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Reaction of 2-(1,2-Epoxycyclohex-1-yl)cyclohexanone Ketal with Boron Trifluoride Etherate[1]

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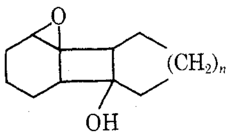
Received June 16, 1975

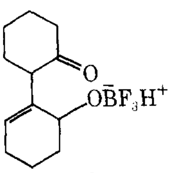
The formation of substituted furans by the action of acids on α,β-epoxy ketones is known,[3,4] and a recent report by Loubinoux and co-workers[5] indicates that in the presence of boron trifluoride etherate β,γ-epoxy alcohols of the type **1** give good yields of furans.



1

We find that the β,γ-epoxy ketal **2** on treatment with boron trifluoride etherate gives 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**5**) in 43% yield. Scheme I illustrates a possible route, though at this stage it seems difficult to distinguish between the two possible pathways, a and b.

Our result would appear to lend support to the suggestion[5] that epoxy alcohols of the type **1** give rise to furans via ketonic intermediates. Thus, for $n = 2$, the system studied by Loubinoux and co-workers is isomeric with the epoxy ketone **3**, and intermediates **4a** and **4b** are isomeric with their proposed intermediate, **6**.



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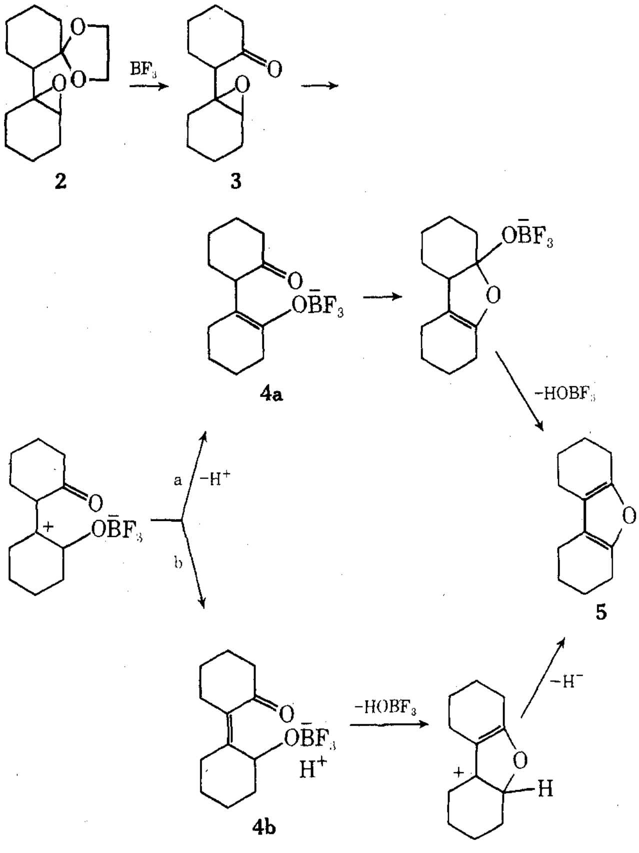
Scheme II outlines the preparation of the title compound.

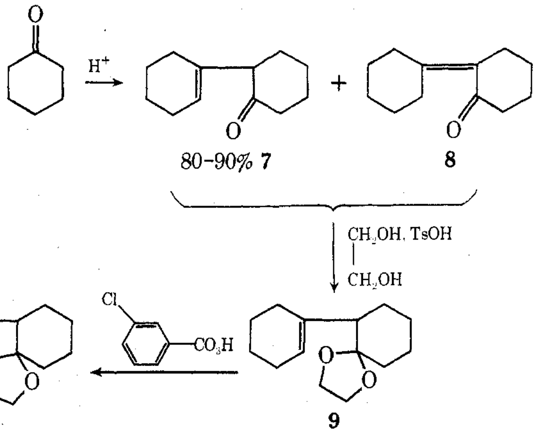
Self-condensation of cyclohexanone in the presence of 60% H_2SO_4[6] gave 2-(cyclohexen-1-yl)cyclohexanone (**7**), together with a small amount of 2-cyclohexylidenecyclohexanone (**8**). The composition was established by ir and NMR analysis, our results agreeing with those of Wenkert and coworkers.[7] However, VPC failed to reveal the presence of the minor component in the mixture. The many reported investigations[7] of the structure of this condensation product do not appear to include a method for the separation of the isomeric mixture. It has been reported,[8] however, that **7** is the more stable isomer thermally, and thus it seemed possible that **8** might have isomerized to **7** while on the VPC column. Heating the mixture to 140° for varying time periods did not produce any appreciable change in the isomer ratio as measured by NMR analysis. However, heating with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid over a period of 7 hr gave the ketal **9**, whose NMR spectrum indicated that it consisted of one isomer only, one olefinic hydrogen being present relative to the four hydrogens from the ethylene glycol residue. This migration of the double bond out of conjugation on ketalization has also been observed in the steroid series.[9,10] [Hydrolysis of **9** in 90% acidified methanol gave 2-(cyclohexen-1-yl)cyclohexanone (**7**).] Ketal **9** reacted smoothly with *m*-chloroperbenzoic acid to give **2**.

Treatment of **2** with boron trifluoride etherate, in either methylene chloride or benzene, gave a dark red oil consisting of four (or five) compounds (TLC), of which the major one was 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**5**). The latter was isolated by dry column chromatography on neutral alumina, followed by distillation, and the structure was established by elemental and spectral analysis.

Scheme I

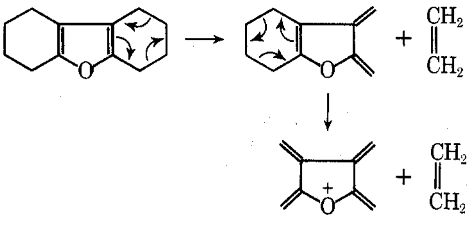


Scheme II



The mass spectrum of **5** proved to be of particular interest. In addition to the previously reported[4] peaks (m/e 176, 148, 120, etc.; see Experimental Section) two "metastables" appeared at m/e 125 and 97.5. These represent respectively the fragmentation of the parent peak at m/e 176 → 148 with loss of 28 mass units, and the m/e 148 peak → 120 with loss of 28 mass units. "Exact mass" measurements on the m/e 148 and 120 peaks suggested that ethylene is the fragment lost in each case, which leads to the fragmentation pattern indicated in Scheme III.

Scheme III



Experimental Section

Ir spectra were recorded on a Beckman IR 33 spectrometer, NMR spectra were determined on a Varian T-60 spectrometer, and the mass spectra on a Varian CH5 mass spectrometer. Microanalyses were performed on a 185 B Hewlett-Packard C, H, N analyser.

Self-condensation of Cyclohexanone.[6] Technical cyclohexanone (500 g, 5.1 mol) was condensed in the presence of 60% H_2SO_4 according to the procedure of Gault and co-workers.[6] The product was a colorless oil (290 g, 63%): ir (liquid film) 1700 (s), 1670 cm^{-1} (sh); NMR ($CDCl_3$) δ 5.4 (m, 0.8 H), 1.0–3.2 (m, 17 H); mass spectrum parent peak m/e 178. Separation of the mixture was attempted, without success, on the following columns: Apiezon, DEGS, XE60, and Carbowax, at temperatures ranging from 180 to 200°. A single, symmetrical peak was observed in every case.

Preparation of Ketal 9.[9] The ketone mixture (8.9 g, 0.05 mol), consisting of 80–90% (**7**), was added to 165 ml of toluene and 60 ml of freshly distilled ethylene glycol containing 0.1 g of p-toluenesulfonic acid, and this mixture was heated with slow distillation for 7 hr, during which time 190 ml of distillate was collected. Fresh toluene was added to maintain the original volume over this period. The organic layer was separated, and, after washing several times with saturated aqueous $NaHCO_3$ and water, the combined aqueous layers were extracted with ether, and the ether layers were washed with water and added to the organic layer. Drying ($MgSO_4$) and removal of the solvent under reduced pressure gave 11.5 g (97%) of a pale yellow oil. Distillation gave a colorless oil: bp 85–89° (0.2 mm); NMR ($CDCl_3$) δ 5.5 (m, 1 H), 3.9 (s, 4 H), 2.2–1.2 (m, 17.2 H). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.08; H, 9.82. Found: 75.38; H, 9.93.

Preparation of 2-(1,2-Epoxycyclohex-1-yl)cyclohexanone Ketal (2).[11] To 11.2 g (0.05 mol) of **7** in 70 ml of methylene chloride in a flask equipped with a thermometer, dropping funnel, stirrer, and condenser was added 11 g (0.054 mol) of m-chloroperbenzoic acid in 120 ml of methylene chloride over a period of 20 min. The temperature was maintained at 25° during the addition, and the stirring was continued for a further 1.5-hr period. The excess peracid was destroyed by the addition of a small amount of 10% aqueous sodium sulfite. The methylene chloride solution was then washed with 5% $NaHCO_3$, water, and saturated aqueous NaCl. Drying ($MgSO_4$) and removal of the solvent left 11.2 g (93%) of a colorless oil: mass spectrum parent peak m/e 238; NMR ($CDCl_3$) δ 3.9 (s, 4 H), 3.1 (m, 1 H), 2.2–1.2 (m, 17 H). Distillation in a Kugelrohr, pot temperature 145° (3 mm), gave a clear liquid. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.81; H, 9.21.

Reaction of 2 with Boron Trifluoride Etherate.[12] The epoxide **2** (4.8 g, 0.02 mol) in 75 ml of methylene chloride at 5° was treated with 8.4 ml of boron trifluoride etherate (48%, technical) added slowly via a dropping funnel. The mixture was stirred at 5° for a further 0.5 hr, and then 75 ml of water was added rapidly. The organic layer was separated and washed with water (2 × 100 ml), saturated, aqueous $NaHCO_3$ (3 × 100 ml), and water (4 × 75 ml). Drying ($MgSO_4$) and removal of the solvent left a pink oil, which turned dark red in 0.5 hr. [The use of benzene (200 ml) as solvent, and the elimination of the 0.5-hr stirring period after the addition of the boron trifluoride etherate, did not appear to have any appreciable effect on the course of the reaction.] Examination of the crude product by TLC indicated that it contained four (or five) components, one well separated and moving very close to the solvent front. The crude red oil was then chromatographed on 400 g of neutral alumina (Woelm), dry column grade, activity III (20 mm), packed in a 2-in. plastic tube. Ether was used as eluant. The bottom ⅛th of the column, which contained the main component of the mixture, gave, on extraction with ether, 1.5 g (43%) of a pale yellow oil. Distillation [bp ∼90° (2 mm), lit.[3] 88–89° (2 mm)] yielded a colorless oil: ir (liquid film) 1600 cm^{-1} (furan ring); NMR ($CDCl_3$) δ 2.0–2.6 (8 H), 1.4–2.0 (8 H); mass spectrum m/e 176, 148, 120, 105, 92, 91, 79, 77, 65, 51, 41, 39, and two "metastables" at 125 and 97.5. Exact mass of 148 peak. Calcd for $C_{10}H_{12}O$: 148.088. Found: 148.087. Exact mass of 120 peak. Calcd for C_8H_8O: 120.057. Found: 120.057. (Perfluoroalkane 225 was used as the reference compound.)

Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.10. Found: C, 81.62; H, 9.19.

Three other materials were isolated from the column and all were ketonic but none was obtained pure enough to warrant a definite structure assignment.

Hydrolysis of Ketal 2 to 2-(Cyclohexen-1-yl)cyclohexanone (7). Hydrolysis of **2** in 90% boiling MeOH acidified with HCl gave 2-(cyclohexen-1-yl)cyclohexanone (**7**): ir (liquid film) 1700 cm^{-1}, and very much reduced shoulder (relative to that observed in the initial mixture of ketones produced by the self-condensation of cyclohexanone) at 1670 cm^{-1}; NMR ($CDCl_3$) δ 5.4 (0.96 H), 1.0–3.2 (17.0 H). The relative areas of the proton peaks in the NMR remained unchanged when the material sat at 25° for 6 days.

Registry No.—**2**, 57090-93-4; **5**, 1010-77-1; **7**, 1502-22-3; **9**, 57090-94-5; cyclohexanone, 108-94-1; boron trifluoride etherate, 109-63-7.

References and Notes

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Demethylation of Labile Aryl Ethers

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Received June 6, 1975

As part of a study of structure–activity relationships of certain synthetic estrogens, the carbinols 3-hydroxy-3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)hexane (I) and 3-hydroxy-3,4-bis(4-methoxyphenyl)hexane (II) were prepared. We also wished to prepare the corresponding free