

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

The Reaction of Epichlorohydrin with the Grignard Reagent

BY J. K. MAGRANE, JR., AND D. L. COTTLE

The reaction of epichlorohydrin with Grignard reagents has been reported by many workers. Some¹ obtained only 1,3-dihalo-2-propanols while others² obtained the same substance as the major product and 1-chloro-3-alkyl(or aryl)-2-propanols. It has long been known that, when a Grignard reagent is treated with ethylene oxide at room temperature or below,³ the main product is an ethylene halohydrin and that the condensation product can be obtained by raising the temperature.⁴ On the other hand, when epichlorohydrin is the oxide, raising the temperature or increasing the time of reaction lowers the yield of the analogous condensation product.^{2b}

It is impossible to explain the above facts with the theory advanced by Grignard⁴ that heating breaks the oxide ring, thus causing it to react with the alkylmagnesium bond and diminishing the quantity of oxide that reacts with the magnesium halide after hydrolysis. On the other hand, there are insufficient data in the literature to support an unqualified explanation by means of the theory advanced by Blaise,³ Ribas and Tapia^{2e,5} and others that ethylene oxides react spontaneously with both the alkylmagnesium and magnesium bromide bonds. It was the purpose of this investigation to test the application to epichlorohydrin of the latter theory which has been used so successfully in explaining the behavior of certain substituted ethylene oxides.⁶

If the more recent theory is correct, it is reasonable to suppose that the alkoxide,⁷ whether formed from epichlorohydrin and magnesium bromide in ether or ether-benzene solutions or from 1-bromo-3-chloro-2-propanol and an alkylmagnesium bro-

(1) Kling, *Compt. rend.*, **137**, 756 (1903); cf. Delaby, *ibid.*, **176**, 1153 (1923); Fourneau and Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1227 (1907).

(2) (a) Iotsitch, *ibid.*, **28**, 920 (1902); **34**, 185 (1905); **32**, 740 (1904); these are abstracts of articles as follows: *J. Russ. Phys.-Chem. Soc.*, **34**, 96 (1902); **36**, 6 (1904); **35**, 554 (1903); (b) Koelsch and McElvain, *This Journal*, **51**, 3390 (1929); (c) **52**, 1164 (1930); (d) Ribas and Tapia, *Añal. soc. españ. fis. quim.*, **28**, 636 (1930); (e) **30**, 944 (1932).

(3) Blaise, *Compt. rend.*, **134**, 552 (1902).

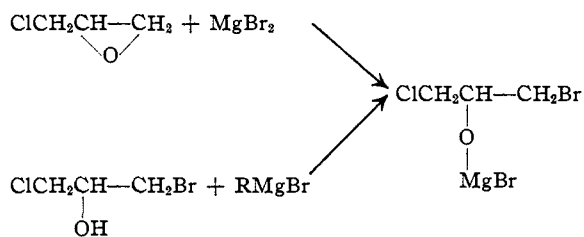
(4) Grignard, *Bull. soc. chim.*, [3] **29**, 944 (1903).

(5) Ribas and Tapia, *Añal. soc. españ. fis. quim.*, **30**, 778 (1932).

(6) (a) Bartlett and Berry, *This Journal*, **56**, 2683 (1934); (b) Cottle and Powell, *ibid.*, **58**, 2267 (1936); (c) Golumbic and Cottle, *ibid.*, **61**, 996 (1939).

(7) No attempt has been made here to differentiate between alkoxy magnesium halides and dialkoxy magnesiums; cf. Huston and Agett, *J. Org. Chem.*, **6**, 123 (1941).

mide, should undergo similar changes on being treated with ethylmagnesium bromide. When the



reaction product from epichlorohydrin and magnesium bromide was treated with ethylmagnesium bromide, ethane, ethylene and a low molecular weight alcohol with the properties that would be expected of cyclopropanol were identified. 1-Bromo-3-chloro-2-propanol, on similar treatment gave, after substitution of the hydroxyl hydrogen, the same substances. Both reactions also produced noteworthy amounts of tar.

Koelsch and McElvain^{2b} observed that ethane, ethylene and hydrogen were produced when epichlorohydrin was allowed to stand with ethylmagnesium bromide. Inasmuch as it was found during the present work that 1-chloro-2-pentanol behaves normally in giving 4-heptanol and neither gas nor tar on treatment with ethylmagnesium bromide, after the hydroxyl hydrogen has been replaced, it is evident that the magnesium salt of the 1,3-dihalopropanol was the cause of the formation of gases and tar.

Our observations on the direct reaction of epichlorohydrin with ethylmagnesium bromide largely parallel those of Koelsch and McElvain^{2b} and Ribas and Tapia^{2d,5} with the exception that we were able to isolate a compound that appears to be cyclopropanol from reaction mixtures that were allowed to stand for some time.

With the above knowledge, a better method for the preparation of 1-chloro-2-pentanol was devised. One mole of magnesiumdiethyl was treated with two moles of epichlorohydrin and 70-83% yields of 1-chloro-2-pentanol were obtained. A non-volatile residue similar in appearance to the tar mentioned above also was obtained. Other workers^{6a,c} have obtained gummy and resinous by-products in treating cyclohexene oxide and styrene oxide with dialkylmagnesiums.

An examination of the lower boiling fractions from the action of ethylmagnesium bromide on magnesium 1-bromo-3-chloro-2-propoxide revealed a small amount of bland liquid, which boiled at 100–103°, (d_{20}^{20} 0.9110, n_D^{20} 1.4129) was completely soluble in water and in ether, contained no halogen and gave a vigorous reaction with sodium, phenyl isocyanate and acetyl chloride. The last reaction gave a water-insoluble product of an ester-like odor but an attempt to obtain isolable quantities from a later specimen gave an indefinite product of wide boiling range. It is concluded that this substance is cyclopropanol (a) because its derivatives from treatment with phenyl and α -naphthyl isocyanates and with dinitrobenzoyl chloride are unlike those obtained with the simple low boiling alcohols, (b) because of its physical properties and (c) because of its change to resins with alkalis, to an aldehyde on heating with formic acid and to propionaldehyde, in one instance, on repeated distillation. The change to an aldehyde is what would be expected from data on previously isolated cyclopropanols.⁸ The conclusion also is supported by the nature of the other products of the reaction and by the isolation in one experiment of 1-chloro-2-propanol. A search of an ether-extracted water layer of one experiment for 1,4-cyclohexanediol was fruitless.

Our subsequent experiments have given cyclopropanol fractions that invariably contained halogen, probably as epichlorohydrin, which fractional distillation or chemical treatment would not remove without damaging the alcohol. However, the work is being continued in an effort to identify the substance beyond question.

Experimental

The Reaction of Ethylmagnesium Bromide with Magnesium 1-Bromo-3-chloro-2-propoxide.—This substance, in experiments 1–6 below, was prepared by adding epichlorohydrin to magnesium bromide in dry ether in a molar ratio of 1:1. In experiments 7–11, it was prepared from 1-bromo-3-chloro-2-propanol and ethylmagnesium bromide. The Grignard column includes the amount of ethylmagnesium bromide used to replace the hydroxyl hydrogen of the dihalopropanol. The reaction mixtures were protected from the air and allowed to stand at room temperature, except as noted, until gas ceased being evolved.

In experiments 1, 2 and 7 the 1-bromo-3-chloro-2-propanol was identified by conversion to the diphenoxy derivative.⁹

(8) Ingold, *J. Chem. Soc.*, **119**, 326 (1921); Lipp and Padberg, *Ber.*, **54**, 1316 (1921); Lipp, Buchkremer and Seeles, *Ann.*, **499**, 8 (1932); Ingold, *J. Chem. Soc.*, **121**, 1197 (1922).

(9) Rössing, *Ber.*, **19**, 64 (1886).

TABLE I

Expt.	Epi-chloro-hydrin or dihalo-propanol in moles	EtMgBr in moles	Total volume of ether used	Time in days	Yield or recov. of dihalo-propanol in %	Cyclopropanol fraction in g.	Tar in g.
1	0.90	0.90	712	8	35	..	6
2 ^h	0.87	0.87	600 ^{a,h}	..	27	1.9 ^a	15
3	0.93	0.93	625	49	53	2.3	27
4	5.4	6 ^b	3860	49	41	59 ^{c,i}	30 ^c
5	2.0	2.0	1630	9 ^d	26	44 ^j	..
6	1.0	2.0	1600	12 ^e	13	6 ^{i,j}	17
7 ^h	0.46	0.93	340 ^g	.. ^h	39	..	4.9
8	0.87	1.76	600	52	47	5.3	5.2
9 ^h	0.44	0.88	325 ^g	.. ^h	36
10	2.6	7.8 ^b	2790	70	46	36 ^{i,j}	25
11	2.2	6.7 ^b	1500	2 ^f	16	54 ^{i,j}	36

^a Not investigated. ^b Moles of ethyl bromide. ^c Approximately a third of this experiment was lost. ^d At the end of nine days another mole of EtMgBr was added and the mixture allowed to stand for five more days. ^e Held at 40° for twelve days. ^f One day at room temperature and one day of refluxing. ^g 300 cc. of benzene was added before refluxing. ^h Refluxed: expt. 2, twelve hours; expt. 7, two hours; expt. 9, five hours. ⁱ The aqueous layer was kept acid throughout hydrolysis. ^j The aqueous layer resulting on hydrolysis was saturated with salt before extraction with ether.

In expts. 1 and 7, ethylene was identified by applying the mixed melting point method to ethylene bromide which was formed by absorbing the gas in bromine.

The gas from expts. 2 and 9 was bubbled through fuming sulfuric acid and 10% sodium hydroxide, saturated with bromine and passed through a U-tube in a sand-bath held at 370°. The resulting ethyl bromide, after distillation, was converted to propionanilide by means of the Grignard reaction and the mixed melting point method applied.

The saturated gases in expt. 7 measured 5 l. and in expt. 9, 6 l. The total gas evolved in expt. 6 was collected over water without removing the ether vapor and measured 19.5 l.

Fractionation of the products from expt. 11 gave 6.7 cc., b. p. 122–126°, and 1.7 cc., b. p. 126–132°. The latter fraction was treated with dinitrobenzoyl chloride and the dinitrobenzoate melted at 75.5–76.7° and contained 9.2% chlorine. The melting point of a dinitrobenzoate of 1-chloro-2-propanol obtained by the hydration of allyl chloride was 76.5–77.3°, and on admixture of the unknown dinitrobenzoate the melting point was 76.5–77.9°. The derivative from allyl chloride was further purified¹⁰ and found to melt at 82.3–83.5°. *Anal.* Calcd. for C₁₀H₉N₂O₆Cl: Cl, 12.24. Found: Cl, 12.28, 12.24.

Experiment 11 also gave 17 g. of a fraction, b. p. 67–71° (15 mm.), which contained halogen and gave a dinitrobenzoate melting at 127.0–128.5°.

In working up the ether extracts, the ether was removed by distillation through a 9-bulb Snyder column and the residues were fractionated by the use of Snyder and Weston columns. In expt. 4, for example, the following were the fractions collected: 87–100°, 3.7 g.; 100–101.5°,

(10) This preparation, the determination of the melting points and the analyses are from work done by C. H. Nielsen, M. E. Wassom and W. A. Raimond on the propylene chlorohydrins, which will be submitted for publication in the near future.

59.4 g.; 101.5–105°, 3.8 g.; 105–116°, 2.1 g.; 116–120°, 3.8 g.; 120–126°, 1.5 g.; 126–130°, 2.7 g.; 60–71° (8 mm.), 8.0 g.; 71–74° (8 mm.) 240 g.; residue 30 g. In expt. 8, the corresponding data are: 80–90°, 3.7 g.; 90–98°, 1.0 g.; 98–105°, 0.6 g.; to 84° (16 mm.), 1.2 g.; 84–88 (16 mm.), 71.2 g.; residue 5.2 g.

The Reaction of 1-Chloro-2-pentanol with Ethylmagnesium Bromide.—1-Chloro-2-pentanol (0.32 mole) was added dropwise to 0.636 mole of ethylmagnesium bromide in 144 cc. of ether and the mixture, protected from the atmosphere, allowed to stand for twenty days. No gas was evolved, after replacement of the hydroxyl hydrogen, and, after hydrolysis, ether extraction and drying, a fraction, b. p. 80–82° (40 mm.), containing 4-heptanol and unchanged 1-chloro-2-pentanol was obtained. There was no tar. The halohydrin was removed from the alcohol fraction as described under expt. 13 below, and the 4-heptanol was characterized by conversion to the α -naphthylurethan¹¹ and application of the mixed melting point method to a derivative prepared from Eastman Kodak Co. 4-heptanol.

Another experiment at lower concentration behaved similarly except that more of the 1-chloro-2-pentanol remained unchanged.

The Direct Reaction of Epichlorohydrin with Ethylmagnesium Bromide.—The following experiments were carried out by adding epichlorohydrin, mole for mole, to the ice-cooled Grignard in approximately 300 cc. of ether.

In expt. 12, 0.91 mole of epichlorohydrin was used, in expt. 13, 0.89 mole and in expt. 14, 0.82 mole. Experiment 12 was hydrolyzed immediately after it came to room temperature; expts. 13 and 14 were allowed to stand seven days and twenty-five days, respectively. These experiments gave the following yields of 1-chloro-2-pentanol (a), 1-bromo-3-chloro-2-propanol (b), cyclopropanol fraction (c) and tar (d): Experiment 12, 13% (a), 61% (b), no (c) and no (d); Experiment 13, 4.5% (a), 36% (b), 2.1 g. (c) and 7.4 g. (d); Experiment 14, 8.7% (a), 41% (b), 4.5 g. (c), and 8.6 g. (d).

The cyclopropanol in expt. 13 was converted to the α -naphthylurethan and the mixed melting point method was applied to it and to a similar derivative that came from a 1-bromo-3-chloro-2-propanol experiment.

In expt. 15, 0.9 mole of ethylmagnesium bromide in 300 cc. of ether was treated with 1.35 moles of epichlorohydrin. After removal of the ice-bath, the mixture refluxed spontaneously for two hours and was then hydrolyzed immediately. The yield, based on the Grignard reagent, was 35% for 1-chloro-2-pentanol and 78% for 1-bromo-3-chloro-2-propanol.

The specific gravity of the 1-chloro-2-pentanol from expt. 13 was low (d^{20}_{20} 0.9912) compared to that of the preparation from magnesiumdiethyl (d^{20}_{20} 1.031) and that from expt. 15 (d^{20}_{20} 1.028). The 1-chloro-2-pentanol from expt. 13 was treated with finely powdered sodium hydroxide in ether and, after filtration, the ether and pentene oxide were removed by distillation. The attempt to derivatize the residue, on the suspicion that it was 4-heptanol, with α -naphthyl isocyanate was fruitless.

The Reaction of Epichlorohydrin with Magnesiumdiethyl.—An ice-cooled solution of magnesiumdiethyl

(0.548 mole in 642 cc. of solution), prepared from ethylmagnesium bromide by the dioxane method, was treated with 1.10 moles of epichlorohydrin, the mixture allowed to reflux spontaneously for about a half-hour, cooled and hydrolyzed. A 70% yield of 1-chloro-2-pentanol (b. p. 66–67° (18 mm.), d^{20}_{20} 1.031, n^{20}_D 1.4422) and 4 g. of tar were obtained. A similar preparation gave a yield of 83%. The 3,5-dinitrobenzoate melted at 84–85°, which is the melting point reported by Koelsch and McElvain.^{2c}

Attempts to Isolate Cyclopropanol.—The ether extract from expt. 3 boiling below 160° was fractionated as follows: 1.8 g., up to 100°; 2.3 g., 100–103°; 3.3 g., 103–160°. On refractionation, the last fraction proved to be almost entirely 1-bromo-3-chloro-2-propanol and two-thirds of the first two fractions boiled at 101–103°. A sodium fusion test for halogen was negative. Inasmuch as later experiments, including those with 1-bromo-3-chloro-2-propanol, always produced a similar fraction containing halogen, the test was repeated at a later date and a negative test again obtained. It (d^{20}_{20} 0.9110 and n^{20}_D 1.4129) gave a typical alcohol test with metallic sodium, a water-insoluble substance with an ester-like odor with acetyl chloride, was soluble in water and in ether and reacted vigorously to give a phenylurethan (*Anal.* Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 8.0) melting at 102°. The derivative from treatment with α -naphthyl isocyanate melted at 101–102° and a mixture of the two urethans showed a lower melting point. Inasmuch as the α -naphthylurethans of isobutyl alcohol, of isopropyl alcohol and of allyl alcohol melt at 104, 106 and 109°, respectively, the melting points of mixtures of these urethans with the derivative from the supposed cyclopropanol were run and depressions were obtained. A derivative obtained on treatment with dinitrobenzoyl chloride melted at 109°, and on mixing with the dinitrobenzoate of methanol (m. p. 107°) the melting point was depressed.

Experiments that were run after this initial discovery were hydrolyzed and the aqueous layer saturated with salt before extracting with ether. The result was greatly increased yields of corresponding fractions (see Table I) that gave different values for the specific gravity and refractive index, the following being typical: d^{20}_{20} 0.9545; n^{25}_D 1.4125. These fractions obtained later invariably gave the same phenyl- or naphthylurethans, but gave strong tests for halogen even when the water layer was kept acid throughout hydrolysis. One fraction was analyzed and found to contain 8.6% halogen, calculated as chlorine. Cyclopropanol fractions from both epichlorohydrin and 1-bromo-3-chloro-2-propanol experiments produced magnesium hydroxide on being added to magnesium chloride solutions. An attempt to remove the halogen-containing compound by treatment with 30% potassium hydroxide gave products that were water-insoluble or resinous. Treatment with powdered sodium hydroxide in ether, solutions of magnesium chloride and precipitation of the halogen-containing substance with water either destroyed the product or did not completely remove the halogen. Treatment with magnesium chloride solution with the intermittent neutralization with acid gave 1,3-dichloro-2-propanol, identified by applying the mixed melting point method to the α -naphthylurethan, and a product boiling rather sharply at 100–101.8° (d^{25}_{25}

(11) Adkins, Connor and Cramer, *THIS JOURNAL*, **52**, 5197 (1930).

0.9426) but still containing a small amount of halogen. This material was lost in attempting to remove the last traces of halogen.

The substance appeared to form a binary with water boiling at 88–90° and an attempt was made to utilize this property but the results were not as satisfactory as with the magnesium chloride method.

The use of potassium carbonate as a drying agent for the supposed cyclopropanol was abandoned early in the work because it converted the product to higher boiling, water-insoluble substances that lost water during further purification by distillation. In a control experiment, in which 0.97 mole of 1-bromo-3-chloro-2-propanol was dissolved in 700 cc. of ether, the mixture saturated with water and dried with potassium carbonate for two weeks, 46% of the halohydrin was converted to epichlorohydrin, b. p. 114–117°.

Anhydrous copper sulfate did not give satisfactory results either and attempts to freeze the water out of ether solutions of the cyclopropanol fraction with dry-ice gave no ice crystals. Calcium sulfate was not tried because in one experiment 4-heptanol was changed to an olefin on being distilled after drying over Drierite. A similar experience with 3-methyl-2-butanol was encountered in this Laboratory.¹²

One cyclopropanol fraction after drying over sodium sulfate, later found to be quite neutral, gave, on several distillations through a 3-bulb Snyder column, a 7% yield of propionaldehyde, b. p. 46–52°, based on the bromochloropropanol used. The propionaldehyde was identified by conversion to the 2,4-dinitrophenylhydrazone and application of the mixed melting point method.

Attempts to Convert Cyclopropanol to Other Substances.—The substance absorbed bromine in carbon tetrachloride

(12) L. S. Powell, Doctor of Philosophy dissertation, 1936, Rutgers University, p. 51.

without evolving hydrogen bromide. Distillation produced considerable coke-like material but no well-defined product.

Concentrated hydrochloric acid, hydrochloric acid-zinc chloride reagent and phosphorus pentachloride all decomposed the compound and no definite product could be isolated. An attempt to acetylate a 6 cc. portion of impure material with 9 cc. of acetyl chloride resulted in a product with an ester-like odor but which distilled over a wide range, 90–118°, and left a residue. When formic acid (1 cc.) was heated with an equal amount of the alcohol, a strong odor of aldehyde was produced.

Attempt to Isolate 1,4-Cyclohexanediol.—An aqueous layer, that remained after hydrolysis and ether extraction of a bromochloropropanol experiment, was treated with potassium carbonate until precipitation was complete. The filtrate was concentrated by distillation, evaporated to dryness and the residue extracted thoroughly with a 50/50 mixture of anhydrous ether and absolute alcohol. Evaporation of the organic solvents gave no significant amounts of organic material.

Summary

The theory that ethylene oxides react spontaneously with both the alkylmagnesium and magnesium bromide bonds of the Grignard reagent was found completely satisfactory when applied to the reaction of epichlorohydrin with ethylmagnesium bromide.

Evidence found during the investigation pointed to the presence of cyclopropanol as a product of the reaction of epichlorohydrin and of 1-bromo-3-chloro-2-propanol with ethylmagnesium bromide.

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RECEIVED JULY 21, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Inhibition of the Proteolytic Action of Trypsin by Soaps

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It has long been known² that soaps are capable of inhibiting the proteolytic activity of trypsin. Earlier workers,³ using trypsin which had not been crystallized, showed that the amount of inhibition brought about in a given system was proportional to the amount of soap present, and that the inhibiting effect appeared to be greater the more unsaturated the soap. The phenomenon has been reinvestigated using crystalline trypsin and pure soaps. A simple quantitative system is described, and some results obtained are discussed.

Experimental

Materials.—In all of the experiments here described, crystalline trypsin was used.⁴ The substrate stock was a 5% solution of casein in 0.1 M phosphate buffer, pH 7.6, prepared as described by Northrop and Kunitz.⁵ The soap solutions were prepared just before use, by neutralization of a weighed sample of fatty acid with the calculated amount of aqueous potassium hydroxide solution and dilution. Oleic and linoleic acids were distilled in nitrogen

(4) (a) M. Kunitz and J. H. Northrop, *J. Gen. Physiol.*, **16**, 267 (1932); **19**, 991 (1935). (b) The preparation employed was a three times recrystallized sample very kindly furnished by Dr. J. H. Northrop, of the Rockefeller Institute for Medical Research. The small amount of magnesium sulfate present could be removed by dialyzing the solution of trypsin in 0.01 N HCl against 0.01 N HCl.

(5) J. H. Northrop and M. Kunitz, *ibid.*, **16**, 362 (1932).

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(2) J. Neumann, *Berl. Klin. Wchnschr.*, **65**, 2066 (1908).

(3) J. W. Jobling and W. Petersen, *J. Exp. Med.*, **19**, 239 (1914).