

THE SYNTHESIS OF DIISOBUTYLETHYLCARBINOL

THESIS

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by

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Introduction

Interest in the general problem of the synthesis of the higher molecular weight, (C_{10} and higher), tertiary alcohols was stimulated by the discovery that in a routine laboratory preparation involving the condensation of ethylmagnesium bromide and diisobutyl ketone the yield of the expected addition product was zero. This was a striking result in view of the fact that ethylmagnesium bromide and diisopropyl ketone give a 77 % yield of the addition product.

A cursory search of the literature revealed that very little information was available concerning the synthesis of the branched-chained tertiary alcohols. It was early recognized that to understand the results of the above attempted condensation, an extensive investigation of the action of Grignard reagents on branched ketones was necessary. The present problem, then, encompasses (1) the preparation and characterization of diisobutylethylcarbinol and (2) the study of the reaction of ethylmagnesium bromide with branched-chained ketones.

Historical Background

Reports throughout the literature on the preparation of the higher molecular weight tertiary alcohols were in agreement concerning the relatively low yields of the expected addition product from the reaction of complex, branched-chained ketones and branched-chained Grignard reagents. It was evident that as the size and complexity of substituent groups increased the percentage yields of the desired tertiary alcohols decreased.

Conant and Blatt² in 1929 reported that very little was known about the general problem of the synthesis of branched-chained, aliphatic tertiary alcohols. Of 38 tertiary alcohols described in the literature to 1910, 32 contained primary alkyl groups only. A further conclusion drawn from their literature search was that the typical addition reaction between ketones and the Grignard reagent ceased to be the main reaction when highly branched compounds were used. When straight-chained ketones and Grignard reagents were used addition was the principal reaction and the desired alcohols were obtained in satisfactory yields.

Whitmore and George⁹ studied a series of ketone-Grignard reagent condensations and determined the extent of addition, reduction and enolization obtained in each case. The ketone used in each case was diisopropylketone.

Grignard reagent	percentage yields			
	enolization	reduction	addition	total
MeMgBr	0	0	95	95
EtMgBr	2	21	77	100
n-PrMgBr	2	60	36	98
i-PrMgBr	29	65	0	94
i-BuMgBr	11	78	8	97

(Table I)

It can be seen from Table I that it was not possible to prepare in satisfactory yeild tertiary alcohols with more than two secondary or tertiary groups . The results obtained by employing branched-chained carbonyl compounds or branched-chained Grignard reagents greatly reduces the usefulness of the method as a means of preparing tertiary alcohols , but it is equally apparent in this case that the reaction is a satisfactory method for reducing highly branched ketones to the corresponding secondary alcohols .

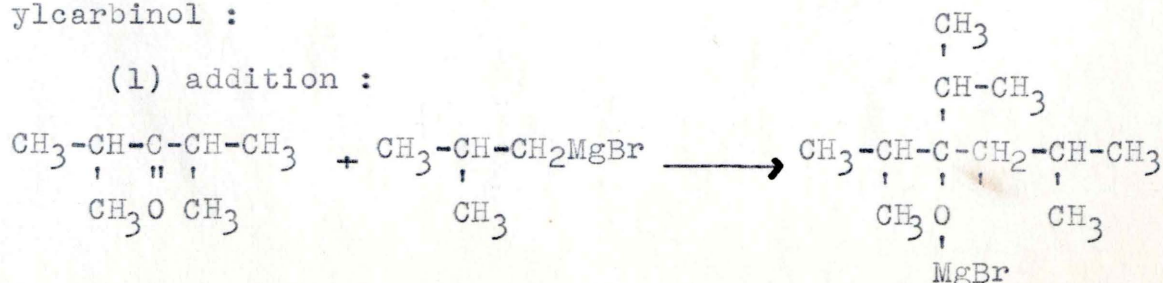
A continuation of the work by Conant and Blatt was undertaken by Whitmore and Lewis¹⁰ in a study of the use of methylmagnesium bromide in the preparation of various tertiary alcohols . As a result of this study it was found that the degree of enolization of the carbonyl compound depended upon the nature of the substituents on the carbon

adjacent to the carbonyl group , and that substitution on the beta carbon had no appreciable effect on the reactions of the carbonyl group .

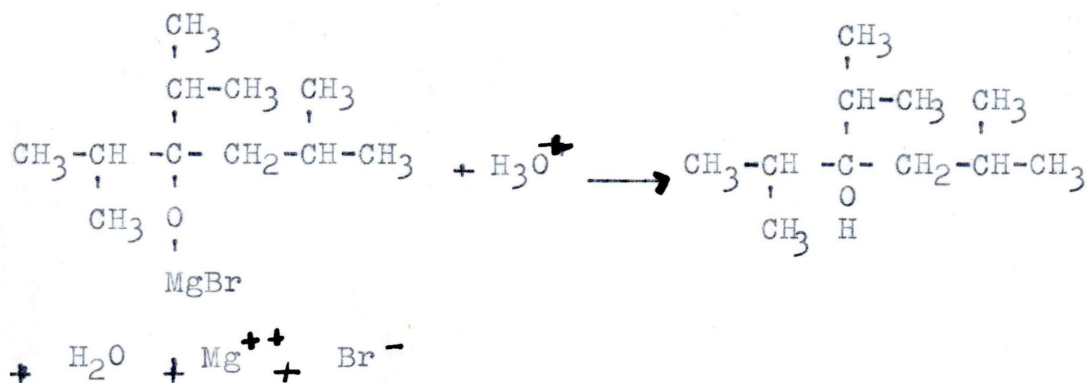
As a possible indication of the instability of the desired addition product , diisobutylethylcarbinol , the work of Meyer and Tuot⁶ was reviewed . In a series of reactions in which the dehydration of substituted carbinols was effected in the presence of anhydrous copper sulfate it was found that the diisobutylmethylcarbinol , (an alcohol very similar to the alcohol under consideration in this research) , was readily dehydrated to 2,4,6-trimethyl-3-heptene , B.P. 158° .

Skroup and Freundlich⁷ , in a study of halochromism in which triisobutyl carbinol was to be prepared as a test reagent , found that the alcohol could not be isolated as it apparently decomposed on distillation in high vacuum .

In a preparation very similar to the reaction under consideration in the present work Amuoroux and Murat¹ , using diisopropyl ketone and isobutylmagnesium bromide succeeded in obtaining a 20 % yield of diisopropylisobutylcarbinol :



(2) hydrolysis :



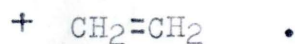
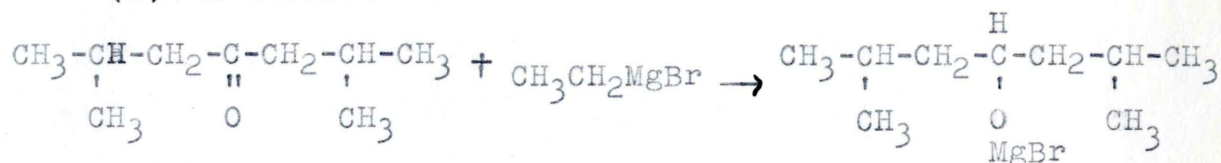
An extensive literature search was conducted to determine whether any of the alkyldiisobutylcarbinols in the series methyl- through butyldiisobutylcarbinol had been previously prepared. The preparation and properties of diisobutylmethylcarbinol were reported by Amouroux and Murat¹. The synthesis was performed by reacting methylisobutyl ketone with isobutylmagnesium bromide. It was noted that a large proportion of the methylisobutyl ketone remained unreacted. The following properties were recorded; bp₇₅₃ 180-2°, d²¹ .823, n_D¹⁸ 1.4334.

No reference was found in the chemical literature to the preparation or properties of diisobutylethylcarbinol, n-butyldiisobutylcarbinol, diisobutyl-n-propylcarbinol, diisobutylisopropylcarbinol. (Triisobutylcarbinol was found to decompose during distillation under high vacuum)?

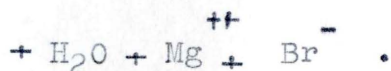
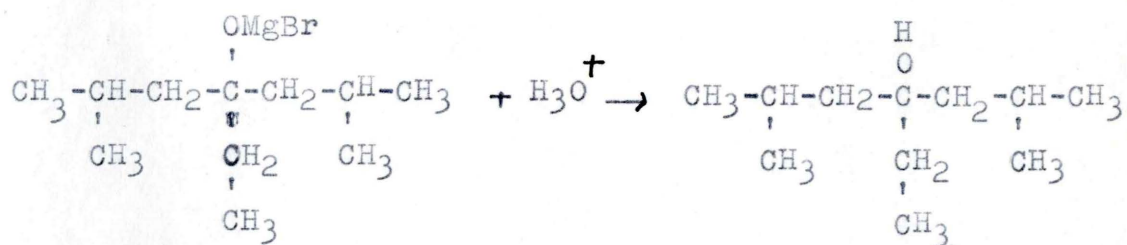
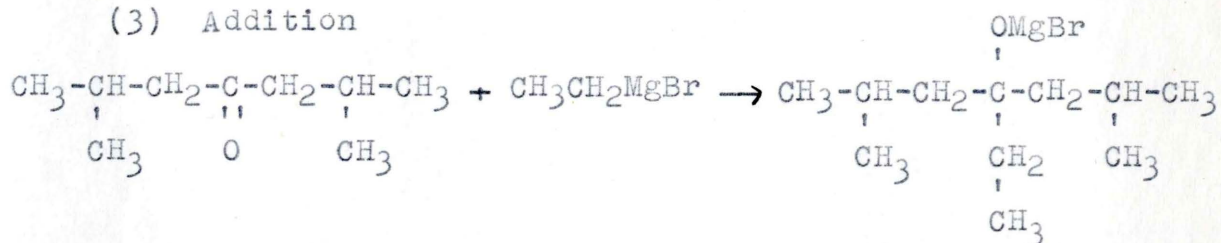
The best and most recent data on the physical properties of diisobutylcarbinol and diisobutyl ketone were reported

by Stross and coworkers⁸. They found for diisobutyl ketone, d^{20} .80600, n_D^{20} 1.41225, and for diisobutylcarbinol, d^{20} .80969, n_D^{20} 1.42314. The boiling points of these compounds were reported as 172-4° (diisobutylcarbinol), and 164-6° (diisobutyl ketone). Checks on this data in this laboratory were made with the following results, for the diisobutyl ketone, n_D^{21} 1.4122, bp_{7mm} 51-6°.

(2) Reduction



(3) Addition



In the case of reactions (1) and (2) the amount of ethane and ethene evolved during the ketone addition to the Grignard reagent would be a measure of the total contribution of (1) and (2). Analysis of the liquid product would, if sufficiently good, present a means of determining the contribution of each to the overall picture. The isolation of the carbinol would determine the extent of reaction (3).

Enolization represents the extent of the acid-base reaction

between the labile hydrogen of the ketone and the basic Grignard reagent . The extent of this reaction would depend upon the base strength of the Grignard reagent and upon the acidity of the ketone .

The mechanistic view of the reduction of the ketone by the Grignard reagent as pictured in equation (2) is supported by experimental evidence⁹ . Thus , this reaction will occur prior to hydrolysis . The amount of gas evolved , in this case ethene , less that amount of gas evolved from the enolization reaction , should be in agreement with the amount of the secondary carbinol found in the liquid product .

In the original condensation reaction as carried out in this laboratory the extent of side reactions was not studied quantitatively . No gas was collected during the addition of the ketone to the Grignard reagent or during hydrolysis . Apparently there was no addition product formed . Equimolar quantities of diisobutyl ketone and freshly prepared ethylmagnesium bromide were used in the laboratory addition with the Grignard reagent dissolved in ether . After hydrolysis of the mixture the ether layer was separated from the aqueous phase. The ether was removed by distillation and the residual liquid was dried over anhydrous Na_2SO_4 . The dried product was distilled under 65 mm. pressure with the greater part of the distillate (114.5 g.)

coming over between 91° and 94° . This temperature, under the pressure stated is in good agreement with the literature value for the boiling point of diisobutyl ketone³. A much smaller portion (10 g.) distilled, under the same pressure at 100° to 115° . The phenylhydrazone of the product was not successfully prepared. It may be possible that under these conditions any diisobutylethylcarbinol formed during the reaction may have dehydrated before the final products were isolated. A total of 1.1 moles of ethylmagnesium bromide were reacted with 1.1 moles of diisobutyl ketone (157 g.). The 124 g. of product isolated represents a weight recovery of 79 %.

In the next run the main objects were (1) to study the effect of using a high-boiling solvent such as benzene in place of the ether in solvating the Grignard reagent and (2) to note the effect of using an excess of Grignard reagent to the ketone. In this case 1.1 moles of Grignard reagent were reacted with .50 moles of diisobutyl ketone. The ether solvent used in the addition of the ethyl bromide to the magnesium was replaced simultaneously by benzene with constant refluxing before the addition of the ketone to the Grignard reagent. The first notable result of this change of conditions was the fact that the boiling range of the product was much greater than in the original work,

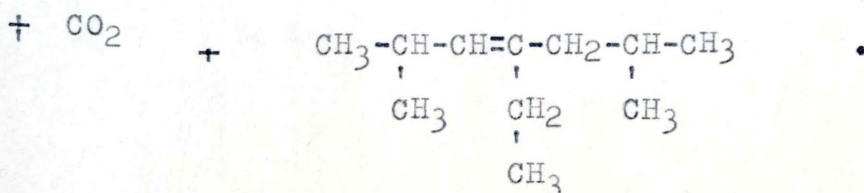
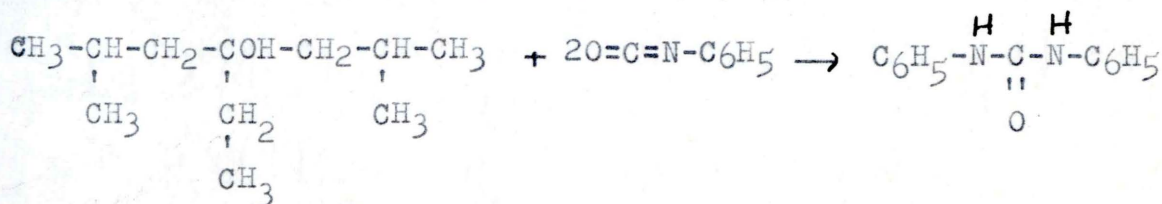
viz., 42° to 54° under a pressure of 7 mm. . Separation of the possible products of enolization , reduction or even dehydration would be extremely difficult since the boiling points of diisobutyl ketone , diisobutylcarbinol and 2,6-dimethyl-4-ethyl-3-heptene are very near to one another . Thus it would be safe to assume that the distillate could contain some quantity of diisobutyl ketone , diisobutylcarbinol , 2,6-dimethyl-4-ethyl-3-heptene and a very small amount of the addition product , diisobutylethylcarbinol , (accounting for the upper range of the distillation) .

Returning the normal procedure insofar as solvent was concerned , the next run of the thesis work was conducted using an excess of Grignard reagent as before with ether as the solvent throughout the reaction . In this run an effort was made to fractionate the product of the Grignard reaction in order to determine the extent of side reactions as well as the extent of the addition reaction . Cuts were taken at the following temperatures : $54-60^{\circ}$ (6.0 g.) , $60-70^{\circ}$ (9.0 g.) , $70-80^{\circ}$ (5.0 g.) , $80-83^{\circ}$ (13.0 g.) . The rate of change of temperature throughout the distillation was fairly constant with the exception of the last cut, ($80-83^{\circ}$) . This could easily be due to the fact mentioned previously that the boiling points of the products of side reactions and dehydration are very similar . Evidence points

to the presence of a fair amount of the addition product in the 80-83° cut . Refractive indices :

50-60° cut	60-70° cut	70-80° cut	80-83° cut
n_D^{24} 1.4278	n_D^{24} 1.4278	n_D^{24} 1.4308	n_D^{24} 1.4342

By comparing the literature values for refractive indices of the possible products of reduction and unreacted ketone , (diisobutylcarbinol n_D^{20} 1.42314 , diisobutyl ketone n_D^{20} 1.41225)⁸ , with the refractive indices of the various cuts taken the following assumptions can be made fairly safely , (1) the 50-60° and 60-70° cuts are mainly diisobutyl ketone with a small amount of the product of dehydration , 2,6-dimethyl-4-ethyl-3-heptene , (2) the 70-80° cut is a mixture of diisobutyl ketone and diisobutylcarbinol , (note the close proximity of the boiling points of these two liquids) , and (3) the 80-83° cut is mainly the addition product , diisobutylethylcarbinol . The phenylurethans of any alcohols present in the distillate could not be prepared because of the ease of dehydration of tertiary alcohols . In each case the reaction ,



predominated and symmetrical diphenyl urea was formed , (mp. 238°) . In this run , for the first time during the thesis work, the gas evolved during preparation of the Grignard reagent and during the hydrolysis was collected . During the addition of the ethyl bromide to the magnesium turnings a total of 2.8 liters (STP) or .12 moles of gas were collected , indicating that enolization and reduction were taking place to the extent of about 20 % . During hydrolysis a total of 12.3 liters (STP) or .55 moles of gas were evolved, an amount readily accounted for by the excess of Grignard reagent used in the run .

The general purpose of the next run of the thesis work , along with again using an excess of Grignard reagent was to improve upon the poor weight recoveries made in the previous runs . This run was made using larger amounts of all reagents but the ratio of Grignard reagent to ketone was maintained at 2:1 . Again the gas evolved was collected during the preparation of the Grignard reagent and during hydrolysis . A good weight recovery was obtained (96 %) . An improvement in the fractionation was effected by using a Vigreux column under reduced pressure , (see Fig .I) . Cuts were taken at seven temperatures and constant pressure and the volumes taken from each cut noted , (see Fig .II) . From the volume-% - temperature curve it may be seen that the large fraction boiling between 87.5 and 92° is composed

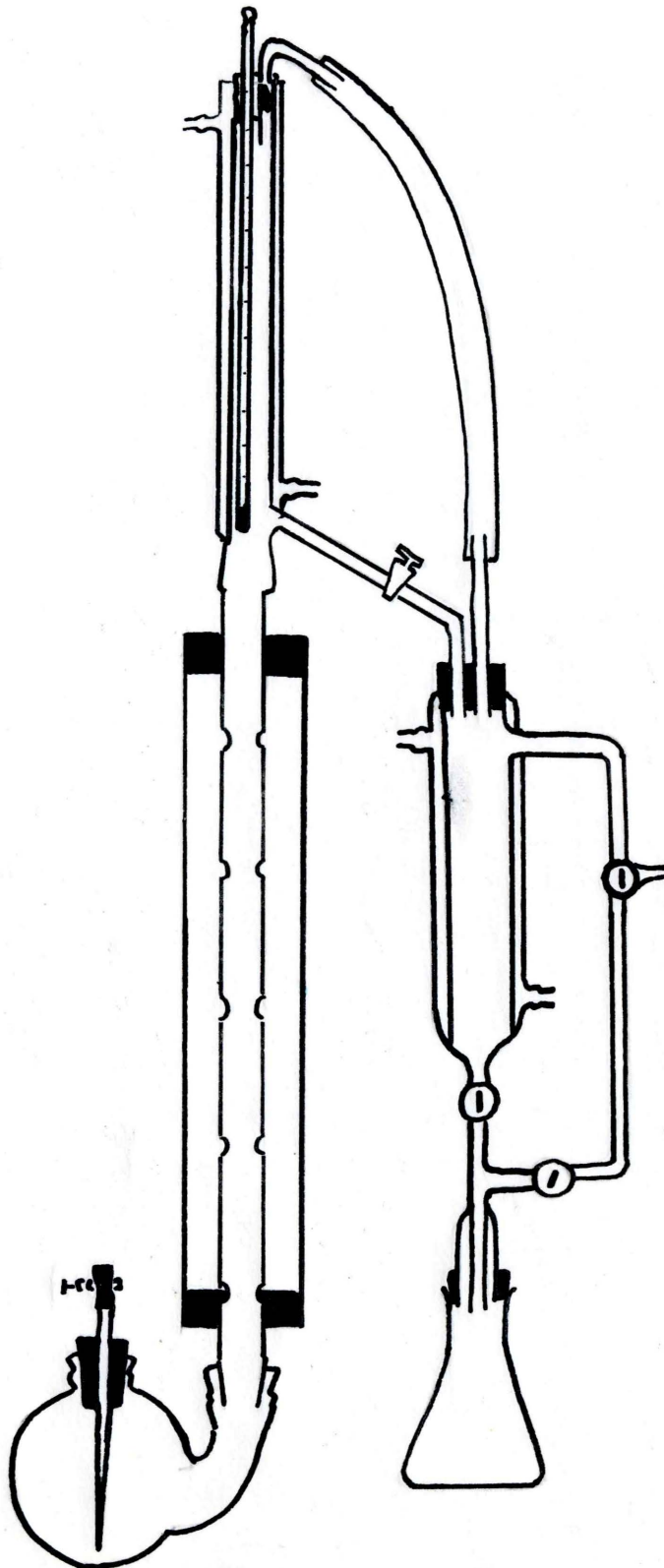


Fig. I.

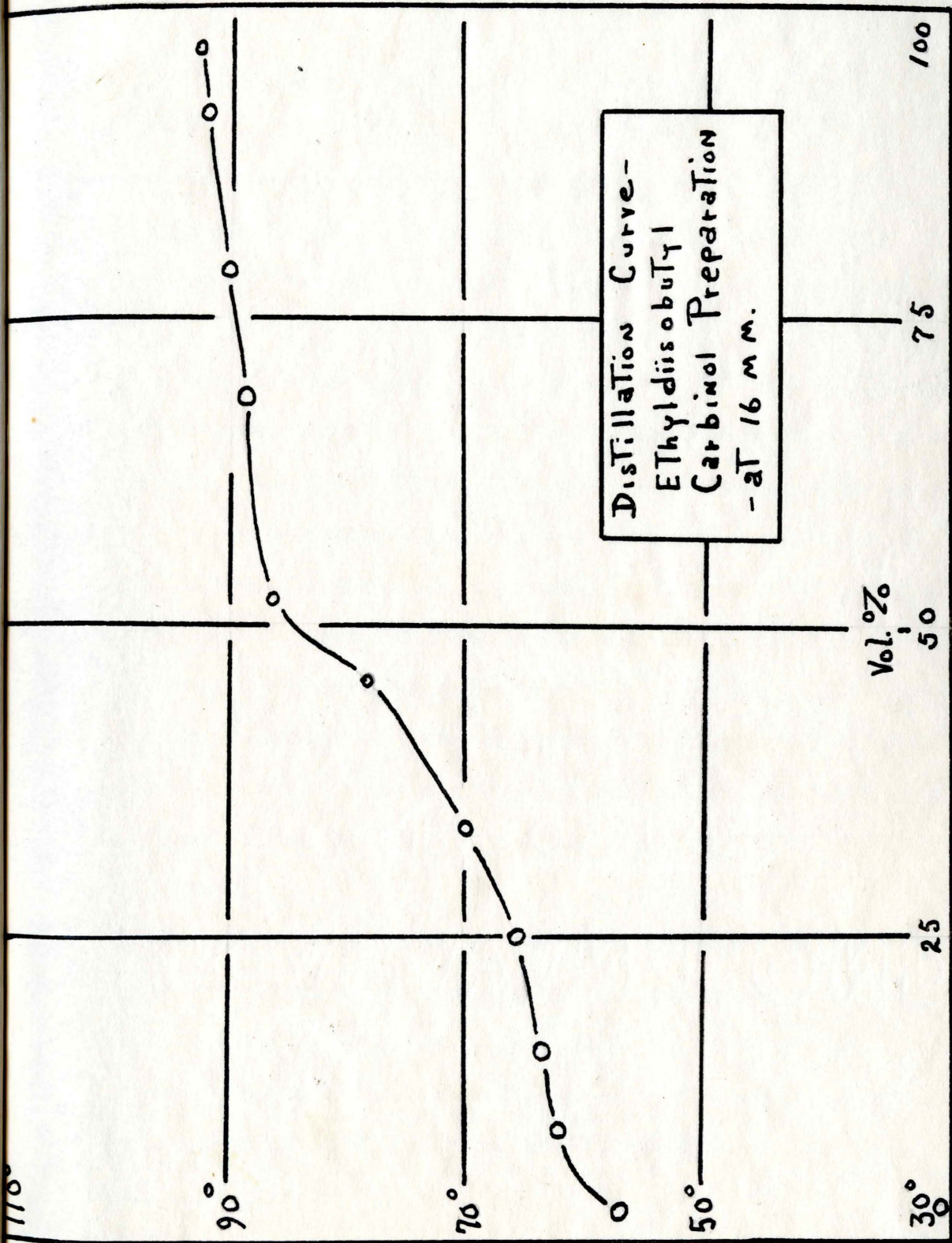


FIG. II

mainly of a single liquid , tentatively identified as diisobutylethylcarbinol . The olefin suspected of being present in the lowtemperature cuts of the previous runs was found in cut 1 of this run , i.e. , the cut boiling from 61 to 67° under 16 mm. pressure . Upon treatment of this cut with 2,4-dinitrophenylhydrazine three phases were found , the 2,4-dinitrophenylhydrazone of the unreacted diisobutyl ketone (mp 92°) , a liquid phase composed of the ethanol used as the solvent in the preparation of the derivative , and a second liquid layer insoluble in the ethyl alcohol solvent . From boiling point data the main constituents of the various cuts can be identified with a reasonable degree of accuracy; cut 1 (61-67°) diisobutyl ketone plus a small amount of the dehydration product 2,6-dimethyl-4-ethyl-3-heptene , cut 2 and 3 (69-87.5°) diisobutyl ketone plus diisobutylcarbinol , cuts 4 to 7 (87.5-93°) diisobutyl-ethylcarbinol .

In an effort to identify the high boiling fraction a small amount of cut 6 was distilled at atmospheric pressure and was found to dehydrate very readily . The boiling point of the dehydrated product was found to agree very well with that predicted from the literature for olefins of this general structure⁵ .

Applying gas collection data as before , it was found

that approximately the same percentage of original ketone was found to undergo enolization and reduction ; 5.2 liters (STP) or .23 moles of gas were evolved during the preparation of the Grignard reagent . During hydrolysis a total of 33.5 liters (STP) or 1.5 moles of gas were evolved . The unreacted ketone in cut 1 was identified as the 2,4-dinitrophenylhydrazone mp . 92° (agrees exactly with the literature).

In view of the evidence found in the analysis of the reaction products , e.g. dehydration by heat in the presence of phenylisocyanate the high boiling fraction is tentatively identified as the new alcohol , diisobutylethylcarbinol .

The physical constants of the new alcohol may be summarized as follows : bp_{16} $88-92^{\circ}$, d_{4}^{25} .8252 , n_D^{25} 1.4347
 M_D^R for diisobutylethylcarbinol 54.52 , M_D^R found in thesis work using n^2 formula 54.48 .

As an indication of the extent of the addition reaction and of the side reactions it may be seen from table II that an excess of Grignard reaction is necessary in order for the reaction to go to any appreciable extent .

Run	EtMgBr	Diisobutyl ketone	Products (moles)			
			solvent	red.	addtn.	unreacted
1	1.1	1.1	ether	0.1	0	0.9
2	1.1	0.5	benzene	0.1	trace	0.4
3	1.1	0.5	ether	0.1	0.2	0.2
4	2.0	1.0	ether	0.2	0.4	0.4

Table II

By comparing the results obtained in this work with those obtained by Conant and Blatt and Whitmore and George for other ketones it can be seen that the introduction of isobutyl groups onto the ketone in the Grignard reagent-ketone preparation of tertiary alcohols decreases the extent to which the addition reaction takes place , (see table III) .

Grignard reagent	Ketone	enolization & reduction	addtn.	total
EtMgBr	diethyl ketone	0	82-8 %	100 %
EtMgBr	diisopropyl ketone	23 %	77 %	100 %
EtMgBr	diisobutyl ketone	20 %	40 %	60 %

Table III .

* Approximately 40 percent of the diisobutyl ketone remained unreacted .

Experimental Data

Run # 1

Ethylmagnesium bromide was prepared by adding 1.1 moles of ethyl bromide (120 g.) to 1.1 moles (26.7 g.) of magnesium turnings in ethyl ether .

The Grignard reagent was reacted with 1.1 moles (157 g.) of diisobutyl ketone with constant refluxing and stirring , time of addition 2 hours .

The reaction mixture was hydrolyzed using 1:1 HCl at the start of hydrolysis and concentrated acid as the reaction became less vigorous . The product was separated , extracted once with ether and dried over anhydrous sodium carbonate .

The dried product was distilled under 65 mm. pressure with the main distillate coming over at 91-94° (114.5 g.) A smaller portion (10 g.) distilled at 100-115° under 65 mm. pressure . The 2,4-dinitrophenylhydrazone of the main distillate was prepared .

Run # 2

Ethylmagnesium bromide was prepared (1.1 moles) by the addition of 1.1 moles of ethyl bromide (120 g.) in 200 cc. of ether to 1.15 moles of magnesium (28 g.) in 50 cc. of ether . The reaction was initiated by seeding with 5 cc. of active Grignard reagent using a crystal of iodine as a catalyst . Time of addition of ethyl bromide was 3 hours .

To the Grignard reagent was added during 3 hours .50 moles (71.1 g.) of diisobutyl ketone with constant refluxing , 2.7 liters (STP) of gas were evolved (. 12 moles) during the addition of the ketone . The ether solvent was distilled off and replaced simultaneously by benzene in equal amounts during 3 hours . The reaction mixture was refluxed at this point for 45 minutes at 75-80° .

Hydrolysis was carried out during 3 hours using 300 cc. of 4. N. HCl , 13 liters (STP) of gas were evolved during hydrolysis , (.58 moles) . The product was separated , washed once with dilute sodium carbonate , once with water , and dried over anhydrous sodium sulfate . The benzene solvent plus the remaining ether were distilled off at 35-55° (ether) and 82° (benzene) .

The product was dried over 12 g. of anhydrous potassium carbonate and distilled at 25 mm. pressure , 64-72° leaving a black , tarry residue of 2.0 g.

The following qualitative data were obtained , (1) the product with acetyl chloride evolved HCl gas (turned blue litmus red) , (2) treatment of the product with Na metal produced a gas , (H₂) , (3) the phenylhydrazone could not be made , (4) the semicarbazone also could not be made .

The product was then redistilled under 7 mm. pressure and 42-54° . The original commercial diisobutyl ketone was

also distilled under 7 mm. pressure at 51-56°. The following data were obtained : product n_D^{21} 1.4260 , residue from the distillation of the reaction product n_D^{21} 1.4283 , the commercial diisobutyl ketone n_D^{21} 1.4122 , residue from the commercial ketone distillation n_D^{21} 1.4283 . From 71.1 g. of diisobutyl ketone at the start of the reaction 46.5 g. of product were isolated , a weight recovery of 65 % .

Run # 3

Ethylmagnesium bromide was prepared exactly as in run # 2 , 1.1 moles of ethyl bromide were added to 1.1 moles of magnesium in ether solvent .

One half mole of diisobutyl ketone were added during 3 hours to the Grignard reagent using ether as the solvent . A total of 2.8 liters of gas (STP) were evolved during the addition of the ketone , (.12 moles) .

Hydrolysis was carried out during 3 hours , 12.3 liters of gas (STP) were collected (.55 moles) . The product was separated , washed once with dilute sodium carbonate , once with water and the ether solvent removed by distillation . The product was dried once over anhydrous sodium sulfate and twice over anhydrous potassium carbonate .

The product was distilled under 26 mm. pressure at 72-95° . A total of 41.0 g. of distillate were obtained leaving a tarry residue of 2.0 g. The distillate was then redistilled under 14 mm. pressure at 55-85° . This distillate

was redistilled at the same temperature and under the same pressure and cuts were taken at 60° , 70° , 80° and 83° .
Refractive indices : $50-60^{\circ}$ cut n_D^{24} 1.4278 , $60-70^{\circ}$ cut n_D^{24} 1.4278 , $70-80^{\circ}$ cut n_D^{24} 1.4308 , $80-83^{\circ}$ cut n_D^{24} 1.4342 . From 71.1 g. of diisobutyl ketone at the start of the preparation 41.0 g. of product were obtained , a weight recovery of 58 % .

Run # 4

Ethylmagnesium bromide was prepared , 2 moles of ethyl bromide (218 g.) in 400 cc. of ether was added to 2 moles (48.6 g.) of magnesium in 100 cc. of ether .

After 30 minutes 1.0 mole of diisobutyl ketone (142 g.), Eastman yellow label P 4306 was added to the Grignard reagent with stirring over 1.5 hours . The mixture was refluxed continuously . A total of 5.8 liters of gas (STP) were evolved during the addition , (.23 moles) .

The reaction mixture was hydrolyzed with 600 cc. of 4. N. HCl during 3.5 hours , 37.22 liters of gas were evolved during hydrolysis (33.5 STP) or 1.5 moles of gas .

The ether and water layers were separated , 50 cc. of conc. HCl were added to the water layer . The water layer was extracted 3 times with 150 cc. portions of ether and the extracts added to the original ether layer . The ether solvent

was distilled off over a water bath leaving 158 g. of higher boiling liquid .

The product was distilled at 16 mm. pressure. The following cuts were taken at the temperatures indicated :

	temp. °C	volume (cc.)	wt. (gms.)
forerun	57-61	3.0	2.4
cut 1	61-67	46.0	36.5
cut 2	69-78	26.0	21.5
cut 3	87.5	13.0	11.0
cut 4	87.5	20.0	17.5
cut 5	88-91	28.0	22.3
cut 6	91-93	26.0	21.1
cut 7	93-93	5.0	4.1

Table IV

A tarry residue weighing 3.0 g. remained after distillation. Data on the refractive indices of these cuts is found in table V . (n_D^{25}).

cut 1	cut 2	cut 3	cut 4	cut 5	cut 6	cut 7
1.4254	1.4286	1.4330	1.4330	1.4340	1.4347	1.4353

Densities of several cuts were taken at 25° using a constant temperature bath and picnometer (see table VI).

cut 1	cut 2	cut 6
d_{4}^{25} .7576	d_{4}^{25} .8189	d_{4}^{25} .8252

Table VI .

Cut # 6 was distilled at $164-7^{\circ}$ under atmospheric pressure (740.4 mm. , corrected 737.3 mm.) . The distillate was dried over anhydrous sodium sulfate and the density and refractive index redetermined ;

n_D^{26} 1.4271 d_{4}^{25} .7562 .

During the distillation dehydration took place to a large extent .

Summary

- (1) A study of the extent of addition and side reactions was made of the reaction between diisobutyl ketone and ethylmagnesium bromide .
- (2) It was found that an excess of Grignard reagent is necessary for the reaction to proceed to any ^{appreciable} extent .
- (3) The use of benzene in place of the ether solvent in the reaction does not improve the yield of addition product .
- (4) The properties of a new alcohol , diisobutylethylcarbinol , have been summarized , (see page 16) .

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