nesium derivative which is formed whenever the dibromo derivative reacts with organic magnesium compounds, several samples obtained with ethylmagnesium bromide were analyzed. As the substance could not be recrystallized its composition was found to be somewhat variable but the results show that it is a dimagnesium bromide derivative.

Anal. Calcd. for $C_{13}H_{10}S_2O_4Br_2Mg_2$: C, 31.0; H, 2.0; S, 12.7; Br, 31.8; Mg, 9.7. Found: C, 31.1; H, 2.3; S, 12.7; Br, 29.0; Mg, 9.5.

The Mono Benzoyl Derivative XX.—A suspension of the dimagnesium derivative which had been obtained in the usual manner in ether–benzene was treated with benzoyl chloride; the mixture was boiled for four hours, during which time it had turned into an orange-brown powder. The usual manipulations resulted in the isolation of a compound which crystallized from acetone–alcohol in colorless cubes melting at 180°.

Anal. Calcd. for $C_{20}H_{16}S_2O_5$: C, 60.0; H, 4.0. Found: C, 59.9; H, 4.2.

The benzoyl derivative does not give a ferric chloride reaction but is soluble in dilute aqueous alkalies and can be recovered from the alkaline solution by acidification.

The Diphenylmethyl Derivative XXI.—When diphenylmethyl bromide was substituted for benzoyl chloride in the preceding experiment the product was a compound which crystallized from acetone–alcohol in small needles melting at 193°.

Anal. Calcd. for $C_{26}H_{22}S_2O_4$: C, 67.5; H, 4.8. Found: C, 67.3; H, 5.0.

Summary

Reactions between organic magnesium compounds and α-halo ketones may result in enolization, metathesis, addition, or elimination of halogen hydride. This communication contains a number of examples which supply a basis for predicting which of these possible reactions is most likely to occur in a given case.

CAMBRIDGE, MASS. RECEIVED NOVEMBER 23, 1934

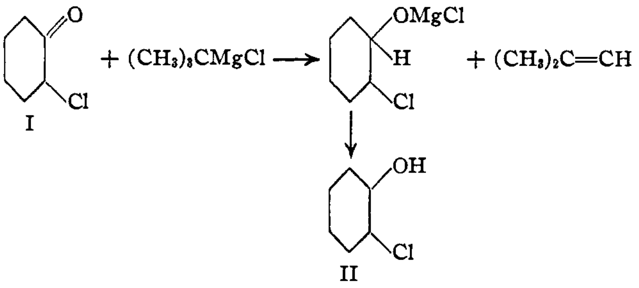
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Cis- and *Trans*-Chlorohydrins of Cyclohexene[1]

BY PAUL D. BARTLETT

It has been observed in two cases[2] that cyclic α-chloro ketones react with the Grignard reagent to give chlorohydrins (designated as "B-isomers") which do not form epoxy compounds, and which on strong alkaline treatment give instead ketones. It is well known that the reaction of secondary and tertiary Grignard reagents upon highly branched ketones[3] and even upon cyclohexanone[4] is primarily one of reduction rather than of addition. If this reduction, applied to 2-chlorocyclohexanone (I), occurs in the same stereochemical sense as the addition of methylmagnesium bromide, then it should yield the hitherto unknown "B"-isomer of 2-chlorocyclohexanol (II). The "A"-isomer of this compound is well known.[5]

Reductions of 2-chlorocyclohexanone were carried out with the cyclohexyl, isopropyl, and tertiary butyl Grignard reagents, with yields of 27, 64 and 72%, respectively, of crude reduction product. Fractionation of this product yielded an oil of b. p. (26 mm.) 93-94°, closely resembling the A isomer.



Refluxed with aqueous sodium hydroxide it gave cyclohexanone, together with a smaller amount of cyclohexene oxide. Since neither the A-isomer, nor cyclohexene oxide itself, is capable of giving cyclohexanone under these conditions, there was evidently a new chlorohydrin present.

The rate of reaction of this product with sodium hydroxide in 50% alcohol was measured at 25° by acid titration. The results, plotted in Fig. 1, show that 27% of the chlorohydrin reacts rapidly, the remainder slowly, with alkali. The fast-reacting fraction has the same rate of reaction with alkali as was determined separately for

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[1] Presented in part before the Organic Division at the Cleveland meeting of the American Chemical Society, September 12, 1934.

[2] Bartlett and Rosenwald, THIS JOURNAL, **56**, 1990 (1934); Bartlett and White, *ibid.*, **56**, 2785 (1934).

[3] Conant and Blatt, *ibid.*, **51**, 1229 (1929).

[4] Kohler and Thompson, *ibid.*, **55**, 3822 (1933).

[5] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, 1932, p. 151.

the A-chlorohydrin, a rate more than 300 times greater than that of the B form.

Treating with cold sodium hydroxide served to convert the A-chlorohydrin in the mixture into cyclohexene oxide, from which the remaining B-chlorohydrin could be separated by distillation. This purified material, on boiling with alkali, gave no oxide, but a 76% yield of cyclohexanone, identified by mixed melting point of its semicarbazone.

The isomeric chlorohydrins of cyclohexene are secondary alcohols and, in contrast to the two isomeric pairs previously described, yield crystalline α-naphthylurethans. A comparison of the properties of the two isomers is given in Table I.

TABLE I

ISOMERIC CHLOROHYDRINS OF CYCLOHEXENE

	Isomer A	Isomer B
d_{35}	1.1233	1.1261
$n^{35}\text{D}$	1.4832	1.4860
B. p. (26 mm.), °C.	93	93–94
Relative viscosities (33°)	1	1.23
M. p. of α-naphthylurethan, °C.	165	94
k (in liter/moles × min.) for reaction with NaOH:		
0°	0.680	....
25°	10.7	0.0334
57°	....	0.853
α in equation $k = \alpha e^{-E/RT}$	1.23×10^{14}	1.10×10^{13}
E, cal.	17,800	19,800

The large difference between the isomers in their rate of reaction with sodium hydroxide offers a convenient titration method of estimating the composition of a mixture of the two. This method of titration, applied to the crude product from reduction of 2-chlorocyclohexanone with the cyclohexyl, isopropyl, and tertiary butyl Grignard reagents, showed in each case 27–28% A-isomer and 72–73% B.

The Addition of Hypochlorous Acid to Cyclohexene.—Hypochlorous acid was added to cyclohexene under a variety of conditions, to determine whether such influences as heat, light, acidity, peroxides, and antioxidants have any important effect in determining *cis* or *trans* addition to the double bond. Under none of the conditions tried was there any reversal of the usual mode of addition. Within the limits of accuracy of the method (two or three per cent.) it appears that pure A-2-chlorocyclohexanol is formed from cyclohexene and hypochlorous acid when the method of "Organic Syntheses"[5] is modified by carrying out the reaction at 50°, or at 0°, in dim light, in bright sunlight, with a two- to six-fold excess of nitric acid, in the presence of cyclohexene peroxide, and with cyclohexanol as an antioxidant.[6]

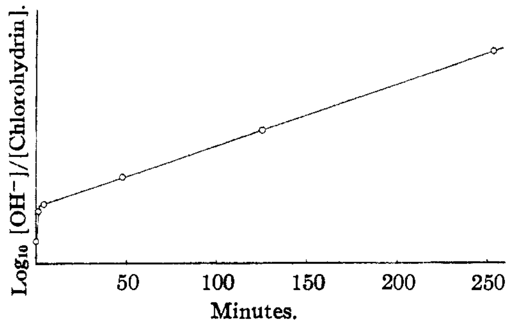
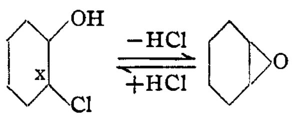


Fig. 1.—Rate of reaction with sodium hydroxide of reduction product of 2-chlorocyclohexanone at 25°.

Opening of the Oxide Ring.—Two methods of opening the oxide ring—the action of zinc chloride in dry ether and the reaction with concentrated hydrochloric acid—gave products titrating for 94 and 99% A-isomer, respectively. In boiling point and in melting point (27°) these were the best samples of isomer A which we obtained. The reaction

(A) 

is then completely reversible, and no conversion of one chlorohydrin isomer into the other can be accomplished by this means.

To test whether Isomer A could be converted into Isomer B by reaction with chloride ion, possibly involving inversion at the point marked x,[7] a 0.1 *M* solution of the chlorohydrin in 50% alcohol was treated with 0.5 *M* potassium chloride at 81° for eight days, at the end of which period it still showed less than 3% of Isomer B.

The Configurations of the Isomers.—Experiments leading to a proof of the configurations of the A and B chlorohydrins are now in progress. The bulk of the evidence is in favor of the common, oxide-forming chlorohydrin (A) possessing the *trans*-configuration, the opening and closing of the oxide ring being attended by complete Walden inversion. This evidence comes from several directions: (1) in a case of oxide forma-

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(6) Small quantities of cyclohexanol inhibit the autoxidation of cyclohexene (H. N. Stephens, private communication).

(7) Compare Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **20B**, 161 (1933).

tion previously studied from the point of view of configuration,[8,9] that of the *cis*- and *trans*-ethylene oxide dicarboxylic acids, there is good evidence that elimination of hydrogen chloride from the chlorohydrins takes place 100% *trans* in each case. (2) *Trans* cleavage of the cyclohexene oxide ring has been established in the addition of water[10] and of dimethyl- and diethylmagnesium.[11] (3) While the stereoisomeric chlorohydrins of the cyclohexane series show but slight differences in their physical properties, their cyclopentane homologs show much larger differences.[12] These differences are in the direction to be predicted on the assumption that the isomer which forms an oxide has the *trans* configuration. (4) According to recent investigations of Polanyi, Bergmann, Olson, and their co-workers,[13] a Walden inversion is the normal course of any one-step substitution reaction occurring at a secondary carbon atom, and involving the replacement of one atom by another of similar polar character.

The possibility of a *trans*-cyclohexene oxide existing has been taken into account in several discussions of this problem.[14] If such a *trans* oxide is capable of existence, it should be related to one of the cyclohexene chlorohydrins as the *cis* oxide is related to the other. Kuhn and Ebel[8] have found that the *cis*- and *trans*-ethylene oxide dicarboxylic acids are formed from their respective chlorohydrins at rates which differ by a factor of 11,000. This is a very much larger difference than is observed (300) between the rates of reaction of the present isomeric chlorohydrins with alkali. Here, evidently, the rate of formation of ketone comes in magnitude between the rates of formation of the isomeric oxides, and shuts off the possibility of obtaining the second oxide. Since only one cyclohexene oxide is known, it seems probable that it is the *cis* form, an assumption which underlies the arguments for the configuration of the chlorohydrins.

Experimental

Reduction of 2-Chlorocyclohexanone with Grignard Reagents.—The procedure was the same in all cases. One mole of *t*-butyl chloride was converted into the Grignard reagent over a five-hour period; 60 g. of 2-chlorocyclohexanone,[2a] freshly redistilled (b. p. 103–105 (27 mm.)) was diluted with twice its volume of anhydrous ether and added to the Grignard reagent under reflux with stirring as rapidly as possible without loss of ether, the flask being cooled with an ice-bath. Gas[15] was copiously evolved. The product was hydrolyzed by pouring on ice, washed with dilute sulfuric acid, water, and sodium carbonate, dried with calcium sulfate, and distilled under 27 mm. pressure. On the first distillation, all but 4.4 g. of residue passed over below 93°. On the second fractionation, the following fractions were obtained: below 80°, 3 g.; 80–90°, 8.8 g. (odor of cyclohexanol); 90–92°, 16.7 g.; 92–93°, 15.3 g.; residue, 6 g. In analyzing various products for halogen, the Stepanov method was at first used; when it was found that this method checked well with the titration method, the latter was used thereafter.

Anal. Calcd. for $C_6H_{11}OCl$: Cl, 26.35. Found: 90–92° fraction, 24.84; 92–93° fraction, 25.23.

Removal of Isomer A.—The combined fractions boiling from 90 to 93° at 27 mm. (32 g.) were added to 2.9 g. of sodium hydroxide dissolved in 5 cc. of water, and enough alcohol added to make a homogeneous solution. The sodium chloride was filtered off, the alcohol distilled, and the product fractionated. Although the isomer A could be removed by this method, a non-chlorine-containing impurity remained in the best fraction of the product (b. p. 93–94° (26 mm.)) which lowered the chlorine content from the calculated 26.35 to 25.23%. No method was found for eliminating this impurity.

Velocity Constants.—Temperature control was obtained with an ice-bath, a thermostat at 25°, and a reaction tube jacketed with the vapor of boiling acetone. Reactions were followed over about 90% of their course, affording a rigorous check of the order of the reaction. The maximum error of the velocity constants reported is about 5%. The reaction was stopped in each sample in the 0° runs by pipetting into a known excess of acetic acid, and titrating back with sodium hydroxide.

Determining the composition of a mixture of the isomeric chlorohydrins was accomplished by the following procedure: six drops of chlorohydrin and 5 cc. of 0.208 *N* sodium hydroxide in 50% alcohol were held at 25° for four minutes, and then titrated with standard acid. Another 5 cc. of the 0.208 *N* alkali was then added, and the mixture held at 80° for five minutes and again titrated. The ratio of the first and second amounts of sodium hydroxide consumed is the ratio of chlorohydrins A and B in the mixture.

α-Naphthylurethans were prepared from the chlorohydrins and equivalent α-naphthyl isocyanate, held at 100° for four hours.

Anal. Calcd. for $C_{17}H_{18}NO_2Cl$: C, 67.2; H, 5.98. Found for A-isomer: C, 67.2; H, 6.08; for B-isomer: C, 67.5; H, 6.05.

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(8) Kuhn and Ebel, *Ber.*, **58**, 919 (1925).

(9) Kuhn and Wagner-Jauregg, *ibid.*, **61**, 483, 504 (1928).

(10) Van Loon, Thesis, Delft, 1919; Böeseken and van Giffen, *Rec. trav. chim.*, **39**, 184 (1920).

(11) Bartlett and Berry, THIS JOURNAL, **56**, 2683 (1934).

(12) Bartlett and White, Ref. 2. These larger differences are attributed to the planar character of the cyclopentane ring, which will prevent interaction of *trans* substituents.

(13) Hartel, Meer and Polanyi, *Z. physik. Chem.*, **19B**, 139 (1932); Bergmann, Polanyi and Szabo, *ibid.*, **20B**, 161 (1933); Olson, *J. Chem. Phys.*, **1**, 418 (1933); Olson and Long, THIS JOURNAL, **56**, 1294 (1934).

(14) See Böeseken, *Ber.*, **58**, 1470 (1925); Kuhn and Ebel, Ref. 8, p. 922; Hückel, "Der Gegenwärtige Stand der Spannungstheorie," p. 58.

(15) Isobutylene: Noller, Grebe and Knox, THIS JOURNAL, **54**, 4690 (1932).

The "relative viscosities" reported in the table are the relative times of flow from a 5-cc. pipet.

Stability of Cyclohexene Oxide to Alkali.—Ten cc. of cyclohexene oxide was refluxed for six hours with 20 cc. of 10% sodium hydroxide solution, separated, dried and distilled. The cyclohexene oxide was unchanged, b. p. 129° (740 mm.).

The author is indebted to the Graduate School of the University of Minnesota for a grant from its research funds, and to Dr. Frank Stodola for the carbon and hydrogen analyses.

Summary

1. Reduction of 2-chlorocyclohexanone with the cyclohexyl, isopropyl, and *t*-butyl Grignard reagents gives predominantly a new isomer of 2-chlorocyclohexanol, which forms cyclohexanone instead of cyclohexene oxide on treatment with alkali.

2. The isomeric chlorohydrins of cyclohexene differ very slightly in their physical properties, but more than 300-fold in their rate of reaction with alkali.

3. Addition of hypochlorous acid to cyclohexene, or hydrogen chloride to cyclohexene oxide, yields only the oxide-forming chlorohydrin.

4. Indirect evidence is discussed that the oxide-forming chlorohydrin has the *trans* configuration.

MINNEAPOLIS, MINN.
CAMBRIDGE, MASS.

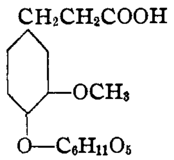
RECEIVED NOVEMBER 28, 1934

NOTE

Glucosidodihydroferulic Acid[1]

BY NELSON K. RICHTMYER AND RAYMOND M. HANN

A recent study has shown that phenyl glucosides may be cleaved to a considerable extent by hydrogenation in the presence of platinum catalysts.[2] The reduction of an ethylenic linkage in the side chain of a substituted phenyl glucoside, however, may be effected quantitatively with the aid of palladium and hydrogen. Thus, tetraacetylglucosidoferulic acid[3] was converted to the dihydro compound, which in turn was smoothly deacetylated by sodium methylate to produce glucosidodihydroferulic acid



Experimental

Tetraacetyl-*β*-*d*-glucosidodihydroferulic Acid (*β*-(3-Methoxy-4-tetraacetyl-*β*-*d*-glucosidophenyl)-propionic Acid).—A solution of 8.5 g. of tetraacetylglucosidoferulic acid in 140 cc. of glacial acetic acid was shaken with 1.7 g. of palladium black in an atmosphere of hydrogen for three hours; 361 cc. of gas, equivalent to one mole, was absorbed. The solution was filtered from the catalyst, and the solvent allowed to evaporate at room temperature in a vacuum desiccator over potassium hydroxide. The residue crystallized spontaneously and represented the theoretical yield of reduced acid.

Tetraacetyl-*β*-*d*-glucosidodihydroferulic acid crystallizes from solution in twenty parts of 50% methyl alcohol in brilliant colorless plates. It melts to a clear colorless oil at 155° (corr.) and shows an $[\alpha]^{20}_{D}$ value of −24.9° (0.2854 g. in 10 cc. of chloroform in a 1-dm. tube rotated 0.71° to the left). Upon recrystallization the $[\alpha]^{20}_{D}$ value was −25.2° (0.2060 g. in 10 cc. of chloroform in a 1-dm. tube rotated 0.52° to the left), and the average value of −25.0° is accepted for the compound.

Anal. Calcd. for $C_{24}H_{30}O_{13}$: C, 54.73; H, 5.75; OCH_3, 5.90. Found: C, 54.77; H, 5.88; OCH_3, 6.21.

***β*-*d*-Glucosidodihydroferulic Acid (*β*-(3-Methoxy-4-*β*-*d*-glucosidophenyl)-propionic Acid).**—Forty and four-tenths cubic centimeters of 0.94 *N* sodium methylate solution was added slowly to a solution of 5.0 g. of the acetylated acid in 100 cc. of dry chloroform at −3°. After one-half hour an equivalent quantity of 5 *N* sulfuric acid was added and the solution was concentrated *in vacuo* to dryness. The glucosido acid was separated from the sodium sulfate by repeated extractions with hot 95% alcohol, and crystallized readily in rosets of short needles upon concentrating and cooling. The crude yield was 3.3 g. (quantitative). It was recrystallized from 3 parts of 95% alcohol.

β-*d*-Glucosidodihydroferulic acid is readily soluble in water and in this medium shows an $[\alpha]^{20}_{D}$ value of −56.9° (0.2620 g. in 10 cc. in a 1-dm. tube rotated 1.49° to the left). It melts at 179–180° (corr.) to a clear colorless oil.

Anal. Calcd. for $C_{16}H_{22}O_9$: C, 53.60; H, 6.19. Found: C, 53.59; H, 6.26.

This work has been materially aided by a grant to one of us (N.K.R.) from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

CHEMICAL LABORATORY OF
BRYN MAWR COLLEGE, AND
NATIONAL INSTITUTE OF HEALTH
U. S. PUBLIC HEALTH SERVICE
WASHINGTON, D. C.

RECEIVED OCTOBER 22, 1934

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(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Richtmyer, THIS JOURNAL, **56**, 1633 (1934).

(3) Hann, *ibid.*, **52**, 5049 (1930); **56**, 1631 (1934).