[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLORADO A. AND M. COLLEGE]

The Reaction of 2,4,6-Trimethylstyrene Oxide with Phenol[1]

BY CYRUS O. GUSS

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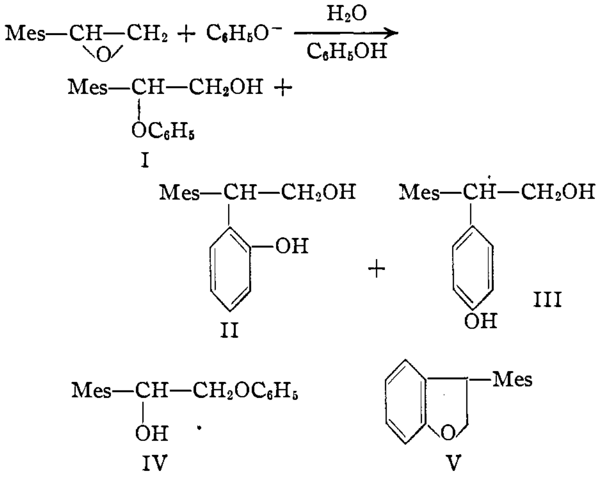
2,4,6-Trimethylstyrene oxide was prepared by solvolysis of the dibromide to the bromohydrin and subsequent treatment of the latter with sodium hydroxide. Reaction of the oxide with phenoxide ion produced the primary alcohol principally and products of nuclear attack. This behavior substantiates the concept of a unimolecular ring opening and the absence of prohibitive steric effects in the reaction of styrene oxides with phenoxide ion to form primary alcohols.

Acetomesitylene, 2,4,6-trimethylbenzoic acid, ethyl 2,4,6-trimethylbenzoate and similarly constituted compounds show a great reluctance to react when an attack on the carbonyl carbon atom is involved.[2] For 2,4,6-trimethylstyrene oxide, a consideration of atomic models and bond distances[3] indicates that free rotation between the oxide ring and the benzene ring is restricted and that a S_N2 attack on the α-carbon atom must be hindered, if not prohibited. Because of this ortho effect, and also the inductive effect of the methyl groups, it follows that, if the opening of the oxide ring in 2,4,6-trimethylstyrene oxide is by way of a bimolecular nucleophilic substitution reaction, attack at the α-carbon atom ought to be less probable than attack at the β-carbon atom. If the ring opening reaction proceeds unimolecularly, steric effects would not be expected to be the directing influence; instead, the resonance stabilization of the resulting carbonium ion, here aided by the methyl groups, would become one of the important factors.

The present investigation was activated by a belief in the validity of this point of view and the desire to obtain more data bearing on the proposal that, with styrene oxide, attack at the α-carbon atom might be influenced by the size of the attacking reagent.[4]

The sequence used in the preparation of 2,4,6-trimethylstyrene oxide proceeded from 2,4,6-trimethylstyrene to 2,4,6-trimethylstyrene dibromide, thence to the bromohydrin by solvolysis of the dibromide in water–dioxane, and finally to the oxide by treatment of the bromohydrin with sodium hydroxide. Purification of the intermediates was not necessary.

The reaction of 2,4,6-trimethylstyrene oxide with phenoxide ion in phenol and water was carried out as in previous work with other styrene oxides.[5] If the reaction proceeded with unimolecular ring opening, the equation shown would indicate the expected products. On the other hand, a bimolecular ring opening might reasonably be expected to lead predominantly to the secondary alcohol IV.



The facile solvolysis of 2,4,6-trimethylstyrene dibromide demonstrated the definite tendency for ionization to occur at the α-carbon atom. From the reaction of the oxide with phenoxide ion, the primary alcohol I was isolated, probably mixed with some of the secondary alcohol IV. The ortho-substituted phenol-alcohol II was presumably present since, by running a cyclization reaction on the alkali-soluble material, a compound having the chemical behavior and correct analysis for the dihydrofuran V was isolated. None of the secondary alcohol IV was isolated, but its presence in minor amount was not excluded. Although the isomeric phenol-alcohol III was a probable product, none was found.

From the acid-catalyzed reaction of 2,4,6-trimethylstyrene oxide with phenol, only products of nuclear attack and polymeric oxide were observed.

The secondary alcohol IV was synthesized and shown to be unlike the predominant alcohol from the reaction of the oxide with phenoxide ion.[6] Synthesis of the primary alcohol I led to the identification of this alcohol as the major constituent of the mixture from the oxide–phenoxide reaction.

These results are in accord with the concept of a unimolecular ring opening and the absence of prohibitive steric effects in the formation of primary alcohols from styrene oxides. If the size of the nucleophilic reagent were a dominant factor,[4] then certainly 2,4,6-trimethylstyrene oxide should allow considerably less attack at the α-carbon atom than would styrene oxide. The observed results contradict this circumstance.

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(1) Scientific Series Paper No. 400 of the Experiment Station.

(2) A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 318; G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 378.

(3) G. L. Cunningham, *et al.*, *J. Chem. Phys.*, **17**, 211 (1949); *ibid.*, **19**, 676 (1951).

(4) R. M. Adams and C. A. VanderWerf, THIS JOURNAL, **72**, 4368 (1950).

(5) (a) C. O. Guss, *ibid.*, **71**, 3460 (1949); (b) C. O. Guss and H. G. Mautner, *J. Org. Chem.*, **16**, 887 (1951); (c) C. O. Guss, *ibid.*, **17**, 678 (1952); (d) C. O. Guss, THIS JOURNAL, **74**, 2561 (1952).

(6) The reaction of 2,4,6-trimethylphenylacetaldehyde with phenol has been studied in experiments not reported here. No compound having the properties corresponding to those of the primary alcohol I was detected.

Experimental[7]

2,4,6-Trimethylstyrene Dibromide.—Acetomesitylene was reduced with lithium aluminum hydride in quantitative yield to the corresponding carbinol, m.p. 67–71° crude (lit.[8] m.p. 71°). This crude product was dehydrated to 2,4,6-trimethylstyrene in 88% yield by the method of Brooks,[9] b.p. 88° (12 mm.), $n^{20}\mathrm{D}$ 1.5323 (lit.[10] b.p. 89.9° (14 mm.), $n^{20}\mathrm{D}$ 1.5323).

To 2,4,6-trimethylstyrene (14.6 g., 0.1 mole) in ether (100 cc.), cooled in an ice-salt-bath, was added bromine (16 g., 0.1 mole) in chloroform (50 cc.) in 40 minutes. Evaporation of the solvent under reduced pressure left 31 g. (100%), light amber oil, $n^{20}\mathrm{D}$ 1.5925 ± 0.0005. Attempts to distil this oil under reduced pressure resulted in some decomposition by loss of hydrogen bromide to give what is believed to be **1-bromo-2-mesitylethylene**, m.p. 55–56°, from dilute acetic acid as white needles (lit.[11] m.p. 53°).

Anal. Calcd. for $C_{11}H_{13}Br$: C, 58.68; H, 5.82. Found: C, 58.54; H, 5.88.

The purest dibromide obtained boiled at 142–143° (4 mm.), $n^{20}\mathrm{D}$ 1.5960.

Anal. Calcd. for $C_{11}H_{14}Br_2$: C, 43.16; H, 4.61. Found: C, 43.53; H, 4.70.

Because of this tendency to lose hydrogen bromide, only crude dibromide was used in subsequent experiments unless otherwise stated.

2,4,6-Trimethylstyrene Bromohydrin.—This solvolysis procedure was patterned after that previously used with *p*-methoxystyrene dibromide.[5d] 2,4,6-Trimethylstyrene dibromide (6.1 g., 0.02 mole, $n^{20}\mathrm{D}$ 1.5960) in dioxane (35 cc.) and water (35 cc.) was stirred at the temperature of a boiling water-bath for 10 minutes. Approximately one bromine was removed by this treatment as shown by a Volhard titration. The resulting mixture, still milky, was diluted with water and extracted with ether. After this solution was dried over anhydrous sodium sulfate, evaporation of the ether under reduced pressure left 4.85 g. (100%) of a colorless oil, $n^{20}\mathrm{D}$ 1.5540. A simple distillation at 124–125° (2 mm.) gave a colorless, viscous oil, $n^{20}\mathrm{D}$ 1.5675, evidently still somewhat impure.

Anal. Calcd. for $C_{11}H_{15}OBr$: C, 54.33; H, 6.22. Found: C, 55.53; H, 6.34.

2,4,6-Trimethylstyrene Oxide.—The route to the oxide did not require the isolation of pure intermediates. Thus, 2,4,6-trimethylstyrene (14.6 g., 0.1 mole) in ether (100 cc.) was brominated in the cold with a solution of bromine (16 g., 0.1 mole) in chloroform (50 cc.). After evaporation of the solvent under reduced pressure, the dibromide was dissolved in dioxane (150 cc.) and water (150 cc.) added. This dispersion was stirred at 50–51° for 1 hour to form the bromohydrin. The temperature and time employed for this solvolysis were chosen after a study of the reaction showed that at room temperature the rate was inconveniently slow while at reflux temperature the further solvolysis of the bromohydrin to 2,4,6-trimethylphenylacetaldehyde was sufficiently rapid to jeopardize the purity of the desired oxide.[12]

The cooled mixture of the bromohydrin in water–dioxane was now treated with sodium hydroxide (10 g.). After being stirred for 15 minutes without heating, all of the bromine initially present in the dibromide was now ionic. The mixture was diluted with water, extracted with ether, and the ether solution dried over anhydrous potassium carbonate. After removal of the ether, the residual oil, $n^{20}\mathrm{D}$ 1.5337, was distilled in a modified Claisen having 2 inches of $^1/_8$ inch glass helices. The fraction boiling at 93–95° (2 mm.), $n^{20}\mathrm{D}$ 1.5280, was the desired oxide, 13.7 g. (84.5% based on the trimethylstyrene). A higher boiling material remained as a residue. The analytical sample of the oxide boiled at 93–94° (2 mm.), $n^{30}\mathrm{D}$ 1.5235, m.p. 29°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.09; H, 8.80.

This oxide did not give a Schiff test in 1 hour although addition of a small amount of 2,4,6-trimethylphenylacetaldehyde produced a positive test within 5 minutes. The oxide was stored for 1 month at room temperature without change in melting point; however, the oxide eventually suffered alteration, and storage in a refrigerator was resorted to when immediate use of the material was not contemplated.

The Reaction of 2,4,6-Trimethylstyrene Oxide with Phenoxide Ion.—The oxide (9.7 g., 0.06 mole) was added in one portion to a solution of phenol (18.8 g., 0.2 mole), sodium hydroxide (2.4 g., 0.06 mole) and water (8 cc.) at the temperature of a boiling water-bath. This one-phase mixture was stirred and heated for 4 hours and formed a dark red solution. After the mixture was poured into iced water containing sodium hydroxide (8 g.) the viscous, insoluble material was taken up in ether and dried over anhydrous potassium carbonate. Evaporation of the ether left 10.7 g. (69%), which was distilled from a Claisen flask. There was obtained 0.5 g. as a forefraction, which gave a Schiff test and presumably contained 2,4,6-trimethylphenylacetaldehyde, and 6.4 g. (41.7%), $n^{20}\mathrm{D}$ 1.5737, b.p. 174–176° (3 mm.), as a very viscous, clear liquid, believed to be chiefly **2-phenoxy-2-(2,4,6-trimethylphenyl)-ethanol** (I). The higher boiling residue (b.p. up to 215° (3 mm.) and above) was not investigated.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.37; H, 8.09.

A **p-nitrobenzoate** (71%, m.p. 110–112°) formed from material so obtained melted at 112.5–113.5°, from dilute ethanol as very pale yellow leaves.[13] The presence of IV as a minor fraction of the total product appears probable.

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.09; H, 5.72. Found: C, 70.79; H, 5.86.

The **3,5-dinitrobenzoate**, recrystallized from ethanol, melted at 130–131°.[13]

Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92. Found: C, 64.09; H, 4.83.

The purest **α-naphthylurethan** obtained melted at 140–142°.

Anal. Calcd. for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40. Found: C, 79.05; H, 6.83.

Each of these derivatives depressed the melting point of the corresponding derivative of IV.

The alkali-soluble material from the reaction of the oxide with phenoxide ion was examined briefly. This fraction, from two runs as just described, phthalic anhydride (15 g.), pyridine (10 cc.) and dioxane (50 cc.) were held at room temperature for 96 hours. The mixture was then dissolved in ether, washed with dilute hydrochloric acid and extracted with four 50-cc. portions of 4% sodium bicarbonate. To the clear bicarbonate extract was added sodium hydroxide (2 g.) in water (40 cc.) and the solution heated for 30 minutes. An insoluble oil was extracted with ether, dried over anhydrous potassium carbonate, and the solvent evaporated to leave 2.8 g. of oil, which slowly solidified. Recrystallization from dilute ethanol gave plates, m.p. 74–75°, assigned the structure **3-(2,4,6-trimethylphenyl)-2,3-dihydrobenzofuran** (V). This structure was inferred from the analyses, the mode of formation, and the fact that analogous compounds have been similarly isolated in our previous studies on the reactions of styrene oxides with phenols.[5]

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.71; H, 7.86.

No other pure compounds were isolated from the alkali-soluble fraction of the oxide-phenoxide reaction although attempts were made to do so, and additional compounds were undoubtedly present.

The Acid-catalyzed Reaction of 2,4,6-Trimethylstyrene Oxide with Phenol.—The oxide (4.9 g., 0.03 mole) was added in 15 minutes, with cooling, to a melt of phenol (9.4 g., 0.1 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) held at 40–45°. After the viscous solution was poured into water containing sodium hydroxide (5 g.), extraction with ether left an aqueous solution and a small amount of an insoluble white solid (not investigated). The ether solution was dried over anhydrous potassium carbonate and the solvent evaporated to give 3.3 g. of a viscous oil. Distillation separated the oil into a small forefraction, shown to contain

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(7) All temperature measurements are uncorrected.

(8) A. Klages and P. Allendorff *Ber.*, **31**, 998 (1898).

(9) L. A. Brooks, THIS JOURNAL, **66**, 1295 (1944).

(10) F. R. Buck, K. F. Coles, G. T. Kennedy and F. Morton, *J. Chem. Soc.*, 2377 (1949).

(11) F. Böck, G. Lock and K. Schmidt, *Monatsh.*, **64**, 399 (1934).

(12) The conversion of bromohydrins to aldehydes is being studied and will be reported at some other time.

(13) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 193.

the dihydrofuran (V), m.p. 74–75° by isolation and mixed m.p., and a major fraction, b.p. 190–205° (2 mm.), which cooled to a glassy solid. This latter material was probably largely polymeric oxide.

Anal. Calcd. for $(C_{11}H_{14}O)_n$: C, 81.44; H, 8.70. Found: C, 81.57; H, 8.13.

The alkali-soluble fraction from the acid-catalyzed reaction of the oxide with phenol was processed in the same manner described for the alkali-soluble fraction of the oxide–phenoxide reaction. A small amount of the dihydrofuran V was isolated after the cyclization step. The ether solution from the bicarbonate extraction of the esterification mixture was freed of solvent, heated with dilute sodium hydroxide, and again extracted with ether. The aqueous layer was now treated with Dry Ice. This caused the separation of an oil which, after washing with water to remove residual phenol, was recrystallized from dilute ethanol, 0.8 g., m.p. 153–154°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.66; H, 7.94.

This compound is isomeric with the ether-alcohol I, it is phenolic, but it is not esterified under the conditions used. Its structure is not entirely clear to us.

Preparation of 2-Phenoxy-1-(2,4,6-trimethylphenyl)-ethanol (IV).—The preparation of 2,4,6-trimethylphenacyl bromide was readily accomplished by the bromination of acetomesitylene in glacial acetic acid, or by the method of Jacobs and Heidelberger[14] from mesitylene and bromoacetyl bromide.

A reaction mixture, consisting of 2,4,6-trimethylphenacyl bromide (24.1 g., 0.1 mole, m.p. 55–56°), phenol (10 g., 0.106 mole), sodium hydroxide (4 g., 0.1 mole), dioxane (50 cc.) and water (35 cc.), was held at reflux temperature with stirring for 4 hours. It was then poured into water and extracted twice with ether. The aqueous layer analyzed for 77% of the theoretical bromide ion. The ether layer was dried over anhydrous sodium sulfate and then distilled from a modified Claisen flask having 2 inches of $^1/_8$ inch glass helices. The **phenoxymethyl mesityl ketone** (12.3 g., 48.4%) boiled at 180–192° (4–7 mm.), n^{20}_{D} 1.5655.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.80; H, 7.45.

Reduction of this ketone with lithium aluminum hydride gave the ether-alcohol IV (80%) as a viscous, colorless liquid, b.p. 185–191° (3–4 mm.), n^{20}_{D} 1.5730.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.26; H, 7.64.

The *p*-**nitrobenzoate**,[13] from dilute ethanol, melted at 114.5–115.5°.

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.09; H, 5.72. Found: C, 70.85; H, 6.03.

The mixture of this *p*-nitrobenzoate with that obtained from the primary alcohol I melted at 95–113°.

The **3,5-dinitrobenzoate**, from ethanol, melted at 126–127°.[13]

Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92. Found: C, 64.07; H, 4.97.

A mixture of the 3,5-dinitrobenzoates of IV and the oxide–phenol reaction product melted at 110–129°.

The **α-naphthylurethan** of IV melted at 138.5–139.5°.

Anal. Calcd. for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40. Found: C, 78.79; H, 6.68.

α-Naphthylurethans of IV and the oxide–phenol reaction product melted at 120–140° when mixed.

Preparation of 2-Phenoxy-2-(2,4,6-trimethylphenyl)-ethanol (I).—A preparation of α-bromo-2,4,6-trimethylphenylacetyl bromide,[15] not purified by distillation, was poured into excess phenol and the mixture warmed for a few minutes. This was then poured into water, extracted with ether, and finally distilled in vacuum to obtain a relatively poor yield of a compound presumed to be phenyl α-bromo-2,4,6-trimethylphenylacetate. This ester (6.3 g.) was added to a mixture of phenol–sodium phenoxide prepared from phenol (14 g.) and sodium (0.5 g.). After being heated 6 hours in a boiling water-bath, the mixture was poured into water, treated with Dry Ice, extracted with ether, and the aqueous layer acidified. The solid thus obtained weighed 1.8 g. after one recrystallization from dilute ethanol. The pure, white needles of **α-phenoxy-2,4,6-trimethylphenylacetic acid** melted at 139–140°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.46; H, 6.94.

This acid (0.5 g.) was reduced with lithium aluminum hydride, and the resulting clear, viscous oil was converted to its *p*-nitrobenzoate (93% yield from the substituted phenylacetic acid), m.p. 112–113.5° alone or when mixed with the *p*-nitrobenzoate derived from the oxide–phenoxide product.

FORT COLLINS, COLORADO

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[14] W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 455 (1915).

[15] R. C. Fuson, L. J. Armstrong and W. J. Shenk, Jr., THIS JOURNAL, **66**, 964 (1944).

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Studies in the Terpene Series. XVI.[1] Hydrogenolysis of Pinane in a Flow Type Apparatus in the Presence of Hydrogenation Catalysts

BY V. N. IPATIEFF,[1a] F. J. PAVLIK[2] AND HERMAN PINES

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The hydrogenolysis of pinane was studied in a flow type apparatus in the presence of nickel–kieselguhr, nickel–alumina, copper–alumina and nickel catalysts. The hydrogenolysis was carried out under 56 atmospheres of pressure and at temperatures ranging from 225 to 295°, using a molar ratio of hydrogen to pinane varying from 2.1 to 11.7. From 35 to 67% of the reacted pinane consisted of alkylcyclopentanes admixed with small amounts of bicyclic dihydroterpenes, the remainder being alkylcyclohexanes. The presence of alkylcyclopentanes indicates that skeletal isomerization accompanied the hydrogenolysis of pinane.

In a previous paper[3] it was shown that pinane undergoes hydrogenolysis when reacting with hydrogen at 175° in the presence of a nickel–kieselguhr catalyst and at 100 atmospheres of hydrogen pressure. The reaction product contained 65% of 1,1,2,3-tetramethylcyclohexane and smaller amounts of 1-methyl-2-isopropyl-, 1-methyl-4-isopropyl- and 1,1,2,5-tetramethylcyclohexane. It was also observed[4] that by using Raney nickel or copper–alumina as catalysts the hydrogenolysis of pinane yielded, in addition to the above-mentioned alkylcyclohexanes, also alkylcyclopentanes. Owing to the difference in the results obtained it was

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[1] For Paper XV of this series see V. N. Ipatieff, G. Czajkowski and H. Pines, *J. Org. Chem.*, **17**, 1431 (1952); (a) Deceased November 29, 1952.

[2] Universal Oil Products Company Predoctorate Fellow 1949–1951.

[3] V. N. Ipatieff, H. Pines and M. Savoy, THIS JOURNAL, **69**, 1948 (1947).

[4] V. N. Ipatieff, G. Czajkowski and H. Pines, unpublished results.