrystallization from ethanol-water, melted at 80–84°, white needles. Reduction with stannous chloride and hydrochloric acid was unsatisfactory.

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59.

Found: C, 72.78; H, 6.36.

The impure amine was diazotized and deaminated in hypophosphorous acid (19). The amine (0.46 g.) was dissolved in 50% hypophosphorus acid (4 g.), and water (3.5 cc.) was added to the clear solution. To this solution, cooled in an ice-salt bath, was added sodium nitrite (0.14 g.) in water (1 cc.). After 30 minutes in the bath and one hour at room temperature, the solid that had formed was filtered off, washed with water, and dried to obtain 0.3 g. (70%) of a cream-colored material, m.p. 50–61°. One recrystallization from heptane (Norit) gave white needles, m.p. 61–64° which melted over the same range when mixed with authentic 2-phenoxy-1-phenylethanol (4), m.p. 63–64°.

The reaction product that remained as an oil and that gave a *p*-nitrobenzoate, m.p. 144–145°, was similarly reduced (80%) and then diazotized and deaminated (53% crude) to give white needles, m.p. 76–80° after one recrystallization. When mixed with authentic 2-phenoxy-2-phenylethanol (4), m.p. 80–81°, the melting point was 76–81°.

An additional indication was obtained of the structure of the components and the ratio of isomers in the alkali-insoluble mixture from *p*-nitrostyrene oxide and phenol. The crude alkali-insoluble mixture, after evaporation of the ether, was reduced catalytically, diazotized, and deaminated in the manner employed for the separated materials. In this manner, from *p*-nitrostyrene oxide (4.1 g., 0.025 mole), there was obtained 1.7 g. (31.8%) of a solid, b.p. 150–160°/2 mm., whose composition, as determined by use of a phase diagram (4), was 64% 2-phenoxy-1-phenylethanol. The solid gave the correct analytical values for a mixture of 2-phenoxy-1-phenylethanol and 2-phenoxy-2-phenylethanol.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.
Found: C, 78.71; H, 6.62.

This result agrees with the composition determined by the separation of the reaction products by fractional crystallization.

Acid-catalyzed reaction of p-nitrostyrene oxide with phenol. *p*-Nitrostyrene oxide (4.95 g., 0.03 mole) was added to a solution of phenol (11.75 g., 0.125 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) at 40°. The addition of the oxide over a 20-minute period maintained the temperature of the reaction mixture at 38–40°. After ten minutes more, the slightly reddish solution was added to sodium hydroxide (10 g.) in water (100 cc.). An insoluble oil was extracted with ether and dried over sodium sulfate. Evaporation of the ether under a vacuum left 2.9 g. (37.3%, assuming ether-alcohols as products) of an amber oil. When the reaction was run at 100° for 10 or 60 minutes, the same yield of alkali-insoluble oil was obtained. In all instances the alkaline solution of the reaction mixture, after removal of the alkali-insoluble products, gave a viscous red oil when acidified.

The alkali-insoluble oil formed a *p*-nitrobenzoate, m.p. 90–135° crude and m.p. 130–145° after one recrystallization from ethanol. A mixture of the latter material with the pure *p*-nitrobenzoate of I did not change the melting point range. When the oil was reduced catalytically and then deaminated, it was possible to isolate white needles, m.p. 75–80°, mixture melting point with pure 2-phenoxy-2-phenylethanol, 77–81°. This indicates only that the alkali-insoluble oil contained I.

The alkali-soluble fraction of the products from this type of reaction is known to be complex (7). There is the possibility of isomeric alkylated phenols being formed by a mechanism presumed to be unimolecular (7), as well as products resulting from the rearrangement of the oxide to the substituted phenylacetaldehyde, which then reacts with the phenol. When the present alkali-soluble oil was esterfied with phthalic anhydride and then subjected to the conditions used in a previous study of the intramolecular displacement of carboxylate ion (11, 12), a solid was obtained, m.p. 77–79°, which is presumed to be the benzofuran that would result from the cyclization of 2-(2-hydroxyphenyl)-2-(4-nitrophenyl)ethanol, a likely component of the alkali-soluble mixture. Further study of the acid-catalyzed reaction has been confined to the use of 2-naphthol as the phenolic reactant (10).

SUMMARY

p-Nitrostyrene oxide was prepared and found to undergo a base-catalyzed reaction with phenol to form a mixture of isomeric ether-alcohols of which the secondary alcohol constituted about two-thirds of the total. The formation of the secondary alcohol is believed to arise from the bimolecular displacement

reaction that is directed by the steric effect of the *p*-nitrophenyl group. The major portion of the products from the acid-catalyzed reaction was alkali-soluble.

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