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

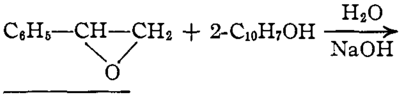
Nuclear Alkylation in the Alkali-catalyzed Reaction of Styrene Oxide with 2-Naphthol

BY CYRUS O. GUSS AND LEONARD H. JULES[1]

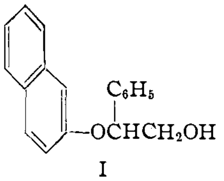
Ethers have been obtained so consistently from the alkali-catalyzed reaction of olefin oxides with alcohols and with phenols that this course of the reaction is presumed to be relatively general. However, there have been reports[2,3] of attack on the nucleus of a phenol in the acid-catalyzed interaction with olefin oxides. It is shown in the following report that the alkali-catalyzed reaction of styrene oxide with 2-naphthol produces the expected ether type of products and also a greater or lesser amount of an alkylated naphthol.

Boyd and Marle[4] investigated the alkali-catalyzed reaction of ethylene oxide and propylene oxide with a number of phenols, including 2-naphthol, and reported good yields of the ethers in every case. Several others[3,5] have reported the results from the use of a variety of olefin oxides, including styrene oxide, with phenol itself, and in these cases the alkali-catalyzed reaction gave the ethers as the only reported product. In the foregoing studies there was no apparent reason to expect nuclear alkylation of a phenol by an olefin oxide in alkaline medium, and, furthermore, since relatively good yields of the ethers were commonly obtained, little effort was made to examine the small amount of reaction product not accounted for as ethers. This pattern would probably have been followed in the present work had not the low yield of the isolated ether emphasized the importance of some other reaction.

Subsequent to a study of the acid-catalyzed reaction of styrene oxide with 2-naphthol, it appeared of some importance to determine the nature of the products formed from these reactants in alkaline medium. When the isolation of products from the alkali-catalyzed reaction in water showed the presence of but 12–17% of a pure, alkali-insoluble compound, the alkali-soluble portion of the reaction mixture was inspected for other products. Isolation of a pure compound was achieved in 46–51% yield. Complete characterization of these two products indicated that the reaction had proceeded, in part, as shown.

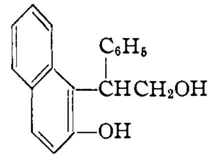


$$\underset{\diagdown\;O\;\diagup}{C_6H_5\text{—}CH\text{—}CH_2} + 2\text{-}C_{10}H_7OH \xrightarrow[NaOH]{H_2O}$$



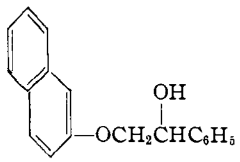
I

+

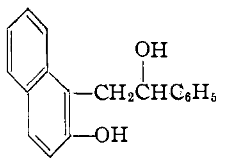


II

Although the oxide ring might have opened to give an ether (III) and a phenol (IV) isomeric with I and II, the formation of these compounds was not evident.



III



IV

Substitution of dioxane for water had been found[3] to increase the relative amount of primary ether–secondary alcohol, analogous to III, in the reaction of styrene oxide with phenol. When dioxane was used in the present work, a 16% yield of the phenol (II) and a 42% yield of a mixture of ether (I) and its isomer (III) were obtained. The composition of the mixture of isomeric ethers was determined by the use of a phase diagram and found to be between 42.5 and 48.5% I. No evidence for the presence of the phenol (IV) isomeric with II was found.

The structures of I and III were determined by comparison with authentic compounds synthesized by the methods[3] used for the preparation of the the analogous compounds obtained from styrene oxide and phenol. The phenol (II) has already been reported.[6]

The structural features necessary to give nuclear alkylation in the alkali-catalyzed interaction of an olefin oxide and a phenol are not clearly defined by these results. Ethylene oxide and propylene oxide[4,5c] have not given nuclear alkylation with 2-naphthol in an alkaline medium, nor has styrene oxide[3] been reported to give nuclear alkylation with phenol in aqueous alkali. Thus, both the structure of the phenolic compound and the olefin oxide are apparently involved in some manner. The isolation of only the single phenol (II) under conditions that gave nearly equal amounts of the isomeric ethers (I and III) seems to indicate that the oxide ring in styrene oxide opens in a specific direction when nuclear alkylation occurs. Additional work is being carried out in an attempt to secure an experimental background for an explanation of this behavior.

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[1] Based on a portion of a thesis submitted by Mr. Leonard H. Jules in partial fulfillment of the requirements for the degree of Master of Science.

[2] Price and Mueller, THIS JOURNAL, **66**, 628 (1944).

[3] Guss, *ibid.*, **71**, 3460 (1949).

[4] Boyd and Marle, *J. Chem. Soc.*, **105**, 2117 (1914).

[5] *E. g.*, (a) Lindeman, *Ber.*, **24**, 2145 (1891); (b) Fairbourne, Gibson and Stephens, *J. Chem. Soc.*, 1965 (1932); (c) Becker and Barthell, *Monatsh.*, **77**, 80 (1947); (d) Sexton and Britton, THIS JOURNAL, **70**, 3606 (1948); (e) Werner and Farenhorst, *Rec. trav. chim.*, **67**, 438 (1948).

[6] Guss and Jules, THIS JOURNAL, **72**, 3462 (1950).

Experimental[7]

Reaction of Styrene Oxide with 2-Naphthol. (a) **In Aqueous Medium**—A solution of 2-naphthol (28.2 g., 0.196 mole) in water (25 cc.) containing sodium hydroxide (4.0 g., 0.1 mole) was heated to the temperature of a boiling water-bath in a three-necked flask equipped with a stirrer, condenser, and dropping funnel. Styrene oxide (12.0 g., 0.1 mole, n^{20}_{D} 1.5351) was added over a thirteen-minute period during which time the mixture turned dark red. After a total time of one hour the reaction mixture, still as one phase, was poured into 200 g. of ice-water containing 4.0 g. of sodium hydroxide. The resulting greenish-blue mixture was extracted with two 100-cc. portions of carbon tetrachloride. and these combined extracts were dried over anhydrous sodium sulfate. The carbon tetrachloride was then removed under vacuum to leave 8.5 g. of a tan residue. Isolation of the pure ether (I) was accomplished by dissolving the residue in heptane, cooling until an insoluble oil separated, and then decanting the heptane solution with subsequent cooling to deposit white needles. The needles were filtered off, and the filtrate was again used to extract the crude product. In this way there was obtained 4.5 g. (17%) of needles, m. p. 103–106°, and 3.6 g. of a brown, gummy residue. The pure product melted at 107–108° and was identified as **2-(2-naphthoxy)-2-phenylethanol** (I) by a mixed melting point determination.

The alkaline solution from the carbon tetrachloride extraction was acidified with acetic acid, and the pink solid that precipitated was filtered off, dried and placed in a sublimation apparatus[8] in which the 2-naphthol was sublimed at 100° and 1 mm. pressure. A total of 12.5 g. (0.087 mole) of 2-naphthol was thus recovered. The last of the 2-naphthol sublimed very slowly, and it is not certain that all that was present was removed. The crystalline cake remaining was dissolved in 30 cc. of hot chloroform, and 30 cc. of carbon tetrachloride was added. The crystals that formed in this solution were filtered, washed with a little heptane, and dried. This light-tan material, 10.3 g., m. p. 120–122°, was identified as **2-(2-hydroxy-1-naphthyl)-2-phenylethanol**[6] (II) by the mixed melting point method. The filtrate was worked up to bring the total yield to 12.3 g. (46.6%).

In another run, using styrene oxide (0.05 mole), 2-naphthol (0.15 mole), sodium hydroxide (0.15 mole) and water (25 cc.), and removing the 2-naphthol from the crude alkali-soluble fraction by steam distillation instead of sublimation, the ether (I) was obtained in 12.1% yield and the phenol (II) in 50.8% yield. An identical experiment was also carried out in which the alkali-soluble fraction was treated with phthalic anhydride and pyridine in dioxane in the manner recently described.[6] By extraction of the half-ester of the phenol (II) with dilute sodium bicarbonate and addition of sodium hydroxide to the extract, a 50.4% yield of the cyclized product, 1-phenyl-1,2-dihydronaphtho(2,1-b)furan,[6] m. p. 94–95°, was isolated.

(b) **In Dioxane.**—In the apparatus used in the foregoing experiments were placed 2-naphthol (28.2 g., 0.196 mole) and dioxane (25 cc.). To this was added small pieces of sodium (2.3 g., 0.1 mole). After the sodium had all reacted, a process hastened by heating, the solution was brought to the temperature obtained by a boiling water-bath. Styrene oxide (12.0 g., 0.1 mole) was then added over a twenty-minute period, and the mixture was heated and stirred for four hours more. This solution was then poured into 200 g. of ice-water containing 6 g. of sodium hydroxide. The alkali-insoluble product was extracted with carbon tetrachloride and worked up by the same method that was used for the similar fraction obtained in aqueous medium. The 18.9 g. of crude product thus isolated gave 7.4 g. of a brown gum and 11.0 g. (41.7%) of a mixture of the isomeric ethers (I and III) which, by the use of a phase diagram drawn from the data in Table I, was found to consist of 42.5% of the primary alcohol (I). One recrystallization of this mixture from heptane gave a product containing 48.5% of I as shown by the phase diagram. The analysis was close to that required for a pure mixture of I and III.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 82.20; H, 6.10.

TABLE I

MELTING POINTS OF KNOWN MIXTURES OF I AND III

I, %	M. p., °C.	I, %	M. p., °C.
30.00	76.0	50.00	84.0
36.36	73.0	60.00	90.0
41.67	77.5	66.67	93.5

This mixture was partially separated into I and III by the method[3] previously used with the analogous mixture resulting from the interaction of styrene oxide and phenol.

The alkali-soluble fraction from the reaction mixture was worked up as before to give 11.2 g. of 2-naphthol by sublimation, 4.3 g. (16.3%) of the phenol (II) and 3.2 g. of a gummy residue. There was no evidence obtained for the formation of the isomeric phenol (IV).

Preparation of 2-(2-Naphthoxy)-2-phenylethanol (I).—Ethyl α-bromophenylacetate[9] (12.2 g., 0.05 mole, n^{20}_{D} 1.5375) in absolute ethanol (10 cc.) was added over a period of forty-five minutes to a refluxing solution of sodium 2-naphthoxide (16.4 g., 0.1 mole) in absolute ethanol (60 cc.). A thick, brown precipitate formed after about half of the ester was added. The mixture was refluxed and stirred for a total period of three hours, then cooled, filtered, and the greenish solid washed with ethanol. This solid was dissolved in water and solid carbon dioxide added, followed by dilute hydrochloric acid. The solid so obtained was washed with water and air-dried; 6.0 g. (43.2%), m. p. 149–152°. Crystallization from ethanol after Nuchar treatment, followed by recrystallization from heptane, gave colorless needles of α-(2-naphthoxy)-phenylacetic acid, m. p. 155–155.5°.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07; neut. equiv., 278. Found: C, 77.69; H, 5.23; neut. equiv., 278.

The ethanol filtrate from the reaction mixture, after dilution with 300 cc. of water, was extracted with ether and the aqueous solution then treated with solid carbon dioxide. The 2-naphthol so precipitated was filtered off and the filtrate acidified to deposit a solid (2.4 g.) which, after crystallization from glacial acetic acid, melted at 186–187°. This was identified as the lactone of α-(2-hydroxy-1-naphthyl)-phenylacetic acid.[6,10]

The anilide of α-(2-naphthoxy)-phenylacetic acid was prepared and crystallized from ethanol–water, m. p. 177–178°.

Anal. Calcd. for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42. Found: C, 81.71; H, 5.51.

When α-(2-naphthoxy)-phenylacetic acid (2.0 g., 0.007 mole) was reduced by the method of Nystrom and Brown[11] with lithium aluminum hydride (0.38 g., 0.01 mole), fine, colorless needles were obtained from dilute acetic acid; 1.3 g. (68.4%), m. p. 104–106°. Recrystallization from heptane was used to obtain the pure 2-(2-naphthoxy)-2-phenylethanol (I), m. p. 107–108°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.81; H, 6.30.

The *p*-nitrobenzoate of this alcohol, obtained as cream-colored needles from ethanol, melted at 117–117.5°.

Anal. Calcd. for $C_{25}H_{19}NO_5$: C, 72.63; H, 4.63. Found: C, 72.83; H, 4.83.

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[7] All melting points are uncorrected. Microanalyses are by the Elek Micro Analytical Laboratories, Los Angeles, California, and the California Institute of Technology, Pasadena, California.

[8] Adams and Johnson, "Laboratory Experiments in Organic Chemistry," The Macmillan Company, New York, N. Y., 1949, p. 85.

[9] Anschütz, *Ann.*, **354**, 127 (1907).

[10] Arventi, *Ann. sci. univ. Jassy*, Pt. I, **23**, 344 (1937).

[11] Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

Preparation of 2-(2-Naphthoxy)-1-phenylethanol (III).—The procedure of Fritz[12] was used to prepare ω-(2-naphthoxy)-acetophenone from 2-naphthol and phenacyl bromide. The product melted at 102–104° compared with m. p. 104–106° reported by Fritz. The oxime derived from this ketone melted at 143–144° while Fritz reported m. p. 144–145°. The 2,4-dinitrophenylhydrazone, crystallized from ethyl acetate, melted at 228.5–229°.

Anal. Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10. Found: C, 65.04; H, 4.16.

Reduction of the ketone with aluminum isopropoxide to the corresponding alcohol, 2-(2-naphthoxy)-1-phenylethanol (III), was accomplished readily (87.5%), m. p. 87–88°. The crystallizing solvent was heptane.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.70; H, 6.16.

The *p*-nitrobenzoate prepared from this alcohol melted at 104–105° after recrystallization from dilute ethanol and then from heptane.

Anal. Calcd. for $C_{25}H_{19}NO_5$: C, 72.63; H, 4.63. Found: C, 72.72; H, 4.75.

Summary

The alkali-catalyzed reaction of styrene oxide with 2-naphthol, in aqueous medium, was found to proceed in part in a manner not previously observed for olefin oxides and phenols under these conditions. In addition to the ether, 2-(2-naphthoxy)-2-phenylethanol (I) there was obtained up to 51% of a naphthol, 2-(2-hydroxy-1-naphthyl)-2-phenylethanol (II).

In dioxane as the solvent the alkali-catalyzed reaction gave a relatively greater amount of the ether (I) and its isomer, 2-(2-naphthoxy)-1-phenylethanol (III). The composition of the isomeric mixture of ethers was determined by the use of a phase diagram.

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RECEIVED FEBRUARY 20, 1950

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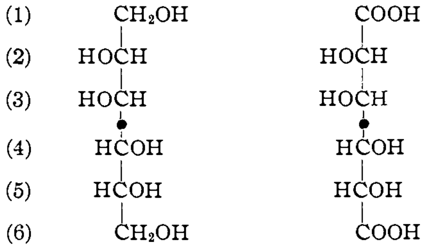
[12] Fritz, *Ber.*, **28**, 3028 (1895).

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

A Direct Proof of the Equivalence of Carbon Atoms 1 and 6 in D-Mannitol and a New Method of Correlating Certain Higher-Carbon Sugars and Alcohols

BY NELSON K. RICHTMYER AND C. S. HUDSON

It has long been recognized in the formulas for D-mannitol (I) and D-mannosaccharic acid (II), each with a center of symmetry between carbon atoms 3 and 4 for 180° rotations within the plane of the paper, that C_1 is equivalent to C_6, C_2 to C_5, and C_3 to C_4. Emil Fischer[1] was the first to draw this conclusion from stereochemical theory and he demonstrated experimentally that it was immaterial whether the C_1 or the C_6 end of the double lactone of D-mannosaccharic acid was reduced with sodium amalgam: one, and only one, hexonic lactone, which was the expected D-mannonic lactone, could be obtained.



$$\begin{array}{lcc}
(1) & CH_2OH & COOH \\
(2) & HOCH & HOCH \\
(3) & HOCH & HOCH \\
(4) & HCOH & HCOH \\
(5) & HCOH & HCOH \\
(6) & CH_2OH & COOH \\
 & \text{I} & \text{II}
\end{array}$$

Utilization of the principle of equivalent symmetry in D-mannitol has enabled one of us[2] to furnish conclusive proof of the structure of turanose. Catalytic hydrogenation of that ketone sugar yielded two alcohols, one of which, the 3-[α-D-glucopyranosyl]-D-mannitol, was found to be identical, by direct comparison of the crystalline nonaacetates, with the 4-[α-D-glucopyranosyl]-D-mannitol obtained by the catalytic hydrogenation of epimaltose. Conversely, if the earlier data[3] suffice to prove the structure of turanose, then the new evidence furnished an experimental proof of the equivalence of the C_3 and C_4 positions in D-mannitol, a result which proves also that C_1 is equivalent to C_6, and C_2 to C_5.

In the present paper we present a simple and more direct experimental proof of the equivalence of carbon atoms 1 and 6 in D-mannitol. This was obtained by desulfurizing D-mannose diethyl mercaptal (III) with Raney nickel and showing that the 1-desoxy-D-mannitol (IVa) thus prepared[4] is identical with the 6-desoxy-D-mannitol (synonym, D-rhamnitol) (IVb) prepared previously in this Laboratory by Haskins, Hann and Hudson.[5] In the earlier work D-mannose was transformed to D-rhamnose (V) through a series of reactions which converted the terminal CH_2OH group at C_6 to a CH_3 group; in the present instance it was the potential CHO group at C_1 that was changed to a CH_3 group. The identity of the two products IVa and IVb thus proves experimentally the

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[1] E. Fischer, *Ber.*, **24**, 1845 (1891).

[2] C. S. Hudson, *J. Org. Chem.*, **9**, 117, 470 (1944).

[3] Especially H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **20**, 773 (1938); E. Pacsu, E. J. Wilson, Jr., and L. Graf, THIS JOURNAL, **61**, 2675 (1939).

[4] A similar desulfurization of D-mannose diethyl mercaptal pentaacetate by G. N. Bollenback and L. A. Underkofler [THIS JOURNAL, **72**, 741 (1950)], followed by deacetylation of the sirupy product, has independently been demonstrated to yield D-rhamnitol. The desulfurization of sugar mercaptals by Raney nickel was first accomplished by M. L. Wolfrom and J. V. Karabinos, THIS JOURNAL, **66**, 909 (1944).

[5] W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **68**, 628 (1946).