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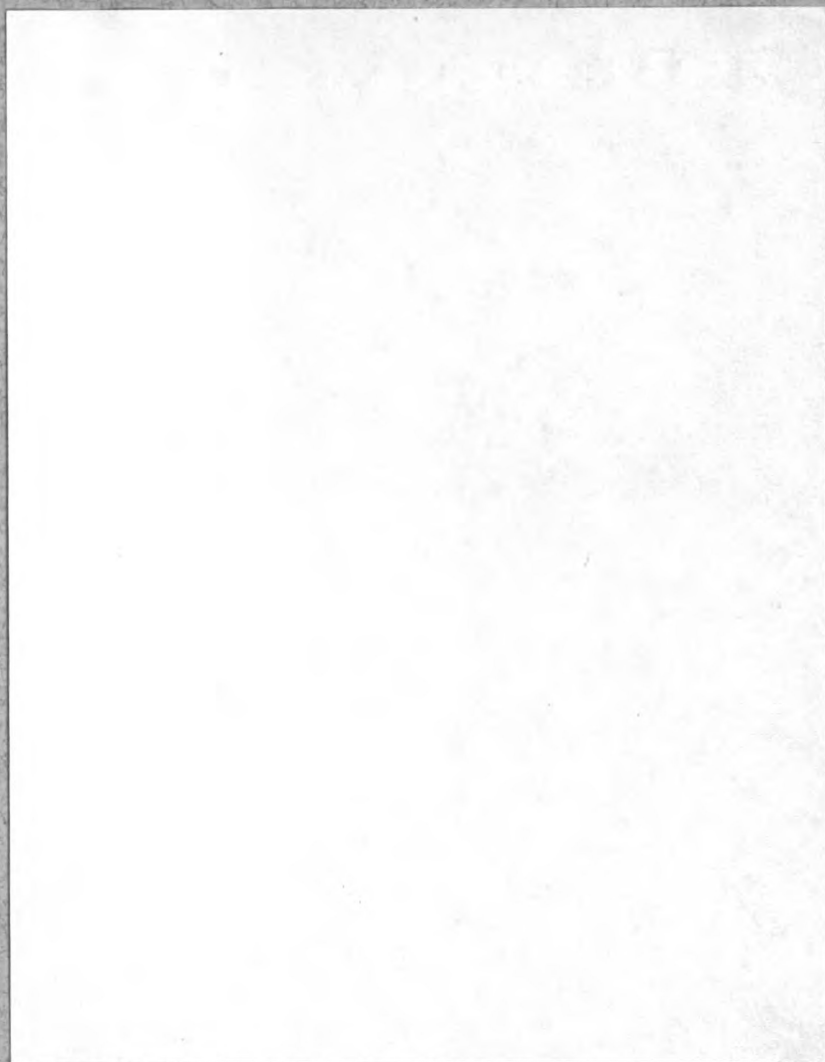
A STUDY OF THE REACTION  
BETWEEN CHLORACETONE AND  
GRIGNARD'S REAGENT

Thesis for the Degree of M. S.  
MICHIGAN STATE COLLEGE  
Boyd Harding Carr Jr.  
1942

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Michigan  
University



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A STUDY OF THE  
REACTION BETWEEN CHLOROACETONE  
AND GRIGNARD'S REAGENT

by  
Boyd Harding Carr Jr.

A THESIS

Submitted to the Graduate School of Michigan  
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#### ACKNOWLEDGMENT

The author wishes to express sincere appreciation for the help tendered by Dr. L. C. Huston, without which the work of this thesis would have been impossible.

## **INTRODUCTION**

The problem of this thesis is an investigation of the reasons why a secondary instead of a tertiary alcohol resulted from the reaction between chloroacetyl chloride and Grignard's reagent.

Much of the work of this laboratory has dealt with the condensation of various alcohols with phenols, benzene and other aromatic hydrocarbons. Many methods of synthesis have been used, and tried, to prepare the many alcohols needed.

One of the methods that was used in attempting to prepare tertiary alcohols was the reaction between halogen acid halides and Grignard's reagent. Huston and Spero<sup>1</sup> utilized this method of synthesis in attempting to prepare di methyl ethyl carbinol. They reacted chloroacetyl chloride and excess methyl Grignard. It was expected that the reaction would proceed as follows:

A methyl group would replace both halogens and a third methyl Grignard would add at the carbonyl group. This reaction would be expected to yield di methyl ethyl carbinol on the hydrolysis of the product. However, the product of the reaction was a secondary alcohol, methyl iso propyl carbinol.

The purpose of this thesis is an attempt to trace the route of the reaction and to investigate the mechanism of the re-arrangement.

In the above reaction, the first intermediate product that was formed was considered to be chloroacetone. The work of this thesis continued the problem from that point.



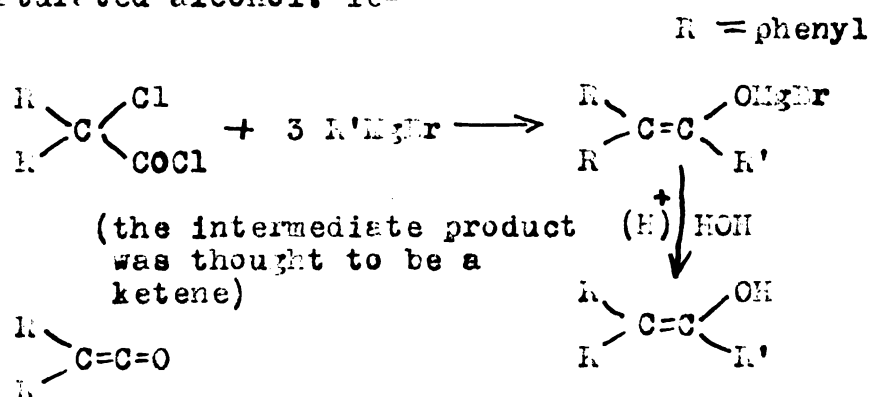
**HISTORICAL**

Though the independent class reactions of either halogen compounds or ketones are many, there has been very little work done on the reaction between alpha halogen alkyl ketones and Grignard's reagent. The literature did yield the following useful reactions.

The secondary alcohol, methyl iso propyl carbinol, was prepared in 1877 by Winogradow<sup>2</sup> by reacting brom-acetyl bromide and excess zinc methyl. And in 1881 Bogomoley<sup>3</sup> carried out the same reactions.

In 1907 Henry<sup>4</sup> synthesized the secondary alcohol, methyl iso propyl carbinol from both chloracetyl chloride and chloroacetone using three and two mols of Methyl Grignard respectively. He also prepared the secondary alcohol from the reaction of isobutylene oxide and isobutyraldehyde with methyl Grignard.

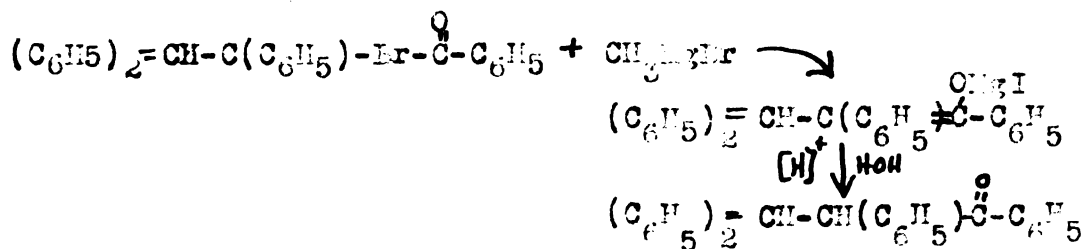
In 1921 McKenzie and Boyle<sup>5</sup> reacted phenyl alpha halogen acid halides with Grignard's reagent and obtained an unsaturated alcohol. ie-



In 1931 Avey<sup>6</sup> prepared some tertiary alcohols of the following nature,

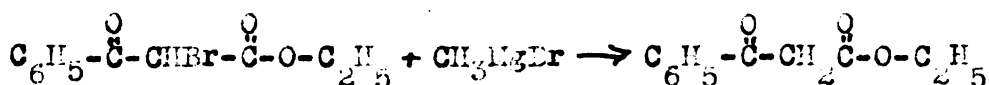
(1)  $\text{R}_2\text{C}(\text{OH})\text{-CHO}$  and (2)  $\text{R}_2\text{C}(\text{OH})\text{-CHCl}_2$   
by reacting Grignard's reagent and ethyl dichloroacetate.

In 1932 Kohler and Tishler<sup>7</sup> reacted phenyl alpha halogen ketones with methyl Grignard. The reactions appeared to go in the same general way. ie-

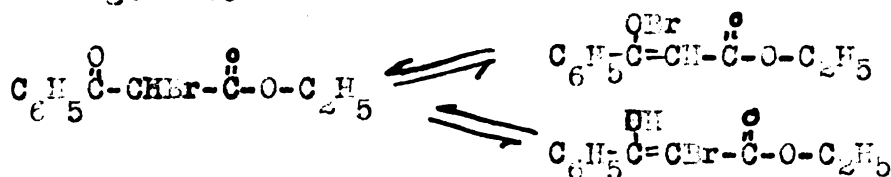


In all of these reactions Kohler and Tishler found only a simple replacement of a halogen by a hydrogen. The carbonyl group entered the reaction as an intermediate enol addition product.

In 1933 Hawk and McElvain<sup>8</sup> carried out some Grignard reactions with ethyl benzoyl bromo acetate. ie-



From the products of the reaction they concluded that a halogen atom proximate to an oxygen may appear in the hypobromite state or the proximity may cause an enol-keto rearrangement.



The reactivity of the resulting molecule must be due to the unsaturation.

In 1940 Tiegler and Connor<sup>9</sup> stated that the reactivity of a halogen proximate to a carbonyl group may be due partly

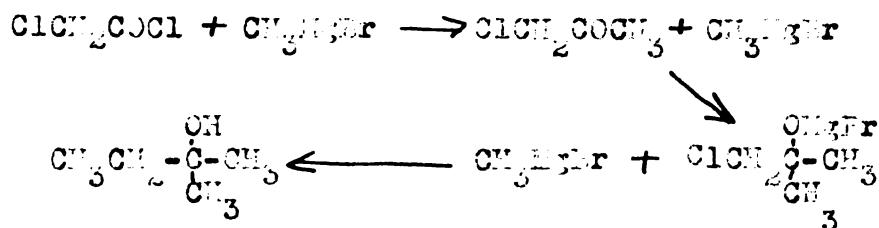
to the effect of the oxygen indirectly on the carbon-halogen link (loosening it) and also to the polarity of the oxygen. The result might be an unsaturated molecule due to a halogen shift, as stated by Hawk and McElvain.

In 1940 Huston and Spero reacted chloroacetyl chloride and chloroacetone with excess methyl Grignard and always obtained the secondary alcohol, methyl iso propyl carbinol as the main product.

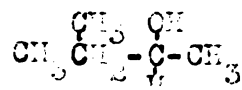
This represents practically all of the work analogous to that of this thesis found.

THEORETICAL  
AND  
DISCUSSION

As stated before, the synthesis of a tertiary alcohol dimethyl ethyl carbinol was attempted in this laboratory in the following way.

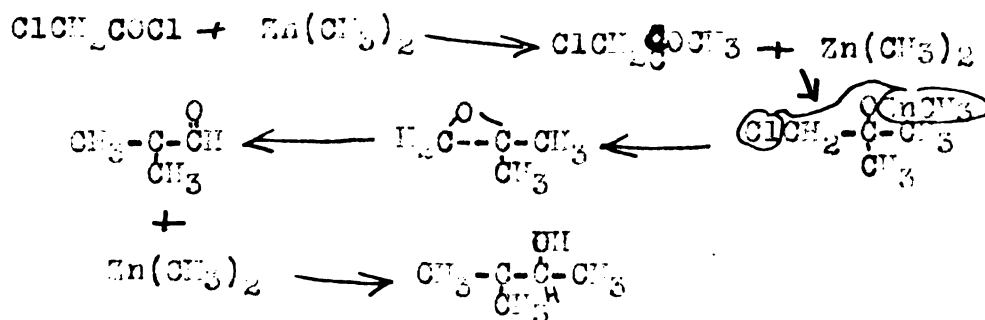


The product was, however, the secondary alcohol, methyl iso propyl carbinol.



This obvious re-arrangement has had several actual attempts at an explanation and in addition there are several somewhat analogous reactions that we can draw from.

Probably the first attempt at an explanation was that by the Russian, Vinogradov in 1877 in his analogous work, preparing methyl iso propyl carbinol from chloroacetyl chloride and excess zinc methyl. Kaschirsky<sup>10</sup> suggested to him that the reason for forming a secondary and not a tertiary alcohol might be as follows.

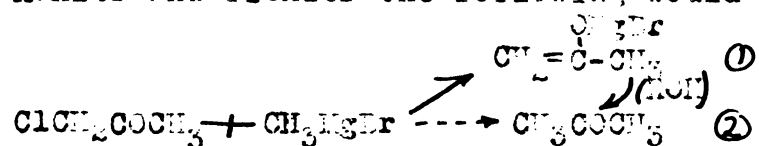




Thus the re-arrangement was suggested to be due to the momentary existence of isobutylene oxide.

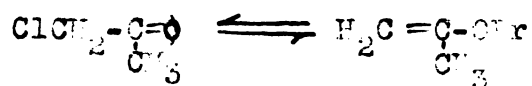
Henry carried out the above reactions in 1907 using methyl Grignard instead of zinc methyl. The results were the same, but in addition Henry reacted isobutylene oxide with methyl Grignard and obtained the secondary alcohol, methyl iso propyl carbinol. However, there was left the question, as to whether the Grignard addition product to chloracetone re-arranges to the oxide.

Kohler and Fiesher stated that all alpha halogen ketones,, provided that the carbonyl group is relatively inactive, reacted in the same way. This statement should be corrected to say that all alpha halogen phenyl ketones may react in this way. If the reactions of this thesis were to undergo the same general sequence as those reported by Kohler and Fiesher the following would happen.



The product of this reaction was not acetone.

Siegler and Connor offer a theory for an alpha halogen ketone re-arrangement. They stated that the carbonyl group increased the reactivity or resonance of the halogen of the ketone. ie-

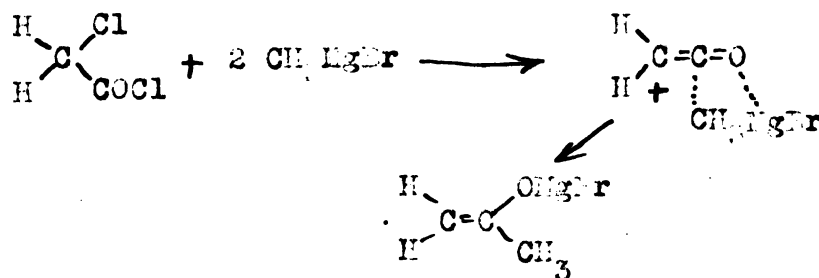


The reactivity of the molecule would then be due to the reactivity of the unsaturated point. However, without

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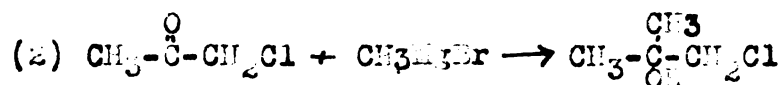
theorizing; farther, Kohler<sup>11</sup> states that Grignards reagents do not add at 1:2 double bonds.

If the McKenzie-Boyle mechanism were to take place then the reactions of this thesis would be as follows.



There was no evidence whatsoever of a ketene being an intermediate. Nor was the final product unsaturated, since the final product was methyl iso propyl carbinol.

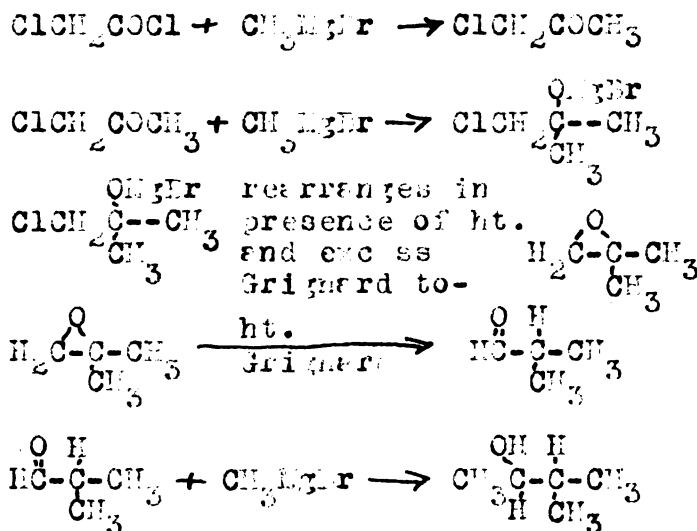
I do not think that the phenyl alpha halogen ketones can be generally considered analogous to chloroacetone in Grignard reactions of this type. By looking closely at the Kohler-Tishler reactants and comparing them to chloroacetone the reason will appear obvious.



In (1) the halogen is tertiary and easily replaced, in (2) it is primary and not as reactive; the benzene nuclei in (1) are themselves unreactive and quite large in comparison to the small reactive hydrogen atoms. For these few reasons alone I do not believe the two different molecules can be expected to give, generally, analogous reactions

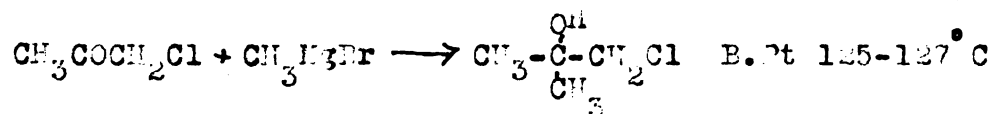
with Grignard's reagent.

From the work of this thesis and from earlier work, the evidence points to the following route of reaction.

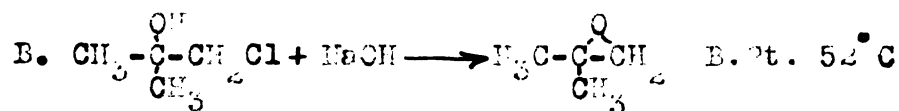


The reasons for believing that the reaction takes the above are as follows. (The assumption was first made that the first product of the reaction between chloroacetyl chloride and methyl Grignard is chloroacetone)

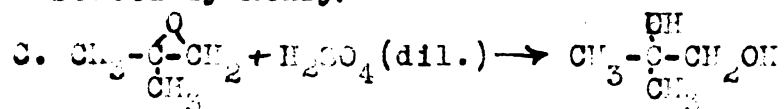
- (1) Chloroacetone on reacting with Grignard's reagent yields isobutylene chlorohydrin in a 61% yield.



A. B. Pt. in Beilstein 125-127°C



The above product (1) reacted in this way as stated by Henry.



B. Pt. 170°C as in the literature (Henry)

(2) Isobutylene chlorohydrin should react with Grignard's reagent on being heated to yield in order,

1. Isobutylene oxide, 2. Isobutyraldehyde, 33.

Methyl iso propyl carbinol. The above reaction was carried out and the following determined.

A. Isobutyraldehyde was isolated as one of the products of the reaction and a derivative was prepared.

B. Methyl iso propyl carbinol was found to be the main product and a derivative was prepared.

Heat must be applied over a fairly long period of time to make the <sup>RE-</sup>arrangement take place.

PROPRIETARY

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## Materials Used

Ether - U.S.P. Dried over Sodium.

Magnesium turnings-

Methyl Alcohol - Pract.- Merck

Chloroacetone - Stabilized - Commercial Solvents Co.

Sodium Bromide - Tech.

Sulfuric Acid - C.P. - Conc.

NaOH - Tech.

Acetone - C.P. - Merck

Sodium

Calcium Chloride - Tech.

$\text{Na}_2\text{SO}_4$

2,4 Dinitro phenylhydrazine - Reagent - Eastman

3,5 Dinitro benzoyl chloride " "

Ethyl Alcohol - C.P. - Merck

$\text{Na}_2\text{CO}_3$  - Tech.

Bromine

$\text{KMnO}_4$

Glacial Acetic Acid - C.P.

HCl - C.P.



## Preparation of Reactants

### Bromacetone: R&E 13

In a 5 liter, 3 neck flask are placed a condenser, glycerine sealed stirrer, a thermometer, and a 500cc dropping funnel. In the flask is placed 1600cc  $H_2O$ , 500cc acetone, and 372cc of glacial acetic acid. The stirrer is started, the flask placed in a water bath at 70-80 C and 754cc  $Br_2$  carefully added. When the reaction mixture decolorizes in 1-2 hours, add 800cc of cold  $H_2O$ , cool to 10 C, and neutralize to Congo red with about 1000 gms  $Na_2CO_3$ . The oil which separates out is taken off, dried over  $Na_2SO_4$  and fractionated. The fraction boiling between 38 and 48 at 13mm pressure is saved and on refractionation that boiling between 40 and 42 C at 13 mm is used. Bromacetone is best stored cold and a little hydroquinone added to prevent oxidation and polymerization. Yield between 420 and 430 gms.

### Methyl Grignard: R&E 14

The methyl Grignards were all prepared in the same way. A three mol run will be for example. All the precautions for anhydrous preparation are used.

First, a methyl bromide generator is set up. A 5 liter round bottom flask is placed in a sand bath with a reflux condenser in it and a delivery tube leading from the condenser to a series of  $H_2SO_4$ - $H_2O$  drying and washing bottles (2  $H_2SO_4$ , 2  $H_2O$ , and 3 safety bottles) To charge for a 45 mol run-place in the flask 220cc of  $H_2O$ , 2200gms  $H_2SO_4$  and 1760cc of methyl alc. (temp. kept below 70 C)

Then 2400 gms of  $\text{H}_2\text{Br}$  are added, the apparatus is sealed and the bath is heated slightly. The gas is evolved immediately and is passed into-

In a 3 liter, 3 neck, round bottom flask is placed a glycerine sealed stirrer, a condenser, a thermometer and a glass entry tube for the gas (large size to prevent plugging) In the flask is placed 77 gms of  $\text{Mg}$  turnings and 800cc of anhydrous ether. The flask is cooled in a salt - ice bath to  $-5^\circ \text{C}$ . The stirrer is started, a few crystals of  $\text{I}_2$  added and the  $\text{CH}_3\text{Br}$  is led into the mixture at such a rate the ether refluxes gently in the condenser. The addition should take from 6 to 8 hours to completely use up all of the  $\text{Mg}$  in a 3 mol run. The Grignard assumes a deep black color.

## Reactions Proper

### Preparation of isobutylene chlorohydrin:

Three mols of anhydrous chloroacetone dissolved in 700cc of anhydrous ether is slowly added to 3 mols of a stirred and cooled methyl Grignard (through a dropping funnel) (the cooling is done by means of a salt-ice bath). The set-up is the same for this reaction as for the preparation of methyl Grignard except that a 500cc dropping funnel replaces the gas delivery tube. The addition is kept at such a rate that the temperature does not get above 5 C. The addition should be complete in 5 to 6 hours and the mixture should be allowed to rise to room temperature. It is then hydrolyzed with acid and ice, extracted, collected and distilled at 17mm of pressure. The fraction boiling between 40 and 45 C should be kept, dried over  $\text{Na}_2\text{CO}_3$  and refractionated. That boiling between 41 and 45 C at 17 mm is used. The yield should be about 186g or 61%. It is best to add the chloroacetone to the Grignard to prevent excess chloroacetone from reacting with itself and any other products which may be present to form resinous masses.

Since the following reactions are mainly all alike I shall describe one and merely tell the varied conditions in the others. They are the reactions between isobutylene chlorohydrin and  $\text{CH}_3\text{MgBr}$ . The conditions were varied to try to establish at what temperature the re-arrangement

takes place from chlorohydrin to isobutylene oxide, to isobutyraldehyde and finally to methyl isopropyl carbinol. The reaction is carried out in excess methyl Grignard.

#### Reaction Of Isobutylene Chlorohydrin and Methyl Grignard at 0 to 5°C.

In a 500cc round bottom, 3 neck flask containing a condenser, glycerine sealed stirrer, and a thermometer was made one half of a mol of  $\text{CH}_3\text{MgBr}$ . To this mechanically stirred and cooled Grignard was added 50 gms of chlorohydrin in 250cc of anhydrous ether. The addition was done so that the temp. did not rise above 5°C. The product was immediately hydrolyzed, extracted, dried and fractionated. The product was chlorohydrin, showing that no reaction took place at this low temperature.

#### Reaction of Isobutylene Chlorohydrin and Methyl Grignard at 28 to 32°C.

The reaction was carried out as above, except that the temperature was kept between 28 and 32°C. Again there was no reaction. No carbinol was formed.

#### Reaction of Isobutylene Chlorohydrin and Methyl Grignard at 45 to 52°C.

The addition of chlorohydrin was carried out at room temperature and then the reaction mixture was placed in a water bath, the ether distilled off and the viscous brown mass remaining was kept at 45 to 52°C for 24 hours.

The product was difficult to isolate because it polymerized in the presence of heat and hydrolyzing acids. However, 3 to 4 cc's of isobutyraldehyde were isolated and a 2,4 dinitro phenylhydrazone derivative was prepared.

Reaction of Isobutylene Chlorohydrin and Methyl Grignard  
at 55 to 65 C.

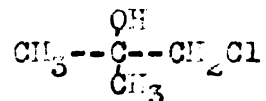
The same technique was followed as in the previous experiment but the heating was carried out for 5 to 6 hours at 55 to 65 C. The product was mainly methyl iso propyl carbinol, 7 or 8 cc's were isolated. A 3,5 dinitro benzoate ester was made of the carbinol.

Reaction of Isobutylene Chlorohydrin and Methyl Grignard  
at 65 to 70 C.

The same technique was used as before but the conditions were changed to a temperature of 65 to 70 C for 6 hours. The product was mainly methyl iso propyl carbinol. About 6 gms of carbinol were isolated and in addition about 2 cc's of isobutyraldehyde were also isolated. A phenyl urethane derivative was prepared of the carbinol and a 2,4 dinitro phenylhydrazone derivative was prepared of the aldehyde.

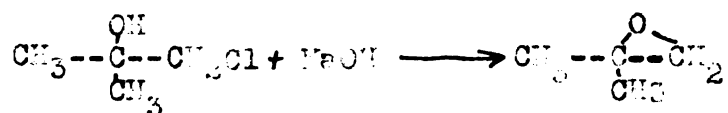
## Proof Of Structure

### Isobutylene Chlorohydrin:

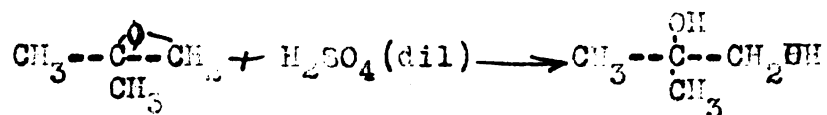


B.pt--125 to 127° C at 760 mm

"      42 to 42° C at 17 mm



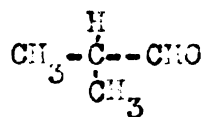
B.pt--52° C



B.pt--170° C

These boiling points are all verified by Henry<sup>4</sup> except that of 42 to 45° C at 17 mm for the chlorohydrin. This was determined during the work of this thesis.

### Isobutyraldehyde:



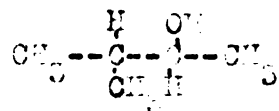
B.pt---63 to 64° C (15)  
Shriner and Fuson

Derivative--2,4 dinitro phenylhydrazine

M.pt-180° C (15)



Methyl Isopropyl Carbinol:

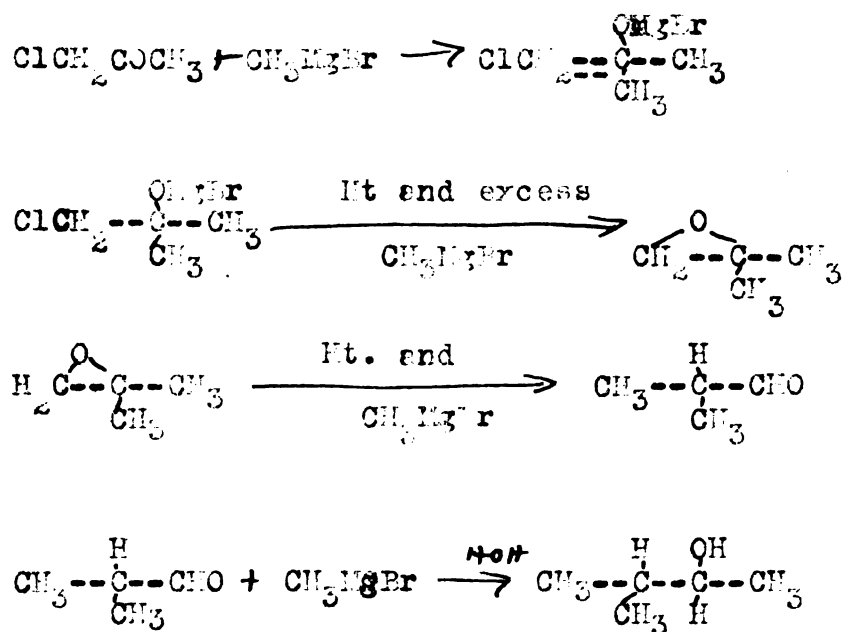


B.pt--110 to 114°C (Spero<sup>1</sup>)

I prepared two derivatives of the carbinol,  
the 3,5 dinitro benzoyl ester(M.pt 70°C)  
and the phenyl urethane(M.pt 72°C)  
(Spero<sup>1</sup>for the ester)

# Conclusions:

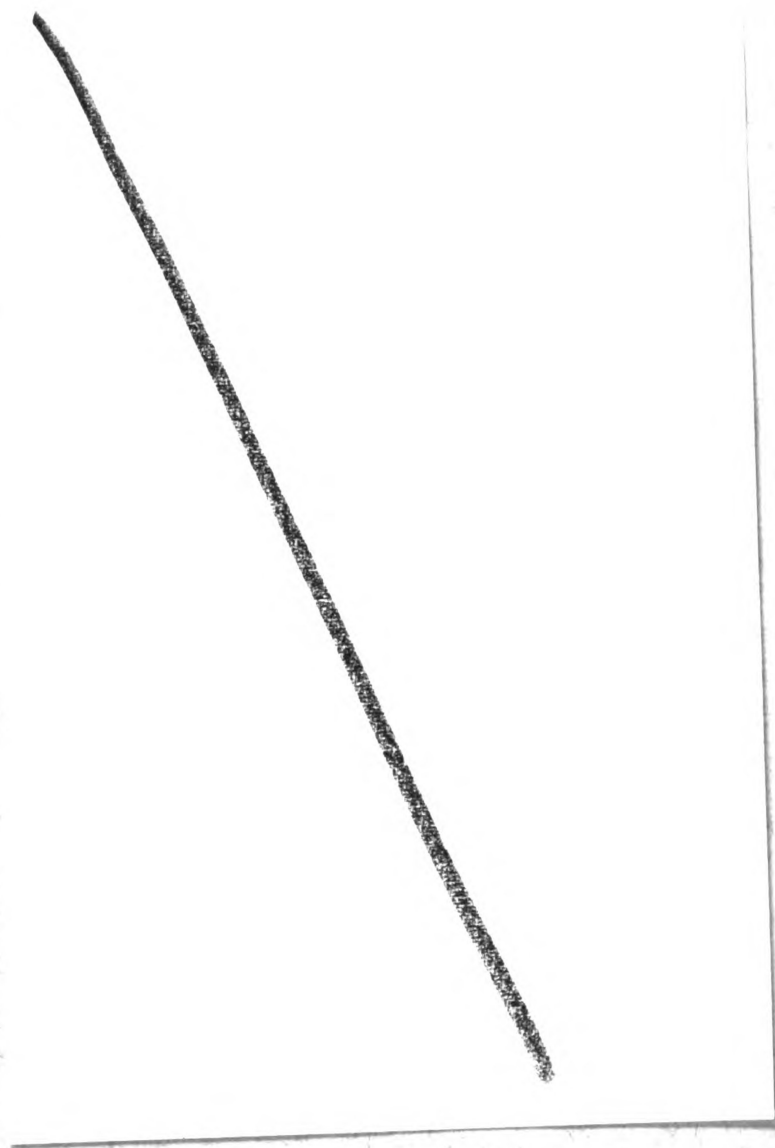
- (1) From the work of this thesis and previous work the indications are that the route of the reaction is as follows.



- (2) That the best way to prepare isobutylene chlorohydrin is to add the chloroacetone to methyl Grignard. It eliminates numerous side reactions and increases the yield.
- (3) That alpha halogen phenyl ketones and chloroacetone are not analogous in their reactions with Grignard's reagent.
- (4) In preparing isobutylene chlorohydrin it is best to distill the product at reduced pressures to prevent polymerization.

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