[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Epoxyethers XIII.[1,2] Determination of Stereochemistry

CALVIN L. STEVENS AND THOMAS H. COFFIELD[3]

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A method for the determination of the stereochemical structures of epoxyethers was developed and applied to the epoxyether I. On the basis of this investigation the epoxyether was assigned the *trans* structure.

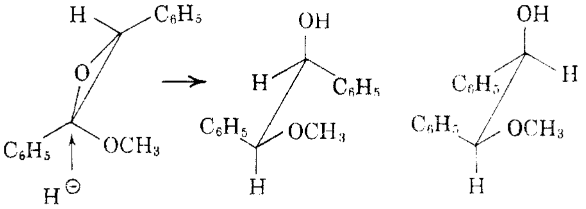
During the course of the investigation of the chemistry of epoxyethers in this laboratory, two solid epoxyethers[4,5] have been isolated from the reaction of *alpha* haloketones with methoxide ion in which both carbon atoms of the epoxide were asymmetric. In each case the product isolated was one of the two possible diastereoisomers as evidenced by the narrow melting point range after repeated recrystallization. In neither case could evidence be obtained for the presence of the other diastereoisomer in the reaction mixture. A consideration of the chemistry of these epoxyethers indicated that a method for the determination of the stereochemistry of the epoxyethers was necessary. The method that was developed in this investigation involved reduction of the epoxyether with hydride ion followed by determination of the stereochemistry of products and assignment of stereochemical structure to the epoxyether on the basis of the assumption that hydride ion attacked the epoxyether with inversion.

The epoxyether chosen for this study was I,[4] since the final products could be related directly to the meso- and DL-hydrobenzoin, which stereochemical structures are known with certainty.

Hydride ion was chosen as the reagent since previous work had indicated attack would occur cleanly at the ketal carbon of the epoxide.[1] Further, since the assignment of the stereochemical structure of the epoxyethers must rest at present upon the prediction of the stereospecificity of the reagent, the known opening of ordinary epoxides by hydride ion with inversion[6] was one stereospecific reaction which was judged likely to proceed with the same stereochemical course in the epoxyether series.

The epoxyether was made in 54% yield by a modification of the procedure previously reported.[4] The product was isolated from the reaction mixture as a low melting solid in substantially pure form. Reduction of the epoxyether with lithium borohydride gave 43% of the monomethyl ether of DL-hydrobenzoin (II) and 1% of the diastereoisomeric monomethyl ether of *meso*-hydrobenzoin-(III). In addition, 9% of benzyl phenyl carbinol-(IV) was isolated. The three products were separated by a combination of fractional crystallization and chromatography.

Of the two diastereomeric compounds, II is the lower melting and more soluble isomer and presumably would be the less stable and the less favored isomer in a non-stereospecific reaction. Considering the difficulty of purifying II in the presence of small amounts of III, the isolation of 43% of II *vs.* 1% of III indicated that the reaction is almost completely stereospecific and, on the assumption that hydride attacks with inversion, shows the epoxyether I to have the *trans* configuration.



I (*trans*) II (*DL*—derivative) III (*meso*—derivative)

The diastereoisomers II and III had been prepared previously in this laboratory[4] and were used for comparison to prove the stereochemical structures of the products of the reaction. The *p*-nitrobenzoate derivatives of II and III were prepared in *ca.* 60% yield and also were identical with authentic samples.

Since the diastereoisomeric *p*-nitrobenzoate derivatives had a reverse melting point and solubility relationship compared with the parent compounds, the reaction products from the reduction were converted directly to a mixture of the derivatives and then separated. This procedure gave 60% of the crude derivative of II without the aid of chromatography and indicated that the amount of II in the reaction mixture was considerably higher.

Although lithium aluminum hydride had been used previously to reduce epoxyethers to the corresponding methoxy alcohols, lithium borohydride was the only hydride useful for epoxyether I.

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(1) The previous paper is "Epoxyethers XII. Reduction with Lithium Aluminum Hydride," *J. Am. Chem. Soc.*, in press.

(2) This work was supported in part by the Office of Ordnance Research, U. S. Army.

(3) U. S. Public Health Service Pre-doctoral Fellow, 1953–1954.

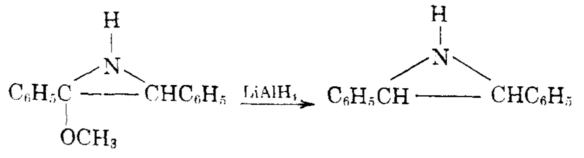
(4) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Am. Chem. Soc.*, **75**, 3977 (1953).

(5) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **76**, 4402 (1954).

(6) L. W. Trevoy and W. C. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).

Lithium aluminum hydride reacted rapidly with I to give 75% of benzyl phenyl carbinol. In view of the fact that the nitrogen analog (V) of the epoxyether I is reduced by lithium aluminum hydride to the corresponding ethylene imine,[7] the formation of the carbinol likely involves a similar displacement of methoxide followed by further reduction of the resulting stilbene oxide.

Sodium borohydride was also unsuited as a reagent for this study since the epoxyether was not reduced by this reagent.



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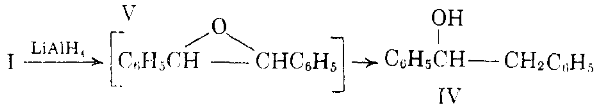

EXPERIMENTAL

1,2-Diphenyl-1-methoxyethylene oxide (I). The compound could be conveniently prepared in 54% yield by allowing equivalent amounts of sodium methoxide and desyl chloride to react in absolute methanol solution for two minutes at the reflux temperature. The solution was then cooled to −80° in a Dry Ice–acetone bath and the solid which precipitated was filtered and recrystallized from a petroleum ether–ether mixture, m.p. 56–57°. The product was identical with the product from the previously published procedure,[4] the yield from which was 33%.

Monomethyl ether of DL-*hydrobenzoin* (*II*) *by lithium borohydride reduction of I.* A mixture of 1.5 g. (0.068 mole) of lithium borohydride and 75 ml. of dry ether was refluxed for 6 hr. The mixture was then allowed to settle and the clear supernatant solution was decanted and cooled to −60°. The solution was stirred and another cooled solution of 6 g. (0.026 mole) of the epoxyether I in 75 ml. of ether was slowly added. The temperature was allowed to rise to room temperature and the mixture was then stirred an additional two hours. Excess saturated ammonium chloride solution was added and the ether layer separated, dried, and concentrated. The residual oil was crystallized from petroleum ether to give 1.3 g. of II, m.p. 56–57°. Alumina chromatography of the filtrate gave an additional 1.3 g. of II, m.p. 56–57°, 0.07 g. (1%) of the monomethyl ether of *meso*-hydrobenzoin III, and 0.5 g. (9%) of phenyl benzyl carbinol, m.p. 65–66°.

The total yield of II was 2.6 g. (43%) and was shown to be identical with an authentic sample made by independent synthesis.[4]

The *p*-nitrobenzoate derivative of II was prepared by the sodium dispersion method previously described.[1] From 0.5 g. of II was obtained 0.4 g. (50%) of product, m.p. 110–112°. The mixture melting point of this derivative with that obtained from the independently synthesized material was undepressed.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 70.26; H, 5.15.

The *p*-nitrobenzoate of the diastereoisomer III was prepared in 60% yield by the same method, m.p. 78–80°. The same derivative was obtained from the product of the reaction mixture or from authentic III.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07. Found: C, 69.71; H, 5.02.

In another experiment the crude reaction mixture was converted to the *p*-nitrobenzoate derivative. Reduction of 17.6 g. (0.075 mole) of I as described above gave 16.5 g. of oil after concentration of the ether solution. Before the product began to crystallize from the oil a 2-g. aliquot was converted to the *p*-nitrobenzoate derivative. One recrystallization of the product from petroleum ether gave 2.1 g. (60%) of the *p*-nitrobenzoate of II, m.p. 105–109°. A second recrystallization gave 1.53 g., m.p. 109–111°.

Reduction of I with lithium aluminum hydride. The epoxyether I was reduced with lithium aluminum hydride in the same manner as described for lithium borohydride except that the reduction was started at 0°. From 3 g. of I was obtained 2.1 g. (75%) of phenyl benzyl carbinol, m.p. 65–66°. A mixture melting point with an authentic sample was not depressed.

DETROIT 2, MICH.

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(7) M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Rearrangement and Condensation of Reissert Compounds with Grignard Reagents. III

NORMAN C. ROSE AND WILLIAM E. McEWEN

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Reissert compounds (1-acyl-1,2-dihydroquinaldonitriles and 2-acyl-1,2-dihydroisoquinaldonitriles) undergo reaction with Grignard reagents in ether-dioxane to form tertiary carbinols containing the 2-quinolyl or 1-isoquinolyl group as one of the substituents bonded to the carbinol carbon atom. The scope of this reaction has been expanded, and evidence has been uncovered which shows that the initial reaction is one between the Reissert compound and RMgX, present in the solid phase of the reaction mixture. A 1-acylisoquinoline or a 2-acylquinoline is formed as an intermediate, and this α-acyl heterocyclic derivative can undergo further reaction to form a salt of the carbinol either with R_2Mg in solution or with RMgX in the solid phase.

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) undergo reaction with Grignard reagents to form tertiary alcohols of structures III and IV, respectively.[1,2] It has been established[2] that the mechanism of the reaction in ether-dioxane solution consists of an

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(1) W. E. McEwen, J. V. Kindall, R. N. Hazlett, and R. H. Glazier, *J. Am. Chem. Soc.*, **73**, 4591 (1951).

(2) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).