THE GRIGNARD REAGENT
AND
ETHYLENE OXIDES

A Thesis

by

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ACKNOWLEDGEMENT

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CLAIM TO ORIGINAL RESEARCH-

Propylene oxide has been treated with t-butyl magnesium chloride for the first time. The reaction was carried out over a wide range of temperatures, -5°C. to 193°C., and over a wide period of reaction times, from immediate decomposition to decomposition following seven weeks standing. These alterations in the operating conditions had no effect on the product obtained. The inter-dependent factors of time and temperature exhibited their usual effect for reactions of this class.

The product isolated as a result of the reaction, ethyl t-butyl carbinol, corresponds to the addition of propionaldehyde to t-butylmagnesium chloride. The isolation of this product iddicates that a rearrangement has taken place. This is the first time that a rearrangement has been observed to take place when propylene oxide is treated with a Grignard reagent.

A simple mechanism has been advanced that will successfully account for the products obtained.

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INTRODUCTION

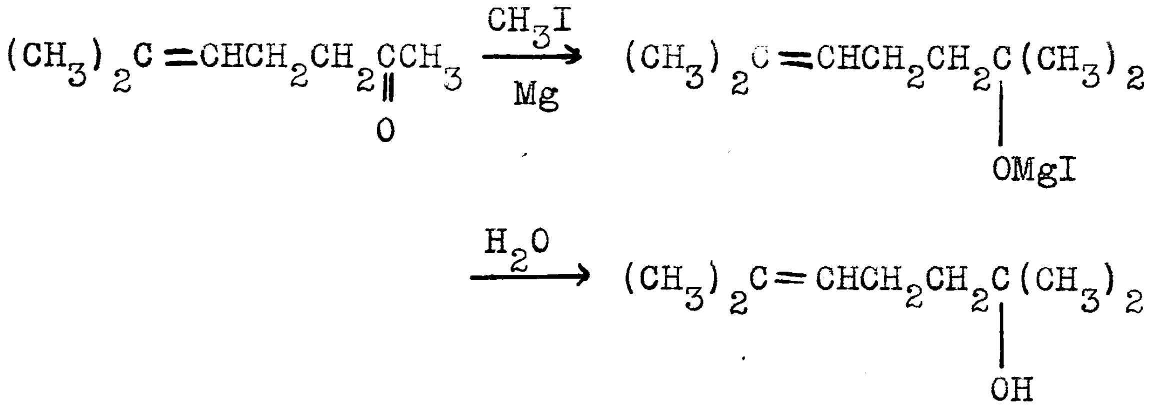
Reactions of synthesis are of prime importance in organic chemistry. The reaction itself may be of practical interest by reason of its uniqueness, smoothness, and the high yield of product which may result from it. From a theoretical point of view, however, the mechanism of the reaction may be of greater importance.

The discovery of a new synthetic method, whether by design or by accident, is followed by a period of expansion wherein the reaction is applied to a great many cases in order to determine the limits of the reaction. The present usefulness of the Grignard reaction is a splendid example of this process of development. The extent of a reaction's usefulness depends upon the variety of ways in which it may be applied, and the fundamental nature of the Grignard reaction may be seen from the fact that new uses for it are constantly being developed.

It is the purpose of the Historical Section of this work to trace in a general way the development of the use of the Grignard reagent and ethylene oxides in the synthesis of alcohols. The limitations of the reaction will be brought out and the mechanism arrived at, as a result of a consideration of these limitations will be given. Particular attention will be paid to the rearrangement of oxides inasmuch as this work indicates quite clearly that a rearrangement takes place when t.butylmagnesium chloride reacts with propylene oxide. The discussion is confined to the simple oxides which have a direct bearing on the problem at hand and, therefore, no attempt is made to discuss rearrangements in the field of terpene oxides and allied substances. Rather, the aim of this work is to present in as simple and straight forward a fashion as possible the development of the Ethylene Oxide-Grignard reaction.

HISTORICAL

Organometallic compounds have been used in reactions of synthesis from the time of Frankland (1), who prepared zinc diethyl. The field of alkyl zinc compounds was not an easy one in which to carry out work, and it is not at all surprising that comparatively little work was done after Frankland's time until Barbier (2) prepared dimethylheptenol from methyl heptenone, methyl iodide, and magnesium in ether.



$$\mathrm{(CH_3)_2C{=}CHCH_2CH_2\underset{\underset{O}{\|}}{C}CH_3} \xrightarrow[\mathrm{Mg}]{\mathrm{CH_3I}} \mathrm{(CH_3)_2C{=}CHCH_2CH_2\underset{\underset{OMgI}{|}}{C}(CH_3)_2}$$

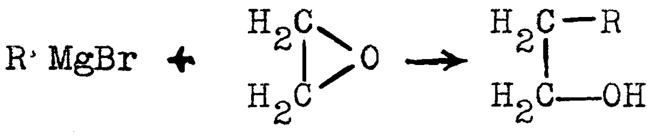
$$\xrightarrow{\mathrm{H_2O}} \mathrm{(CH_3)_2C{=}CHCH_2CH_2\underset{\underset{OH}{|}}{C}(CH_3)_2}$$

It fell to his student Grignard (3) to resolve the reaction into two stages. First, the preparation of the reagent by treating magnesium with the halide in ether and subsequently treating the organometallic compound so prepared with the reactant. The Grignard Reagent, as it is now known, has been the subject of a wide variety of research problems in almost every branch of organic chemistry.

(1) Frankland Ann. 71 213-16 (1849)
(2) Barbier Compt.rend. 128 110-11 (1899)
(3) Grignard Compt.rend. 130 1322-24 (1900)

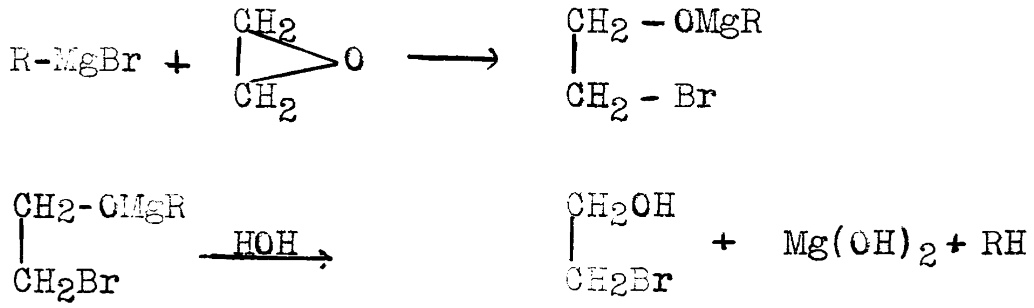
Like any new discovery, it was hailed as a great advance in the science - and, unlike many discoveries, it was able to live up to its advance notices and, in most cases, far outstrip them. The reagent has its limitations, however, and it is perhaps fortunate that they do exist, for instance the failure of RMgX to add to the isolated ethylenic double bond broadens rather than narrows the realm of Grignard chemistry.

In this problem we are particularly concerned with the reaction of the Grignard reagent upon ethylene oxides. Blaise (4) following Grignard's work (5) on the reaction of trioxy methylene with an organomagnesium compound, treated ethylene oxide with a Grignard reagent. As the result of the reaction, he expected to obtain a primary alcohol containing two more carbon atoms than existed in the original radical.

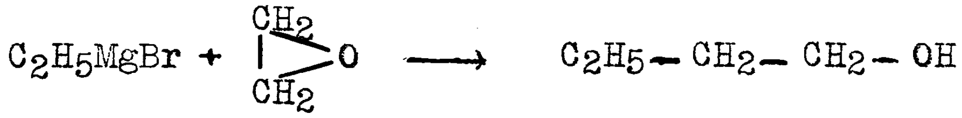


(4) Blaise Compt. rend., 134 551-53 (1902)
(5) Grignard Compt. rend., 134 107-8 (1902)

The products of the reaction, however, were mainly the monobromhydrin of the glycol with only a small amount of the expected alcohol. Blaise accounts for the bromhydrin by assuming that the reaction took the following course rather than that previously outlined.



Grignard, (6) noting that Blaise had formulated the reaction as taking place in a manner that would involve a splitting of the organomagnesium halide into RMg- and -X rather than R- and -MgX as had previously been observed, repeated the work of Blaise and obtained the primary alcohol.



Grignard's method of preparation was to add the oxide to the organomagnesium halide and then distill off the ether, thus removing any unreacted oxide. When the ether was removed, a vigorous reaction set in with the evolution of much heat. The reaction mixture was allowed to cool and then decomposed. The main product being the primary alcohol.

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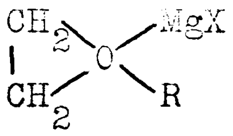
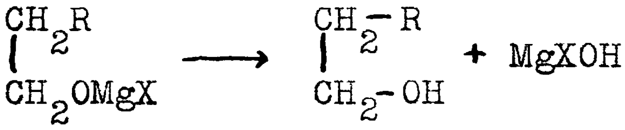
(6) Grignard Compt. rend., <u>136</u> 1260-62 (1903)

Grignard pictured the reaction as taking place in the following manner - first, the oxide replaces the ether in the organomagnesium complex, giving rise to the following structure.



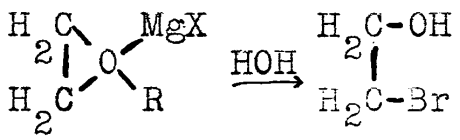
This constitutes the first phase of the reaction, the second phase, which takes place when the ether has been distilled out of the reaction mixture, is the one in which the oxide ring breaks and the oxonium structure is transformed into the intermediate,

which on hydrolysis gives the alcohol.



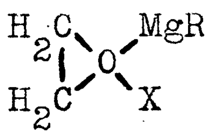
$$\begin{matrix} CH_2R \\ | \\ CH_2OMgX \end{matrix} \longrightarrow \begin{matrix} CH_2-R \\ | \\ CH_2-OH \end{matrix} + MgXOH$$

Grignard found by treating the product of the first phase of the reaction with water that the oxide which was liberated, reacted with the magnesium salts formed by the decomposition of the organomagnesium halide to give the bromohydrin.

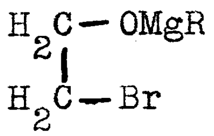


Thus Blaise had not carried the reaction to completion before decomposing the reaction mixture. The increased temperature used by Grignard causes the reaction to enter the "second phase" wherein the oxonium compound rearranges to give the magnesium halide alcoholate, which on hydrolysis yields the alcohol.

The structure of the oxonium compound put forward by Baeyer and Villeger (7)

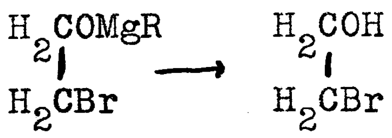


would account for the bromhydrin obtained by Blaise since it would tend to give this rearrangement product



$$\begin{array}{l} H_2C-OMgR \\ \quad | \\ H_2C-Br \end{array}$$

which on decomposition would give rise to the bromhydrin



$$\begin{array}{l} H_2COMgR \\ \quad | \\ H_2CBr \end{array} \longrightarrow \begin{array}{l} H_2COH \\ \quad | \\ H_2CBr \end{array}$$

(7) Baeyer and Villeger Ber. 35 1201 (1902)

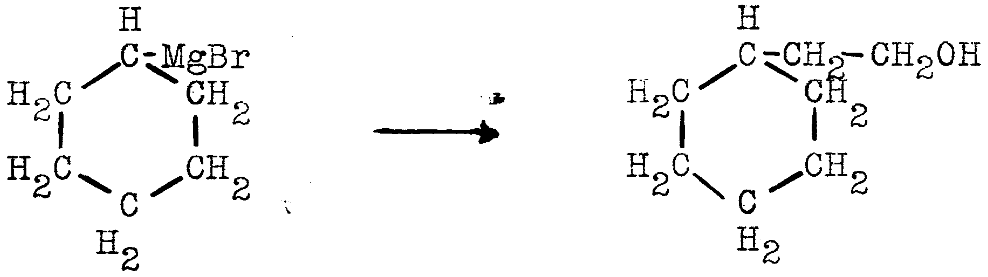
Further evidence in favor of Grignard's mechanism was brought forward by Henry (8) who concluded that the formation of the halohydrin was a result of the temperature of the reaction and the proportion of reagents. Halohydrins have also been isolated by Ribas and Tapia (9) but this is the exception rather than the rule.

As we have shown, ethylene oxide itself gives primary alcohols when treated with organometallic compounds in accordance with the procedure developed by Grignard.

$$C_2H_5MgBr \longrightarrow C_4H_9OH \qquad (6)$$

$$(CH_3)_2CHCH_2CH_2MgBr \longrightarrow (CH_3)_2CH-(CH_2)_4OH \qquad (6)$$

$$(CH_3)_2C=CH-(CH_2)_2-CH(CH_3)MgX \longrightarrow$$
$$(CH_3)_2C=CH-(CH_2)_2-CH(CH_3)-CH_2-CH_2OH \qquad (10)$$



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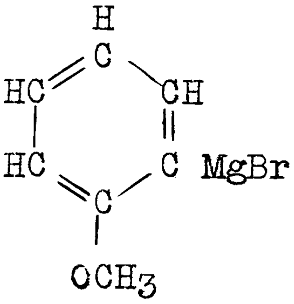
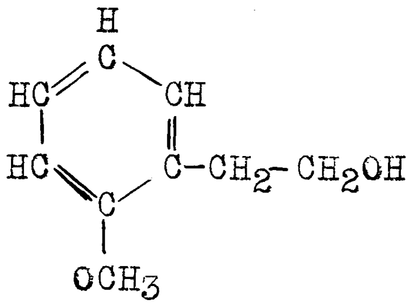
(8) Henry Compt. rend., 145 154-6 (1907)
(9) Ribas and Tapia, Anales soc. espan. Fis Quim 30 778,944 (1930)
(10) German Patent #423544
(11) Hiers and Adams, J.A.C.S. 48 1089-1093 (1926)

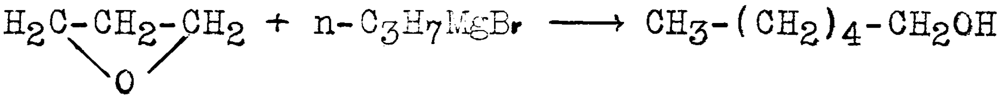




(12)

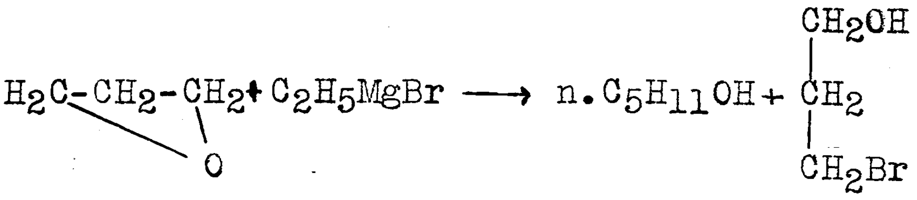
The only exception is the case reported by Whitmore (13), where t.butyl magnesium chloride failed to react with ethylene oxide.

Derick and Bissel (14) have shown that trimethylene oxide reacts with Grignard reagents to give primary alcohols containing three more carbon atoms than are found in the original radical. Thus, propylmagnesium bromide with trimethylene oxide gives n-hexanol.



$$H_2C-CH_2-CH_2 \text{ (—O—) } + n\text{-}C_3H_7MgBr \longrightarrow CH_3-(CH_2)_4-CH_2OH$$

But, there is also a case reported by Beremjo and Aranda (15) in which they obtained approximately equal quantities of n.pentanol and trimethylene glycol bromhydrin as a result of the interaction of ethylmagnesium bromide and trimethylene oxide.



$$H_2C-CH_2-CH_2 \text{ (—O—) } + C_2H_5MgBr \longrightarrow n.C_5H_{11}OH + CH_2OH-CH_2-CH_2Br$$

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(12) Bogert and Haraman, Amer. Perfumer and Essential Oils Rev. <u>25</u> 19-20 (1930)

(13) Whitmore, Homeyer, and Wallingford J.A.C.S. <u>55</u> 4209-4214 (1933)

(14) Derick and Bissel, J.A.C.S. <u>38</u> 2478-86 (1916)

(15) Beremjo and Aranda, Anales Soc. espan. Fis Quim <u>27</u> 798-800 (1929)

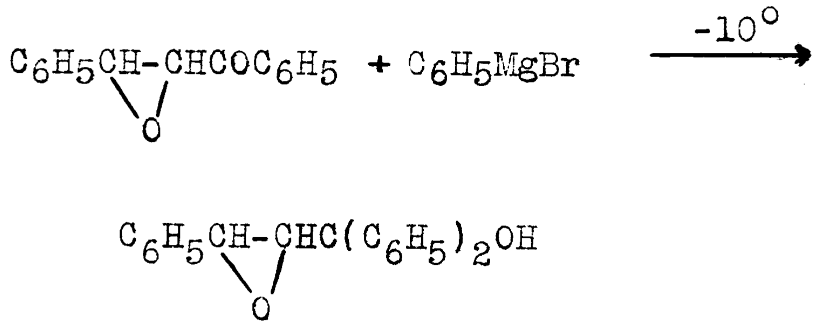
The bromhydrin in all probability arises in the same manner as outlined by Grignard (6) for the simpler oxide.

Larger oxide rings, tetramethylene and pentamethylene oxides, have not been reported to react with the Grignard reagent. If the reactivity of these alkylene oxides is compared with the properties of their cyclic homologues, cyclo-pentane and cyclo-hexane, it is seen that not only are the homologues formed with much greater readiness, but that reppening of the ring is more difficult. These facts are special cases of a general phenomenon, which can be expressed in the form that in similarly constructed ring systems, the stability increases from the three to five-membered ring. The six-membered heterocyclic ring is characterized by very great stability, being very little less stable than the five-membered ring. (16).

The ethylene oxide ring which opens readuly under the influence of the Grignard reagent may be said to bear the same general relationship to the carbonyl group as the cyclopropane ring does to the ethylenic double bond.

(16) Karrer "Organic Chemistry" 219 (Nordemann, N.Y.1938)

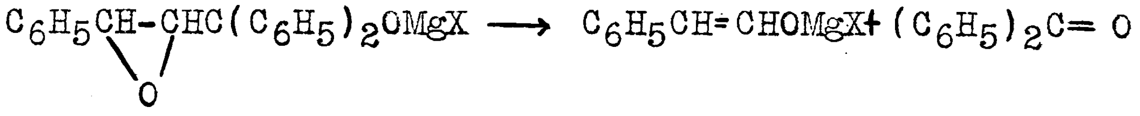
That the oxide ring is less active than the carbonyl group has been shown by Kohler (17), who observed that when organomagnesium compounds react with oxido-ketones they combine with the carbonyl group, and it is possible to secure the corresponding oxido-carbinol by carrying out the reaction at low temperature and decomposing the addition product immediately.



$$C_6H_5\underbrace{CH-CH}_{O}COC_6H_5 + C_6H_5MgBr \xrightarrow{-10^{\circ}}$$

$$C_6H_5\underbrace{CH-CH}_{O}C(C_6H_5)_2OH$$

If, however, the reaction mixture is allowed to warm up before decomposition, the addition product cleaves in the following manner



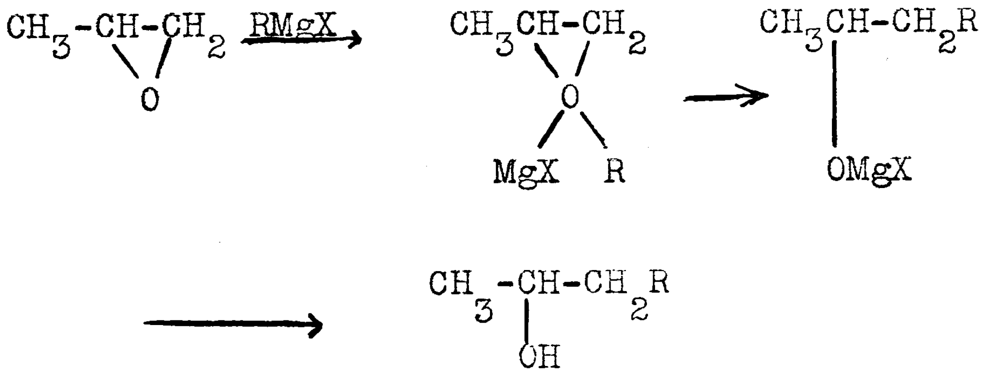
$$C_6H_5\underbrace{CH-CH}_{O}C(C_6H_5)_2OMgX \longrightarrow C_6H_5CH{=}CHOMgX + (C_6H_5)_2C{=}O$$

and in the presence of excess Grignard reagent, these derivatives may be transformed into secondary and tertiary alcohols. Kohler also found that oxidoester were transformed into oxido-ketones by the Grignard reagent and, therefore, gave the same final products as those obtained with ketone.

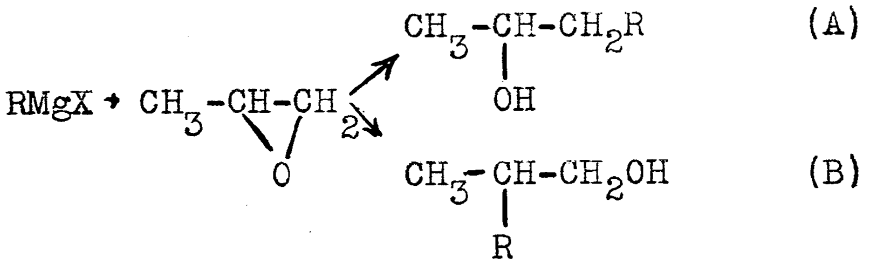
(17) Kohler, Richtmyer, and Hester J.A.C.S. <u>53</u> 205-21 (1931)

Substituted Ethylene Oxides.

A certain number of substituted ethylene oxides react in the same way as ethylene oxide itself. Thus, propylene oxide was reported to undergo opening of the oxide ring between the O and the $-CH_2$ to give a secondary alcohol (18)

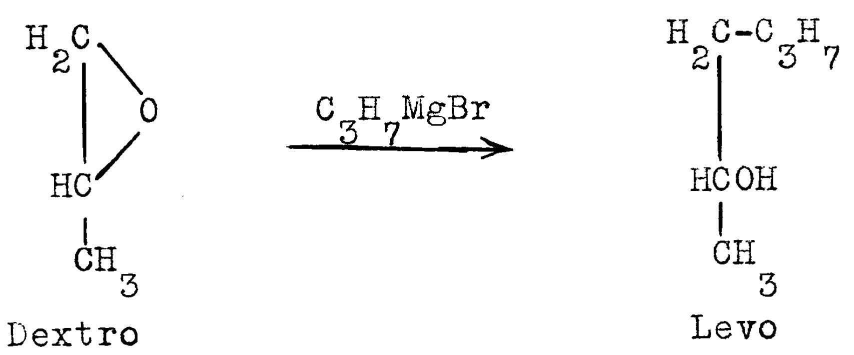


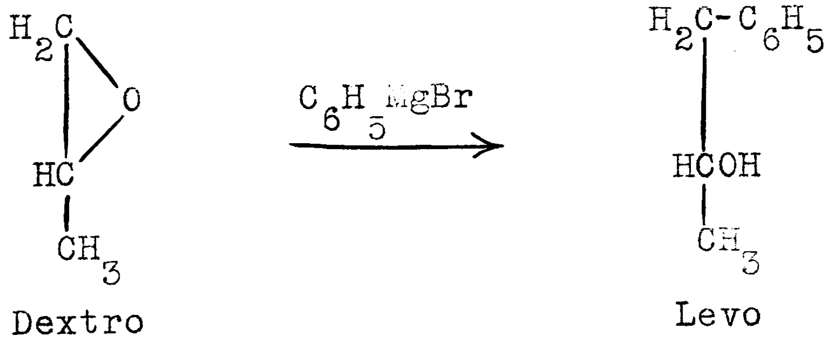
Theoretically, there are two possible products from a break of the oxide ring, but according to Henry (19), Tiffeneau and Fourneau (20), the secondary alcohol, A, alone results, not the primary one, B.



(18) Tiffeneau and Fourneau, Bull Soc. Chim.(3) 33 741 (1905)
(19) Henry, Compt. rend., 145 453-56 (1907)
(20) Tiffeneau and Fourneau, Compt. rend., 145 437-9 (1907)

This work was checked by Levene and Walti (21), who used this method to prepare methybutyl carbinol and methylbenzyl carbinol, and in this way they were able to relate configurationally 1-methylbenzyl carbinol and 1-methylbutyl carbinol.

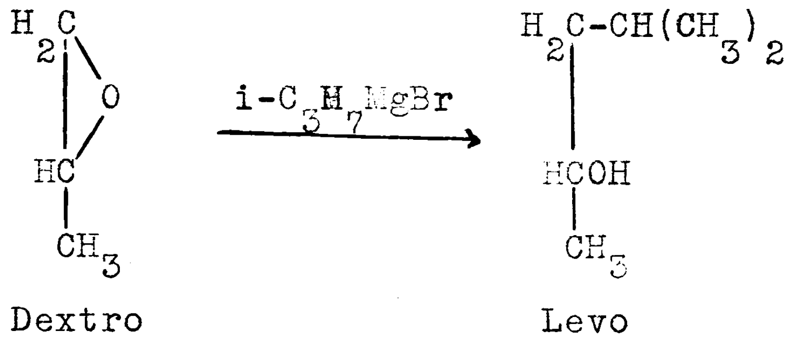




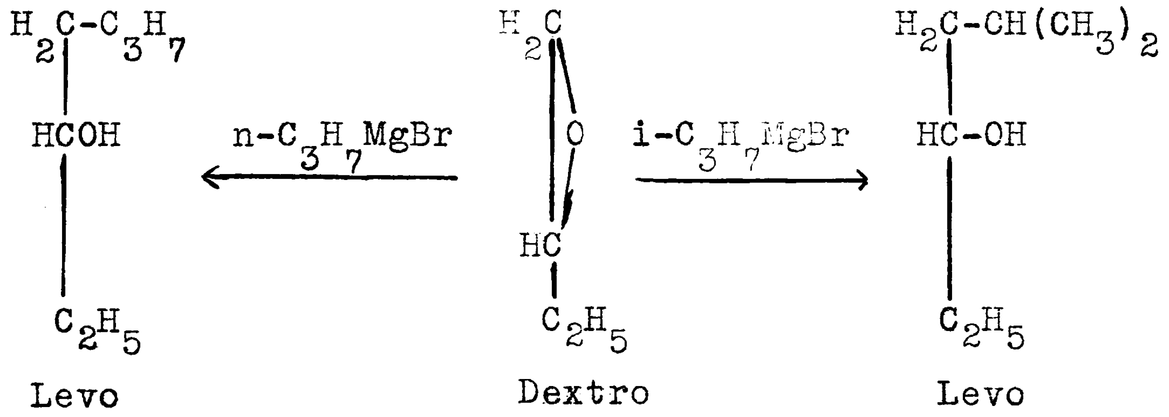
Levene and Walti (22) further showed that propylene oxide on condensation with isopropylmagnesium bromide formed methylisobutyl carbinol, having the same rotation as the methyl n-butyl carbinol derived from the same oxide.

(21) Levene and Walti, J. Biol. Chem. 90 81-88 (1931)
(22) Levene and Walti, J. Biol. Chem. 94 367-72 (1931)

Thus, these two carbinols are configurationally related on the basis of their mode of preparation.

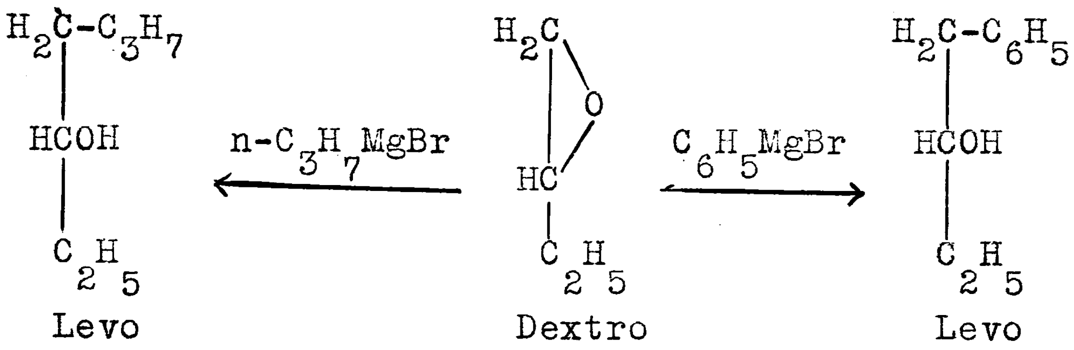


In a similar manner, butylene oxide was used by these authors, (22), to establish the configurational relationship of ethylisobutyl and ethyl-n-butyl carbinols,

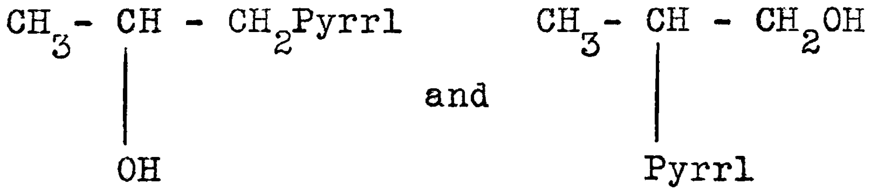


and also the previous conclusions of Levene and Stevens (23), regarding the configurational relationship of 1-ethyl benzyl carbinol and 1-ethyl-n-heptyl carbinol were substantiated by means of the following direct evidence:

(23) Levene and Stevens J. Biol.Chem. <u>87</u> 375 (1930)



Levene and Walti obtained only secondary alcohols as a result of the interaction of the Grignard and the two oxides. Kharasch (24), however, reported the isolation of primary and secondary alcohol from styrene oxide and phenyl magnesium bromide depending upon the order of addition of the reactants. The isolation of primary alcohols as a result of the interaction of an oxide with an organomagnesium compound has also been reported by Hess (25), who found that propylene oxide and pyrrl magnesium bromide reacted to give.



$$CH_3-\underset{OH}{CH}-CH_2Pyrrl \quad \text{and} \quad CH_3-\underset{Pyrrl}{CH}-CH_2OH$$

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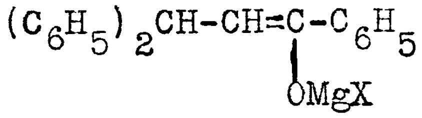
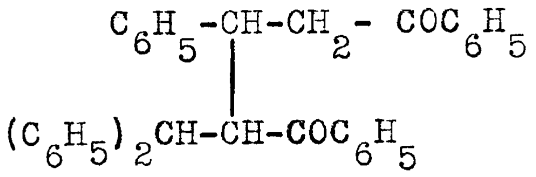
(24) Kharasch, Clapp, J. Org. Chem. (3) 355-60 (1938)
(25) Hess Ber. <u>46</u> 3117 (1913)

Since there is some doubt as to whether pyrryl magnesium bromide is a true Grignard reagent (26), we must accept these results with reservations.

Pyrryl magnesium bromide shows no luminescence when treated with oxygen (27), but nearly all true Grignard reagents do. It will, however, give the Gilman test (28) for an organomagnesium compound, but it may be that in the pyrryl magnesium derivative we have a special case. The position of the metal in the reagent is analagous to the position of the sodium atom in sodium malonate; that is, sodium malonate will add 1-4 to $C_6H_5CH{=}CHCOC_6H_5$, magnesium enolates will do the same, thus  $(C_6H_5)_2CH\text{-}CH{=}\underset{|\atop OMgX}{C}\text{-}C_6H_5$ will add to another mole of benzalacetophenone to give

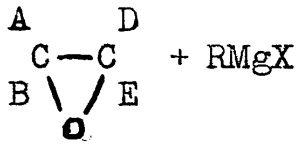


$$\begin{array}{l} C_6H_5\text{-}CH\text{-}CH_2\text{-}\ COC_6H_5 \\ \qquad\quad | \\ (C_6H_5)_2CH\text{-}CH\text{-}COC_6H_5 \end{array}$$

so we might expect that if the enolate adds to Michler's ketone, pyrryl magnesium bromide also would.

(26) Sidgwick, Organic Chem. of Nitrogen 480-481(Oxford 1931)
(27) Mc Cay and Schmidt, J.A.C.S. <u>48</u> 1933 (1926)
(28) Gilman and Shulze, J.A.C.S. <u>47</u> 2002 (1925)

The products obtained from the reaction of substituted ethylene oxides and the Grignard reagent will depend, according to Kayser (29), upon two things.



(I) The direction of the break:-The break may be unilateral to give

AB(OH)C-C(R)DE or AB(R)C-C(OH)DE

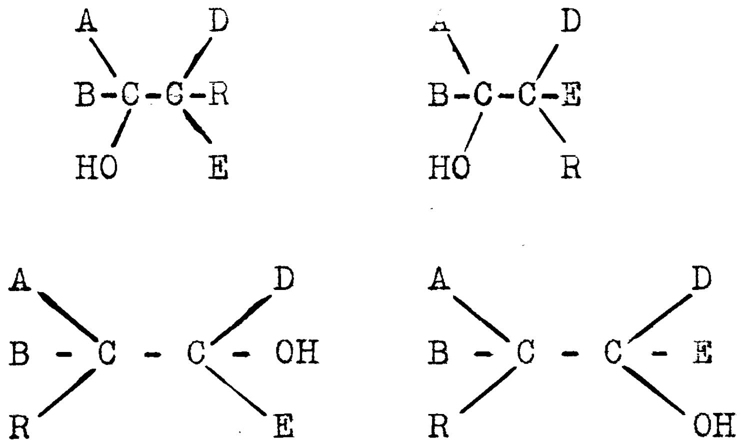
or bilateral to give a mixture of these two alcohols.

(II) The respective position of the substituents:-If the substituents are not modified, an alcohol of the type AB(R)C-C(OH)DE is obtained; if the position of one of the two substituents is modified, (rotation of one of the carbons with relation to the other one in the course of reaction), an alcohol of the type AB(R)C-CD(OH)E will be obtained which is an isomer of the preceding one.

Therefore, in the most unfavorable case, that is to say, if the break is not unilateral and there is partial

(29) Kayser, Ann. de Chim. (11) 6 212-214 (1936)

isomerization, an organomagnesium compound reacting on an oxide will give rise to four alcohols, without considering secondary reactions due to isomerization of the oxide into a ketone or aldehyde, reduction, condensation, or polymerization. The four possibilities are listed below:



In addition to the two foregoing types of reactions, (I and II, page 17), discussed by Kayser, the results of normal cleavage, a third general type was noted by Henry (30), who has shown that isobutylene oxide isomerizes under the influence of the Grignard reagent to isobutenal, and this aldehyde reacts with the Grignard reagent in the usual manner to give the secondary alcohol.

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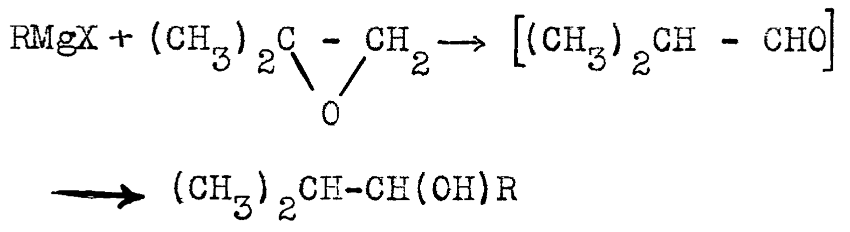
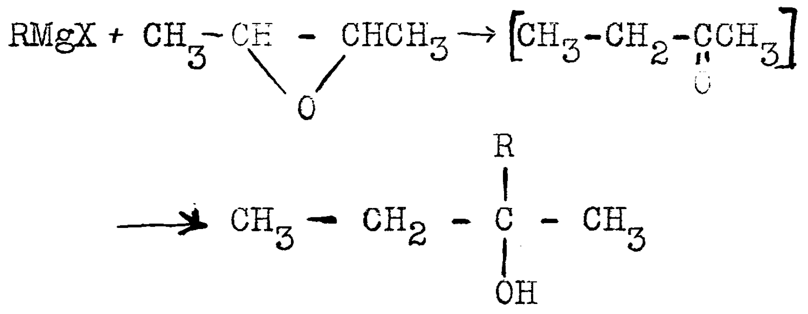
(30) Henry Compt. rend., 145 21 (1907)



Similarly, Henry reported the isomerization of sym. dimethyl ethylene oxide to a ketone (31), and the latter then reacts as such with the Grignard reagent.



A particular case of a di-substituted ethylene oxide is furnished by cyclohexene oxide, studied by Godchot and Bedos (32), (33), and later by Bedos, (34). These authors treated cyclohexene oxide with methylmagnesium iodide, and as a result of their work, stated that, " as the oxide is symmetrically substituted, it does not rearrange into a ketone but functions under the action of the Grignard reagent to give a secondary alcohol".

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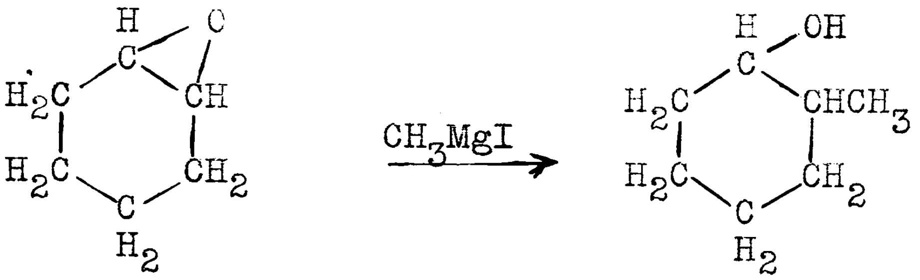
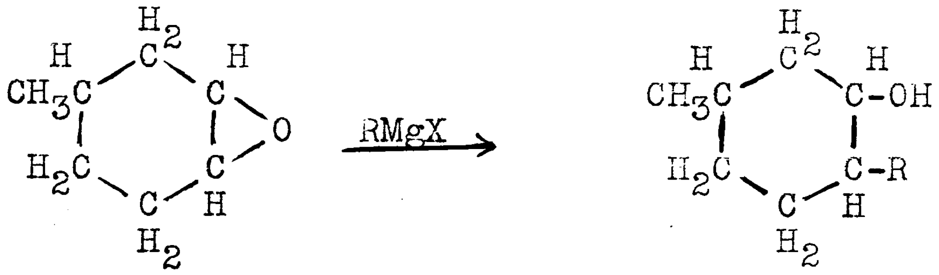
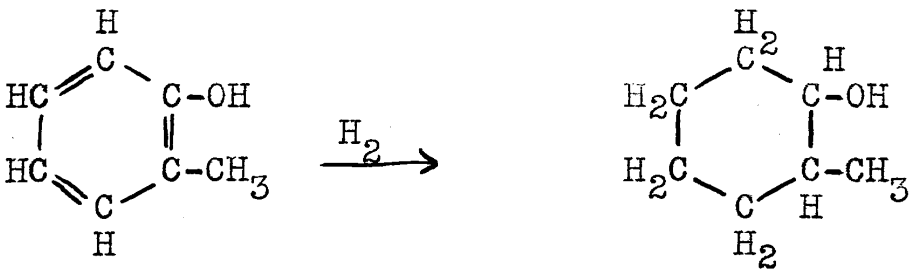
(31) Henry Compt. rend., 145 406-8 (1907)
(32) Godchot and Bedos Compt. rend., 174 461 (1922)
(33) Gpdchot and Bedos Bull.soc.Chim.(4) 31 537 (1922)
(34) Bedos Compt. rend., 177 111-13 (1923)



Godchot and Bedos (35), also reported that 3-methylcyclohexene oxide reacted in the same manner to give the secondary alcohol.



However, the results of Godchot and Bedos, as shown in the preceding equations, have been shown to be incorrect. A synthesis of the two isomeric 2-methylcyclohexanols by reduction of o-cresol by Gough, Hunter, and Kenyon (36), has shown that neither of these compounds are comparable with the reaction product obtained by Godchot and Bedos.



cis and trans.

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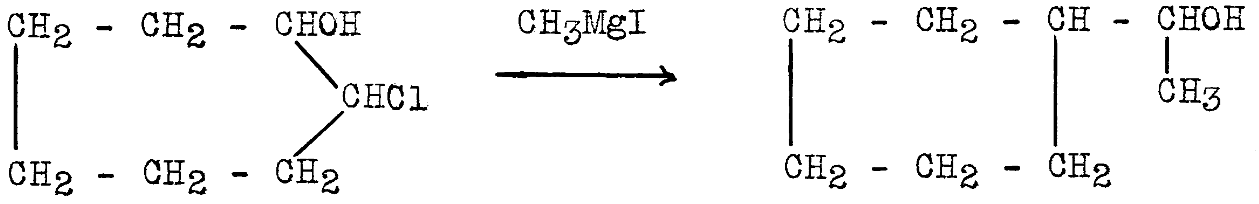
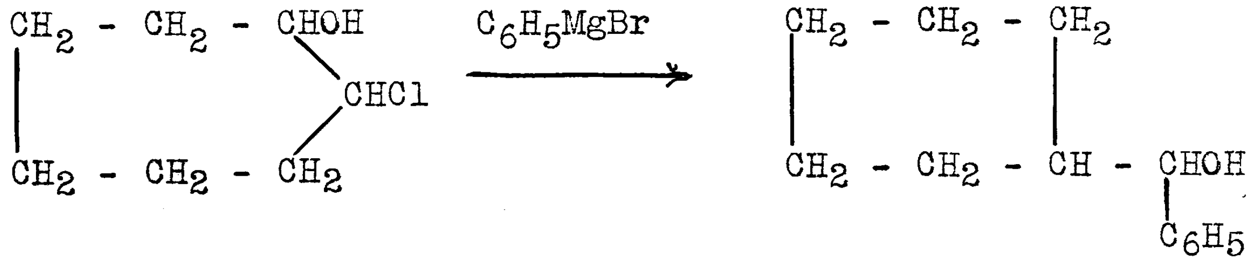
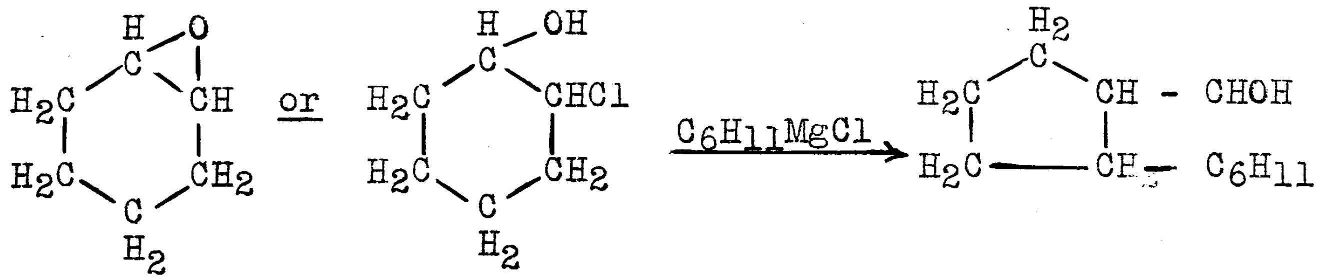
(35) Godchot and Bedos, Bull.soc. Chim. <u>37</u> 1451-66 (1925)
(36) Gough, Hunter, and Kenyon, J.A.C.S. 2052-71 (1926)

This phase of the problem was cleared up by Godchot and Cauquil, (37), (38), and Vavon and Mitchovitch, (39), who showed that the reaction of organomagnesium halides with the oxides or 2-chloro alcohols of the cycloheptane and cyclohexane series led to ring contraction.

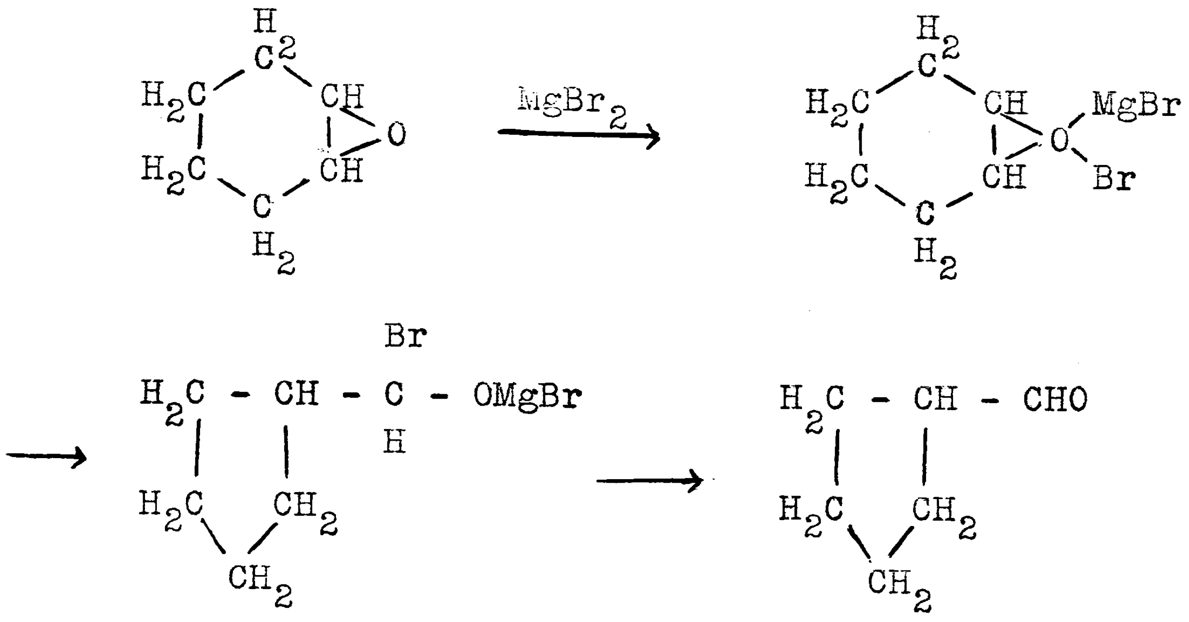




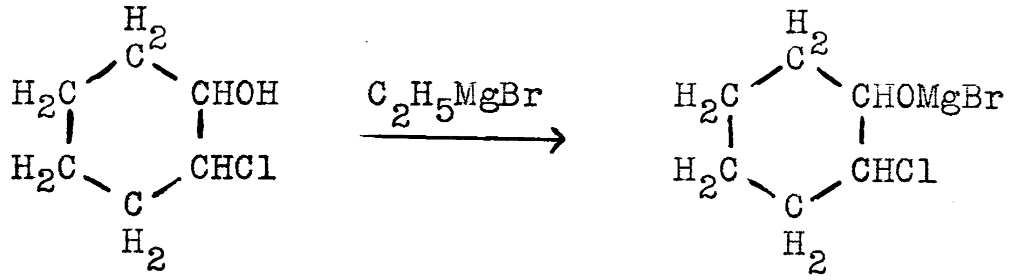


Bedos (40), has further shown that when cyclohexene oxide is heated with magnesium bromide, etherate in dry ether cyclopentylaldehyde was obtained and that the yield of the aldehyde rose to 34% when two moles of the etherate were used to one of the oxide.

(37) Godchot and Cauquil, Compt. rend., <u>186</u> 375-77 (1928)
(38) Godchot and Cauquil, Compt. rend., <u>186</u> 955-57 (1928)
(39) Vavon and Mitchovitch Compt. rend., <u>186</u> 702-5 (1928)
(40) Bedos, Compt. rend., <u>189</u> 255-7 (1929)



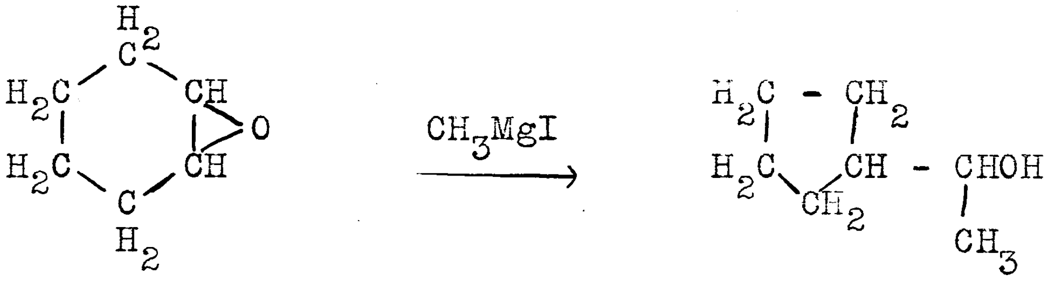
The chlorhydrin, however, when treated in a similar manner gave only traces of the aldehyde, but if the chlorhydrin is treated with ethylmagnesium bromide to form the alcoholate



and then heated with magnesium bromide etherate, the aldehyde was formed in 40% yield. That the foregoing reaction will also take place in the cold was demonstrated by Bedos who carried out the reaction in benzene solution at room temperature, in this case, the yield fell off to 18%.

The magnesium complex obtained from the oxide and the chlorhydrin, reacted as vigorously as the free aldehyde when treated with the Grignard reagent, and gave as a product the cyclopentyl carbinol.

On the basis of this work, the supposed cis-2-methylcyclohexanol of Godchot and Bedos, (32), was then in reality, methylcyclopentyl carbinol arising from ring contraction of the cyclohexene oxide when treated with methyl magnesium oxide.

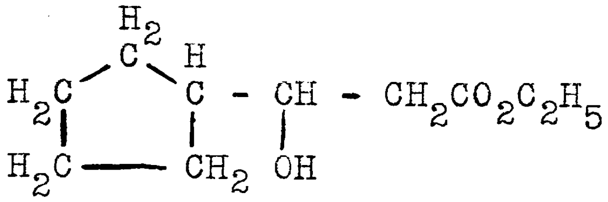


It is interesting to note that cyclohexene oxide on heating over Thorium oxide at 330° gives cyclopentyl aldehyde along with 1, 2-dehydro-benzene (41).

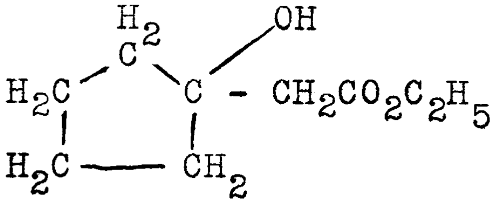
Another example of ring contraction with cyclohexene oxide is found in the work or Clemo and Ormston, (42),

(41) Bedos and Ruyer, Compt. rend., <u>188</u> 962-4 (1929)
(42) Clemo and Ormston, J.-.C.S. (1933) 362

who observed that cyclohexene oxide when treated with ethyl bromoacetate in the Reformatsky reaction gave as a product, the following cyclopentylaldehyde derivative.

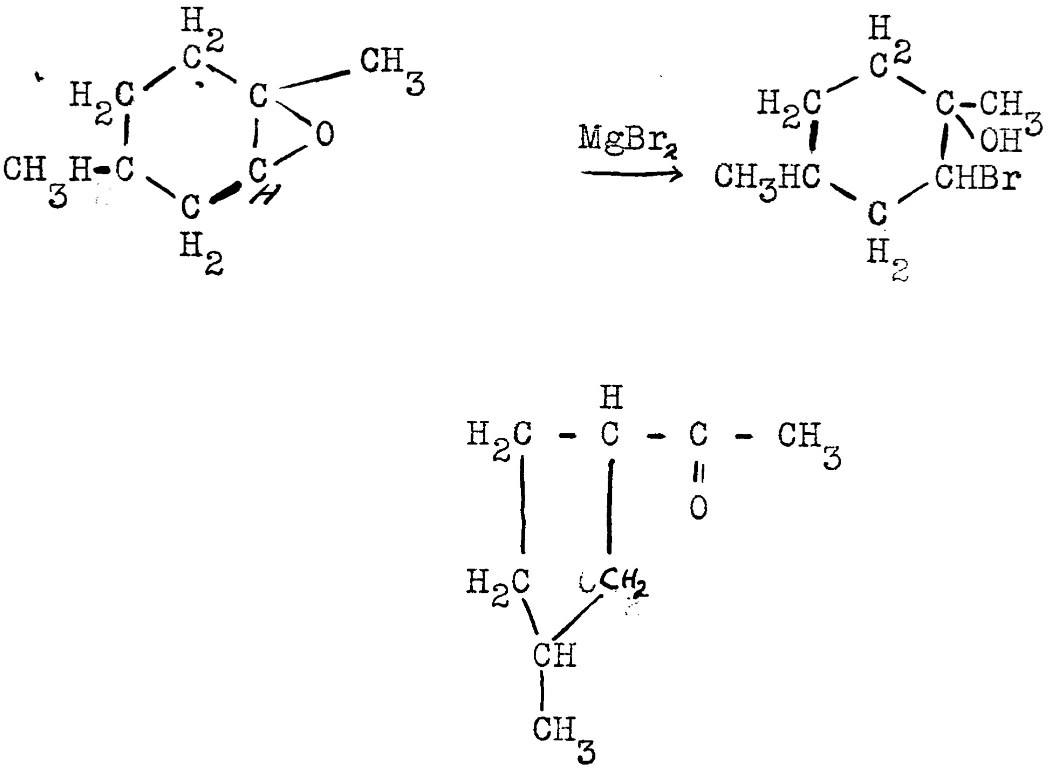


Cyclopentene oxide, however, when treated in a similar manner, did not give ring contraction but rearranged to the ketone cyclopentanone which gave the following product.

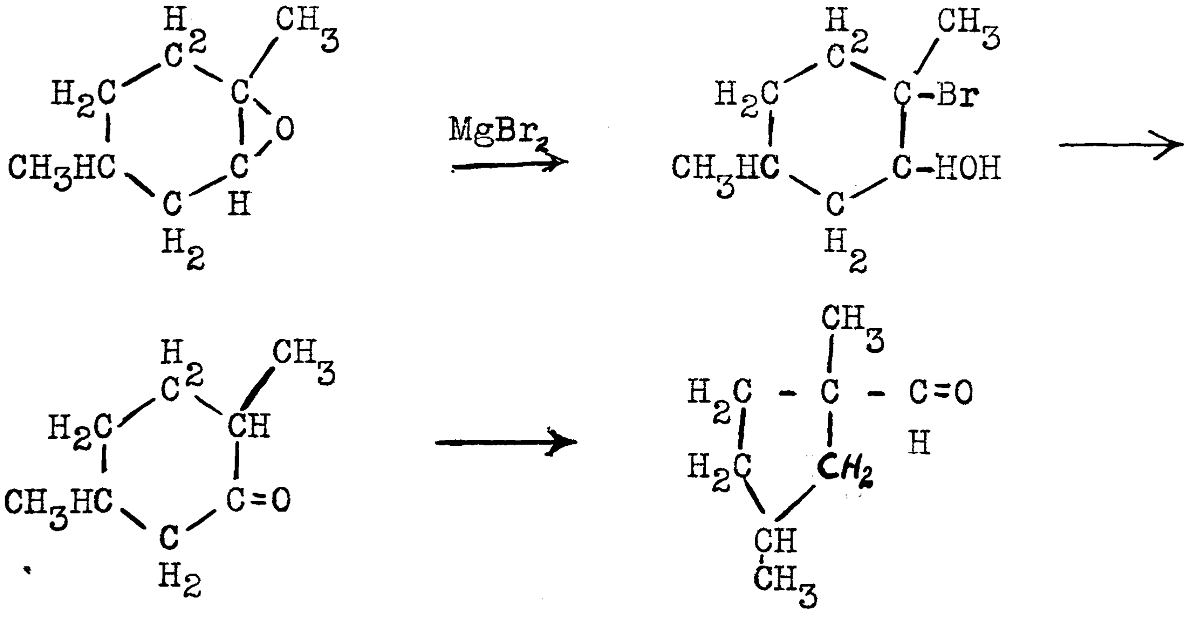


A further example of the extensive rearrangement of epoxycyclohexanes has been given by Tchoubar, (43), who obtained two trans bromohydrins as a result of treating 1,4-dimethyl-1,2-epoxycyclohexane with magnesium bromide-etherate in the cold. It was found that the bromhydrin with the tertiary hydroxyl was stable and by semipinacoline rearrangement gave 3-methyl-1-acetylcyclopetane.

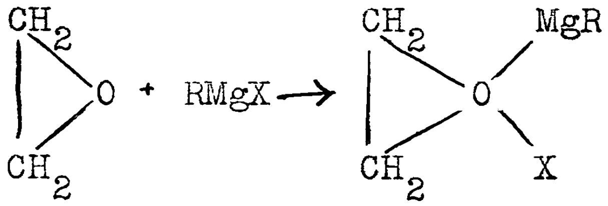
(43) Tchoubar, Compt. rend., <u>208</u> 355-7 (1939)



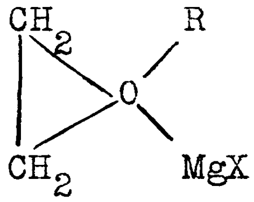
The bromhydrin with the secondary hydroxyl gave, according to the author, two products, 1,4-dimethyl-2-cyclohexanone by migration of hydrogen and 1,3-dimethyl cyclopentyl formaldehyde by a semihydrobenzoin rearrangement.



In considering the problem of the rearrangement of cyclohexene oxide, Bartlett and Berry (44) adopted the Blaise structure for the primary intermediate.



This theory was, we have seen, criticized by Grignard who proposed that the oxide ring broke at a higher temperature and that the intermediate product had the following formula:

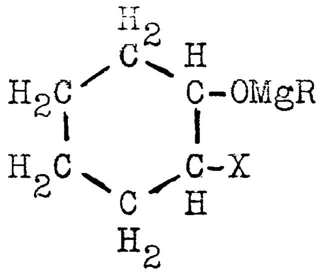


Further evidence in favor of the Blaise form was advanced by Ribas and Tapia, (45), (46), as a result of extensive experiments with ethylene oxide, epichlorhydrin, and 3-methoxy 1,2-epoxy-propane.

These authors have suggested, CH_2Br-CH_2OMgBr and $(CH_2Br-CH_2O)_2Mg$ as possible intermediates in the reaction of ethylene oxide with the Grignard.

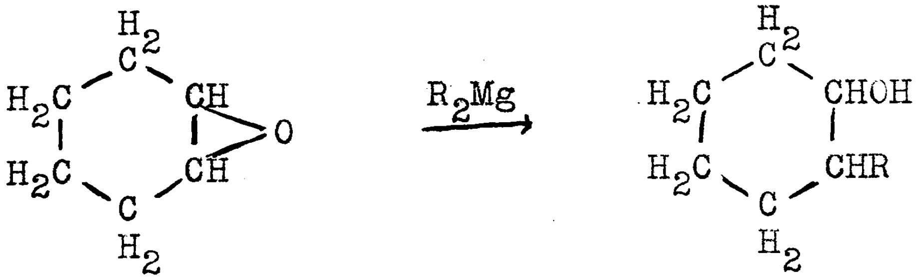
(44) Bartlett and Berry, J.A.C.S. 56 2683-85 (1934)
(45) Ribas and Tapia, Anales.soc.espan.fis quim.30,778-91 (1932)
(46) Ribas and Tapia, Anales.soc.espan.fis quim 30,944-70 (1932)

The intermediate proposed by Bartlett and Berry in the case of cyclohexene oxide follows the Blaise form in that MgR is attached to the oxygen while the halogen is attached to carbon,



and they assume that this intermediate rearranges to cyclopentylformaldehyde instead of reacting through replacement of the halogen by the methyl group.

On the basis of this work, Bartlett and Berry thought that halogen-free organomagnesium compounds would add "normally" to the cyclohexene oxide. They found this to be the case for cyclohexene oxide when treated with diethyl magnesium and dimethyl magnesium. The products of the reaction were the corresponding 2-alkylcyclohexanols.



It is to be noted that the cyclohexanols obtained from this reaction exist principally in the trans configuration. Cyclohexene oxide itself, is a cis modification (47). The predominance of the trans form is also observed when cyclohexene oxide is hydrolyzed to cyclohexanediol.

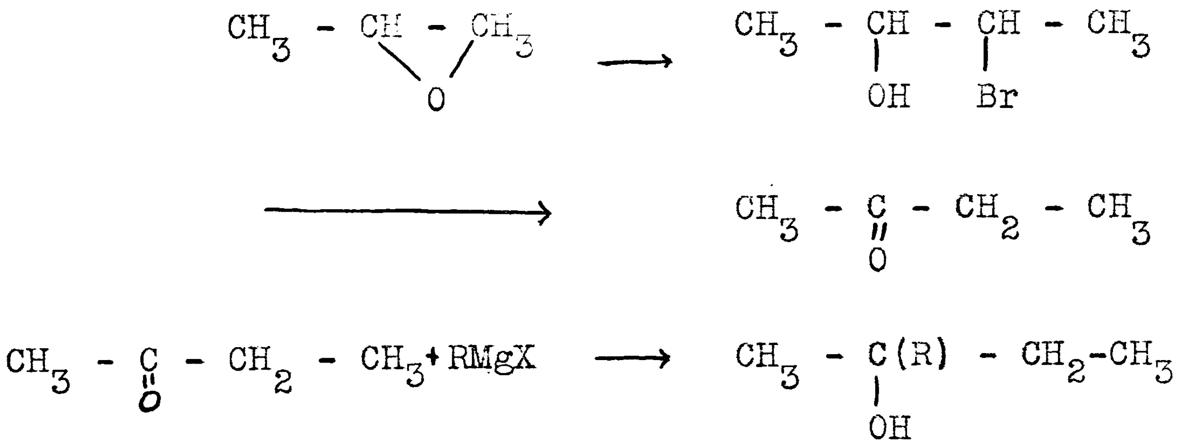
It has been suggested that this latter process involves a Walden inversion. (48)

The reaction mechanism that Bartlett and Berry outlined in their paper (44), was examined by Cottle and Powell, (49). These authors wished to determine whether or not 2,3-epoxybutane would follow the general reaction mechanism outlined by Bartlett and Berry for cyclohexene oxide.

Cottle and Powell state, that if the mechanism as outlined by Bartlett and Berry for cyclohexene oxide (44) holds for 2,3-epoxybutane then, 3-bromo-2-butanol should react with a Grignard reagent and yield a tertiary alcohol

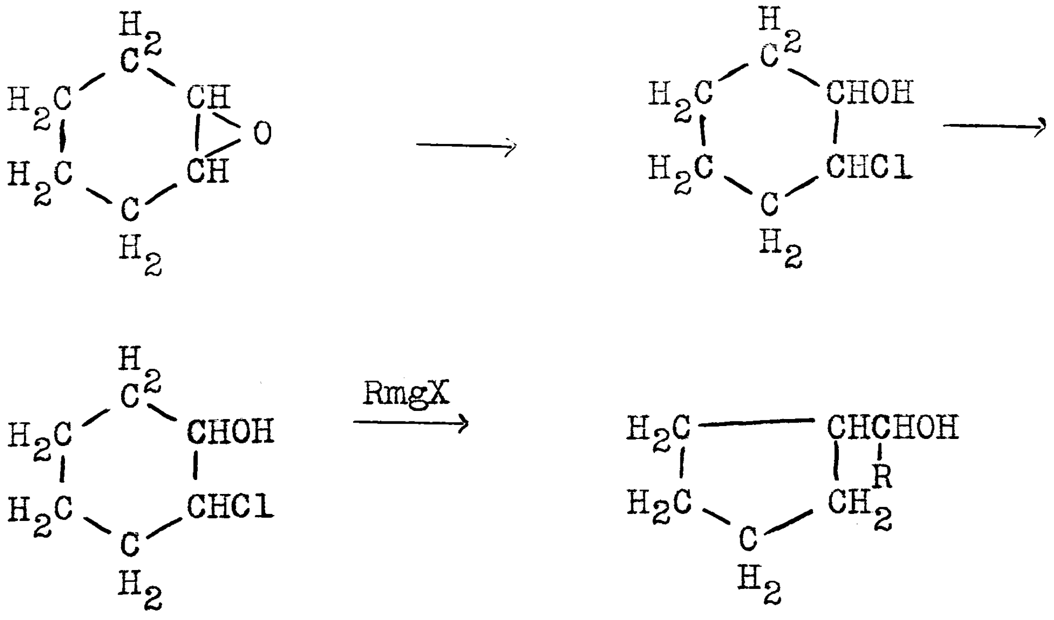
(47) Bartlett, J.A.C.S. 57 224-27 (1935)
(48) Boeseken and Van Griffen Rec.trav.chim.39 183-6 (1920)
(49) Cottle and Powell, J.A.C.S. 58 2267-72 (1936)

as a result of a rearrangement of the bromhydrin to the ketone, butanone-2, since Henry (31), obtained tertiary amyl alcohol when methylmagnesium iodide reacted with the same oxide. The 3-bromo-2-butanol would be an intermediate in the reaction of 2,3-epoxybutane just as 2-chloro-cyclohexanol is in the reaction of cyclohexene oxide.

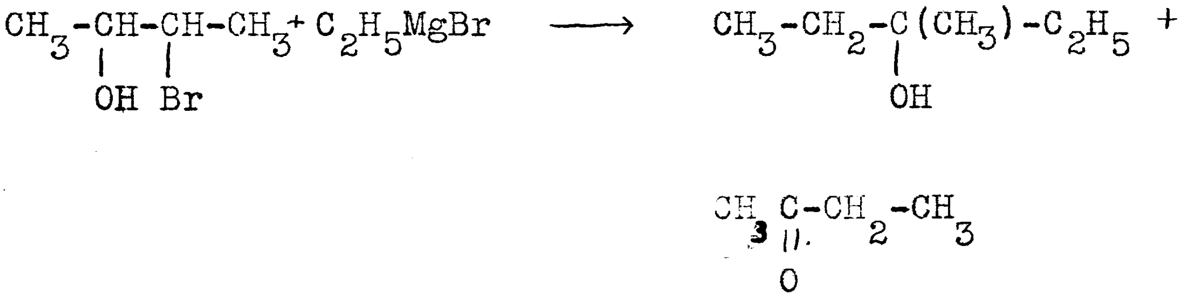


$$CH_3-\underset{OH}{\underset{|}{CH}}-\underset{Br}{\underset{|}{CH}}-CH_3 \longrightarrow CH_3-\underset{O}{\underset{\|}{C}}-CH_2-CH_3$$

$$CH_3-\underset{O}{\underset{\|}{C}}-CH_2-CH_3+RMgX \longrightarrow CH_3-\underset{OH}{\underset{|}{C(R)}}-CH_2-CH_3$$

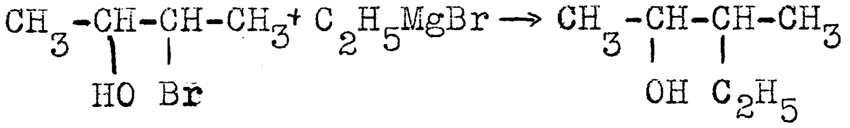


As a result of their work, Cottle and Powell found that 3-bromo-2-butanol reacted with ethyl magnesium bromide without the application of heat to give 3-methyl-3-pentanol and butanone-2, which had been postulated by Henry (31) as the intermediate in the reaction of the Grignard reagent with the oxide.



$$\mathrm{CH_3{-}\underset{OH}{\underset{|}{CH}}{-}\underset{Br}{\underset{|}{CH}}{-}CH_3 + C_2H_5MgBr \longrightarrow CH_3{-}CH_2{-}\underset{OH}{\underset{|}{C}}(CH_3){-}C_2H_5 + CH_3{-}\underset{O}{\underset{\|}{C}}{-}CH_2{-}CH_3}$$

The isolation of the ketone along with the tertiary alcohol indicated that the reaction path as outlined by Bartlett and Berry was applicable to 2,3-epoxybutane. The absence of any 3-methyl-2-pentanol which would result from a replacement of the halogen by the ethyl radical,

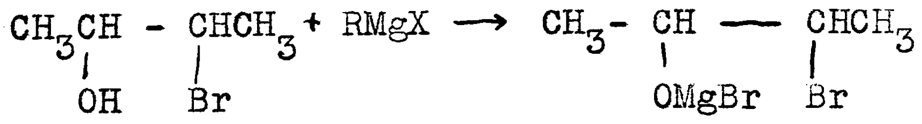


$$\mathrm{CH_3{-}\underset{HO}{\underset{|}{CH}}{-}\underset{Br}{\underset{|}{CH}}{-}CH_3 + C_2H_5MgBr \rightarrow CH_3{-}\underset{OH}{\underset{|}{CH}}{-}\underset{C_2H_5}{\underset{|}{CH}}{-}CH_3}$$

also indicates the general similarity of the reaction mechanisms, as the cyclohexene oxide intermediate was

was not reported by Bedos, (40), to react with the Grignard by halogen replacement.

The fact that the bromide atom does not react with the Grignard reagent at the temperature used is, the authors think, due to the secondary nature of the bromine atom, as ethylene bromhydrin is known to require a higher temperature than was used here for the reaction of the bromine atom, (50). The magnesium salt of 3,bromo-2-butanol, prepared from 2, 3-epoxybutane and magnesium bromide in ether-benzene solution decomposed practically quantitatively at slightly above room temperature to give butanone-2. This would tend to indicate that the ketone, isolated as a result of the reaction of 3-bromo-2-butanol with the Grignard reagent, arose in a similar manner; that is, the Grignard reagent reacted with the 3-bromo-2-butanol to give the magnesium salt,



$$\underset{OH}{CH_3CH} - \underset{Br}{CHCH_3} + RMgX \longrightarrow CH_3 - \underset{OMgBr}{CH} — \underset{Br}{CHCH_3}$$

which then rearranged to the ketone. This would account

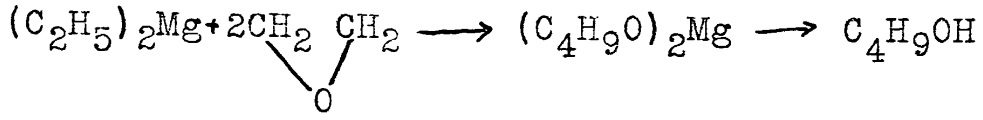
(50)-a-Grignard Bull Soc. Chem. (3) <u>34</u> 918 (1905)
-b-Conant and Kirner, J.A.C.S. <u>46</u> 232-52 (1924)

for the isolation of the ketone since, unless there was an excess Grignard reagent, there would not be sufficient of this reagent present to convert all the ketone formed into the alcohol.

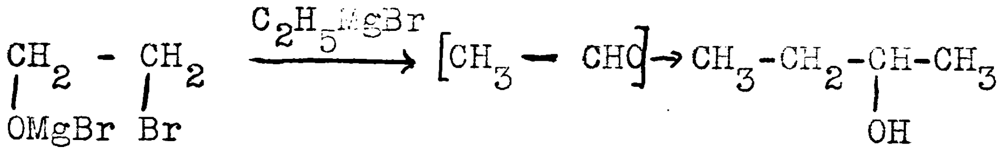
Cottle and Powell, (49), state that although the Blaise theory is satisfactory in predicting the behavior of 3-bromo-2-butanol, the fact that early workers in this field isolated only one alcohol as a result of the reaction between a Grignard reagent and an oxide in cases where rearrangement could occur does not agree with later experimental evidence which indicate that more than one alcohol may be obtained.

A case in point, namely that of a simple oxide giving more than one product, has been reported by Ribas and Tapia, (46). These authors observed, as a result of the reaction of ethylene oxide and ethyl magnesium bromide (in a 2:1 or 1:1 ratio), the formation of n-butyl alcohol, in addition to the bromhydrin. The butyl alcohol arising from the reaction of the dialkyl-magnesium compound present in the equilibrium mixture.

$$2C_2H_5MgBr \rightleftarrows (C_2H_5)_2Mg + MgBr_2$$



They have, however, not reported the isolation of any butanol-2, which would have resulted from a rearrangement of the magnesium salt of the bromhydrin to acetaldehyde followed by reaction with the Grignard reagent.



$$\underset{OMgBr}{CH_2} - \underset{Br}{CH_2} \xrightarrow{C_2H_5MgBr} [CH_3 - CHO] \rightarrow CH_3-CH_2-\underset{OH}{CH}-CH_3$$

The failure of the magnesium salt to rearrange may be due to the fact that the Grignard reagent reacts as R_2Mg, which would then give the normal product n-butanol,

$$2CH_2Br—CH_2OMgBr + (C_2H_5)_2Mg \longrightarrow CH_3CH_2CH_2CH_2OH$$

rather than the abnormal one, butanol-2.

Ribas and Tapia, (46), found that in the case of epichlorhydrin and 1,2-epoxy-3methoxy propane, that the reactivities with magnesium bromide, diethyl magnesium, or diphenyl magnesium were of the same order of magnitude and the composition of the products were correspondingly modified.

The oversight on the part of the early workers may, in some cases, be attributed to the relatively low efficiency of the fractionating columns in use at that time. This fact, combined with the large amount of codistillation that can and does occur with similarly constituted compounds, probably explains the failure to isolate the relatively small amounts of some of the products.

The application of diakyl magnesium compounds has been successfully used in the synthesis of alcohols, as a means of avoiding the rearrangements that so often occur when ethylene oxides are treated with the Grignard reagent in the usual way. Diakyl and diaryl magnesium compounds have been prepared in a great many cases. These compounds were at first prepared from the corresponding organomercury compound.

$$R_2Hg+Mg \longrightarrow R_2Mg+Hg$$

This method was not entirely satisfactory however, in that organomercury compounds are difficult to handle and the organomagnesium compounds resulting from the reaction tend to be spontaneously inflammable in the solid state.

The discovery by Schlenk and Schlenk (51), that Grignard reagents are equilibrium mixtures,

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$

from which the halogen containing compounds are precipated by dioxane made the organomagnesium compounds more readily available and, hence more widely used. Independent evidence in favor of the equilibrium was presented by Cope, (52), who detected the presence of R_2Mg in a study of the reaction of dimethyl sulfate and the Grignard reagent.

Schlenk, Jr., (53) on the basis of his work, made the general statement that the amount of dialkyl magnesium increases with the molecular weight of the hydrocarbon radical. This statement must be modified in view of the work of Noller and Hilmer, (54) to take into consideration the structure of the hydrocarbon radical. Their results indicate that the amount of dialkyl magnesium in the solution of tertiary butylmagnesium bromide

(51) Schlenk and Schlenk, Ber. <u>62</u> 920-4 (1929)
(52) Cope, J.A.C.S. <u>56</u> 1578-81 (1934)
(53) Schlenk, Jr., Ber. <u>64</u> 734-36 (1931)
(54) Noller and Hilmer, J.A.C.S. <u>54</u> 2503-06 (1932)

is lower than in any of the other reagents under examination which included ethyl, propyl, and butyl Grignards.

ALKYL MAGNESIUM BROMIDE	DIALKYL MAGNESIUM EQUIVALENT %
t-Butyl	32
Ethyl	51
Isopropyl	59
s-Butyl	62
n-propyl	71
n-Butyl	74
Isobutyl	78

These results may be compared to those obtained by Johnson and Adkins, (55),

ALKYL HALIDE	DIALKYL MAGNESIUM %
Ethyl Bromide	42
Ethyl Iodide	7
Isobutyl Bromide	79
n-Butyl Bromide	82
n-Butyl Chloride	84
n-Butyl Iodide	76
t-Butyl Bromide	39
t-Butyl Chloride	62

who found that t-butyl chloride when converted to the Grignard reagent contained a far higher percentage of dialkyl magnesium than the corresponding bromide. The amount of dialkyl magnesium compound depends both upon the solvent and upon the temperature. A increase in temperature giving a larger amount of the halogen-free compound.

(55) Johnson, Adkins J.A.C.S. <u>54</u> 1943-47 (1932)

A further increase in the amount of dialkyl magnesium compound isolatable from Grignard reagents treated with dioxane can be made if the Grignard reagent is shaken from four to ten hours before removing the halogen compounds precipated by the dioxane, (56).

The original work of Bartlett and Berry (44) on the action of dialkyl magnesium compounds with epoxides, has been extended by Norton and Hass, (57), to cover a wide variety of types. Norton and Hass quote Houben-Weyl on the general situation in regard to simple oxides.

> "The reaction of epoxyalkanes with the the Grignard reagents may be summarized as follows: Epoxyethane and 1,2-epoxy propane are known to react by a simple splitting of the oxygen to carbon linkage, but the more highly substituted epoxyalkanes rearrange to produce alcohols which can be obtained from the corresponding aldehyde or ketone by use of the same alkyl magnesium halide". (58).

This statement was and is true except for the case reported by Whitmore, (59), wherein ethylene oxide failed to react satisfactorily with t-butyl magnesium chloride, which coupled with the present work on propylene oxide seem to indicate that perhaps the degree of substitution of the alkyl magnesium halide has some bearing on whether or not

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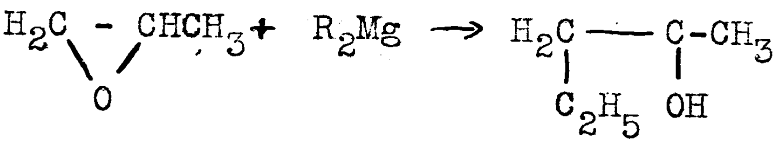
(56) Noller and White, J.A.C.S. 59 1354-56 (1937)
(57) Norton and Gass, J.A.C.S. 58 2147-51 (1936)
(58) Houben-Weyl, 2nd.edition Vol.IV.p.781(G.Thiem,Leipzig (1924)
(59) Homeyer, Whitmore and Wallingford, J.A.C.S.55 4209-14 (1933)

a rearrangement takes place.

Norton and Hass, (57), have prepared a series of carbinols by the action of dialkylmagnesium and alkylmagnesium compounds on ethylene oxides - and conclude :

> 1. "Dialkylmagnesium compounds react with epoxyalkanes to form addition products which yield alcohols when hydrolyzed. These alcohols are the result of a splitting of the oxide linkage and not a rearrangement such as occurs with alkylmagnesium halides".
>
> 2. "Diethyl magnesium reacts with the following compounds".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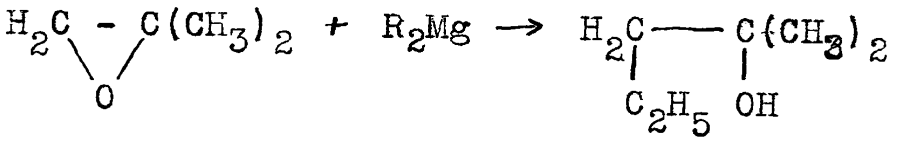
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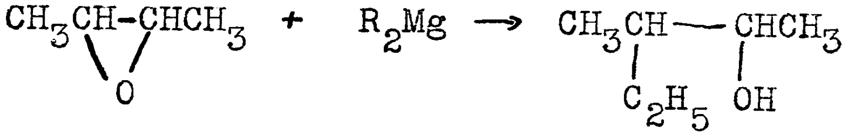
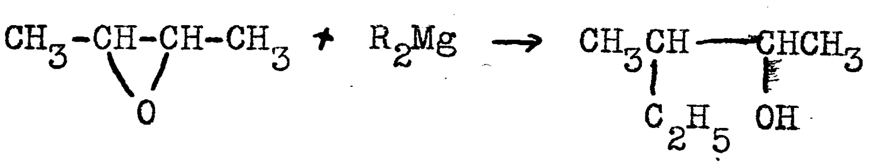
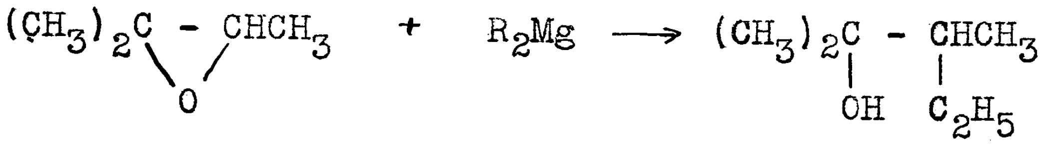

III

Cis A stereoisomeric mixture.

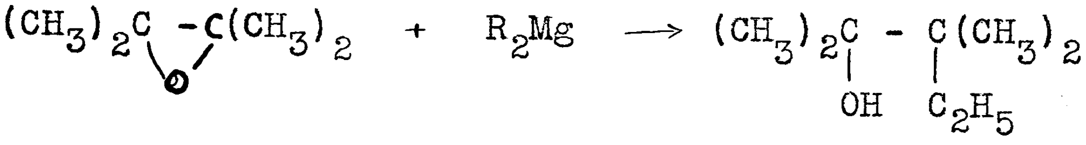

IV

Trans A different racemic mixture.



$$(CH_3)_2C(O)CHCH_3 + R_2Mg \longrightarrow (CH_3)_2C(OH)-CH(C_2H_5)CH_3$$

V



$$(CH_3)_2C(O)C(CH_3)_2 + R_2Mg \longrightarrow (CH_3)_2C(OH)-C(C_2H_5)(CH_3)_2$$

VI

> 3. "When there is a difference between the two carbon valences holding the epoxy oxygen atom, the primary valence breaks rather than the secondary or tertiary, and the secondary rather than the tertiary."

The results obtained by Cottle and Powell, (49), in their work on 2,3-epoxybutane substantiate the general statements made by Bartlett and Berry, (44) and confirm the work of Norton and Hass, (57) in that 2, 3-epoxybutane yields secondary alcohols when treated with diethyl and dimethyl magnesium. Cottle and Powell were also able to isolate secondary alcohols along with the tertiary when 2,3-epoxybutane was treated with a series of ethyl Grignard reagents.

RMgX	SECONDARY ALCOHOL	TERTIARY ALCOHOL
C_2H_5MgCl	27%	30%
C_2H_5MgBr	2%	31%
C_2H_5MgI	trace	27%

The tertiary alcohol arises from the interaction of the organometallic compound and the ketone formed by rearrangement of the oxide, while the secondary alcohol is the result of a reaction of the dialkylmagnesium with the unrearranged oxide. The following table taken from Schlenk, (53) gives the relative proportion of RMgX and R_2Mg in the case of the three reagents listed above.

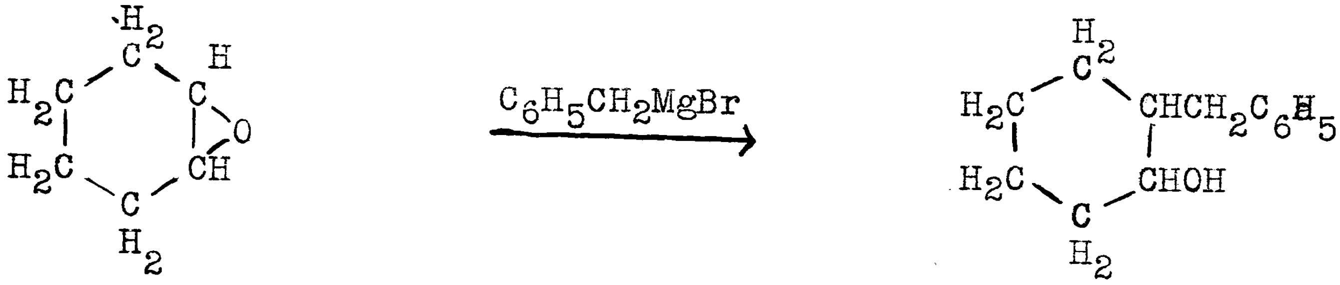
GRIGNARD REAGENT	RMgX	R_2Mg
C_2H_5MgCl	25%	42.5%
C_2H_5MgBr	41%	29.5%
C_2H_5MgI	43%	28.5%

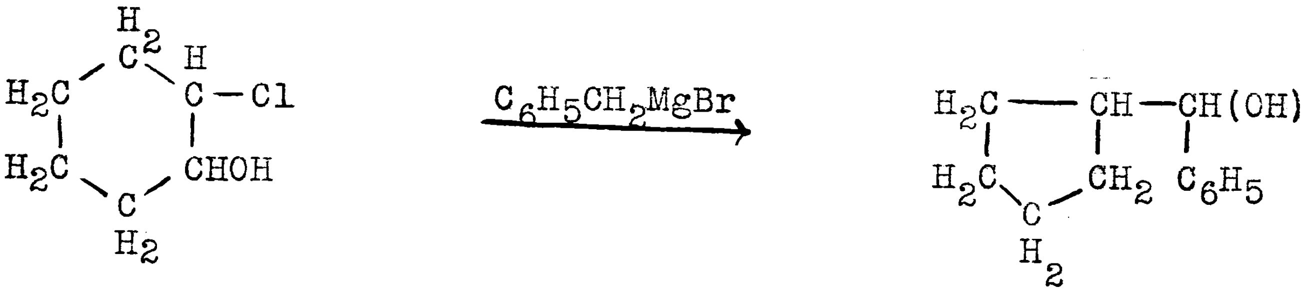
It will be seen from this table that the ethyl magnesium iodide which gave only a trace of the secondary carbinol has the lowest percentage of R_2Mg, while the chloride which gave the greatest percentage of secondary alcohol, has 14% more R_2Mg. The small amount, 2%, is in agreement with the amount of R_2Mg present, it being only slightly higher, 1%, than in the case of the iodide.

Cottle and Powell, (49) attribute the low percentage of secondary alcohol in part, to the fact that aqueous potassium iodide has been shown by Bronsted, (60) to add to glycid and epichlorhydrin faster than the bromide, which in turn, was faster than the chloride. This may be the case, but the relative percentage of RMgX and R_2Mg seem to have a direct bearing here.

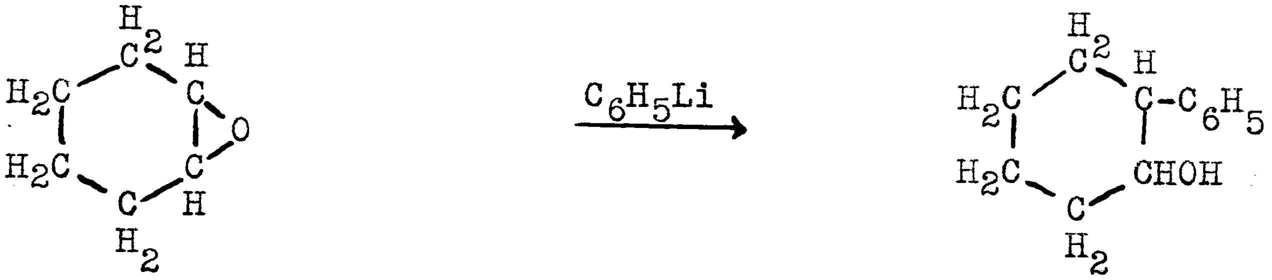
The equilibrium position of the Grignard reagent is not the only factor influencing the course of the reaction for Cook, Hewett, and Lawrence, (61) found that benzylmagnesium chloride reacts with cyclohexene oxide to give as a product, 2-benzyl-cyclohexanol, while at the same time, benzylmagnesium chloride reacted with 2-chloro-cyclohexanol to give a product, which was not 2-benzylcyclohexanol, and by analogy with other cases, was most probably benzylcyclopentyl carbinol.

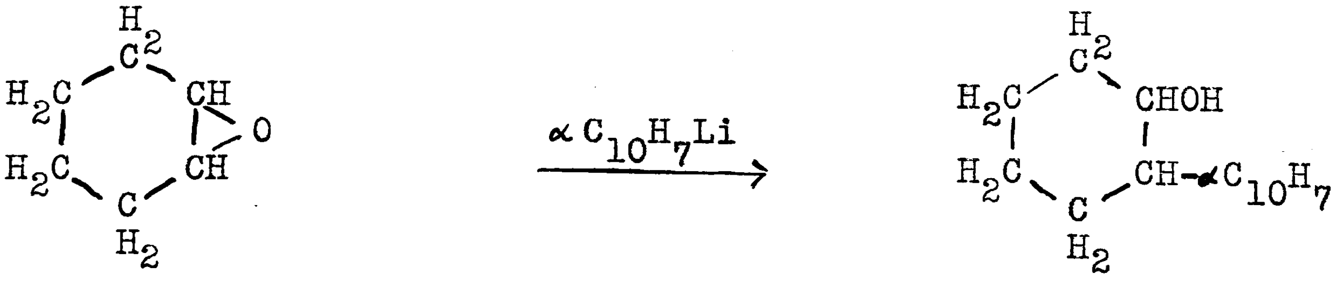
(60) Bronsted, J.A.C.S. <u>51</u> 428-61 (1929)
(61) Cook, Hewett, and Lawrence, J.C.S. (1936) 71-80





Cook, Hewett, and Lawrence, (61) also report that phenyllithium reacts with cyclohexene oxide to give 2-phenyl-cyclohexanol, also α-naphthyllithium gave 2-(α naphthyl)-cyclohexanol.





These results corroborate the conclusions of Bartlett and Berry, (47), that the presence of halide is necessary for the molecular rearrangements which occur under the influence of the Grignard reagent. The abnormal results obtained with benzylmagnesium chloride cannot be ascribed to the equilibrium,

$$2RMgX \rightleftarrows R_2Mg + MgX_2$$

for although it lies mainly to the right, it is not sufficiently different from the equilibrium position of phenylmagnesium bromide and β-phenyl-ethylmagnesium bromide, both of which give ring contraction, (61), (62) to account for the difference.

HALIDE	GRIGNARD REAGENT YIELD %	% PRESENT AS R_2Mg
Benzyl Chloride	93.6	73.4
Phenyl Bromide	94.7	75.8
β-Phenylethyl Bromide	91.6	76.0

These results would lead one to conclude that the dibenzyl magnesium is more reactive towards cyclohexene oxide than the benzylmagnesium chloride portion of the

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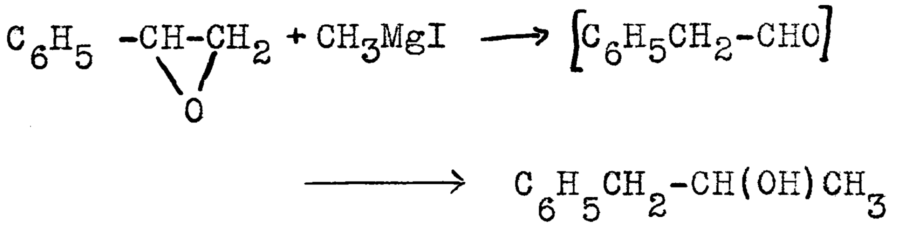
(62) Robinson, J.C.S. (1936) 80.

Grignard equilibrium mixture, whereas in the other cases, the organomagnesium halide is more reactive than the diaryl magnesium compound. The isolation of 2-chlorohexanol in 20% yield in the case of benzyl, Grignard would indicate that some of the benzylmagnesium chloride had reacted with the cyclohexene oxide.

Styrene Oxide

The problem of simple alkyl ethylene oxides has not been pursued further, but the reaction of phenyl-ethylene oxide, (styrene oxide), has received considerable attention and there have been several interesting facts brought to light.

Styrene oxide was found to react with the Grignard reagent as if it were phenyl-acetaldehyde. (63)



$$C_6H_5\text{-}\underbrace{CH\text{-}CH_2}_{O} + CH_3MgI \longrightarrow [C_6H_5CH_2\text{-}CHO]$$

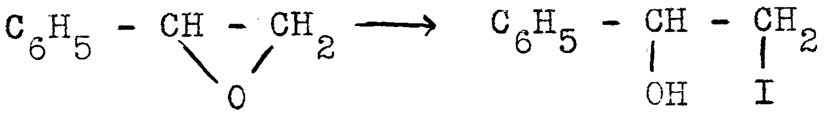
$$\longrightarrow C_6H_5CH_2\text{-}CH(OH)CH_3$$

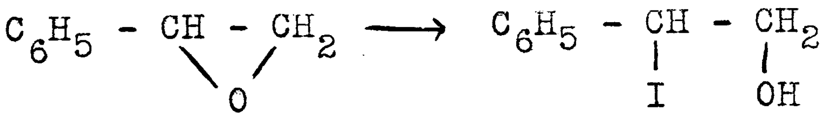
Since the oxide is a mono-substituted ethylene oxide, ring opening can give rise to two products.

(63) Tiffeneau and Fourneau, Compt.rend.,146 697-99 (1908)

Therefore, the mechanism arrived at, as a result of the work with 2,3-epoxybutane and 3-bromobutanol-2, (64) will not be applicable, since 2,3-epoxybutane could only give one product as a result of ring opening with magnesium halide-etherate.

The oxide ring of styrene oxide when opened by the magnesium halide-etherate could give rise to two isomeric halohydrins.

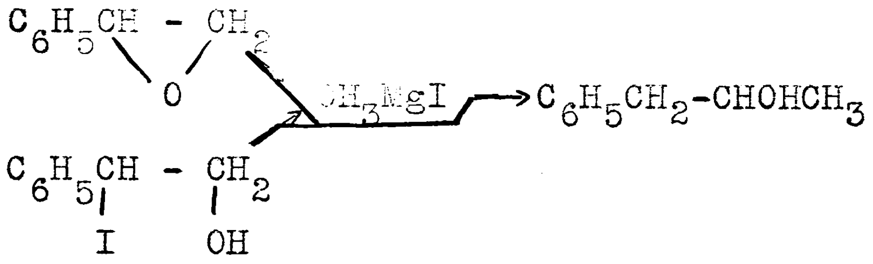

(I)


(II)

Golumbic and Cottle, (64), assumed that the magnesium iodide bond of an alkylmagnesium iodide would add to styrene oxide to give the magnesium derivative of iodohydrin II.

(64) Golumbic and Cottle, J.A.C.S. 61 996-1000 (1939)

In support of this assumption, they found that styrene oxide and iodohydrin II reacted with methyl magnesium iodide in the same manner to give 1-phenyl propanol-2.



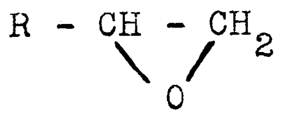
Distillation of the ether from the respective reaction mixtures produced no explosive reactions, such as had been observed by Grignard, (65).

The difference is, the authors think, attributable to the reaction of the secondary iodine atom at temperatures below that used to distill off the ether. They are inclined to agree with Ribas and Tapia, (46) that the explosions were due to a Wurtz-type reaction of the alkylmagnesium bond with the organic halogen of the halohydrin derivative rather than to a cleavage of the oxide ring as had been proposed by Grignard, (65)

(65) Grignard, Bull.soc.Chim. (3) <u>29</u> 944-48 (1903)

The reaction of iodohydrin I with methylmagnesium bromide to give the same alcohol, 1-phenyl-propanol-2, as obtained with styrene oxide and iodohydrin II, was not foreseen by the authors, and no attempt to explain the mechanism by which it occurs.

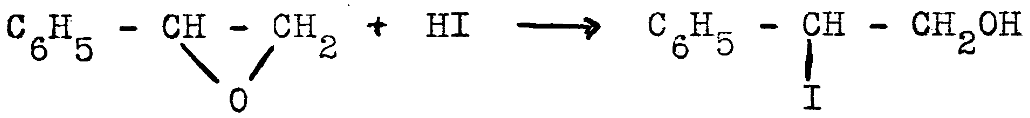
Styrene oxide may be compared to propylene since they are both mono-substituted ethylene oxides. Styrene oxide, however, due to the phenyl group it contains, might be expected to show different reactions than are found in the case of propylene oxide. The position of the break in the oxide ring

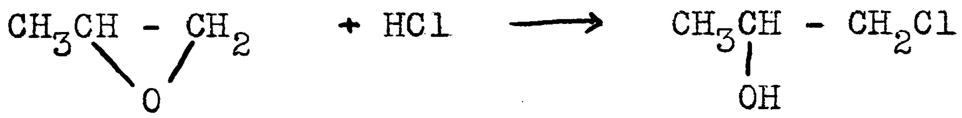


will depend on the nature of the R group. Whitmore and Bernstein, (66) have shown that the methyl group is less electronegative than the phenyl group. The decomposition voltage of the Grignard reagents also indicate the same general relationship, (67).

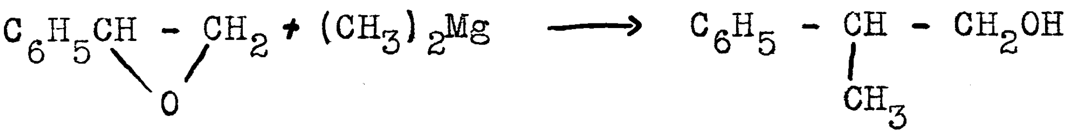
(66) Whitmore and Bernstein, J.A.C.S. <u>60</u> 2626-28 (1938)
(67) Evans, Lee and Lee J.A.C.S. <u>57</u> 489-90 (1935)

Evidence of the difference between the phenyl group and the methyl group is furnished by the reaction of styrene oxide and propylene oxide with hydrogen halides and organomagnesium compounds. Styrene oxide reacts with hydriodic acid to give a primary alcohol, whereas propylene oxide gives a secondary alcohol when treated with hydrochloric acid, (68).



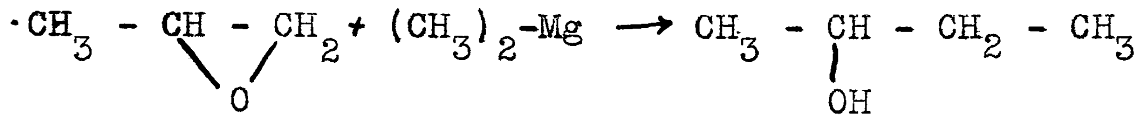


The reaction of styrene oxide with dimethyl magnesium gave as a product the primary alcohol, 2-phenyl-propanol-1. (64).



Whereas, propylene oxide when treated with dimethyl magnesium gave the secondary alcohol, butanol-2, (57).

(68) Henry, Rec. trav.chim. 22 319-48 (1903)



Kharasch, (24) has observed that styrene oxide when treated with phenyl- and p-anisylmagnesium bromide gave primary alcohols. The isolation of primary alcohols, rather than secondary ones in the case of the reaction of styrene oxide and an organomagnesium compound, agrees with reduction data, for styrene oxide gives a primary alcohol on reduction, (63) whereas, propylene oxide yields a secondary alcohol, (69).

Kharasch and Clapp, (24) in their study of the action of Grignard reagents on styrene oxide, used the following as a working hypothesis -"that the reaction product would depend upon two factors: (I), the identity of the Grignard reagent, and (2), the order of addition of reagents. The first factor, presumably of minor importance, has not been investigated as yet."

They state that the second factor should dominate the course of the reaction and the results obtained, seem to bear out this claim, for on addition of the oxide to the Grignard, a primary alcohol was obtained whereas, addition of Grignard to the oxide gave a secondary carbinol.

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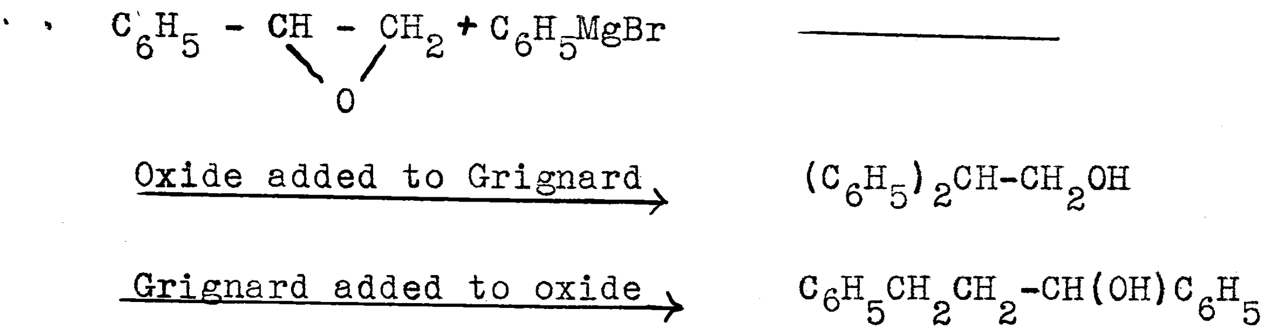
(69) Beilstein's "Handbuch der Organischen Chemie", 4th edition, Vol. XVII p.6



The yields in both cases were about 90%, and the products were identified by synthesis in unimpeachable methods. This work shows then, that for this example at least, the order of addition of the reagent has a definite bearing on the product.

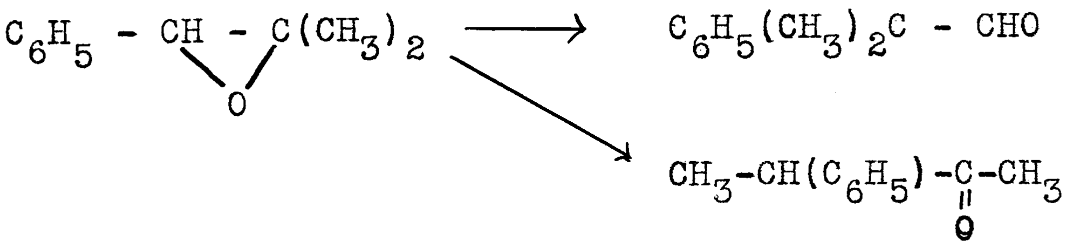
The fact that Kharasch and Clapp, (24) isolated a primary alcohol and Golumbic and Cottle, (64) also obtained a primary alcohol when they treated styrene oxide with dimethyl magnesium, indicates that styrene oxide is a special case for it does not agree with the conclusion put forward by Norton and Hass, (57), "that when there is a difference in the two carbon valences, the primary valence breaks rather than the secondary or tertiary and the secondary, rather than the tertiary."

A further example of a substituted styrene oxide is given by Poctivas and Tchoubar, (70) who have studied the

(70) Poctivas and Tchoubar, Compt.rend., 205 287-88 (1937)

action of C_2H_5MgBr and $MgBr_2$ on the oxide of dimethyl styrene.

There are, as they state, two possibilities, a "normal" breaking of the oxide ring or a rearrangement to a ketone or an aldehyde. The second phase of the reaction will depend on the ease of isomerization of the oxide, and on the part played by the magnesium halide etherate which is present in all organomagnesium compounds. Dimethyl styrene oxide is capable of two rearrangements, for it can rearrange by a semi-hydrobenzoin rearrangement to phenyldimethylacetaldehyde, (71) or by a semi-pinacolin rearrangement to give phenyl-2-butanone-3. (72)



$C_6H_5(CH_3)_2C - CHO$ II

$CH_3-CH(C_6H_5)-\underset{\underset{O}{\|}}{C}-CH_3$ III

Tiffeneau and Levy, (73) have studied the action of C_6H_5MgBr on the oxide and obtained a tertiary alcohol, $(C_6H_5)_2CH - C(OH)\ (CH_3)_2$ which is the result of ring opening.

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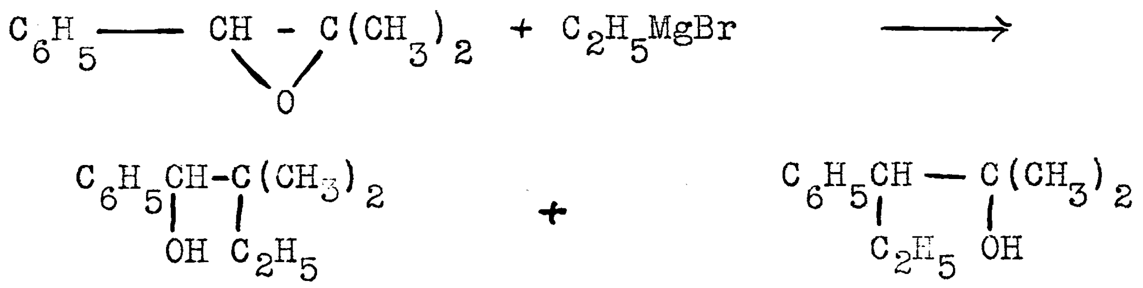
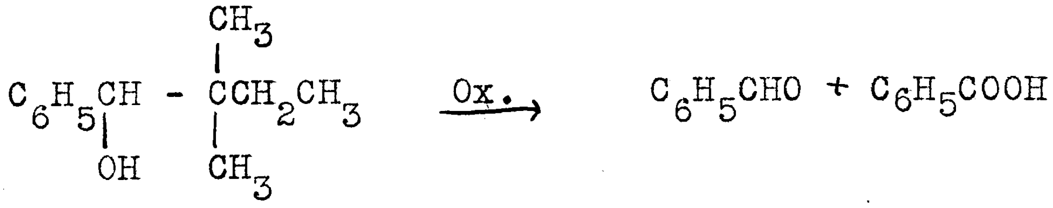
(71) Tiffeneau and Orekhoff, Bull, Soc.Chim.(3) <u>29</u> 809-20 (1921)
(72) J. Levy and Tabart, Bull.Soc.Chim.(4) <u>49</u> 1776-88 (1931)
(73) Tiffeneau and Levy, Bull.Soc.Chim.(4)<u>49</u> 1617-61 (1931)

However, Poctivas and Tchoubar, (70) found that the oxide with $MgBr_2$ etherate at temperatures below 100° affords mainly (90%) phenyldimethylacetaldehyde (II) and a little, (10%), 2-phenyl-butanone-3 (III). The action of ethyl magnesium bromide on the oxide gave 1-phenyl-2, 2-dimethylbutanol-1 (IV), and 3-phenyl -2-methyl pentanol-2 (V) in nearly equal portions.



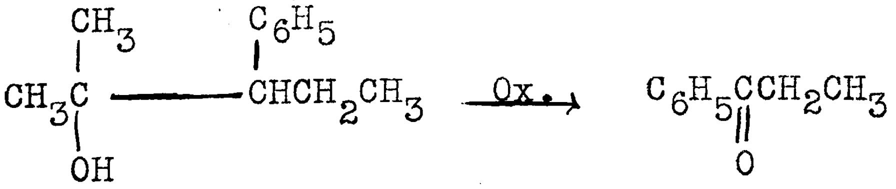
IV V

The alcohols were characterized by oxidation, (CrO_3), of the mixture which gave benzaldehyde and benzoic acid as from the butanol,



$$C_6H_5CH(OH)-C(CH_3)_2CH_2CH_3 \xrightarrow{Ox.} C_6H_5CHO + C_6H_5COOH$$

and Propiophenone as from the Pentanol



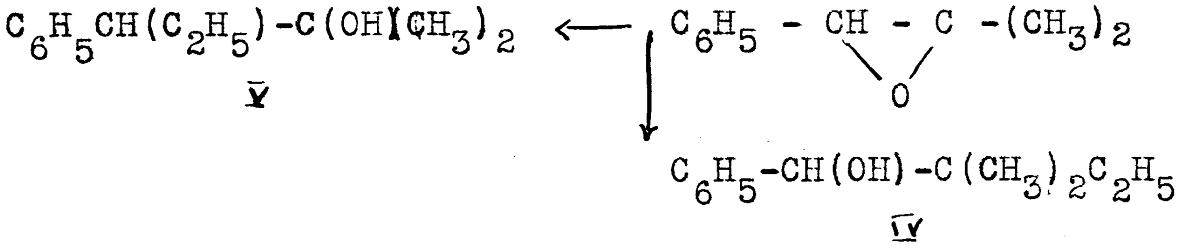
$$CH_3C(CH_3)(OH)-CH(C_6H_5)CH_2CH_3 \xrightarrow{Ox.} C_6H_5C(=O)CH_2CH_3$$

but there was no acetophenone obtained in the oxidation as was the case when the product of interaction of the aldehyde and ketone with the Grignard were oxidized.

$$C_6H_5C(CH_3)_2CHO + C_2H_5MgBr \longrightarrow C_6H_5C(CH_3)_2CH(OH)C_2H_5$$

$$C_6H_5CH(CH_3)COCH_3 + C_2H_5MgBr \longrightarrow C_6H_5CH(CH_3)C(OH)(CH_3)C_2H_5$$

The alcohols IV and V could then, only arise from a reaction of the oxide in its unrearranged form.



Thus, the rate of isomerization of the oxide by $MgBr_2$ is slower than the rate of the reaction with C_2H_5MgBr.

Acetylenic Grignard Reagent

Ethylene oxide has been treated with acetylenic Grignards by Iotsitch, (74), who prepared 3-pentynol, and Faucounau, (75), Danehy, Vogt and Nieuwland, (76), (77), and Bachmann, (78), have also used this reaction to prepare 3-nonyn-1-ol, and 1-phenyl-1-butyn-4-ol. Secondary reaction products have been reported in many cases, (76).

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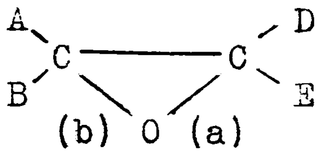
(74) Iotsitch, J.Russ, Phys.Chim.Soc. 39 652 (1907)
(75) Faucounau, Compt. rend., 199 605-7(1934)
(76) Danehy, Vogt and Nieuwland,J.A.C S. 56 2790 (1934)
(77) Danehy, Vogt and Nieuwland,J.A.C:S. 57 2327 (1935)
(78) Bachmann, J.A.C.S. 57 382-3 (1935)

SUMMARY

There are then in general, three paths that may be followed when an ethylene oxide reacts with an organometallic compound.



I. Ring cleavage at (a) with addition.

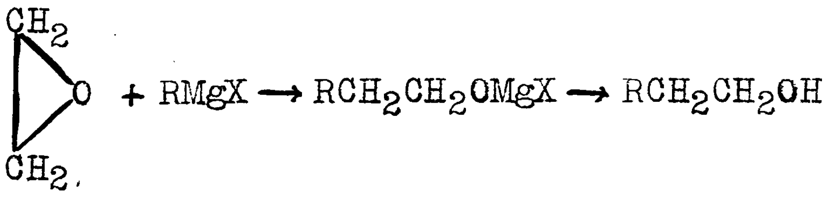
II. Ring cleavage at (b) with addition.

III. Rearrangement to an aldehyde or ketone by MgX_2 followed by addition.

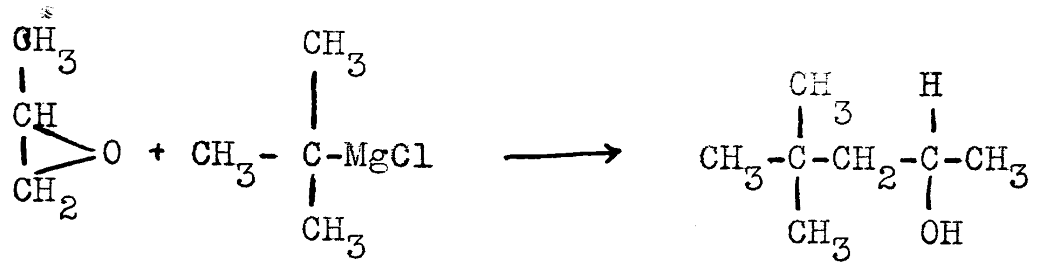
The results then depend on the relative rates of ring opening and isomerization, and these in turn depend on the structure of the oxide and the structure of the organometallic compound.

DISCUSSION

The use of the Grignard Reagent and Ethylene Oxides as a method of synthesis for alcohols is, as we have seen in the historical part of this thesis, almost as old as the Grignard Reagent itself, and has been the means of synthesizing a large number of primary and secondary carbinols. The reaction is comparatively simple and straightforward in the case of the simplest oxide, ethylene oxide, and organomagnesium compounds such as, methyl, ethyl-propyl, and phenyl-magnesium halides. However with more complex cases, anomolies occur with the result that often products are obtained which bear no direct relation to the original reactants.

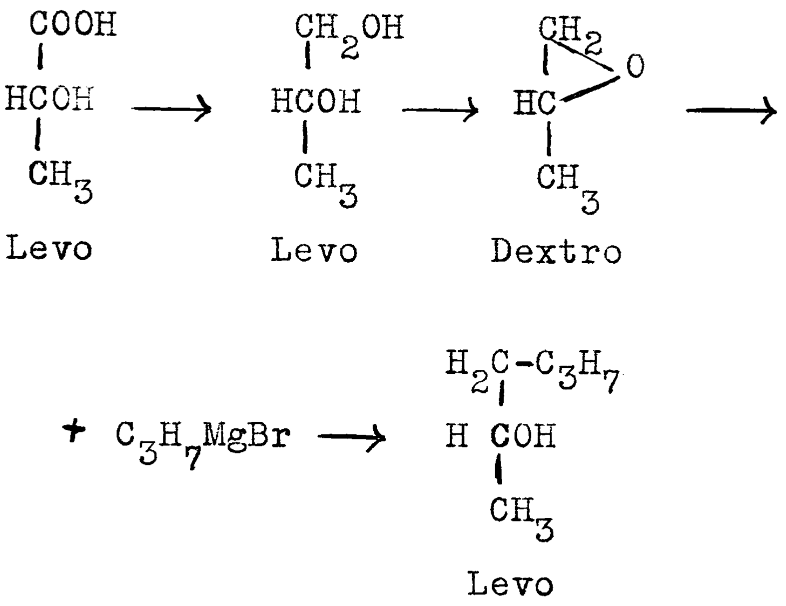


The present investigation was to be a study of the reaction of d-propylene oxide and tertiary butyl magnesium chloride, thereby, expecting to obtain an optically active methylneopentyl carbinol after the manner of Levene and Walti, (21).



This method is based on the condensation of optically active ethylene oxides with alephatic or aromatic radicals by the Grignard reaction.

In order to apply the above reaction for the correlation of the configuration of secondary alcohols to that of propylene oxide, it was necessary to demonstrate first, that the reaction proceeded in a manner leading to secondary carbinols, and second, that the reaction took place without Walden inversion. This was done by Levene and Walti, who found that d-propylene oxide when condensed with propylmagnesium bromide gave 1-methylbutyl carbinol which indicates that the reaction proceeds without an inversion as may be seen from the following set of figures.



In this set of substances, the configuration had previously been established by Levene and Haller, (79).

The methylbutyl carbinol, the propylene glycol and the propylene oxide are each correlated to lactic acid in an identical manner. With this information, then Levene and Walti, (22), and later Levene and Macker, (80), were able to apply the above method of synthesis for the elucidation of the configuration of other carbinols.

(79) Levene and Haller, J.Biol.Chem.79 475-88 (1928)
(80) Levene and Macker, J.Biol.Chem.90 669-75 (1931)

. . This method would then make it possible to relate the configuration of methylneopentyl carbinol to the known series, and enable us to study the effect of removing the center of asymmetry in the molecule one carbon atom away from the branching of the chain.

It is well known that branching of the chain next to the asymmetric center, (81),(82),(83), affects the optical rotation. It is important also to see whether or not the fully branched chain group like the tertiary butyl would resemble the isopropyl group when once removed from the asymmetric center. This would be equivalent to studying the effect of the neopentyl group, which is already known to have chemical peculiarities. Thus, Whitmore, (84),(85),(86), has shown that neopentyl halides are remarkably inert and that when these halides are hydrolyzed, rearrangement occurs almost exclusively. It is of particular interest, therefore, to see if there is any parallel between their constitution and optical rotatory power, a study already started by Levene and later continued by Stevens in regard to branched chain groups.

(81) Stevens, J.A.C.S. 54 3737-38 (1932)
(82) Stevens, J.A.C.S. 55 4237-40 (1933)
(83) Stevens, Higbee and Armstrong, J.A.C.S. 60 2658-60 (1938)
(84) Whitmore and Fleming, J.A.C.S. 55 4161-62 (1933)
(85) Whitmore, Wittle and Popken, J.A.C.S. 61 1586-90 (1939)
(86) Whitmore and Fleming, J.C.S. (1934) 1269

It might be expected that groups with quaternary carbon atoms which influence to such a great extent neighboring replacement reactions, as with neopentyl alcohol, should likewise exert an influence on the optical rotation. A positive and definite direct correlation could be then used to check a similar correlation by Freudenberg's Rule, and so show whether or not Freudenberg's Rule is valid with highly branched chain compounds.

The reaction of mono-substituted ehtylene oxides depends, as we have seen, to a great extent upon the substituent or group surrounding the oxide ring.

Thus, styrene oxide, except for the one case reported by Kharasch, (24), almost always rearranges when treated with the Grignard reagent, while the propylene oxide gives normal addition products with primary and secondary Grignard reagents.

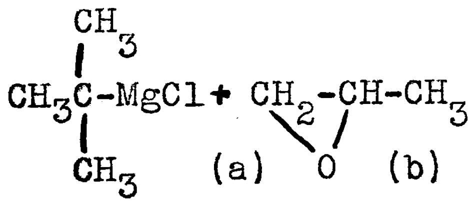
That the order of addition can affect the mode of reaction has been shown by Kharasch, who uses this as a premise in his work with styrene oxide. Kharasch found that when styrene oxide was added to phenyl- and p-anisylmagnesium bromides, normal addition occurred whereas if the order of addition of the reagents was reversed, a rearrangement took place.

In view, however, of the many exceptions frequently found in the reaction of Grignard reagents and oxides as mentioned above, we felt that we should investigate the reaction of t-butylmagnesium chloride with the more readily accessible racemic propylene oxide. This was particularly advisable because little or no successful work has been reported with tertiary Grignard reagents and oxides. Furthermore, it is known that tertiary Grignard reagents are peculiarly prone to react differently from most other Grignard reagents, for example, as in the addition of t. butylmagnesium chloride to $\alpha\beta$-unsaturated aldehyde and ketones where the tertiary groups yield considerably more 1,4-addition than primary or even secondary Grignard reagents, (87). We expected then anomalies might occur, and so proceeded directly to the general study of tertiary Grignard reagents with <u>dl</u>-propylene oxide.

(87) Stevens, J.A.C.S. <u>57</u> 1112-16 (1935)

The only previous reports of tertiary butyl magnesium halides and oxides are those of Whitmore, (13), and Chaletski, (88). Whitmore reported no success with ethylene oxide and the tertiary Grignard, and Chaletski found that the disubstituted oxide, methyl phenyl ethylene oxide, rearranged to the aldehyde. The rearrangement of the disubstituted oxide, as observed by Chaletski, is not unusual nor could it be attributed entirely to the tertiary Grignard for previous workers as far back as the time of Henry had observed that disubstituted oxides tended to rearrange even when treated with simple Grignard reagents. It was necessary, therefore, to start from the beginning in our study.

From previous work, it can be seen that the reaction can take several courses.



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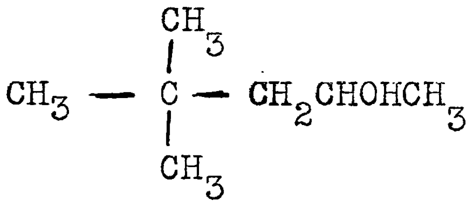
(88) Chaletski J.Gen. Chem. U.S.S.R. <u>6</u> 1-14 (1936)

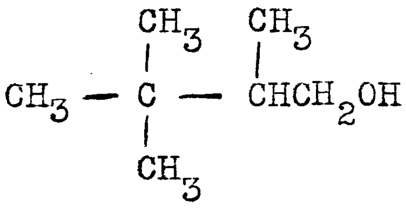
(A). The oxide ring opening at (a), would give as a product, methylneopentyl carbinol, (4,4-dimethyl pentanol-2),



$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2CHOHCH_3$$

which is the desired product.

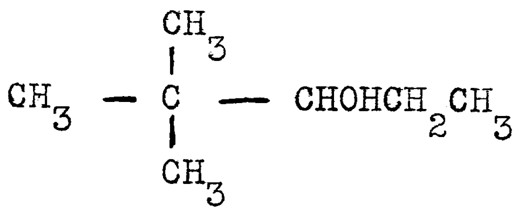
(B). The oxide ring could break at (b) to give methyl t.butyl ethanol, (2,3,3-trimethyl butanol-1),



$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2OH$$

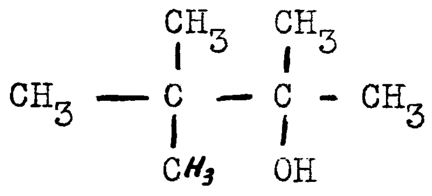
which would correspond to the primary alcohol obtained by Kharasch, (24), as a result of adding styrene oxide to phenyl magnesium bromide.

(C). The oxide might rearrange to propionaldehyde under the influence of the Grignard Reagent and the product would then be ethyl t-butyl carbinol, (2,2-dimethylpentanol-3).



$$CH_3 - \underset{CH_3}{\overset{CH_3}{C}} - CHOHCH_2CH_3$$

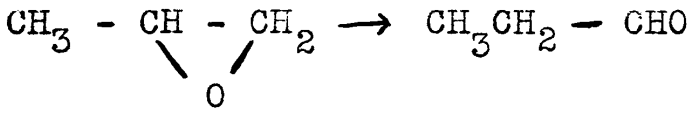
(D). The fourth and last possibility, pentamethyl ethanol, (2,3,3-trimethyl butanol-2),



$$CH_3 - \underset{CH_3}{\overset{CH_3}{C}} - \underset{OH}{\overset{CH_3}{C}} - CH_3$$

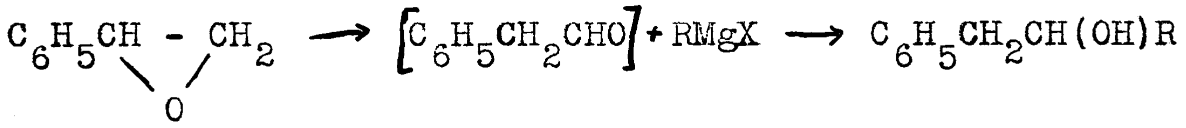
would result from the oxide having rearranged to the ketone, (CH_3COCH_3) rather than to the aldehyde.

The rearrangement of the oxide to the aldehyde



$$CH_3 - CH \underset{O}{-} CH_2 \longrightarrow CH_3CH_2 - CHO$$

might be expected to occur since we have seen that there is a tendency for other oxides to rearrange to aldehydes under the influence of the Grignard reagent. The final product of the reaction would then be the same as if propionaldehyde had been treated with t-butylmagnesium chloride; thus, Tiffeneau and Faucouneau, (63), reported the isolation of $C_6H_5CH_2CH(OH)CH_3$ and $C_6H_5CH_2CH(OH)C_2H_5$ as a result of the addition of methyl- and ethyl-magnesium bromide to styrene oxide, and these products could only arise as a result of the rearrangement of the oxide to phenyl acetaldehyde.



$$C_6H_5CH\underset{O}{\diagdown\diagup}CH_2 \longrightarrow [C_6H_5CH_2CHO] + RMgX \longrightarrow C_6H_5CH_2CH(OH)R$$

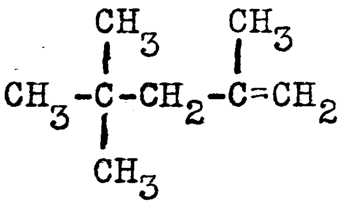
Kharasch and Clapp, (24), and later Golumbic and Cottle, have confirmed Tiffeneau's results, in that they have also obtained products arising from a rearrangement of styrene oxide, to the aldehyde under the influence of the Grignard reagent.

Further evidence that the rearrangement of the oxide to an aldehyde, merits consideration is found in the fact that propionaldehyde, (89) and acetaldehyde, (90),(91), results from the pyrolysis of the corresponding aldehyde. Ipatiew, (92), found both propionaldehyde and acetone among the pyrolysis products of propylene oxide, but as yet, there is no record of propylene oxide rearrangement to the ketone under the influence of the Grignard reagent.

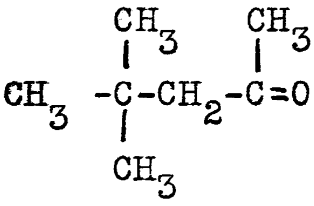
(89) Hurd, Pyrolysis of Carbon Compounds, 177 Chemical Catalog Company, New York. (1929)
(90) Nef. Ann. 355 200 (1904)
(91) Peytral, Bull.soc.chim.(4) 39 206-14 (1926)
(92) Ipatiew and Leontowitsch, Ber. 36 2017 (1903)

There is, of course, no reason why this reaction could not occur, for Tiffeneau and co-workers, (71), (72),(73), have observed that certain styrene oxides can be made to rearrange to either the aldehyde or the ketone depending upon the reagent used to bring about the isomerization. Although, the reaction with MgX is not exactly similar, the possibility that such a reaction occurs must not be overlooked.

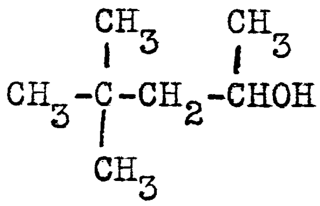
Of the four possible products, (A) methylpentyl carbinol, (B) methyl t.butyl ethanol, (C) ethyl t.butyl carbinol, and (D) pentamethyl ethanol, all but methyl t-butyl ethanol were known as a result of previous work. Methylneopentyl carbinol has been prepared by Whitmore and Homeyer, (93) by the reduction of methylneopentyl ketone obtained from the dichromate oxidation of the diisobutylene.



$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{CH_3}{C}=CH_2$



$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{CH_3}{C}=O$



$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{CH_3}{CHOH}$

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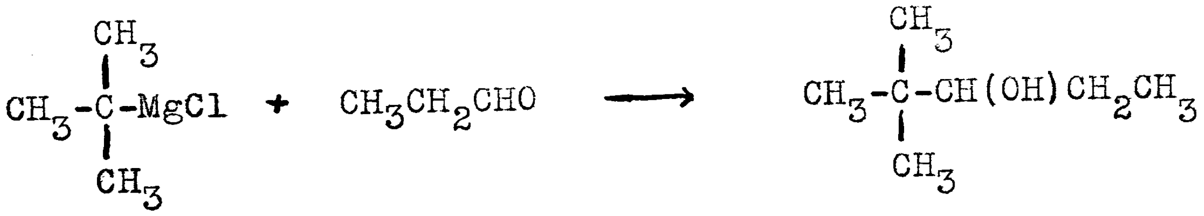
(93) Whitmore and Homeyer, J.A.C.S. 55 4149-6 (1933)

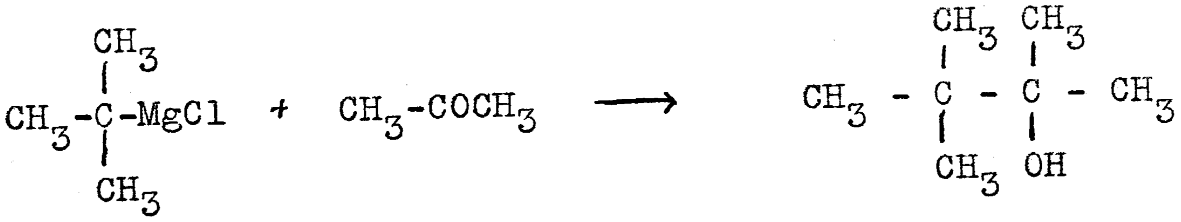
Whitmore and Homeyer report the carbinol as boiling at 137-137.5°C (736mm) naphthylurethan m.86.5 to 87°C., 3.5 dinitro benzoate m.95.2-95.7°C. Ethyl t.butyl carbinol has been prepared by Favorski, (94) and also by Ginnings and Hauser, (95), as a result of the action of t.butyl magnesium chloride on propionaldehyde.



$$\mathrm{CH_3-\underset{CH_3}{\overset{CH_3}{C}}-MgCl + CH_3CH_2CHO \longrightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH(OH)CH_2CH_3}$$

Favorski reported the boiling point of the carbinol as being 132-135°C but Ginnings and Hauser, report it as being 134.7-135.1°C.,(760 mm), however, neither of these authors report any derivative.

The product resulting from a rearrangement of the oxide to the ketone namely, pentamethyl ethanol,



$$\mathrm{CH_3-\underset{CH_3}{\overset{CH_3}{C}}-MgCl + CH_3-COCH_3 \longrightarrow CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3}$$

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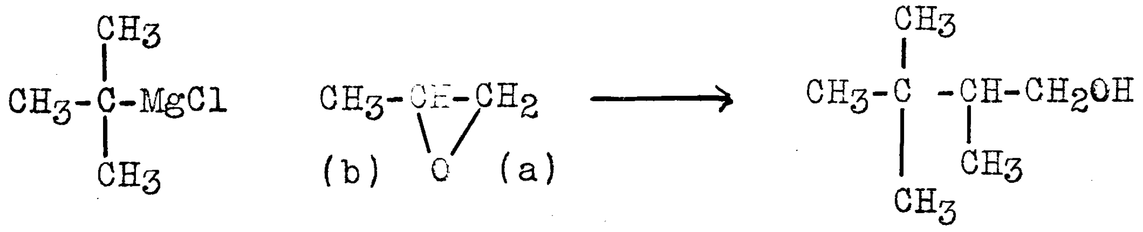
(94) Favorski and Aschmarin, J.prakt.chem.(2) 88 675-79 (1913)

(95) Ginnings and Hauser, J.A.C.S. 60 2581-2 (1938)

has been prepared by several previous workers by the action of t.butylmagnesium chloride on acetone, (96), by the action of methylmagnesium iodide on pinacolone (97),(98),(99), and by the action of methylmagnesium iodide on tetramethyl ethylene oxide, (100). These authors all report a boiling point in the range of 130 to 132°C. at atmospheric pressure. It is a tertiary alcohol and has a pronounced tendency to form a crystalline hydrate. The presence of the alcohol is readily discernable due to the tendency of this hydrate to crystallize out at room temperature, even from ether solutions.

The primary alcohol, methyl t.butylethanole, which would result from ring cleavage at (b) has not been



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-MgCl \qquad \underset{(b)\quad\quad O\quad\quad (a)}{CH_3-CH-CH_2} \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\underset{CH_3}{CH}-CH_2OH$$

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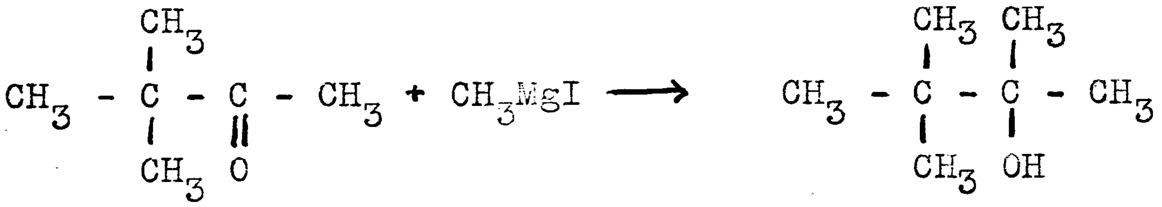
(96) Henry, Compt. rend., 143 20-22 (1906)
(97) Butlerow, Ann. 177 176-86 (1875)
(98) Richard, Ann. de chim. et phys. (8) 21 323-406 (1910)
(99) Henry, Rec. trav. chim. 26 107-116 (1907)
(100) Henry, Rec. trav. chim. 26 414-437 (1907)

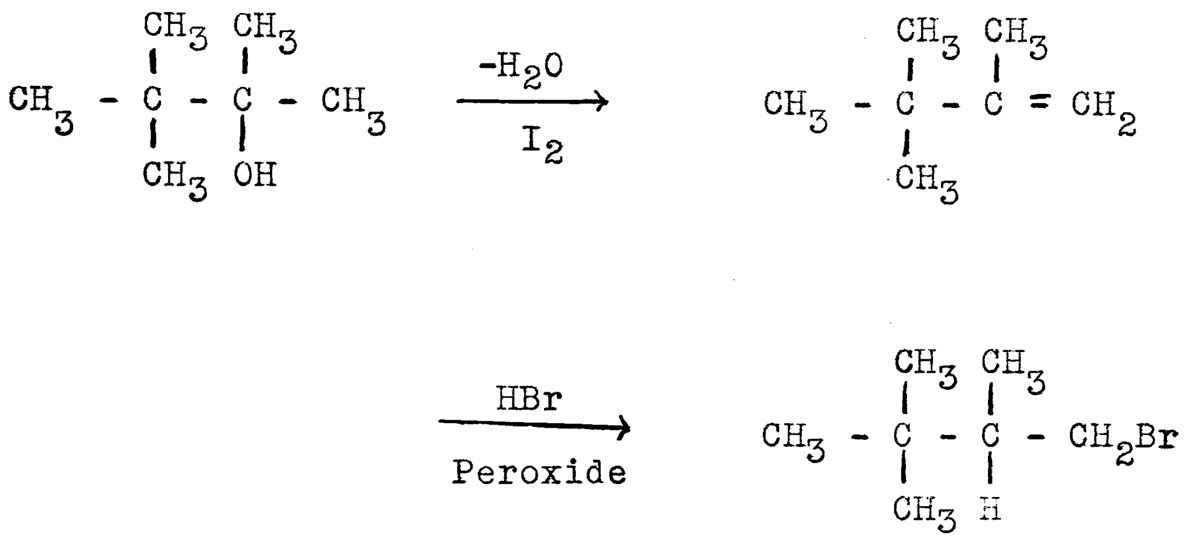
reported as such in the literature. Therefore, it was necessary to synthesize this isomer by an entirely different method in order that its physical constants might be determined. The synthesis was accomplished by the following series of reactions. Pinacolone was treated with methylmagnesium iodide and the product, pentamethylethanol, (b.130-131.2°C. at 757 mm)



$$CH_3 - \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} - \underset{\displaystyle O}{\overset{\|}{C}} - CH_3 + CH_3MgI \longrightarrow CH_3 - \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} - \overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}} - CH_3$$

This carbinol was, as we have seen, one of the possible isomers and it was observed to form the characteristic crystalline hydrate with great ease. The pentamethyl ethanol was dehydrated by distillation in the presence of iodine, (101), to give the olefine, methyl t-butylethylene, (b.78.0°C. at 750 mm). Hydrogen bromide was then added to the olefine in the presence of a peroxide, (ascaridole), using the technique developed by Kharasch, (102), and used by Michael and Weiner, (103), with trimethylethylene.

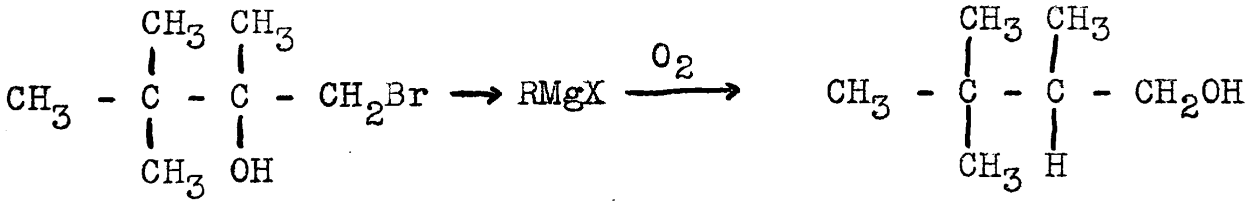
(101) Hibbert, J.A.C.S. <u>37</u> 1748-63 (1915)
(102) Kharasch, Kleiger and Mayo, J.Org.Chem. <u>4</u> 428-35 (1939)
(103) Michael and Weiner, J.Org.Chem. <u>4</u> 531-42 (1939)



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{OH}{C}}-CH_3 \xrightarrow[I_2]{-H_2O} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{C}=CH_2$$

$$\xrightarrow[\text{Peroxide}]{HBr} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{H}{C}}-CH_2Br$$

The olefine had previously been prepared by Richard, (98), and Favorski, (104), who report essentially the same boiling point, 78-80°C. at atmospheric pressure, but no reference exists to the bromide which was found to distil at 73-75°C. (45 mm). The bromide was converted to the Grignard reagent in the usual way, and this treatment with oxygen gave the desired carbinol.



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{OH}{C}}-CH_2Br \longrightarrow RMgX \xrightarrow{O_2} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{H}{C}}-CH_2OH$$

It was found to have a boiling point of 159.5-162°C.

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(104) Favorski, (1918) J. Russ.Phys.Chem.soc. 50 43-80

(at 761 mm.) n_d^{25} 1.4288 (*). The only previous reference to this alcohol, or what might be this alcohol, is one by Faget, (105), who isolated from wine fusel oil an alcohol of the same emperical formula, ($C_7H_{16}O$), b.155-160°C.

In order to study the reaction of t-butylmagnesium chloride with propylene oxide, we proceeded in the usual way, treating the previously prepared Grignard reagent with the oxide at 0°C. It was soon found, as reported by Levene and Walti, (21), that the reaction proceeded very slowly and that considerably more time was necessary than the seven days, which they allowed for the reaction in the case of phenylmagnesium bromide and the oxide. It was finally found necessary to let the reaction mixture stand for seven weeks, at 20-25°C. to obtain an appreciable yield of products arising from the addition of the Grignard radical to the oxide.

(*) Thanks are due to Mr. J. Calder, (Honor Student of McGill University), who prepared this alcohol.

(105) Faget, Ann. <u>124</u> 355-357 (1862)

The first attempt to prepare the carbinol by the addition of propylene oxide to t-butylmagnesium chloride, gave excluding fore-runs of low boiling material, a fraction in the range 135-137°C. (760 mm.). Although the fraction obtained was too small to permit of its identification after being purified through the phthalate, the boiling point, (135-137°C), was close to that reported by Whitmore and Homeyer, (93), for methylneopentyl carbinol. It was thought, therefore, that normal addition had taken place and a preparation on a larger scale would give enough of the carbinol to permit of a definite characterization.

The reaction was carried out a second time using larger amounts, of starting materials and permitting the reaction mixture to stand for several days before decomposing the Grignard addition product. A carbinol was obtained which, on purification through the phthalate, boiled at 135-137°C. (774 mm.). A second portion of the same reaction mixture yielded a carbinol boiling at 130 to 133° C. without being put through the phthalate. This fraction was later found to contain chlorine, and it is probable that the boiling point was due to the inclusion of some of the lower boiling propylene chlorhydrin.

The high boiling fraction gave a 3,5-dinitro benzoate which was recrystallized from ethyl alcohol and then from methyl to a constant melting point of 92.5-93°C. and not 95.2-95.7°C. as reported by Whitmore and Homeyer, (93). This indicated that the product of the Grignard reaction was not methylneopentyl carbinol, the desired product, (see A page 63) in spite of the similarity of the boiling points.

Since the product obtained might well be the result of a rearrangement of propylene oxide to propionaldehyde with subsequent addition of the Grignard reagent to give ethyl t-butyl carbinol, it was,therefore, decided to prepare this carbinol by the direct addition of propionaldehyde to t-butylmagnesium chloride and to compare the resulting product with that obtained from the reaction of the Grignard reagent with propylene oxide, as described above. The product obtained from the propionaldehyde reaction was found to boil at 132-135°C., a value which corresponds to that reported by Favorski, (94), and by Ginnings and Hauser, (95).

As no derivatives of this carbinol had previously been prepared, we undertook to prepare the 3,5-dinitro and the naphthylurethan. They were found to melt at 92.5-93°C. and 107-108°C. respectively. The melting point of the 3,5-dinitro benzoate agrees with that obtained from the product of the reaction of t-butyl magnesium chloride and propylene oxide. A mixed melting point showed no depression. The same was also found to be true when a mixed melting point of the two naphthylurethans was taken. This, then indicated that the product isolated as a result of the interaction of t-butylmagnesium chloride and propylene oxide under the foregoing conditions was ethyl t-butyl carbinol.

At this point, it was realized that this method would not be satisfactory for preparing methylneopentyl carbinol unless it were possible to prevent the rearrangement of the oxide by changing the conditions.

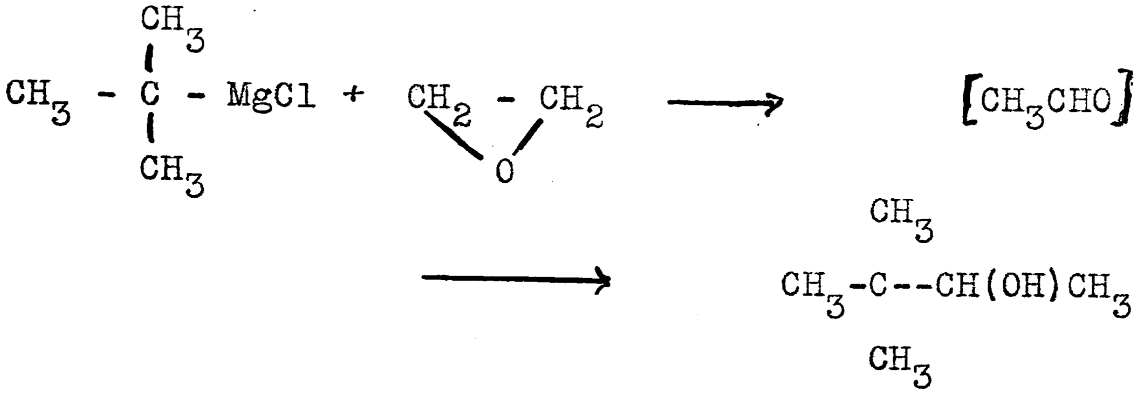
The conditions under which the reaction was carried out were varied in several ways. The aldehyde, resulting from a rearrangement of the oxide, may be competing with the unrearranged oxide in the reaction with the Grignard. If such is the case, an increase in temperature should favor one or the other.

Accordingly, the reaction was carried out with benzene (b.80 °C.) and decalin, (b.173-196 °C.) as the solvent but the increased temperature of operation made possible by the use of these solvents did not alter the mode of addition. Since the order of the addition of the reagents might have some influence on the product in a manner similar to that observed by Kharasch, (24), in his work with styrene oxide, the order of addition was reversed, but here again the only product isolated was ethyl t-butyl carbinol.

It remained then to see if there were some small amounts of normal addition product which had escaped detection in the smaller runs. With this in view, the reaction was carried out on a larger scale, but the desired methylneopentyl carbinol could not be isolated even though the reaction mixture was allowed to stand for seven weeks before working it. The object of letting the reaction mixture stand for such a long period of time was to permit the primary addition complex of the Grignard and the oxide to assume its final structure. This period of standing at room temperature takes the place of the higher temperature of reaction used by Grignard, (6). Since our previously described experiments in benzene and decalin did not prevent the rearrangement of the oxide to the aldehyde. It was hoped that a long period of standing at room temperature, (20-25^{o}C.), might permit the isolation of at least a small quantity of methyneopentyl carbinol, which we had not been able to obtain by allowing the reaction mixture to stand for shorter periods of time.

As we have seen, no previous case of rearrangement has been reported with propylene oxide and the Grignard reagent, although the substituted oxide methylphenyl ethylene oxide had been found to rearrange when treated with the t-butylmagnesium chloride, (88). Whitmore, (13), reported no success when ethylene oxide was allowed to react with the t-butylmagnesium chloride and he suggests, (106), that tertiary Grignard reagents will not react with ethylene oxides to give carbon chain lengthening. He does not state, however, whether or not any 3,3-dimethylbutanol-2 was isolated as a result of the reaction of t-butylmagnesium chloride with ethylene oxide. This product would be obtained if the ethylene oxide rearranged to acetaldehyde and then reacted with the Grignard reagent.

(106) Whitmore, "Organic Chemistry" <u>124</u> (D.Van Nostrand, New York) 1937.



The situation is,therefore, open for discussion and probable mechanisms for the production of the product obtained may be advanced.

We have seen that in the case of t-butylmagnesium chloride, the position of the equilibrium favors the formation of the dialkylmagnesium compounds, there would then be a correspondingly large amount of magnesium halide etherate present. The rearrangement of cyclohexene oxide and dimethylethylene oxide, as well as others, has been shown to be brought about by magnesium halide-etherate, therefore, it is to be expected that the rearrangement of propylene oxide to propionaldehyde is also to be brought about by the same mechanism.

The question of whether or not a rearrangement will occur depends upon the relative rates of reaction of the organomagnesium compound and the magnesium halide-etherate with the oxide.

Other Grignard reagents were not observed to cause a rearrangement of propylene oxide for Levene, (21), (22),(80), used this method to configurationally relate a series of straight and branched chain carbinols.

There are marked differences in the reaction rates of Grignard reagents with a particular reactant, just as there are marked differences in the rates of reaction of a particular Grignard reagent with a series of reactants having different functional groups.

The relative reactivities of some Grignard reagents have been determined in a variety of ways.* The several series do not give wholly concordant results but the following table gives the results obtained by Gilman, (107) in the series established by the reaction with benzonitrile.

$$C_6H_5CN + RMgX \longrightarrow C_6H_5CR$$

The time in hours for complete reaction of the organometallic compound with an excess of the nitrile are given.

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* A summary of the methods used with references is given in Gilman's"Organic Chemistry" Vol.I p.433 (Wiley, New York, 1938)

(107) Gilman, St.John, St.John and Lichtenwalter, Rec. trav.chem. 55 577-85 (1936)

GRIGNARD REAGENT	TIME IN HOURS
C_6H_5MgBr	0.31
C_2H_5MgBr	0.85
n-C_4H_9MgBr	4.57
n-C_4H_9MgCl	7.35
n-C_4H_9MgI	7.50
sec.-C_4H_9MgBr	11.65
t.-C_4H_9MgBr	25.5

It will be seen that n-butylmagnesium bromide reacts faster than the corresponding chloride, therefore, it is likely that t-butylmagnesium chloride would be even slower than the t-butylmagnesium bromide which is given in the table.

Although the reaction with the oxide may not be exactly similar to that with the benzonitrile, the comparative reaction times will be of the same general order and the reaction of the t-butylmagnesium chloride with the oxide would be extremely slow.

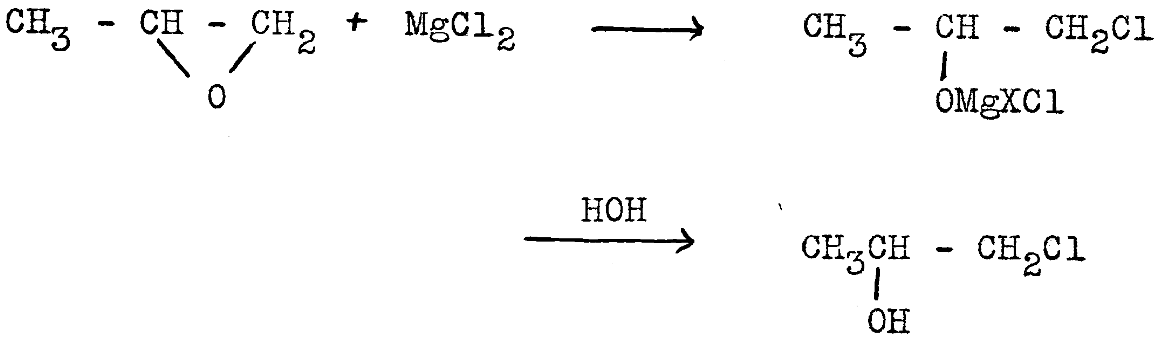
The slowness of this particular Grignard reagent in adding to the propylene oxide would allow sufficient time for the magnesium chloride-etherate present to add to the oxide with the consequent production of the chlorhydrin. Propylene oxide when treated with primary and secondary Grignard reagents was not observed to give rearrangement products. This may be attributed to the more rapid reactions of the Grignard reagent with the oxide.

Further evidence that the t-butylmagnesium chloride tends to be sluggish in its reactions is found in the fact that there is a tendency for products other than those resulting from addition reaction, to arise when reactants are treated with the tertiary Grignard, for example, isobutyraldehyde gives reduction as well as addition when treated with t-butylmagnesium chloride and pinacolone when treated in a similar manner gives no addition whatsoever, (108).

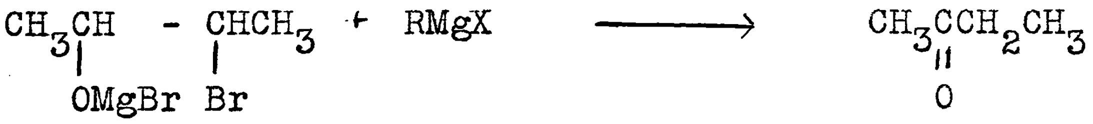
Propylene chlorhydrin was found to be present in all cases and in one, it constituted the major portion of the product.

(108) Gilman, "Organic Chemistry", Vol.I, p.556 (Wiley, New York, 1938)

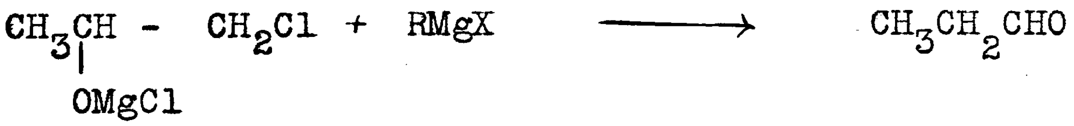
The isolation of the chlorhydrin indicates that the magnesium chloride-etherate present in the Grignard reagent has added to the oxide, giving rise to the magnesium salt of the chlorhydrin which on hydrolysis, gives the chlorhydrin itself.



The magnesium salt, once formed, would rearrange to the aldehyde under the influence of the Grignard reagent just as the magnesium salt of 3-bromo-2-butanol rearranged to butanone-2 when treated with the Grignard reagent, (49).



$$\underset{\text{OMgBr}}{\underset{|}{\mathrm{CH_3CH}}} - \underset{\text{Br}}{\underset{|}{\mathrm{CHCH_3}}} + \mathrm{RMgX} \longrightarrow \mathrm{CH_3}\underset{\text{O}}{\underset{\|}{\mathrm{C}}}\mathrm{CH_2CH_3}$$

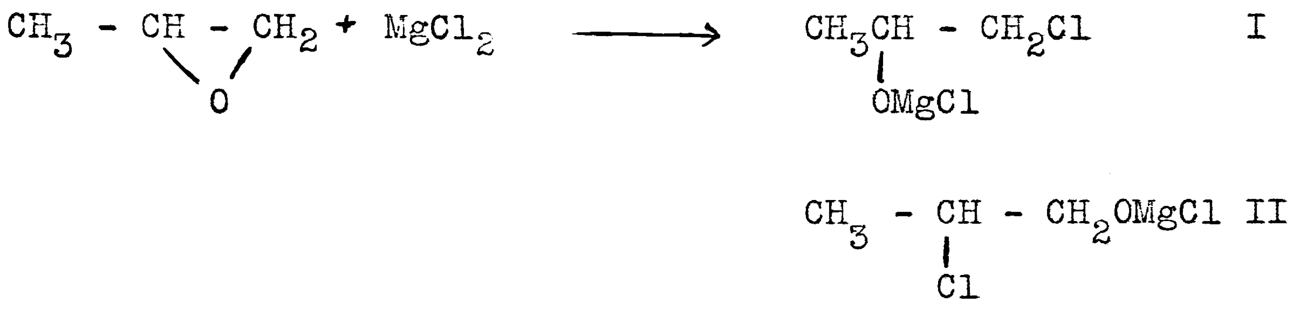


$$\underset{\text{OMgCl}}{\underset{|}{\mathrm{CH_3CH}}} - \mathrm{CH_2Cl} + \mathrm{RMgX} \longrightarrow \mathrm{CH_3CH_2CHO}$$

The rearrangement of this magnesium salt when treated with the Grignard reagent may be considered to follow along the same line as that observed by Golumbic and Cottle, (64), in the case of the iodohydrins of styrene. They observed that both the iodohydrins $C_6H_5CH(OH)CH_2I$ and $C_6H_5CHICH_2OH$, when treated with the Grignard reagent in a manner similar to that used in this work, gave the addition product that corresponded to that obtained by the addition of phenylacetaldehyde to the Grignard.

As we have seen the rearrangement of the iodohydrin, with the primary alcohol, to the aldehyde through the magnesium salt, follows that observed in the case of the 3-bromo-2-butanol.

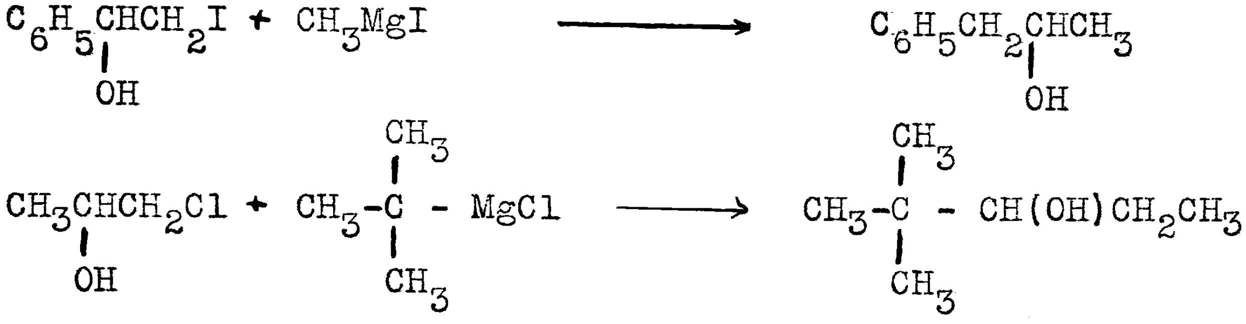
In this work, we have observed the formation of 1-chloro-2-propanol, (CH_3-$CH(OH)CH_2Cl$), which we have attributed to the hydrolysis of the corresponding magnesium salt. By analogy with styrene oxide, we must consider the possibility of the formation of the other chlorhydrin as well. Thus, propylene oxide when treated with an organomagnesium compound would, as a result of the action of magnesium halide-etherate, give the two isomeric chlorhydrins.



$$CH_3CH(OMgCl) - CH_2Cl \quad \text{I}$$

$$CH_3 - CH(Cl) - CH_2OMgCl \quad \text{II}$$

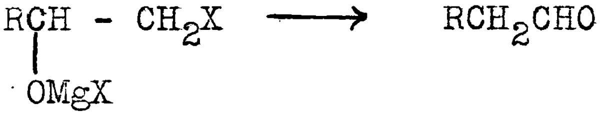
The failure to isolate any of the chlorhydrin which would correspond to the hydrolysis product of II may be attributed to the similarity in boiling points of the two chlorhydrins, ($CH_3CHOHCH_2Cl$, 127-128°C., $CH_3CHClCH_2OH$, 133-134°C.) but it is more probable that this compound II when formed, would rearrange to the aldehyde and react as such with the Grignard reagent to give rise to the ethyl-butyl carbinol. The isolation of n-propyl alcohol, which corresponds to ring break in the same position as that necessary for the formation of the magnesium salt of the chlorhydrin II, would indicate that the ring probably does break in this position.
The formation of 1-phenyl-2-propanol, ($C_6H_5CH_2CH(OH)CH_3$), observed by Golumbic and Cottle, (64), as a result of the interaction of $C_6H_5CHOHCH_2I$ with $CH_3CHOHCH_2Cl$ and t-C_4H_9MgCl.



$$\underset{\substack{|\\ OH}}{C_6H_5CH}CH_2I + CH_3MgI \longrightarrow C_6H_5CH_2\underset{\substack{|\\ OH}}{CH}CH_3$$

$$CH_3\underset{\substack{|\\ OH}}{CH}CH_2Cl + CH_3-\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ CH_3}}{C}} - MgCl \longrightarrow CH_3-\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ CH_3}}{C}} - CH(OH)CH_2CH_3$$

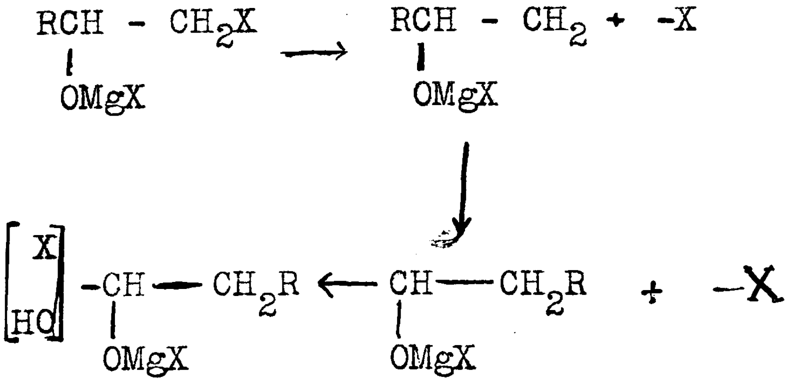
From the equations above, it will be seen that in order to give the product obtained, a rearrangement of the following type must have taken place.



$$\underset{\substack{|\\ OMgX}}{RCH} - CH_2X \longrightarrow RCH_2CHO$$

It can be thought of as taking place in the following way.

Preliminary loss of X in the basic medium followed by a migration of the group, R, to give an unstable intermediate which then, adds the -X or an -OH to fill the vacancy left by the R group.

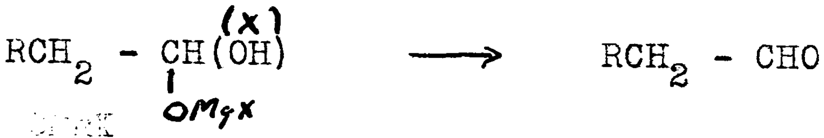


$$\underset{\substack{|\\ OMgX}}{RCH} - CH_2X \longrightarrow \underset{\substack{|\\ OMgX}}{RCH} - CH_2 + -X$$

$$\downarrow$$

$$\begin{bmatrix} X \\ HO \end{bmatrix} -\underset{\substack{|\\ OMgX}}{CH} — CH_2R \longleftarrow \underset{\substack{|\\ OMgX}}{CH} — CH_2R + -X$$

Then having this unstable structure, it would tend to split out MgX_2 (or MgXOH) and thus give rise to the aldehyde.

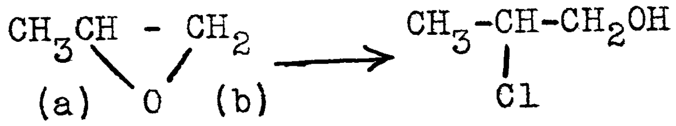


$$RCH_2 - \underset{OMgX}{CH(\overset{(X)}{OH})} \longrightarrow RCH_2 - CHO$$

The aldehyde would then react with the Grignard reagent as soon as it was formed either to give the addition product, (ethyl t-butyl carbinol), or by reduction to give n-propanol which was also isolated. The same mechanism will apply to iodohydrin, $C_6H_5CH(OH)CH_2I$, studied by Golumbic and Cottle, (64).

Thus, we can account for the formation of the chlorhydrin and this ethyl t-butyl carbinol by the action of magnesium-chloride-etherate on the oxide giving rise to the magnesium salt of the chlorhydrin which, then rearranges to the aldehyde and then reacts as such with the Grignard reagent. That all the magnesium salt of the chlorhydrin is not rearranged may be attributed to the relative slowness with which the tertiary Grignard reacts, and the stability of the chlorhydrin, since it contains a primary chlorine.

The failure to isolate any of the chlorhydrin corresponding to a ring break at (a)



has been attributed to the greater ease with which the magnesium salt of this chlorhydrin, containing as it does a secondary chlorine, would rearrange to the aldehyde. The formation of the n-propanol isolated has also been accounted for.

EXPERIMENTAL.

Description of Apparatus-

One of the most commonly used methods of separating liquids is by fractional distillation. The successful separation depends to a large extent upon the type of equipment used, and the care taken in controlling the operating conditions.

In an investigation such as the one under consideration where liquid products are obtained whose boiling points lie in the same range, and whose structures are closely related to one another, an efficient fractionating column is a necessity if there is to be any degree of separation attained. This type of mixture whose components tend to codistil the fractionation must be done very carefully.

The performance characteristics of any fractionating column used must be known in detail. It is essential that the operator be accustomed to the type of column used and, it may even be said, to the particular column used if the maximum separation is to be obtained. Constant attention is necessary in any fractionation as small changes in pot and jacket temperature can markedly alter the column efficiency.

The fractionating columns used in this work were of two types. The first type for fractionation of relatively large amounts of material was of the Whitmore and Lux type, (109), being a total condensation variable take-off column equipped with an electrically heated jacket, as described by Lauflin, Nash and Whitmore, (110). The jacket in this case was equipped with a two-stage electrical heater rather than a three-stage heater as described by these authors. The packing consisted of glass helices and they were inserted one at a time to obtain an even distribution, thereby, avoiding the possibility that the column might have a variation in the height equal to a theoretical plate. The two columns of the type that were used had 18 and 24 theoretical plates.

The second type of column used for relatively small samples, was a modified Podbielniak. The column had a gold plated Nichrome wire spiral (Brown and Sharpe gauge No.20) for packing. The spiral had from six to seven turns per inch and was fitted into a tube 3.5 mm. inside diameter.

(109) Whitmore and Lux, J.A.C.S. 54 3448-52 (1932)
(110) Lauflin, Nash and Whitmore, J.A.C.S. 56 1395-96 (1934)

The head was a simple distilling head of sufficiently larger bore than the main column to take a standard thermomenter. The column was provided with a vacuum jacket and equipped with a Nichrome ribbon wound around the column itself as a means of supplying the heat necessary to distill high boiling fractions as the vacuum jacket was not efficient enough.

A column of this type must be operated very carefully and the rate of distillation must be kept down or the efficiency of the column will be lost. The column described has a 34 inch spiral and about 14 theoretical plates when operating at maximum efficiency.

The columns described above were quite satisfactory but a more efficient column would undoubtedly give cleaner cuts and facilitate the separation of the fore-run into its various components.

<u>NOTE</u>- An excellent discussion of fractional distillation with references is to be found in Morton's, "Laboratory Technique in Organic Chemistry". (McGraw-Hill, New York 1938)

The Action of t-Butylmagnesium Chloride on Propylene Oxide.

(A) Preparation of Tertiary Butylmagnesium Chloride.

The Grignard reagent was prepared after the manner of Whitmore and Badertscher, (111), with some variations. The reagent was in general prepared immediately prior to use, although sometimes it was stored for various periods of time. The activity of the reagent did not appear to decrease markedly on standing. One sample that had been stored for two years and used at various times as a starter for other preparations, developed large clear crystals as distinct from the fine grey precipitate. The dark black colour remained in the solution although it seemed to be lighter after standing for some time. A typical preparation of the reagent is as follows: In a 3 liter 3-necked round bottomed flask fitted with a Hershberg stirrer, a Freidrich condenser and a dropping funnel are placed a few crystals of iodine and then 98 g. (4 moles) of fresh magnesium turnings (Mallinckrodt or Eastman Grignard magnesium was found to be quite satisfactory.

(111) Whitmore and Badertscher, J.A.C.S. 55 1559-1567 (1933)

The turnings were washed with two 50 ml. portions of dry ether to remove all traces of grease. It was found that freshening the surface of the magnesium by grinding under ether in a mortar materially reduced the induction period. Magnesium so treated was placed in the flask and then the flask was gently heated, to vaporize the iodine, and allowed to cool before adding the halide. (The purple iodine vapour serves as a good indicator for the dryness of the apparatus, a brown colour develops if the glassware is not thoroughly dry, usually in the neck of the flask and on the condenser. This fault may be remedied by rinsing out the apparatus with dry ether.) An alternative procedure may be followed to avoid the use of iodine, which according to Grignard, (112), promotes coupling. The alternative procedure consists in starting the reaction with a little methyl iodide - no more than 2 ml. dissolved in 10 ml. of dry ether are necessary to start the reaction.

(112) Grignard and Tcheoufaki, Compt.rend., <u>188</u> 357 1929.

The reaction having started, twenty-five to thirty mls. of a solution of four moles, (400 mls.) of the chloride in five hundred mls. of dry ether is added from the dropping funnel, followed by the addition of two hundred mls. of ether. (This is most conveniently added through the condenser. If the addition is not too rapid, there will be no plugging of the condenser).

The initial reaction is allowed to subside and the halide addition is commenced. Approximately half, (500 mls.) of the ether halide mixture is added drop by drop at a rate just sufficient to keep the ether refluxing slowly. When this amount of ether halide mixture has been added, the remainder diluted with some three hundred mls. of dry ether, is added at the same rate, (three to five mls. per minute).

The ether volume may need to be supplemented by further additions to replace losses due to leakage through the condenser. Efficient stirring is essential and stirring should be continued for an hour at least after the last of the halide mixture is run in.

There is no need for cooling the reaction and an ice bath is unneccessary except as a precautionary measure in case the reaction starts with violence. Once the reaction is proceeding smoothly, it should be allowed to reflux by the heat of the reaction, or refluxed gently on the water bath. This does not decrease the yield, (113).

(B) Preparation of the Carbinol-

Run #1- This was a trial run carried out at 0°C. using one-fifth of a mole of Grignard and one-sixth of a mole of propylene oxide, dissolved in 200 mls. of dry ether. The reaction product was decomposed immediately using ice and ammonium chloride. The ether was separated, washed twice with water, dried over anhydrous potassium carbonate and fractionally distilled. After removal of the ether, a fraction in the range of 70-90°C. was obtained. The main portion of this fraction came over at 80-85°C. The other main fraction distilled at 135-137°C. As the fraction was quite small, (1 gram), and as it contained some unsaturated substance, an attempt was made to purify it through the phthalate.

(113) Gilman and Zoellner, J.A.C.S. 50 425-428 (1928)

The phthalate, however, did not crystallize and there was not sufficient carbinol present on decomposition to permit identification. It was found that small runs tended to give a considerable amount of coupling product which was absent from the product in large runs.

Preparation of the Phthalate-

The general procedure for the preparation of the phthalate was as follows:

One equivalent of carbinol,1.2 equivalent of phthalic anhydride and 1.4 equivalents of dry pyridine were allowed to stand overnight in a stoppered flask, followed by heating on the water bath for an hour. The reaction mixture was allowed to cool, poured into ice water and acidified with dilute (1;1) sulphuric acid. The cold acid solution now extracted three or four times with chloroform, and the chloroform extract washed with very dilute sulphuric acid. This washing should be repeated until the odor of pyridine is absent from the chloroform layer.

The chloroform is evaporated in vacuo leaving the phthalate, the anhydride, unreacted carbinol, and any other substance present as a viscous residue. The residue is dissolved in excess sodium carbonate solution and extracted with ether three or four times to remove the anhydride, unreacted carbinol, and the extraneous material, thus, leaving the phthalate in solution as the sodium salt. To this alkaline solution is now added cold dilute 20% sulphuric acid until the solution converts the sodium salt to the acid salt which is extracted with chloroform, dried, and the chloroform removed at reduced pressure, (15 mm.). If the phthalate fails to crystallize, the carbinol may be recovered by the addition of excess sodium hydroxide solution followed by steam distillation, and the distillate extracted with ether, dried, and distilled. The purification through the phthalate gives as a product, a carbinol of carbinols, if there are more than one present in the starting material, free from any other type of compound.

Run #2-

One mole, (58 g.) of propylene oxide, dissolved in 150 mls. of dry ether, was slowly added to 1.5 moles of t-butylmagnesium chloride cooled in an ice bath. The reaction mixture was allowed to warm up to room temperature as the ice melted and then left to stand overnight. In the morning, the mixture was stirred for thirty minutes and tested for excess Grignard reagent, using the method of Gilman, (28) and Shultze. The test indicated that there was Grignard reagent present. The reaction flask was now stoppered and allowed to stand for ten days before decomposition.

(a) Three hundred mls. of the ethereal solution was decomposed in the usual manner with ice and ammonium chloride at -5°C. A camphor-like odor, which might be classified as a musty odor, was observed, there was also observed an "apple-like odor" which indicated the presence of unreacted propylene oxide.

Distillation gave a fraction boiling in the range of 80-84°. The material in the flask tended to darken markedly so the distillation was discontinued and this material, (10 g), was put through a phthalate purification. Some difficulty was encountered in the recovery of the carbinol, but the addition of a few mls. of ether enabled the distillation to take place smoothly.

(28) Gilman and Shultze, J.A.C.S. <u>47</u> 2002-5 (1925)

The ether extract, when dried and distilled, gave a fraction, (5 ml) boiling in the range of 136-137°C. at 774 mm. The 3,5-dinitrobenzoate of this fraction melted poorly at 85-88°C. and after repeated recrystallization from ethylene alcohol and methyl alcohol. A melting point of 92°-92.5°C. was obtained.

(2b) The remainder of the Grignard reaction mixture was decomposed after standing an additional ten days. This time, the decomposition was carried out in a 2 litre erlenmeyer flask surrounded by an ice-salt bath, and the decomposition was carried out as rapidly as possible to minimize losses, for although the carbinol boils at over 130°, the vapour pressure at room temperature is such that it evaporates very rapidly.

The product of the decomposition was distilled and fractions obtained in the range 80-85°C., 100-110°C., 125-127°C. and 130-133°C. The 80-85°C. was found to consist of n-propanol, (3,5-dinitrobenzoate, m.73°). The boiling point lies closer to that of isopropyl alcohol, (b.83°C.) but the lowering of the boiling point may be due to a co-distillation of propylene oxide ether and alcohol.

The 100-110°C. fraction solidified in the side arm of the column, which as characteristic of hexamethyl ethan with which it was found to be identical, (m.pt. 104°C). The fraction distilling at 125-127° was later identified as propylene chlorhydrin. The 133° fraction failed to give a positive iodoform reaction, and was found to contain chlorine probably due to the chlorhydrin although it could not be identified as such.

Owing to the small amount of carbinol present, sodium chloride was added to the reaction flask. This "salting" effect permitted a maximum recovery of the carbinol. The ether extract, when dried and distilled, gave a fraction, (5 ml.), at boiling point in the range of 136-137°C. at 774 mm. The 3,5-dinitrobenzoate of this fraction melted poorly at 85-86°C. and after repeated recrystallization which indicated that the product was impure.

RUN #3

Propylene oxide, (1 mole), dissolved in dry ether and kept at 0°C. was added to an excess of the Grignard reagent and which was kept at 0°C. to 5°C. by an ice salt bath. When all the oxide mixture had been added to the Grignard reagent, the reaction was stirred for some time, and three hundred mls. of dry, thiophene free benzene were added. The ether was distilled off up to 55°C. and the benzene solution was then refluxed for one hour. The decomposition with ice and ammonium chloride required the addition of more benzene as the reaction mixture tended to collect as a stiff, jelly-like mass. Excess ammonium chloride was added and the solution filtered to facilitate handling.

The benzene ether extract was dried and fractionated. The results of the fractionation following the removal of the ether and the benzene were as follows:

BOILING POINTS at 757 mm.	VOLUME in mls.
110- 29°	30 mls.
130-132°	20 mls.
132-133°	less than 1 ml.
133-134°	less than 1 ml.
134-135°	less than 1 ml.
135-136°	less than 1 ml.
136-137°	less than 1 ml.
over 137°	very little

The fraction 110-129°C. was found to consist mainly of propylene chlorhydrin, (b.127-128°C.). The main fraction, 130-132°C. gave a 3.5 dinitrobenzoate that melted at 92.5-93°C. and was identical with the same derivative prepared from ethyl t-butyl carbinol. The higher boiling fraction, of which so little was obtained, was later found to be due to the increased temperature in the still pot, and column jacket which tended to drive out some of the normal hold-up of the column.

Run #4

Two hundred mls. of an ether solution of t-butyl magnesium chloride containing 0.5 mole of reagent was added to two hundred mls. of dry decalin and the ether removed by distillation. To the decalin solution was added an equimolecular quantity of propylene oxide dissolved in dry decalin. The reaction mixture was then heated at a temperature of 135°C. for two and one-half hours. During this time, the reaction mixture jelled and it was impossible to stir the mass. There was little tendency for the propylene oxide to distill out of the reaction mixture indicating complex formation of the oxide and the Grignard. On standing overnight, the mass set to a solid. The solid exhibited little tendency to react with water or air inasmuch as the jelly-like mass could be handled without any heating effect being noticed and on immersion of samples in water, no decomposition was observed over a period of an hour.

In an attempt to put the jelly-like mass in solution, 100 mls. of benzene was added and the mixture was allowed to stand on the steam bath. Another portion of benzene was added, and the reaction mixture transferred to an oil bath and heated to 105°C. The mass softened but the stirrer could not be operated. The mass was, therefore, transferred to a 2 liter flask and another portion of the benzene was added. There was no indication that the substance would go into solution and in view of the difficulty encountered in decomposing the previous run with benzene as the solvent, it was decided to steam distill the mixture. Benzene was distilled off up to 110°C. at which point, distillation ceased. The remainder of the mass was then steam distilled. The distillation was accomplished by first adding water dropwise to the reaction mixture, stirring and heating at the same time. Finally, the stirrer could be removed and the actual distillation commenced. The ether-benzene-decalin fraction was separated and dried, and then fractionated. The following samples were obtained:

TEMP. °C.	VOLUME in mls.
80-81°	0.5
98	0.5
120-130°	small
132	12
132-5°	1
135-136°	5
136-140°	2

Some distillate above 140°C. was obtained, but it consisted of a hydrocarbon fraction.

(Note). The various fractions obtained from 132-140°C. in this run were combined, and carefully refractionated through a 20 plate column, and one fraction compound of ethyl t-butyl carbinol (b. 132-133°C.). The 3,5 dinitrobenzoate melted at 92-92.5°C. after repeated recrystallization from ethyl and methyl alcohol.

Run #5

Propylene oxide, (2.75 moles) dried over aluminum oxide, (114), and dissolved in dry ether, was added dropwise with stirring to a 4 mole run of tertiary butylmagnesium chloride at room temperature. The reaction mixture was allowed to stand overnight and stirred the following day for an hour. After standing for five days, 1500 mls. of the ethereal solution were syphoned out and decomposed. The following day, two liters more of the ethereal solution were syphoned out and decomposed.

In these decompositions, a large amount of gas was given off, which at first was thought to be due to excess Grignard reaction, but in view of later work, it was recognized that a portion of it, at least, was the result of reduction of the oxide with the consequent formation of isobutylene.

(114) Allen and Hibbert, J.A.C.S. 56 1398-1403 (1934)

The ether extract from the decomposition was washed, dried, and the ether removed by distillation, under a 12 plate column to reduce losses of higher boiling material. The ether distillate contained propylene oxide, but no separation was possible due to the similarity of boiling points. It was noted that the oxide-ether mixture necessitated more careful control of the heating during the fractionation to avoid flooding. Following the removal of the majority of the lower boiling material, the flask was changed for a smaller one and the distillation continued.

The higher boiling fractions are distilled through a Claisen flask to remove them from the decomposition products that were accumulating in the flask, (difficulty was encountered in getting the material to distil). The material continued to decompose on distillation, and gave a fraction boiling at 33°C. After several hours heating, a fraction boiling at 127-128° was obtained. It was identified as propylene chlorhydrin. The distillate composing the 33°C. fraction was identified as propylene oxide, arising from the decomposition of the chlorhydrin by the high temperature necessary to distill it.

Temperatures given below indicate the operating conditions:

BATH	VAPOR over liquid	VAPOR AT COLUMN HEAD
112°C.	102°C.	33-34°C.
140 "	112 "	" "
155 "	120 "	" "
170 "	128 "	55 small fraction
185 "	129 "	110-123°C. 1.1g
200 "		125-128°C.5.5 g.

The distillation did not proceed smoothly due to the decomposition that took place. Distillation would cease, the temperature of the bath would be raised and distillation would commence again more of the 33-34°C. material, (propylene oxide), resulting.

Distillation of the chlorhydrin was accompanied by extensive decomposition the first three times. Data for the final distillation are given below

The weight of the sample previously collected at 125-128°C. was -55 grams.

BATH TEMP.	COLUMN JACKET Bottom	COLUMN JACKET Top	TAKE OFF	Yield
155°	125°	122°	126°	
162°	127°	125°	126.5-7,0°	37g
175°	127°	124°	127°	5g
Low boiling material				5g
Residue				2g
TOTAL				49g

This represents a loss of 6 grams of material, with 42 grams collected at 126.5 - 7.0° at 755 mm. The 3,5-dinitrobenzoate of this material twice recrystallized from ethyl alcohol melted at 69°C. This melting point agrees with the melting point of a similar derivative prepared from the 127-130°C. fraction of previous runs.

All these various fractions were found to contain chlorine, and a carbon and hydrogen analysis indicated:

semi micro	C 40.94%	H.8.17%
	49.19%	H.15.45%
micro	42.22%	H.8.25%

Whereas actually, the percentages are:

C 38.09% H.7.30%

which indicates, that although the fraction is mainly propylene chlorhydrin, there is some other material present which cannot be separated from it by fractionation. Evidence of impurity is obtained also from the refractive index of the material which was 1.4332 at 20° as compared to the value given by Heilbron, (115), for 1-chloro isopropyl alcohol, n_d^{20} 1.4392.

(115) Heilbron Dictionary of Organic Compounds, (Eyre & Spottiswoode, London, 1934)

RUN #6

Addition of Grignard reagent to oxide -1 mole of tertiary butylmagnesium chloride was added to 0.8 moles of propylene oxide dissolved in dry ether and cooled to $0^{o}C$.

The addition product was decomposed after standing four days at room temperature. The decomposition was carried out in the following manner: The Grignard addition was forced over by nitrogen pressure from the reaction flask into a 2-liter flask containing an ammonium chloride-ice mixture. This flask was fitted with a stirrer, and an efficient reflux condenser through which ice water was circulated. The condenser was connected to a trap cooled in a dry ice-acetone bath. The liquid collecting in the trap was sealed in a bomb tube for further investigation. The nitrogen pressure was regulated through a by-pass so that a constant stream of Grignard addition product was being added to the ice-ammonium chloride decomposition material.

The ether extracts were washed and dried, but still contained ammonia.

The trapping system used, prevented the ammonia from escaping from the system as it had previously done. The ammonia was distilled out of the solution under a 12 plate column. The first ether fraction, (28-32°C.) was found to contain ammonia which would account for the low boiling point. Also, the receiver, cooled in dry ice acetone, was found to contain some small solid particles which melted on warming up to room temperature. These were identified as ice particles which were forzen out by the low temperature of the bath. The ether was removed and a fraction in the range 82-84°C. was obtained. The material in the flask tended to turn brown and gave signs of decomposition so the whole was converted into a phthalate. The phthalate was steam distilled from an alkaline media to regenerate the carbinol.

The receiver was cooled in ice and two traps were used in an attempt to separate any low boiling material. The first trap was cooled in a calcium chloride-ice mixture while the second trap was cooled in dry ice-acetone. The characteristic "apple-like" odor of propylene oxide could be detected through the dry-ice trap. Other than small amounts of ether found in the first trap, no noticeable amount of material was recovered from either trap.

The steam distillate was extracted with ether and distilled, only a small amount of material, less than 1 cc, was recovered from the distillate. More sodium hydroxide was added to the reaction flask and the steam distillation continued for several hours - but no further material was recovered. The products of the reaction could not have escaped and we were forced to conclude that no reaction had taken place other than possibly some reduction of the oxide by the Grignard reagent. This was borne by the fact that the material collected in the dry-ice trap during the decomposition of the Grignard oxide addition product consisted of ammonia and an unsaturated material which boiled between 6° - $10^{\circ}C$. This material most probably consisted of isobutylene (b.pt.-6°) the unsaturated portion, and isobutane, (b.pt. -10°) from unreacted Grignard.

RUN # 8

To a six mole run,(150 g. of Mg and 552 g. of t-C_4H_9Cl) of tertiary butylmagnesium chloride, was added 220 grams (3.8 mole) of propylene oxide. The reaction mixture was allowed to stand for seven weeks, at room temperature, with occasional shaking, at the end of which time, it was decom-

-posed in two portions - using the technique outlined in the previous case; that is, blowihg the ethereal solution into the decomposition mixture with nitrogen under pressure. The procedure was modified inasmuch as the ethereal solution was retained in a graduated dropping funnel to give better control of the addition to the ice and ammonium sulfate that was used for decomposition.

The ammonium sulfate was used rather than the chloride in an attempt to cut out possible chlorhydrin formation due to interaction of the halide and the oxide. Having decomposed both portions, there remained some crystalline magnesium etherate in the flask. This was decomposed by adding ice and the ammonium salt and extracting with ether. The ether extracts were then combined. The water layer which contained some undissolved sulfate was acidified with dilute sulfuric acid at 0°C. extracted twice with ether and this ether added to the main volume, (total volume five liters). The ether extract was then treated with one liter of 10% sodium hydroxide (2.8 moles NaOH), the purpose of the hydroxide being to hydrolyze any chlorhydrin that might be present and convert it to the glycol, (b. 189°C.).

The flask containing the mixture of ethereal solution and caustic was shaken thoroughly, placed under a 20 plate column and the ether distilled off. The receiver was cooled in an ice bath and protected with a dry ice-acetone trap. The material collected in the trap consisted of ammonia, some ether and an unsaturated substance, (isobutylene). The ether distilled contained some lower boiling material 32-33° and the "apple-like" odor of propylene oxide was noted.

The ether fraction having been removed, the remainder of the material was refluxed for five hours at a temperature of 125-135° and allowed to cool. The next step in the process was steam distillation, whereby the soluble glycol remained behind.

The reaction mixture was steam distilled directly from the flask with the addition of excess caustic to the already alkaline liquor. The possibility of loss was minimized by the use of the Frudrich condenser, backed by a dry ice-acetone trap, on the three-necked flask used as a receiver. Some two hundred and fifty mls. of material were separated from the water layer and dried.

It possessed the characteristic camphor-like odor that had been observed in previous preparations, and was halogen free. The water layer was extracted twice with halogen free,ether and both portions of ether were dried over anhydrous carbonate. The product was next distilled from a modified Claisen flask. The ether washings being used to rinse out the flask in which the product had been dried. The ether was distilled off and the remaining distillate collected in a three-necked flask which was to be used for the fractionation. The temperature rose gradually during the fractionation, from 55° to 137° at which point the material in the still pot commenced to fume and noticeably darken. The pot temperature at this point was 165-170°. The residue, (42 g), which gave an acid reaction was transferred to another flask, some potassium carbonate added, and stored for further investigation.

The fractionation gave 39 grams of material boiling at 137-138° at 762 mm. The fore-run after the removal of the ether consisted of the following amounts:

	TEMP. °C.	VOLUME
	80- 86	18 mls.
	86-100	12 "
	100-110	10 " (solid in CO_2)
	110-122	5 "
	122-130	3 "
	132-134	0.5 "
	134-135	3 "
762 mm.	135-135.5	10 "

There was a definite change in the odor of the product at 80° and up. The fraction in the lower range 69-78° had a definite benzene-like odor. The fraction coming over at 100-110° solidified on immersion in a dry-ice bath but not on immersion in a freezing mixture. It is probable that it contains some water.

Derivatives were prepared of the 137-138°C. fraction. The 3,5-dinitrobenzoate melted at 92.5-93°C. which checks with that obtained from ethyl t-butyl carbinol. The naphthylurethan was found to melt at 107-108°C. which agrees with the same derivative, prepared from ethyl t-butyl carbinol. Analysis of the naphthylurethan of carbinol $C_{18}H_{23}NO$ C - 75.7%, H. 8.13% as against C - 75.4%, H. 8.3% found. The high boiling residue (42 g) from the previous distillation was combined with the residue from the Claiser flask distillation and put through a phthalate purification. It was expected that if any of the product resulting from a oxide ring break to give a primary alcohol were present, it would be found in this fraction. There was, however, no fraction boiling above 135°C. at 755 mm. obtained; hence, we may conclude that the primary alcohol is absent.

PREPARATION OF METHYL NEOPENTYL CARBINOL.

Preparation of Carbinol from Diisobutylene-

An attempt was made to prepare the carbinol by the oxidation of diisobutylene and reducing the ketone so formed to the carbinol, (93). Yields on the oxidation step were very low and this process was abandoned in favor of the preparation from neopentyl ethylene.

(a) Preparation of Neopentyl Ethylene: Neopentyl ethylene was prepared after the manner of Whitmore and Homeyer, (116), 1 mole (85 mls) of allyl bromide (b.70-71°C.), at 767 mm. diluted with 125 mls. of dry ether was placed in a one liter three-necked flask fitted with a mercury sealed stirrer, a thermomenter, and a graduated separating funnel. The flask was cooled in an ice-salt bath at about -10°C. while 2 moles of a filtered ethereal solution of tertiary-butylmagnesium chloride were added slowly. The temperature of the solution was kept below 5°C.

(116) Whitmore and Homeyer, J.A.C.S. 55 4555-9 (1933)

Stirring was continued for several hours on completion of the addition, and the presence of excess Grignard was determined by the Gilman test,(114). After standing for ten days, with occasional stirring, the addition product was decomposed with ice and ammonium chloride, the ether layer separated, (washed with ammonical ammonium sulfate solution to remove magnesium salts) and dried over calcium chloride. The aqueous layer was steam distilled and the distillate extracted with ether, washed and combined with the first ether extract.

The ether was removed under a 14 plate column, and the fractionation continued under the same column. The fraction 70-72°C. (755 mm.) was collected as neopentyl ethylene. It was found that this fraction contained halogen so it was heated with an excess of NaOH solution for six hours, separated, washed and dried over anhydrous potassium carbonate. Analysis indicated that some halogen containing compound, (allyl bromide b.71°C. was still present. The heptene was freed from the halogen containing material by prolonged shaking with silver oxide. The halogen free heptene was then converted to the iodide by treatment with anhydrous hydrogen iodide as described.

(b) Preparation of 4,4-dimethyl-2-iodpentane: The hydrogen iodide was prepared after the manner of Hauben, (117), by dropping iodine dissolved in tetralin to boiling tetralin. The HI so generated was passed through a red phosphorus and glass wool filter (cooled in an ice bath), through a thirty inch phosphoric acid anhydride drying tube, then led below the surface of the sample. The sample was kept at 0°C. during the addition of the iodide - and the addition was carried out in the dark.

The iodide obtained after passing HI through the heptene until saturated, was washed with sodium bisulfite to remove any excess hydrogen halide. At this point, some Skelly solve B from which all unsaturated material had been removed, was added to facilitate the handling. The solution was then dried over sodium sulfate. The iodide had previously been prepared by Kharasch and Hannum, (118), in a similar manner and they reported the boiling point as 57.6°C. at 15 mm. This preparation had a boiling point of 52-58° at 7-12 mm. The iodide was slightly pink after standing, but the addition of a few drops of mercury clarified it.

(117) Houben, Boedler and Fischer, Ber. 69B,1766-88 (1936)
(118) Kharasch and Hannum, J.A.C.S. 56 1782-84 (1934)

(c) Conversion of the Iodide to the Carbinol-

(1) Ten grams, (0.044 moles) of the iodide so prepared were treated with 7.4 grams, (0.044 moles), of dried silver acetate at -5°C.followed by filtration to remove the silver iodide, and saponification with sodium hydroxide. The ether solution following steam distillation was dried and fractionated but no fraction boiling over 100° was obtained.

(2) Ten grams of the iodide were converted to the Grignard reagent. The Grignard reagent so prepared was converted to the carbinol by passing in dry oxygen gas for several hours until no more oxygen was absorbed. The addition product was decomposed with ice and ammonium chloride and the whole steam distilled following the addition of excess sodium hydroxide. The distillate was extracted with ether, separated, dried and distilled. A fraction was obtained which had a boiling point of 137°C. at 755 mm. The distillation was carried out in a modified Podbielniak column. The carbinol was converted to the 3,5-dinitrobenzoate which on recrystallization from alcohol was found to melt at 95-96°C. substantially in agreement with the derivative prepared by

by Whitmore, (93), from methylneopentyl carbinol, (3,5-dinitrobenzoate, 95.2 - 95.7 °C). A mixed melting point of this 3,5-dinitrobenzoate with a similar derivative prepared from ethyl t-butyl carbinol, (93.5-93°C.)was taken and the melting point obtained was 87-90°C. Another mixed sample method at 89-90°C.

PREPARATION OF ETHYL TERTIARY BUTYL CARBINOL-

(a) Propionaldehyde was prepared by dichromate oxidation of normal propyl alcohol using a reflux condenser through which chloroform was circulated as a separator the chloroform, (b.61°C.) served to condense the propyl alcohol, (b.97°C.), and return it to the system, but at the same time allowed the aldehyde, (b.48°C.) to pass over into the receiver. The aldehyde was fractionated and the fraction distilling between 48-49°C. was collected, the yield, 45 grams.

(b) Preparation of the Carbinol-

Thirty mls. of the aldehyde prepared above were dissolved in ether and added to an excess of Grignard reagent. The reaction was quite vigorous and the reaction mixture tended to solidify to a jelly-like mass.

The decomposition was accomplished by using ammonium chloride and ice as before. The product of the decomposition was fractionally distilled, the main fraction coming over at 132-135°C. The carbinol had previously been prepared by Ginnings and Hauser, (95), but no experimental details were given in their paper. The boiling point is reported by these authors as being 134.7-135.1 C. at 760 mm.

A low boiling fraction 80-90°C. was obtained which was identified as n-propyl alcohol, (3.5-dinitrobenzoate 72.5-73°C). This is lower than the normal boiling point of n-propyl alcohol but it corresponds to a similar fraction obtained in the Grignard oxide runs.

Refractionation of Carbinol prepared from Propionaldehyde and t-butyl Magnesium Chloride:

This carbinol had previously been separated into five fractions including material boiling from 120-135°C. The five fractions were now combined, washed and dried, and carefully refractionated through a modified Podbielniak column. The first fraction, excluding the fore-run of ether, was obtained at 125-127°C. followed by a fraction at 127°C. which solified in the dry ice cooled receiver. This was followed by a sharp rise to 133°C. where the main body of the material came over. This material, ethyl-butyl carbinol, (b.pt. 133°C. 756 mm), was converted into a 3,5-dinitrobenzoate, m.pt.92.5-93.0°C. and an naphthylurethan m.pt. 107.5 - 108°C. These melting points checked with those obtained from the carbinol resulting from the interaction of propylene oxide and tertiarybutyl magnesium chloride. Mixed melting points of the dinitrobenzoate of the known ethyl t-butyl carbinol and the methylneopentyl carbinol showed a definite depression (m.85-87°C.) as did the mixed melting point of the reaction product (oxide and Grignard) and methylneopentyl carbinol, (m.89-90°C).

SUMMARY

The reaction of t-butylmagnesium chloride with propylene oxide has been studied over a wide variety of conditions. The effect of low temperatures, (-5 to 0°C.), and high temperatures, (81°C. and 178-193°C.), in the solvents ether, benzene, and toluene, has been studied. The effect of time on standing before decomposition has also been studied. In all cases, the only product corresponding to an addition of the t-butyl group was ethyl t-butyl carbinol.

The other possible isomers, methyl neopentyl carbinol, methyl t-butyl, and pentamethyl ethanol were were synthesized and found to be absent from the product obtained as a result of the reaction of t-butyl magnesium chloride and propylene oxide. In the process of the investigation methyl t-butyl ethanol was synthesized under the direction of the authors. This alcohol had not previously been reported as such in the literature. The methyl neopentyl carbinol has been prepared by a new method.

It is suggested that this synthesis be repeated using ditertiary butyl magnesium or t-butyl lithium.

The use of either of these compounds would avoid the possibility of rearrangement of the oxide through the action of the magnesium halide etherates and should lead to the desired product, methyl neopentyl carbinol. This would make it possible to configurationally relate the carbinol to the members of the straight chain series. A more efficient fractionating column would be advisable as it should make possible the separation of the lower boiling isomers, some of which may be of theoretical interest.

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