[From the Kedzie Chemical Laboratory, Michigan State College]

THE REACTION OF PROPYLENE OXIDE WITH ORGANOMAGNESIUM BROMIDES

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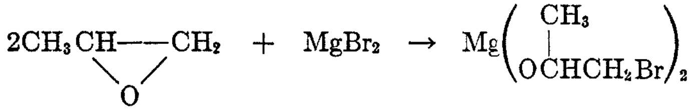
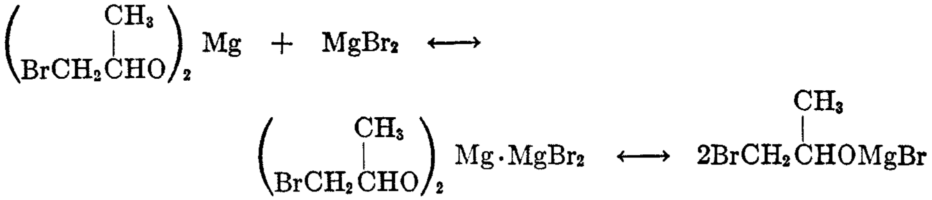
The addition of one mole of ethylene oxide to one mole of ethylmagnesium bromide resulted in the immediate precipitation of a compound which gave the correct analysis for dibromodiethoxy magnesium and which was hydrolyzed to ethylene bromohydrin (1). The same precipitate was formed immediately when ethylene oxide was added to a solution of magnesium bromide in ether.

The addition of one mole of propylene oxide to one mole of ethylmagnesium bromide caused no precipitation. When propylene oxide was added to a solution of one mole of magnesium bromide, in ether, there was no precipitation during the addition of the first mole. During the addition of the second mole, a precipitate was formed which had a bromine and magnesium content corresponding to dibromodiisopropoxymagnesium,



and which gave upon hydrolysis an 80% yield of propylene bromohydrin. The absence of precipitation during the addition of the first mole and the solubility of dibromodiisopropoxymagnesium in excess of magnesium bromide etherate are attributed to the solubility of bromoisopropoxymagnesium bromide and/or the formation of an addition compound of dibromodiisopropoxymagnesium and magnesium bromide.



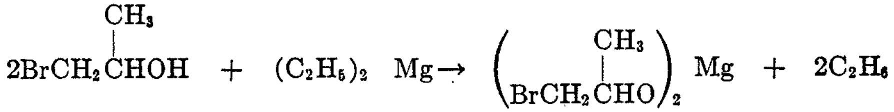
$$\left(BrCH_2\overset{\overset{CH_3}{|}}{C}HO\right)_2 Mg + MgBr_2 \longleftrightarrow \left(BrCH_2\overset{\overset{CH_3}{|}}{C}HO\right)_2 Mg\cdot MgBr_2 \longleftrightarrow 2BrCH_2\overset{\overset{CH_3}{|}}{C}HOMgBr$$

When the reaction is between mole equivalents of propylene oxide and ethylmagnesium bromide, intermediates may be formed by the addition of the propylene oxide to one or both of the bromomagnesium bonds of magnesium bromide, to either the bromomagnesium bond or the ethylmagnesium bond of ethylmagnesium bromide or to both of these or to one or both of the ethylmagnesium bonds of diethylmagnesium.

When mole equivalents of ethylene oxide and ethylmagnesium chloride reacted, the addition was predominantly with the ethylmagnesium bonds, and the yield of butyl alcohol was more than twice as great as that of ethylene chlorohydrin (2), while with the higher alkylmagnesium chlorides, yields of alcohol and chlorohydrin were more nearly equal. In some cases, the yield of chlorohydrin exceeded that of the alcohol. It appears that the rate of addition of this epoxide to the alkylmagnesium bond decreases with the increase in size of the alkyl group and with branching.

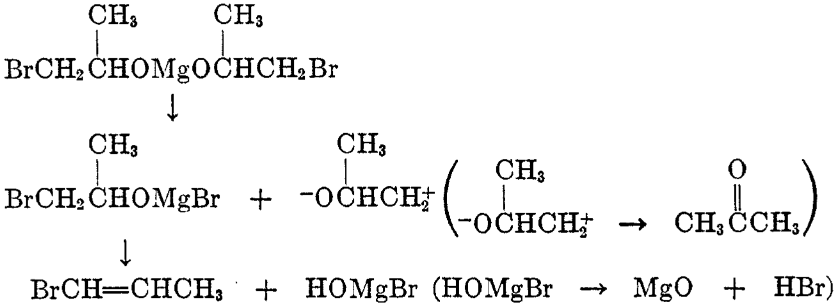
When one mole of propylene oxide reacted with one mole of ethylmagnesium bromide in the cold and was allowed to stand at room temperature for two days (without refluxing), the addition was predominantly with the magnesium bromide bonds. The yield of propylene bromohydrin was approximately five times that of 2-pentanol (3, 4, 5). In general, reactions of this epoxide with the higher alkylmagnesium bromides give yields of bromohydrin of 60–70% while the yields of secondary alcohols were not greater than seven per cent. With arylmagnesium bromides, on the other hand, yields of alcohols exceeded those of the bromohydrin (Table I).

When the dried precipitate $(\mathrm{BrCH_2\overset{\overset{CH_3}{|}}{C}HO})_2\mathrm{Mg}$, prepared either by treating magnesium bromide solution with propylene oxide or by adding two moles of propylene bromohydrin to one mole of diethylmagnesium, was heated in an atmosphere of nitrogen, it first melted and then decomposed.



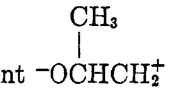
$$2\mathrm{BrCH_2\overset{\overset{CH_3}{|}}{C}HOH} + (\mathrm{C_2H_5})_2\ \mathrm{Mg} \rightarrow \left(\mathrm{BrCH_2\overset{\overset{CH_3}{|}}{C}HO}\right)_2\mathrm{Mg} + 2\mathrm{C_2H_6}$$

Acetone, bromopropylene, and hydrobromic acid distilled over while the residue in the flask became dark colored and viscous. Heating the dibromodiisopropoxymagnesium in air at 500° gave pure magnesium oxide. The following scheme is representative of the type of breakdown involved.



$$\mathrm{BrCH_2\overset{\overset{CH_3}{|}}{C}HOMgO\overset{\overset{CH_3}{|}}{C}HCH_2Br}$$
$$\downarrow$$
$$\mathrm{BrCH_2\overset{\overset{CH_3}{|}}{C}HOMgBr} + {}^{-}\mathrm{O\overset{\overset{CH_3}{|}}{C}HCH_2^{+}} \left({}^{-}\mathrm{O\overset{\overset{CH_3}{|}}{C}HCH_2^{+}} \rightarrow \mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_3}\right)$$
$$\downarrow$$
$$\mathrm{BrCH{=}CHCH_3} + \mathrm{HOMgBr}\ (\mathrm{HOMgBr} \rightarrow \mathrm{MgO} + \mathrm{HBr})$$

It is proposed that the transformation of ${}^{-}\mathrm{O\overset{\overset{CH_3}{|}}{C}HCH_2^{+}}$ to $\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_3}$ requires the intermediate formation of a protonized double bond.

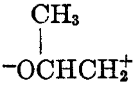
Attempts to increase the yield of 2-pentanol by heating the reaction mixture of equimolecular equivalents of ethylmagnesium bromide and propylene oxide were not successful (1). When the ether was distilled off and replaced with benzene, refluxing for six hours gave a 24% yield of a mixture of pentanols. This was separated by fractionation into approximately equal parts of 2-pentanol and 2-methyl-2-butanol which were identified by their boiling points, densities, refractive indices, and 3,5-dinitrobenzoates. There was also isolated a small fraction (4 ml.) of acetone which was identified as its 2,4-dinitrophenylhydrazone. The heating also reduced the yield of bromohydrin from 60% to approximately 10%. These results indicate that, at the boiling temperature of benzene, there is decomposition of dibromodiisopropoxymagnesium and bromoisopropoxymagnesium bromide with the formation of the fragment  $^{-}\mathrm{O}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCH_2^+}$ which rearranges to acetone, which in turn reacts with ethylmagnesium bromide or diethylmagnesium. Cottle and co-workers (6) have also noted the formation of aldehydes and ketones by the decomposition and rearrangement of intermediates formed by the addition of epoxides to Grignard reagents.

When two moles of propylene oxide reacted with one mole of ethylmagnesium bromide, the yield of 2-pentanol was 54% as compared with 13% when the reactants were in a 1.1 ratio, while the yield of bromohydrin was increased from 62% to 76% (Table I). After all of the propylene oxide had been added, a precipitate formed slowly and, within two days, the entire reaction mixture set to a hard mass. In one experiment, the precipitate was removed after twenty hours and dried. Upon hydrolysis, this particular mixture of intermediates yielded bromohydrin and 2-pentanol in a 2:1 ratio.

In all reactions of the series in which two moles of propylene oxide were added to one mole of alkylmagnesium bromide, the mixture was allowed to stand at room temperature until a negative test was obtained with Michler's ketone. In all cases, a very stiff gel or solid was formed.

The yields of secondary alcohols from primary alkylmagnesium bromides, excepting isobutylmagnesium bromide, were more than 50% and from secondary alkylmagnesium bromides more than 30%. Tertiary butylmagnesium bromide required a period of forty-five days to give a negative test with Michler's ketone and gave a yield of 15%. This time is of the same order as that required for the reaction between di-*t.*-butylmagnesium and ethylene oxide (1).

In all cases where two moles of propylene oxide were allowed to react with one of alkylmagnesium bromide, there was an evolution of gas which lasted for several days. These gases were passed through bromine and the following alkenes were identified as their dibromides: ethene, propene, 1-butene, 2-butene, and 2-methylpropene. The evolution of gas was most pronounced in the reaction with isobutylmagnesium bromide, which gave the smallest yield of bromohydrin.

In all reactions, small amounts of acetone were isolated from the distillates which came over at 50–60°. This indicates that some  $^{-}\mathrm{O}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCH_2^+}$ is formed and rearranged at or below room temperatures.

There was left a viscous residue after 2-pentanol had been distilled off. A small amount of mesityl oxide was removed by distillation and identified as its 2,4-dinitrophenylhydrazone. It is probable that the residue consisted, for the most part, of polymers and condensation products of both propylene oxide and acetone.

Mesityl oxide was also found as a by-product in the preparation of 2-hexanol, 4-methyl-2-pentanol and 2-heptanol.

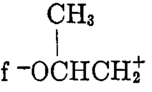
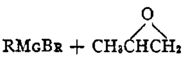
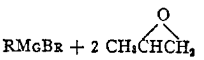
The formation of  $^{-}O\overset{\overset{CH_3}{|}}{C}HCH_2^{+}$ and its rearrangement or polymerization appears to be favored when both propylene oxide and magnesium bromide are present. When propylene oxide was allowed to stand with, or was refluxed with, diethylmagnesium, 2-pentanol was the only alcohol isolated and there was no evidence of the formation of acetone or of polymerization.

TABLE I

YIELDS OF ALCOHOLS FORMED BY THE REACTION OF PROPYLENE OXIDE WITH ORGANOMAGNESIUM BROMIDES

GRIGNARD REAGENT PREPARED FROM	 RMgBr + $CH_3\overset{O}{CHCH_2}$			 RMgBr + 2 $CH_3\overset{O}{CHCH_2}$		
	Time (days)	% Yield Bromohydrin	% Yield Alcohol	Time (days)	% Yield Bromohydrin	% Yield Alcohol
Ethyl bromide	2	62	13	2	76	54
Propyl bromide	2	69	4	6	74	51
sec.-Propyl bromide	2	50	7	7	76	38
n-Butyl bromide	2	67	5	8	70	56
sec.-Butyl bromide	2	62	4	21	62	31
iso-Butyl bromide	2	64	4	25	28	15
tert.-Butyl bromide	2	62	4	45	52	15
Phenyl bromide	1	39	47	1	74	67
Mesityl bromide	1	35	58			

EXPERIMENTAL

Apparatus. For the preparation of Grignard reagents and magnesium bromide etherate and the reaction of these with propylene oxide, a 2-liter, three-necked, round-bottom flask, fitted with a condenser, mercury-seal stirrer, and a Hershberg dropping-funnel or separatory funnel, was used. A nitrogen gas inlet was provided for all reactions. All Grignard reagents and magnesium bromide etherates were protected from atmospheric moisture and CO_2 by calcium chloride and soda-lime tubes. For all distillations a heated glass helix-packed column 12¼ in. long was used. The head was of the total reflux, partial take-off, type. The pot was heated with a Glas-col mantle.

Preparation of Grignard reagents. One mole of redistilled organic bromide was mixed with 150 ml. of anhydrous ether (previously dried over sodium for a week). Twenty-six grams of magnesium and 100 ml. of ether were placed in the reaction flask. Ten to fifteen milliliters of the bromide-ether solution was added and the magnesium stirred until reaction started. The aromatic bromides sometimes required refluxing to start the reaction. Two hundred twenty-five milliliters of ether was then added and the remainder of the bromide—ether solution was added dropwise. The Grignard reagent was stirred over an hour after all of the bromide was in and then allowed to stand under a nitrogen atmosphere overnight.

The aryl and normal alkyl Grignard reagents were prepared by adding the bromide mixture to the uncooled magnesium and ether as fast as the condenser and ice placed on top of the flask would allow. The yield of Grignard reagent was over 90%.

Secondary and iso-alkyl Grignard reagents were prepared by adding the bromide-ether mixture more slowly and not allowing the reaction mixture to get above 35°. The yield of Grignard reagent with isopropyl, *sec.*-butyl, and isobutyl bromide was between 85 and 90%.

tert.-Butylmagnesium bromide was prepared in 50 to 55% yields from the same proportion and quality of reagents. The reaction mixture was cooled in a mixture of salt and ice and the bromide-ether solution added very slowly.

Analysis of the Grignard reagent. The Grignard reagent was forced through a glass wool plug from the unreacted magnesium by nitrogen pressure. Its volume was measured in a 500-ml. graduated cylinder. Five milliliters was pipetted out and analyzed for the organomagnesium content by Gilman's procedure (7). One milliliter was pipetted out and analyzed by the Volhard method for bromide ion.

Reaction with propylene oxide. The Grignard reagent was poured, under a stream of nitrogen, into the reaction flask filled with nitrogen. This was cooled in salt and ice and a mixture of propylene oxide and an equal volume of ether added slowly. The salt and ice bath was allowed to warm up to room temperature and removed the next day.

When the ratio of reactants was 1:1, the reaction was allowed to stand for two days. With the 1:2 ratio reactions, the reaction mixture was allowed to stand until the test with Michler's ketone was faint or negative.

The reaction mixture was cooled with ice and then 150–200 ml. of saturated ammonium bromide solution was added dropwise. This minimized loss of bromohydrin due to reaction with basic magnesium compounds. The ether solution was decanted from the precipitated magnesium salts and dried over Na_2SO_4. Water was added to the magnesium salts until they were pasty. This paste was extracted with benzene.

The dried hydrolysis products were refluxed with a mixture of 40 g. of NaOH and 150 ml. of water for one hour with vigorous stirring. The mixture was cooled and the layers separated. The water layer was extracted with benzene, and the benzene and ether extracts dried over Na_2SO_4. The NaOH layer was heated to boiling to expel excess benzene, cooled, and diluted to one liter. A five-ml. aliquot portion was titrated for bromide ion by Volhard method.

The ether-benzene solution of products was distilled at atmospheric pressure until all of the ether and nearly all of the benzene was removed. For most of the alcohols, reduced pressure was used to prevent decomposition.

In all of the distillations, propylene oxide and acetone were obtained. The acetone was checked by a mixed melting point of its 2,4-dinitrophenylhydrazone. Mesityl oxide (identified by the melting point of its 2,4-dinitrophenylhydrazone) and other unsaturated ketones caused difficulty in the separation of some of the alcohols in the pure state. With several Grignard reactions, a wax-like product was precipitated out of the residue by adding petroleum ether. It has a softening point at 62–63°.

A small fraction (2 ml. or less) was isolated from each reaction mixture, which had a boiling range and refractive index approximately that of the tertiary alcohol that would be formed from acetone and the particular alkylmagnesium bromide. All of these fractions gave positive tests when treated with ceric ammonium nitrate. They were too small and impure to give esters or α-naphthylurethans of definite melting points.

In all reactions of two moles of propylene oxide with one mole of alkylmagnesium bromide, the unsaturated compound corresponding to the alkyl group of the reacting Grignard reagent was isolated from the evolved gases. The gases were passed through bromine and the dibromides were identified by boiling points and refractive indices. No attempt was made to determine quantitatively the yields of these alkenes. The amounts of dibromide collected in periods of six hours varied from more than twenty grams in the case of isobutylmagnesium bromide to less than six grams in the case of ethylmagnesium bromide.

Effect of heat on the reaction. One mole of propylene oxide was added to one mole of ethylmagnesium bromide cooled in ice. Half of the ether was distilled off and replaced with benzene. The mixture was refluxed for six hours and then allowed to stand overnight. Decomposition with saturated ammonium bromide and analysis indicated a yield of fourteen grams of 1-bromo-2-propanol (10%). Distillation of the ether-benzene solution gave a fraction of twenty grams between 100° and 120°. Refraction of this gave seven grams at 100–104° (40%) and eleven grams at 117–120° (60%). The 100–104° fraction was identified by its boiling point, density, refractive index, and α-naphthylurethan as 2-methyl-2-butanol. The 117–120° fraction was identified as 2-pentanol.

TABLE II

DERIVATIVES OF THE ALCOHOLS AND CORRESPONDING KETONES

ALCOHOL	DERIVATIVES	M. P. °C	% N' CALCD	% N FOUND
1-Bromo-2-propanol (9) B.p. 49.6°(12 mm.); n_{D}^{20}, 1.4801	3,5-Dinitrobenzoate (9) α-Naphthylurethan 2,4-Dinitrophenylhydrazone	85–87 116–116.5 128	 4.54 17.66	 4.33 17.56
2-Pentanol (5) B.p.118.8° (745 mm.); n_{D}^{20}, 1.4068	3,5-Dinitrobenzoate (5) α-Naphthylurethan (10) 2,4-Dinitrophenylhydrazone(10)	59–61 75 143–145*		
2-Hexanol (15) B.p.139.5° (740 mm.); n_{D}^{20}, 1.4155	3,5-Dinitrobenzoate (11) 2,4-Dinitrophenylhydrazone (10)	36–37 106–108*		
4-Methyl-2-pentanol (10) B.p. 68°(52 mm.); n_{D}^{20}, 1.4120	3,5-Dinitrobenzoate (11) α-Naphthylurethan (4) 2,4-Dinitrophenylhydrazone(10)	61–62 94–95.5 91–92*	5.16	4.96
2-Heptanol (10) B.p. 77°(24 mm.); n_{D}^{20}, 1.4214	3,5-Dinitrobenzoate (10) 2,4-Dinitrophenylhydrazone	47.5–48.5 72.5–73.5*		
4-Methyl-2-hexanol (12) B.p. 85.5° (44 mm.); n_{D}^{20}, 1.4223	3,5-Dinitrobenzoate (12) Semicarbazone (12)	62.5–63.5 128–129*	9.03	9.09
5-Methyl-2-hexanol (16) B.p. 73° (32 mm.); n_{D}^{20}, 1.4227	3,5-Dinitrobenzoate 2,4-Dinitrophenylhydrazone (10)	34–36 94–96	9.03	8.97
4,4-Dimethyl-2-pentanol (13) B.p. 65° (40 mm.); n_{D}^{20}, 1.4248	3,5-Dinitrobenzoate (13)	48–50		
1-Phenyl-2-propanol (10, 14) B.p. 95° (7 mm.); n_{D}^{20}, 1.5221	α-Naphthylurethan (14) Semicarbazone (10)	88–89.8 193		
1-Mesityl-2-propanol B.p. 137° (9 mm.); n_{D}^{20}, 1.5282	3,5-Dinitrobenzoate α-Naphthylurethan Semicarbazone	153.8–154.8 114.8–115.2 206–206.5	7.42 3.97	7.36 3.84

* Checked by a mixed m.p. with a known derivative.

Derivatives. The 3,5-dinitrobenzoates were made by using pyridine and 3,5-dinitrobenzoyl chloride. Another method was developed for any type of alcohol (primary, secondary, or tertiary) or phenol which made use of ethylmagnesium bromide. The alcohol must not contain any contaminant that forms an alcoholate with Grignard reagent. After the slight excess of alcohol had been added to the cooled Grignard reagent (evolution of ethane ceased), 0.5–1 g. of 3,5-dinitrobenzoyl chloride was added. The tube was stoppered with a calcium chloride tube and allowed to stand overnight or longer if the alcoholate was slow in reacting. Water was added to precipitate the magnesium salts and the ether layer filtered off and evaporated.

α-Naphthylurethans were prepared from α-naphthyl isocyanate using a drop of trimethyl amine-ether solution as catalyst.

As further proof, the secondary alcohols were oxidized to ketones with a saturated solution of $KMnO_4$ in 1 to 6 *N* H_2SO_4 and filtered. The 2,4-dinitrophenylhydrazones were made by adding this filtrate to three ml. of a solution of 2.4 g. of 2,4-dinitrophenylhydrazine in a mixture of 80 ml. of water and 40 ml. of 72% perchloric acid. The semicarbazones were made by separating the ketone from the water and using the method for water-insoluble ketones.

Preparation of magnesium bromide etherate and reaction with propylene oxide. Twenty-nine grams of magnesium was placed in the reaction flask and covered with 500 ml. of ether. One hundred sixty grams (26 ml.) of bromine was added dropwise. After all of the bromine had been added, the reaction mixture was refluxed for an hour and allowed to stand overnight. The magnesium bromide solution was removed from the excess magnesium, measured, and titrated for bromide ion. The reaction with 2 moles of propylene oxide was carried out in the same manner as with the Grignard reagent.

Two hours after addition of all the epoxide, the precipitate was placed in centrifuge bottles, stirred with anhydrous ether, and centrifuged. The ether layer was decanted and the process of washing repeated. The precipitate was dried in a vacuum desiccator over calcium chloride for several days at 12 mm. or less. The amount of bromine was determined by the Parr bomb method.

Anal. Calc'd for $C_6H_6BR_2MgO_2$: Br, 53.2; Mg, 8.1.
Found: Br, 51.7; Mg, 8.5.

Reaction of diethylmagnesium with two mole equivalents of bromohydrin. The calculated amount of bromohydrin was mixed with 200 ml. of benzene, placed in the reaction flask, and cooled. The diethylmagnesium solution (8) was added from the dropping-funnel. The resulting white solid (which formed immediately) was washed with ether by centrifuging and dried in a vacuum desiccator under reduced pressure.

Anal. Calc'd for $C_6H_6Br_2MgO_2$: Br, 53.2; Mg, 8.1.
Found: Br, 51.2; Mg, 8.5.

Reaction of diethylmagnesium with one mole equivalent of bromohydrin. The diethylmagnesium solution was placed in the reaction flask and the bromohydrin, mixed with an equal volume of benzene, was added slowly. A white precipitate formed. The reaction mixture was allowed to stand four days, refluxed six hours, and hydrolyzed. Part of the bromohydrin was recovered along with some alcohol. On oxidation, the alcohol gave 2-pentanone which was checked by a mixed melting point of its 2,4-dinitrophenylhydrazone with a known derivative.

SUMMARY

1. When one mole of propylene oxide was added to one mole of alkylmagnesium bromide, both alkylmagnesium bonds and magnesium bromine bonds reacted but the reaction was predominantly with the magnesium bromine bonds. The yield of secondary alcohol was small as compared with that of propylene bromohydrin. When one mole of propylene oxide was added to one mole of aryl-

magnesium bromide, the addition was predominantly at the arylmagnesium bond and the yield of alcohol exceeded slightly that of the bromohydrin.

2. The addition of a second mole of propylene oxide to alkylmagnesium bromide (excepting isobutylmagnesium bromide and *tert.*-butylmagnesium bromide) gave a slight increase in the yield of bromohydrin. In all cases, addition to the alkylmagnesium bond occurred. This addition was relatively slow, the rate depending upon the size of the alkyl group and branching. The yields of secondary alcohols from normal primary alkyl bromides were more than 50%; from secondary alkyl bromides, more than 30%; and from isobutyl and *tert.*-butyl bromides, 15%.

3. Refluxing the reaction mixture from ethylmagnesium bromide and propylene oxide at the boiling temperature of benzene, caused partial decomposition of the intermediates with the formation of acetone and 2-methyl-2-butanol. That this type of decomposition and rearrangement takes place to some extent at room temperatures or below was evidenced by the presence of small amounts of acetone in all reaction mixtures.

EAST LANSING, MICH.

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