[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

## THE REACTION OF ETHYLENE OXIDE AND ETHYLENE BROMOHYDRIN WITH *n*-BUTYLMAGNESIUM BROMIDE

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The Organic Syntheses method for the preparation of 1-hexanol involves the addition of ethylene oxide to an ethereal solution of n-butylmagnesium bromide (1a). The over-all reaction may be represented by the following equation:

 $\mathrm{C_4H_9MgBr} \ + \ \mathrm{CH_2CH_2O} \ \rightarrow \ \mathrm{C_4H_9CH_2CH_2OMgBr}$ 

1-Hexanol is, of course, obtained upon hydrolysis of the magnesium salt.

The mechanism suggested by the above equation would be a nucleophilic attack by the carbanion of the Grignard reagent upon one of the carbon atoms of the ethylene oxide:

 $C_4H_9^-$  +  $CH_2CH_2O$   $\rightarrow$   $C_4H_9CH_2CH_2O^-$ 

However, such a mechanism does not account for the 2-hexanol which, as was found during the present work, is always one of the reaction products.

Evidence has been obtained by Huston and Agett (and by others whose work is reviewed by these authors) that the insoluble product of the reaction between one mole of ethylene oxide and one mole of alkylmagnesium bromide is the same as that obtained by passing the oxide into an etheral solution of magnesium bromide. The insoluble product may be represented by the empirical formula  $C_4H_8Br_2MgO_2$  (2). This material reacts with the dialkylmagnesium upon heating to yield magnesium bromide and the condensation product.

It has long been known that, when one mole of ethylene oxide is passed into one mole of Grignard reagent at room temperature or below, the main product obtained upon hydrolysis of the unheated solution is an ethylene halohydrin.

The structure of the ethylene oxide-magnesium bromide complex is unknown. Earlier workers favored  $(BrCH_2CH_2O)_2Mg$ , but according to Huston and Agett about half the bromine is ionic (2). It may be imagined that the structure is  $BrCH_2CH_2OMgBr \cdot CH_2CH_2O$ . Whatever the structure, condensation of this material with the dialkylmagnesium may involve to some extent the nucleophilic reaction mentioned previously, but most probably involves the following reaction to a greater extent:

 $C_4H_9^- + BrCH_2CH_2O^- \xrightarrow{\triangle} C_4H_9CH_2CH_2O^- + Br^-$ 

Neither of these nucleophilic reactions should give rearrangement (3).

Two pieces of evidence found during the present work support a theory that the  $BrCH_2CH_2O^-$  particle may, upon heating, lose a bromide ion (perhaps as

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a result of an electrophilic attack by magnesium) and then rearrange to acetaldehyde.

1. A violent reaction which occurred during the reaction of n-butylmagnesium bromide with ethylene bromohydrin resulted in a much higher yield of 2-hexanol than was obtained in a similar experiment in which the violent reaction did not take place.

2. The product of the reaction between ethylene oxide and magnesium bromide underwent a further violent reaction when heated in a bomb. The product of the final reaction appeared to be an acetaldehyde resin. In a parallel experiment, acetaldehyde gave a similar resin, but no violent reaction.

The possibility of the formation of acetaldehyde by dehydrobromination of the  $BrCH_2CH_2O^-$  particle under the influence of the proton acceptor RO<sup>-</sup> (or R<sup>-</sup>) cannot be ignored:

 $\begin{array}{l} (\mathrm{BrCH_2CH_2O})^- + \mathrm{RO}^- & \longrightarrow \mathrm{ROH} + (\mathrm{BrCH_2CHO})^- \\ (\mathrm{BrCH_2CHO})^- & \longrightarrow \mathrm{Br}^- + (\mathrm{CH_2CHO})^- \\ (\mathrm{CH_2CHO})^- + \mathrm{ROH} & \longrightarrow \mathrm{CH_3CHO} + \mathrm{RO}^- \end{array}$ 

However, it is to be expected that the removal of a second proton from ethylene bromohydrin could be accomplished only with such difficulty (cf. the second ionization of a dibasic acid) that such a mechanism seems unlikely.

Preparation of 1-hexanol. 1-Hexanol was prepared by the reaction of ethylene oxide with *n*-butylmagnesium bromide in 65% yield, and by the reaction of ethylene bromohydrin with the same Grignard reagent in 51% yield. 2-Hexanol constituted 13.4% of the total hexanols obtained in the former preparation, and 10.1% in the latter.

The yield of 1-hexanol in the reaction of ethylene oxide with dibutylmagnesium at  $0-15^{\circ}$  was 44%, with only 1.84% of the hexanols being 2-hexanol.

Since both condensations with *n*-butylmagnesium bromide are known to involve the ethylene bromohydrin salt, it was to be expected that the amount of rearranged material would be about the same in both reactions.

The reaction of ethylene oxide with dibutylmagnesium involves a nucleophilic attack of the carbanion upon a carbon atom of the oxide. Such a reaction should give no rearrangement. Since there is little evidence that ethylene oxide should rearrange under the conditions of the condensation, no 2-hexanol was expected in this reaction. The 1.84% 2-hexanol isolated may represent acetaldehyde present in the reagents despite every effort to remove it, or it may have been produced by unknown side reactions.

The "violent" reactions. The vigorous reaction which may set in during the reaction between ethylene oxide and *n*-butylmagnesium bromide is well known, and adequate warning as to precautions to prevent it are given in Organic Syntheses (1a). Since this reference attributes the vigorous reaction to the rearrangement of an oxonium-type complex of ethylene oxide, a similar reaction was not anticipated with ethylene bromohydrin. One reaction mixture was heated with considerably less care than that employed with ethylene oxide, and the resulting vigorous reaction forced some of the mixture through the reflux

condenser. The yield of 1-hexanol actually recovered was 38% and it was estimated that approximately one-fifth of the reaction mixture was lost. However, 22.8% of the total hexanols recovered was 2-hexanol, in contrast to 10.1% 2-hexanol in a similar reaction in which the violent reaction did not take place.

It seems probable that the violent reaction mentioned in Organic Syntheses may involve the transition of the magnesium salt of ethylene bromohydrin to acetaldehyde. The statement is made in Organic Syntheses that the yield of 1-hexanol will be low if the violent reaction is allowed to take place.

Other examples in which an oxide reacts with the Grignard reagent to a greater or lesser extent as though it were a carbonyl compound are known. Styrene oxide reacts as though it were phenyl acetaldehyde (4) and 2,3-epoxybutane reacts as though it were butanone (5). An instance of the isolation of an aldehyde monomer after the treatment of an oxide with magnesium bromide etherate has been reported (6).

## EXPERIMENTAL

Preparations of 1-hexanol were carried out essentially according to the directions of Organic Syntheses (la), except that refluxing at 35° was continued for five hours instead of one.

The products were separated by Snyder columns into fractions distilling in the following ranges: (a) below 136°, (b) 136-140°, (c) 140-154°, (d) 154-157°. The 154-157° fraction was assumed to be l-hexanol. The 140-154° fraction usually amounted to considerably less than 1% of the l-hexanol. The 136-140° fractions were identified as 2-hexanol by the 3,5-dinitrobenzoate and the *alpha*-naphthylurethan.

The melting points of the 3,5-dinitrobenzoates from all the experiments fell within the range  $37.0-38.2^{\circ}$ . Previous values given are  $38.6^{\circ}$  (7) and  $38^{\circ}$  (8a).

The *alpha*-naphthylurethans were heavy oils which could not be recrystallized in the usual fashion. An isothermal recrystallization was carried out as follows: The yellow oil was dissolved in about ten volumes of 95% alcohol. To this, water was added dropwise until approximately half of the oil had reprecipitated. This oil extracted the yellow material from the alcohol solution. The clear solution was transferred to another flask and an equal volume of water was added rapidly. The milky supernatant liquid was decanted from any oil which formed in five minutes, and set aside at room temperature. After 24 hours the voluminous, white, crystalline precipitate was filtered off and air dried.

The urethans melted in the range 59.3-60.5°. Previous values given are  $60.5^{\circ}(9)$  and  $58-62^{\circ}(9)$ .

All reagents were tested for acetaldehyde with a supersensitive Schiff reagent (10) by visual comparison with known standards consisting of acetaldehyde in water. Acetaldehyde contents estimated in this manner were as follows: benzene, dioxane, and *n*-butyl bromide: 0.000%; ethylene bromohydrin: 0.013%; the ether used in the vigorous reaction between ethylene bromohydrin and *n*-butylmagnesium bromide: 0.04%; and the ether used in all other preparations of 1-hexanol: 0.006%. However, more significance was attached to the fact that no 2-hexanol (or other material boiling above 118°) could be found in the products from the preparation and hydrolysis of *n*-butylmagnesium bromide in an aliquot portion of the ether used in the preparations of 1-hexanol.

"Blank" preparation. A large batch of about fifteen liters of anhydrous ether was kept over powdered potassium hydroxide for several months prior to use. Portions of this ether were used in this reaction and in the next three preparations to be described.

*n*-Butylmagnesium bromide was prepared from 297 g. (2.17 moles) of *n*-butyl bromide in 3,650 ml. of ether and 53 g. (2.32 atoms) of magnesium. After hydrolysis, the reaction mixture was treated according to the Organic Syntheses directions for working up l-hexanol. There were obtained 28.2 g. of material boiling between 80 and 118°, mostly benzene and n-butanol, and a negligible amount of material boiling above 118°.

Failure to isolate any 2-hexanol from this experiment was taken to indicate that the amount of acetaldehyde present in the ether was insufficient to account for the 2-hexanols found in the experiments in which ether from this same batch was used.

Reaction of ethylene oxide with n-butylmagnesium bromide. This reaction was carried out essentially according to the Organic Syntheses procedure for the preparation of 1-hexanol. The ethylene oxide was passed through two or three tubes connected in series (2.5 cm. in diameter, 150 cm. over-all length) packed with freshly powdered potassium hydroxide, to remove acetaldehyde, then directly into the reaction mixture. The brown acetaldehyde polymer formed only in the first 25 cm. or so of the first tube. Ethylene oxide thus treated gave a negative test with ordinary Schiff reagent.

The tubes had to be watched carefully for the development of unpredictable "hot spots" which indicated that the ethylene oxide was polymerizing in that region. A tube was replaced with a fresh one whenever a "hot spot" was detected, to keep the losses of ethylene oxide due to polymerization to a minimum.

The Grignard reagent was prepared from 827 g. (6.04 moles) of *n*-butyl bromide in 2,000 ml. of ether (from the batch, a portion of which was used in the previous experiments) and 153 g. (6.30 atoms) of magnesium, and 300 g. (6.80 moles) of ethylene oxide were added. There were obtained 400 g. (65.0% yield) of 1-hexanol and 61.9 g. of 2-hexanol.

Reaction of ethylene bromohydrin with n-butylmagnesium bromide. The procedure was essentially that used in the previous experiment except, of course, two moles of Grignard reagent had to be used because one was destroyed by the active hydrogen of the bromohydrin.

The Grignard reagent was prepared from 1,430 g. (10.42 moles) of *n*-butyl bromide in 3,600 ml. of ether (from the batch, portions of which were used in the previous experiments) and 260 g. (10.70 atoms) of magnesium. To this was added dropwise 650 g. (5.20 moles) of ethylene bromohydrin under the same conditions used for the addition of ethylene oxide in the previous experiment.

The bromohydrin was prepared according to the directions of Organic Syntheses (1b) and was distilled twice, the fractions collected being:  $48.0-57.3^{\circ}$  at 9.2-10.4 mm. and  $49.6-50.0^{\circ}$  at 5.5-5.9 mm. The bromohydrin was analyzed for bromine by the sodium in alcohol method (8b).

Anal. Calc'd for C<sub>2</sub>H<sub>5</sub>BrO: Br, 63.95. Found: Br, 63.88, 63.99, 64.00.

The yield of 1-hexanol was 268 g. (50.6%) and that of 2-hexanol was 30.0 g.

Reaction of ethylene oxide with dibutylmagnesium. The ether used was from the batch, portions of which were used in the previous preparations.

Dibutylmagnesium was prepared from the Grignard reagent by precipitation of the halogen-containing compounds with dioxane. Dioxane was added to the Grignard solution with vigorous stirring at room temperature, at a rate such that no refluxing took place.

The condensation step of the reaction was carried out in two separate batches. In the first 597 g. (6.78 moles) of dioxane freshly distilled from bright sodium was added to 5.01 moles of *n*-butylmagnesium bromide in 1,600 ml. of ether. In the second 772 g. (8.77 moles) of dioxane was added to 6.04 moles of Grignard solution in 2,600 ml. of ether.

The precipitates were not separated from the dibutyImagnesium solutions. Instead, the yields of dibutyImagnesium were estimated by the preparation of a third, smaller batch in which 61.6 g. (0.70 moles) of dioxane was added to 0.50 moles of Grignard solution in 300 ml. of ether. The mixture was centrifuged and 258 ml. of solution containing 1.232 mmol. Mg./ml. were decanted. The precipitate was stirred with fresh ether, centrifuged until the precipitate occupied the same volume as before, and 319 ml. of solution containing 0.1699 mmol. Mg./ml. was decanted.

In the following equation, X is the volume of solution entrapped in the precipitate:  $X \cdot 1.232 = (319 + X) 0.1699$ 

$$X = 51 \text{ ml.}$$

$$(258 + 51) \cdot 1.232 = 380.5$$
 mmol. Mg.

The yield of dibutylmagnesium is thus 76.1%, and it was estimated that the first batch contained 1.90 moles, and the second 2.30 moles, of dibutylmagnesium. To the first was added 200 g. (4.53 moles), and to the second was added 300 g. (6.80 moles) of ethylene oxide, purified and added as described previously.

The mixtures were hydrolyzed with distilled water after standing for eight hours at  $0-15^{\circ}$ . After hydrolysis was complete, the magnesium hydroxide was dissolved in dilute sulfuric acid, the mixtures were combined and worked up together.

The yield of 1-hexanol was 373 g. (43.5%) and that of 2-hexanol, 7.0 g.

A vigorous reaction between ethylene bromohydrin and n-butylmagnesium bromide. The reaction was carried out as the previously described condensation between these reagents except that the refluxing at  $35^{\circ}$  was for only one and a half hours instead of five. When part of the ether was replaced with benzene and the temperature raised to about  $65^{\circ}$ , a vigorous reaction set in which forced about one-fifth of the material through the reflux condenser.

This Grignard reagent was prepared from 250 g. (10.33 atoms) of magnesium and 1,370 g. (10.00 moles) of *n*-butyl bromide, in 3,840 ml. of ether which was estimated to contain 0.04% acetaldehyde, as has been described.

The bromohydrin used was distilled three times, the fractions collected being:  $50-77^{\circ}$  at 23.5 mm.,  $46.0-48.0^{\circ}$  at 4.2-4.8 mm., and  $48-49^{\circ}$  at 3.0-3.1 mm. The bromohydrin was analyzed for bromine by the sodium in alcohol method (8b).

Anal. Calc'd for C<sub>2</sub>H<sub>5</sub>BrO: Br, 63.95. Found: Br, 63.78, 63.89, 63.78.

There were obtained 184 g. (38.0%) of 1-hexanol and 54.6 g. of 2-hexanol.

Reactions of acetaldehyde with n-butylmagnesium bromide. These reactions were carried out to determine if the vigorous refluxings or other steps in the procedure involved in the preparation of 1-hexanol might destroy or in some manner cause the loss of appreciable amounts of 2-hexanol.

Two simultaneous preparations were carried out as follows, portions of the same reagents being used for each:

One hundred grams (0.73 mole) of *n*-butyl bromide in 300 ml. of ether was added to 18.5 g. (0.76 atom) of magnesium. The Grignard solution was cooled to  $-5^{\circ}$  and the addition of 50 g. (1.14 moles) of acetaldehyde in 300 ml. of cooled ether was begun. The temperature was maintained at -10 to  $-5^{\circ}$  and the acetaldehyde was added over an hour and a half.

One solution was allowed to stand at room temperature for ten days. At the end of this time the mixture was hydrolyzed, and the oily layer was separated. The water layer was thoroughly extracted with ether. The combined ether extracts were fractionally distilled. The yield of 2-hexanol was 34.4 g. (46.2%).

The second solution was treated exactly according to the method previously described for the preparation of 1-hexanol from ethylene oxide and *n*-butylmagnesium bromide. The yield of 2-hexanol was 38.7 g. (52.0%).

These experiments demonstrate that appreciable loss of 2-hexanol in the previous experiments is unlikely.

Resinification of ethylene oxide. The anhydrous magnesium bromide solution was prepared by the addition of 188 g. (1.18 moles) of bromine (dried by shaking with concentrated sulfuric acid) to 28.5 g. (1.18 moles) of magnesium in 1,000 ml. of ether.

The mixture (two layers) was cooled to below 10° and the addition of 100 g. of ethylene oxide was started. The ethylene oxide was passed through a tube, 2.5 cm. in diameter, packed with 20 cm. of 8 mesh soda-lime, and then as a gas directly into the magnesium bromide. The oxide was readily absorbed at all times, although the temperature rose somewhat above 10°.

The mixture stood for fifteen hours at room temperature, and finally was refluxed for four hours. Part of the ether was distilled off, replaced with benzene, and refluxing at 65° was continued for three hours, during which most of the precipitate dissolved.

Half of this material was placed in a steel bomb fitted with a themocouple and a pressure

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guage. The temperature was raised to 84° and held there for half an hour, with vigorous shaking. This treatment appeared to effect no change in the solution.

The second half of the solution was heated as before except that the temperature was raised to 95° at the rate of about 0.8° per minute, at which temperature a violent reaction set in as evidenced by a sudden, sharp increase in temperature and pressure. Heating was discontinued as soon as the reaction set in, but the temperature had reached a maximum in 3 minutes 8° above that expected, and the pressure had increased from twenty-one pounds at the start of the vigorous reaction to thirty-three pounds at the maximum. The product of this reaction was a dark brown resin with the characteristic caramel-like odor noted when acetaldehyde is treated with concentrated alkali.

The resin washed successively with dilute potassium hydroxide and dilute hydrochloric acid contained 62.3% C, 7.1% H and 2.0% Br.

Resinification of acetaldehyde. The anhydrous magnesium bromide solution was prepared from 160 g. (2.00 moles) of bromine, 25 g. (1.03 atoms) of magnesium, and 700 ml. of ether. The upper layer of the solution was discarded. One-half of the lower layer plus an equal volume of benzene was used for each of the following preparations.

Acetaldehyde was not readily absorbed by the cooled magnesium bromide solution, so the liquid acetaldehyde (22 g., 0.5 mole) was added to the cooled material in the bomb. The temperature was raised as before except there was no sudden increase in temperature or pressure at any time, therefore the temperature was raised to 110° and held there for an hour. The product of this reaction was identical in odor with the resin from ethylene oxide, but was somewhat softer and darker in color. The resin contained 62.9% C and 7.9% H.

Particular care was taken to insure the absence of magnesium metal in the above reaction mixture. In the second preparation in which 5 g. of magnesium turnings was added to the mixture the product could not be distinguished from the first by appearance or odor. The resin contained 59.6% C and 7.2% H.

A solution consisting of 24 g. of acetaldehyde in 200 ml. of ether and 200 ml. of benzene was heated at 110° with no change in the appearance of the solution except for a very slight discoloration. The material was completely volatile on the steam-bath except for a trace of yellowish residue.

The resins from ethylene oxide and acetaldehyde were all insoluble in water and dilute acids and bases, very slightly soluble in benzene and aliphatic hydrocarbons, partially soluble in the lower alcohols, and completely soluble in chloroform. Because the composition of these resins is dependent upon the degree of dehydration, and therefore may vary widely (11), little significance was attached to elemental analyses. More dependence was placed upon the characteristic odor, the solubility characteristics, and the general appearance of the resin.

The carbon and hydrogen determinations reported in this paper were run by Mr. M. J. Gardella.

## SUMMARY

Evidence is presented which supports the theory that the anion of the magnesium salt of ethylene bromohydrin may rearrange in part during the reaction of ethylene oxide with alkylmagnesium bromides, giving rise to products which must have come from acetaldehyde.

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