[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Epoxyethers. II. The Epoxyether from α-Halocyclohexyl Phenyl Ketone[1]

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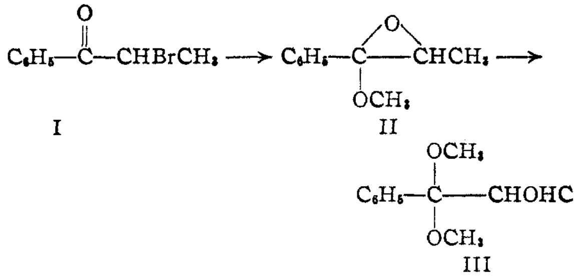
The epoxyether of α-halocyclohexyl phenyl ketone has been prepared. This α-haloketone had previously been reported to undergo a Favorski type rearrangement in the presence of base. The epoxyether of the α-haloketone was shown not to be an intermediate in this type of rearrangement. A new modification for the preparation of epoxyethers is introduced, and cleavage reactions of the epoxyether with water, alcohol, and organic acids are reported. The reactions through the epoxyether intermediate provide an excellent method of preparing, in good over-all yield from the ketone, an α-keto *t*-alcohol, or that derivative of the keto alcohol in which the ketone is protected by a ketal group, or the *t*-alcohol is protected by a benzoate group.

Recently the reaction of α-halopropiophenone (I) with sodium methoxide to give an epoxyether (II) was reported.[2] This epoxyether (II) was shown to react rapidly with alcohol to give a hydroxyketal (III) which confirmed the mechanism postulated by Kohler and by Ward[3] for the reaction of certain α-haloketones with alcoholic sodium alkoxides to give hydroxy ketals.



Various investigators[4] have postulated epoxyethers as intermediates in Favorski type rearrangements of α-haloketones to acids or esters in the presence of bases. Mousseron[5] recently claimed that the epoxyether, isolated from the reaction of chlorocyclohexanone and sodium cyclohexanolate, rearranged to give cyclohexyl cyclopentanecarboxylic ester. However, Loftfield[6] has presented evidence that the most reasonable intermediate in the reaction of this haloketone with sodium amylate to give the amyl ester is a cyclopropane derivative.

The primary purpose of this work was to investigate the properties of an epoxyether of an α-haloketone which had previously been reported to undergo rearrangement in the presence of base but which could not form a cyclopropanone intermediate to determine whether the epoxyether is an intermediate in this type of rearrangement.

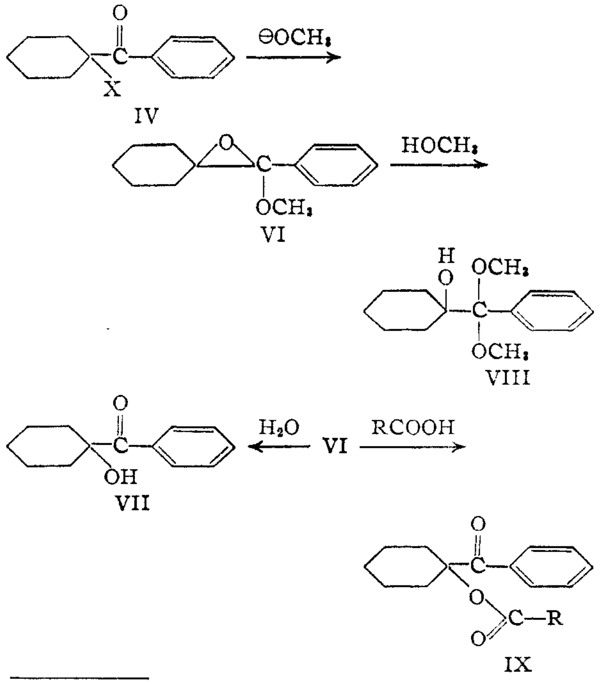
The results of the investigation show that the epoxyether does not undergo rearrangement to an acid derivative. Also, this work further extends the scope of the reaction for the formation of the epoxyethers and shows that the preparation and certain simple cleavage reactions proceed in yields sufficiently high to make the reactions useful in organic synthesis. In this respect, a new simple modification for the preparation of epoxyethers is introduced.

The α-haloketone chosen for this work was α-halocyclohexyl phenyl ketone (IV). Tchoubar[7] has reported that IV (X is Cl) rearranged in the presence of sodium hydroxide in ether to give 40% of 1-phenylcyclohexanecarboxylic acid (V). The remainder of the reaction product was reported to be cyclohexenyl phenyl ketone.

The epoxyether, 2-methoxy-2-phenyl-1-oxaspiro-[2.5]octane (VI), could readily be prepared from the α-haloketone (IV, X is Br) using dry sodium methoxide in ether, as in the procedure previously described,[2] in 83% yield.

A high yield (82.5%) of epoxyether could also be obtained by the following modification. The haloketone was allowed to react with an alcoholic solution of sodium methoxide for a short reaction time, after which the reaction mixture was poured into a large volume of ice, extracted with ether and purified by distillation. The epoxyether prepared by both procedures had identical properties.

Chemical evidence for the structure of the epoxyether was obtained from the rapid cleavage reactions with water, alcohol and organic acids. Water containing a small amount of acid hydrolyzed the epoxyether in 90% yield to the



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[1] Presented before the Organic Division at the 118th Meeting of the American Chemical Society in Chicago, Illinois, Sept. 6, 1950. Sponsored in part by the Research Corporation of New York.

[2] C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4758 (1950).

[3] E. P. Kohler and C. R. Addinall, *ibid.*, **52**, 3728 (1930); A. M. Ward, *J. Chem. Soc.*, 1544 (1929).

[4] J. G. Aston and R. B. Greenburg, THIS JOURNAL, **62**, 2590 (1940); W. D. McPhee and E. Klingsberg, *ibid.*, **66**, 1132 (1944).

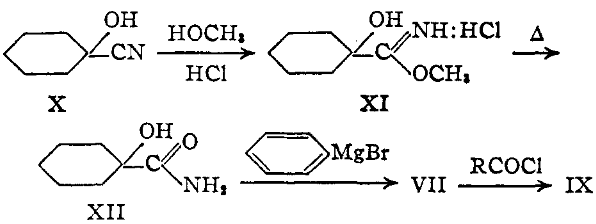
[5] M. Mousseron and R. Jacquier, *Compt. rend.*, **229**, 374 (1949).

[6] R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).

[7] B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

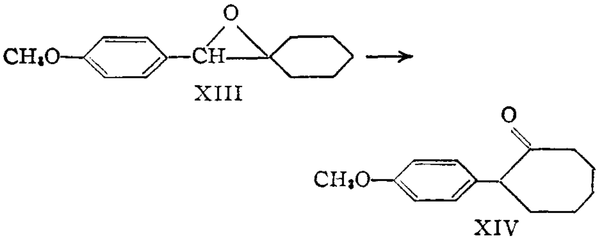
hydroxyketone (VII). The epoxyether reacted exothermically with an excess of methyl alcohol to give a 92% yield of hydroxyketal (VIII). Benzoic acid reacted rapidly with the epoxyether to give the α-ketoester (IX, R is C_6H_5) in 92% yield. Physical data support the epoxyether structure in that the infrared absorption spectrum shows no absorption band corresponding to a carbonyl group.

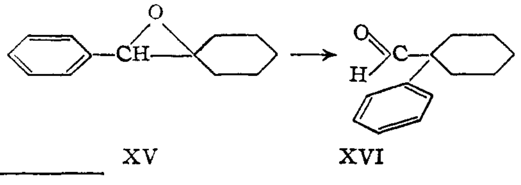
Further, the hydroxyketal (VIII) was hydrolyzed to the hydroxyketone (VII) and the hydroxyketone and benzoate were prepared by the following independent synthesis. The cyanohydrin of cyclohexanone (X) was converted in 92% yield to the methyl iminoester hydrochloride (XI) which was pyrolyzed to give α-hydroxycyclohexanecarboxamide (XII) in 82% yield. The α-hydroxyamide (XII) with excess phenylmagnesium bromide gave 11% of the α-hydroxyketone (VII). The low yield in this reaction is comparable to those yields reported in the literature for similar reactions.[8] Benzylation of the α-hydroxyketone gave the α-ketoester (IX, R is C_6H_5) in 54% yield.



The epoxyether (VI) after preparation and isolation or after pyrolysis at 200° for one hour in the presence of a small amount of base contained no rearranged ester of 1-phenylcyclohexanecarboxylic acid (V), since saponification of the product by procedures which are known to saponify alkyl esters of V gave no acid.

The fact that the epoxyether (VI) does not rearrange to an ester can be correlated with the fact that anisalcyclohexane oxide (XIII), which is a vinylog of VI, is reported[9] to rearrange with ring enlargement (XIV) and not with migration of the aromatic group, while benzalcyclohexane oxide (XV) rearranges with migration of the aromatic group to give XVI.





The refractive index of the pyrolysate was only slightly different from that of the starting epoxyether and contained mostly VI as shown by reaction with alcohol to give the hydroxy-ketal. Exhaustive fractionation was not attempted to determine whether the pyrolysate contained a small amount of material analogous to the compound (XIV) with ring enlargement.

Experimental

α-Halocyclohexyl Phenyl Ketones.—Cyclohexyl phenyl ketone, m.p. 53–54°, was prepared in 84% yield by the oxidation of the corresponding carbinol with aqueous sodium dichromate solution following the directions of Sidorova.[10] The carbinol, m.p. 49–50°, was prepared in 81% yield from benzaldehyde and cyclohexylmagnesium bromide.

α-Chlorocyclohexyl phenyl ketone[5] (IV, X is Cl) was prepared by dissolving 8 g. of cyclohexyl phenyl ketone in 40 ml. of freshly distilled sulfuryl chloride. After the solution had been heated under reflux for 12 hours, the reaction was poured into 100 g. of cracked ice. The crude haloketone solidified, and after filtration and recrystallization from low boiling petroleum ether, a 7.82-g. (81%) yield of pure α-chlorocyclohexyl phenyl ketone, m.p. 53–54°, was obtained. The chlorine content of this ketone was 16.0% (calcd. 15.7%).

α-Bromocyclohexyl phenyl ketone (IV, X is Br) was prepared in 87% yield by slowly adding 26.7 g. (0.16 mole) of bromine dissolved in 20 ml. of acetic acid to a refluxing solution of 20 g. (0.1 mole) of the cyclohexyl ketone in 50 ml. of acetic acid. After the bromine color disappeared the reaction was poured onto 200 g. of cracked ice and the precipitated bromoketone was filtered and recrystallized from low-boiling petroleum ether, m.p. 50–51°.

Anal. Calcd. for $C_{13}H_{15}OBr$: Br, 29.5. Found: Br, 29.6.

Preparation of the Epoxyether (VI).—To a refluxing solution of 15 g. (56.2 millimoles) of α-bromocyclohexyl phenyl ketone in 30 ml. of absolute methyl alcohol was added a solution of 56.2 millimoles of sodium methoxide in 40 ml. of alcohol. After 1.5 minutes at the reflux temperature titration of an aliquot indicated that 98% of the base had reacted. The reaction was immediately poured onto 500 g. of cracked ice and the organic material extracted with ether. After the ether solution had been dried two hours with anhydrous sodium sulfate, 20 ml. of benzene was added and the solvents then were evaporated at room temperature under reduced pressure. The residual liquid was distilled from a 25-ml. Claisen-type flask with an 8-cm. Vigreux column. The yield of 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane (VI) was 10 g. (83%), b.p. 97–100° (0.4 mm.); n^{25}_D 1.5179; d^{25}_4 1.052. The chloroketone gave a 79% yield.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; CH_3O, 14.2. Found: C, 77.04; H, 8.35; CH_3O, 14.4.

By the method previously described,[3] the *t*-bromoketone (IV, X is Br) gave an 83% yield of epoxyether.

Pyrolysis of the Epoxyether (VI).—Two drops of 2 *M* sodium methoxide solution in absolute methyl alcohol were placed in a 10-ml. distilling flask. The alcohol was evaporated under reduced pressure leaving the dry sodium methoxide as a catalyst. The flask was protected from moisture with a drying tube, and 2 g. of epoxyether (VI), n^{25}_D 1.5182, added to the catalyst. The epoxyether was heated at 200° for one hour and then at 260° for five minutes. After this treatment the boiling point was unchanged and the refractive index only slightly changed, n^{25}_D 1.5192. That the material was composed largely of unchanged epoxyether was shown by rapid reaction with alcohol to give hydroxyketal (VIII). That the material contained no ester of 1-phenylcyclohexanecarboxylic acid was shown by application of the saponification procedure of Rubin and Wishinsky,[11] which is known to saponify the ethyl ester of 1-phenylcyclohexanecarboxylic acid in 100% yield. No acid was produced from the saponification of the pyrolysate and titration showed no base was used during the saponification procedure.

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[8] S. S. Jenkins, L. A. Bigelow and J. S. Buck, THIS JOURNAL, **52**, 5198 (1930).

[9] M. Tiffeneau, *et al.*, *Compt. rend.*, **201**, 277 (1935); **195**, 1284 (1932).

[10] N. G. Sidorova and I. P. Tsukervanik, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 2073 (1940); *C. A.*, **35**, 3979 (1941).

[11] M. Rubin and H. Wishinsky, THIS JOURNAL, **68**, 929 (1946).

α-Hydroxycyclohexyl Phenyl Ketone.—A mixture of 20 ml. of water and 0.82 g. of epoxyether containing one drop of concentrated hydrochloric acid was heated to reflux for one hour. The resultant oil solidified on cooling and was filtered and recrystallized from low-boiling petroleum ether to give 0.68 g. (90%) of the hydroxyketone (VII), m.p. 48–49°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.45; H, 7.92. Found: C, 76.50; H, 8.20.

The semicarbazone of this ketone melted at 208–210°.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33. Found: C, 64.32; H, 7.31.

The Dimethyl Ketal of α-Hydroxycyclohexyl Phenyl Ketone (VIII).—To 10 ml. of absolute methyl alcohol was added 1.08 g. (4.9 millimoles) of the epoxyether (VI). Upon addition the solution became warm and on cooling the hydroxyketal (VIII) crystallized, m.p. 100–101°. Further evaporation and crystallization gave a total of 1.15 g. (92%) of the ketal. An analytical sample was recrystallized from petroleum ether, m.p. 100–101°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 71.7; H, 8.75; CH_3O, 24.8. Found: C, 71.92; H, 8.78; CH_3O, 24.5.

α-Hydroxycyclohexyl Phenyl Ketone Benzoate.—To a solution of 0.41 g. (3.3 millimoles) of benzoic acid in 10 ml. of dry ether was added 0.73 g. (3.3 millimoles) of the epoxyether (VI). After one-half hour the ether was evaporated and the resulting solid recrystallized from low boiling petroleum ether to give 0.97 g. (92%) of the ketobenzoate (IX, R is C_6H_5), m.p. 83–84°.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.89; H, 6.54. Found: C, 77.70; H, 6.80.

Hydrolysis of Hydroxyketal (VIII) to Hydroxyketone (VII).—The hydroxyketal (0.61 g.) was hydrolyzed in a solution of 20 ml. of methyl alcohol and 5 ml. of concentrated hydrochloric acid by refluxing the mixture for 3 hours. The product was isolated by dilution of the reaction with water, extraction with ether and evaporation of the solvent. The yield of hydroxyketone was 0.34 g. (68%). The product of this reaction was identical with VII from the hydrolysis of the epoxyether (VI).

Methyl Cyclohexaneiminocarboxylate Hydrochloride.—Cyclohexanone cyanohydrin was prepared from 60 g. (0.61 mole) of cyclohexanone, 68 g. (0.71 mole) of sodium bisulfite and 50 g. (1.0 mole) of sodium cyanide by the procedure described by Fieser.[12] The yield of cyanohydrin, b.p. 70–72° (2 mm.), was 57.9 g. (74%).

Dry hydrogen chloride was bubbled into a solution of 31 g. (0.25 mole) of cyclohexanone cyanohydrin and 8.0 g. (0.25 mole) of anhydrous methanol which was cooled in an ice-bath until a gain in weight indicated 2.0 g. (0.25 mole) of gas had been adsorbed. The reaction mixture was allowed to stand 10 hours at 0° during which time the material solidified. The solid was washed with dry ether and dried *in vacuo* to give 44.5 g. (92%) of the imino ester.

Anal. Calcd. for $C_8H_{16}O_2NCl$: Cl, 18.34. Found: Cl, 18.65.

α-Hydroxycyclohexanecarboxamide.—The iminoester hydrochloride (44.5 g., 0.23 mole) was heated to 120° in a flask protected from the moisture of the air. A vigorous evolution of gas occurred with the formation of liquid. After the gas evolution ceased, the flask was cooled and the solid product recrystallized from ethyl acetate to give 26.5 g. (82%) of α-hydroxycyclohexanecarboxamide,[13] m.p. 120–121°. A small amount of by-product, insoluble in ethyl acetate, was obtained which was not further investigated.

Independent Synthesis of α-Hydroxycyclohexyl Phenyl Ketone and Benzoate.—To a Grignard reagent made with 33 g. (0.21 mole) of bromobenzene, 5.1 g. (0.21 atom) of magnesium and 70 ml. of ether was added 10 g. (0.07 mole) of the hydroxyamide. After the reaction had been refluxed for 8 hours with stirring, the mixture was hydrolyzed with 300 ml. of cold 10% sulfuric acid solution. The organic material was extracted with ether, and after the ether solution had been dried and the ether evaporated, the remaining liquid was distilled through a 25-ml. Claisen-type flask. The fraction boiling at 95–100° (0.2 mm.) was collected and amounted to 2.65 g. During some experiments the hydroxyketone slowly crystallized from this fraction, m.p. 48–49°, the melting point of a mixture of this ketone and that ketone from the hydrolysis of the epoxyether (IV) was not depressed. An aliquot of the distillate was converted to a semicarbazone derivative, m.p. 208–210°. The melting point of a mixture of this derivative and a similar derivative of VII, was not depressed, 208–210°. The total yield[14] of α-hydroxycyclohexyl phenyl ketone, isolated as the semicarbazone, was found to be 11%. That the hydroxyketone is stable to distillation was shown by a distillation of 5 g. of pure crystalline hydroxyketone at 1 mm. pressure.

The hydroxyketone (1 g., 4.9 millimoles), 0.8 g. (5.7 millimoles) of benzoyl chloride and 3 ml. of pyridine were refluxed for 12 hours and then poured onto 10 ml. of H_2O. The organic material was extracted with ether and the ether evaporated. The product was recrystallized from low-boiling petroleum ether to give 0.88 g. (54%) of α-hydroxycyclohexyl phenyl ketone benzoate, identical with IX (R is C_6H_5) by mixture melting point determination.

DETROIT 1, MICHIGAN RECEIVED AUGUST 7, 1951

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(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 94.

(13) P. J. Tarbouriech, *Compt. rend.*, **149**, 604 (1909).

(14) *Cf.* reference 6 in which this type of reaction is used to prepare β-*p*-dimethylaminobenzoin in 25% yield.