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Stereochemistry of the Prins Reaction with Cyclohexene

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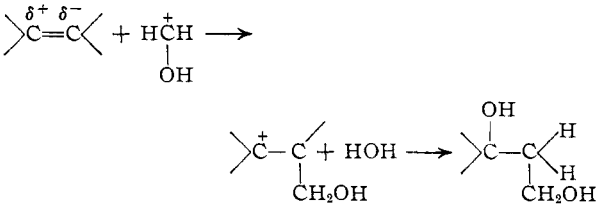
The reaction of formaldehyde with cyclohexene in acid media has been shown to give *trans*-2-hydroxymethyl-1-hydroxycyclohexane as the only 1,3-diol. No *cis*-diol was obtained.

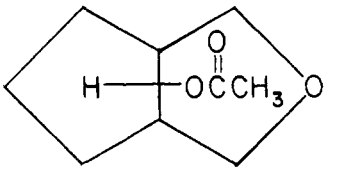
The mechanism of the Prins reaction has been reviewed and reported by Franzen and Krauch[1] to involve the initial protonation of formaldehyde followed by attachment of the hydroxymethyl carbonium ion to the double bond and finally solvolysis of the resulting carbonium ion. We have



investigated the stereochemistry of this reaction using cyclohexene and have found that only *trans*-diol is formed. Blomquist and Wolinsky[2] have studied this same reaction and have obtained the same results. We prepared the *cis*- and *trans*-2-hydroxymethyl-1-hydroxycyclohexane by reduction of 2-carbethoxycyclohexanone. Catalytic reduction gave predominantly *cis*-2-carbethoxycyclohexanol.[3] The *trans*-2-carboxycyclohexanol was obtained by epimerization of the *cis* compound in basic solution. The *cis*- and *trans*-2-carboxycyclohexanol esters were reduced to the corresponding 1,3-diols with lithium aluminum hydride. The *cis*-diol was shown to be a solid while the *trans*-diol and the product obtained from the Prins reaction were viscous liquids. Infrared spectra of *trans*-diol and the Prins reaction product were superimposable while the *cis*-diol spectra were found to differ markedly above the 8μ region.

The configuration has been shown to be *trans*. The exact mechanism of the reaction cannot be postulated until the conformational aspects have been studied. If the mechanism reported in the paper of Franzen and Krauch[1] was correct, a mixture of *cis*- and *trans*-diol should be obtained. If the initial attack of the hydroxymethylcarbonium ion is axial, then the resulting *trans*-diol must go to the flip conformation to produce the acetonide which we isolated. The conformational study would require a system incapable of undergoing a change in conformation once it is formed.

Other products are obtained during the Prins reaction, and these have been discussed by Olsen and Padberg[5] and more recently by Blomquist and Wolinsky.[2] One of the most important of these is hexahydrophthalanyl acetate, reported by Blomquist and Wolinsky to have the structure



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Experimental

Preparation of *trans*-2-Hydroxymethyl-1-hydroxycyclohexane by the Prins Reaction.[4]—Two hundred grams (2.22 moles) of trioxane, 1200 ml. of glacial acetic acid and 100 ml. of concentrated sulfuric acid were placed in a 2-l. three-necked flask. The mixture was heated (100–110°) until the trioxane depolymerized. The solution was allowed to cool to room temperature and 480 g. (5.84 moles) of freshly distilled cyclohexene was added dropwise over a period of 2 hr., the temperature being maintained between 45 and 65°. After completion of addition, the mixture was heated for 1.5 hr. at 65° and then stirred for 24 hr. at room temperature. One liter of water was then added to the mixture and the solution was extracted with three 750-ml. portions of ether. The ether was washed with water, saturated sodium bicarbonate solution until neutral and then with water. After concentration the crude product was fractionally distilled. The following higher boiling fractions containing the desired product were obtained: 1, b.p. 78–87° (0.80 mm.), 164 g.; 2, b.p. 88–93° (0.80 mm.), 179 g. Fraction 2 consisted, for the most part, of the diacetate of 2-hydroxymethyl-1-hydroxycyclohexane. Fraction 1 was found to contain only about 50% of the desired diacetate of the 1,3-glycol, the remainder consisting of the hexahydrophthalanyl acetate postulated by Olsen and Padberg.[5]

Fraction 2 (179 g.) was saponified with a solution of 94 g. of potassium hydroxide dissolved in 300 ml. of 6:1 aqueous alcohol. The solution was concentrated *in vacuo* and then extracted with ether. Fractional distillation gave a quantitative yield of a very viscous, water-clear, odorless glycol, b.p. 101–103° (0.96 mm.), $n^{25}D$ 1.4840, bis-phenylurethan, m.p. 159–160°.

Saponification of fraction one (163.4 g.) yielded only 42 g. (49%) of the desired glycol. The remainder consisted of hexahydrophthalanol whose structure was postulated by Olsen and Padberg.[5]

The over-all yield of *trans*-2-hydroxymethyl-1-hydroxycyclohexane (configuration proved by infrared comparison with stereospecifically prepared *trans*-glycol) was found to be 150 g. (19.7%). Acid hydrolysis of the formaldehyde acetal of 2-hydroxymethyl-1-hydroxycyclohexane also yields the *trans*-glycol. This acetal is found in lower boiling fractions and is stable to base.

Preparation of 2-Carbethoxycyclohexanol.—Seventy-three and eight-tenths grams (0.433 mole) of 2-carbethoxycyclohexanone,[6] 70 ml. of absolute ethanol and 1.5 g. of Adams catalyst were placed in a hydrogenation apparatus.[7] The mixture was hydrogenated for 48 hr. at room temperature and five atmospheres pressure. The theoretical amount of

(1) V. Franzen and H. Krauch, *Chem. Ztg.*, **79**, 335 (1955).
(2) A. Blomquist and J. Wolinsky, THIS JOURNAL, in press.
(3) J. Pascual, J. Sistane and A. Regas, *J. Chem. Soc.*, 1943 (1949).
(4) J. Matti, *Bull. soc. chim. France*, **51**, 974 (1932).
(5) S. Olsen and H. Padberg, *Z. Naturforsch.*, **1**, 448 (1946).
(6) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 531.
(7) Reference 6, Coll. Vol. I, p. 61.

hydrogen was consumed and on fractional distillation, 65 g. (87%), of *cis*-2-carbethoxycyclohexanol, b.p. 125–217° (27 mm.), $n^{25}D$ 1.4585 (lit.[3] 117–118° (17 mm.)).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.94; H, 9.47.

Preparation of *cis*-2-Carboxycyclohexanol.—A mixture of 14.5 g. (0.08 mole) of 2-carbethoxycyclohexanol (95% *cis*) and 45 ml. of 25% aq. sodium hydroxide was stirred for 12 hr. The sodium salt of *cis*-2-carboxycyclohexanol acid separated and was filtered. It was dissolved in a small amount of water and the solution made acid to congo red with 10% hydrochloric acid. The aqueous solution was saturated with ammonium sulfate and extracted with ether. The ether-soluble material was recrystallized from a small amount of ether to give 5.4 g. (44%) of the *cis*-acid, m.p. 79–80° (lit.[3] 80–81°).

Preparation of *cis*-2-Carbomethoxycyclohexanol.—To a cooled solution of 5.1 g. (0.035 mole) of *cis*-2-carboxycyclohexanol in 25 ml. of ether was added an ether solution of diazomethane at 0–5°. Fractional distillation gave a quantitative yield of the desired ester, b.p. 87.5–88.5° (3 mm.), $n^{25}D$ 1.4647 (lit.[3] b.p. 105° (14 mm.), $n^{25}D$ 1.4645).

Preparation of *cis*-2-Hydroxymethyl-1-hydroxycyclohexane.—To a solution of 1.44 g. (0.038 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether, we added 5.4 g. (0.034 mole) of *cis*-2-carbomethoxycyclohexanol in an equal volume of ether at such a rate as to maintain slow refluxing. After addition was complete, the mixture was refluxed and stirred for an additional 1.5 hr. The excess lithium aluminum hydride was decomposed with moist ether followed by water and the metal alkoxides with cold dilute sulfuric acid. The aqueous solution was saturated with ammonium sulfate and extracted with ether. Distillation of the resulting glycol yielded a very viscous, colorless oil, b.p. 124° (2 mm.). On standing several hr. the glycol crystallized, m.p. 48–49° (lit.[8] 49–50°).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.65; H, 10.48.

The di-*p*-nitrobenzoate of *cis*-2-hydroxymethyl-1-hydroxycyclohexane was prepared by the usual procedure for these derivatives, m.p. 133.5–134 (lit.[9] 134°). The mono-*p*-nitrobenzoate, previously unreported, also was isolated, m.p. 95–96°.

Anal. Calcd. for $C_{14}H_{17}O_5N$: C, 60.28; H, 6.14; N, 5.02. Found: C, 59.60; H, 6.03; N, 5.00.

Preparation of *trans*-2-Carboxycyclohexanol.—The mother liquors from the preparation of *cis*-2-carboxycyclohexanol were concentrated *in vacuo* and refluxed with 7.5 *N* potassium hydroxide. The mixture was cooled, acidified to congo red with sulfuric acid and saturated with ammonium sulfate. The aqueous solution was extracted several times with ether. The *trans*-acid was recrystallized from ethyl acetate, m.p. 109–111° (lit.[3] m.p. 111°).

In a similar epimerization 12.1 g. (0.072 mole) of sodium *cis*-cyclohexanol-2-carboxylate was transformed into the *trans*-acid by refluxing with base. The yield was 5.6 g. (54%) of pure *trans*-acid.

Preparation of *trans*-2-Carbomethoxycyclohexanol.—The procedure was identical to that used for the *cis*-ester. Fractional distillation yielded a quantitative amount of the *trans*-methyl ester, b.p. 99.8–101.8° (2 mm.), m.p. 34–35°, $n^{25}D$ 1.4632.

Preparation of *trans*-2-Hydroxymethyl-1-hydroxycyclohexane.—The procedure was identical to that used to prepare the *cis*-diol above. A solution of 1.3 g. (0.032 mole) of lithium aluminum hydride in 100 ml. of ether was used to reduce 4.54 g. (0.029 mole) of *trans*-2-carbomethoxycyclohexanol. Fractional distillation yielded 2.4 g. (63%) of a viscous, colorless oil, b.p. 103.5–104° (0.9 mm.), $n^{25}D$ 1.4829, which was shown by comparison of infrared spectrum to be identical with the glycol obtained from the Prins reaction.

The acetonide of *trans*-2-hydroxymethyl-1-hydroxycyclohexane was prepared, b.p. 106–107° (30 mm.), 214–216° (740 mm.), $n^{25}D$ 1.4602.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.60; H, 10.75.

The bis-phenylurethan of *trans*-2-hydroxymethyl-1-hydroxycyclohexanol melted at 159–160.5° (lit.[5] m.p. 160–161).

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

Epoxyethers. XI. O→O Acyl Migrations with α-Hydroxyacylals

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1,2-Epoxy-1-methoxy-2-methylpropane (X) was isolated in good yield from the reaction of α-haloisobutyraldehydes with dry sodium methoxide. This epoxyether X reacted with organic acids to form relatively stable α-hydroxyacylals XI (pseudoesters) which readily underwent O → O acyl migration with the loss of alcohol to give esters of α-hydroxyisobutyraldehyde (XIII). At 150°, the 3,5-dinitrobenzoate pseudoester XI eliminated 3,5-dinitrobenzoic acid to form the dioxane derivative IX.

The reaction of an organic acid with an epoxyether has been shown previously to give an α-ketoester. In one example, the intermediate α-hydroxyacylal could be isolated and was shown to undergo irreversible O→O acyl migration to form the α-ketoester and alcohol.[3] Acylals derived from aldehyde epoxyethers were found to be relatively more stable than those from ketone epoxyethers, one being distilled under reduced pressure without decomposition.[4] Since the O→O acyl migration is accompanied by formation of a carbonyl group in α-hydroxyacylals, these compounds provide unique and simple examples for the study of such migrations. The present work demonstrates that the more stable acylals from aldehyde epoxyethers can also be made to undergo acyl migration.

The aldehyde epoxyether chosen for this study was that from isobutyraldehyde. The starting α-chloroaldehyde I was prepared in 60% yield by direct chlorination of isobutyraldehyde using a modification of the method of Brown and Ash.[4,5]

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(2) Abstracted from the dissertation submitted by B. T. Gillis in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Wayne University, 1956.

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