Novel Addition of an Alcohol to an Enol Ether. Isomerization of 1,4,5,6-Tetrahydro-3-methoxybenzyl Alcohol to 1-Methoxy-7-oxabicyclo[3.2.1]octane

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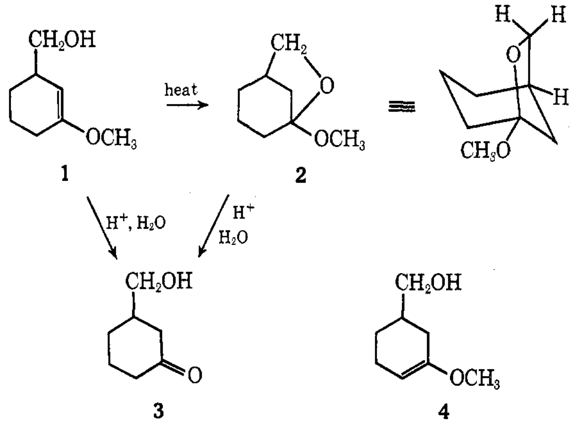
The acid[1-3] or base[1,2] catalyzed addition of alcohols to enol ethers is well known. The closely related formation of α-halo ketals by the reaction of enol ethers with a source of positive halogen in alcohol solvent apparently involves initial addition of the positive halogen followed by the alcohol.[1] We have encountered a facile, and possibly uncatalyzed, internal addition of an alcohol group to an enol ether forming the isomeric ketal.

When 1,4,5,6-tetrahydro-3-methoxybenzyl alcohol (**1**) was injected into a 5-ft 10% Carbowax 20M on Aeropak-30 glc column (150°) or a 10-ft Reoplex 400 on Chromosorb W column (170°), the eluent was previously unreported 1-methoxy-7-oxabicylo[3.2.1]octane (**2**). Experiments in lowering the column temperature of the Carbowax 20M column indicate that the isomerization occurs above 100°. Vacuum distillation of **1** through a spinning band column with condensate vapor reaching a temperature of 74-82° did not cause isomerization. However, an attempted simple distillation of **1** with the temperature of the condensing vapor reaching 150-300° also caused conversion of **1** to **2**.



While the reaction appears to be uncatalyzed, we have not rigorously excluded the possibility that trace amounts of acids may be present in the glc columns or introduced during work-up and may catalyze the reaction.

That the hydroxymethyl group in the pseudoaxial position has its oxygen in the proximity of the methoxy-substituted vinyl carbon undoubtedly contributes to the ease of this reaction. Other reactions leading to similar bicyclic ring systems have been reported, such as the acid-catalyzed formation of 1,6-anhydrohexoses from aldohexoses,[4] the base-catalyzed conversion of veracevine to cevine *via* cevaginin,[5] and the methoxide ion catalyzed formation of methyl 3,6-anhydro-β-D-glucopyranose from methyl 3-*O*-tosyl-β-D-glucopyranoside.[6] However, such ring systems do have some strain.[7]

1 was prepared by one-step reduction of *m*-methoxybenzamide with 8 or more equiv of sodium in liquid ammonia plus ethanol as proton source. The product was assigned structure **1** rather than the alternate possibility, 1,2,5,6-tetrahydro-3-methoxybenzyl alcohol (**4**), on the basis that the observed nmr signal for the single vinyl hydrogen (δ 4.53, $CDCl_3$) was split into a doublet rather than a triplet and on the basis of the expected course of the reduction in which the *m*-methoxybenzamide ring is probably reduced first to the 1,4,5,6-tetrahydro-3-methoxybenzamide (analogous to the reduction of *m*-methoxybenzoic acid[8]) followed by reduction of the amide group to the alcohol *via* the aldehyde.[9,10]

2 showed absence of OH and C=C absorption in the ir as well as absence of vinyl hydrogen in the nmr that **1** had exhibited. Thus **2** was assigned the structure shown on basis of ir and nmr spectra and the fact that 3-hydroxymethylcyclohexanone (**3**) formed upon acid hydrolysis. **3** also formed by acid hydrolysis of **1**. The mixture melting point of 2,4-dinitrophenylhydrazone samples of **3** from each gave no depression.

Experimental Section[11]

1,4,5,6-Tetrahydro-3-methoxybenzyl Alcohol (**1**).—To a stirred, refluxing (−33°) mixture of 1400 ml of NH_3, 270 ml of absolute ethanol, and 40.0 g (0.264 mol) of *m*-methoxybenzamide was added (5-10 min) 48.6 g (2.11 g-atoms) of sodium in small pieces. After the deep blue color disappeared, 200 g of NH_4Cl was added and the NH_3 was allowed to evaporate. The solid residue was dissolved in water and the organic material was removed by CH_2Cl_2 extractions, which were dried ($MgSO_4$). Evaporation of solvent yielded 31.4 g of liquid, which was distilled through an Annular Teflon spinning band column (0.5 mm) yielding fractions totaling 14.2 g (0.10 mol) (38%) of **1**, bp 74-82° (corrected) [lit.[12] bp 102-104° (2.75 mm)], $n^{25}{}_D$ 1.4883-1.4890, and polymeric material: ir (neat) 2.95 (-OH), 5.99 μ (enol C=C); nmr (DMSO-d_6) δ 1.05-2.6 (m, 7, ring CH_2 and CH), 3.23 (t, 2, J = 5-6 Hz, CH_2OH), 3.42 (s, 3, OCH_3), 4.40 (t, 1, J = 5-6 Hz, primary -OH), 4.58 (d, J = 2-3 Hz, CH=C); nmr ($CDCl_3$) δ 2.55 (s, broad, 1, -OH), 3.45 (d, 2, J = 5-6 Hz, CH_2OH, with downfield half of doublet coinciding with the $-OCH_3$ absorption at δ 3.59, s), 4.53 (d, 1, CH=C).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.92; O, 22.5. Found: C, 67.5; H, 9.72; O, 22.7.

1-Methoxy-7-oxabicyclo[3.2.1]octane (**2**).—Injection of 15 μl of **1** onto a 5-ft 10% Carbowax 20M on 80/100 mesh Aeropak-30 column (Aerograph Model A-90-P, column 150°, injector 205°,

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[1] S. Patai, "The Chemistry of the Ether Linkage," Interscience, New York, N. Y., 1967, p 322.

[2] M. F. Shostakowskii, A. V. Bogdanova, and G. I. Plotnikova, *Russ. Chem. Rev.*, **33**, 66 (1964).

[3] M. L. Wolfrom, S. S. Bhattacharjee, and R. M. De Lederkremer, *Carbohyd. Res.*, **11**, 148 (1969).

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 415-417.

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[7] Reference 4, pp 381, 405.

[8] M. E. Keuhne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

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[10] A. J. Birch, *J. Roy. Inst. Chem.*, **81**, 100 (1957).

[11] Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected unless otherwise stated. Analyses were by Bernhardt Mikroanalytisches Laboratorium, Elbach uber Engelskirken, West Germany. Ir spectra were obtained on a Perkin-Elmer 137B. Nmr spectra were obtained with a Varian A-60 with tetramethylsilane as internal standard. The ammonia for reduction solvent was distilled from its metal cylinder and condensed in the reduction flask but not dried before use. The sodium was freshly cut free of oxide and hydroxide just before use.

[12] O. L. Chapman and P. Fitton, *J. Amer. Chem. Soc.*, **85**, 41 (1963).

detector 200°, collector 190°, helium at 40 psi, and flow rate of 200 ml/min) yielded a small unidentified peak (2% of eluate) at 15 sec and a peak at 6 min which was **2**. Repeated injections and collections yielded sufficient material for characterization (although only about 50% of injected material was accounted for): n^{25}D 1.4641; ir (neat) no absorption at 6.0 (no enol C=C), no absorption at 2.95 (no -OH), 9.18 μ; nmr (CDCl$_3$) δ 4.02 (double doublet, 1, A of ABX pattern, J_{AB} = 7–8 Hz, cis J_{AX} = 4 Hz, -OCH$_A$H$_B$CH$_X$<), 3.78 (d, 1, B of ABX pattern, J_{AB} = 7–8 Hz, trans J_{BX} = 0), 3.32 (s, 3, -OCH$_3$), 1.2–2.6 (m, 9, cyclohexane ring CH$_2$ and CH).

Anal. Calcd for C$_8$H$_{14}$O$_2$: C, 67.6; H, 9.92; O, 22.5. Found: C, 67.4; H, 9.76; O, 22.7.

The conversion of **1** into **2** was also observed on a 10-ft Reoplex 400 on Chromosorb W column (injector 200°, column 170°, detector 250°). Distillate from an unsuccessful simple distillation of crude reduction product in which vapor temperature reached 150–300° was combined with additional crude reduction product and separated on a spinning band column, yielding pure samples of **2**, bp 40° (0.3 mm), and impure **1**, bp 78–86° (0.3 mm), and polymer.

Lowering the column temperature of the Carbowax 30M column below 100° resulted in **1** not being converted into **2**.

3-Hydroxymethylcyclohexanone (3).—Hydrolysis of 0.68 g (0.0048 mol) of **1** with 25% H$_2$SO$_4$ yielded 0.47 g (0.0037 mol) of **3** (77% yield): n^{25}D 1.4806; nmr (CDCl$_3$) showed absence of both vinyl hydrogen and -OCH$_3$, δ 3.6 ("filled in" d, 2, J = 4 Hz, -CH$_2$OH), 2.7–0.9 (m, 10, ring and -OH hydrogens); ir (neat) 2.88 (-OH), 5.84 μ (C=O).

Anal. Calcd for C$_7$H$_{12}$O$_2$: C, 65.6; H, 9.44; O, 25.0. Found: C, 65.2; H, 9.62; O, 24.8.

3 was converted to its 2,4-dinitrophenylhydrazone,[13] mp 120–122° (inserted at 26°), 119–120° (inserted at 70°) (other derivatives[14]).

Anal. Calcd for C$_{13}$H$_{16}$N$_4$O$_5$: C, 50.6; H, 5.23; N, 18.18; O, 26.0. Found: C, 50.5; H, 5.53; N, 17.96; O, 26.1.

Sample of **3** made from acid hydrolysis of **2** had the same ir and nmr spectra and yielded 2,4-dinitrophenylhydrazone which gave no mixture melting point depression.

Registry No.—**1**, 34407-89-1; **2**, 34407-90-4; **3**, 32916-58-8; **3** DNP, 34407-91-5.

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[13] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965, p 254.

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The Alkaline Hydrolysis of Aryl α-Disulfones[1]

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In alkaline solution aryl α-disulfones **1** undergo rapid hydrolysis to ArSO$_3^-$ and ArSO$_2^-$ (eq 1). Several years ago Allen and Conway[2] reported some kinetic data on this reaction in ethanol whose accuracy was later called into serious question by Kice and Kasperek.[3] The latter authors measured the rate of hydrolysis, k_h, of several **1** in various Et$_3$N-Et$_3$NH$^+$ buffers in 60% glyme at constant ionic strength. They found that under such conditions k_h was given by eq 2, where the first term is due to eq 1 and the second to general base catalysis of the hydrolysis of **1** by Et$_3$N. Their results showed that k_{OH} was apparently much more dependent on aryl group substituents (ρ = +3.7) than reported by Allen and Conway[2] (ρ = +0.3). However, the lack of values of K_w and $K_a^{Et_3NH^+}$ for 60% glyme prevented Kice and Kasperek from determining the absolute magnitude of k_{OH} for any of their α-disulfones under their reaction conditions.

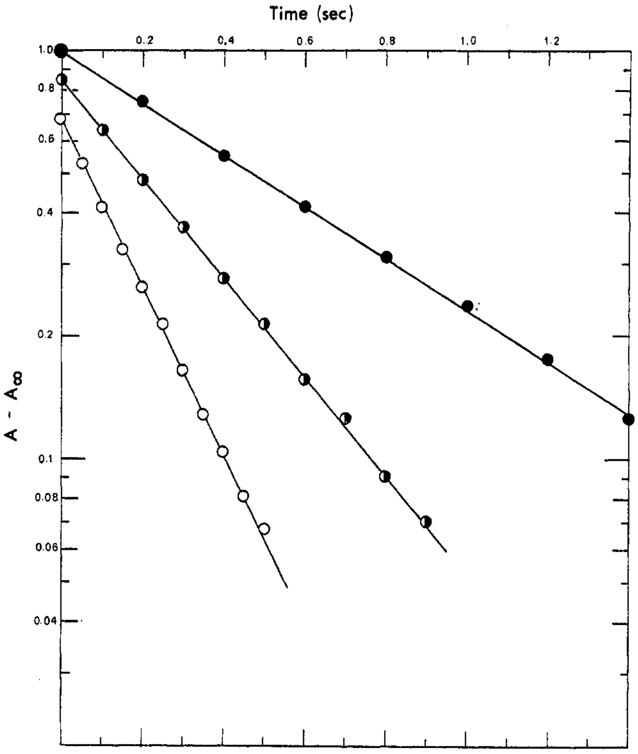
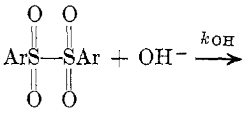


Figure 1.—Plot of log ($A - A_\infty$) *vs.* time for the alkaline hydrolysis aryl α-disulfones at 25°: ●, PhSO$_2$SO$_2$Ph, 3.7 × 10^{-5} M, [OH]$^-$, 0.02 M, 60% dioxane as solvent; ◑, PhSO$_2$SO$_2$Ph, 2.6 × 10^{-5} M, [OH$^-$], 0.01 M, ethanol as solvent; ○, p-chlorophenyl α-disulfone, 1.6 × 10^{-5} M, [OH$^-$], 0.01 M, 60% dioxane as solvent.



$$\mathrm{ArS(O_2){-}S(O_2)Ar} + \mathrm{OH^-} \xrightarrow{k_{OH}}$$

1

$$\mathrm{ArSO_2^-} + \mathrm{ArSO_3H} \xrightarrow[\text{fast}]{\mathrm{OH^-}} \mathrm{ArSO_2^-} + \mathrm{ArSO_3^-} \qquad (1)$$

$$k_h = k_{OH}\left[\frac{K_w}{K_a^{Et_3NH^+}}\right]\frac{(Et_3N)}{(Et_3NH^+)} + k_{Et_3N}(Et_3N) \qquad (2)$$

In the present work, by using a stopped-flow spectrophotometer to follow the very rapid disappearance of **1**, we have been able to measure k_{OH} at 25° for several aryl α-disulfones directly in solutions 0.01 or 0.02 M in NaOH in either 60% dioxane (v/v) or ethanol as solvent. Figure 1 shows plots of the data for representative runs. One can see that under the conditions used, where hydroxide ion is present in huge stoichiometric excess over **1**, excellent first-order kinetics are obtained. Table I summarizes the kinetic data for the various runs. In it k_1 is the experimental first-order rate constant for a run as obtained from the slope of a plot such as shown in Figure 1. Hence $k_{OH} = k_1/(OH^-)$.

Several aspects of the results merit discussion. First,

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[1] This research was supported by the National Science Foundation, Grant GP-25799.

[2] P. Allen, Jr., and P. J. Conway, *Can. J. Chem.*, **47**, 873 (1969).

[3] J. L. Kice and G. J. Kasperek, *J. Amer. Chem. Soc.*, **92**, 3393 (1970).