[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE UNIVERSITY]

Epoxyethers. V. The Reaction of Perbenzoic Acid with Vinyl Ethers

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The reaction of perbenzoic acid with the vinyl ether, 2-methyl-1-ethoxy-1-phenylpropene (II), was shown to give the epoxyether, 1,2-epoxy-2-methyl-1-ethoxy-1-phenylpropane (I), in 90% yield. With the alicyclic vinyl ether, 1-cyclohexenyl ethyl ether (VI), the benzoic acid formed in the initial reaction mixture reacted with the epoxyether to give the ketobenzoate (IV). Evidence is presented that the alcohol formed in this latter reaction further reacts with epoxyether to give the hydroxyketal V. Also, perbenzoic acid was shown to cleave an epoxyether VIII to give an ester IX.

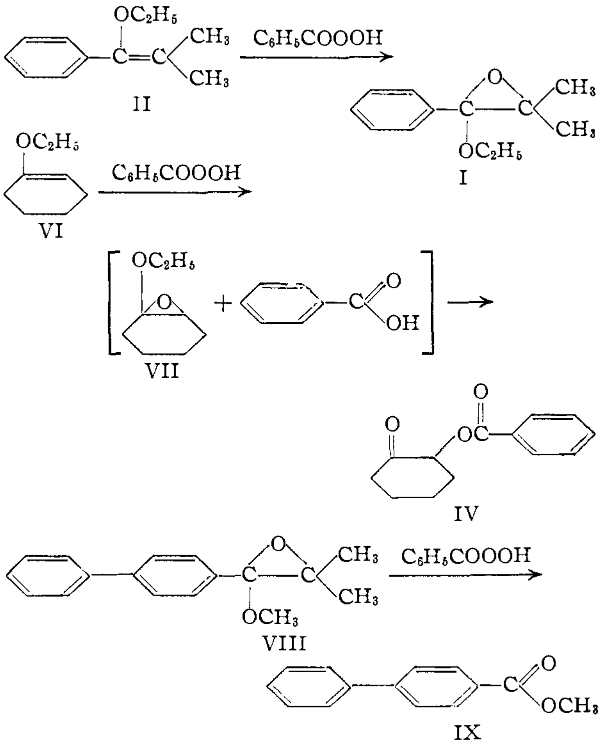
The present investigation resulted in the isolation of a pure epoxyether I from the reaction of a vinyl ether II with perbenzoic acid. With 1-cyclohexenyl ethyl ether (III) and perbenzoic acid the resulting epoxyether and benzoic acid reacted together too rapidly to permit isolation of the epoxyether.

As early as 1921, Bergmann[2] reported that the reaction of vinyl ethyl ether with perbenzoic acid gave an epoxyether. Later he discussed the compound in terms of a dimer.[3]

Hurd[4] in 1949 claimed the isolation of a crude epoxyether from the reaction of dihydropyrane with perbenzoic acid. Recently, Mousseron[5] reported that 1-cyclohexenyl ethyl ether and excess perbenzoic acid gave after 12 hours 75% of the corresponding epoxyether.

Epoxyethers have been prepared and characterized recently in this Laboratory.[6] A characteristic of the various epoxyethers isolated thus far has been their rapid reaction with benzoic acid. After the reaction of a vinyl ether with perbenzoic acid the main components of the reaction mixture should be the epoxyether and benzoic acid. A further complication in the peracid reaction was indicated by the work of Gallagher,[7] who presented evidence that an epoxyether also reacted with a peracid. Since authentic epoxyethers were available in this Laboratory for comparison and determination of suitable isolation procedures, a study of the peracid reaction was undertaken.

The first epoxyether chosen for synthesis was 1,2-epoxy-2-methyl-1-ethoxy-1-phenylpropane (I). Of the epoxyethers isolated in this Laboratory, those from α-bromoisobutyrophenone[8] were among the least reactive with benzoic acid. Preliminary rate determinations indicated that the corresponding vinyl ether, 2-methyl-1-ethoxy-1-phenylpropene (II), reacted much more rapidly at 0° with perbenzoic acid than the epoxyether I reacted with benzoic acid.



The pure epoxyether I could be synthesized in 90% yield by allowing an ether solution of the vinyl ether II and perbenzoic acid to react for a short reaction time (30 seconds), after which the benzoic acid was removed by passing the reaction mixture rapidly (30 seconds) through a column containing activated alumina. The identity of the epoxyether was established by comparison of the infrared spectrum with an infrared spectrum of an authentic sample as well by the preparation of the ketobenzoate derivative.

The initial reaction mixture could not be separated satisfactorily by extraction with dilute sodium hydroxide solution, since partial hydrolysis of the epoxyether occurred.

Until the present investigation, the structures of the epoxyethers have been assigned on the basis of the physical properties (particularly the infrared spectra) and the ring opening reactions. The independent synthesis recorded here completes an unequivocal proof of structure of the epoxyether I and is considered to confirm the structural assignments of the other epoxyethers, which have properties similar to I and which were made from α-bromoketones.

Mousseron[9] reported the isolation of epoxyethers

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(1) Parke, Davis and Co. Postdoctoral Fellow, 1952–1953.

(2) M. Bergmann and A. Miekeley, *Ber.*, **54**, 2153 (1921).

(3) M. Bergmann and A. Miekeley, *ibid.*, **62**, 2297 (1929).

(4) C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, **14**, 680 (1949).

(5) M. Mousseron and R. Jaquier, *Bull. soc. chim. France*, 698 (1950).

(6) (a) C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4758 (1950); (b) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952); (c) C. L. Stevens, M. L. Weiner and R. C. Freeman, *ibid.*, **75**, 3977 (1953).

(7) B. Belbau and T. F. Gallagher, *ibid.*, **74**, 2816 (1952).

(8) Epoxyethers from α-bromoisobutyrophenone were first prepared in this Laboratory by Mr. Thomas H. Coffield and I had been prepared previously by Mr. Donald L. Dorward.

(9) M. Mousseron and R. Jaquier and A. Fontaine, *Bull. soc. chim. France*, 767 (1952).

from the reaction of α-chlorocyclohexanone with base and from the reaction of the enol ether of cyclohexanone and perbenzoic acid. Since this alicylic epoxyether was needed in this Laboratory for other studies, α-chlorocyclohexanone was allowed to react with sodium methoxide in alcohol following the directions of Mousseron as closely as possible. A product was isolated which had the same physical properties as those recorded by Mousseron but which proved to be α-hydroxycyclohexanone dimethyl ketal (III). The infrared spectrum indicated a hydroxyl group and a solid 3,5-dinitrobenzoate as well as a benzoate derivative of the hydroxyketal was prepared. The ketal group of the ketalbenzoate was preferentially cleaved with dilute acid to give the crystalline benzoate of α-hydroxycyclohexanone (IV).[10] With alcoholic sodium ethoxide, chlorocyclohexanone gave the diethyl ketal V which was characterized in a similar manner.

The ether solution of the ethyl enol ether of cyclohexanone (VI) was allowed to react with an ether solution of perbenzoic acid for 30 seconds at 0° and then quickly (30 seconds) passed through a column of activated alumina. From the effluent 61% of the benzoate of α-hydroxycyclohexanone (IV) was isolated and proven by comparison with the authentic sample prepared above. From the previous work[6] a ketobenzoate IV is the expected product of the reaction of an epoxyether with benzoic acid.

Since an infrared spectrum of the remaining oil indicated the presence of α-hydroxyketal (V), a small amount of ethyl alcohol was added to the reaction of the enol ether VI and perbenzoic acid. From this reaction a 74% yield of the α-hydroxycyclohexanone diethyl ketal was isolated and the structure proved by comparison with the authentic sample prepared above and by the preparation of a solid derivative. Previously, epoxyethers have been shown to react with alcohols[6] to give α-hydroxyketals.

These experiments indicate that the epoxyether VII is an intermediate in the reaction of perbenzoic acid with 1-cyclohexenyl ethyl ether (VI), but that the benzoic acid reacts very rapidly with the epoxyether. The alumina column did not catalyze the latter reaction, since the ketobenzoate could be isolated in 42% yield when the initial reaction was quenched after 30 seconds with sodium carbonate solution.

Also, the experiments indicate that the reaction between ethyl alcohol and the epoxyether competes successfully with the reaction between the epoxyether and benzoic acid. Since the reaction of the epoxyether with benzoic acid liberates a mole of alcohol, these facts readily explain the formation of some α-hydroxyketal V from the reaction of pure enol ether VI with pure perbenzoic acid.

Further attempts to isolate the epoxyether from the peracid reaction with the vinyl ether by allowing the benzoic acid to react preferentially with diazomethane failed.

Gallagher[7] recently reported the reaction of excess perbenzoic acid with a vinyl ether to give cleavage of the vinyl ether with the formation of an ester. He proposed that an epoxyether was an intermediate in this cleavage. Since this reaction represented a further complication in the synthesis of epoxyethers from vinyl ethers, a pure solid epoxyether,[11] 1,2-epoxy-1-methoxy-2-methyl-1-(*p*-biphenyl)-propane (VIII), was treated with perbenzoic acid. The proposal of Gallagher was confirmed in that the perbenzoic acid reacted slowly with the epoxyether and from the reaction 27% of solid ester IX was isolated. The structure was proven by comparison with an authentic sample prepared independently.

Experimental

1,2-Epoxy-2-methyl-1-ethoxy-1-phenylpropane (I).—This epoxyether was prepared by a procedure[8] which involved the reaction of the bromoketone with dry sodium ethoxide suspended in ether followed by isolation of the epoxyether by pouring the reaction mixture on ice and extraction with ether. From 50 g. (0.23 mole) of α-bromoisobutyrophenone and alcoholic sodium methoxide made from 6 g. (0.26 g. atom) of sodium and 100 ml. of absolute ethanol was isolated 31 g. (70%) of the epoxyether I, b.p. 73–74° (1.0 mm.), $n^{25}\text{D}$ 1.4840, $d^{25}{}_4$ 0.9900.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.16; H, 8.51.

3,5-Dinitrobenzoic acid reacted with the epoxyether to give the 3,5-dinitrobenzoate derivative of α-hydroxyisobutyrophenone, m.p. 151–152°.

Anal. Calcd. for $C_{17}H_{14}N_2O_7$: C, 56.98; H, 3.91. Found: C, 56.96; H, 3.81.

The ketobenzoate derivative of the epoxyether, α-hydroxyisobutyrophenone benzoate, melted at 63–64° and was obtained in 70% yield in an experiment starting with 15 millimoles of the epoxyether.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.98; H, 6.01.

Isobutyrophenone Diethyl Ketal.—The procedure employed was an adaptation of the method of Beals and Gilfillan.[12] From 155 g. (1.1 moles) of ethyl orthoformate, 190 ml. of absolute ethanol, 140 g. (0.95 mole) of isobutyrophenone and 0.5 ml. of concentrated hydrochloric acid was obtained 95 g. (39%) of isobutyrophenone diethyl ketal, b.p. 119–122° (15 mm.). An analytically pure sample had b.p. 113–114° (10 mm.), $n^{23}\text{D}$ 1.4803.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.64; H, 9.97.

2-Methyl-1-ethoxy-1-phenylpropene (II).—To a solution of isobutyrophenone diethyl ketal (23 g., 0.103 mole) and 60 ml. of pyridine was added 29 g. (0.20 mole) of phosphorus pentoxide. The mixture was vigorously stirred and heated to 100° for a period of five hours. The cooled mixture was filtered and the precipitate was washed with 50 ml. of anhydrous ether. The filtrate was concentrated and the residue was distilled to give 13.1 g. (72%) of enol ether II, b.p. 96–97° (8 mm.), $n^{23}\text{D}$ 1.51828.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.67; H, 9.41.

Epoxylation of 2-Methyl-1-ethoxy-1-phenylpropene (II).—The perbenzoic acid was prepared by the method of Braun,[13] recrystallized from *n*-hexane and analyzed prior to use.

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(10) Previously the benzoate prepared from α-hydroxycyclohexanone was reported to melt at 122° (A. Kötz, K. Blendermann, R. Rosenbush and E. Sirringhaus, *Ann.*, **400**, 62 (1913)) and 87° (M. Bergmann and M. Gierth, *ibid.*, **448**, 72 (1926)). The above series of reactions, which gave the ketobenzoate melting at 85–86°, is considered to prove the structure of this product. Sheehan (J. C. Sheehan, R. C. O'Neill and M. A. White, THIS JOURNAL, **72**, 3376 (1950)) recently showed solid α-hydroxycyclohexanone to be a dimer with a dioxane-type structure. The benzoate, m.p. 122°, is undoubtedly the benzoate of this dimer.

(11) C. L. Stevens and S. J. Dykstra, THIS JOURNAL, **75**, 5975 (1953).

(12) E. L. Beals and F. A. Gilfillan, *J. Am. Pharm. Assoc.*, **25**, 426 (1936).

(13) G. Braun, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 431.

To a solution of 1 g. (5.7 millimoles) of enol ether II in 10 ml. of absolute ether, which had been cooled to 0°, was added a solution of perbenzoic acid (98% pure, 5.7 millimoles) in 5.3 ml. of absolute ether cooled to 0°. After shaking the flask in an ice-bath for 30 seconds, the ether solution was rapidly (30 seconds) passed through a column containing activated alumina (15 × 125 mm.) and the column was washed with 25 ml. of absolute ether. The effluent was concentrated *in vacuo* and 0.98 g. (90%) of epoxyether I was obtained. The structure was proved by comparison of the infrared spectrum with that of authentic epoxyether prepared above and by preparation of the ketobenzoate derivative. From 0.7 g. (3.6 millimoles) of the epoxyether a 62% yield of the benzoate of α-hydroxyisobutyrophenone, m.p. 60–62°, was isolated after reaction with benzoic acid. A mixture melting point with the ketobenzoate prepared above was not depressed.

α-Hydroxycyclohexanone Dimethyl Ketal (III).[14]—Following the directions of Mousseron as closely as possible, 7 g. (0.052 mole) of α-chlorocyclohexanone[15] in 50 ml. of absolute methanol was added to a solution of 2.99 g. (0.13 g. atom) of sodium in 150 ml. of anhydrous methanol cooled to 5°. After 12 hours at room temperature the mixture was poured onto cracked ice and quickly extracted with ether. The ether solution was dried with anhydrous sodium sulfate and the ether evaporated. After distillation of the cyclopentanecarboxylic acid ester, 2 g. (24%) of colorless α-hydroxycyclohexanone dimethyl ketal (III), b.p. 85–86° (12 mm.), $n^{23}\text{D}$ 1.4645, was obtained.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.91; H, 10.03.

An infrared spectrum indicated the presence of a hydroxyl group and a 3,5-dinitrobenzoate derivative was prepared from 1 g. of the hydroxyketal, 1.45 g. of 3,5-dinitrobenzoyl chloride and 3 ml. of anhydrous pyridine. After recrystallization from ligroin, the derivative melted at 97–98°.

Anal. Calcd. for $C_{15}H_{18}N_2O_8$: C, 50.84; H, 5.12; OCH_3, 17.45. Found: C, 50.34; H, 5.03; OCH_3, 17.78.

From 3 g. of the hydroxyketal III and 2.7 g. of freshly distilled benzoyl chloride was obtained 2.9 g. (57%) of the benzoate of α-hydroxycyclohexanone dimethylketal, b.p. 138–140° (2 mm.), $n^{24}\text{D}$ 1.5122.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.27; H, 7.55.

The ketal group was cleaved by heating at the reflux temperature for one hour a solution of 0.85 g. of the ketal benzoate in 12 ml. of methanol and 3 ml. of concentrated hydrochloric acid. After the solvents were removed under reduced pressure, the residue crystallized and was recrystallized from ligroin to give 0.34 g. (49%) of α-hydroxycyclohexanone benzoate, m.p. 85–86°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.03; H, 6.63.

α-Hydroxycyclohexanone Diethyl Ketal (V).—The procedure described above for the preparation of the dimethyl ketal was used. From 40 g. of α-chlorocyclohexanone and alcoholic sodium ethoxide 6 g. (11%) of α-hydroxycyclohexanone diethyl ketal was obtained, b.p. 96–97° (8 mm.), $n^{21}\text{D}$ 1.4528.

Anal. Calcd. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.49; H, 10.34.

The 3,5-dinitrobenzoate was prepared in 46% yield from 0.5 g. of the hydroxy diethyl ketal, m.p. 110–112°. Recrystallization from *n*-hexane raised the melting point to 112–113°.

Anal. Calcd. for $C_{17}H_{22}N_2O_8$: C, 53.41; H, 5.80. Found: C, 53.44; H, 5.98.

1-Cyclohexenyl Ethyl Ether (VI).—Cyclohexanone diethyl ketal was prepared in 71% yield according to the directions of Böeseken,[16] b.p. 70–72 (10 mm.), $n^{24}\text{D}$ 1.4336. The enol ether VI was prepared according to the directions of Arbuzov[17] and obtained in 50% yield, b.p. 49–50° (9 mm.), $n^{25}\text{D}$ 1.4550.

Epoxylation of 1-Cyclohexenyl Ethyl Ether (VI).—A solution of 1-cyclohexenyl ethyl ether (0.9 g., 7.15 millimoles) in 10 ml. of absolute ether was cooled to 0° and to this solution was added 7 ml. of a cooled solution (0°) of recrystallized perbenzoic acid (90% pure, 7.15 millimoles) in ether. After the mixture was shaken for 30 seconds, the ether solution was rapidly passed through an activated alumina column (12 × 130 mm.). The column was washed with 50 ml. of additional ether. The effluent was concentrated *in vacuo* and the crystalline residue was washed with *n*-pentane to give 0.95 g. (61%) of the benzoate of α-hydroxycyclohexanone (IV) as colorless needles, m.p. 80–82°. Recrystallization from *n*-hexane raised the melting point to 84.5–85.5° and admixture of this sample with an authentic sample prepared above did not depress the melting point. The infrared spectra of the two products were identical.

The above experiment was repeated using chloroform as solvent. Under these conditions, a 52% yield of the ketobenzoate IV, m.p. 81–83°, was isolated.

This experiment was further modified by quenching the reaction mixture after thirty seconds with 10% sodium carbonate solution. From the reaction a 42% yield of ketobenzoate, m.p. 82–84°, was obtained.

α-Hydroxycyclohexanone Diethyl Ketal (V) from VI.—A solution of 1 g. (7.9 millimoles) of enol ether VI in 10 ml. of chloroform was cooled to 0° and treated with a cooled solution (0°) of recrystallized perbenzoic acid (90% pure, 8.1 millimoles) in 3 ml. of absolute ethanol and 8.5 ml. of chloroform. After 30 seconds, the solution was warmed to room temperature (three minutes) and passed through an activated alumina column (17 × 150 mm.). The column was washed with additional chloroform and the combined effluent was concentrated to constant weight (1.1 g., 74%). The infrared spectrum of this product was found to be identical in all respects to the spectrum obtained from an authentic sample of V.

The 3,5-dinitrobenzoate derivative was prepared from the above product in 50% yield, m.p. 110–112°. Admixture of this product with an authentic sample did not depress the melting point.

Reaction of an Epoxyether (VIII) with Perbenzoic Acid.—A solution of 2.0 g. (7.9 millimoles) of 1,2-epoxy-2-methoxy-1-methyl-1-(*p*-biphenyl)-propane[11] (VIII), m.p. 78–79°, and recrystallized perbenzoic acid (90% pure, 8 millimoles) in 30 ml. of benzene was allowed to stand at room temperature for 24 hours and then heated to the reflux temperature for 5 hours. The cooled solution was extracted with 50 ml. of 10% sodium carbonate solution. After extracting the aqueous layer twice with 20-ml. portions of ether, the ether and benzene layers were combined and concentrated. The residue was dissolved in a small amount of ether and the solution passed through an activated alumina column (17 × 190 mm.). The colorless plates obtained from the first effluent fraction were recrystallized from *n*-hexane to give 0.35 g. (27%) of methyl *p*-phenylbenzoate, m.p. 113–115°. Sublimation of a portion of this material gave an analytically pure sample, m.p. 114–115°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.25; H, 5.70. Found: C, 79.31; H, 5.75.

A cold solution of 1 g. (5.0 millimoles) of *p*-phenylbenzoic acid, m.p. 223–226°, in 50 ml. of ether was treated with an ethereal solution of diazomethane. After one hour, the ether was removed under reduced pressure and the remaining residue was recrystallized from *n*-hexane to give 0.82 g. (77%) of colorless plates of methyl *p*-phenylbenzoate, m.p. 114–115°. The identity of this product with that obtained from the peracid reaction was established by a comparison of their infrared spectra and by a mixture melting point determination.

Acknowledgment.—The authors wish to thank Mr. Michael Papo and Miss Phylis Tocco, who performed the microanalyses.

DETROIT 1, MICHIGAN

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(14) This experiment was performed by Dr. E. Farkas.

(15) Prepared by the method of M. S. Newman and M. D. Farbman (THIS JOURNAL, **66**, 1551 (1944)) in 62% yield.

(16) J. Böeseken and F. Tellegen, *Rec. trav. chim.*, **57**, 133 (1938).

(17) A. E. Arbuzov and B. M. Mikhailova, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 390 (1936).