STUDIES IN THE SYNTHESIS OF PURE HYDROCARBONS

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SUMMARY

Research into the synthesis of pure hydrocarbons received much stimulus during the war years, when the characteristics of as large a number of pure hydrocarbons as possible were needed. The present study formed part of a wide scheme for this purpose. During the work on synthesising hydrocarbons the author found that, inasmuch as the synthesis of pure hydrocarbons depended to a large extent on the Grignard reaction, it was necessary to try to obtain a better understanding of this reaction.

This Thesis therefore serves two purposes. It describes the author's investigation of the abnormal reaction of Grignard reagents with carbonyl compounds, and it describes the synthesis of two hydrocarbons, 2:4:6-trimethylheptane and 2:3:5-trimethylhexane, and the preparation of four others, believed to be new:

3:4-dimethylnonane, 3:4-dimethyloctane,
2:4:5-trimethylheptane, 2:6-dimethyl-4-*iso*butylheptane

The investigation of the Grignard reaction occupies the larger part of the thesis, and is devoted to a survey on some of the past work on abnormal Grignard reactions, to a discussion of the mechanisms of abnormal reactions, and

the application of the author's results to these mechanisms.

The author's results lead him to refute the "alcoholate" and "addition" mechanisms, and to postulate that all Grignard reagents can dissociate homolytically and heterolytically, the extent to which any Grignard reagent does so depending on the nature of the Grignard reagent and the nature of the second reactant.

The author concludes that, for this reason, the mechanism of reduction of carbonyl compounds by Grignard reagents is one of free radicals, whereas that of enolisation and condensation is ionic.

Acknowledgements

The author wishes to thank Prof. E.E. Turner, F.R.S., for his advice and guidance during the course of this work.

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The Infra-red absorbtion graphs are included in the text by permission of Dr. G.B.B.M. Sutherland, Pembroke College, Cambridge, by whose colleagues they were determined.

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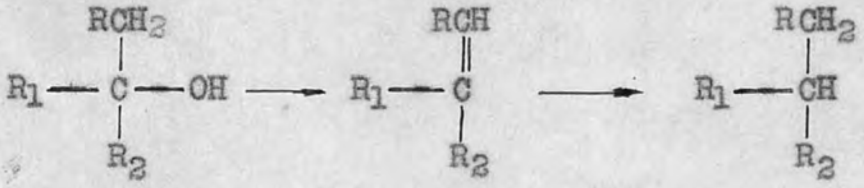
INTRODUCTION

The scope in reactions enabling the synthesis of saturated aliphatic hydrocarbons in a high degree of purity is not large, and when one comes to the higher hydrocarbons, say beyond C_8, the scope becomes even more limited, ending practically in the use of one reaction - the Grignard reaction. The general scheme of synthesis of the pure hydrocarbon is to aim for a tertiary carbinol corresponding with the hydrocarbon, for in most cases the tertiary carbinol is easily dehydrated and reduced to the hydrocarbon.



$$R_1-\overset{\overset{\displaystyle RCH_2}{|}}{\underset{\underset{\displaystyle R_2}{|}}{C}}-OH \longrightarrow R_1-\overset{\overset{\displaystyle RCH}{\|}}{\underset{\underset{\displaystyle R_2}{|}}{C}} \longrightarrow R_1-\overset{\overset{\displaystyle RCH_2}{|}}{\underset{\underset{\displaystyle R_2}{|}}{CH}}$$

The difficulties in the synthesis of pure aliphatic hydrocarbons therefore lie not so much in the synthesis of the hydrocarbon as in the synthesis of the tertiary carbinol. Once the carbinol is obtained it is not unlikely that the course to the hydrocarbon will be simple and easily followed. Admittedly there are the possibilities of molecular rearrangement and of polymerisation in going from the tertiary carbinol to the hydrocarbon, but they are small compared with the difficulties of arriving at pure tertiary carbinol. Once the tertiary carbinol stage has been reached there is no possibility of purifying products other than by fractional distillation or crystallisation at low temperatures. Therefore synthesis of tertiary carbinols must be those which have the largest possible likelihood of giving a pure product or those from which the tertiary carbinol is most easily separable. It may not at the start be apparent that to satisfy these conditions one would not from choice use the Grignard reaction as a general method. However, in the majority of cases there is no choice. It is necessary to use the Grignard reaction only a few times to realise its limitations. This realisation came early in the course of the present work, and led to a study of the abnormalities of the Grignard reaction. As an introduction to this study a review is given in Part I of this thesis of the earlier work on the side reactions of Grignard reagents with carbonyl compounds.

PART I.

THE ABNORMALITIES OF THE GRIGNARD REACTION

The side reactions of the Grignard reaction have long been known and accepted. Indeed they occur so frequently and readily that a more appropriate name for them would be the abnormalities of the Grignard reaction, for in many cases the "abnormal" reaction becomes the main reaction and the "main" reaction becomes insignificant. To such an extent does this occur that one may choose a Grignard reaction in order to synthesise the "abnormal" product.

There are several abnormal reactions and the frequency and extent with which any one occurs is different from that of another. They may be classified as follows:

(1) abnormal behaviour of the Grignard reagent itself.

(2) abnormal interaction of the Grignard and a second reagent.

Of the two the second has the greater interest and importance, but any work on reactions of the second class must take into consideration those of the first class. The reason for this will appear later. Reactions of class (1) are

(a) the coupling of the Grignard radical. i.e. from a Grignard reagent RMgX there is obtained the compound R-R. This is said to occur frequently but usually to a small extent.

(b) disproportionation of the Grignard radical. i.e. from the mutual oxidation and reduction of two R radicals there are obtained a saturated hydrocarbon and an olefin.

The present study deals with abnormal reactions of Grignard reagents with carbonyl compounds, and since reactions of this type give rise to saturated and unsaturated hydrocarbons, the possibilities of disproportionation (b) must not be overlooked.

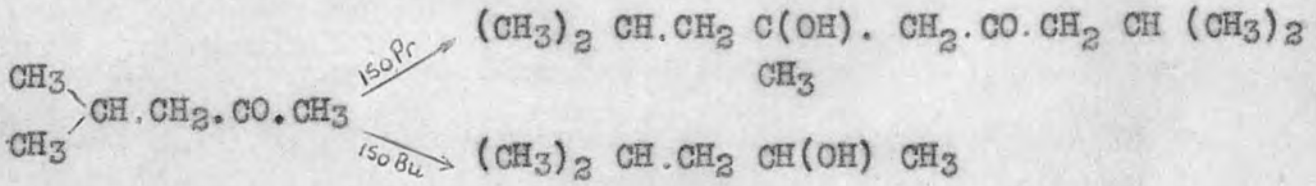
Of the second class of abnormal reactions the chief of those which concern reaction with carbonyl compounds are known as:

(c) reduction, in which the carbonyl compound is reduced to a primary alcohol in the case of aldehydes, or a secondary alcohol in the case of ketones.

(d) enolisation, in which the carbonyl compound is obtained unchanged in the reaction product.

(e) condensation, in which the carbonyl compound is obtained in a multimolecular form.

This study arose as the result not so much of the observation of one of these reactions, but of the observation of two reactions, namely reduction and condensation. For it was found that whereas interaction of one Grignard reagent, *iso*propylmagnesium bromide with methyl *iso*propyl ketone caused considerable condensation of the ketone to its ketol, interaction of the same ketone with *iso*butylmagnesium bromide caused little condensation, but considerable reduction of the ketone to the corresponding secondary carbinol:-



$$\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!\!>\mathrm{CH.CH_2.CO.CH_3}\ \begin{matrix}\xrightarrow{\text{isoPr}}\ \mathrm{(CH_3)_2\ CH.CH_2\ \underset{CH_3}{C}(OH).\ CH_2.CO.CH_2\ CH\ (CH_3)_2}\\ \xrightarrow{\text{isoBu}}\ \mathrm{(CH_3)_2\ CH.CH_2\ CH(OH)\ CH_3}\end{matrix}$$

It seemed therefore that reduction and condensation of ketones by Grignard reagents were not to be thought of as separate behaviours, but that the mechanisms of condensation and reduction were closely allied. Reduction of carbonyl compounds was recognised early in the history of Grignard chemistry and a good deal of work has been done in investigating the conditions and causes of reduction. Condensation of carbonyl compounds however, although equally long recognised, has not been the subject of so much attention, and it has been the practice of many workers, even those working on reduction, to speak of "higher boiling residues" in the reaction products and to describe them either as condensation products or merely as "probably" being condensation products. There has not been the same urge in identifying and explaining these condensation products as there has been with reduction products. It was evident therefore that if there was a link between the causes of reduction and condensation a scheme of reactions should be undertaken in which both reduction and condensation products must be isolated and identified as quantitatively as possible and correlated with the quantities of normal and other products from the respective reactions.

This meant that the controversies which have reigned over both reduction and condensation must be investigated and brought into line with each other. This was not all however. There were two other problems to be considered. They were enolisation and the nature of the Grignard Reagent. The former is an important factor in abnormal reactions, as will be seen. The latter is important, for it is not possible to attempt any consideration of reaction mechanisms without having an idea of the nature of the reagent involved.

Investigation of the earlier work on these abnormal reactions showed that it is suitable to divide a review of this work in the following manner

(A) Reduction

(B) Condensation and Enolisation

It was also found that in (A) and (B), after the first few papers had been published, development in mechanisms proceeded in definite stages. They are in (A)

(1) The HMgX and alcoholate theories.

(2) Mechanisms involving radicals.

and in (B)

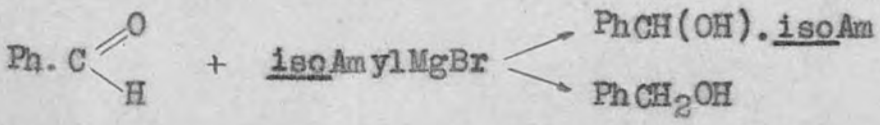
(1) The alcoholate theories.

(2) Steric influence and complexity of reactants.

(3) Electromeric influence

REDUCTION

This type of abnormal reaction of the Grignard reagent was first noticed and reported by *Grignard* (1901)[1]. Nothing more was reported than that from the interaction of *iso*amylmagnesium bromide and benzaldehyde there was obtained a little *iso*amylphenylcarbinol and some benzyl alcohol.



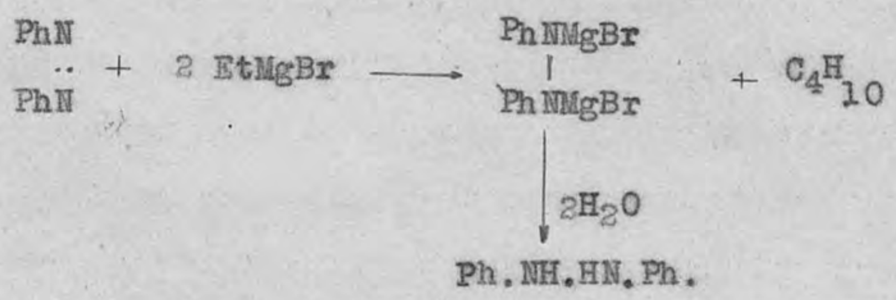
$$\mathrm{Ph.C}\begin{matrix}\nearrow\!\!\!{}^{\,O}\\ \searrow\!\!\!{}_{\,H}\end{matrix} + \textit{iso}\mathrm{AmylMgBr}\begin{matrix}\nearrow \mathrm{PhCH(OH).}\textit{iso}\mathrm{Am}\\ \searrow \mathrm{PhCH_2OH}\end{matrix}$$

Sabatier and Mailhe (1904)[2] however were the first chemists to report an investigation of reduction and to suggest a way in which it might occur. They had noticed that the action of *iso*butylmagnesium bromide on *cyclo*hexanone gave only a 15% yield of the tertiary carbinol, the major part of the product being *cyclo*hexanol, and they thought at that time that the formation of the *cyclo*hexanol occurred at the hydrolysis stage by the breakdown of the normal addition product to *cyclo*hexanol and butylene. They found subsequently that the butylene was produced abundantly on the addition of the *cyclo*hexanone to the Grignard reagent, and this led them to suggest that when the MgBr went to the carbonyl oxygen it took hydrogen with it and left butylene to be evolved. From experiments with other ketones and Grignard reagents they obtained the following results:

Ketone	Grignard	Yield t-OH	Yield redn. prod
Acetone	*iso*BuMgBr	50%	fair amount
*cyclo*hexanone	MeMgI	major	little
*cyclo*hexanone	EtMgI	major	little
*cyclo*hexanone	PrMgI	-	50%
*cyclo*hexanone	*iso*AmMgI	-	20%
*cyclo*hexanone	*iso*AmMgBr	-	20%
*cyclo*hexanone	*iso*PrMgI	-	75%
p-Me*cyclo*hexanone	s-octylMgI	25%	25%
*cyclo*hexanone	*cyclo*hexylMgCl	20%	-
Benzophenone	*cyclo*hexylMgCl	-	almost entirely
di*cyclo*hexylketone	*cyclo*hexylMgCl	-	almost entirely
*cyclo*hexanone	PhMgBr	major	-

It was also stated that the reduction of aliphatic and aromatic aldehydes was slight except in the case of chloral. They were the first authors to attribute to the nature of the Grignard reagent a great influence in reduction.

An explanation of the reducing action of Grignard reagents on azo compounds was offered by Franzen & Diebel (1905)[3]. They found that azobenzene and azotoluene were reduced by ethylmagnesium bromide to the respective hydrazo compounds.

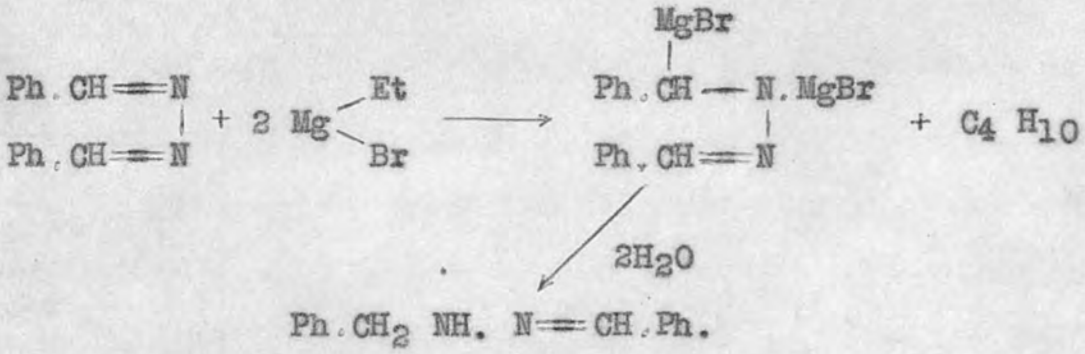


$$\begin{matrix}PhN\\ \cdot\cdot\\ PhN\end{matrix} + 2\ EtMgBr \longrightarrow \begin{matrix}PhNMgBr\\ |\\ PhNMgBr\end{matrix} + C_4H_{10}$$

$$\begin{matrix}PhNMgBr\\ |\\ PhNMgBr\end{matrix} \xrightarrow{2H_2O} Ph.NH.HN.Ph.$$

In these cases however they depict a mechanism which includes the formation of butane.

Similarly with aldazine and benzaldazine they reported the formation of hydrazone derivatives of the corresponding primary hydrazines according to the following mechanism:



$$\begin{array}{l} Ph.CH{=}N \\ \qquad\;\; | \\ Ph.CH{=}N \end{array} + 2\,Mg\begin{array}{l} Et \\ Br \end{array} \longrightarrow \begin{array}{l} \qquad MgBr \\ \qquad\;\; | \\ Ph.CH - N.MgBr \\ \qquad\qquad\;\; | \\ Ph.CH{=}N \end{array} + C_4H_{10}$$

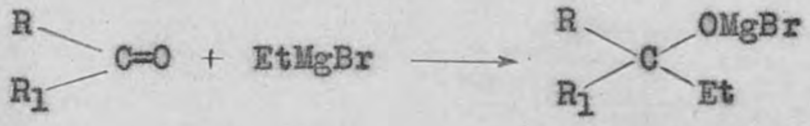
$$\xrightarrow{2H_2O} Ph.CH_2\;NH.\;N{=}CH.Ph.$$

Lucas (1910)[4] found that whereas the action of MeMgI, EtMgI, PhMgBr, and benzylMgCl on trimethylacetophenone gave the expected addition product, isoPrMgBr gave the reduction product

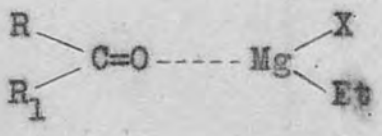
THE HMgX HYPOTHESIS AND ALCOHOLATE THEORIES

It had occurred to Hess & Rheinboldt (1921)[5] that the influential factor in the reducing action of Grignard reagents might be the hydrogenmagnesiumhalide HMgX. Their attempts to synthesise and isolate such a halide were unsuccessful, but they were of the opinion that it did exist in the form of an intermediate addition product having the reducing properties which one might expect from HMgX. They found moreover that the interaction of EtMgBr and benzaldehyde could be directed in two ways. By warming the reactants in ether solution on a water bath they obtained after hydrolysis benzyl alcohol, but when hydrolysis was carried out with preliminary warming they obtained a smaller yield of benzyl alcohol and some of the normal product, ethylphenylcarbinol

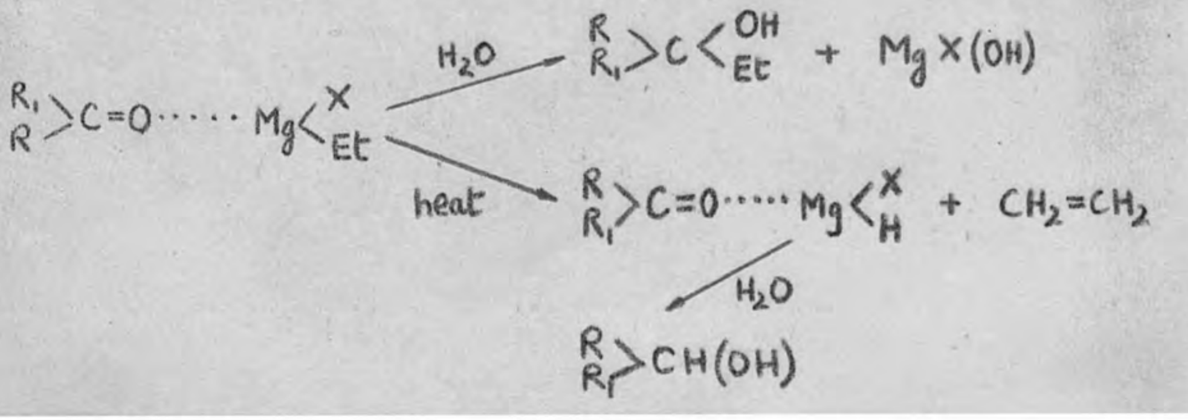
They concluded therefore that in the reaction between a Grignard reagent and an aldehyde a product must be formed which could easily give the required secondary carbinol, but which could also easily lose the olefin corresponding with the original Grignard reagent. The possibility that such a compound could be formed by the addition across the double bond of the carbonyl group was excluded by them, since they

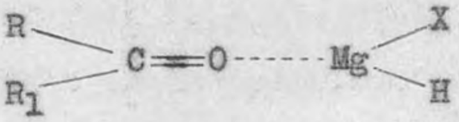


considered the loss of an olefin from such a compound at moderate temperatures to be unlikely. Instead they postulated that a compound is formed containing a less stable linkage such as a coordinate link, and they formulated this as



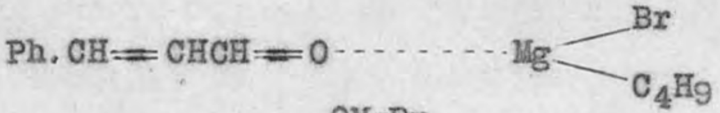
adding that in certain cases it might be possible that several carbonyl compound molecules and ether molecules participated in the coordination around the central Mg atom. The coordination compound was then depicted as undergoing two reactions:



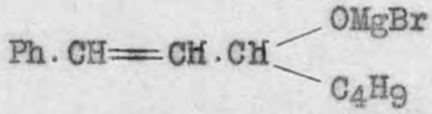
Support for the intermediate  $R(R_1)C{=}O\cdots Mg(X)(H)$ was said to exist in known ketone metallic salt complexes.

The HMgX hypothesis was further propagated by <u>Hess & Wustrow</u> (1924)[6] in their studies on the cinnamaldehyde-<u>iso</u>BuMgBr reaction. The type of evidence supplied is similar to that of Hess and Rheinboldt. (i.e.) the compound resulting from the addition of cinnamaldehyde to <u>iso</u>BuMgBr was shown to consist only of one molecule of each reactant, was found to give cinnamyl alcohol on hydrolysis without previous heating, but was found to give <u>iso</u>butylene and C_9H_9OMgBr by warming to room temperature or, better, in boiling ether.

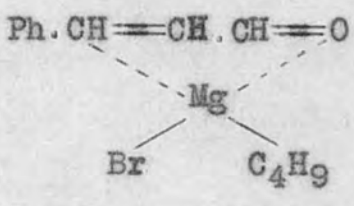
This behaviour was taken as showing clearly the coordinate nature of the coupling between the magnesium and the aldehyde, and to confirm this the same authors discussed the type of compound likely to be formed from such a reaction as theirs and the products likely to be obtained therefrom. The possibilities were.

(1) 

$Ph.CH{=}CHCH{=}O\cdots Mg(Br)(C_4H_9)$

(2) 

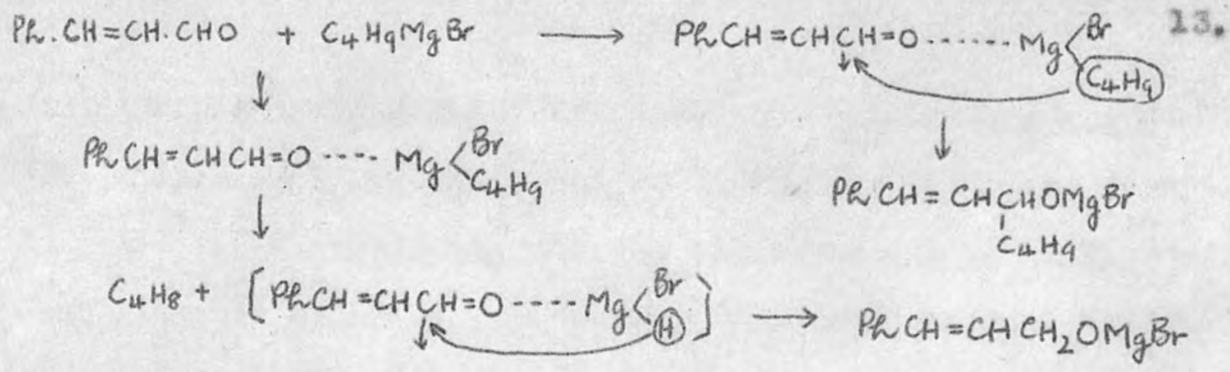
$Ph.CH{=}CH.CH(OMgBr)(C_4H_9)$

(3) 

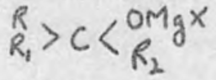
As far as (3) was concerned they felt that the addition of water to this would give the substituted aldehyde $PhCH(C_4H_9)CH_2{-}CHO$, and since this had not been observed formula (3) was excluded. Formula (2) was excluded on the grounds that an analogous compound made by the interaction of isobutylstyrylcarbinol and EtMgBr failed to give isobutylene on warming, and on hydrolysis gave only the secondary carbinol or its anhydride $PhCH{=}CHCH{=}CHC_3H_7$.

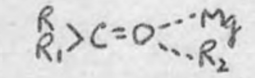
A second differentiating reaction quoted was that involving acetyl chloride. The authors found that from the reaction between acetyl chloride and (1) cinnamaldehyde was reobtained in 40% yield. On the other hand the action of acetyl chloride on (2) gave only the acetate $PhCH{=}CHCH\genfrac{}{}{0pt}{}{\diagup OCOCH_3}{\diagdown C_4H_9}$ or the anhydride $PhCH{=}CHCH{=}C_3H_7$. Hence it was concluded that the compound formed by the addition of cinnamaldehyde to isoBuMgBr and given formula (1) was certainly different from the isomeric compound (2)

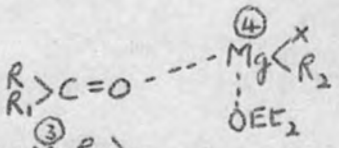
Further the action of acetyl chloride on the butylene-free C_9H_9OMgBr gave only the acetate of cinnamyl alcohol and therefore the possibility that this compound existed as $PhCH{=}CHCH{=}O \cdots\cdots Mg\genfrac{}{}{0pt}{}{\diagup Br}{\diagdown H}$ was excluded too. However it was believed that it was necessary to consider this hydrogenmagnesium halide to be an intermediate in the formation of the alcoholate C_9H_9OMgBr, and the following scheme was proposed:-

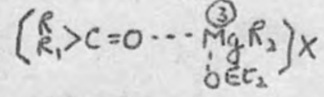


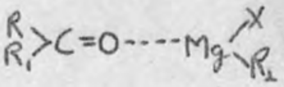
Rheinboldt and Roleff (1924)[7] in a later contribution to the HMgX theory considered in the same way as Hess and Rheinboldt the possible structures of a Grignard-carbonyl complex which might lead to both normal addition and reduction. However, they stressed that it was impossible to generalise with the knowledge in existence at that time and they therefore confined themselves to individual Grignard reagents and ether-free complexes. The formulations discussed were:

(1) Grignard's alcoholate  $\genfrac{}{}{0pt}{}{R}{R_1}>C<\genfrac{}{}{0pt}{}{OMgX}{R_2}$

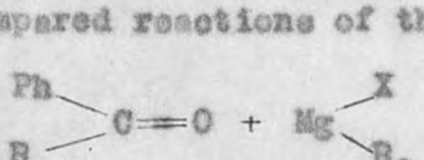
(2) Braun's oxonium  $\genfrac{}{}{0pt}{}{R}{R_1}>C=O\genfrac{}{}{0pt}{}{\cdots Mg}{\cdots R_2}$

(3) Meisenheimeimer's coordinate  $\genfrac{}{}{0pt}{}{R}{R_1}>C=O\cdots\overset{④}{Mg}<\genfrac{}{}{0pt}{}{X}{R_2}$, $\vdots\ OEt_2$

(4) Trivalent coordination  $\left(\genfrac{}{}{0pt}{}{R}{R_1}>C=O\cdots\overset{③}{Mg}R_2\right)X$, $\vdots\ OEt_2$

(5) Hess & Rheinboldt's coordinate  $\genfrac{}{}{0pt}{}{R}{R_1}>C=O\cdots Mg<\genfrac{}{}{0pt}{}{X}{R_2}$

Since it was already known that PhMgX did not cause reduction they compared reactions of the type

(A)  (B) 

and they found that in the series B, in which PhMgBr and *cyclo*hexylMgCl were used, no reduction occurred, but in series A, in which *iso*BuMgBr had been used, extensive reduction occurred.

They therefore concluded that since heating a compound of the B series, in which R_2 was linked to the carbonyl carbon, did not cause reduction, then in the series A in which reduction had ~~not~~ been observed the R_2 could not be joined to carbonyl carbon.

They also prepared several alcoholates analogous to (1) by interaction of a Grignard reagent and an alcohol, and found that heating these alcoholates did not form olefins.

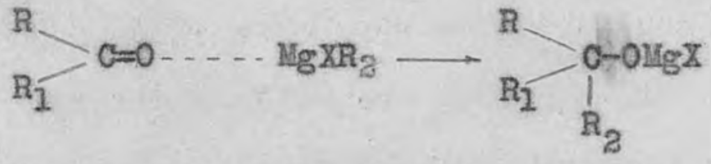
Formulation (1) was therefore ruled out on two counts, and an ether-free complex (5), analogous to complexes formed between carbonyl compounds and metallic salts, was given preference. This formulation had some support in that it could be envisaged as the precursor to the halogenomagnesiumhalide HMgX which, if formed by the liberation of the olefin, would be a ready agent of reduction.

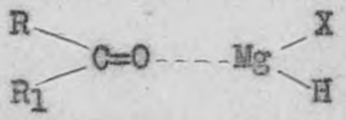
Rheinboldt and Roleff (1925)[8] contimued this hypothesis with the investigation of the influence of temperature on reduction, and the dependance of reduction on the nature of the Grignard radical and the carbonyl compound.

They found that the yields of benzhydrol from the action of EtMgBr, *iso*BuMgBr, and *cyclo*hexylMgCl on benzaldehyde were increased by working in boiling ether solution, and more so by changing from ether to the higher boiling solvent benzene.

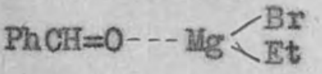
Ketones investigated were benzophenone, phenyl *iso*butyl ketone and pinacolone. It was found that *iso*BuMgBr caused more reduction than *cyclo*hexylMgCl, but although benzophenone and phenyl isobutyl ketone were quantitatively reduced by isoBuMgBr, pinacolone was reduced only to the extent of 75%.

Their conclusions were as follows: Reaction first produced the addition product (I)

(I)  (II)

and (I) could lose olefin to form 

However (I) could also change to (II), and since (II) could not lose olefin the fact that reduction is not always quantitative is explained. The two reactions occurred together and the easier the first so the smaller the extent of the second. In this respect the nature of the carbonyl compound had an influence, for if R and R_1 had a steric influence on the carbonyl group then addition of R_2 would be slowed down, thus increasing the tendency to lose olefin.

Objections to the HMgX hypothesis were started by Meisenheimer (1925)[9] on the grounds that addition of water to  $PhCH{=}O{-}{-}{-}Mg\begin{smallmatrix}Br\\Et\end{smallmatrix}$ should give back benzaldehyde rather than PhCH(OH)Et. He quotes reactions in which the original reactants were obtained at the end of the reaction but these he says are to be explained by special influences (steric hindrance) which prevent the formation of a complex (III) which he postulates as the active agent in Grignard reactions.

PhCHO-----MgBrEt ——— PhCH.(OMgBr)Et (III)

Meisenheimer discusses his findings in the reactions of benzaldehyde with EtMgBr and _iso_BuMgBr. He had found that the products of reaction depended on temperature to a small extent, on the solvent to a greater extent, but to the greatest extent on the time of reaction and the ratio of reactants. A good yield of secondary carbinol was obtained if EtMgBr was used in excess, but a large amount of reduction product was obtained if there was an excess of benzaldehyde, and also if benzene was used as solvent.

The explanation of these findings was given as follows: The initial reaction product (I) rapidly changes to (II)

(I) PhCH$=$O----MgBrEt---ether —— PhCH(OMgBr)Et---ether (II)

and a crystalline product is obtained consisting mainly of (II) and a little (I). It was possible that (I) could break down to $PhCH_2.OMgBr$----ether + $CH_2=CH_2$ but although this might apply to a large extent with _iso_BuMgBr, in the case of EtMgBr a new reaction occurs with the excess benzaldehyde:

$PhCH.(OMgBr)Et + PhCHO \longrightarrow Ph.CO.Et + PhCH_2.OMgBr.$

Confirmation of such a reaction was taken to be the isolation of propiophenone, a fact which had also been noticed earlier by _Marshall_ (1914,1915) [10], and the influence of solvent. In benzene, the formation of the organo-magnesium complex was believed to be slow, resulting in a greater excess of benzaldehyde and thus an increased double decomposition reduction reaction.

Gilman & Pickens (1925)[11] finally established certain cases of reduction in which there could be no H for making HMgX. They repeated the work of Franzen and Diebel on azobenzene and EtMgI. Gilman and Pickens used PhMgBr, obtaining diphenyl and hydrazobenzene, and concluded that since no olefin was formed there could not have been any HMgX.

Support to the works of Meisenheimer and Marshall was given by that of Gomberg and co-workers. This work involved the reducing action of the system $Mg + MgX_2$, attributed by Gomberg to the radical MgX.

Gomberg and Bachmann (1927)[12] found that the reaction between benzophenone, magnesium, and an aryl halide produced benzpinacol, and it was found subsequently that this reduction was in no way due to the Grignard reagent itself. It was postulated therefore that the free radical MgX was formed

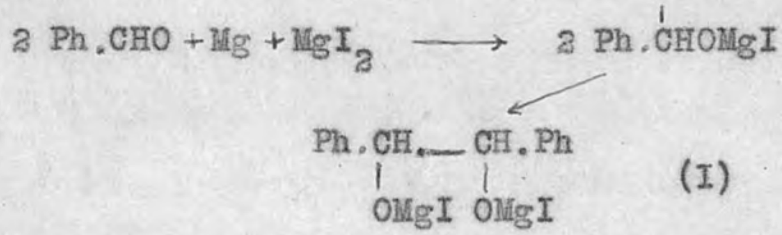
$$Mg + MgX_2 \rightleftharpoons 2\,MgX$$

and that this united with the oxygen atom of the C=O group forming a ketyl free radical $R_2\dot{C}OMgI$. The ketolate radicals were then able to dimerise to form a pinacolate.

$$2\,R_2\cdot\dot{C}OMgI \longrightarrow \begin{array}{l} R_2-COMgI \\ \quad\ | \\ R_2-COMgI \end{array}$$

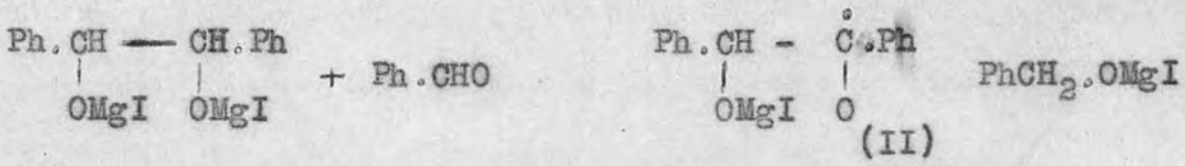
Much evidence derived from the study of the action of $Mg + MgX_2$ on ketones was supplied in support of this postulate. Later papers showed the application of this mechanism to the action of $Mg + MgI_2$ on diketones [13, 14], on acids and esters[15], on aromatic halogeno ketones[16], and on aldehydes[17].

The paper on aldehyde reduction is of particular interest, for it led later to the conclusion by Shankland and Gomberg (1930)[18] that reduction by Grignard reagents is a function of the addition product and not of the Grignard reagent itself. (i.e.) Gomberg and Bachmann found that $Mg + MgI_2$ reacted with benzaldehyde to produce benzoin, benzyl alcohol, tetraphenylerythritol and a high M.wt. polymer of the last. The explanation of these products was that the benzaldehyde was firstly reduced by MgI to the iodobenzoinate (I).



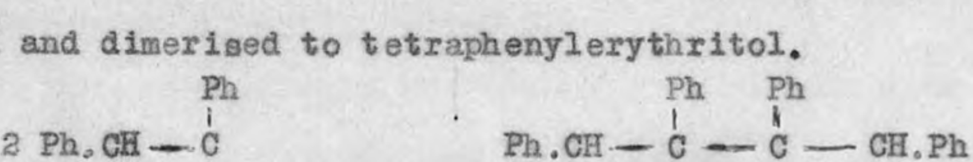
$$2\ Ph.CHO + Mg + MgI_2 \longrightarrow 2\ Ph.\overset{|}{C}HOMgI \swarrow \quad \underset{OMgI}{Ph.CH}-\underset{OMgI}{CH.Ph} \qquad (I)$$

Some of the benzoinate was immediately oxidised by more benzaldehyde, the latter being reduced to benzyl alcohol



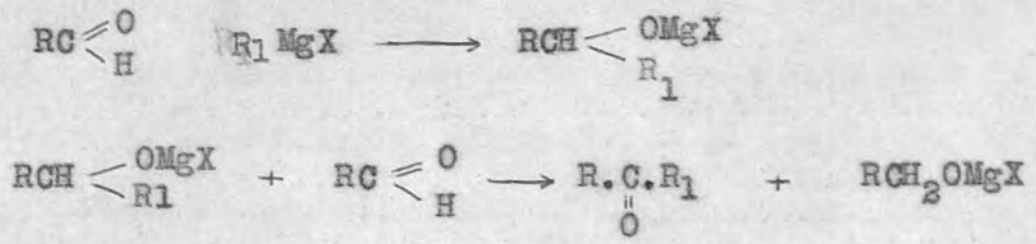
$$\underset{OMgI}{Ph.CH}-\underset{OMgI}{CH.Ph} + Ph.CHO \qquad \underset{OMgI}{Ph.CH}-\underset{O}{\dot{C}.Ph} \quad PhCH_2.OMgI \qquad (II)$$

and the oxidised benzoinate (II) was subsequently reduced by MgI and dimerised to tetraphenylerythritol.



$$2\ \underset{OMgI}{Ph.CH}-\underset{OMgI}{\overset{Ph}{C}} \qquad \underset{OMgI}{Ph.CH}-\underset{OMgI}{\overset{Ph}{C}}-\underset{OMgI}{\overset{Ph}{C}}-\underset{OMgI}{CH.Ph}$$

This work led Shankland and Gomberg to the conclusion that reduction by aromatic Grignard reagents proceeds as follows:



$$\mathrm{RC}{\genfrac{}{}{0pt}{}{\nearrow O}{\searrow H}}\quad \mathrm{R_1MgX} \longrightarrow \mathrm{RCH}{\genfrac{}{}{0pt}{}{\nearrow OMgX}{\searrow R_1}}$$

$$\mathrm{RCH}{\genfrac{}{}{0pt}{}{\nearrow OMgX}{\searrow R1}} + \mathrm{RC}{\genfrac{}{}{0pt}{}{\nearrow O}{\searrow H}} \longrightarrow \mathrm{R.}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{.R_1} + \mathrm{RCH_2OMgX}$$

involving merely the transfer of MgX and H from one molecule to another.

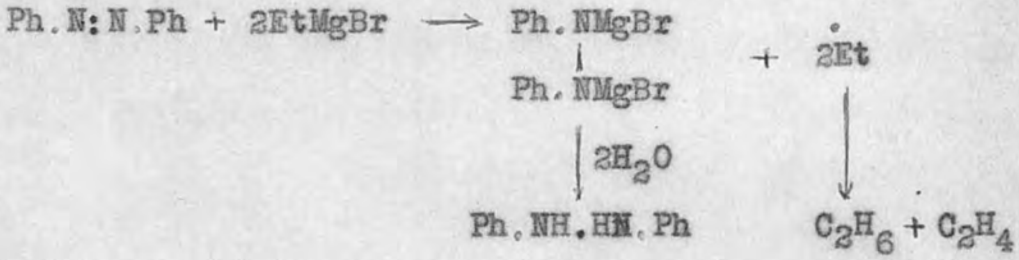
The experimental evidence for this conclusion was given by the reduction of a number of aldehydes and ketones by the iodo-magnesium salt of hydrobenzoin. The interaction of an aldehyde or ketone with this salt resulted in the formation of benzoin and the reduced aldehyde or ketone.

The results given by Shankland and Gomberg are as confirmation of the same explanations, given by Marshall and Meisenheimer, of the behaviour of aromatic ketones only when an excess of aldehyde was used.

When aliphatic Grignard reagents were used, as Shankland and Gomberg found, reduction was accompanied by the formation of saturated or unsaturated hydrocarbons, or both.

Mechanisms involving radicals.

Movement towards the theories of reduction by Grignard radicals and ions began in 1928 when Rheinboldt and Kirberg (1928) 19 reported their investigations of the reduction of azobenzene. Franzen and Diebel had reported that reaction of azobenzene with EtMgBr was accompanied by evolution of butane. Rheinboldt and Kirberg, however, repeated these experiments and found the evolved gas consisted of a mixture of ethane and ethylene the composition of which was independent of the amount of EtMgBr used. They believed, therefore, that the formation of hydrazobenzene occurred at the hydrolysis stage, whilst the formation of gas during reaction was due to the mutual oxidation and reduction of the Grignard alkyl radical.



$$\begin{tikzcd} Ph.N{:}N.Ph + 2EtMgBr \arrow[r] & \begin{array}{c}Ph.NMgBr\\ | \\ Ph.NMgBr\end{array} \arrow[d, "2H_2O"] & + \; 2\dot{E}t \arrow[d] \\ & Ph.NH.HN.Ph & C_2H_6 + C_2H_4 \end{tikzcd}$$

A reaction such as this should be independent of the Grignard reagent used and as confirmation of this the authors reported that MeMgX and PhMgX behaved similarly except that coupling of the radicals occur giving ethane and diphenyl, whilst the use of _iso_butyl bromide resulted in _iso_butylene, _iso_butane, and di-_iso_butyl.

Somewhat similar conclusions were drawn by Gilman and Fothergill (1929)[20]. After experimenting on the constitution of Grignard reagents they arrived at the conclusion that, although the chief constituent of a Grignard reagent was RMgX (existing in equilibrium with R_2Mg),

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

in some cases dissociation may occur

$$RMgX \rightleftharpoons R- + -MgX$$

The existence of MgX was then associated with the formation of benzpinacol from the action of Grignard reagents with benzophenone. A table of results was given showing the variation in yield of benzpinacol with the nature of the Grignard reagent and the condition of use. It would seem from earlier remarks in the authors' paper that the variation in pinacol yield is due to the variation in dissociation and formation of MgX. No reference is made to the reducing capabilities of the radical R.

	Grignard (gm.mol)	Magnesium (gm.atom)	Benzophenone (gm.mol)	Pinacol (%yield)	tert-OH (%yield)
MeMgI	0.2	0.2	0.4	0.057	27.9
MeMgI	0.3	0.3	0.3	3.6	81.3
EtMgCl	0.3	0.3	0.3	0.0	4.5
n-BuMgI	0.3	0.3	0.3	10.0	36.3
n-BuMgI	0.3	0.3	0.3	17.3	26.1
n-BuMgI	0.2	0.0	0.2	0.0	0.0
tert-BuMgCl	0.3	0.0	0.3	0.0	0.0
PhMgBr	0.2	0.2	0.4	0.0	36.9
PhMgBr	0.3	0.3	0.3	Trace	79.3
$PhCH_2MgCl$	0.3	0.3	0.3	0.0	85.2
$PhCH_2MgCl$	0.2	0.2	0.4	0.75	9.5
$PhCH_2MgBr$	0.25	0.0	0.25	0.0	51.0
$Ph_3C.MgCl$	0.03	0.0	0.043	22.0	7.8
$Ph_3C.MgCl$	0.03	0.0	0.043	31.6	4.3

Blicke and Powers (1929)[21], however, also experimenting on benzophenone, included the reducing capabilities of the radical R. They found that with benzophenone

(1) MeMgI gave no benzhydrol
(2) EtMgI gave little benzhydrol
(3) nPrMgI gave benzhydrol corresponding to 50% of the ketone even at 0°.

To account for the formation of benzhydrol they suggested that trivalent carbon radicals are formed as intermediate reaction products and as to be expected of such radicals undergo either addition, mutual oxidation and reduction, or polymerisation.

$$\begin{matrix}R\\ \end{matrix}\!\!>C=O + R_1MgX \longrightarrow \underset{(1)}{\begin{matrix}R\\ \end{matrix}\!\!>C - OMgX} + \underset{(2)}{R_1}$$

$$R_2 \qquad\qquad\qquad\qquad R_2$$

Then

(a) (1) and (2) may unite to give the tertiary carbinol

(b) they may undergo mutual oxidation and reduction to give the secondary carbinol and unsaturated hydrocarbon

(c) polymerisation of (1) may give the pinacol and of (2) the hydrocarbon R'-R'

(d) two R' radicals may react to give saturated and unsaturated hydrocarbons.

They state finally, however, that in all cases it may be possible that molecular addition occurs first.

Noller (1931)[22] explained the well known reducing power of *iso*BuMgBr as due to the dialkyl $Mg(isoBu)_2$. He investigated the action of *iso*BuMgBr on benzophenone in two ways (1) as the ordinary Grignard reagent, (2) after the $MgBr_2$ had been precipitated by 1:4-dioxan. He found that $Mg(isoBu)_2$ solution gave a 64% yield of benzhydrol and that the reaction product was soluble in the ether. With the ordinary Grignard solution, however, a yield of 83.5% benzhydrol was obtained and during reaction a copious precipitate was formed. Thirdly the addition of anhydrous $MgBr_2$ to the solution after reduction by $Mg(isoBu)_2$ gave a copious precipitate.

He concluded that reduction is possible by $Mg(isoBu)_2$

alone to give an ether soluble product $Ph_2CHO.MgOCHPh_2$, but that when the ordinary Grignard reagent is used reduction is caused by the Grignard reagent only even though the solution may consist of 75% Mg(isoBu)$_2$. The reduction product in this case is insoluble in ether and by determination of the benzhydrol : basic hydroxyl group and benzhydrol : halide ratios after the decomposition of the precipitate by water he concluded that the formula of the precipitate was $(Ph)_2.CHOMgBr$.

In discussing this evidence, Noller refers to the work of Schlenk and Schlenk (1929)^{23}, in which evidence was given for the existence of the equilibrium

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

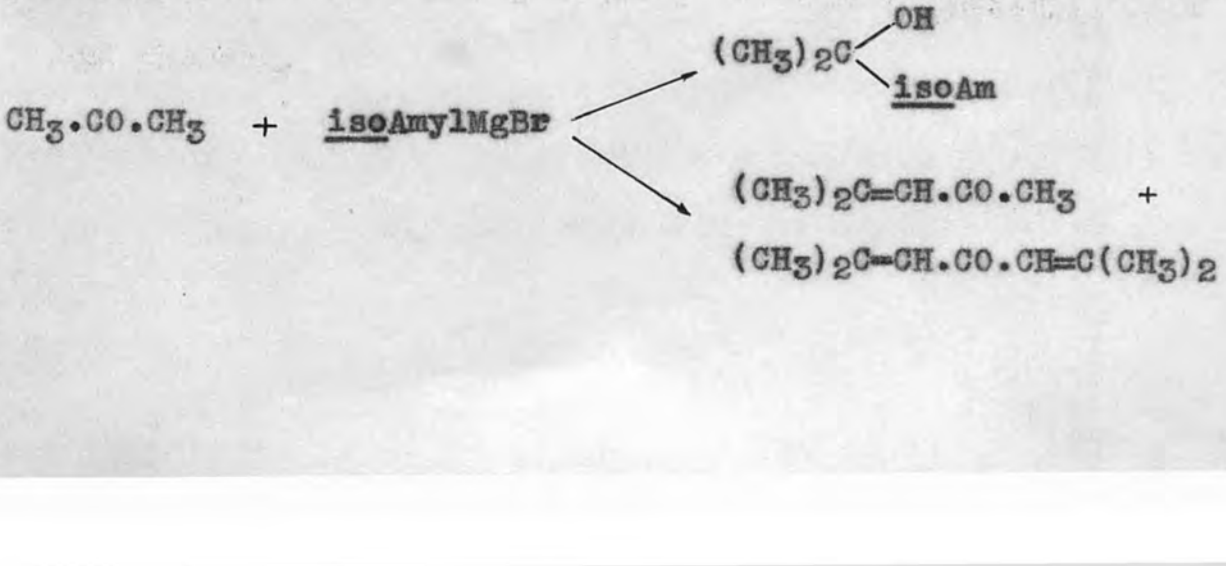
He says he cannot see why in the case of isoBuMgBr which appears to exist in the form Mg(isoBu)$_2$ to an extent of 75% there should be the rapid shift to the RMgX form during reduction when both RMgX and R_2Mg cause reduction. Schlenk and Schlenk indicated that the rate of attaining equilibrium varies with the Grignard reagent. Noller says finally, therefore, that the reactions he has reported are best explained by assuming the equilibrium in solution

$$R_2Mg.MgX_2 \rightleftharpoons R_2Mg + MgX_2$$

and that no isobutylMgBr exists in solution. The precipitate from the benzophenone reaction would then have the formula $(Ph_2CHO)_2Mg.MgBr_2$ since reactions involving the simple formation of addition products would be expected to take place more rapidly than metathetical reactions in a slightly ionizing solvent such an anhydrous ether. With such a formula only MgR_2 would be responsible for reduction.

CONDENSATION AND ENOLISATION

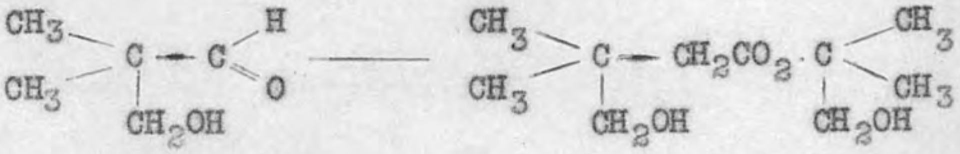
It is rather remarkable that in the time which has elapsed since the first definite recognition of condensation of a carbonyl compound by a Grignard reagent, no intensive investigation of the phenomen has been undertaken. Condensation and reduction were both reported for the first time by Grignard himself in his first paper (1901)[1] on the Grignard reaction. The difference between the attention which has since been given to reduction and the attention which has been given to condensation is considerable. Grignard chemistry began to displace the use and importance of organozinc compounds as synthetic reagents, and in his first paper Grignard says: "an advantage which the use of organomagnesium halides has over the use of organozinc compounds is that with the former secondary reactions are less important. Reactions with ketones of the type $R.CO.CH_3$ are possible, whereas in the Saytzeff reaction, with the exception of allyl methyl ketones, condensation or no reaction occurs." It is in this paper that he records the action of isoamylmagnesium bromide on acetone as giving a 46% yield of the expected carbinol with small amounts of mesityl oxide and phorone.



$$CH_3.CO.CH_3 + \text{isoAmylMgBr} \rightarrow (CH_3)_2C\begin{matrix} OH \\ \text{isoAm} \end{matrix}$$

$$CH_3.CO.CH_3 + \text{isoAmylMgBr} \rightarrow (CH_3)_2C{=}CH.CO.CH_3 + (CH_3)_2C{=}CH.CO.CH{=}C(CH_3)_2$$

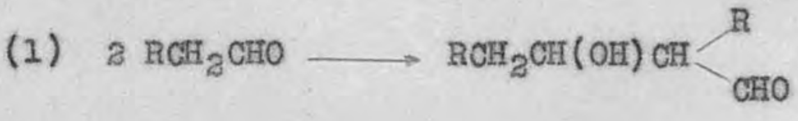
The next report of condensation is given by *Francke and Kohn* (1904)^{24} and on this occasion it is the condensation of an aldehyde. Francke and Kohn found that the action of MeMgBr on α-hydroxymethyl *iso*butyraldehyde gave only an hydroxypivalic ester.



There then seems to have been a gap until 1909, when *Carre* (1909)^{25}, investigating the action of the three xylyl magnesium bromides on carbonyl compounds found that whereas *m*-xylylMgBr and acetone gave the expected tertiary carbinol, the interaction of *o*-xylylMgBr gave only a small amount of the expected tertiary carbinol but a large amounts of polymerisation products consisting chiefly of phorone.

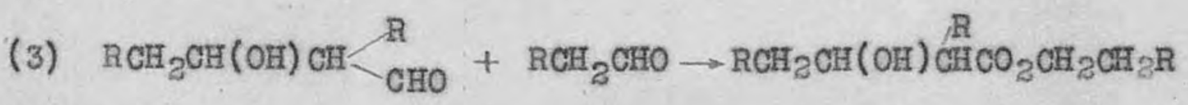
The Alcoholate Theories

Research into carbonyl condensation, however, seems not to have begun until 1923, and in this year there began what one might term the alcoholate theories. The condensation of aldehydes by aluminium alcoholates had been discovered in 1906 by *Tistchenko*^{26}, who found that the product of interaction of an aldehyde and aluminium alcoholate* included (1) the aldol (2) the ester from two molecules of aldehyde (3) the ester from one molecule of aldehyde and one molecule of aldol.



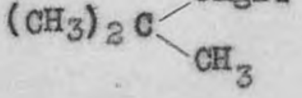
$$(1)\quad 2\,\mathrm{RCH_2CHO} \longrightarrow \mathrm{RCH_2CH(OH)CH}{<}\begin{smallmatrix}\mathrm{R}\\ \mathrm{CHO}\end{smallmatrix}$$

$$(2)\quad 2\,\mathrm{RCH_2CHO} \longrightarrow \mathrm{RCH_2CH_2CO_2CH_2R}$$



$$(3)\quad \mathrm{RCH_2CH(OH)CH}{<}\begin{smallmatrix}\mathrm{R}\\ \mathrm{CHO}\end{smallmatrix} + \mathrm{RCH_2CHO} \rightarrow \mathrm{RCH_2CH(OH)}\overset{\mathrm{R}}{\mathrm{C}}\mathrm{HCO_2CH_2CH_2R}$$

Grignard and Dubiens (1923)[27] drew an analogy between condensation by Grignard reagents and the Tistchenko condensations, which was sufficient at that time to lead to a good deal of work on alcoholate condensation. According to Grignard, the initial reaction between a Grignard reagent and a carbonyl compound is normally the formation of an alcoholate. i.e. if acetone and MeMgBr were the reactants the alcoholate first formed would be magnesium bromo-*tert*-butylate



$$\mathrm{(CH_3)_2C}{<}\begin{smallmatrix}\mathrm{OMgBr}\\ \mathrm{CH_3}\end{smallmatrix}$$

Therefore, said Grignard and Dubiens, it would seem that in the case of condensation by a Grignard reagent condensation is not caused by the Grignard reagent itself but by the alcoholate formed as the first stage of the Grignard reaction. With this

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* Although the term alcoholate is better replaced by the term alkoxide, the present writer proposes to retain the term alcoholate in view of its historical significance in Grignard chemistry. The same applies to the terms enolate and ketolate further on in the text.

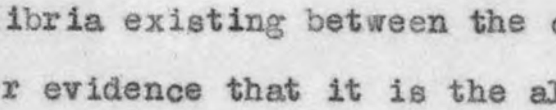
in mind they investigated the action of EtOMgI on butyraldehyde, and on acetone. Interaction of EtOMgI and butyraldehyde gave them ethyl butyrate, butyl butyrate, dibutyraldehyde, and a high boiling residue which was thought to consist of polymers of dibutyraldehyde. The explanation of this result was that the EtOMgI caused the condensation of the aldehyde to the aldol. At the same time there was a slow catalysed Tistchenko reaction giving butyl butyrate. Finally the butyl butyrate and EtOMgI underwent double decomposition, forming ethyl butyrate and BuOMgI.

$$EtCH_2CO_2CH_2CH_2Et + EtOMgI \longrightarrow EtCH_2CO_2Et + C_4H_9OMgI$$

The authors say that apparently the butyl alcohol which should be obtained after the final hydrolysis is lost in the washing processes.

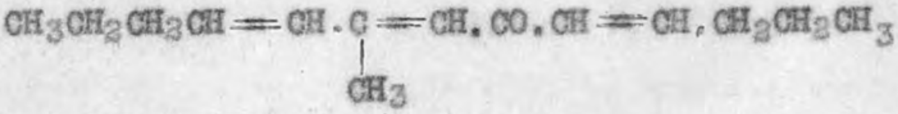
The interaction of EtOMgI and acetone gave only diacetone alcohol and it was said that condensation here was incomplete owing to equilibria existing between the condensing compounds.

As further evidence that it is the alcoholate of the Grignard reaction which causes condensation the authors prepared the alcoholate which would be produced by the interaction of MeMgI and butylideneacetone (i.e.) the iodomagnesium salt of dimethyl-α-pentene carbinol:



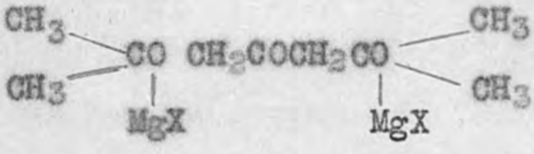
$$CH_3CH_2CH_2CH = CH.C\Big\langle\begin{matrix}OMgBr\\(CH_3)_2\end{matrix}$$

They condensed this with butylideneacetone and obtained the compound



$$CH_3CH_2CH_2CH=CH.\underset{\substack{|\\CH_3}}{C}=CH.CO.CH=CH.CH_2CH_2CH_3$$

This work was continued by <u>Grignard and Fluchaire</u> (1924)[28] These authors recorded the condensation of aldehydes and ketones by halogeno magnesium alcoholates. This paper however mainly recalls the work of Grignard and Dubiens, and adds only that ketols were obtained from methyl ethyl ketone, methyl propyl ketone, and diethyl ketone. In a second short paper (1926)[29] they state that ketone condensation is checked after a while by the condensation products. (i.e.) the ketols formed decompose the alcoholates, and the magnesiumhalogeno-ketolates formed in the decomposition are either inactive or only slightly active. What precisely is meant by the activity is not clear. They say in the case of acetone the trimolecular ketoglycolate formed is active:



$$\substack{CH_3\\CH_3}\!>\!\underset{\substack{|\\MgX}}{CO}\ CH_2COCH_2\underset{\substack{|\\MgX}}{CO}\!<\!\substack{CH_3\\CH_3}$$

They record the ketols of methyl <u>iso</u>butyl, methyl <u>n</u>-amyl, and dipropyl ketones, and of ethylidene and propylidene acetone.

A more detailed investigation was reported in the third paper by <u>Grignard and Fluchaire</u> (1928)[30]. Experiments on the condensation of aldehydes and ketones by magnesium halogeno alcoholates were carried out, and the relative condensing action of several alcoholates was investigated. They observed that as far as aldehydes were concerned some of the aldehyde formed the aldol, some formed the ester, and some reacted with the aldol to form a more complex ester. Of the ketones used they found that those possessing the grouping $-CO.CH_3$ showed the greatest tendency to condense, but it was possible to condense ketones with two polycarbon groups such as in dipropyl ketone. The influence of the alcohol radical was summarised as in the following table:

	% cond^{n}		% cond^{n}
MeOMgI	18	MeOMgCl	5
EtOMgI	20		
PrOMgI	78		
BuOMgI	80	BuOMgCl	65
*iso*AmOMgI	84		
PhCHOMgI	81		

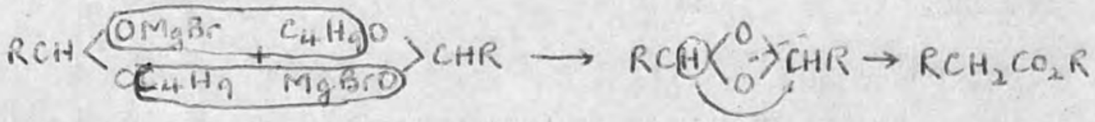
Condensation appeared to increase slightly with the molecular weight of the alcohol and was said to be of the same order for alcohols of the same size. The small yield from MeOMgI and EtOMgI was attributed to the small solubility of the alcoholates. It is only with PrOMgI that solubility becomes appreciable. They concluded that in general the alcoholates of the primary alcohols cause slightly more condensation than the alcoholates of the corresponding secondary and tertiary alcohols. The mechanism by which condensation was believed to occur was presented as follows:

A hemiacetal addition complex is formed between the carbonyl compound and the halogeno alcoholate:

$$RCHO + C_4H_9OMgBr \longrightarrow RCH\begin{matrix} OMgBr \\ OC_4H_9 \end{matrix}$$

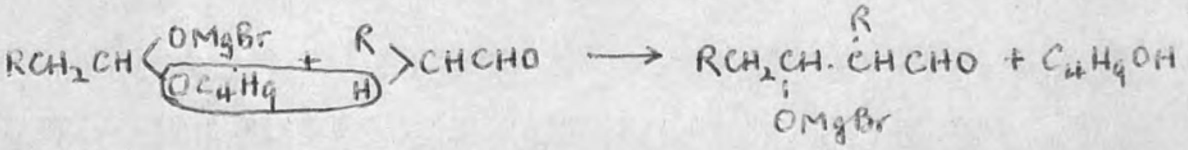
The hemiacetal can react in several ways:

(1) with itself; this was termed a Cannizzaro-Tistchenko reaction.



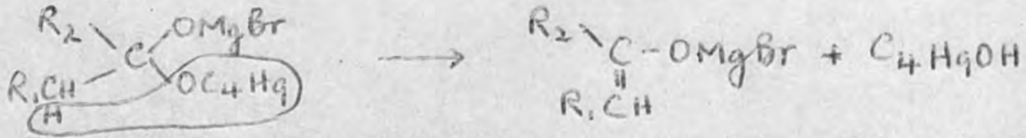
$$RCH\begin{matrix} OMgBr \\ OC_4H_9 \end{matrix} + \begin{matrix} C_4H_9O \\ MgBrO \end{matrix}CHR \longrightarrow RCH\begin{matrix} O \\ O \end{matrix}CHR \rightarrow RCH_2CO_2R$$

(2) with a second molecule of the carbonyl compound; this is aldolisation or ketolisation.



$$RCH_2CH\begin{matrix} OMgBr \\ OC_4H_9 \end{matrix} + \begin{matrix} R \\ H \end{matrix}CHCHO \longrightarrow RCH_2\underset{OMgBr}{CH}\cdot\overset{R}{C}HCHO + C_4H_9OH$$

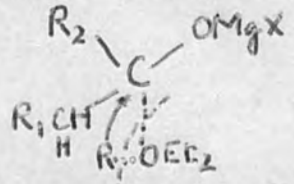
That the catalyst is not regenerated here was said to be due to the greater acidity of the aldol or ketol compared with that of the C_4H_9OH. This reaction was therefore said to be limited. Both reactions (1) and (2) occur with aldehydes but in the case of ketones only reaction (2) occurs. The addition complex was used to explain enolisation of ketones too. (i.e.) an intramolecular elimination occurs:



$$\begin{matrix} R_2 \\ R_1CH \\ H \end{matrix}C\begin{matrix} OMgBr \\ OC_4H_9 \end{matrix} \longrightarrow \begin{matrix} R_2 \\ R_1CH \end{matrix}C{-}OMgBr + C_4H_9OH$$

Recognition of enolisation was already well established when Grignard and Savard (1927) [31] carried out a systematic investigation of the enolisation of pulegone. Their investigation included the action of a series of Grignard reagents on the ketone. It was found that in all cases the yield of carbinol was mediocre, nearly all the pulegone being recovered, except in those cases in which condensation occurred, which was attributed to the influence of the initial stage alcoholate. Since the extent of ketone recovery varied with the Grignard reagent used and the conditions of reaction, the behaviour could not be attributed to the reactivity of the enolic form of the ketone but to the enolising action of the Grignard reagent. Another factor in favour of this opinion was that pulegone was found not to react as an enol with organo-zinc compounds.

Enolisation was explained by the formation of an oxonium complex and its ability to decompose in two ways; (i.e.) in normal addition the R group in the complex



migrates to the C atom of the carbonyl group, but in enolisation it extracts a hydrogen atom from the CH_2R grouping, giving the hydrocarbon RH and the enolate $R_1CH{=}C\genfrac{}{}{0pt}{}{\diagup OMgX}{\diagdown R_2}$
The reaction occurring in any case was said to depend on the operating conditions, the nature of the Grignard reagent, and that of the ketone, which vary the stability of the complex and the relative speeds of the two reactions.

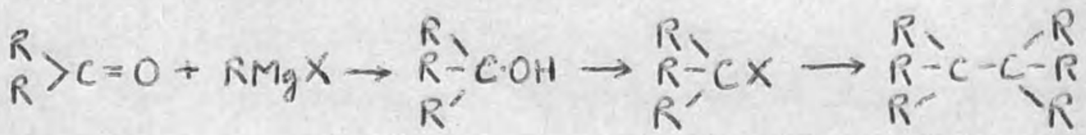
The extent of enolisation caused by the Grignard reagents used is given below: (Figures indicate % enolisation by RMgX)

R	RMgCl	RMgBr	RMgI
Me		33	26
Et	50	47	40
n-Pr		56	45
n-BU		59	45
n-Am		60	47
isoPr		100	72
isoBu		54	40
secBu		100	-
tertBu		100	-
isoAm		72	-
Ph		41	35
Benzyl		44	39

and it was concluded from these results that (1) enolisation of pulegone diminishes with increasing atomic weight of the Grignard halogen (2) enolisation increases with increasing reaction temperature (3) concentration does not influence enolisation but condensation diminishes with dilution.

INFLUENCE OF COMPLEXITY & STERIC HINDRANCE

The influence of the complexity of the groups constituting the reactants in a Grignard reaction was first stressed and critically investigated by Conant & Blatt (1929)[32]. This paper seems to be the turning point in the aim to which research into the mechanisms of Grignard reactions was devoted. For although a mechanism of reaction is not proposed in this paper, the way in which the results of a number of particular reactions is presented, and indeed, the way the reactions for discussion were chosen, indicates that a relationship was believed to exist between the products of reaction and the structure of the reactants. The work of Conant and Blatt arose from the difficulties encountered in attempting to synthesise complex tertiary alcohols. They desired to prepare hexa-alkylethanes as indicated below:



$$\begin{matrix}R\\R\end{matrix}\!>C=O + RMgX \rightarrow \begin{matrix}R\\R-C\cdot OH\\R'\end{matrix} \rightarrow \begin{matrix}R\\R-CX\\R'\end{matrix} \rightarrow \begin{matrix}R\quad\;\;R\\R-C-C-R\\R'\quad\;\;R\end{matrix}$$

Where R was a secondary or tertiary group however the stage $R_3C.OH$ was never reached for it was found that when highly branched compounds were used the normal Grignard reaction ceased to be the main reaction, so much so, that when all three radicals of a proposed tertiary alcohol were either secondary or tertiary no normal reaction occurred. Conant and Blatt therefore tabulated as below their own results with results which had already been reported by other workers.

In this table A E R and C refer to normal addition, enolisation, reduction, and condensation. Where the yield of a particular product exceeded 50% this is indicated by doubling the letter indicative of the type of reaction by which the product was obtained. The results which were taken from papers by other workers are so indicated.

	MeMgI	n-PrMgBr	isoPrMgBr	n-Bu MgBr	tertBu MgBr
$(CH_3)_2CHO$	AA a		A		AA
$(CH_3)_2CH.CHO$	A b		AA		AR
$(CH_3)_3C.CHO$		AA d	RA d		RRdd
$CH_3.CO.CH_3$	AA a		AA e		A b
$CH_3CH_2.CO.CH_2CH_3$	AA g		AA g	AA	C
$CH_3.CO.CH(CH_3)_2$	AA g		AARg		

$CH_3.COC(CH_3)_3$	AA f	EC	AR	EC
$(CH_3)_2CH.CO.CH(CH_3)_2$	AA g	RR		RR
$(CH_3)_2CH.CO.C(CH_3)_3$	AA	RR		RR
$(CH_3)_3C.CO.C(CH_3)_3$	AA	R		RR
$(CH_3)_2CH.CO_2Et$		RR g		
$(CH_3)_3C.CO_2Et$				no reaction
$PhCh_2CO_2Et$		EECC		

(a) Grignard (A.ch.phys.1901(7),24,464)
(b) Pickard & Kenyon(J.C.S.1912,101,628)
(c) Conant et al (J.A.C.S.1929,51,1246)
(d) Ziegler (Ann.1924, 437,244)
(e) Henry(Bl.Soc.roy. belg.1906,352)
(f) Stas(Bl.Soc.chim. belg.1926,35,379)

From these results Conant and Blatt drew the following conclusions: (1) which of the four major reactions resulting from the interaction of a Grignard reagent and a carbonyl compound will occur in a given case depends on the nature of the groups in both the Grignard reagent and the carbonyl compound. Although the addition reaction seems to predominate in reactions involving primary groups, complications arise when branched alkyl groups are present in either or both of the reactants. (2) tertiary alcohols containing more than two secondary or tertiary groups cannot be prepared. E.g.

isobutyrone + isoPrMgBr
$(CH_3)_2CH.CO.CH(CH_3)_2$
isobutyrone + tertBuMgCl

80% yield of
$(CH_3)_2CH.CH(OH).CH(CH_3)_2$

(3) the amount of reduction product increases not only with the size of the alkyl group in the Grignard reagent but also with its complexity.

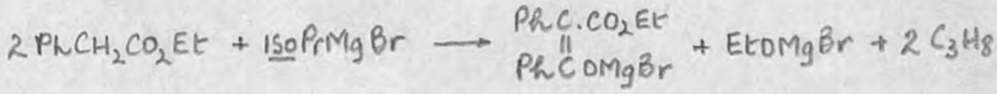
	MeMgI	n-PrMgBr	n-BuMgCl	tertBuMgCl	
pinacolone	0	20	30	-	% reduction
isobutyrone			13	80	"

(4) the amount of reduction similarly increases with the size and complexity of the groups in the carbonyl compound.

	Et.CO.Et	$(CH_3)_2CH.CO.CH(CH_3)_2$	$(CH_3)_3C.CO.CH_3$	
n-BuMgBr	0	13	30	% redn.

(5) enolisation and reduction would appear to be limited to those ketones which contain a CH_3 group or a CH_2 group adjacent to the carbonyl group.

(apart from the considerable condensation or phenylacetic ester



$$2\,PhCH_2CO_2Et + \underline{iso}PrMgBr \longrightarrow \begin{array}{c} PhC.CO_2Et \\ \| \\ PhC\,OMgBr \end{array} + EtOMgBr + 2\,C_3H_8$$

they did not isolate or identify any other condensation product, but considered high boiling products under this name)

(6) any discussion of mechanism must largely be a restatement of experimental facts. It seemed however that the most satisfactory way of interpreting Grignard reactions was as follows: The A reaction decreases with increasing size of the groups and their complexity. When the A reaction is sufficiently slowed down, other reactions normally too slow to be observed and which are less subject to steric hindrance become predominant. When hindrance to A is great and the structure of the ketone cannot lead to R and E then no reaction occurs.

<u>Grignard & Blanchon</u> (1931)^{33} tried to establish a relationship between the constitution of a ketone, the extent of its enolisation by a Grignard reagent, and the stability of the enol. Although a relationship could not be established

some important conclusions were drawn.

The extent of enolisation was measured by the volume of saturated gas liberated during the reaction, whilst the stability of an enol was measured by isolating the enol as the acetate, hydrolysing with oxalic acid, and then measuring the percentage enol in the keto-enol mixture obtained. The enol acetate was obtained by adding acetyl chloride to the Grignard-ketone reaction mixture.

The measurement of saturated gas was not believed to indicate the full extent of enolisation in every case, since they found in certain cases that the evolution of gas was slow and occupied several hours. E.g. with menthone although evolution started immediately it continued for over two hours, and with butyrone gas was evolved for 0.75 hour. (In this respect it should be noted that the Grignard reagent was added in excess and in bulk to an ethereal solution of the ketone) Some of their results are given in the table below: Figures represent % enolisation.

	RMgCl	RMgBr	RMgI
Methyl			7.5 7.5
Ethyl		6.9 6.8	7.2 7.5
Propyl		8.7 8.3	8.2 8.5
Butyl		6.3 6.3	5.8 5.1
*iso*Propyl		15.8 16.3	15.9 15 6

*iso*Butyl		13.9 13.7	14.1 13.8
*tert*Butyl	19.7 20.4		

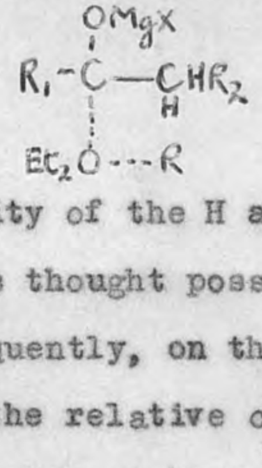
The authors concluded from their results and from consideration of the results Grignard and Savard obtained with pulegone that (1) although supplementary negative groups may favour enolisation, enolisation is possible without such groups. The presence of a double bond, above all if it is conjugated with the carbonyl group, favours enolisation. (2) Grignard chlorides cause less enolisation than bromides and iodides, whilst generally the iodides cause slightly less enolisation than bromides. (3) raising the temperature of the reaction mixture increases the extent of enolisation but usually only slightly.

The mechanism of enolisation accepted by Grignard and Blanchon is that suggested earlier by Grignard; i.e. one of complex formation and subsequent decomposition. The possibility that interaction may occur between a Grignard reagent and the enolic form of a ketone was not acceptable to them, for they measured first the initial enol content of the ketones used:

Acetone	0%	*Cyclo*hexanone	8.2
Butyrone	0%	*p*-Me*Cycl*ohexanone	6.3
Dibutylketone	0%	Menthone	0
Dibenzylketone	0%	Carvone	0
Acetophenone	0%	Thujone	0
*Cycl*opentanone	0%	Mesityl oxide	6.3

and found that although the ketones which already existed to some extent in the enolic form figured among those ketones undergoing much enolisation, so did butyrone and menthone which contained no enol. It seemed therefore that, if the initial presence of enol did not give rise to higher enolisation, it was not possible to invoke the great reactivity of a liberated enol and its regeneration by displacement of equilibrium. Moreover if it were possible it seemed that the extent of enolisation should be independent of the Grignard reagent.

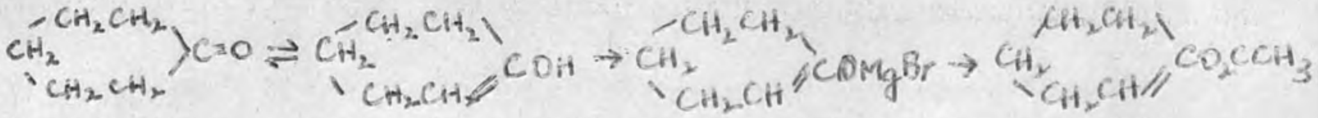
Therefore they were bound to conclude that the already proposed oxoniumcomplex mechanism was correct. The oxonium which was first formed decomposed in a way depending on the aptitude of R to give or accept a hydrogen atom,



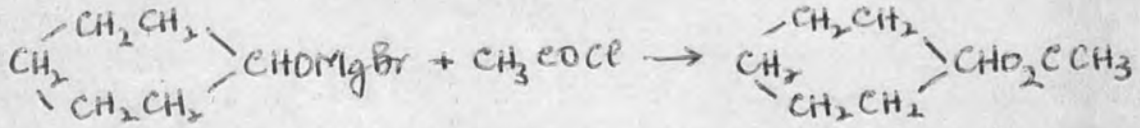
$$\begin{array}{l} \quad\;\; OMgX \\ \qquad | \\ R_1-C-\underset{H}{C}HR_2 \\ \qquad \vdots \\ Et_2O\cdots R \end{array}$$

and on the mobility of the H atom near the carbonyl group. This mobility was thought possibly to depend also on the OMgX group and, consequently, on the halogen. Final equilibrium might depend on the relative concentrations of the alcoholate and enolate, and also on temperature, the raising of which enhanced the evolution of gas, and therefore might increase the extent of enolisation.

The conclusion by Grignard and Blanchon[33] that the action of *iso*PrMgBr on some saturated ketones resulted in the formation of enolates which reacted as true enolates was invalidated by *Kohler and Thompson* (1933)[34]. Grignard and Blanchon described the product from the addition of acetyl chloride to the enolate of *cycl*ohexanone as *cycl*ohexenyl acetate.

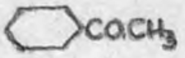
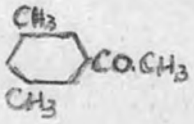
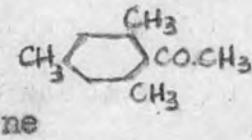
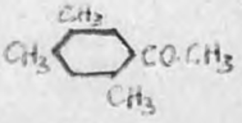
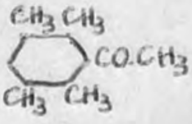
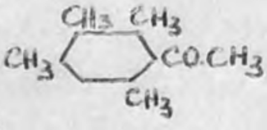
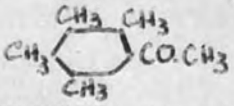
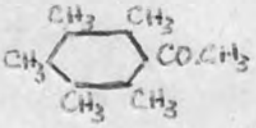
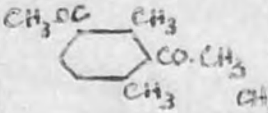
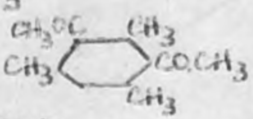
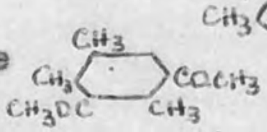
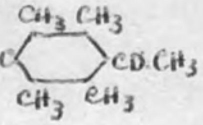
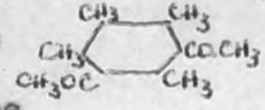
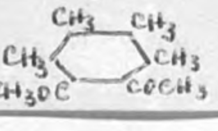


Kohler and Thompson however obtained only cyclohexyl acetate from this reaction. They therefore allowed *iso*PrMgBr to react with *cycl*ohexanone in as nearly as possible the same conditions as in the experiments of Grignard and Blanchon, and found the only products to be those of reduction and condensation. (i.e.) they obtained a 68% yield of *cycl*ohexanol and a 26% yield of *cycl*ohexylidene*cycl*ohexanone. Presumably therefore the *cycl*ohexyl acetate is formed from the interaction of the *cycl*ohexylate and acetyl chloride:



They concluded that (1) Grignard and Blanchon identified the reaction products incorrectly, (2) in reality it is not enolisation which is favoured by raising the temperature but reduction, since they obtained a 28% yield of *cycl*ohexanol at -5^{0}, (3) Grignard reagents containing secondary or tertiary groups frequently act as condensing and reducing agents, but there was no evidence to suggest that they were any more effective in inducing enolisation than others, (4) there was no evidence that any Grignard reagent could convert a monoketone into a enolate unless hindrance prevented addition.

Smith and Guss (1937)[35], like Kohler and Thompson, were of the opinion that the nature of the Grignard reagent had no influence in causing enolisation. Using a Kohler "Grignard machine", and working in xylene solution, they examined the enolisation caused by MeMgBr in a number of hindered ketones. From their results they concluded that enolisation was mainly a function of hindrance in the ketone, since only when hindrance was at a maximum, i.e. when both o-positions were methylated, was 100% enolisation realised. When only one o-position was methylated the extent of enolisation was affected by the positions of the other groups in the benzene ring. In the diketones however the positions of the acetyl groups did not affect the extent of enolisation. The following is a tabulation of their results:

		%E	%A
Acetophenone		2.5	102.5
Aceto-m-xylene		5	102
Acetomesitylene		103	0
5-acetopseudocumene		25	79
Acetodurene		97	4
Acetoisodurene		94	7
Acetoprehnitene		75	27
Acetopentamethylbenzene		93	1
Diaceto-m-xylene		8	81
Diacetomesitylene		91	13
Diacetopseudocumene		88	22
Diacetodurene		81	27
Diacetoisodurene		86	24
Diacetoprehnitene		84	23

Further evidence of the great influence of steric hindrance on the course of the Grignard reaction is given in a series of papers by Whitmore and co-workers.

Whitmore and George (1942)[36] invalidated the conclusion drawn by Smith and Guss that enolisation was primarily a function of hindrance in the ketone, the branching of the chain in the Grignard reagent being of minor importance. In an investigation of the enolisation of di*iso*propyl ketone, Whitmore and George found that enolisation varied from 0% with MeMgBr to 90% with neopentylMgBr, and reduction from 0% with MeMgBr to 78% with *iso*BuMgBr. By consideration of the extents to which A, E, and R took place in the action of various Grignard reagents on di*iso*propyl ketone, and, in some cases, measuring and identifying the gases evolved during reaction, they concluded that reduction is a function of the hydrogen atoms on the β carbon atom of the Grignard radical. Their results are tabulated below:

	A	E	R	Structure	No. & type of H on β C
MeMgBr	95	0	0	CH_3	none.
EtMgBr	77	2	21	CH_3CH_2	3 primary.
n-PrMgBr	36	2	60	$CH3CH_2CH$	2 secondary.
*iso*PrMgBr	0	29	65	$(CH_3)_2CH$	6 primary.
*iso*BuMgBr	8	11	78	$(CH_3)_2CHCH_2$	1 tertiary
neoPenMgCl	4	90	0	$(CH_3)_3C.CH$	none.

That is, where there is no β C or no H on the β C there is no reduction. The greatest aptitude for reduction is shown by *iso*Bu which has one tertiary H on the β C atom, whilst the lowest is shown by Et which has three primary H on the β C atom. The slight increase in reduction between the two propyl groups was attributed not only to the β C effect but to steric hindrance too.

Whitmore and George record:

(1) 2 mols di*iso*propyl ketone + 2 mols *iso*PrMgBr gave 43.6 L of gas, which is a 97.2% theoretical yield based on the yields of enolisation and addition. Passage through 82.5% sulphuric acid and explosion of the unabsorbed gas showed a composition of 63.4% propylene and 33.8% propane.

(2) 4.5 mols di*iso*propyl ketone + 5 mols *iso*BuMgBr gave 90.3L gas, which is 98.4% theory. Analysis showed 88.4% butylene and 9.6% *iso*butane.

The application of steric factors to the course of the Grignard reaction was continued by *Whitmore and Lewis* (1942)[37], who showed that enolisation occurred to a great extent even with MeMgBr when the carbonyl compound contained highly branched groups. They investigated 15 carbonyl compounds and concluded from their results that enolisation is dependent on the nature of the substituents on the C atom adjacent to the carbonyl group, whereas substitution on the β C had no noticeable affect on the reactivity of the carbonyl group. Their results are given below:

Compound	% Enol^{n}.	% Add^{n}.
$Et_3C.CO.Me$	94	0
$Et_2CH_3C.CO.Me$	84	0
$EtMe_2C.CO.Me$	14	74
$Me_3C.CO.Me$	5	86
$Me_3C.CH.CO.Me$	0	100
$Et_3C.CO.CH_2CHMe_2$	85	0
$Et_3C.CO.CH{=}CH_2$	0	58

$Et_3C.CO_2Et$	0	0
$Et_3C.CO_2Me$	0	0
$Et_2CH_3C.CO_2Et$	25	45
$Et_2CH_3C.CO_2Bu$	22	60
$EtMe_2C.CO_2Et$	0	100
$Et_3C.CO.CH_2CH_2OH$	58	27
$(Et_3C.CO)_2CH_2$	91/2	55/2
$(Et_3C.CO)_2CHCH_2$	79/2	19/2

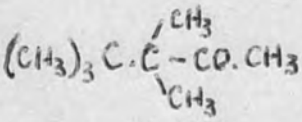
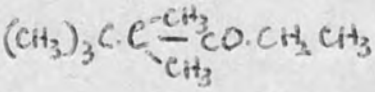
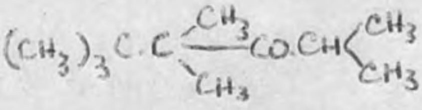
In the case of $Et_3C.CO.Me$ they isolated the pseudo-enolate* $Et_3C.CO.CH_2MgBr$ and showed this to act as a true Grignard reagent in that it reacts

(1) with CO_2 to form the keto acid $Et_3C.CO.CH_2CO_2H$

(2) with formaldehyde to form the ketol $Et_3C.CO.CH(OH)CH_2$

(3) with triethyl acetyl chloride to form the diketone $Et_3C.CO.CH_2CO.CEt_3$

By increasing the size and complexity of the groups adjacent to the carbonyl group Whitmore and Randall (1942)[38] obtained more evidence of extensive enolisation. Using a Kohler type "Grignard machine" they obtained by the action of EtMgBr enolisation of the following three tertbutylneopentyl ketones:

		% Enolⁿ.	% Addⁿ.
(1) Methyl	 $(CH_3)_3C.C(CH_3)_2-CO.CH_3$	94	0
(2) Propyl	 $(CH_3)_3C.C(CH_3)_2-CO.CH_2CH_3$	57	0
(3) isopropyl	 $(CH_3)_3C.C(CH_3)_2CO.CH(CH_3)_2$	25	0

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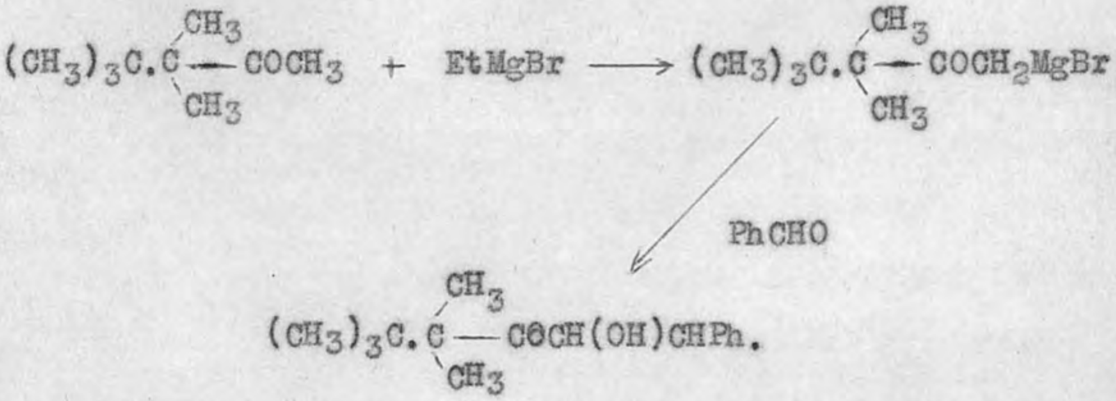
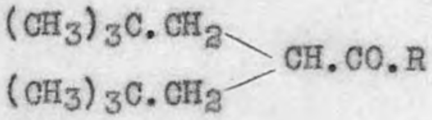
* The present writer proposes to use the term "pseudo-enolate" for compounds of this type

The pseudo-enolate of (1) was obtained as a precipitate and was shown to act as an ordinary Grignard reagent by its ketol formation with benzaldehyde.



$$(CH_3)_3C.\overset{CH_3}{\underset{CH_3}{C}}-COCH_3 + EtMgBr \longrightarrow (CH_3)_3C.\overset{CH_3}{\underset{CH_3}{C}}-COCH_2MgBr \xrightarrow{PhCHO} (CH_3)_3C.\overset{CH_3}{\underset{CH_3}{C}}-COCH(OH)CHPh.$$

This dependency of enolisation on the second group of the ketone even when the first group has a structure associated with high steric hindrance was shown too by <u>Whitmore and Lester</u> (1942)[39]. They prepared five dineopentyl ketones



$$\left.\begin{matrix}(CH_3)_3C.CH_2 \\ (CH_3)_3C.CH_2\end{matrix}\right\rangle CH.CO.R$$

in which R was successively Me, Et, Ph, <u>o</u>-tolyl, and <u>p</u>-tolyl, and found that the Me and Et ketones gave quantitative enolisation even with highly branched Grignard reagents which frequently cause reduction. With MeMgBr however the Ph, <u>o</u>-tolyl, and <u>p</u>-tolyl ketones gave quantitative addition, and it was concluded that if the second group of the ketone does not contain a labile H atom enolisation cannot occur and normal addition results. They prepared the <u>pseudo</u>-enolates of the Me and Et ketones and showed them to act as true Grignard reagents by forming ketols with benzophenone:

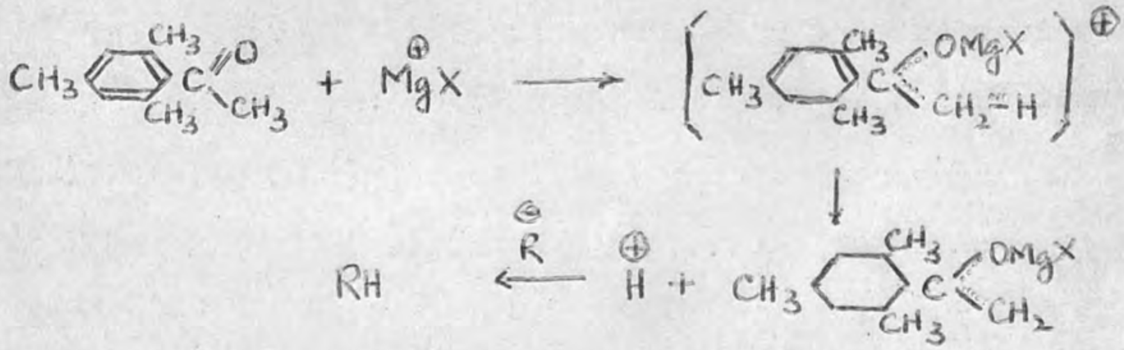
$(Np)_2CH.CO.CH_2MgBr + Ph_2C{=}O \longrightarrow (Np)_2CH.CO.CH.C(OH).Ph_2$

Although Whitmore *et al.* established that steric hindrance promotes enolisation, *Whitmore and Block* (1942)[40], by working on simpler ketones, concluded that steric hindrance around the C atom of the carbonyl group retards both addition and enolisation. Using MeMgBr, and assuming condensation to be negligible, they obtained the results summarised below:

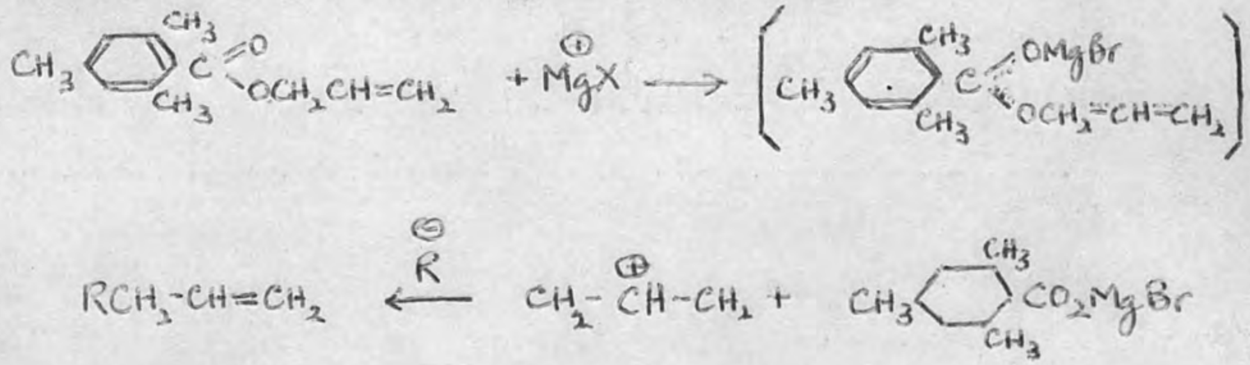
	% Enol^n.	% Add^n.
Me.CO.*iso*Pr	0	100
Et.CO.*iso*Pr	0	100
Me.CO.*tert*Bu	5	86
Et.CO.*tert*Bu	9	86
Me$_5$acetone	0	49
Me.CO.pinacolyl	48	47
Et.CO.pinacolyl	62	33
Me.CO.*sec*Bu	32	-
Pr.CO.*sec*Bu	53	40
2:2Me$_2$4-Et-3hexanone	5	19
2:2:4:6:6:-Me$_5$3:5-heptadione	13	64

Electromeric Influences

The first indication of an electromeric influence of substituents appears to come in a paper by *Arnold and Liggett* (1941)[41], but the explanation given is incomplete, since it is one of effect and not cause. They say that the reaction between sterically hindered ketones and Grignard reagents to form enolates and hydrocarbons may not necessarily be preceded by simple enolisation of the ketone. A more probable mechanism involves the coordination of a halomagnesium cation, MgX, with the carbonyl oxygen followed by direct ionisation of a proton from the α C atom. E.g. with acetomesitylene:

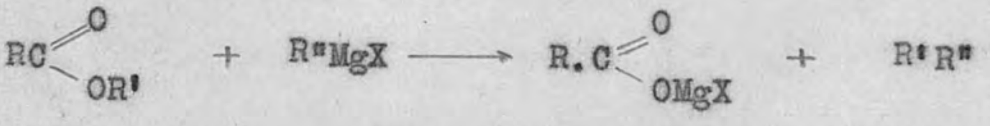


Assuming that the thermodynamic stability of the resonating systems allyl, benzyl, and crotyl should enable them to act similarly to a proton, the authors studied the reaction of sterically hindered allylic esters with a Grignard reagent and obtained the allylic hydrocarbon corresponding with RH of the usual cases. With allyl isodurylate and PhMgBr they obtained a 67-70% yield of allyl benzene, and with o-tolylMgBr they obtained a 67-70% yield of o-Me-allyl benzene.



The analogous reaction with allyl benzoate gave however only the normal addition product in yields of 86% and 68% respectively, which led these authors to the conclusion that only in sterically hindered ketones will the loss of a proton (and of the allyl radical) occur.

Some indication of the cause is given in a second paper by Arnold and Liggett (1942)[42] in which the dependency of the nature of the groups in the ester is described. It is said here that the reaction



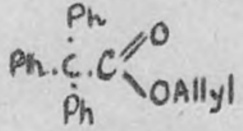
$$RC\begin{matrix}\diagup O \\ \diagdown OR'\end{matrix} + R''MgX \longrightarrow R.C\begin{matrix}\diagup O \\ \diagdown OMgX\end{matrix} + R'R''$$

will only occur if (1) the group R' is sufficiently thermodynamically stable as the cation $\overset{+}{R}'$, and (2) the group R presents sufficient steric hindrance to the carbonyl group. If, however, R' has little tendency to form a cation but on the other hand the group -OR' will readily form an anion then the following reaction occurs:

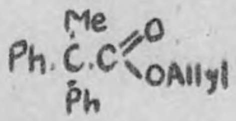
$$R.C\begin{matrix}\diagup O \\ \diagdown OR'\end{matrix} + R''MgX \longrightarrow RC\begin{matrix}\diagup O \\ \diagdown R''\end{matrix} + R'OMgX$$

To illustrate this PhMgBr was made to react with the following allylic esters

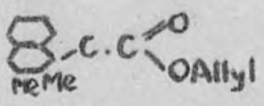
(1)



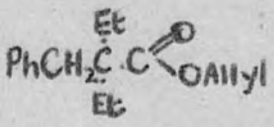
(2)



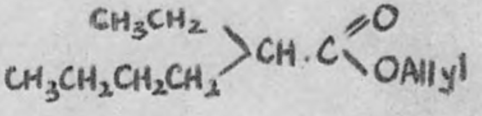
(3)



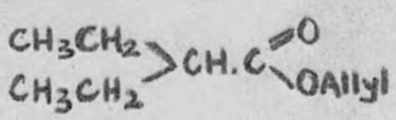
(4)



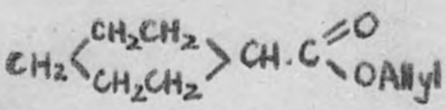
(5)



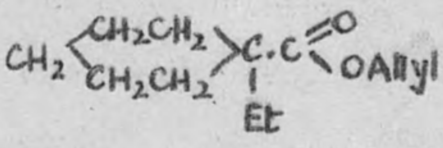
(6)



(7)



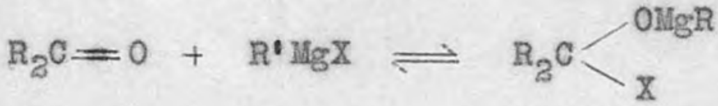
(8)



With (1), (2), (3), and (4) complete cleavage of the O-allyl bond occurred. With (7) and (8) complete cleavage of the C-Oallyl bond occurred. With (5) and (6) both reactions were said to proceed at comparable rates.

They concluded that in (1), (2), (3), and (4) the groups corresponding with R highly hindered the carbonyl group. With regard to (8) they said that although the Et group usually offers considerable steric hindrance owing to the area through which the Me component can freely rotate, the rigidity of the ring system in (8) prevents free rotation and as a consequence there is no steric hindrance.

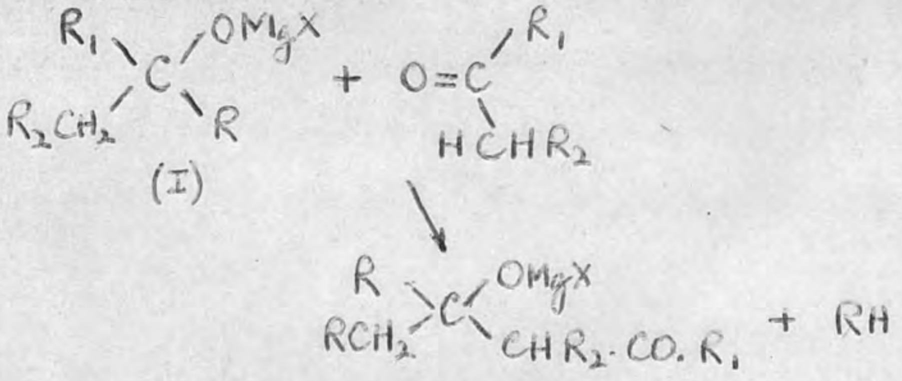
Whereas it was the custom in the past years to argue between an addition mechanism and an ionic mechanism for explaining the abnormal reactions of the Grignard reagent, Evans and Pearson (1942)[43] used the abnormal reactions as evidence for the ionic nature of the Grignard reagent. Their paper consists mainly of conductivity measurements and transport studies on a number of Grignard reagents, but in a section headed "chemical evidence" it is said that:- "In the majority of its reactions the Grignard reagent behaves as an $\bar{R}$ anion and $\overset{+}{Mg}X$ cation. The anion with its unshared pair of electrons goes on to an atom with an open sextet, and the cation adds on to an atom with an unshared pair of electrons" ..... Instead of an atom with an open sextet an ionisable H may furnish the necessary orbital for the unshared pair of the anion in which case the anion acts as a base. The H ion may come from an OH, SH, NH, or an activated CH. The behaviour of the Grignard reagent in enolisation and condensation is due to this reaction. The reducing effect of Grignard reagents is particularly noticed in the case of highly branched $\bar{R}$ anions and branched chain carbonyl compounds. Here, due to steric factors, a hydride ion, $\bar{H}$, adds to the carbonyl group giving a reduction product and an olefin....The reaction is carried to completion by the irreversibility of the formation of a C-C or C-H bond. Because of this only the $\bar{R}$ anion seems to react.....Actually, (because of the dissociation $RMgX \rightleftharpoons \overset{+}{RMg} + \bar{X}$) the anion $\bar{X}$ must be undergoing the same reactions but to a lesser degree owing to the lower basicity of the halide ion compared with an alkide ion



$$R_2C{=}O + R'MgX \rightleftharpoons R_2C\begin{matrix} \diagup OMgR \\ \diagdown X \end{matrix}$$

In such cases, however, the reaction is readily reversible because of the lability of a C-X bond α to an oxygen atom."

On the other hand, however, <u>Dubois</u> (1947)[47] reiterates the prior addition mechanism of condensation. Dubois' interpretation is that normal addition occurs and that if conditions are such that the addition reaction is slow there is enhanced opportunity of unreacted ketone reacting with the addition complex to form the ketol (i.e.)



The stability of the addition complex (I) is described as a function of steric effects and the polarity of the groups R_1, and R_2 and R.

In the following results for the condensation of pinacolone to 2:2:5:6:6-pentamethylheptanol-5-one-3

	MeMgBr	EtMgBr	<u>n</u>-PrMgBr	<u>iso</u>PrMgCl
%	6	7.5	19	62

the increase due to <u>iso</u>PrMgCl is attributed to the slowing down of the addition reaction by the steric hindrance of the <u>iso</u>Pr group.

Dubois explains also the increase in condensation by going from <u>iso</u>PrMgBr to <u>iso</u>PrMgCl:

	<u>iso</u>PrMgBr	<u>iso</u>PrMgCl
% ketol	30	62

as due to the slowing down of the addition reaction this is said to be due to the decrease in reactivity of chlorides.

<u>Dubois</u> (1947)[45], discussing the condensation of ketones by Grignard reagents, says: "one can no longer maintain the hypothesis that the enol of the ketone, or the tertiary alcohol, or the alcohol of reduction act in the form of magnesium

alcoholates, even though the latter are condensing agents. In fact one can condense diethyl ketone without difficulty using <u>iso</u>propylmagnesium chloride, but one obtains only six to eight grams of the ketol in ninety hours when a magnesium alcoholate is used."

The following law is then given: "When a ketone condenses to a ketol, the group CH_3 gives hydrogen to the receptive molecule more easily than the group CH_2, and the latter more easily than the group CH."

PART II

GRIGNARD REACTIONS

RESULTS

When the following series of reactions were started, it was intended to isolate and identify the products of the abnormal action of a number of Grignard reagents on a number of ketones, and also to find if there were a correlation between the quantities of the abnormal reaction products and the quantities of the gases evolved during reaction. The Grignard reagents chosen were:

n-propylmagnesium bromide
*iso*propylmagnesium bromide
n-butylmagnesium bromide
*iso*butylmagnesium bromide
sec-butylmagnesium bromide
tert-butylmagnesium bromide

and the ketones chosen were:

methyl ethyl ketone
methyl *n*-propyl ketone
methyl *iso*propyl ketone
methyl *n*-butyl ketone
methyl *iso*butyl ketone
methyl *tert*-butyl ketone
methyl *n*-amyl ketone
di-*iso*propyl ketone
di-*iso*butyl ketone

The scheme undertaken was to cause the interaction of the Grignard reagents and ketones under specific conditions, to measure the amount of gas evolved and to determine the saturated and unsaturated components, to fractionate the liquid products of the reactions, and to find whether there was an exact relationship between the liquid products and the gases evolved.

The gas evolved in a reaction was collected by freezing out in traps immersed in ethanol/CO_2 baths at - 72°, and, after the reaction had run its specific time, allowing the gas to boil into a calibrated brine aspirator, from which it was forced by brine inflow, through sulphuric acid, into another brine aspirator.

The liquid products were fractionated through a 12 inch column packed with Fenske helices, and fitted with a total-reflux-variable-take-off still head. The fractional distillates were collected in small tared test-tube receivers made to fit the standard joint of the take-off. This permitted a reasonably accurate weighing of each fraction, and the measurement of the refractive indáx of small amounts of distillate.

However, it was soon found that an exactly quantitative correlation between liquid product and evolved gases could not be made. The reason for this lay entirely with the fractionation of the liquid products. For although what might be called large quantities of reagents for such a series of reactions were used, the amount of product obtained from a reaction was in the region of 90 to 130 gm. This meant that a restriction was placed on the size of the column to be used. Each reaction gave a product consisting of four or five compounds. That is, the product could contain (1) the original ketone, (2) the secondary carbinol, (3) the tertiary carbinol, (4) the ketol, and (5) the dehydrated ketol. Three other possible constituents were (6) small amounts of ether, (7) small amounts of olefin if the tertiary carbinol had broken down slightly, and (8) water from the breakdown of tertiary carbinol and ketol.

Apart from these factors, the nature of the products made fractionation more difficult. It was necessary to fractionate the tertiary carbinol and ketol at reduced pressure. In many cases the boiling point of the tertiary carbinol prevented fractionation at the low pressure needed for the ketol, so that a water pump pressure had to be used for the tertiary carbinol, and a "hivac" pressure for the ketol. This meant that there was some incomplete separation in the change over region from water pump to "hivac". The use of vacuum distillation, moreover, meant that some material must be carried over to the freeze trap in the vacuum line.

Again, the use of reduced pressure meant that the unchanged ketone and secondary carbinol in a product must be removed first, for their boiling points would not permit the use of too low a pressure. To accomplish this separation the ketone and secondary carbinol were, in most cases, removed under reduced pressure through a six inch column packed with Fenske helices, but through a Kon trinagle set-up, the received of which was immersed in a trap at -40°. The vacuum line was arranged to go through this receiver, so that no vapours could by-pass the trap. Once again however, there could be no exact separation at the boundary regions. This meant that since the ketone and secondary carbinol were later fractionated at atmospheric pressure, any tertiary carbinol that may have come over stood the chance of being dehydrated, and that any ketone or secondary carbinol that did not come over stood the chance of being carried through the vacuum line when the remainder of the product was fractionated at reduced pressure.

This so far indicates that complete separation of constituents might have been possible but for the small amounts left at the boundary regions. This of course was not so, since the restriction on column size hindered complete separation anyway.

Although it was not feasible to construct refractive inddx charts for mixtures of constituents owing to the number of variables, some indication of the constitution of the boundary region distillates is given by the progression of the refractive index. This is used for comparing the results of some ketone-secondary carbinol fractionations. (A gradual change in refractive index is most noticeable for the change from dehydrated ketol, the refractive indices of which are of the order of 1.5, to higher boiling ketol, the refractive indices of which are characteristic of the tertiary carbinol group, and lie in the 1.3 to 1.4 region.)

Therefore, as the experimental results show, the order of the amounts of constituents could be determined, and it is in considering the order of amounts that some correlation between liquid and gaseous products can be made. *That is where a large amount of olefin was obtained, a large amount of reduction product was obtained, and where a large amount of saturated gas was obtained, a large amount of unchanged ketone, ketol, and/or dehydrated ketol was obtained*. Although only a few of the experiments were repeated[*] the regularity in the correlation between the order of quantities and the nature of the gas evolved justifies the use of gas volumes as an indication of the extent and nature of anomalous reaction occurring. For this reason, out of the 47 reactions recorded, the liquid products of only 32 have been fractionated.

Before discussing the relationship between the reagents and the nature and quantity of gases evolved, it is convenient to deal with the liquid products that were obtained and identified.

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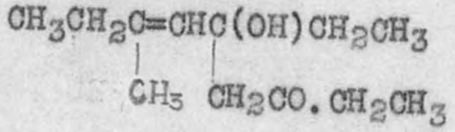
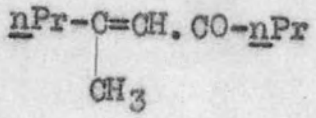
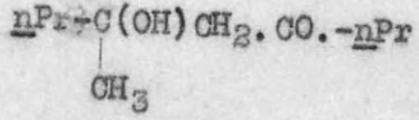
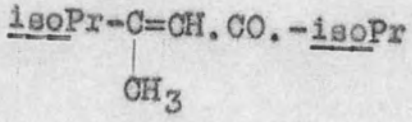
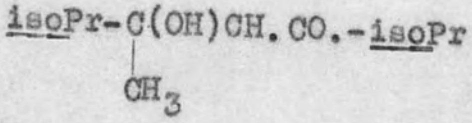
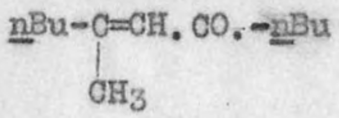
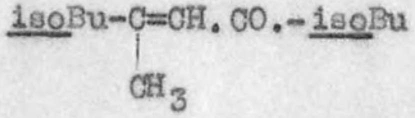
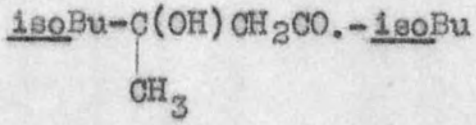
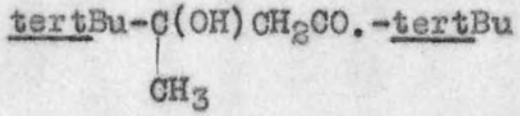
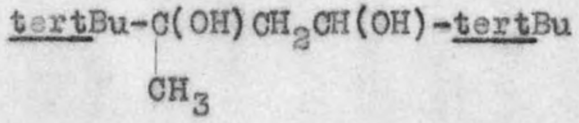
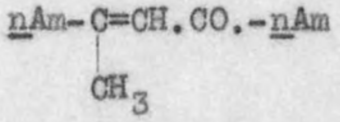
[*] i.e. repeating the reactions between methyl *iso*butyl ketone and (1) *n*-propylmagnesium bromide (2) *iso*propylmagnesium bromide (3) *sec*-butylmagnesium bromide gave the following results.

	Total vol.	saturated	unsatd.	% satd.
(1)	8,500	3,900	4,600	45.8
	8,200	3,700	4,500	45.0
(2)	19,500	15,950	3,600	81.4
	19,000	15,200	3,800	80.0.
(3)	20,000	13,100	6,900	65.6
	20,400	12,800	7,600	63.0

KETONE	RMgBr	CONDENSATE	B.P. n_d	"2:4-dinitrophenyl-hydrazone"
Methyl ethyl	*tert*-Bu *iso*Pr	 $CH_3CH_2\underset{CH_3}{C}=CH\underset{CH_2CO.CH_2CH_3}{C}(OH)CH_2CH_3$	93-93°/2.5mm $n_D^{21\cdot5}$ 1.4645	yellow needles 146-147°
Methyl *n*-propyl	*iso*Pr.	 $\textit{n}Pr-\underset{CH_3}{C}=CH.CO-\textit{n}Pr$	63-63°/3.0mm $n_D^{9\cdot5}$ 1.4557	liquid
	sec-Bu	 $\textit{n}Pr-\underset{CH_3}{C}(OH)CH_2.CO.-\textit{n}Pr$	63°/1.0 mm n_D^{20} 1.4390	liquid
Methyl *iso*propyl	*iso*Pr	 $\textit{iso}Pr-\underset{CH_3}{C}=CH.CO.-\textit{iso}Pr$	43-44°/2.0mm n_D^{16} 1.4528	golden cubes 85°
	sec-Bu	 $\textit{iso}Pr-\underset{CH_3}{C}(OH)CH.CO.-\textit{iso}Pr$	64-65°/2.0mm $n_D^{20\cdot75}$ 1.4368	golden cubes 85°

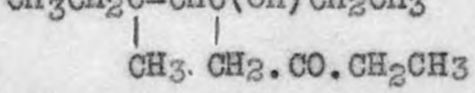
KETONE	RMgBr	CONDENSATE	B.P n_D	"2:4-dinitrophenyl-hydrazone"
Methyl <u>n</u>-butyl	<u>iso</u>Pr <u>sec</u>-Bu	 $\underline{n}\text{Bu-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{=CH.CO.-}\underline{n}\text{Bu}$	83-83°/2.0mm $n_D^{16.5}$ 1.4569	liquid
Methyl <u>iso</u>butyl	<u>iso</u>Pr <u>sec</u>-Bu	 $\underline{\text{iso}}\text{Bu-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{=CH.CO.-}\underline{\text{iso}}\text{Bu}$	69-70°/3.0mm $n_D^{22.5}$ 1.4511	brilliant red plates 126-127°
	<u>sec</u>-Bu	 $\underline{\text{iso}}\text{Bu-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{(OH)CH}_2\text{CO.-}\underline{\text{iso}}\text{Bu}$	87°/3.0 mm $n_D^{22.5}$ 1.4379	
Methyl <u>tert</u>-butyl	<u>iso</u>Pr <u>sec</u>-Bu	 $\underline{\text{tert}}\text{Bu-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{(OH)CH}_2\text{CO.-}\underline{\text{tert}}\text{Bu}$	80-81°/4.0mm n_D^{18} 1.4444	yellow needles 147-148°
	<u>iso</u>Pr <u>sec</u>-Bu	 $\underline{\text{tert}}\text{Bu-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{(OH)CH}_2\text{CH(OH)-}\underline{\text{tert}}\text{Bu}$	M.P. 92-93°	
Methyl <u>n</u>-amyl	<u>iso</u>Pr	 $\underline{n}\text{Am-}\underset{\substack{\vert\\ \text{CH}_3}}{\text{C}}\text{=CH.CO.-}\underline{n}\text{Am}$	110°/2.0 mm n_D^{18} 1.4558	liquid

Products of Condensation

On pages 58&59 are listed the condensation products obtained, with their characteristic physical properties. Where it was possible to obtain, by Brady's method, a 2:4-dinitrophenylhydrazone, this is listed.

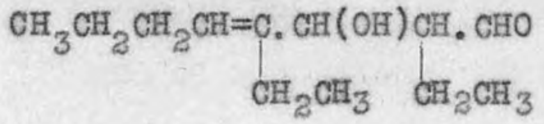
It will be noticed that the "2:4-dinitrophenylhydrazone" recorded for the ketol of methyl isopropyl ketone is the same as that recorded for the dehydrated ketol. It was found too that the "2:4-dinitrophenylhydrazone" prepared from the ketol of methyl tert-butyl ketone was really the derivative of the dehydrated ketol. This means that by using Brady's method the ketols are dehydrated at their tertiary hydroxyl group.

There seems to be one exception to this however, in the case of methyl ethyl ketone. Analysis of the condensate and its derivative show that the condensate has a formula $C_{12}H_{22}O$ and must have the structure



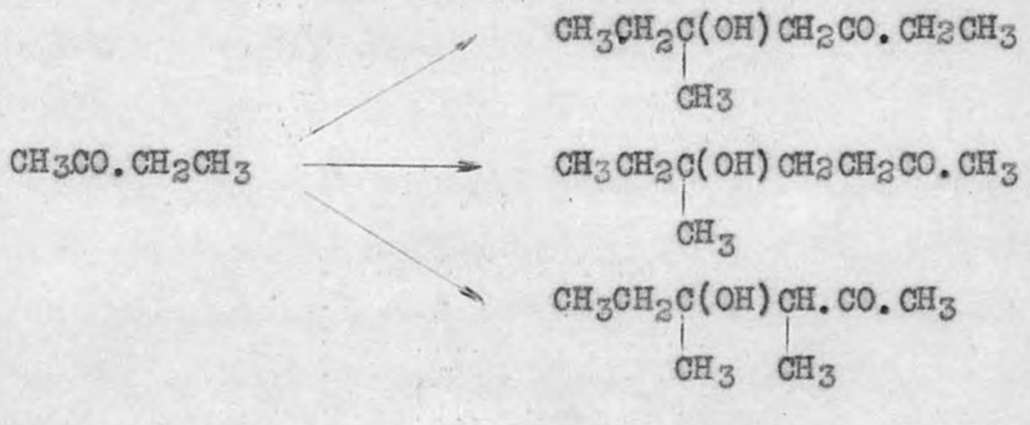
$$\begin{array}{l}\mathrm{CH_3CH_2C{=}CHC(OH)\,CH_2CH_3} \\ \qquad\quad | \qquad\ | \\ \qquad\ \mathrm{CH_3.\ CH_2.CO.CH_2CH_3}\end{array}$$

Analysis of the 2:4-dinitrophenylhydrazone showed that this is a derivative of the above compound and not of the dehydrate, which means that in this case dehydration of the tertiary hydroxyl group does not occur. An analogous compound has been obtained by Gorhan (1905)[46] by heating n-butyraldehyde with 16% sulphuric acid, and is given the probable constitution



$$CH_3CH_2CH_2CH{=}\underset{CH_2CH_3}{C}.CH(OH)\underset{CH_2CH_3}{CH}.CHO$$

With regard to methyl ethyl ketone, it was also found that the bimolecular condensate, corresponding with the ketols of the other ketones, consisted of two compounds. This result was obtained with both <u>iso</u>propylmagnesium bromide (Expt 3) and <u>tert</u>-butylmagnesium bromide (Expt.31). Evidence showing this lies in the preparation of the 2:4-dinitrophenylhydrazone. Two derivatives were obtained, but could not be completely separated. It is believed the two compounds are formed by ketolisation in two of three possible ways:



$$CH_3CO.CH_2CH_3 \rightarrow \begin{cases} CH_3CH_2\underset{CH_3}{C}(OH)CH_2CO.CH_2CH_3 \\ CH_3CH_2\underset{CH_3}{C}(OH)CH_2CH_2CO.CH_3 \\ CH_3CH_2\underset{CH_3}{C}(OH)\underset{CH_3}{CH}.CO.CH_3 \end{cases}$$

A law has recently been stated by Dubois[45] to the effect that in the condensation of ketones the carbon atom involved in condensation is that carbon atom adjacent to the carbonyl group, which is least substituted. This law is really a statement of very obvious facts. The present writer believes however, that of the three possible condensations of methyl ethyl ketone the first and the second are those occurring.

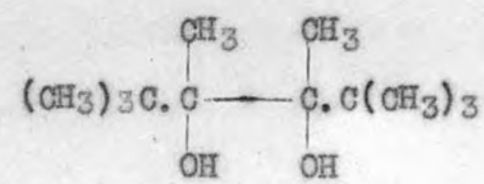
It is necessary to deal in more detail with the condensates of methyl *tert*-butyl ketone. It will be seen that, of the two recorded, the second is the reduction product of the first. This reduction product was obtained from the residues of the reaction between pinacolone and (1) *iso*propylmagnesium bromide, and (2) *sec*-butylmagnesium bromide. Well defined crystals formed in the cold residues and were hardly in need of purification after they had been washed with a cold solvent.

Although the solid condensation product was obtained by the use of *iso*propylmagnesium bromide and *sec*-butylmagnesium bromide, it was not obtained by the use of *iso*propylmagnesium chloride, nor by the use of *sec*-butylmagnesium chloride.

These observations are discussed in a later section.

When the solid product was first obtained, it was thought to be a trimolecular condensate of pinacolone. Analysis showed that it had the necessary empirical formula, but determination of the M.Wt. showed this to be 200 instead of the 300 required by a trimolecular condensate. The M.Wt. determinations also showed that the compound was highly associated in benzene and bromoform solutions.

The only solid "polymer" of pinacolone recorded in the literature is the pinacol



$$(CH_3)_3C.\overset{CH_3}{\underset{OH}{C}}-\overset{CH_3}{\underset{OH}{C}}.C(CH_3)_3$$

which was prepared by Friedel and Silva (1873)[47], and by Delacre (1907)[48], by the action of sodium on pinacolone in the presence of water. The M.Ps. recorded are respectively 69° and 70-72°. The M.P. of the solid obtained from the Grignard reactions was 92-93°.

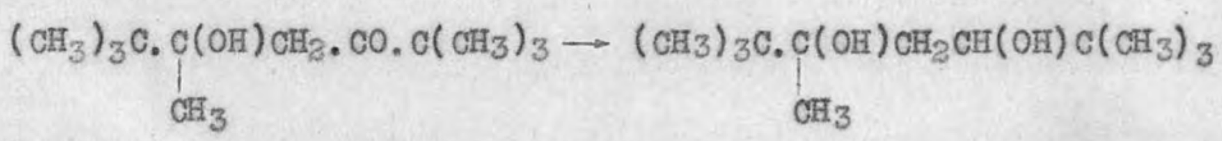
Although it was found impossible to oxidise this solid by Criegee's lead tetra-acetate method, indicating that it was not a glycol, it was thought advisable to go back over the preparations of pinacolone pinacol to see whether another form of the pinacol existed. It was not possible to prepare the pinacol by the method for other pinacols given by Gomberg and Bachmann[12]. Repetition of Delacre's work showed the recorded M.P. of 70° to be correct.

It was found that the solid from the Grignard reactions could be dehydrated by distilling over naphthalene-2-sulphonic acid, did not give any of the common derivatives of primary or secondary alcohols, and did not form a 2:4-dinitrophenylhydrazone by Brady's method.

It was noticed that although dilute acids had no effect on the solid, concentrated nitric acid converted it into a liquid, and that this liquid was very similar to the product of the action of concentrated nitric acid on the ketol of pinacolone.

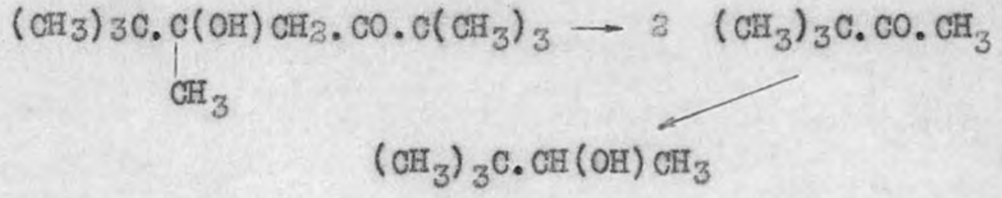
Therefore the ketol was reduced by sodium and ethyl alcohol; two products were formed:

(1) the solid condensate M.P. 92-93°, and (2) pinacolyl alcohol. This meant that the solid condensate could have been produced in two ways: either (i) by the direct reduction of the ketol



$$(CH_3)_3C.\underset{\displaystyle CH_3}{\underset{|}{C}}(OH)CH_2.CO.C(CH_3)_3 \rightarrow (CH_3)_3C.\underset{\displaystyle CH_3}{\underset{|}{C}}(OH)CH_2CH(OH)C(CH_3)_3$$

or (ii) by the breakdown of the ketol into pinacolone, and subsequent repolymerisation of the pinacolone. The pinacolyl alcohol must have resulted from the preliminary breakdown of the ketol



$$\begin{aligned}&(CH_3)_3C.\underset{\displaystyle CH_3}{\underset{|}{C}}(OH)CH_2.CO.C(CH_3)_3 \rightarrow 2\ \ (CH_3)_3C.CO.CH_3\\ &\qquad\qquad\qquad\qquad\qquad\qquad\swarrow\\ &\qquad\qquad\qquad (CH_3)_3C.CH(OH)CH_3\end{aligned}$$

It was unlikely that the solid would have been produced by (ii) since the only product, beside pinacolyl alcohol, that is obtained by the similar action of sodium on pinacolone in aqueous ether is the pinacol.

To verify that reduction (i) had occurred, the ketol was reduced in alcohol solution by the method of Carothers and Adams (1923)[49] involving hydrogen at four atmospheres pressure and Adams PtO_2 catalyst activated by ferrous chloride. Using this method it was unlikely that the ketol would break down to pinacolone. The solid, M.P. 92-93°, was obtained.

- - - - - - - - - - - -

A solid product was also obtained by the action of *iso*butylmagnesium bromide on pinacolone (Expt. 20), but although this had a composition corresponding with the formula $(C_6H_{12}O)x$, it had an M.P. 115°. Insufficient of this solid was obtained to enable the determination of its M.Wt.

- - - - - - - - - - - -

The Usefulness of the Condensates.

The unsaturated ketones formed by the dehydration of ketol condensates can be used to make long chain saturated ketones and alcohols. For example, the dehydrated ketol of methyl *iso*butyl ketone was reduced catalytically (Expt. 56a) to the saturated ketone,

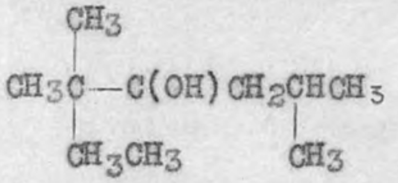
$$(CH_3)_2CHCH_2CH(CH)_3.CH_2CH_2CO.CH_2CH(CH_3)_2$$

while the catalytic reduction of the keto group has already been discussed in the case of pinacolone ketol. The selective reducing action of PtO_2 in the absence of a promoter removes the possibility of reducing both the double bond and keto group of an unsaturated ketone at the same time, as is illustrated by Fig 2 for mesityl oxide. Hence the saturated ketone and alcohol can be obtained at will. Although no Grignard reactions were carried out on a saturated ketone obtained in this manner, it is very probable that Grignard reagents such as methyl, ethyl, *n*-propyl, *n*-butyl, and possibly phenyl magnesium halide would react to form the corresponding tertiary carbinols.

Tertiary Carbinols

Below are listed those tertiary carbinols obtained by the present writer, which have not been found to be recorded elsewhere.

(1) 2:2:3:5-tetramethylhexanol-3



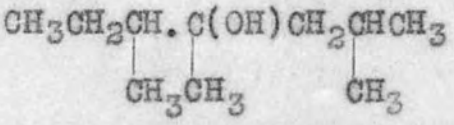
$CH_3\overset{CH_3}{\underset{CH_3}{C}}-\underset{CH_3}{C}(OH)CH_2\underset{CH_3}{C}HCH_3$

83-85 °/29 mm

$n_D^{23.5}$ 1,4358

Obtained by the action of <u>tert</u>-butylmagnesium bromide on methyl <u>iso</u>butyl ketone, in 8% yield.

(2) 2:4:5-trimethylheptanol-4



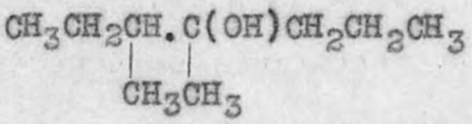
$CH_3CH_2\underset{CH_3}{C}H.\underset{CH_3}{C}(OH)CH_2\underset{CH_3}{C}HCH_3$

54-55 °/3 mm

n_D^{20} 1.4382

Obtained by the action of <u>sec</u>-butylmagnesium bromide on methyl <u>iso</u>butyl ketone, in 11.5% yield.

(3) 3:4-dimethylheptanol-4



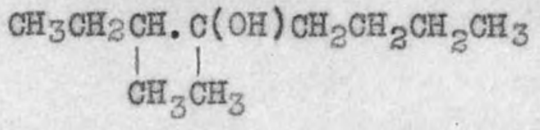
$CH_3CH_2\underset{CH_3}{C}H.\underset{CH_3}{C}(OH)CH_2CH_2CH_3$

83-85 °/25 mm

n_D^{21} 1.4388

Obtained by the action of <u>sec</u>-butylmagnesium bromide on methyl <u>n</u>-propyl ketone, in 16% yield.

(4) 3:4-dimethyloctanol-4



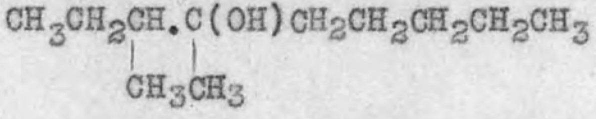
$CH_3CH_2\underset{CH_3}{CH}.\underset{CH_3}{C}(OH)CH_2CH_2CH_2CH_3$

64-65 °/3 mm

n_D^{23} 1.4406

Obtained by the action of sec-butylmagnesium bromide on methyl n-butyl ketone, in 16.75% yield.

(5) 3:4-dimethylnonanol-4



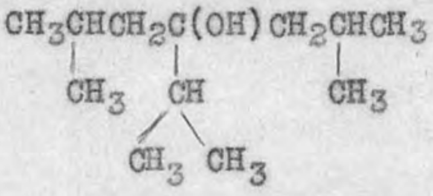
$CH_3CH_2\underset{CH_3}{CH}.\underset{CH_3}{C}(OH)CH_2CH_2CH_2CH_2CH_3$

68-69 °/2 mm

n_D^{22} 1.4422

Obtained by the action of sec-butylmagnesium bromide on methyl n-amyl ketone, in 13.5% yield.

(6) 2:6-dimethyl-4-isopropylheptanol-4



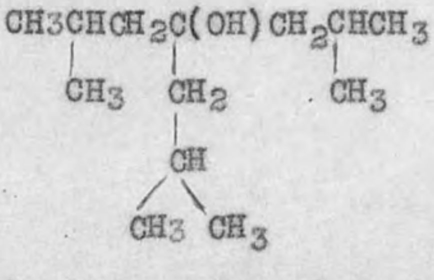
$CH_3\underset{CH_3}{CH}CH_2\underset{\underset{CH_3\ CH_3}{CH}}{C}(OH)CH_2\underset{CH_3}{CH}CH_3$

48-49 °/1 mm

$n_D^{22.5}$ 1.4438

Obtained by the action of isopropylmagnesium bromide on di-isobutyl ketone, in 7.25% yield.

(7) 2:6-dimethyl-4-isobutylheptanol-4



$CH3\underset{CH3}{CH}CH_2\underset{\underset{\underset{CH3\ CH_3}{CH}}{CH_2}}{C}(OH)CH_2\underset{CH_3}{CH}CH_3$

72-73 °/2 mm

n_D^{17} 1.4402

Obtained by the action of isobutylmagnesium bromide on di-isobutyl ketone, in 13.5% yield.

The Composition of the Gases

Table I shows the volumes of the gases collected for the series of reactions. The table shows the total volume of gas obtained from each reaction, and the volumes of the saturated and unsaturated components.

These results are expressed individually for the Grignard reagents and ketones in tables II to XVII. In interpreting the results of these reactions, it is necessary to see both the effect of steric hindrance in the reactants, and their reactivity. Table I shows that all the Grignard reagents used caused some kind of anomalous reaction, and the fractionation tables (pp153-205) confirm this. Confirmation of small amounts of enolisation and reduction is not as easy as the confirmation of small amounts of condensation, but it was possible in several cases, and there is no reason to believe that in those cases in which, say, reduction is indicated by the gas collected, but in which the reduction product could not be separated, that reduction had not really taken place.

It has been shown by Whitmore and Lewis[37] (p43) that provided there was sufficient hindrance in the ketone, enolisation could be caused by a methyl Grignard reagent, while Stas (1926)[50] obtained a 78% yield of di*iso*propylcarbinol by the action of methylmagnesium bromide on di*iso*propyl ketone.

The present author (pp123-4) has found that methylmagnesium bromide also causes reduction in di*iso*butyl ketone and in *iso*propyl *iso*butyl ketone. Grignard and Blanchon[33] (p36) were unable to show any relationship between ketone and yield of saturated gas in the experiments they carried out, while Smith and Guss[35] (p41) concluded that the only factor effecting enolisation was hindrance in the ketone.

The results indicated in Table I, however, were obtained with some ketones and Grignard reagents in which there is no great steric hindrance. Therefore what is necessary is that these results should be arranged in such a way as to allow an interpretation of not only steric hindrance but of reactivity.

The tables show that in general there is an increase in the extent of anomalous reaction as steric hindrance in the ketone and Grignard radical increases, but there are several cases in which it is obvious that the extent of anomalous reaction is not due to hindrance alone. The tables are also designed to show the variation in the *kind* of anomalous reaction. For this reason each table is arranged to show initially the increase in total volume of gas per change in variable, but with each table the percentage of saturated gas is given, and it will be seen that this does not follow the same order as the increase in total volume.

In the methyl ketone tables II to VI it will be seen that there is a common order in the increase of anomalous reaction proceeding in the order of RMgBr

*n*Bu < *n*Pr < *iso*Bu < *sec*Bu < *iso*Pr

but this order breaks down for di*iso*butyl ketone (Table VII), and for di*iso*propyl ketone (Table VIII), the order of RMgBr being

Table VII   *n*Bu < *iso*Pr < *iso*Bu < *sec*Bu

Table VIII   *n*Bu < *n*Pr < *iso*Pr < *sec*Bu

These tables indicate therefore, that while in the methyl ketones the extent to which total anomalous reaction varies with Grignard reagent seems to be a function of hindrance plus a reactivity factor, in di*iso*butyl ketone and di*iso*propyl ketone the extent of anomalous reaction seems to be entirely a function of hindrance.

The same tables show also that there is a common order for the increase in the percentage of saturated gas, which for each ketone, except di*iso*propyl ketone, goes

*iso*Bu < *n*Pr < *n*Bu < *sec*Bu < *iso*Pr

This order is entirely different for di*iso*propyl ketone, being

*sec*Bu   *n*Bu < *n*Pr < *iso*Pr

The tables IX to XIII show that the order in which total volume of gas increases for a series of ketones is not the same for each Grignard reagent. This is what one might expect when there are two factors influencing anomalous reaction. It is better to take the tables individually to discuss this.

Table IX for n-propylmagnesium bromide indicates that there is no great reactivity factor in the Grignard reagent and that the extent of anomalous reaction depends mainly on the hindrance of the ketone.

Table X for isopropylmagnesium bromide indicates that with this Grignard reagent hindrance is subjugated by reactivity, for this reactivity is brought into play with methyl isopropyl ketone and methyl tert-butyl ketone.

Table XI for n-butylmagnesium bromide shows similarity with table IX, except for methyl tert-butyl ketone.

Table XII for isobutylmagnesium bromide indicates that the extent of anomalous reaction is a function of hindrance, except in the case of the highly reactive methyl tert-butyl ketone.

Table XIII for sec-butylmagnesium bromide indicates that the extent of anomalous reaction increases with steric hindrance.

The above tables show again, however, that the order in which the extent of the kind of anomalous reaction increases is very different from the order in the total anomalous reaction. (i.e.) the order of increase of percentage of saturated gas per change in ketone is as follows:

n-PrMgBr	di*iso*Pr < *tert*Bu < *iso*Pr < *iso*Bu < *n*-Pr < *n*-Am
n-BuMgBr	di*iso*Pr < *tert*Bu < di*iso*Bu < *iso*Pr < *iso*Bu < *n*-Pr < *n*-Am
*iso*PrMgBr	di*iso*Pr < *n*-Pr < *n*-Am < *tert*Bu < *iso*Pr < *iso*Bu < di*iso*Bu
sec-BuMgBr	di*iso*Pr < di*iso*Bu < *tert*Bu < *iso*Pr < *n*-Am < *n*-Pr < *iso*Bu
*iso*BuMgBr	*n*-Pr < *n*-Am < *iso*Bu < di*iso*Bu < *iso*Pr < *tert*Bu

How these results fit in with the mechanism of reaction will be discussed in Part III of this thesis.

Key to Tables I to XVII

Unless otherwise mentioned in the text, these tables show the volumes of gas, in mls., obtained when 1 gm.mol. of each ketone was added to a solution of the appropriate Grignard reagent made from 2 gm. atoms of magnesium.

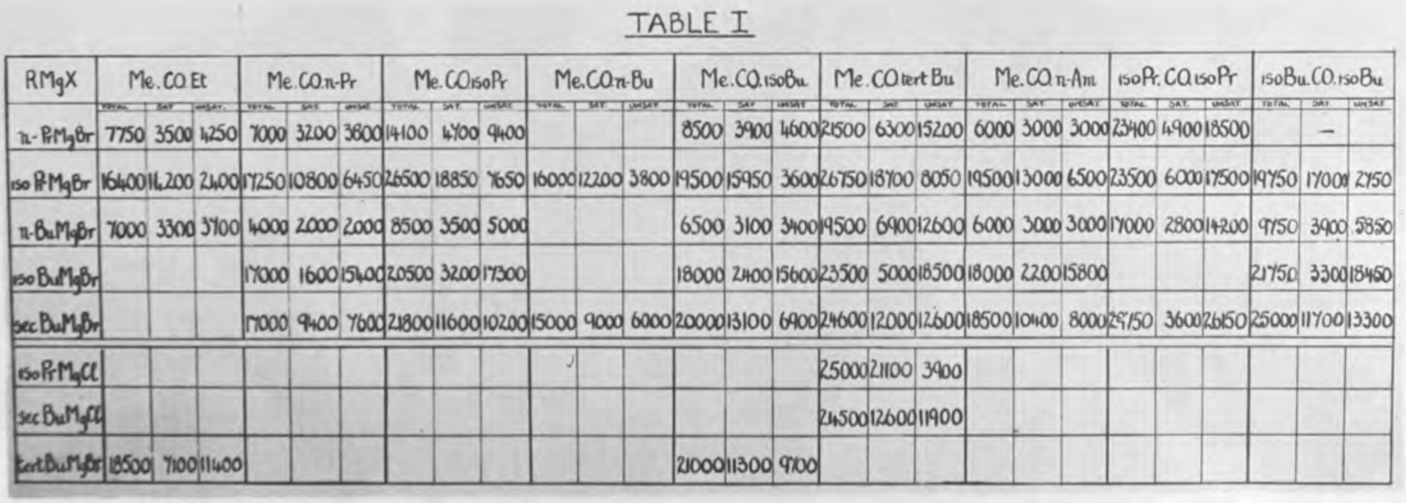


TABLE I

RMgX	Me.CO.Et			Me.CO.n-Pr			Me.CO.isoPr			Me.CO.n-Bu			Me.CO.isoBu.			Me.CO.tert Bu			Me.CO.n-Am			isoPr.CO.isoPr			isoBu.CO.isoBu		
	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.	TOTAL	SAT.	UNSAT.
n-PrMgBr	7750	3500	4250	7000	3200	3800	14100	4700	9400				8500	3900	4600	21500	6300	15200	6000	3000	3000	23400	4900	18500		—	
iso PrMgBr	16400	14200	2400	17250	10800	6450	26500	18850	7650	16000	12200	3800	19500	15950	3600	26750	18700	8050	19500	13000	6500	23500	6000	17500	19750	17000	2750
n-BuMgBr	7000	3300	3700	4000	2000	2000	8500	3500	5000				6500	3100	3400	19500	6900	12600	6000	3000	3000	17000	2800	14200	9750	3900	5850
iso BuMgBr				17000	1600	15400	20500	3200	17300				18000	2400	15600	23500	5000	18500	18000	2200	15800				21750	3300	18450
sec BuMgBr				17000	9400	7600	21800	11600	10200	15000	9000	6000	20000	13100	6900	24600	12000	12600	18500	10400	8000	29750	3600	26150	25000	11700	13300
iso PrMgCl																25000	21100	3900									
sec BuMgCl																24500	12600	11900									
tert BuMgBr	18500	7100	11400										21000	11300	9700												

Table II

Methyl n-propyl ketone

RMgBr	Total vol.	saturated	unsaturated	%satd.
n-Bu	4,000	2,000	2,000	50.0
n-Pr	7,000	3,200	3,800	45.7
isoBu	17,000	1,600	15,400	9.4
sec-Bu	17,000	9,400	7,600	55.5
isoPr	17,250	10,800	6,450	61.3

Table III

Methyl isopropyl ketone

RMgBr	Total vol.	saturated	unsaturated	%satd.
n-Bu	8,500	3,500	5,000	41.2
n-Pr	14,100	4,700	9,400	33.3
isoBu	20,500	3,200	17,300	15.6
sec-Bu	21,800	11,600	10,200	58.5
isoPr	26,500	18,850	7,650	71.2

Table IV

Methyl isobutyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	6,500	3,100	3,400	47.6
n-Pr	8,500	3,900	4,600	45.8
isoBu	18,000	2,400	15,600	13.3
isoPr	19,500	15,950	3,600	81.4
sec-Bu	20,000	13,100	6,900	65.6

Table V

Methyl tert-butyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	19,500	6,900	12,600	35.4
n-Pr	21,500	6,300	15,200	29.3
isoBu	23,500	5,000	18,500	21.3
sec-Bu	24,600	12,000	12,600	48.8
isoPr	26,750	18,700	8,050	70.0

Table VI

Methyl n-amyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	6,000	3,000	3,000	50.0
n-Pr	6,000	3,000	3,000	50.0
isoBu	18,000	2,200	15,800	12.2
sec-Bu	18,500	10,400	8,100	56.2
isoPr	19,500	13,000	6,500	66.6

Table VII

diisobutyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	9,750	3,900	5,850	40,0
isoPr	19,750	17,000	2,750	86.0
isoBu	21,750	3,300	18,450	15.4
sec-Bu	25,000	11,700	13,300	46.8

Table VIII

diisopropyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	17,000	2,800	14,200	16.5
n-Pr	23,400	4,900	18,500	20.9
*iso*Pr	23,500	6,000	17,500	25.5
sec-Bu	29,750	3,600	26,150	12.1

Table IX

n-propylmagnesium bromide

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.*n*Am	6,000	3,000	3,000	50.0
Me.*n*Pr	7,000	3,200	3,800	45.7
Me.*iso*Bu	8,500	3,900	4,600	45.8
Me.*iso*Pr	14,100	4,700	9,400	33.3
Me.*tert*Bu	21,500	6,300	15,200	29.3
Di*iso*Pr	23,400	4,900	18,500	20.9

Table X

isopropylmagnesium bromide

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.*n*-Pr	17,250	10,800	6,450	62.6
Me.*n*-Am	19,500	13,000	6,500	66.6
Me.*iso*Bu	19,500	15,950	3,550	81.8
Di*iso*Bu	19,750	17,000	2,750	86.0
Di*iso*Pr	23,500	6,000	17,500	25.5
Me.*iso*Pr	26,500	18,850	7,650	71.2
Me.*tert*Bu	26,750	18,700	8,050	70.0

Table XI

n-butylmagnesium bromide

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.*n*-Pr	4,000	2,000	2,000	50.0
Me.*n*-Am	6,000	3,000	3,000	50.0
Me.*iso*Bu	6,500	3,100	3,400	47.6
Me.*iso*Pr	8,500	3,500	5,000	41.2
Di*iso*Bu	9,750	3,900	5,850	40.0
Di*iso*Pr	17,000	2,800	14,200	16.5
Me.*tert*Bu	19,500	6,900	12,600	35.4

Table XII

isobutylmagnesium bromide

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.*n*-Pr	17,000	1,600	15,400	9.4
Me.*n*-Am	18,000	2,200	15,800	12.2
Me *iso*Bu	18,000	2,400	15,600	13.3
Me.*iso*Pr	20,500	3,200	17,300	15.6
Di*iso*Bu	21,750	3,300	18,450	15.3
Me.*tert*Bu	23,500	5,000	18,500	21.3

Table XIII

sec-butylmagnesium bromide

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.n-Pr	17,000	9,400	7,600	55.5
Me.n-Am	18,500	10,400	8,100	56.2
Me.isoBu	20,000	13,100	6,900	65.5
Me.isoPr	21,800	11,600	10,200	53.2
Me.tertBu	24,600	12,000	12,600	48.8
DiisoBu	25,000	11,700	13,300	46.8
DiisoPr	29,750	3,600	23,150	12.1

Table XIV

Methyl ethyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
n-Bu	7,000	3,300	3,700	47.1
n-Pr	7,750	3,500	4,250	45.2
isoPr	16,400	14,200	2,400	86.8

Table XV

Methyl n-butyl ketone

RMgBr	Total vol.	saturated	unsaturated	% satd.
sec-Bu	15,000	9,000	6,000	60.0
isoPr	16,000	12,200	3,800	76.2

The results obtained with methyl ethyl ketone and methyl n-butyl ketone are not included in tables II to XIII since they would interrupt the completeness of these tables. Instead they are given separately, but are discussed with the other results in Part III.

Tertiary butylmagnesium bromide

Only two experiments were made with this reagent, because the difficulty in preparing the Grignard solution, and the amount of decomposition that occurs in its preparation, do not allow a fair comparison with the other Grignard reagents used, and the conclusions drawn from the results obtained would be only tentative. The following results were obtained with *tert*-butylmagnesium bromide.

Table XVI

Ketone	Total vol.	saturated	unsaturated	% satd.
Me.Et	18,500	7,100	11,400	38.3
Me.*iso*Bu	21,000	11,300	9,700	53.8

The fractionation tables (pp 200-4) are in agreement with these results. An important feature in these reactions is the formation of di-*tert*-butyl (hexamethylethane), which distilled with the low boiling product of each reaction. In the methyl ethyl ketone reaction a distillate of di-*tert*-butyl and methylethylcarbinol was obtained, while in the methyl *iso*butyl ketone reaction a distillate of di-*tert*-butyl and methyl *iso*butyl ketone was obtained. Earlier attempts (Expts.32) to prepare di-*tert*-butyl by normal Grignard methods had failed. The only way in which a small amount, 0.5 gm, of di-tert-butyl was obtained was from the action of anhydrous cupric chloride on tert-butylmagnesium bromide. (The use of cupric chloride in such a reaction was first reported, for diphenyl, by Krizewsky and Turner (1919)[75]) None was obtained from the ordinary Grignard reactions

tert-BuMgBr + tert-BuBr

tert-BuMgCl + tert-BuCl

and none was obtained when anhydrous cobalt chloride was used in an attempt to promote the formation of free radicals. Yet the influence of the two ketones raises the yidld of di-tert-butyl to several gm. This certainly means that the Grignard reagent dissociates into free radicals, and it seems that the union, if not the presence, of free radicals, is promoted by the ketones.

Experiments using Grignard Chlorides.

The probability that a change in the halide of a Grignard reagent influences the extent and type of reaction taking place necessitated some experiments being made with alkylmagnesium chlorides. Grignard and Savard[31] (p 33) concluded that the enolisation of pulegone diminishes with increasing atomic weight of the Grignard halogen, and Grignard and Blanchon[33] reported that less enolisation was caused by Grignard chlorides than by bromides, but that in general iodides caused less enolisation than bromides too. Dubois[44] (p 51) found that isopropylmagnesium chloride caused

62% condensation of pinacolone, whereas *iso*propylmagnesium bromide caused only 30%.

Experiments were made using *iso*propyl and *sec*-butyl magnesium chlorides on pinacolone. In the table below the volumes of gas collected are compared with those from the use of the bromides. (In the case of *sec*-butylmagnesium chloride only half quantities were used, so that the gas volumes have been doubled for the purpose of comparison.)

Table XVII

Grignard reagent	Total vol.	saturated	unsatd.	% satd.
*iso*PrMgBr	26,750	18,700	8.050	70.0
*iso*PrMgCl	25,000	21,100	3,900	82.2
sec-BuMgBr	24,6000	12,000	12,600	48.8
sec-BuMgCl	24,500	12,600	11,900	51.4

These tables show that in each case the amount of saturated gas is greater for the chlorides, and that the percentage of the total volume represented by the saturated gas is also greater for the chlorides.

Instead of the great difference in the amounts of ketol obtained by Dubois, the experiments with *iso*propyl magnesium bromide and chloride (Expts.10 & 15) show the following results.

Table XVIII

Grignard reagent	gm pinacolone	gm pinacolyl-OH	gm ketol
*iso*PrMgBr	20	10	44
*iso*PrMgCl	36	5	35

Where Expt. (10) differs from Dubois too is, as already noted, in the formation of the reduced ketol, of which 6 gm were obtained. (This is included in the 44 gm above)

The experiments with sec-butylmagnesium bromide and chloride show the following results:

Table XIX

Grignard reagent	gm pinacolone	gm pinacolyl-OH	gm ketol
sec-BuMgBr	-	45/2	38/2
sec-BuMgCl	7	17	15

Inspection of Expt. (29) will show that the figures for pinacolone and pinacolyl alcohol are computed from refractive indices, since the separation of the ketone and alcohol was not sharp. The figure for the ketol from the bromide includes the reduced ketol, of which 5 gm were obtained.

Experiments using low temperatures.

The theory that reduction, enolisation, and condensation by Grignard reagents go through an addition stage has been upheld by many workers. One of the props of this theory was that the extent of anomalous reaction is diminished by working at low temperatures, and increased by working at high temperatures, the significance being that the breakdown of an addition complex is influenced by temperature. This has been discussed by Rheinboldt and Roleff[7,8](pp13-15) for reduction, and by Grignard and Savard[31] (p33) for enolisation. Condensation has not had a temperature restriction placed upon it. This is probably due only to the fact that condensation was not fully recognised as such. Meisenheimer[9] (p16) however, says that temperature influences reduction only to a small extent, while Blicke and Powers[21] (p21) found that the action of n-propylmagnesium iodide on benzophenone gave 50% yield of benzhydrol at 0°. Kharasch and Weinhouse (1936)[51] found that the reduction of benzophenone by n-butylmagnesium bromide varied only slightly when the reaction was carried out at low temperatures. The view that temperature influences reduction only to a small extent is indeed correct, and applies equally to condensation and enolisation. The present writer finds that interaction of isopropylmagnesium bromide and methyl isobutyl ketone at -10° to -20° (Expt. 8), of isobutylmagnesium bromide and methyl isobutyl ketone at -40° to -50° (Expt. 19), and sec-butylmagnesium bromide and methyl isobutyl ketone at -45° to -50° (Expt. 26), neither prevented nor markedly diminished the reduction, enolisation, and condensation already found to occur in these reactions.

Below are given the results obtained from these reactions compared with the same reactions in boiling ether.

Table XX

isoBuMgBr + methyl isobutyl ketone

Product	Boiling Solution (Ex.18)	Cold (Ex.19)
	gm	gm
Ketone	0	10
sec-OH	48	50
tert-OH	45	35
Ketol	2	2

Table XXI

sec-BuMgBr + methyl isobutyl ketone

Product	Boiling Solution (Ex.25)	Cold (Ex.26)
	gm	gm
Ketone	-	10
sec-OH	16	7
tert-OH	18	18
Ketol	57	59

Table XXII

isoPrMgBr + methyl isobutyl ketone

Product	Boiling Solution (Ex.7)	Cold (Ex.8)
	gm	gm
Ketone	2·5	-
sec-OH	2·5	0
tert-OH	31·0	34
Ketol	53·0	46

These results indicate that there is no prevention of anomalous reaction, but there is a tendency for reaction to be incomplete at the low temperatures used, as shown by the ketone and tertiary carbinol in Table XX, and the ketone in Table XXI

If the volume of gas evolved in the cold experiments were taken as an indication of the extent of anomalous reaction, then one would indeed conclude that these reactions were inhibited. However, the small volume of gas evolved in each case is due entirely to the solubility of the gases in ether at low temperatures.

The following solubilities are given in the literature:

Propane 9.26 vols. dissolve in 1 vol ether at 16.6°
Lebeau (1905)[52]

Propylene 16 vols dissolve in 1 vol ether
Berthelot (1855)[53]

The Influence of Cobalt Chloride.

The work of Kharasch and co-workers[54] has shown that small amounts of anhydrous cobaltous chloric catalytically promotes free radical mechanisms in Grignard reactions. An experiment (9) was therefore made using the procedure of Kharasch, in which the reaction between isopropylmagnesium bromide and methyl isobutyl ketone was carried out in the presence of cobaltous chloride. There was a pronounced increase in the amount of methylisobutylcarbinol obtained from this reaction compared with the amount contained from a similar reaction containing no cobaltous chloride (Expt.8).

Table XXIII

Product	no $CoCl_2$	$CoCl_2$
	gm	gm
sec-OH	0	14
tert-OH	34	25
ketol	46	39

At the same time there was a decrease in the amounts of tertiary carbinol and ketol formed.

PART III

Discussion

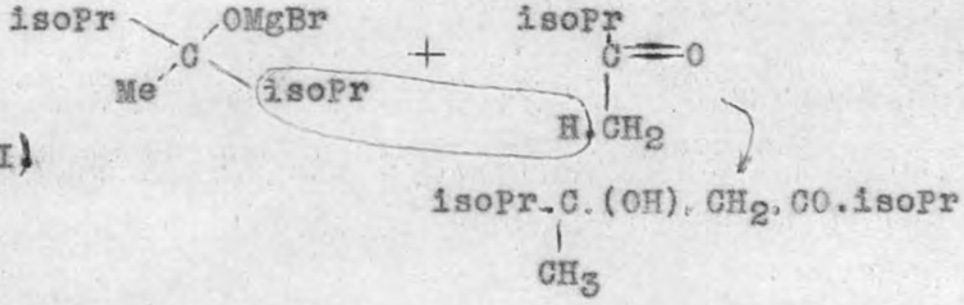
In discussing the mechanism by which a Grignard reagent and a carbonyl compound may react abnormally it is first necessary to distinguish between the two types of mechanism already reported; that is, between the mechanism of preliminary addition, and the mechanism involving a dissociated Grignard reagent.

The Mechanism of Preliminary Addition.

The theory that reduction and condensation of carbonyl compounds by Grignard reagents went through a preliminary addition stage developed from the HMgX hypothesis of Hess and Rheinboldt[5] in the case of reduction, and from the condensing action of aluminium alcohates (Tistchenko[26]) in the case of condensation. The HMgX hypothesis led through a series of papers on coordination complexes and their liability to break down, up to the opinion of Shankland and Gomberg[18] that reduction was a function of the alcoholate formed by addition of the Grignard reagent to the carbonyl compound. Alcoholate condensations were investigated at length by Grignard and Dubiens [27], and by Grignard and Fluchaire[30], and were applied to enolisation by Grignard and Savard[31]. Condensation via addition was also recently reiterated by Dubois [44]; but questioned by the same author in a later paper[45]; no alternative was suggested.

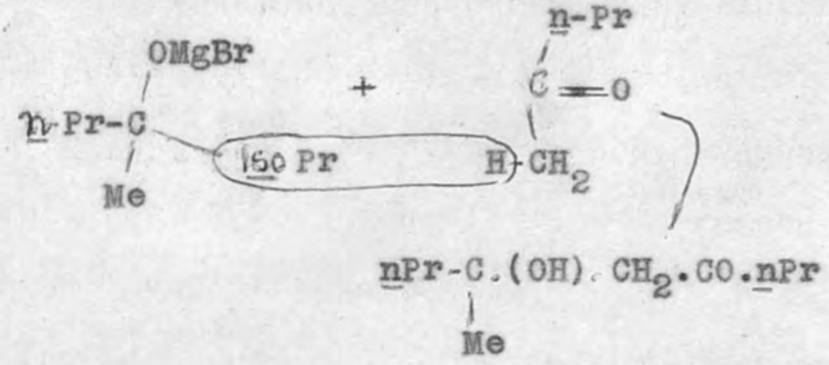
However, whether or not these mechanisms of reduction, enolisation, and condensation by alcoholates are those suggested by the various authors is not under discussion. What is in question is whether these mechanisms are applicable to Grignard reactions. There are several reasons for believing they are not.

First, suppose that condensation does go through a stage of preliminary addition. In the reaction between isopropylmagnesium bromide and methyl isopropyl ketone the major product has been shown to be the condensate (Expt.5). Using an addition mechanism, the condensate is formed as follows: the initially formed alcoholate (I) reacts with the ketone to form the ketolate, which on hydrolysis gives the ketol, the condensate of Expt.5.

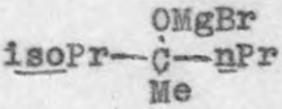

(I)

In the reaction between isopropylmagnesium bromide and methyl n-propyl ketone (Expt. 4) it has been shown that although the major product is the tertiary carbinol, a fair amount of condensate is formed. In an addition mechanism therefore, the following happens.

II



However, in the reaction between n-propylmagnesium bromide and methyl isopropyl ketone (Expt. 2) only a very small amount of condensate is formed, nearly all the product being the tertiary carbinol. That is, the addition complex III



$$\mathit{iso}\mathrm{Pr}\text{—}\overset{\mathrm{OMgBr}}{\underset{\mathrm{Me}}{\mathrm{C}}}\text{—}n\mathrm{Pr}$$

III

has not been inclined to condense with methyl isopropyl ketone.

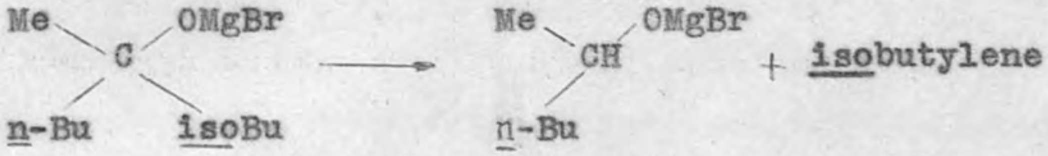
Surely, if alcoholate II will condense with methyl isopropyl ketone, is it not likely that alcoholate III will condense with methyl isopropyl ketone too? Alcoholate II shows a readiness to lose its isopropyl group. It is identical with alcoholate III. Yet when the Grignard reagent used is n-propylmagnesium bromide, only a small amount of condensation occurs.

The same reasoning may be applied to the reactions

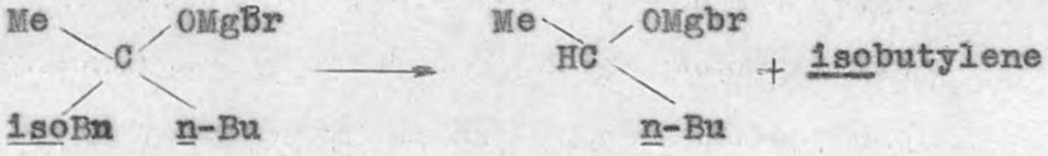
isopropylmagnesium bromide + methyl isopropyl ketone
isopropylmagnesium bromide + methyl n-butyl ketone
n-butylmagnesium bromide + methyl isopropyl ketone.

With reduction, too there is an identical failure of the alcoholate theory. The action of isobutylmagnesium bromide on methyl isobutyl ketone causes much reduction. The action of isobutylmagnesium bromide on methyl n-propyl ketone again causes much reduction. Yet the action of n-propylmagnesium bromide on methyl isobutyl ketone causes little reduction. If reduction were occurring by way of the break down of an addition complex, the following reactions would have occurred:

(1) 

(2) 

but NOT

(3) 

Is it not to be asked why the third reduction does not take place? There are of course the possibilities that in the freshly formed alcoholate the entering group is not fully attached to the central carbon atom; that is, as if it were a stranger in a new home and had not yet settled down, or that the placing of coordinated ether molecules alters the respective relative arrangement of the groups in each alcoholate

The work of the HMgX and coordinate school of chemists would uphold such possibilities, as indeed Rheinboldt and Roleff have done in reactions involving isobutyl-and phenylmagnesium bromides, but the present writer feels that such conceptions as these are stretching the addition theories to breaking point.

Preliminary addition as a step towards reduction, enolisation, and condensation is again questionable in the light of steric hindrance. The effect of hindrance on the extent of enolisation has been shown fully by the work of Whitmore et al (pp 42-46), while Conant and Blatt[32] have investigated its effect on reduction. The present writer's experiments on diisopropyl and diisobutyl ketones also show the influence of hindrance on enolisation and reduction. It is therefore difficult to envisage these anomalous reactions as going through an addition stage if they are increased by prevention of addition. And if condensation involves the enolate ion or radical, as is discussed later, one cannot give to condensation a mechanism which is preceded by addition.

Finally there is the mainstay of the addition mechanisms: the influence of temperature. As is reported on pp. 83-4, low temperatures do not prevent anomalous reactions, and temperature has no great influence on these reactions.

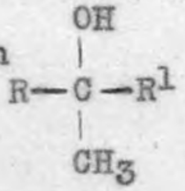
It is the writer's conclusion, therefore, that these anomalous reactions do not involve an addition stage, but are the result of the action of dissociated Grignard reagents. How the mechanisms of dissociated Grignard reagents work will now be discussed.

The Mechanisms of Dissociated Grignard Reagents.

In order to come to any reasonable conclusions about the mechanism of the anomalous interaction of dissociated Grignard reagents and carbonyl compounds, it is expedient to begin by first considering what mechanisms are possible, and then to see how experimental evidence supports any speculation on mechanism. The greater part of the present work concerns the interaction of methyl ketones and Grignard reagents, and it is therefore preferable to confine discussion for the moment to methyl ketones, and to consider changing the methyl group later.

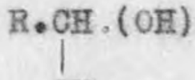
The products into which a methyl ketone $R.CO.CH_3$ may be converted by the action of a Grignard reagent containing the group R^1 are at least four in number. That is:

(1) by addition



$R-\overset{OH}{\underset{CH_3}{C}}-R^1$

(2) by reduction

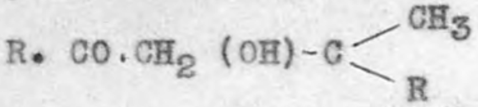


$R.\underset{CH_3}{CH}.(OH)$

(3) by enolisation

$R.\ CO.\ CH_3$

(4) by condensation

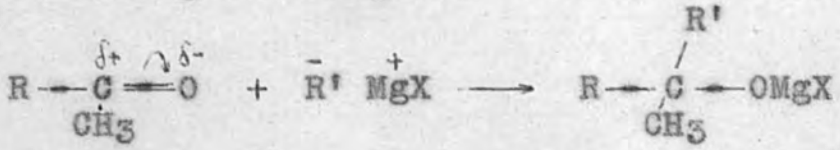


$R.\ CO.CH_2\ (OH)-C{<}^{CH_3}_{R}$

Therefore it is necessary to consider a condition from which the ketone may be converted into any one of the above products. Furthermore, since in many cases it is possible to obtain all four products from the same reaction, it is necessary to consider a condition of the ketone which can lead to the simultaneous formation of all of these products. Again, the ketone must be in a condition from which it is possible to obtain not only the dimer (4), but also the trimer, and possibly a four or more molecule polymer.

The formation of compounds (2), (3), and (4) is accompanied by the evolution of gaseous products in those cases in which the R' radical of the Grignard reagent can form a gaseous product, and the evolution of gas has been observed to take place immediately contact between the two reactants is established. It is reasonable to suppose that for a ketone to take part in several reactions at the same time leading to widely different products it must be in an unusually active condition; and it is also reasonable to suppose that, since evolution of gas begins immediately contact is made between the ketone and Grignard reagent, this contact brings the ketone into its active condition.

It is well known that the carbonyl group is polarised, and that this polarisation is a permanent feature. Therefore it may be suggested that the activity of the ketone lies in its polarised carbonyl group. This is quite acceptable if one wishes to explain perhaps the normal addition of a Grignard reagent:



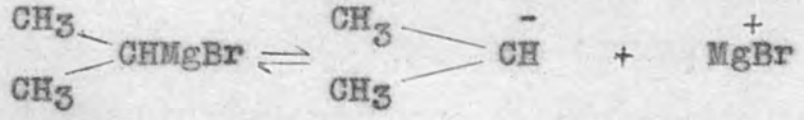
$$R-\underset{CH_3}{\overset{\delta+}{C}}=\overset{\delta-}{O} + \overset{-}{R'}\,\overset{+}{Mg}X \longrightarrow R-\underset{CH_3}{\overset{R'}{C}}-OMgX$$

It is required to explain, however, a higher and variable activity within the molecule, an activity which varies with the Grignard reagent used. That is, an activity which is subject to the demand made upon it. Such an activity is associated with the inductomeric effect, and it seems that in this effect and the demands made for its operation lies some of the explanation of these abnormal reactions with Grignard reagents.

With this in mind it is now pertinent to consider the anomalous reactions.

Enolisation and Condensation.

It has been found that *iso*propylmagnesium bromide causes considerable condensation of methyl ketones, and in doing so is reduced to propane. The simplest way in which to envisage the reduction of an *iso*propyl radical is by an *iso*propyl ion accepting a proton. That is, there is in solution a partly ionised Grignard reagent, the equilibrium



$$\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!>\!\mathrm{CHMgBr} \rightleftharpoons \begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!>\!\overset{-}{\mathrm{CH}} + \overset{+}{\mathrm{MgBr}}$$

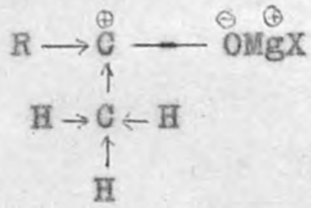
of which ionisation proceeds to the right as the ions are used up. On the addition of the already polarised ketone to the Grignard solution, the MgX cation joins to the oxygen of the carbonyl group, and in its approach to this group, makes a demand on the inductomeric capability of the molecule, causing the following inductomeric shift:

The $\bar{\text{O}}$ and the MgBr unite. It is insufficient to say, however, merely that the MgX cation of the Grignard reagent unites with an atom possessing an unshared pair of electrons, such as the oxygen atom of the carbinol group. If the union of the MgX cation with the oxygen atom is accompanied by an inductomeric shift in the ketone molecule, it is probable that a variation in the nature of the cation will cause some variation in the extent and nature of the reactions which follow. That is, a variation in the nature of the cation would cause a variation in the magnitude of the demand made for an inductomeric shift. In the series of cations

$$\overset{+}{\text{MgF}} \qquad \overset{+}{\text{MgCl}} \qquad \overset{+}{\text{MgBr}} \qquad \overset{+}{\text{MgI}}$$

the electrophilic nature of the cations will increase from left to right. (By virtue of the high electronegativity of the fluorine atom, MgF may of course be electronegative, $\overset{-}{\text{MgF}}$) If therefore, a carbonyl compound were presented separately with two cations, one more electrophilic than the other, there is no doubt that union with the oxygen of the carbonyl group would occur in both cases, but the request made for the inductomeric shift by the more electrophilic cation would be greater than that made by the less electrophilic cation.

As evidence for such an effect of the cation the difference in yields of normal addition product is not likely to be conclusive. It is likely that the effect of the cation would be seen more clearly in the yields and nature of the abnormal reaction products. The union of the oxygen atom and the cation produces a state in which the hyperconjugation of the methyl group hydrogen atoms is included in the inductomeric shift.



Withdrawal of electrons from the C-H bonds of the methyl group loosens the hold on the hydrogen atoms and may result in the loss of a proton. Whether a proton will be lost or not depends (1) on the extent of electron withdrawal, and (2) on the nature of the Grignard radical R'. It is apparent therefore, that a variation in the electrophilic nature of the cation may be noticeable under (1).

If in the presence of an isopropyl anion there is a molecule from which a proton can easily be removed, it will be removed. The following happens:

(I)

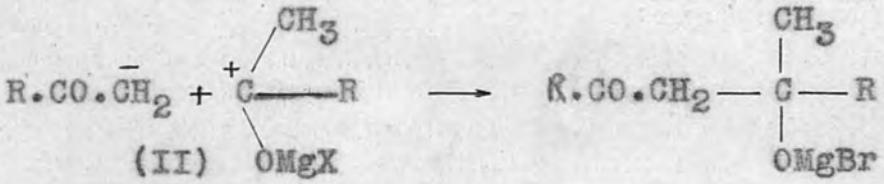
The enolate (I) however, does not remain as an enolate but passes into the pseudo-enolate.

$$R.CO.CH_2MgBr$$

In a number of cases such pseudo-enolates have been isolated It is such a pseudo-enolate which is involved in condensation. The pseudo-enolate may be assumed to exist in equilibrium with its ions:

$$R.CO.CH_2MgBr \rightleftharpoons R.CH.\overset{-}{C}H_2 + \overset{+}{M}gBr$$

and in condensation the pseudo-enolate ion unites with an original alcoholate ion II



$$R.CO.\overset{-}{C}H_2 + \overset{+}{C}(CH_3)(R)(OMgX) \longrightarrow R.CO.CH_2-C(CH_3)(R)-OMgBr$$

(II)

so that on hydrolysis the ketol $R.CO.CH_2\underset{CH_3}{\underset{|}{C}}(OH).R$ is formed.

There is a point to be settled, however:

Why at this stage does the alcoholate cation react as an alcoholate instead of losing a proton as in the earlier stage? The answer is this: After the initial formation of the pseudo-enolate ion R.CO.CH$_2$*, any further alcoholate molecules formed are subject to attack by yet another ion,the pseudo-enolate ion. Whether or not this will behave in the

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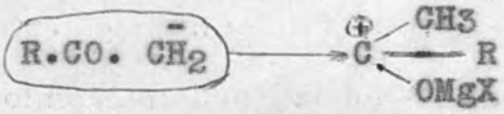
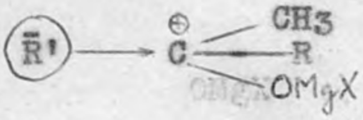
*Although this ion is called the pseudo-enolate ion by the author, it is possible that there exists a mesomeric state between the true enolate ion and the pseudo-enolate ion.

same way as the $\bar{R}'$ ion of the Grignard reagent naturally depends on the ion. There is no reason to believe that it does not do so. For if $R.CO.\overset{-}{CH_2}$ takes a proton from the original alcoholate, the original ketone is formed and will continue reaction. If $R.CO.\overset{-}{CH_2}$ enters into ketolate formation, however, there is an obvious conclusion to be drawn. That is, if $R.CO.\overset{-}{CH_2}$ can take part in the following reaction,



$$\boxed{R.CO.\overset{-}{CH_2}} \longrightarrow \overset{\oplus}{C}\begin{matrix} CH_3 \\ R \\ OMgX \end{matrix}$$

then in the majority of cases the $\bar{R}'$ ion of the Grignard reagent should be able to take part in the similar normal addition reaction.



$$\boxed{\bar{R}'} \longrightarrow \overset{\oplus}{C}\begin{matrix} CH_3 \\ R \\ OMgX \end{matrix}$$

This means that in the majority of cases in which condensation occurs the normal addition reaction should occur too. This obviously cannot apply to all reactions, because the structure of the $\bar{R}'$ ion may hinder approach to the alcoholate, whereas the $R.CO\bar{C}H_2$ may have free approach. If, however, both $\bar{R}'$ and $R.CO\bar{C}H_2$ have structures which combined with the steric hindrance in the alcoholate, prevent both kinds of addition, the only reaction occurring throughout will be enolisation.

This means at once that enolisation and condensation are not caused entirely by the inability for normal addition to take place. The greater the hindrance in a ketone then the less the condensation, but this does not mean that enolisation is a direct result of great hindrance in the ketone. Enolisation is caused by the reactivity of the reactants. It is not true to say that enolisation occurs only because there is difficulty in normal addition. It is true however, that if normal addition is difficult, there is more chance for enolisation to occur.

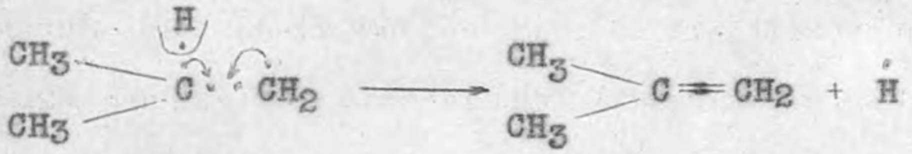
Reduction

Reduction of carbonyl compounds by a Grignard reagent, however, presents a different problem from condensation. It is easy enough to say that since reduction consists in the donation of hydrogen and the formation of an olefin that the hydrogen comes from the same molecule as the olefin. Evans and Pearson[43] have assumed that this is accomplished by the donation of a hydride ion by the Grignard anion $\overset{-}{R}'$. That is, with a polarised ketone $R_2.\overset{\delta+}{C}\overset{\curvearrowright\delta-}{=}O$ and an ionised Grignard reagent $\overset{-}{R}'\ \overset{+}{MgX}$, the anion $\overset{-}{R}'$ has in some way to supply the $\overset{\delta+}{C}$ with a hydrogen atom carrying a negative charge. This is as unlikely as it is unusual. Furthermore, if the approach of $\overset{+}{MgX}$ to the carbonyl group causes an inductomeric shift in the ketone molecule, one must ask why the $\overset{-}{R}'$ anion should give up $\overset{=}{H}$ instead of accepting $\overset{+}{H}$.

In reduction, there is one definite piece of evidence to bear in mind; an olefin is produced. Therefore it is pertinent to ask which form of the R' radical is most likely, under present conditions, to lose hydrogen and become an olefin. The answer to this is that the R' radical should be as a free radical. This means that the Grignard reagent must undergo homolytic scission:

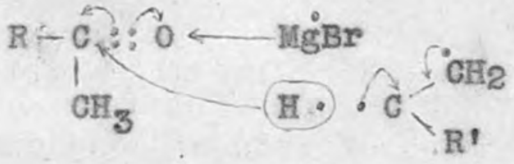
$$R\cdot \vdots \cdot MgX$$

It is known that a free radical will tend to stabilise itself in the easiest way possible, and in the case of reduction this stabilisation must come by the loss of a hydrogen atom, the free electron of the radical becoming one of a pair:



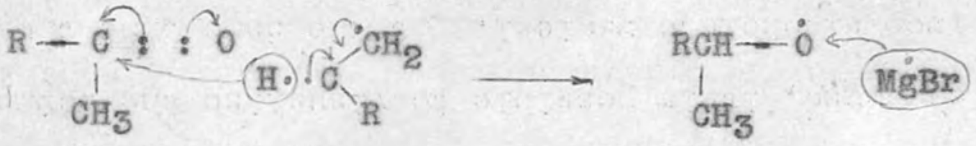
Homolytic scission requires that free MgX radicals are present. In the work of Gomberg *et al* (pp 17-19) the formation of pinacols by free radical mechanism is presented as follows:

so that by analogy, in reduction one should have:-



The movement of electrons from the carbonyl double bond is not unlikely. The whole stability of free radicals containing phenyl groups lies in the ability of the phenyl group to distribute a charge, thereby increasing the uncertainty of position and decreasing the molecular free energy. If similar distribution can occur in the carbonyl compound, it is possible to visualise the formation of a free alcoholate radical. At the same time there is no demand for the inductomeric shift of the condensation mechanism, and enolisation and condensation should be small.

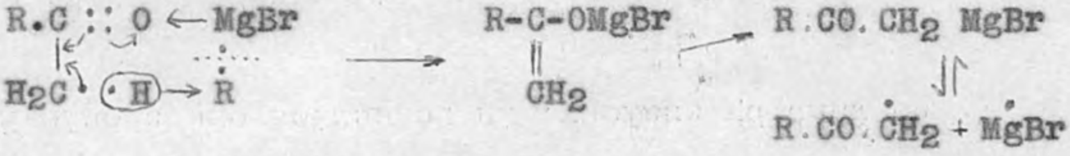
Whether the above formulation shows the right sequence of reaction cannot be said. It may be that the first addition to take place is at the carbon atom:



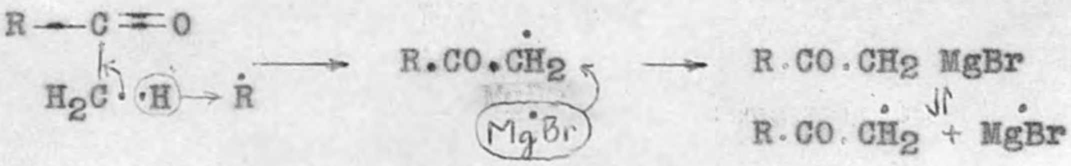
Enolisation and Condensation by Free Radicals:

The possibility that enolisation and condensation may take place by a free radical mechanism will be apparent. For this to happen there must be free pseudo-enolate radicals in solution, and the origin of these may be formulated in three ways:

(1)



(2)



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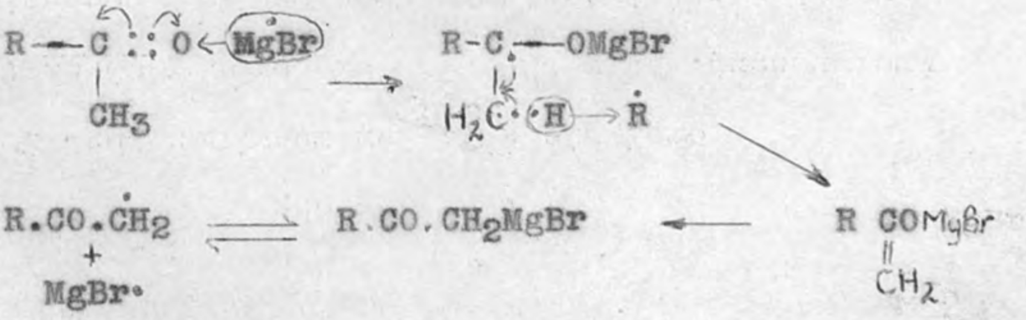
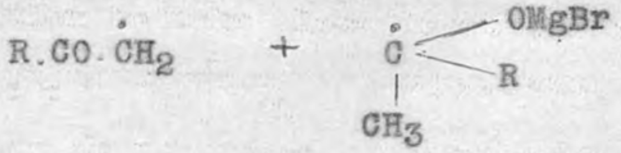


Since condensation would be effected by the union of a pseudo-enolate radical and an alcoholate radical,



it seems that formulation (3) is most probable.

If both reduction and condensation can take place by a free radical mechanism, one may perhaps explain the preference for reduction by some radicals, and condensation by others, by the difference in stability of the radicals. It has already been said that a free radical will take the easiest way of stabilising itself, so that whereas in certain cases this stability is attained by giving up a hydrogen atom, in others it may be attained by accepting a hydrogen atom. And it would follow that where a free radical, which normally stabilised itself by accepting a hydrogen atom, has no easily acceptable hydrogen atom to accept, it would take the second less easy way of giving up a hydrogen atom.

On the other hand, if the mechanisms of reduction and condensation are those of free and charged radicals respectively, one must make the following observations:

(1) The same Grignard reagent may react either as a charged or neutral radical, for the present writer finds that most Grignard reagents cause both reduction and condensation.

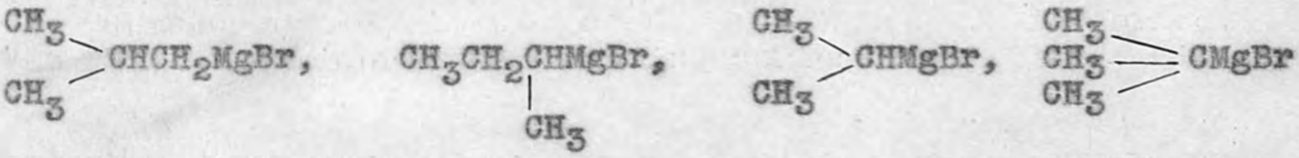
(2) A Grignard reagent may react both as a charged and neutral radical at the same time, for the present writer finds that in many cases reduction, enolisation and condensation occur together.

Application of Results and Further Considerations of Mechanisms.

Dissociation of a Grignard reagent into ions has been interpreted by the following equilibrium:

$$RMgX \rightleftharpoons \overset{-}{R} + \overset{+}{MgX}$$

Yet if one considers the following series



$$(CH_3)_2CHCH_2MgBr, \quad CH_3CH_2CH(CH_3)MgBr, \quad (CH_3)_2CHMgBr, \quad (CH_3)_3CMgBr$$

it is seen that the tendency to ionize into $\overset{-}{R}$ and $\overset{+}{MgX}$ should decrease in the order given.

The results obtained and reported in part II show that the tendency for hydrogen acceptance by a number of Grignard reagents is in the order

$$R = \underline{iso}Bu < \underline{n}\text{-}Pr < \underline{n}\text{-}Bu < \underline{sec}\text{-}Bu < \underline{iso}Pr$$

so that one would conclude that hydrogen acceptance is not a function of alkyl ions, and one is left with the alternative that the magnitude of hydrogen acceptance is a function of free alkyl radicals; that is, that in all cases the Grignard reagent does not ionise but reacts by homolytic scission.

This, however, does not permit of an explanation of the difference between Grignard reagents containing different halogens; that is, if the mechanism of reactions involves only free radicals, there should be little difference between using *iso*propylmagnesium chloride and *iso*propylmagnesium bromide, or between *sec*-butylmagnesium chloride and *sec*-butylmagnesium bromide. It is not sufficient to invoke a difference in the speed of reaction, such as Dubois has done, for if the difference lay only in the speed of reaction, the ratio of the products formed should be unchanged. The difference in the products of the above reactions is such that can be explained only by a difference in structure of the Grignard reagents. This explanation cannot be given if all Grignard reagents only react by homolytic scission, but it can be given if a Grignard reagent can react both homolytically and heterolytically. For if the ratio in which Grignard chlorides react homolytically and heterolytically is smaller than that with which Grignard bromides react, the ratio of hydrogen donation to proton acceptance will be smaller for chlorides.

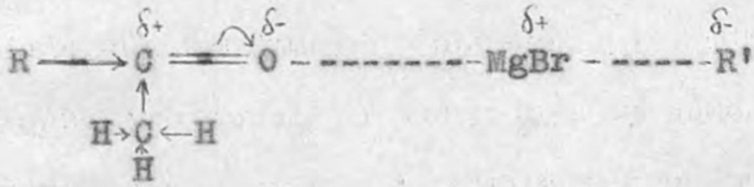
The fact that the deliberate promotion of free radicals by cobaltous chloride increases the amount of hydrogen acceptance in the case of <u>iso</u>propylmagnesium bromide supports the above postulation.

Where it is possible to include ionisation in this postulation is if the Grignard reagent is considered to exist not in ionic equilibrium of dissociation, but in the polar state $\overset{\delta-}{R}\overset{\delta+}{Mg}X$.

In this way the formation and stability of such a polar state would increase in the order:-

<u>iso</u>BuMgBr < <u>sec</u>BuMgBr < <u>iso</u>PrMgBr < <u>tert</u>-BuMgBr

The dissociation of the polar molecule would occur in the presence of a reactant permitting nucleophilic attack, and one may envisage the ionic mechanism of enolisation and condensation occurring. It is possible that this may go through the transition state



$$R \longrightarrow \underset{\substack{\uparrow \\ H\rightarrow C\leftarrow H \\ \uparrow \\ H}}{\overset{\delta+}{C}} = \overset{\delta-}{O} \text{ - - - - - - - - - } \overset{\delta+}{MgBr} \text{ - - - - - - } \overset{\delta-}{R'}$$

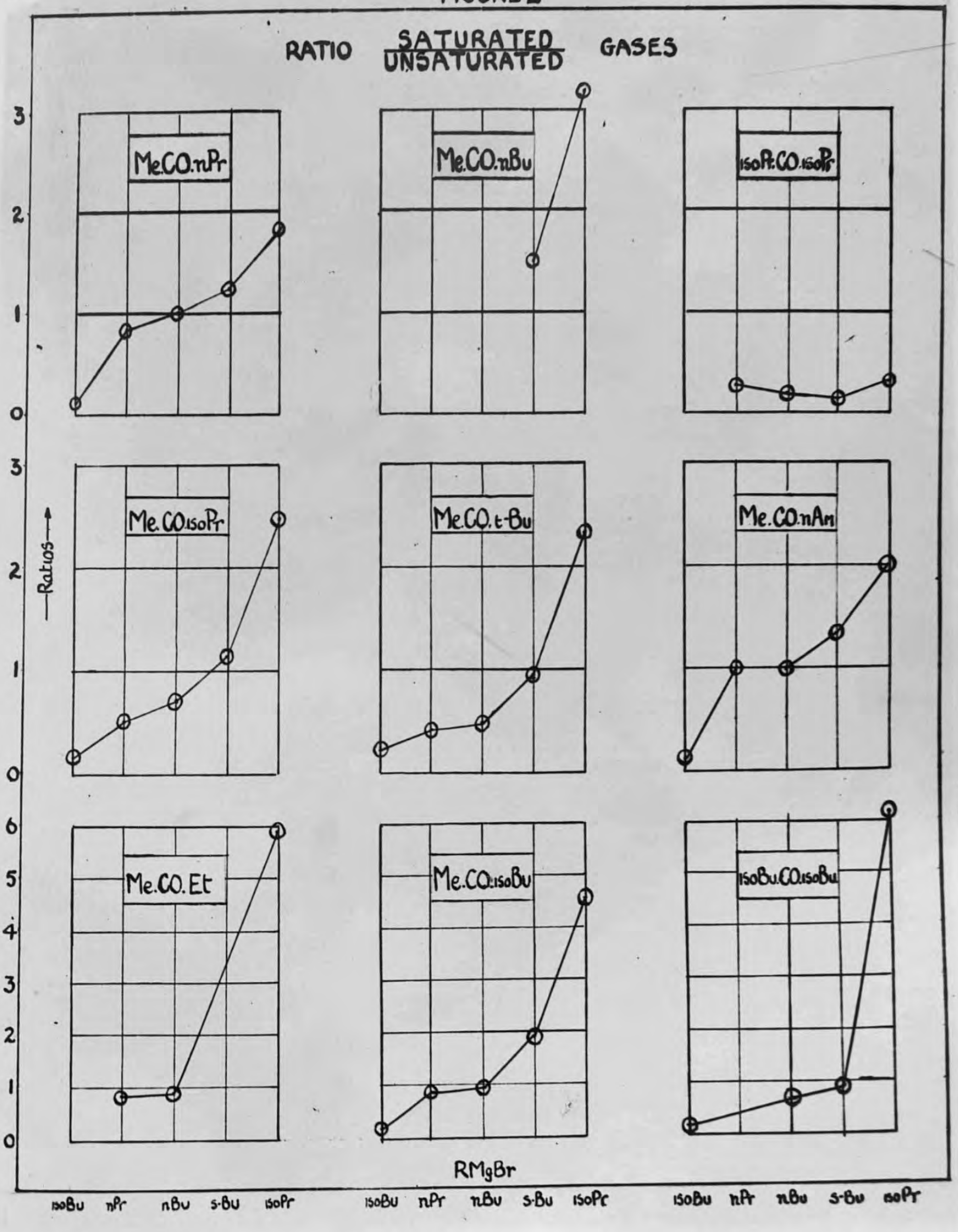
which is followed by the ejection of the R' ion. There is as yet no evidence to show the nature of the transition state.

One may visualise further that the greater the tendency toward the polar state the less likely that a free radical mechanism will occur, and that, therefore, Grignard reagents participate in the following equilibria

$$\dot{R} + \dot{Mg}X \underset{(1)}{\rightleftharpoons} RMgX \underset{(2)}{\rightleftharpoons} \overset{\delta-}{R}\text{- - - - -}\overset{\delta+}{Mg}X$$

and that the tendency for either equilibrium (1) or (2) varies

FIGURE 1


RATIO SATURATED/UNSATURATED GASES
Me.CO.nPr
Me.CO.nBu
isoPr.CO.isoPr
Me.CO.isoPr
Me.CO.t-Bu
Me.CO.nAm
Me.CO.Et
Me.CO.isoBu
isoBu.CO.isoBu
Ratios
0
1
2
3
0
1
2
3
0
1
2
3
4
5
6
RMgBr
isoBu
nPr
nBu
s-Bu
isoPr
isoBu
nPr
nBu
s-Bu
isoPr
isoBu
nPr
nBu
s-Bu
isoPr

not only with the Grignard reagent, but with the reactant presented to the Grignard reagent.

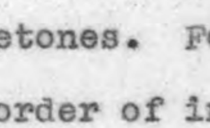
Such a postulate is in agreement with the results obtained for the interaction of each ketone with the series of Grignard reagents. That is, as Figure I shows, the proportion of saturated gas in the total amount of gas formed increases for each ketone, except di*iso*propyl ketone, in the order

R = *iso*Bu < *n*-Pr < *n*-Bu < *sec*-Bu < *iso*Pr

indicating that the above Grignard reagents show a tendency to exist in the polar state in that order.

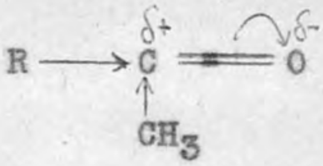
It must be admitted, however, that it is much more difficult to apply the postulate to the results when they are considered for individual Grignard reagents reacting with a series of ketones. For it can be seen from Figure I that although the order of increase in the ratio of saturated gas to unsaturated gas is constant, the magnitude of the increase varies with the ketone, and it is in explaining fully the part played by the ketone that one meets with difficulties.

The function of the second group in the methyl ketones cannot be consistently explained by the results which have been obtained. If the general ketone



$$R{-}\underset{\displaystyle CH_3}{\overset{}{C}}{=}O$$

is considered, one might ask whether an increase in the electron donation from the group R will suppress the withdrawal of electrons from the C-H bonds of the methyl group.



$$\underset{\overset{\uparrow}{CH_3}}{R \longrightarrow \overset{\delta+}{C}} = \overset{\delta-}{O}$$

This is likely to be the case, since the flow of electrons towards the C atom of the carbonyl group depends on the electron density on that carbon atom. Therefore, in any series of ketones, although the size of the R group may cause an increase in the amount of anomalous reaction, its nature may cause a decrease in the reaction giving rise to the saturated gas.

That is, one would expect that in using the ketones

Me.CO.*iso*Bu Me.CO.*iso*Pr Me.CO.*tert*-Bu

the amount of anomalous reaction would increase in this order, but that, owing to the increase in the electron donation of the second group, the order of increase in percentage of saturated gas would be the reverse.

It will be seen that this is true for *n*-propyl, *n*-butyl, *sec*-butyl, and *iso*propyl magnesium bromides, but that the order is exactly the opposite for *iso*butylmagnesium bromide.

However, it will also be seen that these remarks should not be restricted to the three ketones above, but should include the straight chain ketones used. That is, the series should be written for total anomalous reaction as

Me.CO.*n*Pr $<$ Me.CO.*n*Am $<$ Me.CO.*iso*Bu $<$ Me.CO.*iso*Pr $<$ Me.CO.*tert*Bu and for percentage of saturated gas as

Me.CO.tertBu $<$ Me.CO.isoPr $<$ Me.CO.isoBu $<$ Me.CO.n-Pr $<$ Me.CO.nAm

The results obtained are partly erroneous in this light. Those obtained for n-propyl- and n-butylmagnesium bromides are in agreement with this order, but the straight chain ketones are misplaced for isopropyl- and sec-butylmagnesium bromides.

In the case of isobutylmagnesium bromide the great diversion may be because this Grignard reagent exists for the greater part in the free radical equilibrium, and is thus very different from the other Grignard reagents, which show a capability of existing, for a goodly part, in the polar state. When one considers Figure I, one is bound to ask why there should be so great a fall in the ratio for isobutylmagnesium bromide. Purely on the strength of inductive capability these graphs should rise in the order:-

R = n-Bu   n-Pr   isoBu   sec-Bu   isoPr

The author must admit that the fact that the order is in each case

R = isoBu   n-Pr   n-Bu   sec-Bu   isoPr

is unexpected on purely inductomeric reasoning, and it may be possible that in the case of isobutyl bromide there is another factor involved.

In mechanisms involving free radicals one cannot overlook the possibility of mutual oxidation and reduction of the alkyl radical. If this were to happen in the case of *iso*butylmagnesium bromide, the percentage of saturated gas would be higher than the postulated equilibria allow instead of lower. There is also the possibility of interaction of free radicals with the solvent, but the author is of the opinion that if this did occur, it would do so only to a small extent, and would not contribute very much to the results obtained. For he believes that if dissociation into free radicals is enhanced by a ketone, there are in solution much more reactive molecules than those of the solvent, so that while the possibility of solvent attack is not refuted, its magnitude is believed not to be of prime importance.

With methyl ethyl ketone the probability that this ketone undergoes condensation in two ways when it reacts with *iso*propylmagnesium bromide leads one to expect a high percentage of saturated gas, and this is obtained, the percentage being higher than that from the other methyl ketones.

Yet with *n*-propylmagnesium bromide and *n*-butylmagnesium bromide the percentage of saturated gas is smaller than the corresponding percentages for the other straight chain ketones. It may be that in view of the small tendency of *n*-propylmagnesium bromide and *n*-butylmagnesium bromide to react in the polar form, the likelihood of condensation occurring at two carbon atoms in the ketone is small. In this way the electron donation from the ethyl group, being greater than in n-propyl and n-amyl groups, should cause a decrease in the percentage saturated gas, and the order of increase in percentage saturated gas would proceed, for the ketones Me.CO.R:-

R == n-Am n-Pr Et isoBu isoPr tert-Bu

The results obtained are not in serious disagreement with this, the percentages obtained being:-

R =	n-Am	n-Pr	Et	isoBu	isoPr	tert-Bu
n-PrMgBr	50.0	45.7	45.2	45.8	33.3	20.9
n-BuMgBr	50.0	50.0	47.1	47.6	41.2	35.4

tert-Butylmagnesium bromide

If it is so that in a Grignard reagent RMgBr the greater the electron donation of the group R the less the tendency to form free radicals, the results obtained with tert-butylmagnesium bromide are entirely erroneous, for one would expect the percentage of saturated gas to be the highest of all the Grignard reagents used. As noted on page 79 , tert-butylmagnesium bromide needs a more detailed investigation, and the author does not think that the results obtained for this Grignard reagent can be used for comparison with those of the other Grignard reagents.

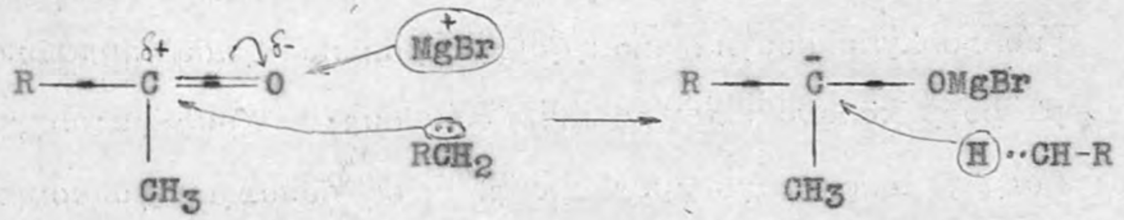
Diisopropyl ketone and diisobutyl ketone.

The behaviour of diisopropyl ketone is entirely different from that of the other ketones in that it undergoes reduction by the Grignard reagents which are capable of causing much enolisation and condensation. It is to be concluded from this that the difficulty in removing a proton from the isopropyl groups in this ketone causes the Grignard reagents to function mostly in the way demanded by the ketone, that is, as hydrogen atom donors.

Diisobutyl ketone, however, behaves more like the methyl ketones in that the type of reaction is controlled by both ketone and Grignard reagent. That is, with isopropylmagnesium bromide the ketone gives up a proton as readily as the Grignard reagent can accept it, while with sec-butylmagnesium bromide, which in general is able both to give and to take hydrogen (in the appropriate form) with equal ease, diisobutyl ketone undergoes almost equal amounts of reduction and enolisation. In the case of n-butylmagnesium bromide the result obtained is again not unexpected.

The work of Kharasch and Weinhouse [51]

In a systematic investigation of the reduction of benzophenone the above authors conclude that reduction by Grignard reagents is caused by charged radicals, but only those of intermediate electronegativity. The term electronegativity is given as meaning affinity for electrons. The proposal is that a Grignard reagent dissociates into ions, and the alkyl ion gives up both electrons in reduction. The authors do not deal further with the mechanism of the reduction, and one assumes therefore, that they intend that the carbonyl group should receive two electrons from the alkyl ion, to be followed later by a proton from the same ion.



With this mechanism in mind they give a series of radicals in order of decreasing electronegativity, and with each radical is given the amount of reduction of benzophenone caused when the radical is used as a Grignard reagent:

Radical	% reduction
Ethyl	2
n-propyl	58
n-butyl	59
iso-butyl	91
*cyclo*pentyl	94
sec-butyl	40
*iso*amyl	30
$C_6H_5(CH_2)_2$	33
$C_6H_5(CH_2)_3$	20
*cyclo*hexyl	7
allyl	ca. 5

The gradual increase and subsequent fall is attributed not to a decrease in reducing tendency, but to a masking of the reducing tendency by an increasing addition velocity. That is, the more electronegative a radical is, the slower is its speed of addition reaction. Evidence is given for the relationship between electronegativity and speed of reaction by the results of competitive reactions, in which Grignard solutions containing a mixture of radicals of different electronegativity were allowed to react with benzophenone. It was found that the radical which took part in addition was that which had the smaller electronegativity.

One might concludd from this, therefore, that if addition were not possible, the amount of reduction would increase in the order given for decreasing electronegativity. That is, extracting the alkyl radicals from the above table the order of reduction is

R = *n*-Pr < *n*-Bu < *iso*-Bu < *sec*-Bu < *iso*Am

and from statements in the text one concludes that since *tert*-Bu is less electronegative than *iso*Bu, the amount of reduction to be expected if addition were not possible would be

tert-Bu > *iso*Bu

One can see further that the term electronegativity may be paralleled with the inductive effect in the alkyl groups:-

Electronegativity: *n*-Pr ≃ *n*-Bu > *iso*Bu > *sec*-Bu > *tert*-Bu
Inductive effect : *n*-Pr ≃ *n*-Bu < *iso*Bu < *sec*-Bu < *tert*-Bu

so that one may include in the order of decreasing electronegativity that of the *iso*propyl radical:-

Electronegativity: *n*-Pr ≃ *n*-Bu > *iso*Bu > *sec*-Bu > *iso*Pr > *tert*-Bu
Inductive effect : *n*-Pr ≃ *n*-Bu < *iso*Bu < *sec*-Bu < *iso*Pr < *tert*-Bu

From this one concludes that the order of reducing tendency in the absence of addition must be

R = *n*-Pr ≃ *n*-Bu < *iso*Bu < *sec*-Bu < *iso*Pr < *tert*-Bu

In actual fact the present author has found that for the first five radicals the opposite is true, for the tendency for reduction, interpreted in a way intended to overcome the variations of hindrance (whether steric or of velocity), is in the order:

R = *iso*Bu > *n*-Pr ≃ *n*-Bu > *sec*-Bu > *iso*Pr

This has been found so whether addition can take place or not.

Furthermore the concept of electronegativity and reduction by ions does not satisfy the variation in the halide of the Grignard reagent. In the two reagents,

RMgCl and RMgBr,

electronegativity being akin to nucleophilic power, one concludes that RMgCl will dissociate with greater ease than RMgBr, and therefore be capable of causing, in a given time, more reduction than RMgBr. In fact the difference in reducing powers for a given ketone should be one of time of reaction only. Kharasch and Weinhouse find that n-butylmagnesium bromide causes less reduction than n-butylmagnesium chloride, a result which is contrary to the findings of the present author and of other workers for other Grignard bromides and chlorides.

Conclusion.

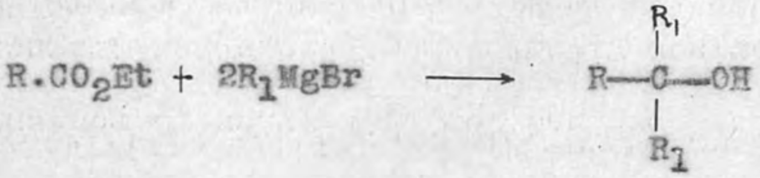
Kharasch *et al* [54] concluded that a Grignard reagent could act by either an ionic or free radical mechanism for the reaction between methyl magnesium halides and mesitoyl chloride.

The present author has come to the conclusion that this possibility of reacting as ions or free radicals is true of all Grignard reagents. It is believed however, that ionic mechanisms do not involve a completely ionised reagent, but that the Grignard reagent can dissociate into ions as required by the second reagent. It is further concluded that whereas reduction of carbonyl compounds is a function of free radicals, enolisation and condensation are a function of ions, and that the differences observed in the change of Grignard reagent and the change of carbonyl compound result from the call made for these two types of reaction and the ability of the Grignard reagent to answer to the call.

It must be borne in mind that some of the experimental results obtained do not bear out the reasoning which has been applied to the causes which make the mode of reaction vary, and the author stresses that a more detailed analysis must be made of a larger number of reactions.

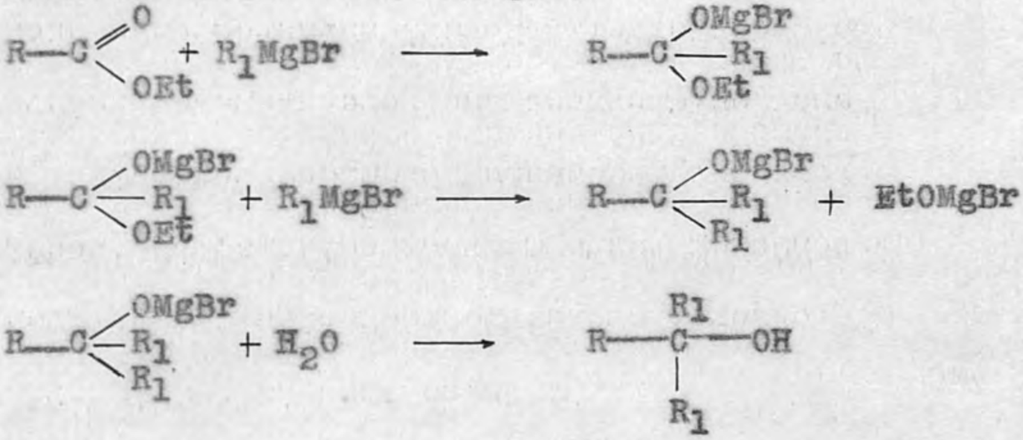
The Reaction of esters with Grignard Reagents

The interaction of an ester and Grignard reagent is designed to give a tertiary carbinol as the final product



$$R.CO_2Et + 2R_1MgBr \longrightarrow R-\overset{R_1}{\underset{R_1}{C}}-OH$$

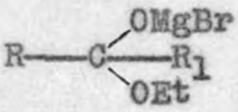
and the mechanism proposed by Grignard (1901)[55] for such a reaction was one of three stages:-



However, it was found by Boyd and Hatt (1927)[56] that pinacols are formed in good yield when esters are treated with Grignard reagents in the presence of excess magnesium, and these authors consequently suggested that this is due to the preliminary formation of a ketone.

$$R.CO_2Et + R_1MgBr \longrightarrow R.CO.R_1 + EtOMgBr$$

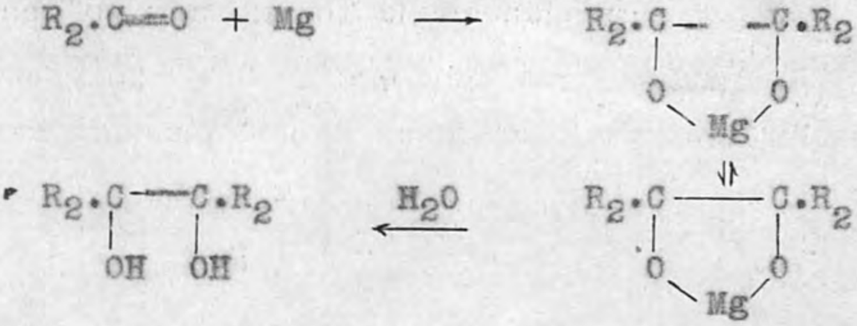
Blaise and Courtot(1905)[57] had already isolated ketones from ester reactions, but according to Boyd & Hatt, this could have resulted from the hydrolysis of the addition complex



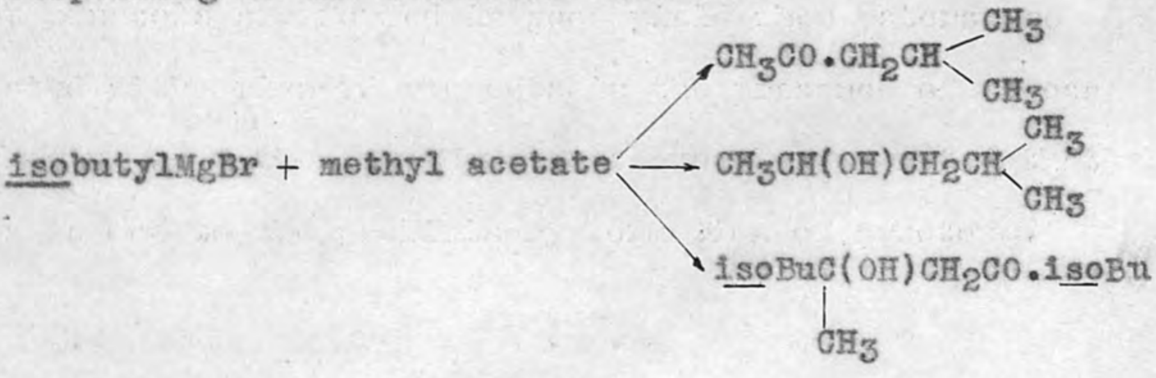
$$R{-}C(OMgBr)(R_1)(OEt)$$

which might go through the reaction without breaking down to the ketone.

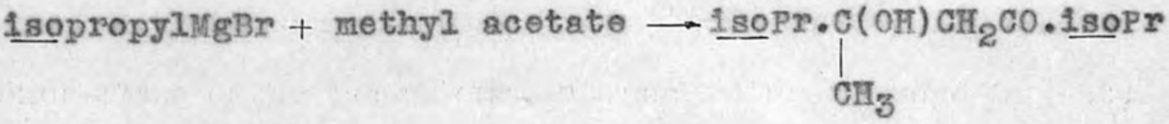
The formation of pinacols left Boyd and Hatt in no doubt, however, that the ketone was formed during reaction, and they suggested the following mechanism:



The present author has found that the action of Grignard reagents on methyl acetate gives the same products as the action of the Grignard reagents on the ketone corresponding to the reaction. That is



$$\text{\underline{iso}butylMgBr} + \text{methyl acetate} \longrightarrow \begin{cases} CH_3CO.CH_2CH(CH_3)_2 \\ CH_3CH(OH)CH_2CH(CH_3)_2 \\ \text{\underline{iso}Bu}C(OH)(CH_3)CH_2CO.\text{\underline{iso}Bu} \end{cases}$$



$$\text{\underline{iso}propylMgBr} + \text{methyl acetate} \longrightarrow \text{\underline{iso}Pr}.C(OH)(CH_3)CH_2CO.\text{\underline{iso}Pr}$$

The above findings are further evidence that the ketone must exist during reaction. Free ketone was obtained and characterised in the isobutylmagnesium bromide reactions (pp. 127). The products of anomalous reaction in the esters are moreover of the same extent as the products of anomalous reaction in the ketones. That is, *iso*butylmagnesium bromide gave a large amount of secondary carbinol, while *iso*propylmagnesium bromide gave a large amount of ketol, although comparison of the volumes of gas obtained from corresponding ester and ketone reactions indicate that the total anomalous reaction is somewhat greater in the case of the ketones:

isoPrMgBr on	Total vol.	satd.	unsatd.	% satd.
Methyl acetate	19,500	14,800	4,700	75.9
Me.CO.*iso*propyl	26,500	18,850	7,650	71.2

n-PrMgBr on	Total vol.	satd.	unsatd.	% satd.
Methyl acetate	6,500	3,000	3,500	46.0
Me.CO.*n*-propyl	7,000	3,200	3,800	45.7

isoBuMgBr on	Total vol.	satd.	unsatd.	% satd.
Methyl acetate	16,500	5,700	10,800	34.5
Me.CO.*iso*butyl	18,000	2,400	15,600	13.3

While insufficient work has been done on ester reactions to permit any discussion of mechanism, these results are given as further evidence of the existence of free ketone during reaction.

PART IV

2:4:6-Trimethylheptane

This hydrocarbon has been synthesised by Tuot(1933)[58]. The most suitable basis of the hydrocarbon is 2:4:6-trimethylheptanol-4. This was made by Tuot and is the carbinol on which the present synthesis was based.

There are three straightforward methods of making 2:4:6-trimethylheptanol-4. They are:

(1) by the interaction of methyl *iso*butyl ketone and *iso*butylmagnesium bromide

$(CH_3)_2CHCH_2.CO.CH_3 + (CH_3)_2CH_2CHMgBr$

(2) by the interaction of an acetic acid ester and *iso*butylmagnesium bromide

$CH_3CO_2R + (CH_3)_2CHCH_2MgBr$

(3) by the interaction of di*iso*butyl ketone and methyl-magnesium bromide

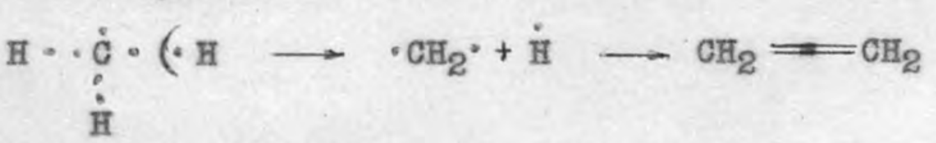
$(CH_3)_2CHCH_2.CO.CH_2CH(CH_3)_2 + CH_3MgBr$

Each method was tested and it was found that for the purpose of preparing a pure hydrocarbon method (1) is most suitable. However, method (2) was used for preparing most of the hydrocarbon. Methods (1) and (2) suffer from the two great disadvantages in using *iso*butyl magnesium bromide. Firstly the preparation of pure *iso*butylbromide is difficult and exacting. (A part of this thesis describes the difficulties encountered in the preparation of this reagent). Secondly the action of *iso*butyl magnesium bromide on carbonyl compounds is accompanied by reduction of the carbonyl group.

Method (2) was chosen since methyl *iso*butyl ketone was not available, and since it gave better yields than (1).

From the point of view of Grignard reagent it might appear that methods (1) and (2) bear no comparison with method (3). In the last case however it was found that reduction of the ketone to the secondary carbinol occurred to a larger extent than was expected. That any appreciable reduction occurs in this method makes it immediately questionable, for the separation of the secondary and tertiary carbinols would be difficult; their respective B.Ps. are 180° and 174°. It was indeed found that by fractionation at reduced pressure (Expt.45), the major part of the reaction product was obtained as an azeotrope of the tertiary and secondary carbinols boiling at 33-34°/0.75 mm.Hg and having n_D^{22} 1.4309.

At first sight one would not expect a methyl Grignard reagent to cause reduction, since reduction necessitates the formation of methylene radicals and their linking to form ethylene:



$$H\cdot\cdot\underset{\dot{H}}{\dot{C}}\cdot(\cdot H \longrightarrow \cdot CH_2\cdot + \dot{H} \longrightarrow CH_2 = CH_2$$

Although it was not found possible to separate the azeotrope by fractionation at a different pressure (Expt 46) it was possible to obtain a phenylurethane by heating one of the lower boiling fractions with phenylisocyanate. The M.P of the phenylurethane was 152-153°. SKita (1908)[59] gives that of diisobutylcarbinol as 154°. Treatment of the same fraction with 2:4-dinitrophenylhydrazone by Brady's method failed to give a ketone derivative.

Similar reduction by methylmagnesium bromide was reported by Stas[50] who obtained a 78% yield of the secondary carbinol from di<u>iso</u>propyl ketone. Whitmore and George[36], however, say that this reaction is accompanied by neither reduction nor enolisation.

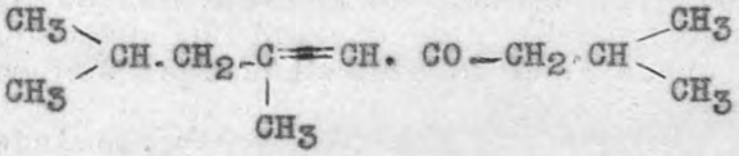
It was found possible however, to separate (virtually) the two carbinols by dehydration. By distilling over naphthalene-2-sulphonic acid (Expt.46d) only 2:4:6-trimethylheptane was obtained, B.P. 144-145° n_D^{23} 1.4204, which on reduction gave 2:4:6-trimethylheptane, B.P. 145-146° n_D^{23} 1.4075. The characteristics of 2:6-dimethylheptene and 2:6-dimethylheptane are respectively B.P. 132° and B.P. 133-134° n_D^{23} 1.4067.

Although it was possible to obtain the desired olefin and parafin from this reaction it is nevertheless preferable to use a reaction such as (1) and (2) from which a pure product representative of each stage in the synthesis can be obtained.

Method (1) was that used by Bodroux and Tabory(1908)[60], the first occasion on which 2:4:6-trimethylheptanol-4 was synthesised. In a series of Grignard reactions between methyl <u>iso</u>butyl ketone and certain Grignard reagents they record yields of the corresponding tertiary carbinols between 40 and 60%, indicating that their yield of 2:4:6-trimethylheptanol-4 was in this region. They reported that in the cases of ethylMgBr, *n*-propylMgBr, and *iso*butylMgBr (a) considerable amounts of unchanged ketone remained, (b) the unsaturated hydrocarbon corresponding to the tertiary carbinols were obtained but could not be separated from the near boiling ketone, (c) ethane, propane, and *iso*butane were evolved, and (d) a small amount of high boiling liquid was formed.

Whereas Bodroux and Tabory worked with equimolar proportions, in the present preparation of the carbinol an excess of *iso*butylmagnesium bromide was used and there were obtained a 21% yield of the tertiary carbinol and a 38% yield of the secondary.

A more detailed investigation (Part II) of this reaction showed that the high boiling liquid (d) obtained by Bodroux and Tabory was probably the unsaturated ketone

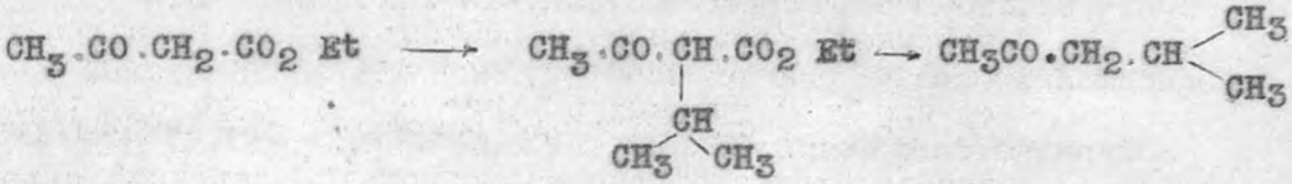


$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH.CH_2\text{-}\underset{\displaystyle CH_3}{\underset{|}{C}}=CH.\ CO-CH_2.CH\!\!<\!\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

resulting from the condensation of two molecules of methyl *iso*butyl ketone, and that the gas (c) evolved during reaction was probably not *iso*butane but *iso*butylene.

In no case was it possible to obtain such a high yield of tertiary carbinol as 40%.

For the above reactions the methyl *iso*butyl ketone was made firstly from acetoacetic ester



$$CH_3.CO.CH_2.CO_2\,Et \longrightarrow CH_3.CO.\underset{\underset{CH_3\quad CH_3}{CH}}{CH}.CO_2\,Et \longrightarrow CH_3CO.CH_2.CH\begin{matrix}CH_3\\CH_3\end{matrix}$$

and then, when mesityl oxide was available, by the catalytic reduction of this unsaturated ketone.

The difficulties experienced in preparing methyl-isobutyl in the quantities required, particularly from acetoacetic ester, made method (2), the interaction of methyl acetate and isobutylmagnesium bromide, preferable.

2:4:6-trimethylheptanol-4 was prepared in a similar way by Halse (1914)[61] using ethyl acetate and isobutylmagnesium bromide. No experimental details of this reaction were given.

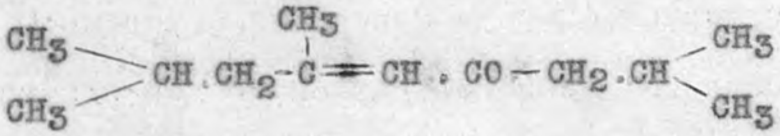
Reaction between excess isobutylmagnesium bromide and methyl acetate gave yields of 2:4:6-trimethylheptanol-4 varying between 20 and 33%. These yields were obtained by varying the ratio of reactants, the time of reflux, and the source of the isobutyl bromide. The latter variable does not seem to be of much account (p.213). Although the lowest yields of tertiary carbinol were obtained when isobutyl bromide made by the hydrobromic acid method was used, some yields using this bromide were also obtained comparable with those using isobutyl bromide made by the phosphorous tribromide method. The results tabulated on p. do not really enable definite conclusions to be drawn about the effect of conditions on the yield of tertiary carbinol. It is noticeable however, that the two highest yields were obtained with the shortest time of reflux.

From these reactions three by-products were obtained and identified. They were (1) methyl *iso*butyl ketone and (2) methyl *iso*butylcarbinol, both found in the low boiling reaction product, and (3) methyl *iso*butyl ketone ketol constituing the high boiling reaction product.

Only small amounts of methyl *iso*butyl ketone were obtained (Expt.51), but considerable amounts of methyl*iso*butylcarbinol (Expt.52). The carbinol was characterised by the preparation of the *p*-toluenesulphonate and the 3:5-dinitrobenzoate. The only solid derivatives of this carbinol recorded are the phenylurethane, the 1-naphthylurethane, and the allophanate. All attempts to prepare the phenylurethane were unsuccessful. Attempts to prepare a solid hydrogenphthalate were also unsuccessful, a very viscous liquid being obtained, which, even after purification by the usual sodium bicarbonate extraction method, remained liquid.

The *p*-toluenesulphonate has a M.P. 39-40°, and the 3:5-dinitrobenzoate has a M.P. 60.5-61.5°.

The ketol of methyl *iso*butyl ketone was obtained in the dehydrated form



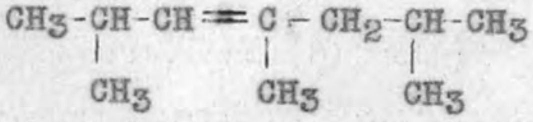
$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH.CH_2-\overset{\overset{CH_3}{|}}{C}=CH.CO-CH_2.CH<\!\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

and was identified by analysis, M.wt., and the preparation and analysis of the 2:4-dinitrophenylhydrazone (Expts. 55 and 56).

These findings led to further study of the interaction of esters and Grignard reagents, and are discussed in Part III of this thesis.

Dehydration of 2:4:6-trimethylheptanol-4

Dehydration of this carbinol gives 2:4:6-trimethylheptene-3:



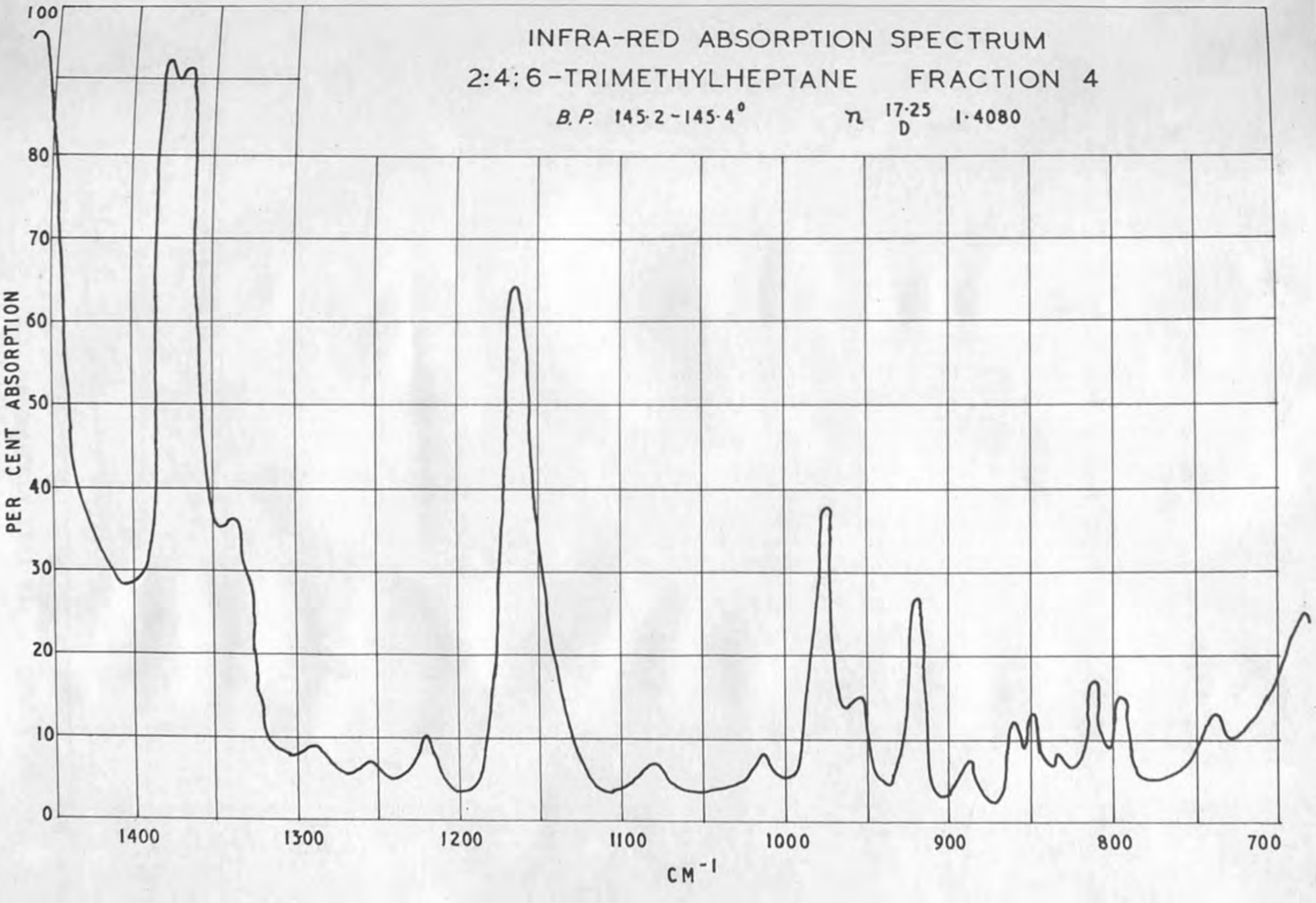
$$CH_3-\underset{CH_3}{\underset{|}{CH}}-CH=\underset{CH_3}{\underset{|}{C}}-CH_2-\underset{CH_3}{\underset{|}{CH}}-CH_3$$

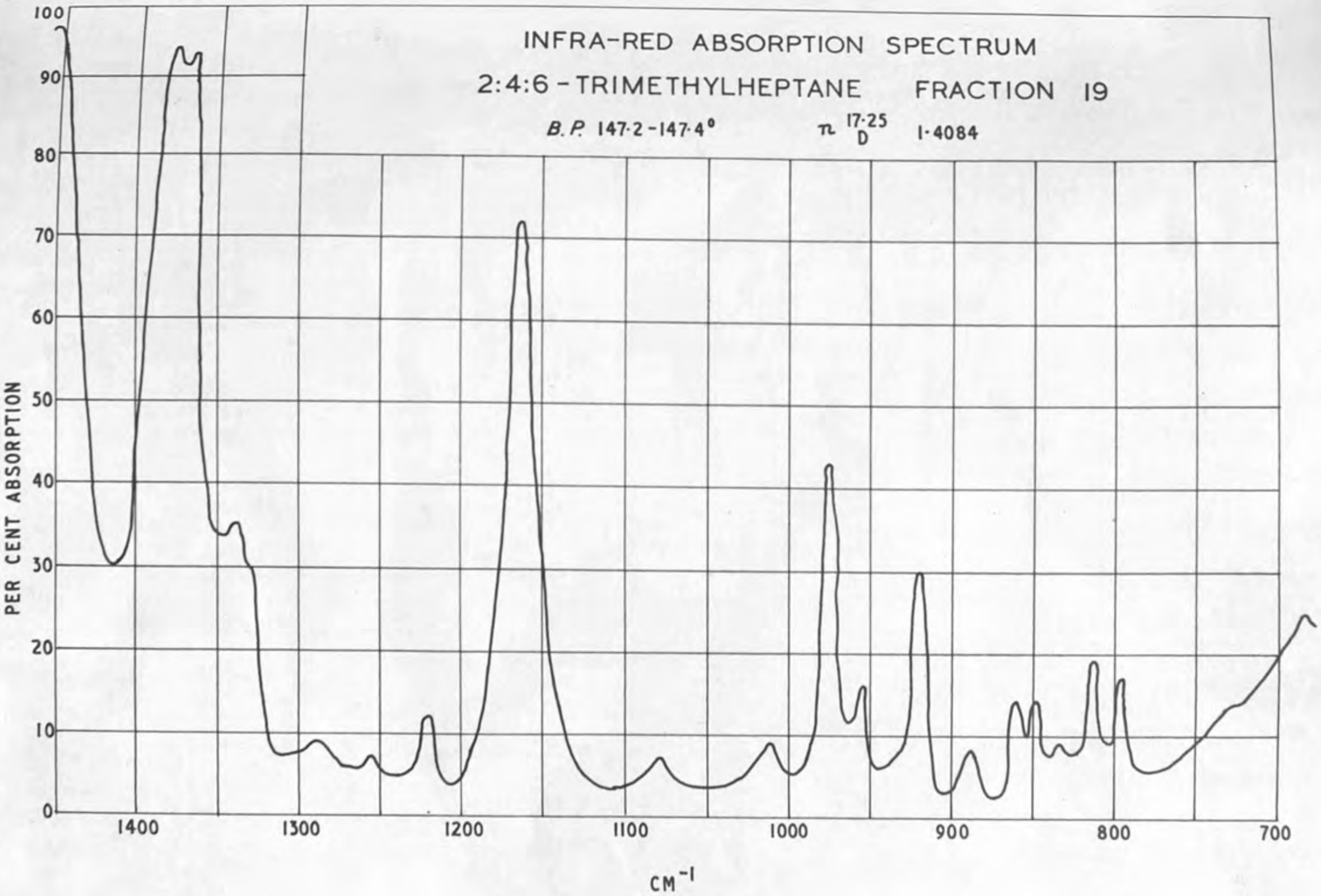
This was first made by Tuot (1933)[62]. Tuot used anhydrous copper sulphate as the dehydrating agent because of the possibility of tar formation and conversion to organic acids and other products harmful to the yield and purity of the unsaturated hydrocarbon when acid catalysts such as $KHSO_4$, oxalic acid, H_2SO_4, $ZnCl_2$, and $Al_2(SO_4)_3$, are used, and because the necessity of passing the carbinol over the catalysts several times for complete dehydration frequently causes isomerisation and transposition.

In the present synthesis naphthalene-2-sulphonic acid was used as dehydrating catalyst. No trouble was given by this catalyst.

Reduction: From the dehydration 2:4:6-trimethylheptene-3 $n^{20}_{D}1.4214$ was obtained, and this was fractionally distilled and reduced to the saturated hydrocarbon with Adam's PtO_2 catalyst and hydrogen at three atmospheres pressure. This heptene has been reduced in a similar manner by Tuot[58].

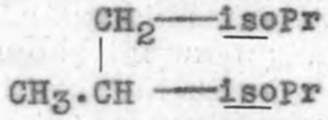
After several fractionations over sodium and several re-reductions a product was obtained free from olefin. This was fractionated and collected in 5 ml portions of which the fourth B.P. 145.2 - 145.4° $n_D^{17.25}$ 1.4080 and the nineteenth B.P. 147.2 - 147.4° $n_D^{17.25}$ 1.4084 were examined by infra-red spectroscope. The accompanying photographs of the absorption spectra of these two fractions show the similarity of the two fractions.


INFRA-RED ABSORPTION SPECTRUM
2:4:6-TRIMETHYLHEPTANE FRACTION 4
B.P. 145·2–145·4°
$n_D^{17·25}$ 1·4080
PER CENT ABSORPTION
100
80
70
60
50
40
30
20
10
0
1400
1300
1200
1100
1000
900
800
700
CM⁻¹


INFRA-RED ABSORPTION SPECTRUM
2:4:6 - TRIMETHYLHEPTANE FRACTION 19
B.P. 147·2 - 147·4°
$n_D^{17\cdot25}$ 1·4084
PER CENT ABSORPTION
100
90
80
70
60
50
40
30
20
10
0
1400
1300
1200
1100
1000
900
800
700
CM^{-1}

2:3:5-Trimethylhexane

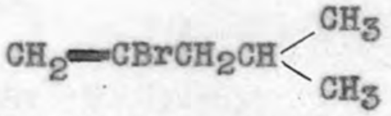
This hydrocarbon was first prepared by Silva(1872)[63] as a by-product in the attempted preparation of di*iso*propyl. The action of sodium amalgam on *iso*propyl iodide at 140° gave little di*iso*propyl but some gases and a hydrocarbon boiling at 130° whose composition and vapour density corresponded with the formula



$$\begin{array}{l} CH_2\text{——}\underline{iso}Pr \\ \;| \\ CH_3.CH\text{——}\underline{iso}Pr \end{array}$$

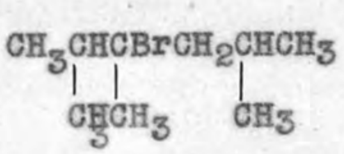
The same hydrocarbon was also obtained in the attempted preparation of zinc di*iso*propyl

Reference is also made by Lespieau(1921)[64] to the possible bromide of 2:3:5-trimethylhexane. The action of *iso*propylmagnesium bromide on propylene dibromide gave two bromides:

(1) 

$$CH_2{=}CBrCH_2CH\begin{matrix}\diagup CH_3 \\ \diagdown CH_3\end{matrix}$$

and (2) a liquid containing 38.1% bromine which he suggested was the monobromide



$$\begin{array}{l} CH_3CHCBrCH_2CHCH_3 \\ \quad\;\;|\;\;\;| \qquad\quad\;\; | \\ \quad CH_3CH_3 \quad\;\; CH_3 \end{array}$$

formed by the action of *iso*propylmagnesium bromide on (1)

The hydrocarbon was synthesised by Tuot[58], who started with 2:3:5-trimethylhexanol-3, dehydrated this to 2:3:5-trimethylhexene-2, and reduced the latter to the saturated hydrocarbon. No information is given by Tuot other than the method of preparation and the physical constants. He describes

2:3:5-trimethylhexanol-3 as new and gives the preparation as the action of isopropylmagnesium bromide on methyl isobutyl ketone.

2:3:5-trimethylhexane has also lately been synthesised by Howard et al (1947)[65] by the action of isopropylmagnesium chloride on 1-chloro-2:3-dimethylbutene-2. This gave 2:3:5-trimethylhexene which was then catalytically reduced to the hexane. This reaction however, gives also another hydrocarbon 2:3:3:4-tetramethylpentene-1. The two hydrocarbons are thought to result from the action of isopropylmagnesium chloride on the two isomers of the dimethylchlorobutene, 1-chloro-2:3-dimethylbutene-2 and 3-chloro-2:3-dimethylbutene-1. Howard and co-workers obtained the two hydrocarbons in a ratio of 18:1, while Cline (1940)[66] using the bromobutene instead of the chlorobutene obtained a ratio of 1.6:1.

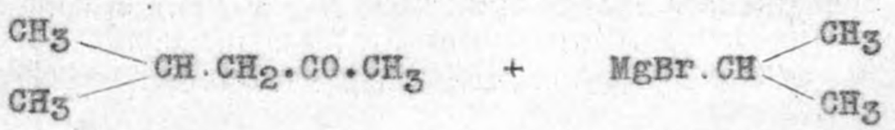
The physical properties of the two saturated hydrocarbons are respectively

B.P. 131.9° n_D^{20} 1.4060

B.P. 141.9° n_D^{20} 1.4218

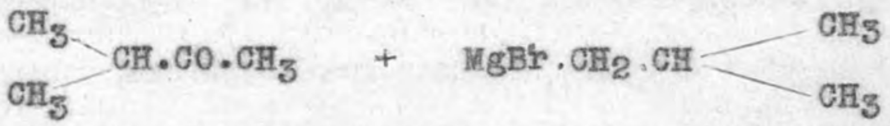
Although the difference in B.P. and refractive index is comparatively large for two nonanes, the fact that two hydrocarbons are produced from the one reaction, and that these hydrocarbons are separable only by physical methods, makes the choice of such a reaction unwise for preparing a spectroscopically pure hydrocarbon.

In the present work the hydrocarbon was synthesised from 2;3;5-trimethylhexanol-3. The carbinol can be prepared by three methods, each of which was investigated. They are (1) the interaction of isopropylmagnesium bromide and methyl isobutyl ketone



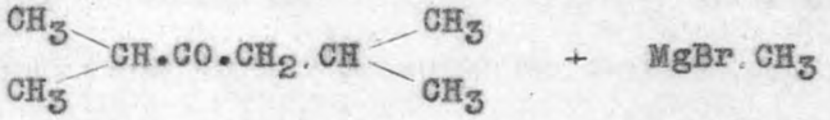
$$\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!>\mathrm{CH.CH_2.CO.CH_3} \quad + \quad \mathrm{MgBr.CH}<\!\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}$$

(2) the interaction of isobutylmagnesium bromide and methyl isopropyl ketone



$$\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!>\mathrm{CH.CO.CH_3} \quad + \quad \mathrm{MgBr.CH_2.CH}<\!\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}$$

(3) the interaction of methylmagnesium bromide and isopropyl isobutyl ketone



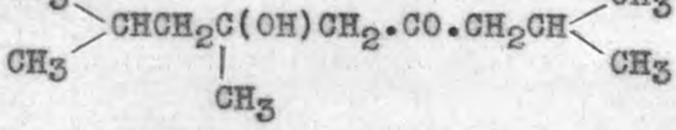
$$\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\!>\mathrm{CH.CO.CH_2.CH}<\!\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix} \quad + \quad \mathrm{MgBr.CH_3}$$

Method (1)

It was found that this method, far from being simple as might be imagined from Tuot's brief description, is accompanied by difficulties in operation and by poor yields. In six of the preparations carried out an average yield of 16% was obtained.

One of the surprising features of the preparations was the necessity to vacuum separate the reaction product into two portions. The usual procedure in the preparation of tertiary carbinols had been to vacuum distil the whole of the product and to fractionate the distillate at atmospheric pressure. When this procedure was applied to 2:3:5-trimethylhexanol indication of much cracking was given and fractionation at atmospheric pressure was found too difficult unless the reaction product was first separated by vacuum distillation into two distillates boiling (a) below - 100°/30 mm Hg (b) between 100-140°/30 mm Hg. Fractionation of the former gave the tertiary carbinol without difficulty, whereas fractionation of the latter was always accompanied by heavy cracking. The top distillates from (b) always contained water, and from their boiling points should have been in portion (a) unless they were the result of decomposition when (b) was distilled at atmospheric pressure. It was then found that these top distillates from (b) contained considerable amounts of methyl isobutyl ketone

Reference has already been made (p. 125) to the ketolisation of methyl isobutyl ketone. In the above reactions between isopropylmagnesium bromide and methyl isobutyl ketone it was obvious that the same ketolisation was occurring but to a greater extent. The ketol



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>CHCH_2\underset{\underset{\displaystyle CH_3}{|}}{C}(OH)CH_2.CO.CH_2CH<\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

formed the high boiling distillate (b) and not only did this suffer dehydration at the tertiary carbinol group when distilled at atmospheric pressure but also broke down to the original ketone.

This is in accordance with the analogous findings of Usherwood (1923)[67] that the distillation of *iso*butyraldol gave 33% of the original *iso*butyraldehyde. (Recently, however, as is discussed by Owen in Annual Reports 1944, addition compounds have been shown to be formed between aldols and aldehydes, which, on distillation, break down to the aldol and aldehyde again. It may be possible that such addition products can be formed by ketols and ketones, but in the present case of methyl *iso*butyl ketone the results obtained point more to the breakdown of the ketol only).

Because of the large amount of ketolisation occurring it was attempted to minimise the ketolisation by altering the conditions of reaction. It was thought that this might be effected by increasing the ratio of Grignard reagent to ketone or by decreasing the concentration of ketone in solution. Neither increase in the amount of Grignard reagent nor adding the ketone in ether solution gave any marked alteration in the relative amounts of tertiary carbinol and ketol. Again no great alteration was obtained by the reverse addition of the Grignard solution to an ether solution of the ketone, or by increasing the time of refluxing the reactants after addition.

The table below shows the results obtained from some of the reactions. The tertiary carbinol was obtained by fractionating distillates (a). The aqueous distillate (denoted by Aq.), which contained methyl *iso*butyl ketone, and the dehydrated ketol (denoted by dK) were obtained by fractionating distillates (b).

Expt	gm.mol ketone	gm.mol Grignard	Hours Reflux	gm. tert-OH	gm. Aq.	gm. dK	gm. Aq-dK
(61)	1.0	1.16	1	22.5	13.0	22	35
(62)	1.0	2.3	1	28.0	9.0	28	37
(63)	1.0	2.3	1	25.5	5.5	33	38.5
(64)	0.5	1.16	1	12.5	-	-	-
(65)	1.0	2.3	6	22.0	18.0	15	33
(66)	1.0	1.23	8	25.5	5.0	32	37

In Expt.(63) the ketone was added as a 20% solution in anhydrous ether.
In Expt.(64) the Grignard was added to an ether solution of the ketone.

Later experiments showed that it was possible to increase the amount of tertiary carbinol by using a better fractionating technique, and by working at a lower temperature. It was also found that *iso*propylmagnesium chloride gave a lower yield than the bromide:

Experiment	*iso*PrMgBr(boiled) (7)		*iso*PrMgBr(cold) (8)		*iso*PrMgCl (15a)	
	gm	yield %	gm	yield %	gm	yield %
tertiary-OH	31	21.5	34	23.6	21	13.9
ketol	53		46		55	

Method (2)

Only one experiment using this method sufficed to show that it possessed no advantage of yield over method (1) to counterbalance the disadvantages of the preparation of *iso*butyl bromide (pp.227-233) and methyl *iso*propyl ketone. From 1 gm.mol of ketone and 2 gm.mols of Grignard reagent there were obtained 25 gm. of the tertiary carbinol and nearly 50 gm. of the secondary carbinol resulting from the reducing action of the Grignard.

The methyl *iso*propyl ketone was prepared from *tert*-amyl alcohol (Organic Syntheses Coll. Vol. 2, 408)

Method (3)

This method has an outstanding difficulty even before the reaction can be investigated. (i.e) the preparation of the ketone. When this had been prepared (pp.141-142) its interaction with methylmagnesium bromide showed that as a method of preparing a pure hydrocarbon method (3) is unsatisfactory. As with di*iso*butyl ketone and methylmagnesium bromide (p.123) reduction occurred and it was impossible to completely separate the secondary and tertiary carbinols.

From the interaction of 0.5 mol. Grignard reagent and 0.33 mol. ketone a product of 34 gm. (70% yield) B.P. 162-167° was obtained. When this was fractionated a range of distillates was obtained from 157° to 166° with a range of $n_D^{20.5}$ from 1.4240 to 1.4321.

isopropylisobutyl carbinol B.P. 156-158° n_D^{20} 1.4246
2:3:5-trimethylhexanol-3 B.P. 165-166° n_D^{20} 1.4321

Although it is probable that by the use of larger quantities of reactants some tertiary carbinol would be obtained (none was obtained from diisobutyl ketone and methylmagnesium bromide), the preparation of large amounts of the ketone is very difficult, and much time was spent in preparing the small amount used in the above experiment.

2:3:5-trimethylhexene and 2:3:5-trimethylhexane.

The 2:3:5-trimethylhexanol-4 was dehydrated by three methods, only two of which were found suitable. It was attempted to avoid using naphthalene-2-sulphonic acid as a dehydrating agent for although 2:3:5-trimethylhexanol-4 is easily dehydrated by this catalyst a gummy residue remained and the olefin had a boiling range of 10°. Therefore anhydrous copper sulphate was used, and an attempt was also made to dehydrate the carbinol by refluxing with acetic anhydride and sodium acetate.

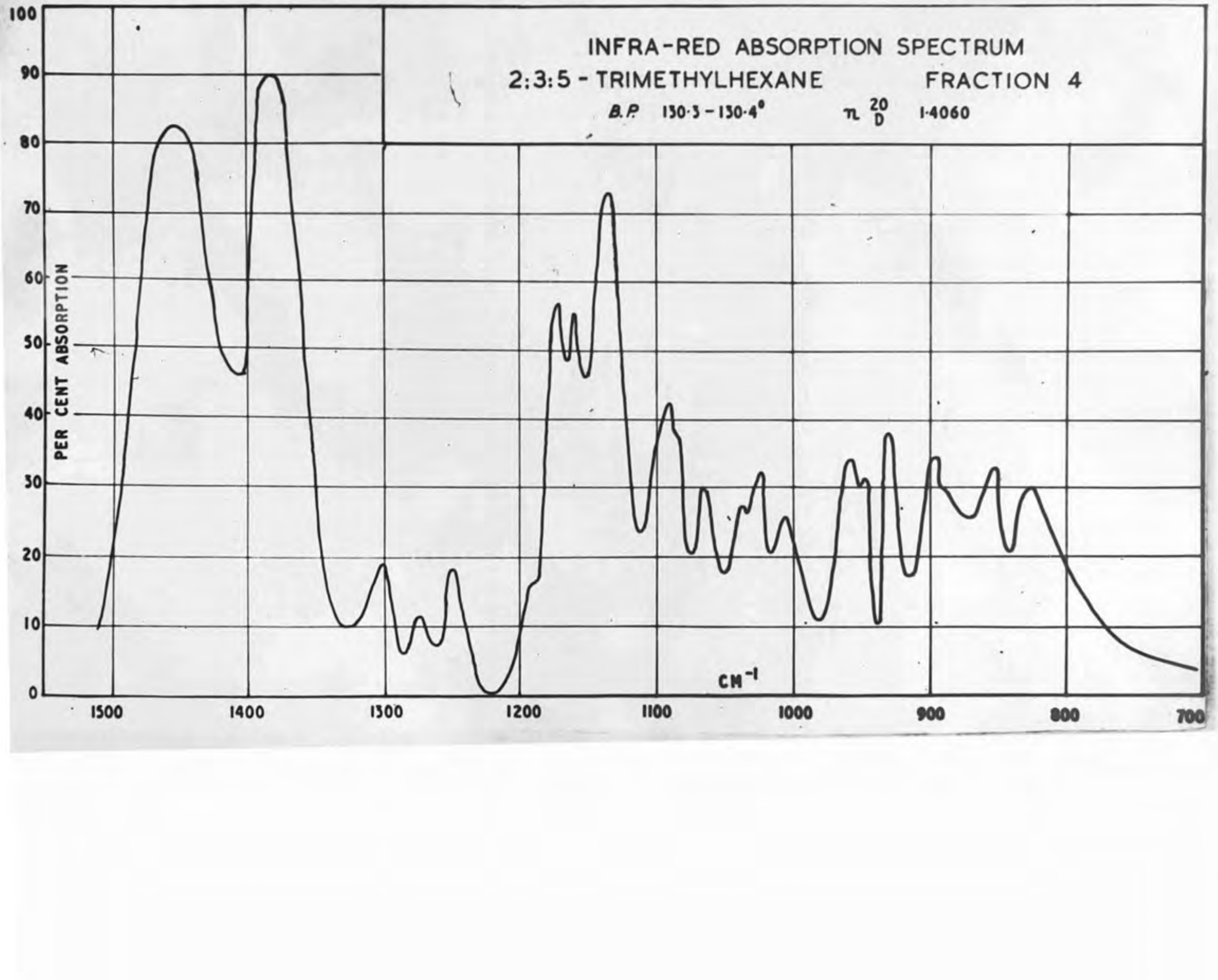
Dehydration by the acetic anhydride method did not go to completeness even after several hours reflux.

The use of copper sulphate was successful in one respect only. Dehydration occurred and was complete after one or two hours reflux, and it was possible to obtain a clean product. (Some of the olefin is absorbed by the copper sulphate but can be liberated by dissolving out with water and added to another dehydration of the same carbinol). The use of copper sulphate however, did not improve the boiling range of the product.

When a product with a 10° boiling range was obtained from the naphthalene-2-sulphonic acid dehydrations it was thought that this was due to either (1) incomplete dehydration or (2) position isomerism of the double bond in the olefin. Prolonged reflux over the catalyst completely altered the product from n_D^{20} 1.4280 to 1.4448 so that the boiling range seemed due to position isomerism. The possibility that dehydration by naphthalene-2-sulphonic acid goes through an esterification stage increases the likelihood of position isomerism, and hence it was thought that the use of copper sulphate would avoid this. The same range of boiling point was obtained however. This fact is not mentioned by Tuot. There is no doubt that isomerism of the double bond had occurred because separate reductions of the low and high boiling olefins gave parafins of the same refractive index. (i.e)

Olefin		Parafin
126-130°	n_D^{20} 1.4208	n_D^{13} 1.4092
130-135°	n_D^{20} 1.4268	n_D^{13} 1.4096

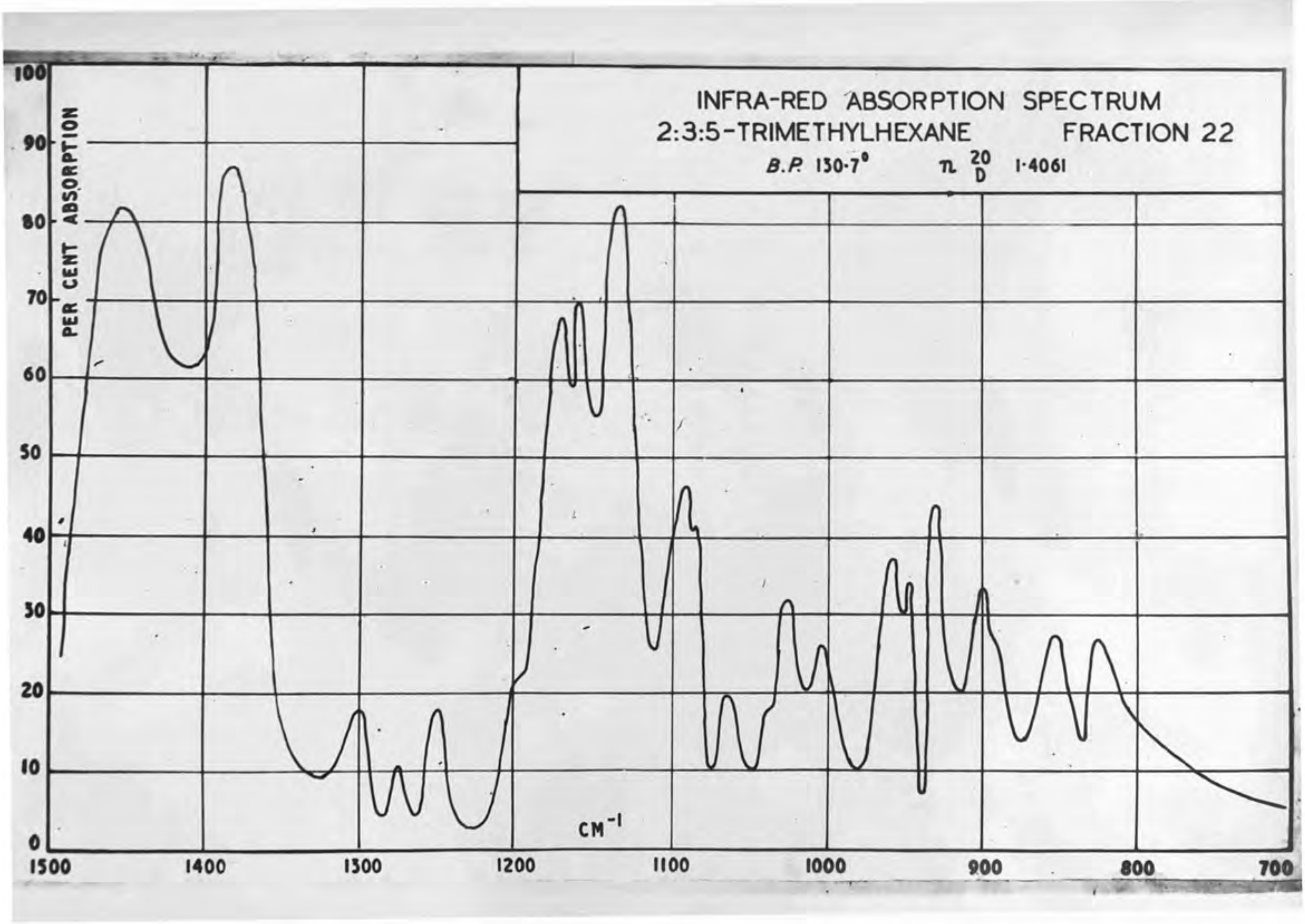
Reduction of the bulk of the olefin, furthermore, gave a constant boiling hydrocarbon (Expt.74). Examination of the Infra-red absorbtion spectra with their characteristic wave bands shows the close similarity between the two end fractions of the hydrocarbon.



INFRA-RED ABSORPTION SPECTRUM

2:3:5 - TRIMETHYLHEXANE FRACTION 4

B.P. 130·3 – 130·4° n_D^{20} 1·4060


INFRA-RED ABSORPTION SPECTRUM
2:3:5-TRIMETHYLHEXANE
FRACTION 22
B.P. 130·7°
n_D^{20} 1·4061
PER CENT ABSORPTION
100
90
80
70
60
50
40
30
20
10
0
CM⁻¹
1500
1400
1300
1200
1100
1000
900
800
700

iso*Propyl*iso*butyl ketone*

This ketone has already been prepared by the following workers, but their methods were not considered suitable for large amounts of ketone.

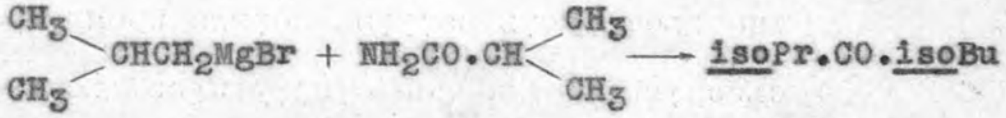
(1) *Ponzio*(1900)[68] by the action of zinc dimethyl on *iso*butyryl chloride.

(2) *Faworski* (1913)[69], and Mayberry(1934)[70] by the oxidation of *iso*propyl*iso*butylcarbinol with chromic acid.

(3) *Sernagiotto*(1919)[71] by the oxidation of 2;5-dimethylhexandiol with dilute suphuric acid.

Two other methods of preparing the ketone were tried and both were found to be unsuitable for large amounts of ketone.

The first consisted in the action of *iso*butymagnesium bromide on *iso*butyramide

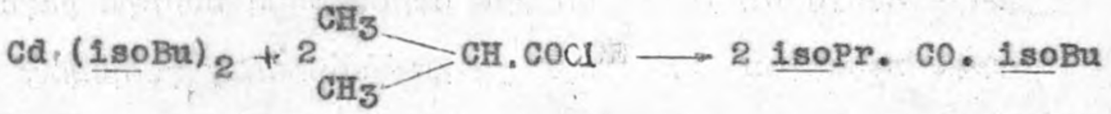


$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>CHCH_2MgBr + NH_2CO.CH<\!\!\begin{matrix}CH_3\\ CH_3\end{matrix} \longrightarrow \underline{iso}Pr.CO.\underline{iso}Bu$$

Using a ratio of 3 mols Grignard reagent to 1.5 mol *iso*butyramide this reaction gave only 19 gm *iso*propyl *iso*butyl ketone, which is a yield of 16%. On the other hand nearly twice this amount of *iso*butyronitrile was formed by the dehydration of the amide by the Grignard reagent.

Apart from the poor yield of ketone, this method suffers from the disadvantage of the awkward preparation of both *iso*butyl bromide and *iso*butyramide, and of the necessity of adding an insoluble solid reagent to a Grignard solution, or conversely, of adding an easily decomposable Grignard solution to a solid.

The second method of preparing the ketone was the interaction of cadmium di*iso*butyl with *iso*butyryl chloride



$$\mathrm{Cd.(\underline{iso}Bu)_2 + 2\ (CH_3)_2{>}CH.COCl \longrightarrow 2\ \underline{iso}Pr.\ CO.\ \underline{iso}Bu}$$

Since this was a novel reaction to the author's laboratory, a preliminary excursion into the use of cadmium dialkyls was made, and therefore, although the yields of *iso*propyl *iso*butyl ketone are given below, more information is given in the section dealing with cadmium dialkyls.

From the two preparations of *iso*propyl *iso*butyl ketone by this method yields of 14% and 21% were obtained (Expts.78 & 79)

The reactions carried out were between cadmium di*iso*butyl and three acyl chlorides: acetyl, propionyl, and *iso*butyryl, leading respectively to methyl *iso*butyl ketone, ethyl *iso*butyl ketone, and *iso*propyl *iso*butyl ketone.

(1) Methyl iso*butyl ketone* (Expts 75 and 76)

$$\mathrm{Cd.(\underline{iso}Bu)_2 + 2\ CH_3.COCl \longrightarrow 2\ Me.Co.\underline{iso}Bu}$$

This reaction was performed twice, giving in each a 10% yield of the ketone. A considerable amount of ethyl acetate was obtained from each reaction.

The formation of ethyl esters from such reactions as these has been examined by several workers (1947)[72] and is attributed to the following reaction:

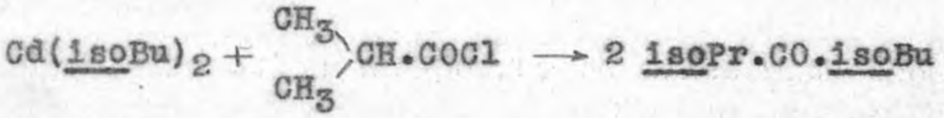
$$R.CO.Cl + (C_2H_5)_2O \xrightarrow{Mg} RCO_2C_2H_5 + C_2H_5Cl$$

(2) *Ethyl* iso*butyl ketone.* (Expt.77)

$$Cd(\underline{iso}Bu)_2 + CH_3CH_2COCl \longrightarrow 2\ Et.CO.\underline{iso}Bu$$

This reaction was performed only once and gave a yield of ketone of 26%.

(3) iso*propyl* iso*butyl ketone* (Expts. 78 and 79)



$$Cd(\underline{iso}Bu)_2 + \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>CH.COCl \longrightarrow 2\ \underline{iso}Pr.CO.\underline{iso}Bu$$

This reaction was performed twice with the following results:

Excess of Cd dialkyl	Yield of ketone
50%	14%
100%	21%

Conclusions:

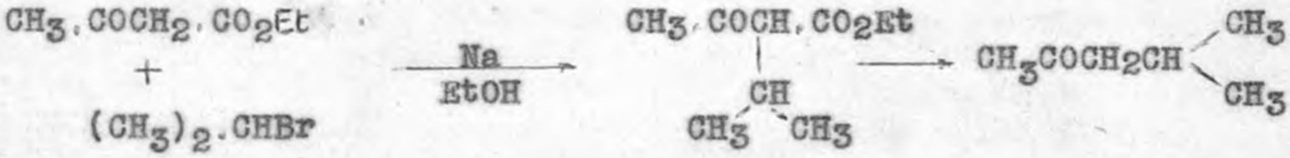
The yields of ketones obtained were much lower than expected. No references have been found to the use of cadmium di*iso*butyl for preparative purposes, and it is not known whether other workers have experienced the same low results. The time spent in preparing the *iso*butyl bromide, *iso*butyrul chloride and anhydrous cadmium chloride, coupled with the difficult experimental conditions, does not favour the use of this reaction for preparing large amounts of *iso*propyl *iso*butyl ketone.

It is probable that increasing the ratio of cadmium dialkyl to acyl halide will increase even more the yield of ketone, but in doing this the difficulty of working conditions is increased. The higher the concentration of cadmium dialkyl the more difficult becomes stirring and addition of the acyl halide.

Methyl isobutyl ketone

Notes on the preparation of this ketone are included since some attempts were made to improve on a known method (1), and to introduce a new method (2).

Method (1) The first method was that of an acetoacetic ester substitution (following the method given for methyl n-amyl ketone in Organic Syntheses Coll. Vol. 2, 248) in which an isopropyl group was substituted into acetoacetic ester using isopropyl bromide.

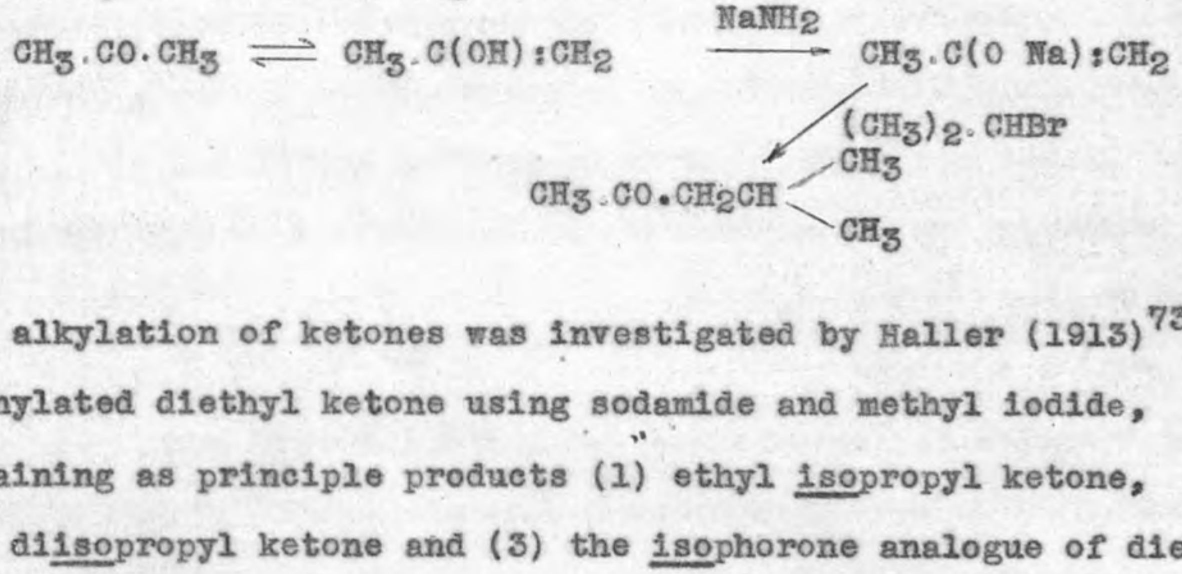


$$CH_3.COCH_2.CO_2Et + (CH_3)_2.CHBr \xrightarrow[EtOH]{Na} CH_3.COCH(CH(CH_3)_2).CO_2Et \longrightarrow CH_3COCH_2CH(CH_3)_2$$

A yield of ketone of 20% theory was obtained, and a control experiment (80) was therefore run in which a small amount of potassium iodide was added to the sodio-acetoacetic ester-isopropyl bromide solution before refluxing. The idea was to see if any influence could be brought to bear on the exchance of groups by the two reactants, by the possible exchange of halide between isopropyl bromide and potassium iodide. A similar experiment containing no potassium iodide was run at the same time. The yields of substituted ester obtained were KI(40%), no KI (37%). Since an earlier preparation of the ketone gave a 39% yield of the substituted ester then it appears that the addition of potassium iodide does not enhance the speed or extent of reaction.

A third experiment (Expt. 81) to see whether an increased time of refluxing caused an increase in yield of substituted ester gave a 29% yield after boiling under reflux for 36 hours. Whitmore (Org. Synth.) speaks of the low yield of methyl isobutyl ketone due to the less complete reaction between the secondary alkyl bromide and the sodio acetoacetic ester.

Method (2) Further experiments on the preparation of methyl isobutyl ketone included attempts to isopropylate acetone according to the following scheme:



$$CH_3.CO.CH_3 \rightleftharpoons CH_3.C(OH):CH_2 \xrightarrow{NaNH_2} CH_3.C(O\ Na):CH_2 \xrightarrow{(CH_3)_2.CHBr} CH_3.CO.CH_2CH\begin{matrix} CH_3 \\ CH_3 \end{matrix}$$

The alkylation of ketones was investigated by Haller (1913)[73] who methylated diethyl ketone using sodamide and methyl iodide, obtaining as principle products (1) ethyl isopropyl ketone, (2) diisopropyl ketone and (3) the isophorone analogue of diethyl ketone.

The first attempt (Expt.82) to introduce an isopropyl group into acetone resulted in the formation of mesityl oxide and a pale yellow liquid B.P. 215-220°. No product corresponding to methyl isobutyl ketone nor to diisobutyl ketone was obtained.

Since the only reaction that appeared to have occurred was the condensation of the acetone, a second experiment (Expt.83) was started in which the sodamide was added in small amounts to acetone cooled in ice slurry. It was hoped thereby to prevent the condensation of the acetone by moderating the reaction, but at the lower temperature used reaction between the sodamide and the acetone would not commence. This experiment was therefore carried no further.

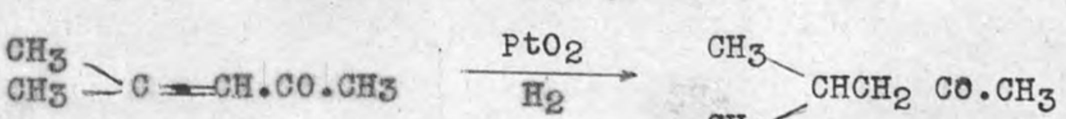
A third experiment (Expt.84) was tried in which the acetone was diluted with dry benzene, and the product obtained from this consisted mostly of the 213-220° liquid and of some mesityl oxide.

The liquid boiling between 213-220° was found on fractionation to consist mostly of a pale yellow liquid B.P. 211-215°, with a small amount of an orange liquid B.P. 243-244°.

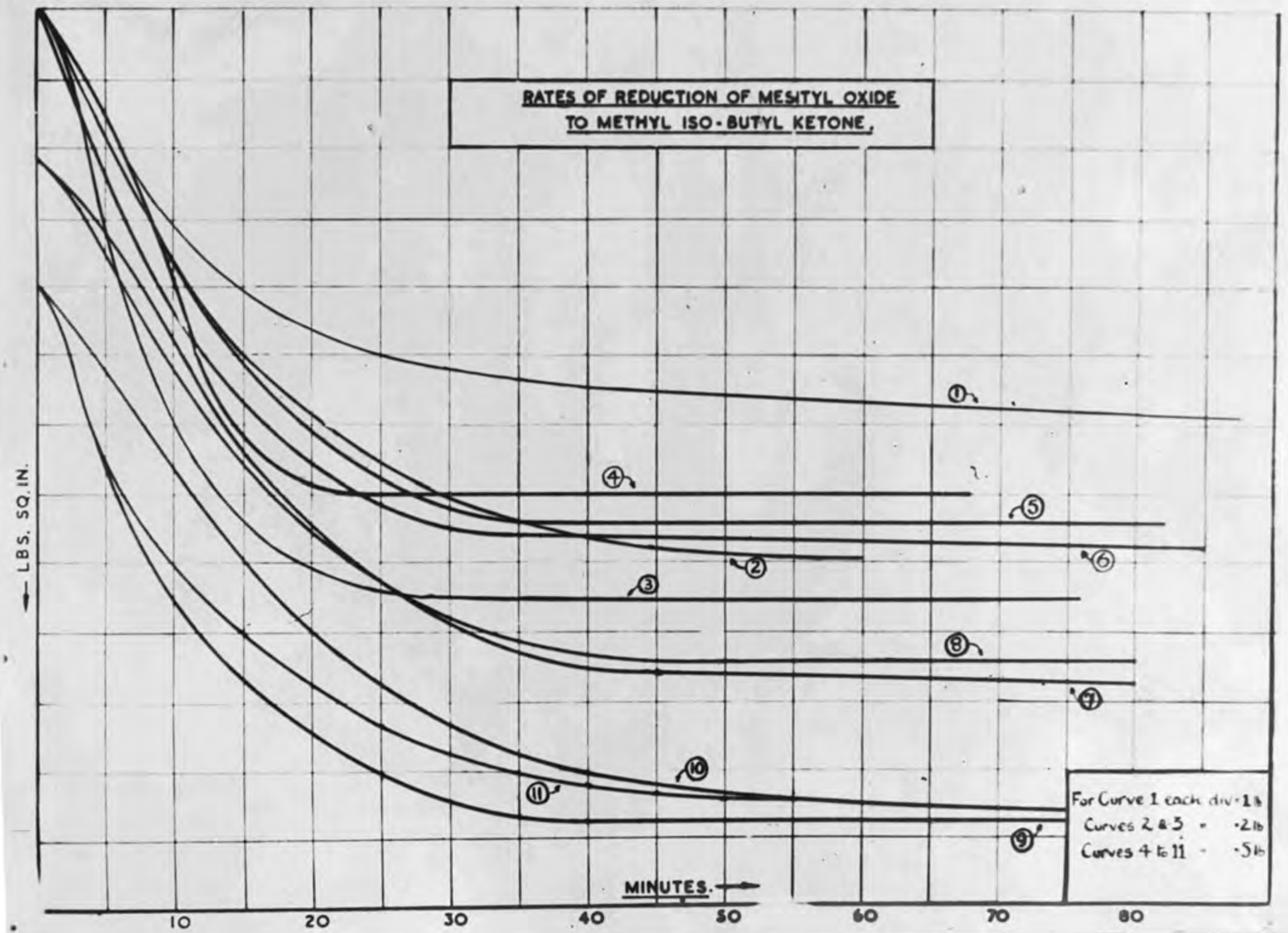
The liquid boiling between 213-215° was identified by analysis and by analysis of its semicarbazone as <u>iso</u>phorone.

The liquid boiling between 243-244° is believed to be a-<u>iso</u>xyliton. This, described as of uncertain constitution, was obtained by <u>Knoevenagel & Schwartz</u> (1906)[74] by the action of sodium ethoxide on acetone. The semicarbazone prepared by these workers had a M.P. 158-159°. That prepared from the 243-244° liquid had a M.P. 157-158°. There was insufficient for analysis.

<u>Method (3)</u> Methyl <u>iso</u>butyl ketone was finally prepared in large quantities by the reduction of mesityl oxide.



$$(CH_3)_2C{=}CH.CO.CH_3 \xrightarrow[H_2]{PtO_2} (CH_3)_2CHCH_2\,CO.CH_3$$



RATES OF REDUCTION OF MESITYL OXIDE TO METHYL ISO-BUTYL KETONE.

The reductions were carried out in glacial acetic acid solution using Adam's PtO_2 and H_2 under pressure. It was found that the speed of reduction increased as the amount of catalyst was increased, but that no further reduction than to the saturated ketone occurred. This is very apparent from the accompanying graphs (Fig.2) of the rate of absorption of hydrogen. Heat was developed during each reduction. Fractionation of the products gave a yield of at least 70% methyl isobutyl ketone B.P. 115-117°.

One reduction was tried using ethyl alcohol as solvent. This was discarded since the rate of absorption of hydrogen was much too slow, and apparently ceased long before the calculated absorption had been reached.

PART V.

EXPERIMENTAL

EXPERIMENTAL

GRIGNARD REACTIONS

In the following series of Grignard reactions the procedure adopted was the same in every case, except where the nature of the products of a reaction demanded alteration.

The Grignard reagent was prepared from two gm atoms of pure magnesium in ketone reactions, and three gm atoms in ester reactions. The requisite halide was added to the magnesium under anhydrous ether. The total volume of ether used in each reaction was 1250 ml. At the end of the addition of the halide the solution was refluxed for 0.5hours on a water bath to expel dissolved gases. The solution was allowed to cool and then decanted from any undissolved magnesium through glass wool into a clean flask. To this solution was added 1 gm mol. of the requisite ketone or ester over a period of two to three hours. Brisk stirring by a mercury seal stirrer was maintained during addition and during reflux after addition was complete. The period of reflux was 1 hour except in those cases in which a longer reflux seemed necessary. The gaseous product of reaction was collected in two traps, T_1 at $-10^{\circ}C$ and T_2 at 72°. The first trap held back most of the ether carried over by the gas, although some ether was always found in T_2. At the end of the reflux the traps were disconnected and connected by rubber tubing to a brine aspirator immersed in a brine tank. The gases were allowed to boil gently into the aspirator and then water was passed into the traps to wash out the gas dissolved in the ether. No liquid was allowed to pass from trap to aspirator. The volume of the collected gas was measured at Atmospheric Pressure and the gas was then forced by brine solution from an overhead tank through three successive traps containing conc. sulphuric acid into a second aspirator in which the volume of unabsorbed gas was measured. The passage of the gas through the sulphuric acid usually took two or three days.

In the working up of the Grignard solution, this when cool was poured onto an ice slurry and dissolved out with concentrated hydrochloride acid. The aqueous layer was extracted twice with ether and the collected ether layers were then washed once with 20% sodium chloride, once with 10% sodium hydroxide and twice with water. After drying with potassium carbonate the ether was removed through an 8 inch helices-packed column. The residue was then separated by vac. distillation, using a Kon triangle, into one, two, or three portions depending on the reaction. These portions were then fractionated, usually at reduced pressure, through a 12 inch column fitted with a total-reflux-variable-take-off still head, and an electrically heated jacket, and packed with Fenske helices.

The fractions so obtained were identified for purity by refractive index and, for nature by analysis and, where possible, by analysis of a solid derivative.

Preparation of Reagents

The alkyl bromides used in the following reactions were prepared by the sulphuric acid-hydrobromic acid method (Organic Syntheses Coll. Vol. 1, 25), with the exception of *iso*butyl bromide and tertiary butyl bromide. The alcohols used were fractionated through a 2 ft. column packed with stainless steel gauze θ rings of 1/16th inch mesh, and fitted with a total-reflux-variable-take-off still head. Only the products boiling over a 1° range were used. After washing with sulphuric acid the bromides were steam distilled, dried over potassium carbonate, and fractionated through a similar column packed with Fenske helices.

The *iso*butyl bromide was prepared by Messrs. British Drug Houses Ltd., according to the author's specifications. The method used was the phosphorous tribromide method (Organic Syntheses Coll. Vol 2, 358), and a boiling range of 1° was stipulated. Before use the bromide was shaken with water for 12 hours and dried over potassium carbonate.

The tertiary butyl bromide was prepared from crystallised tertiary butyl alcohol and an excess of hydrobromic acid. The bromide was separated, washed with cold water, distilled under reduced pressure, dried over sodium sulphate, and fractionated under reduced pressure.

The alkyl chlorides, *iso*propyl and *sec*-butyl, were prepared by the zinc chloride-hydrochloric acid method (Organic Syntheses Coll. Vol. 1, 142).

The *ketones* were fractionated through the gauze ring-packed column.

Methyl ethyl, methyl *n*-propyl, methyl *n*-amyl, methyl *iso*butyl, di*iso*propyl, and di*iso*butyl ketones were purchased.

Methyl *iso*propyl ketone was prepared from tertiary amyl alcohol (Organic Syntheses Coll. Vol.2, 408).

Methyl *n*-butyl ketone was prepared from aceto-acetic ester and *n*-propyl bromide (Organic Syntheses Coll. Vol. 1, 248).

Methyl *tert*-butyl ketone was prepared from pinacol hydrate (Organic Syntheses Coll. Vol. 1, 462), the pinacol hydrate being prepared from acetone (Organic Syntheses Coll. Vol. 1, 459).

(1) n-Propyl<u></u>MgBr on Methyl n-propyl ketone

Addition reaction was not as vigorous as with isopropylMgBr.

Volume of gas collected 7000 ml. Volume unabsorbed 3200 ml.

Distillation at reduced pressure left about 3 ml. residue.

The distillate was fractionated at reduced pressure.

No.	B.P.	mmHg	gm	n_D 19.5
1	45.0 - 51.0	23	1.0	1.4088
2	49.0 - 65.0	23	3.0	1.4125
3	61.0 - 65.0	23	1.5	1.4169
4	-	18	2.5	1.4220
5	62.0 - 65.0	18	4.0	1.4250
6	65.0 - 66.0	18	5.0	1.4214
7	66.0 - 67.0	18	6.5	1.4218
8	67.0 - 67.0	18	6.5	1.4218
9	67.0 - 67.0	18	5.5	1.4223
10	67.0 - 67.5	18	11.5	1.4219
11	67.5 - 68.0	18	10.0	1.4218
12	67.0 - 68.0	18	6.5	1.4218
13	67.0 - 67.0	18	4.0	1.4210
14	64.5 - 64.5	17	10.0	1.4219
15	64.5 - 64.5	17	13.5	1.4219
16	66.5 - 66.0	17	4.5	1.4219
17	66.0 - 67.0	17	9.5	1.4220
18	67.0 - 67.0	17	1.5	1.4268

The residue from the preliminary distillation was distilled at 1 mmHg giving a product which although unidentified was similar in smell and B.P. to the end fractions of Experiment (4), isoPrMgBr on Me.CO.n-Pr

	B.P.	n_D^{20}
(1)	→40°	-
(2)	40-100°	1.4462 pale yellow
(3)	100-105°	1.4500 pale yellow

(2) n-PropylMgBr on Methyl isobutyl ketone

Addition reaction slightly vigorous.

Volume of gas collected:8500 ml. Volume unabsorbed:3,900ml

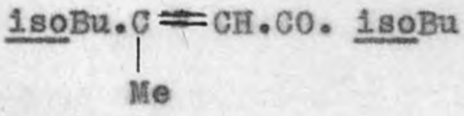
Distillation at reduced pressure left a small residue. The distillate was fractionated at reduced pressure.

No.	B.P.	mmHg	gm.	$n_D^{15.5}$
1	47-53	13	2.0	1.4190
2	53-56	13	1.5	1.4179
3	50-61	13	2.5	1.4233
4	55-60	13	3.0	1.4245
5	60-62	13	3.5	1.4275
6	60-62	13	6.0	1.4282
7	70-75	13	1.5	1.4280
8	69-70	13	4.0	1.4298
9	66-68	13	4.0	1.4310
10	67-67	13	4.5	1.3212
11	64-67	13	5.0	1.4318
12	65-67	13	6.0	1.4318
13	64-65	13	9.5	1.4319
14	64-65	13	7.0	1.4320
15	64-65	13	10.0	1.4321
16	70-70	20	9.5	1.4320
17	70-70	20	10.0	1.4320
18	70-70	20	13.5	1.4321
19	70-70	20	12.0	1.4320
20	70-70	20	2.5	1.4322

The small residue of the preliminary distillation was distilled at 0.5 mmHg giving fractions each of about 0.5 ml.

(1)	n_D^{15}	1.4428
(2)	"	1.4523
(3)	"	1.4524

The 2:4-dinitrophenylhydrazone of (3) had M.P.126-127°, this being the same as that of the condensate



$\underline{iso}Bu.\underset{\substack{|\\ Me}}{C}=CH.CO.\ \underline{iso}Bu$ obtained in Expt. (56)

(3) isoPropylMgBr on Methyl ethyl ketone

Volume of gas collected: 16,400 ml. Volume unabsorbed: 14,200 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into
(a) below 30°/25 mm Hg (b) residue. Fractionation of (a) left only a small residue after the ether had been removed, and the residue was added to (b).

Fractionation of (b).

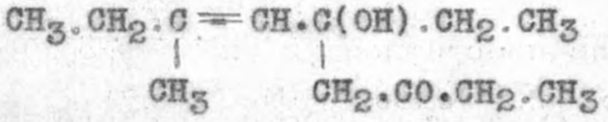
No.	B.P.	mm	gm	$n_D^{20.5}$
1	—69	77	1.0	
2	69-72	77	3.0	1.4255
3	72-73	77	3.5	1.4288
4	69-70	62	7.5	1.4292
5	68-69	57	7.5	1.4297
6	66-67	52	8.0	1.4297
7	66-67	52	5.0	1.4298
8	Trap		5.0	1.4122
9	56-57	28	0.5	1.4308
10	56-57	28	0.5	1.4311
11	57-61	28	0.5	1.4301
12	61-64	28	2.0	1.4415
13	64-71	25	1.5	1.4490
14	71-72	25	4.0	1.4493
15	72-75	25	1.5	1.4491
16	Trap		6.0	1.4327
17	32-33	3	1.5	1.4497
18	33-60	3	1.0	1.4456
19	60-76	3	2.5	1.4505
20	76-92	3	2.5	1.4605
21	92-93	3	0.5	1.4628
22	Trap	-	3.0	1.4482
23	Resid	-	3.0	-

The residue (23) was distilled at 86-88°/0.6 mm Hg. The 2:4-dinitrophenylhydrazone prepared from this was

(contd.)

recrystallised from aqueous ethyl alcohol. M.P. 143.5°.

Analysis of distilled residue; Fd. C 71.53 H 12.06



$$CH_3.CH_2.\underset{|\atop CH_3}{C}=CH.\underset{|\atop CH_2.CO.CH_2.CH_3}{C}(OH).CH_2.CH_3$$

req: C 72.71 H 11.11

Analysis of the 2:4-dinitrophenylhydrazone:

Found C 56.65 H 6.9 N 14.5

Req: C 57.14 H 6.76 N 14.8

(4) isoPropylMgBr on Methyl n-propyl ketone

Volume of the gas collected; 21,500 ml.

Volume unabsorbed: 10,250 ml.

The reaction product was separated by Kon triangle distillation at 25 mm. into two parts (a) below 90° (b) residue.

Fractionation of (a) at 25 mmHg.

No.	B.P.	gm	$n_D^{14.5}$
1	52.0 - 53.0	0.5	-
2	50.0 - 54.0	1.5	1.4161
3	57.0 - 59.0	4.0	1.4272
4	60.0 - 61.5	13.0	1.4340
5	59.0 - 60.0	11.0	1.4345
6	59.0 - 59.5	11.5	1.4345
7	59.5 - 60.0	0.5	1.4345
8	60.0 - 70.0	1.5	1.4345
9	70.0 - 85.0	1.5	1.4372
10	87.0 - 89.0	3.0	1.4504
11	89.0 - 90.0	2.0	1.4544

Fractionation of (b) at 3 mmHg

			$n_D^{9.5}$
12	62.5 - 64.0	2.0	1.4555
13	62.5 - 63.0	2.0	1.4560
14	64.0 - 67.0	2.0	1.4558
15	64.0 - 65.0	4.0	1.4556
16	61.5 - 63.0	2.5	1.4560
17	64.0 - 65.5	2.0	1.4554
18	62.0 - 63.0	3.0	1.4560
19	62.0 - 63.0	2.0	1.4559
20	85.0 - 90.0	0.5	1.4569
21	90.0 - 95.0	0.5	1.4580
22	95.0 - 97.0	0.5	1.4592
23	100.0 -105.0	0.5	1.4600
24	105.0 -110.0	0.5	1.4611

The 2:4-dinitrophenylhydrazone prepared from fraction (15) remained as a dark red viscous oil.

Analysis of (4)	Found	C 72.07	H 11.58
nPr.isoPr.Me-Carbinol	Req.	C 72.73	H 15.15

Analysis of (15) Found C 75.84 H 11.15

$CH_3.CH_2.CH_2.\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH.CO.CH_2CH_2CH_3$ Req.C77.93 H 11.69

(5) isoPropylMgBr on Methyl isopropyl ketone

Volume of the gas collected: 26,500 ml.

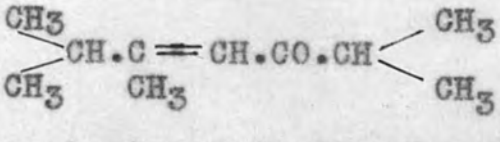
Volume unabsorbed: 18,850 ml.

Fractionation:

No.	B.P.	mmHg	gm	n_D^{16}
1	20.0-25.0	290	6.0	(ether)
2	20.0-25.0	290	5.0	(ether)
3	23.0-25.0	100	0.5	-
4	23.0-25.0	50	0.5	-
5	26.0-27.0	2	2.5	-
6	25.0-27.5	2	2.0	1.4339
7	26.5-27.5	2	7.0	1.4371
8	27.0-22.5	2	3.5	1.4390
9	22.5-43.5	2	2.0	1.4472
10	43.5-44.0	2	0.5	1.4523
11	44.0-44.0	2	3.0	1.4526
12	44.0-44.0	2	10.0	1.4528
13	44.0-44.0	2	12.5	1.4528
14	44.0-44.0	2	2.0	1.4528
15	43.5-44.0	2	4.5	1.4527
16	43.5-45.0	2	3.0	1.4522

The 2:4-dinitrophenylhydrazone prepared from (13) was recrystallised from ethyl alcohol. M.P. 85°. Bright golden yellow crystals.

Analysis of fraction (7) diisoPr.Me.carbinol		Found Req.	C 73.72 C 73.84	H 13.71 H 13.84
Analysis of fraction (13)		Found Req.	C 78.3 C 77.9	H 11.40 H 11.60



$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!>CH.\underset{CH_3}{C}=CH.CO.CH<\!\begin{matrix}CH_3\\ CH_3\end{matrix}$$

Analysis of dinitrophenylhydrazone

Found	C 57.51	H 6.57	N 14.4
Req.	C 57.14	H 7.45	N 16.35

(6) isoPropylMgBr on Methyl n-butyl ketone

Volume of gas collected 16,000 ml.

Volume unabsorbed 12,200 ml.

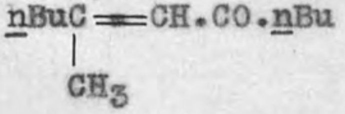
Distillation at 17 mmHg using a Kon triangle gave 8 gm. smelling of methyl n-butyl ketone having $n_D^{19.5}$ 1.4250. $n_D^{19.5}$ for Me.Co.n -Bu is 1.4235. The bulk of the product was therefore fractionated at reduced pressure.

No.	B.P.	mmHg	gm	$n_D^{16.5}$
1	70.0 - 72	20	0.5	-
2	77.5 - 78	"	6.5	1.4392
3	77.5 - 81	"	6.0	1.4389
4	77.5 - 78	"	1.5	1.4389
5	77.5 - 78	"	4.0	1.4393
6	77.5 - 78	"	4.5	1.4392
7	78.0 - 83	"	2.0	1.4392
8	77.5 → 60	"	2.0	1.4391
9	75.0 - 80	"	7.5	1.4381
10	76.0 - 77	"	2.5	1.4383
11	77.0 - 83	"	1.5	1.4388
12	78.0 - 95	"	2.5	1.4397
13	86.0 -105	"	1.5	1.4400
14	78.0 - 80	"	0.5	1.4566
15	80.0 - 81	"	0.5	1.4563
16	81.0 - 82	"	2.0	1.4569
17	82.0 - 83	"	3.0	1.4569
18	83.0 - 84	"	5.0	1.4569
19	82.0 - 84	"	4.5	1.4572
20	84.0 - 85	"	4.5	1.4569
21	84.0 - 87	"	2.0	1.4571
22	85.0 - 87	"	1.0	1.4572
23	83.0 - 88	"	6.0	1.4574
24	86.0 - 88	"	1.0	1.4573

The small residue was transferred to a 50 ml distilling flask and distilled at 2 mmHg.

	B.P.	gm.	$n_D^{16.5}$
25	→ 100	0.5	1.4576
26	96- 99	1.0	1.4572
27	100-108	0.5	1.4571
28	103-108	0.5	1.4571

Analysis of fraction (18) Found C 79.12 H 12.17



$\underset{\displaystyle CH_3}{\underline{n}BuC}=CH.CO.\underline{n}Bu$ Req. C 79.12 H 12.37

(7) isoPropylMgBr on Methyl isobutyl ketone (1)

In this experiment decomposition at the end of the reaction was carried out by pouring on to a suspension of ammonium chloride in ice slurry instead of using hydrochloric acid. Dissolution was not complete, and the remaining sludge was washed several times with ether. The rest of the procedure was as usual.

Volume of gas collected; 19,500 ml. Volume unabsorbed; 15,950 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into;

(a) below 30°/24 mm (b) residue

Fractionation of (a) left only a 2 gm residue n_D^{21} 1.3957 after the ether had been taken off.

Fractionation of (b) at reduced pressure;

No.	B.P.	mm	gm	n_D^{21}
1	→ 59	25.0	0.5	1.4176
2	59-65	25.0	1.0	1.4184
3	65-72	25.0	1.5	1.4288
4	Trap	-	0.5	1.4030
5	29-29	1.5	4.0	1.4327
6	29-30	1.5	8.0	1.4328
7	29-30	1.5	9.5	1.4328
8	Trap	-	4.5	1.4301
9	30-32	1.5	0.5	1.4329
10	32-46	1.5	2.0	1.4331
11	46-62	1.5	0.5	1.4468
12	62-67	1.75	3.0	1.4512
13	67-68	1.75	3.0	1.4509
14	Resid	-	47.0	-
15	Trap	-	3.0	1.4313

(8) *iso*PropylMgBr on Methyl *iso*butyl ketone (2)

*Iso*propylMgBr made from 2 gm atoms of magnesium in 1250 ml. anhydrous ether was cooled to -10/-20° in a CO_2/ethanol bath. The ketone was added over a period of 3.5 hours, stirring being continued for 1 hour after addition. The reactants were allowed to stand overnight, the apparatus remaining untouched, the gas trap being still connected to the reaction flask and kept at -73°.

The volume of gas collected after standing 15 hours: 6,500 ml. Volume unabsorbed: 5,200 ml.

Decomposition by pouring on to ice was very vigorous as if neat *iso*propylMgBr solution was being decomposed.

Kon triangle distillation gave 5.5 gm. low boiling liquid. This was distilled through a six inch helices-packed column and gave only mixtures of methyl *iso*butyl ketone and the olefin corresponding to the tertiary carbinol.

	B.P.	gm		B.P.	gm	
1	-120	0.5	4	127-129	1.0	
2	120-125	1.0	5	129-131	1.0	
3	125-127	1.0	6	131-133	1.0	containing water

Attempts to prepare a *p*-toluene sulphonate and a 3:5-dinitrobenzoate of fraction (5) were unsuccessful.

(contd.)

Fractionation of major liquid product.

No.	B.P.	mmHg	gm.	$n_D^{22.5}$
1	72.73	26	3.0	1.4306
2	73-74	26	11.0	1.4312
3	73-74	26	10.0	1.4313
4	73-74	26	7.5	1.4314
5	74-75	26	3.5	1.4312
6	75-75	26	2.5	1.4311
7	34-65	2	1.0	1.4378
8	34-64	2	2.0	1.4496
9	64-65	2	2.0	1.4498
10	65-66	2	10.0	1.4508
11	65-66	2	8.0	1.4511
12	64-65	2	5.5	1.4512
13	Resid.		18.0	
14	Trap		4.0	

The trap contents smelled slightly of methyl *iso*butyl ketone.

(9) iso<u>PropylMgBr on Methyl</u> iso<u>butyl ketone</u> (3)

The <u>iso</u>propylMgBr made from 2 gm. atoms of magnesium in 1250 ml. anhydrous ether was cooled to -10/20° and 12.9 gm. (5 mol%) of freshly prepared anhydrous $CoCl_2$ were added. Stirring was continued for half an hour and the ketone was then slowly added over 2.5 hours. There was no gas in the gas traps at the end of the addition. The apparatus was left as assembled overnight, the gas traps being kept at -72° during this time.

Volume of gas collected after 14 hours: 8,750 ml.
Volume unabsorbed 6, 200 ml.

The dark brown solution was poured on to ice in the usual way. Decomposition was not at all vigorous. The ether extracts were filtered from the insoluable black sludge.

The liquid product was separated by Kon triangle distillation into (a) below 50°/125 mm. (b) residue

Fractionation of (a) at atmospheric pressure

No.	B.P.	gm.	n_D^{24}
1	124	1.0	1.4011
2	124-126	1.0	1.4045
3	126-128	2.0	1.4064
4	128-130	2.0	1.4079

The p-toluenesulphonate prepared from fraction (4) using pyridine and p-toluenesulphonyl chloride was recrystallised from 60-80° P.E. and had a M.P. 39-40°.

(contd.)

Fractionation of (b)

No.	B.P.	mm.	gm.	$n_D^{23.5}$
1	52.54	26	1.5	1.4095
2	54-55	26	3.0	1.4100
3	55-61	26	2.5	1.4125
4	61-70	26	1.0	1.4246
5	74-75	26	8.0	1.4303
6	74-75	26	10.0	1.4305
7	75-77	26	4.5	1.4301
8	75-77	26	2.0	1.4306
9	66-66	2	1.0	1.4359
10	65-66	2	1.5	1.4407
11	66-70	2	1.5	1.4407
12	70-70	2	3.0	1.4416
13	70-75	2	2.5	1.4431
14	73-75	2	2.0	1.4427
15	75-75	2	3.0	1.4426
16	75-76	2	3.0	1.4426
17	75-78	2	3.0	1.4428
18	75-83	2	2.0	1.4407
19	83-86	2	1.0	1.4411
20	86-86	2	1.5	1.4387
21	Resid.	-	15.0	-
22	Trap	-	6.0	-

The following refractive indices are to be noted:

methyl isobutyl ketone	n_D^{20}	1.3964
methyl isobutyl carbinol	n_D^{20}	1.411 (literature)

(10) isoPropylMgBr on Methyl tert-butyl ketone

Volume of gas collected: 26,750 ml.

Volume unabsorbed: 18,700 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/25 mm (b) residue

Fractionation of (a) at reduced pressure:

No.	B.P.	mmHg	gm	n_D^{22}
1	22-24	60	1.0	1.3969
2	23-24	60	2.0	1.3964
3	24-25	60	1.0	1.3968
4	24-25	60	1.0	1.3965
5	23-24	60	1.0	1.3967
6	23-27	36	1.0	1.3965
7	26-27	36	1.0	1.3966
8	26-27	36	1.0	1.3963
9	25-26	36	2.0	1.3969
10	25-26	36	1.0	1.3981
11	24-26	26	0.5	1.4013
12	26-27	26	0.5	1.4000
13	27-37	26	1.0	1.4051
14	37-38	26	1.0	1.4115
15	36-37	26	2.5	1.4116
16	37-38	26	2.0	1.4119
17	37-38	26	2.0	1.4123
18	38-39	26	1.0	1.4129
19	39-60	26	0.5	1.4229
20	Resid	-	1.0	-
21	Trap	-	3.0	1.3972

(contd.)

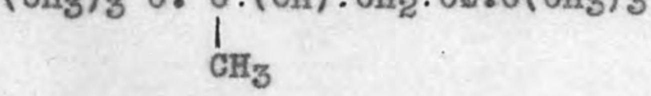
Fractionation of (b) at reduced pressure:

No.	B.P.	mmHg	gm	$n_D^{13.5}$
22	→ 75	4	0.5	1.4350
23	75-78	4	0.5	-
24	75-78	4	0.5	-
25	75-78	4	0.5	1.4443
26	75.78	4	0.5	1.4439
27	75-78	4	1.0	1.4450
28	77-78	4	1.0	1.4450
29	78-78	4	2.5	1.4440
30	78-79	4	2.5	1.4437
31	79-80	4	3.0	1.4439
32	80-81	4	6.0	1.4439
33	80-81	4	3.5	1.4438
34	81-81	4	4.5	1.4439
35	81-81	4	2.0	1.4439
36	73-74	2	3.0	1.4438
37	73-74	2	3.0	1.4439
38	73-74	2	2.5	1.4438
39	Drain	-	3.0	-

The residue in the still pot set overnight to a mass of well formed crystals. These were shaken out and washed with 40-60° petroleum ether at -40° five times, and had an M.P. 92-93°. Crystallisation from aqueous ethyl alcohol gave the same M.P.

The 2:4-dinitrophenylhydrazone prepared from fraction (32) was recrystallised as bright yellow needles from aqueous ethyl alcohol M.P. 147-148°.

Analysis of fraction (32) Found C 72.8 H.12.48



$(CH_3)_3C.\underset{\displaystyle CH_3}{\underset{|}{C}}.(OH).CH_2.CO.C(CH_3)_3$ Req. C 72.0 H.12.0

Analysis of the 2:4-dinitrophenylhydrazone:

Found	C	59.89	H 7.28	N 15.1
Req:	C	59.68	H 7.18	N 15.47

Analysis of the crystalline product from the still pot

Found C 71.29 H 12.71

(11) isoPropylMgBr on Methyl n-amyl ketone

Volume of gas collected: 19,500 ml. Volume unabsorbed: 13,000 ml.

The product was fractionated at 2 mmHg:

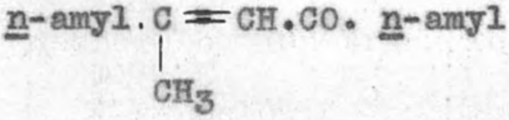
No.	B.P.	gm	n_D^{17}
1	20-21	0.5	-
2	21-22	1.5	1.4208
3	22-22	1.0	1.4211
4	22-37	1.0	1.4219
5	37-54	3.0	1.4241
6	54-56	0.5	1.4261
7	55-56	9.0	1.4391
8	55-56	2.0	1.4391
9	56-57	5.0	1.4399
10	56-57	5.5	1.4400
11	56-57	0.5	1.4398
12	57-58	0.5	1.4399
13	58-59	1.5	1.4399
14	58-59	2.5	1.4400
15	58-60	2.0	1.4400
16	59-60	3.0	1.4400
17	57-59	3.0	1.4401
18	58-60	2.0	1.4401
19	57-58	5.0	1.4400
20	59-63	2.0	1.4394
21	63-73	2.5	1.4404
22	103-105	0.5	1.4402
23	105-105	2.5	1.4555
24	105-107	0.5	1.4555
25	107-107	1.0	1.4555
26	107-109	3.5	1.4555
27	109-110	3.5	1.4557
28	110-110	1.0	1.4555
29	110-110	0.5	1.4555
30	110-111	3.0	1.4559
31	110-112	4.0	1.4567
32	110-112	6.0	1.4563
33	112-115	3.0	1.4563
34	115-116	1.5	1.4565

(contd.)

Analysis of fraction (19) Found: C 76.93 H 13.95

Methyl-*n*-amyl-*iso*propyl-carbinol req: C 75.95 H.13.92

Analysis of fraction (32) Found: C 80.44 H 11.94



$n\text{-amyl.}\underset{\substack{|\\ CH_3}}{C}=CH.CO.\;n\text{-amyl}$ Req: C 80.47 H 11.96

The 2:4-dinitrophenylhydrazone prepared from fraction (32) remained as a dark red viscous oil.

(12) isoPropylMgBr on diisopropyl ketone

The addition of the ketone to the Grignard solution was not accompanied by signs of vigorous reaction. It seemed that considerable gas was evolved during the reflux period, which was therefore extended to 1.5 hours.

Volume of gas collected: 23,500 ml. Volume unabsorbed: 6,000 ml.

The liquid product was distilled at 20 mmHg, leaving a small amount of residue. The distillate was fractionated at 20 mmHg.

No.	B.P.	gm	$n_D^{11.25}$
1	43.0-45.0	0.5	1.4106
2	43.0-45.0	2.5	1.4080
3	41.0-42.0	13.5	1.4086
4	42.0-45.0	2.0	1.4095
5	45.0-47.5	2.5	1.4092
6	45.0-47.0	2.0	1.4110
7	45.0-48.0	6.5	1.4134
8	43.0-47.0	9.0	1.4180
9	41.5-42.0	14.0	1.4234
10	42.0-52.0	0.5	-
11	52.0-52.5	3.5	1.4213
12	52.0-52.5	2.0	1.4265
13	52.0-53.0	2.0	1.4273
14	53.0-54.0	8.5	1.4280
15	54.0-54.0	5.0	1.4284
16	53.0-54.0	8.5	1.4284

Owing to the inconclusiveness of this fractionation, fractions (1) to (12) were bulked and fractionated at atmospheric pressure.

(contd.)

No.	B.P.	n_D^{12}
1	124-128	1.4109
2	126-128	1.4103
3	126-127	1.4105
4	128-129	1.4113
5	129-130	1.4120
6	130-130	1.4123
7	130-131	1.4138
8	130-133	1.4158
9	131-132	1.4175
10	133-136	1.4208

The following refractive indices are to be noticed:

di<u>iso</u>propyl ketone	n_D^{12}	**1.4048**
di<u>iso</u>propyl carbinol	n_D^{20}	**1.42259 (literature)**

Fraction (16) was analysed:

	Found	C 72.86	**H 13.32**
$(\underline{iso}Pr)_2$ CHOH	req:	C 72.41	**H 13.79**

(13) isoPropylMgBr on diisobutyl ketone

The addition of the ketone to the Grignard solution was accompanied by vigorous reaction.

Volume of gas collected: 19,750 ml. Volume unabsorbed: 17,000 ml.

Fractionation of the liquid product:

No.	B.P.	mmHg	gm	$n_D^{22.25}$
1	26.0-28.5	2.0	-	1.4123
2	26.0-27.0	1.5	7.0	1.4123
3	23.0-29.0	1.5	8.0	1.4126
4	27.0-32.0	1.5	6.5	1.4130
5	27.0-30.0	1.5	5.0	1.4128
6	29.0-30.0	1.5	4.0	1.4135
7	29.0-31.0	1.5	5.5	1.4129
8	31.0-32.0	1.5	5.5	1.4138
9	32.0-35.0	1.5	2.5	1.4143
10	31.0-35.0	1.5	3.0	1.4146
11	35.0-37.0	1.5	1.5	1.4173
12	37.0-42.5	1.0	1.5	1.4249
13	42.5-45.0	1.0	3.5	1.4288
14	41.0-43.0	1.0	2.5	1.4288
15	43.0-46.0	1.0	1.5	1.4319
16	45.0-48.0	1.0	2.5	1.4357
17	48.0-48.5	1.0	2.5	1.4371
18	48.5-49.0	1.0	1.0	1.4387
19	48.0-49.0	1.0	2.0	1.4388
20	48.5-49.0	1.0	2.5	1.4388
21	48.5-49.0	1.0	1.5	1.4389
22	49.0-49.5	1.0	2.5	1.4389
23	49.0-49.5	1.0	1.5	1.4390
24	49.5-50.0	1.0	1.0	1.4392
25	50.0-50.5	1.0	1.0	1.4392
26	50.0-50.5	1.0	1.0	1.4392

Analysis of fraction (22)

	Found	C 77.67	H 13.92
isopropyldiisobutylcarbinol	req:	C 77.43	H 13.98

(14) isoPropylMgBr on Methyl acetate

In this reaction the Grignard reagent was prepared from 3 mol magnesium and 3.3 mol isopropyl bromide. Only 1 mol of the ester was used. When about three quarters of this had been added a greyish green sludge began to form, and became thicker during the rest of the addition.

Volume of gas collected: 19,500 ml. Volume unabsorbed: 14,800 ml.

The product was fractionated at 1.8 mmHg. It was omitted to weigh the fractions collected.

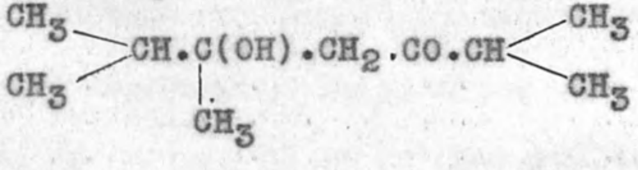
No.	B.P.	$n_D^{12.5}$
1	47-49	1.4443
2	49-50	1.4421
3	50-51	1.4407
4	52-55	1.4401
5	52-55	1.4396
6	53-59	1.4391
7	58-59	-
8	59-59	1.4391
9	59-59	1.4394
10	59-59	1.4400
11	58-59	1.4400
12	58-59	1.4405
13	59-59	1.4406
14	59-59	1.4408
15	58-59	1.4403
16	58-59	1.4403
17	58-59	1.4404
18	59-59	1.4406
19	59-57	1.4410
20	57-54	1.4408

Fraction (10) to (19) became discoloured on standing, the colours varying from pale blue to blue-green.

(contd.)

2:4-dinitrophenylhydrazones were prepared from fractions (6) and (12). These were recrystallised from ethyl alcohol and had M.Ps. of 85° and 84-85° respectively. Mixed M.Ps. with the 2:4-dinitrophenylhydrazone from Expt.(5) were the same.

Analysis of fraction (12) Found C 69.98 H 11.66



Req: C 69.82 H 11.64

(15) isoPropylMgCl on Methyl tert-butyl ketone

The preparation of the Grignard solution was not so difficult as in Expt. (15a), since it was now known that heating is required to start the reaction. Pieces of solid began to settle out after about a third of the ketone had been added. On cooling at the end of reflux a thick sludge settled out leaving a clear supernatant liquor. The decomposition by pouring onto ice slurry was very vigorous.

Volume of gas collected: 25,000 ml. Volume unabsorbed: 21,000 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/20 mm (b) residue

Fractionation of (a)

No.	B.P.	mm.	gm	$n_D^{22.5}$
1	→ 103	759	1.0	-
2	103-105	759	1.5	1.3948
3	105-106	759	2.0	1.3967
4	106-107	759	3.5	1.3972
5	107-108	759	10.5	1.3978
6	107-108	759	2.5	1.3976
7	107-108	759	1.5	1.3973
8	107-108	759	4.0	1.3976
9	29-30	30	0.5	-
10	30-32	30	2.0	1.4018
11	32-40	30	1.0	1.4065
12	40-45	30	0.5	1.4138
13	44-45	30	1.0	1.4146
14	Trap	-	10.0	1.3988

The phenylurethane of fraction (11) was prepared by heating together equal volumes of fraction (11) and phenylisocyanate

(contd)

at 110° for half an hour. The mixture set solid overnight, and was broken up in 100-120° petroleum ether. The petroleum ether solution was evaporated at room temperature, and the solid so obtained was recrystallised from petroleum ether, giving a product M.P. 78-79°. The phenyurethane of pinacolyl alcohol is recorded in the literature as having an M.P. 79°.

Fractionation of (b)

No.	B.P.	mm	gm	n_D^{23}
14	60-63	2.0	1.0	1.4470
15	63-65	2.0	1.5	1.4460
16	65-66	2.0	2.0	1.4443
17	66-67	2.0	2.0	1.4439
18	67-68	2.0	2.5	1.4438
19	68-72	2.5	2.0	1.4440
20	72-72	2.5	2.0	1.4422
21	72-73	2.5	3.5	1.4418
22	73-74	2.5	5.0	1.4408
23	74-75	2.5	3.0	1.4406
24	75-75	2.5	3.0	1.4403
25	75-76	2.5	3.0	1.4400
26	75-76	2.5	1.5	1.4395
27	Resid	-	3.0	-
28	Trap	-	4.0	-

The residue (27) was not at all solid, nor did it solidify when immersed in a bath at -60°.

(15a) iso<u>PropylMgCl on Methyl</u> iso<u>butyl ketone</u>

The preparation of the Grignard solution gave some difficulty at first. It was found necessary to reflux the ether solution for an hour even after adding some magnesium treated with ethyl bromide. The addition of the bulk of the <u>iso</u>propyl chloride followed smoothly.

A sludge began to settle out after about one quarter of the ketone had been added. On cooling after the reflux period this sludge settled out very thickly, leaving a clear supernatant liquor. Decomposition by pouring onto ice slurry was very vigorous.

The gas from this experiment was lost by breakage of the gas line.

The liquid product was separated under reduced pressure into (a) below 40^{o}/25 mm (b) residue

<u>Fractionation of (a)</u> at atmospheric pressure

No.	B.P.	gm
1	93 - 115	0.5
2	115 - 117	1.5
3	117-118	3.5
4	Residue	1.0

(contd.)

Fractionation of (b)

No.	B.P.	mm	gm	n_D^{23}
5	38-39	2.5	1.0	1.4310
6	39-40	2.5	6.5	1.4314
7	40-40	2.5	4.0	1.4317
8	40-36	2.5	1.0	1.4319
9	Trap	-	9.0	1.4300
10	→62	1.7	1.0	1.4340
11	66-67	2.0	0.5	1.4490
12	66-67	2.0	1.5	1.4499
13	69-70	2.0	1.5	1.4498
14	72-73	2.0	2.5	1.4488
15	73-75	2.0	2.0	1.4478
16	75-76	2.0	4.5	1.4473
17	76-78	2.0	2.0	1.4463
18	78-79	2.0	2.0	1.4458
19	80-82	2.0	2.5	1.4450
20	82-83	2.5	3.0	1.4449
21	83-84	2.5	3.5	1.4444
22	82-83	2.0	5.0	1.4435
23	83-85	2.5	2.5	1.4420
24	84-85	2.5	2.5	1.4433
25	81-83	1.7	2.5	1.4390
26	83-84	1.7	2.5	1.4386
27	84-85	1.7	1.5	1.4385
28	Resid	-	13.0	-
29	Trap	-	6.0	

The trap contents (29) smelled strongly of 2:3:5-trimethylhexanol, and not of ketol.

(16) isoButylMgBr on Methyl n-propyl ketone

Volume of gas collected: 17,000 ml. Volume unabsorbed: 1,600 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 55°/20mm (b) 55-70°/20mm (c) small residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	$n_D^{21.25}$
1	39-40	-	-
2	39-40	-	-
3	40-115	1.5	1.3933
4	110-116	0.5	1.3966
5	116-118	3.0	1.4032
6	118-119	4.5	1.4053
7	119-120	4.0	1.4056
8	119-120	5.5	1.4070
9	120-121	5.5	1.4067
10	121-125	2.5	1.4069
	Residue	15.0	-

The residue from (a) was transferred to (b), which was then fractionated at 22 mm Hg

11	40-44	3.0	1.4073
12	45-50	5.0	1.4083
13	50-53	3.5	1.4095
14	53-55	2.5	1.4101
15	71-72	0.5	1.4231
16	72-73	3.0	1.4298
17	73-73	4.0	1.4300
18	73-73	7.0	1.4301
19	73-73	7.0	1.4301
20	73-73	8.5	1.4301
21	73-73	6.5	1.4301

A hydrogenphthalate was prepared from fractions (8) and (9) by heating with pyridine and phthalic anhydride for 3 hours

(contd)

at 105-110°. Recrystallisation from 100-120° petroleum ether gave a hydrogenphthalate M.P. 59-60°. The M.P. of methyl-n-propylcarbinol hydrogenphthalate is given in the literature as 60-61°.

(17) isoButylMgBr on Methyl isopropyl ketone

Volume of gas collected: 20,500 ml. Volume unabsorbed: 3,200 ml.

Some of the liquid product of this reaction was lost by fire. However, the proportion of products from an identical reaction carried out earlier, but without gas measurements, is to be seen on p. 246 .

Of importance, however, is the small residue left after the Kon triangle distillation in the present experiment. This residue was distilled to give 2 ml of condensate. The 2:4-dinitrophenylhydrazone prepared from this had an M.P. 85°. The mixed M.P. with the 2:4-dinitrophenylhydrazone from Expt. (5) was also 85°.

(18) isobutylMgBr on Methyl isobutyl ketone (1)

Volume of gas collected: 15,000 ml. Volume unabsorbed: 2,000 ml.

Kon triangle distillation gave only (a) ether (b) residue.

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	$n_D^{21.75}$
1	52	25	0.5	1.4082
2	52-53	25	6.5	1.4091
3	53-54	25	9.0	1.4102
4	53-54	25	7.0	1.4107
5	54-55	26	7.5	1.4111
6	53-54	25	9.0	1.4112
7	53-54	26	1.5	1.4112
8	54-55	26	5.5	1.4113
9	55-63	26	2.0	1.4118
10	46-47	3	1.0	1.4312
11	46-47	3	7.5	1.4316
12	46-47	3	10.0	1.4316
13	47-47	3	10.5	1.4315
14	47-47	3	9.0	1.4317
15	47-48	3	7.5	1.4317
16	Resid	-	5.0	-
17	Trap	-	5.0	1.4016 (dried)

The residue (16) was distilled at 1 mm Hg using a Kon triangle, and from the 2.0 gm residue a 2;4-dinitrophenylhydrazone was prepared, and crystallised from ethyl alcohol M.P. 126-127°.

(19) isobutylMgBr on Methyl isobutyl ketone (2)

This experiment was carried out with the reaction flask immersed in an ethanol/CO_2 bath at -50°. Stirring was continued for 1 hour after the addition of the ketone, which took 3 hours, and the apparatus was left assembled overnight. The gas traps were left connected and at a temperature of -72°.

Volume of gas collected: 300 ml. Volume unabsorbed: 230 ml.

The reaction product was separated under reduced pressure by Kon triangle distillation into:

(a) below 50°/29 mm (b) residue

Fractionation of (a) at 25 mm Hg:

No.	B.P.	gm	n_D^{22}
1	43.0-45.0	0.5	1.4040
2	45.0-51.0	1.5	1.4040
3	51.0-52.5	1.5	1.4078
4	52.5-53.5	1.5	1.4094
5	53.5-54.0	7.0	1.4101
6	54.0-54.5	8.0	1.4102
7	54.0-54.5	7.0	1.4105
8	54.0-54.5	5.5	1.4105
9	54.0-54.5	8.0	1.4106
10	54.0-54.5	2.5	1.4105
11	Residue	0.5	
12	Trap	10.0	1.3940

(contd.)

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	n_D^{22}
11	54.0-54.5	26	8.5	1.4106
12	54.0-54.5	26	4.0	1.4104
13	43.0-44.0	2	0.5	1.4294
14	43.5-44.0	2	3.0	1.4306
15	43.5-44.0	2	4.5	1.4308
16	44.0-44.5	2	5.0	1.4308
17	44.0-44.5	2	9.0	1.4310
18	44.5-45.0	2	9.0	1.4310
19	45.0-45.5	2	4.0	1.4310
20	Residue	-	6.0	-
21	Trap	-	4.0	1.4162

The residue from (b) was distilled at 1 mm Hg using a Kon triangle, and two fractions of 1 gm each were taken off.

1	35-39	n_D^{22} 1.4340
2	39-40	" 1.4360

This left a golden yellow residue from which was prepared a 2:4-dinitrophenylhydrazone M.P. 126-127°.

(20) isoButylMgBr on Methyl tert-butyl ketone

The addition reaction was not very vigorous. The quantity of trap content increased considerably during reflux.

Volume of gas collected: 23,500 ml. Volume unabsorbed: 5,000 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/25 mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	n_D^{15}
1	105	0.5	1.3986
2	105-110	2.5	1.4070
3	110-110	4.5	1.4078
4	118-118	5.0	1.4078
5	117-118	2.5	1.4126
6	118-121	3.0	1.4153
7	121-123	8.0	1.4160
8	121-123	7.5	1.4166
9	121-123	8.0	1.4168
10	121-123	8.0	1.4172
11	121-123	9.0	1.4173
12	121-123	9.0	1.4176

Fractionation of (b) at 15 mm Hg:

13	40-66	1.0	1.4241
14	66-70	1.0	1.4385
15	70-82	1.5	1.4400
16	82-84	3.5	1.4423
17	84-94	4.0	1.4452
18	85-87	2.0	1.4473
19	87-95	2.5	1.4496
20	95-100	4.5	1.4492
21	100-103	4.5	1.4462
22	103-105	4.0	1.4441
23	103-105	0.5	1.4430

(Contd.)

The 2:4-dinitrophenylhydrazone prepared from fraction (20) was recrystallised from ethyl alcohol as bright yellow needles, M.P. 147-147.5°. The mixed M.P. with the 2:4-dinitrophenylhydrazone from Expt. (10) was 147-147.5°.

The small residue from the fractionation deposited a few milligrams of solid. This was filtered and washed several times with 40-60° petroleum ether at -60°, and was recrystallised twice from 100-120° petroleum ether, giving long white needles, M.P. 115° at each crystallisation.

Analysis: C 71.8 H 12.33

This gives an empirical formula of $C_6H_{12}O$.

(21) isoButylMgBr on diisobutyl ketone

The addition of the ketone to the Grignard solution was not at all vigorous. A good deal of gas collected in the traps before refluxing.

Volume of gas collected: 21,750 ml; Volume unabsorbed: 3,300 ml.

The product was separated by Kon triangle distillation into: (a) below 90°/18 mm Hg (b) residue. Fractionation of (a) at 21 mm Hg:

No.	B.P.	gm	n_D^{15}
1	→60	0.5	1.4130
2	60-70	2.0	1.4183
3	68-70	2.0	1.4206
4	68-70	2.0	1.4206
5	69-70	2.5	1.4208
6	70-74	5.0	1.4218
7	70-73	4.0	1.4213
8	71-75	5.0	1.4221
9	73-75	5.0	1.4221
10	75-78	5.0	1.4230
11	78-81	5.0	1.4248
12	79-81	6.5	1.4254
13	80-84	5.5	1.4266
14	80-82	5.5	1.4260
15	82-85	6.5	1.4272
16	81-85	4.5	1.4271
17	81-85	4.0	1.4274
18	81-85	7.0	1.4274
19	81-83	6.5	1.4272
20	81-86	5.5	1.4277
21	82-86	4.0	1.4280

The residue from (a) was transferred to (b), which was then fractionated at 2 mm Hg.

(contd.)

Fractionation of (b)

No.	B.P.	gm	n_D^{15}
22	48-49	1.0	1.4268
23	49-55	2.0	1.4272
24	55-60	4.0	1.4318
25	60-71	2.0	1.4338
26	71-73	4.0	1.4398
27	72-73	3.0	1.4401
28	72-73	5.5	1.4403
29	72-73	7.0	1.4402
30	73-74	6.0	1.4403
31	73-74	5.5	1.4404
32	Resid	7.0	-

n_D^{15} for di<u>iso</u>butyl ketone is 1.4160

n_D^{21} for di<u>iso</u>butyl carbinol is 1.423[76]

Analysis of fraction (30)	Found:	C 77.64	H 13.91
Tri-<u>iso</u>butyl carbinol	req:	C 78.0	H 14.0

(22) sec-butylMgBr on Methyl n-propyl ketone

Volume of gas collected: 16,300 ml. Volume unabsorbed: 9,050 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/21 mm Hg (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	$n_D^{21.25}$
1	→ 103	1.0	-
2	100-103	1.0	1.3993
3	103-107	4.5	1.4015
4	107-108	4.0	1.4028
5	108-111	5.0	1.4032
6	111-113	2.5	1.4038
7	113-116	2.0	1.4044
8	116-116	0.5	1.4045
9	Residue	6.0	-

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	$n_D^{21.25}$
10	→ 83	25	0.5	1.4372
11	83-83	25	3.0	1.4378
12	83-84	25	3.5	1.4383
13	82-83	25	4.5	1.4386
14	83-86	25	3.0	1.4391
15	83-86	25	2.5	1.4384
16	83-85	25	1.5	1.4388
17	85-86	25	1.0	1.4397
18	85-87	25	3.0	1.4397
19	39-42	1	2.5	1.4415
20	42-43	1	1.5	1.4449
21	43-44	1	2.0	1.4464
22	45-47	1	2.0	1.4500
23	47-49	1	1.0	1.4509
24	49-50	1	1.0	1.4515
25	49-51	1	1.0	1.4535
26	51-52	1	1.0	1.4538
27	52-55	1	1.0	1.4495
28	55-60	1	1.0	1.4427
29	60-62	1	1.0	1.4394

(contd)

Analysis of fraction (30) Found: C69.9 H 11.3

Methyl *n*-propyl ketone ketol req: C 69.7 H 11.6

Analysis of fraction (12) Found: C 76.35 H 12.25

Methyl-*n*-propyl*sec*-butylcarbinol req: C 75.0 H 13.9

(23) sec-butylMgBr on Methyl isopropyl ketone

The addition of the ketone to the Grignard solution was accompanied by vigorous reaction.

Volume of gas collected: 21,800 ml. Volume unabsorbed: 11,600 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 35°/20mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm.	n_D^{20}
1	34-95	3.5	-
2	95-101	3.5	1.3945
3	101-103	2.0	1.4008
4	103-104	3.5	1.4030
5	103-104	2.0	1.4032
6	104-105	2.5	1.4042
7	104-106	2.5	1.4042
8	105-106	2.0	1.4051
9	106-108	3.0	1.4057
10	108-110	1.5	1.4073
11	110-111	1.5	1.4087
	Residue	1.0	-

(contd.)

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	$n_D^{20.75}$
12	35-39	1.5	1.0	1.4453
13	39-40	1.5	4.0	1.4462
14	40-41	1.5	2.5	1.4484
15	40-41	1.5	1.5	1.4490
16	41-41	1.5	4.0	1.4500
17	40-45	2.0	1.0	1.4502
18	45-65	2.0	1.0	1.4375
19	64-65	2.0	2.5	1.4368
20	64-65	2.0	7.0	1.4368
21	64-65	2.0	2.5	1.4368
22	64-65	2.0	2.0	1.4368
23	64-65	2.0	1.5	1.4368
24	Resid	-	2.0	-
25	Trap	-	11.0	-

Fractions (11) and (12) developed a brown colour on standing.

Analysis of fraction (20) Found: C 70.01 H 12.06

Methyl <u>iso</u>propyl ketone ketol Req: C 69.77 H 11.63

(24) sec-butylMgBr on Methyl n-butyl ketone

The addition reaction of the ketone to the Grignard was vigorous.

Volume of gas collected: 15,000 ml. Volume unabsorbed: 9,000 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/20mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	$n_D^{20.5}$
1	→115	0.5	1.4003
2	115-125	1.0	1.4039
3	125-130	1.0	1.4055
4	residue	6.0	-

The residue from (a) was transferred to (b), which was then fractionated at reduced pressure:

No.	B.P.	mm	gm	n_D^{23}	No.	B.P.	mm	gm	n_D^{23}
1	55-57	25	2.5	1.4133	14	→85	3	1.0	1.4499
2	56-57	21	4.0	1.4137	15	85-87	3	4.5	1.4552
3	55-56	21	2.0	1.4142	16	81-82	3	7.5	1.4553
4	36-60	3	0.5	1.4237	17	87-90	3	3.5	1.4549
5	61-63	3	1.0	1.4392	18	90-90	3	1.0	1.4553
6	63-64	3	4.5	1.4407	19	90-73	1	0.5	1.4548
7	64-67	3	3.0	1.4408	20	73-77	1	2.5	1.4556
8	64-67	3	3.0	1.4406	21	74-76	1	1.5	1.4558
9	64-65	3	2.5	1.4405	22	77-80	1	1.5	1.4510
10	63-68	3	4.0	1.4407	23	80-87	1	1.0	1.4510
11	63-68	3	5.0	1.4406	24	85-90	1	1.0	1.4516
12	64-65	2	1.5	1.4409	25	90-92	1	1.0	1.4449
13	63-65	2	3.0	1.4406	26	90-92	1	1.0	1.4430
	Trap	-	5.0	1.4215	27	90-92	1	1.0	1.4421
						Trap	-	5.0	-

Analysis of fraction (9) Found: C 76.79 H 14.04

Methyl-n-butylsec-butylcarbinol Req: C 76.32 H 14.45

(25) sec-<u>butylMgBr on Methyl</u> iso<u>butyl ketone</u> (1)

The addition reaction of the ketone to the Grignard was vigorous.

Volume of gas collected: 20,000 ml. Volume unabsorbed: 13,100 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/18 mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	n_D^{19}
1	→107	1.0	-
2	107-114	3.5	1.4018
3	110-114	3.0	1.4028
4	114-118	1.5	1.4039
5	118-123	0.5	1.4046
6	123-127	1.0	1.4066
7	127-129	1.5	1.4088
8	129-131	1.5	1.4107
9	131-133	2.5	1.4118

(contd)

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	n_D^{20}
10	53-54	3	0.5	1.4384
11	53-53	3	2.6	1.4386
12	53-54	3	2.0	1.4382
13	54-55	3	3.0	1.4382
14	54-54	3	1.0	1.4382
15	55-58	3	2.0	1.4388
16	55-58	3	2.5	1.4387
17	55-60	3	1.5	1.4388
18	57-60	3	1.5	1.4386
19	57-60	3	2.0	1.4409
20	55-64	3	1.0	1.4411
21	55-67	3	2.5	1.4439
22	63-69	3	2.0	1.4478
23	67-70	3	3.0	1.4502
24	71-72	3	4.5	1.4520
25	71-72	3	6.0	1.4521
26	72-72	3	9.0	1.4520
27	67-70	2	2.5	1.4521
28	69-72	2	3.0	1.4521
29	72-74	2	6.5	1.4521
30	69-73	2	1.5	1.4515
31	72-74	2	2.0	1.4513
32	75-77	2	2.0	1.4462
33	77-80	2	1.5	1.4480
34	80-85	2	1.5	1.4462
35	82-87	2	1.5	1.4442
36	87-87	2	2.0	1.4402
37	87-87	2	0.5	1.4389

Analysis of fraction (13) Found: C 76.35 H 13.9

Methyl-*iso*butyl*sec*-butylcarbinol Req: C 75.95 H 13.9

(24) sec-butylMgBr on Methyl isobutyl ketone (2)

In this experiment the reaction flask was immersed in a bath maintained at -45° to -50°. The ketone was added over 2.5 hours. Volume of gas collected: 200 ml. Volume unabsorbed: 100 ml.

The liquid product was separated under reduced pressure into: (a) below 40°/25 mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	n_D^{23}
1	40-90	2.0	- (wet)
2	90-96	2.0	1.3908(dried)
3	96-100	3.0	1.3968 "
4	100-110	3.0	1.3977 "
5	110-116	2.0	1.3993 "

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	n_D^{23}	No.	B.P.	mm	gm	n_D^{23}
6	46-53	25	0.5	1.4060	18	52-53	2.0	5.5	1.4378
7	53-54	25	1.0	1.4088	19	53-62	1.5	1.5	1.4455
8	53-54	25	0.5	1.4097	20	62-63	1.5	1.5	1.4491
9	Trap	-	5.0	1.4138	21	61-63	1.5	2.5	1.4488
10	47-49	2	1.0	1.4356	22	63-64	1.5	6.0	1.4501
11	50-51	2	1.5	1.4367	23	64-65	1.5	7.0	1.4503
12	51-53	2	1.5	1.4370	24	64-65	1.5	2.0	1.4502
13	52-53	2	2.0	1.4373	25	65-67	1.5	5.0	1.4501
14	52-53	2	2.5	1.4374	26	66-67	1.5	5.5	1.4499
15	50-52	2	2.5	1.4374	27	67-68	1.5	3.5	1.4499
16	52-53	2	4.0	1.4378	28	Resid	-	23.0	-
17	52-53	2	1.5	1.4380	29	Trap	-	2.0	-

(27) sec-butylMgBr on Methyl tert-butyl ketone

The addition reaction of the ketone to the Grignard was not at all vigorous. The trap contents increased much during the reflux period.

Volume of gas collected: 24,600 mm. Volume unabsorbed: 12,000 ml.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 35°/20 mm (b) residue

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	n_D^{22}
1	108-109	4.0	1.4013
2	109-110	4.5	1.4023
3	110-112	5.5	1.4038
4	112-112	3.5	1.4042
5	112-113	2.5	1.4041
6	113-114	4.5	1.4052
7	114-116	5.5	1.4072
8	116-118	5.0	1.4086
9	118-119	2.5	1.4111
10	120-120	1.0	1.4118
11	120-120	1.5	1.4126

(contd.)

Fractionation of (b) at 2 mm Hg.

No.	B.P.	gm	n_D^{18}
12	49-52	2.0	1.4178
13	59-60	0.5	1.4510
14	59-63	3.0	1.4500
15	63-65	2.0	1.4474
16	64-67	1.5	1.4465
17	68-70	2.0	1.4490
18	70-74	3.5	1.4442
19	74-77	2.0	1.4444
20	75-77	3.0	1.4446
21	76-80	3.0	1.4444
22	78-81	3.0	1.4442
23	80-81	1.5	1.4442
24	Trap	3.0	-
25	Drain	5.0	-

The residue from (b) solidified overnight in the still pot. Solid matter was found in the whole length of the column up to the thermometer. The pot contents were drained at the pump and the solid product was washed with 40-60° petroleum ether at -30° several times. This gave 5 gm clear white needles, which when recrystallised from aqueous ethyl alcohol had an M.P. 92-93°.

(28) sec-butylMgBr on Methyl n-amyl ketone

Volume of gas collected: 18,500 ml. Volume unabsorbed: 10,400 ml.

Fractionation of the liquid product:

No.	B.P.	mm	gm	n_D^{22}
1		20	1.0	1.4100
2	50-63	20	0.5	1.4200
3	67-70	20	4.0	1.4192
4	68-70	20	5.5	1.4204
5	70-71	20	12.5	1.4202
6	→ 65	2	0.5	1.4408
7	60-60	1	0.5	1.4421
8	60-60	1	1.5	1.4422
9	60-61	1	1.5	1.4421
10	60-60	1	2.0	1.4421
11	60-63	1	0.5	1.4421
12	67-68	2	3.0	1.4422
13	68-69	2	3.0	1.4422
14	68-69	2	3.5	1.4422
15	70-72	3	1.5	1.4423
16	75-75	3	1.5	1.4422
17	74-74	3	3.5	1.4423
18	→ 68	2	1.0	1.4422
19	68-68	2	1.0	1.4422
20	68-90	2	1.5	1.4437
21	90-110	2	2.5	1.4500
22	108-110	2	3.0	1.4571
23	110-110	2	6.0	1.4570
24	-	2	1.0	1.4580
25	-	2	0.5	1.4573
26	Residue	-	26.0	-

It appeared that break up of the ketol began to occur, since the freeze trap became blocked several times during the latter part of the distillation, and the trap contents smelled of methyl n-amyl ketone. Fractionation was therefore stopped.

Analysis of fraction (14) Found: C 76.19 H 14.1

Methyl-n-amylsec-butylcarbinol Req: C 77.02 H 14.4

(29) sec-butylMgCl on Methyl tert-butyl ketone

In this reaction the Grignard solution was prepared from 1 mol magnesium in 750 ml ether. 20% excess chloride was needed to dissolve the magnesium. To the decanted solution were added 50 gm (0.5 mol) pinacolone. Solid began to settle out after about 10 gm ketone had been added, and when the reaction was completed a thick white sludge settled.

Volume of gas collected: 200 ml. Volume unabsorbed: 100 ml. The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 40°/25 mm (b) residue

Fractionation of (a) at atmospheric pressure

No.	B.P.	gm	$n_D^{21.5}$	No.	B.P.	gm	$n_D^{21.5}$
1	→74	3.0	-	7	107-109	3.0	1.4007
2	74-99	2.0	1.3952	8	109-110	3.5	1.4018
3	99-101	1.0	1.3982	9	110-112	3.0	1.4027
4	101-104	2.0	1.3984	10	112-113	2.5	1.4042
5	104-106	2.5	1.3988	11	113-115	2.5	1.4038
6	106-107	1.5	1.3987	12	Residue	1.5	-

Fractionation of (b) at 3.5 mm Hg

No.	B. P.	gm	$n_D^{21.5}$
13	→72	1.0	1.4476
14	72-78	2.0	1.4450
15	77-78	5.0	1.4430
16	78-79	6.0	1.4420
17	Resid	0.5	-
18	Trap	2.5	1.4208

The residue (17) was washed out with ether, filtered, and the ether evaporated. No solid matter was observed.

(30) tert-butylMgBr on Methyl isobutyl ketone

The preparation of the Grignard was not as easy as with the other Grignard reagents used. A black sludge formed and some of the magnesium remained undissolved although nearly 25% excess tert-butyl was used.

After the addition of the ketone the solution was refluxed for 70 minutes, by which time gas was being evolved only very slowly.

Volume of gas collected: 21,000 ml. Volume unabsorbed: 11,300 ml.

On cooling, the solution deposited colourless crystals around the wall of the reaction flask. It was attempted to wash the crystals with ether, and to work them up separately from the main solution. Only 1.5 gm of liquid were obtained, however, this being too small an amount to enable identification as a pure component of the reaction product.

The liquid product was separated under reduced pressure by Kon triangle distillation into:

(a) below 50°/28 mm (b) residue

Fractionation of (a) at atmospheric pressure: This was made difficult by the solidification of part of the distillate in the take off channel, so that only intermittent take off could be used.

No.	B.P.	gm	
1	→ 100	2	liquid at room temperature
2	100-105	4	partly solid at room temperature
3	105-110	4	" "
4	110-115	1	" "
5	110-115	3	" "
6	115-120	1	" "
7	118-120	1	liquid at room temperature

Each of the fractions was warmed until the solid had dissolved, and then allowed to cool. The solid which crystallised out was filtered off in a cooled filter funnel, and the filtrates were cooled in ice slurry, and the process repeated. The filtrates smelled strongly of methyl *iso*butyl ketone.

The solid was identified by its great tendency to sublime, and its M.P. 105°, as di-*tert*-butyl.

The residue from (a) was transferred to (b), which was fractionated at reduced pressure.

No.	B.P.	mm	gm	n_D^{22}	No.	B.P.	mm	gm	n_D^{22}
1	51-53	29.0	1.0	1.4078	16	47-55	1.75	1.0	1.4375
2	54-55	29.0	2.5	1.4108	17	55-62	1.75	2.5	1.4439
3	54-55	29.0	2.5	1.4110	18	60-62	1.75	2.0	1.4445
4	55-56	29.0	2.0	1.4118	19	61-62	1.75	4.0	1.4466
5	55-56	29.0	1.0	1.4119	20	61-62	1.75	3.5	1.4473
6	56-80	29.0	1.0	1.4278	21	62-64	2.0	2.0	1.4481
7	80-82	29.0	1.0	1.4354	22	65-66	2.0	1.5	1.4485
8	82-84	29.0	2.0	1.4357	23	65-66	2.0	4.0	1.4490
9	82-84	29.0	2.5	1.4363	24	65-66	2.0	6.0	1.4495
10	84-85	29.0	2.0	1.4365	25	66-67	2.0	6.5	1.4498
11	83-85	29.0	1.5	1.4365	26	66-67	2.0	5.0	1.4501
12	33-34	1.5	2.0	1.4368	27	66-67	2.0	8.0	1.4503
13	34-35	1.5	1.5	1.4365	28	Resid	-	1.0	-
14	35-44	1.5	1.5	1.4361	29	Trap	-	5.0	-
15	44-47	1.5	1.5	1.4369					

(contd.)

The *p*-toluenesulphonate prepared from fraction (3) was recrystallised from 100-120° petroleum ether, and had an M.P. 38-38.5°.

Analysis of fraction (11) Found: C 75.75 H 13.97
Analysis of fraction (14) Found: C 75.98 H 14.16
Methyl-*iso*butyl-*tert*-butylcarbinol req: C 75.95 H 13.97

(31) tert-butylMgBr on Methyl ethyl ketone

The preparation of the Grignard was again difficult.

Volume of gas collected: 18,500 ml. Volume unabsorbed: 7,100 ml.

The liquid product was separated under reduced pressure into: (a) 50 gm below 40°/22 mm (b) 46 gm residue.

Fractionation of (a) at atmospheric pressure:

No.	B.P.	gm	$n_D^{21.5}$	
1	34-36	11.5	-	
2	34-36	6.0	-	
3	36-74	0.5	-	liquid at room temperature
4	74-86	1.5	-	partly solid at room temperature
5	86-91	3.0	-	" "
6	91-94	4.0	-	" "
7	92-95	4.0	-	" "
8	95-98	4.0	1.3981	liquid at room temperature
9	98-100	3.0	1.3975	" "
10	99-100	1.0	1.3975	" "
11	Resid	4.0	-	

Fractions (3) to (10) were immersed in ice slurry, and those that were partly solid at room temperature became almost entirely solid, whereas those that were liquid at room temperature showed no solid matter at all at 0°. The solid matter was filtered off, and when dry amount to 3·2 gm.

(contd.)

Fractionation of (b) at reduced pressure:

No.	B.P.	mm	gm	n_D^{22}	No.	B.P.	mm	gm	n_D^{22}
12	60-61	26.0	0.5	1.4349	24	57-58	2.5	1.5	1.4352
13	61-62	26.0	3.0	1.4351	25	57-56	2.5	1.0	1.4353
14	61-62	26.0	2.0	1.4356	26	56-87	2.5	0.5	1.4404
15	62-62	26.0	5.5	1.4358	27	87-90	2.5	0.5	1.4634
16	62-63	26.0	3.5	1.4363	28	90-91	2.5	0.5	1.4649
17	63-64	26.0	2.0	1.4374	29	91-93	2.5	1.5	1.4645
18	64-65	26.0	2.5	1.4392	30	93-93	2.5	1.0	1.4645
19	65-67	26.0	2.5	1.4417	31	93-94	2.5	1.5	1.4651
20	67-68	26.0	2.0	1.4432	32	94-95	2.5	1.5	1.4658
21	35-40	3.0	1.0	1.4474	33	Resid	-	1.0	-
22	40-57	2.5	1.5	1.4393	34	Trap	-	6.0	-
23	57-58	2.5	0.5	1.4348					

The 2;4-dinitrophenylhydrazone prepared from fraction (29) was recrystallised from ethyl alcohol, and had an M.P. 146-147°.

The 2:4-dinitrophenylhydrazone prepared from fraction (24) consisted of two compounds which could not be separated completely. The original, when crystallised from ethyl alcohol, melted between 110-120°. Repeated crystallisations raised the M.P. to 127-128° and freezing of the mother liquors of the first crystallation gave a product M.P. 85-96°. Further crystallisations gave an ever diminishing product still having a melting range. There was insufficient for analysis, and insufficient of fraction (24) to prepare more.

Analysis of fraction (15 Found: C 73.4 H 13.39
req: C 73.8 H 13.84

Analysis of fraction (24) Found: C 66.37 H 11.08
req: C 66.66 H 11.11

Analysis of fraction (29) Found: C 70.21 H 10.39
req: C 72.71 H 11.11

Analysis of fraction (31) Found: C 70.21 H 11.32
req: C 72.71 H 11.11

Analysis of 2:4-dinitrophenylhydrazone from fraction (29)
Found C 56.46 H 6.8 N 15.1
Req: C 57.14 H 6.76 N 14.8

(32) Attempted preparations of di-*tert*-butyl

(a) *tert*-butylMgCl + *tert*-butyl chloride

A solution of *tert*-butylMgCl was made in 1000 ml anhydrous ether from 1 mol. magnesium. The solution deposited a black sludge during preparation, and again after decanting through glass wool. To this solution was slowly added 1 mol. *tert*-butyl chloride, and the solution was then refluxed for 1 hour. After cooling, water was added slowly, and the product was worked up in the usual way. Only a very small residue was obtained. This contained no di-*tert*-butyl.

(b) *tert*-butylMgCl + $CuCl_2$

The solution of *tert*-butylMgCl was made as in (a). To the solution was added 1 mol. freshly prepared anhydrous $CuCl_2$, and the solution was then stirred under reflux for 2 hours. After standing overnight water was added with continuous stirring. Ferric chloride was added to oxidise insoluable copper salts, but this was not effective. The ether solution was washed until both ether and washing water were colourless. After drying and removing the ether through an 8 inch column, a small residue was obtained from which a few milligrams of solid di-*tert*-butyl were obtained.

(c) tert-butylMgCl + tert-butylCl + $CoCl_2$

The tert-butylMgCl solution was made as before, and cooled in an ethanol/CO_2 bath at 0°. To the solution were added 6.5 gm (5 mol %) freshly prepared anhydrous $CoCl_2$, and the solution was stirred for half an hour. 1 mol. tert-butyl chloride was then added over 1.25 hours. The bath was kept at 0° to - 5° during the addition. The addition was accompanied by effervescence. After stirring for 1 hour, the solution was allowed to stand for two days. A heavy sludge of brown and white granules formed. Water and dilute acetic acid were added, and the ether layer was separated and washed several times with sodium bicarbonate and water. After drying with calcium chloride the ether was removed through an 8 inch column. The residue was distilled through a 6 inch column filled with Fenske helices; the distillate was collected in five portions between 100-104°.

No.	n_D^{15}	gm	No.	n_D^{15}	gm
1	1.3978	1.0	4	1.4058	3.0
2	1.4048	1.5	5	1.4067	1.0
3	1.4052	2.0			

The refractive index of diisobutylene at 15° is 1.4115. No di-tert-butyl was obtained.

(d) tert-butylMgBr + tert-butyl bromide

The same procedure was used as in (a). No di-tert-butyl was obtained.

(33) Identification of Solid from E xpts 10 & 27

(a) Analysis of the recrystallised solid M.P. 92-93°. Found: C: 71.29 H: 12.71 This indicates a formula approximating $(C_6H_{12}O)x$.

(b) The M.Wt of the solid was determined by cryoscopic measurements in benzene. The M.Wt. was determined at three concentrations, and the values found were extrapolated to zero concentration. The cryoscopic constant for the benzene was determined using naphthalene as solute. The M.Wt of the solid was found to be 210. (This is within experimental error of 200).

(c) Some of the solid was dissolved in pyridine, and benzoyl chloride was added. The solution became purple and deposited needles of pyridine hydrochloride. Dilute HCl was added, and an oil separated out. This solidified after two weeks, and was recrystallised from 100-120° petroleum ether. The M.P. was 121-122°, and indicated that the product was only benzoic acid.

(d) The same procedure was carried out as in (c) using p-toluenesulphonyl chloride. The only product obtained was the original p-toluenesulphonyl chloride.

(e) Some of the solid was heated with acetic anhydride on a steam bath for one hour, cooled, and diluted with water. The oil which separated soon solidified, and when washed and dried had an M.P. 92-93°.

(f) Some of the solid was refluxed with acetic anhydride and sodium acetate on a sand bath for one hour. On diluting with water a small amount of sweet smelling oil separated, but could not be identified.

(g) Some of the solid was dissolved in a freshly prepared solution of lead tetra-acetate in acetic acid. No visible reaction took place either in the cold or on warming or on refluxing the solution.

(h) Attempted synthesis of pinacolone pinacol. Using the method of Gomberg and Bachmann[12], a solution of MgI was made from 7.5 gm magnesium and 21 gm iodine. To this were added 15 gm pinacolone. After continuing as directed no other product than pinacolone was obtained.

(i) As in (h) but refluxed several hours after adding the pinacolone. Once again only pinacolone was obtained.

(j) Synthesis of pinacolone pinacol. Using the method of Delacre[48] 20 gm pinacolone were reacted with 12 gm sodium in a mixture of ether and water. The washed and dried product consisted mostly of pinacolyl alcohol, but on evaporating this a small amount of solid residue was obtained. This was washed with 40-60° petroleum ether at -60°, and was then crystallised from petroleum ether. M.P. 69-70°. The M.P. given by Delacre is 72°. That given by Friedel and Silva[47] is 69°.

(k) Some of the solid was dehydrated by distilling over naphthalene-2-sulphonic acid. Only a small amount of olefin and water was obtained. There was insufficient for identification.

(l) Reduction of pinacolone ketol. (1) 4 gm of the ketol from Expt. (27) were dissolved in ethyl alcohol, and 1 gm sodium was added in small pieces. The solution was diluted with water and an upper layer was obtained smelling of pinacolyl alcohol. Solid matter began to be deposited, and the upper layer, on separation and evaporation, gave a considerable amount of solid. This was recrystallised from aqueous ethyl alcohol, and had an M.P. 92-93°. The mixed M.P. with the "unknown" solid was 92-93°.

(m) Reduction of pinacolone ketol (2) 3.5 gm of the ketol were dissolved in 20 ml ethyl alcohol, and 3 ml N $FeCl_3$ solution were added. The solution was shaken with Adam's PtO_2 catalyst and hydrogen at 50 lb sq. in. pressure for 12 hours. The filtered solution was diluted with water, and extracted with ether, and the ether solution was washed with water several times. After drying with calcium chloride the ether was evaporated, leaving a liquid which slowly deposited crystals around the perimeter. These were removed and purified by repeated evaporation of their ether solution. The crystals so obtained were recrystallised from aqueous ethyl alcohol, and had an M.P. $92.5-93.5^{o}$. The mixed M.P. with the "unknown" solid was $92.5-93-5^{o}$.

Summary of Experimental work on 2:4:6-Trimethylheptane

(A) On the syntheses of 2:4:6-trimethylheptanol-4

Experiments (34) to (45) deal with the three syntheses used (i.e.)

(34) The interaction of methyl *iso*butyl ketone and *iso*butylMgBr.

(35) to (44) The interaction of methyl acetate and *iso*butylMgBr.

(45) The interaction of di*iso*butyl ketone and methylMgBr.

(B) On the dehydration of 2:4:6-trimethylheptanol-4 and the reduction of 2:4:6-trimethylhexene.

Experiments (46) to (49)

(C) On the identification of the by-products from the methyl acetate syntheses.

Experiments (50) to (55)

(D) On the preparation of *iso*butyl bromide

Experiment (56)

N.B. Notes on the preparation of methyl *iso*butyl ketone are given in the experimental work on 2:3:5-trimethylhexane (pp.255-60)

2:4:6-Trimethylheptanol-4

In the eleven preparations of 2:4:6-trimethylheptanol-4 described below the following procedure was adopted. The isobutylMgBr solution was made by adding the desired amount of iso-butyl bromide to an excess of magnesium under anhydrous ether. When all the bromide had been added the solution was boiled under reflux for half an hour, cooled, and decanted from unused magnesium through glass wool into a second dry flask. The second reagent was then added dropwise to the Grignard solution. After this reagent had been added the solution was refluxed for a determined time, cooled, and poured on to crushed ice. The mixture was then dissolved out with concentrated hydrochloric acid, separated and extracted with ether. The ether solution was washed twice with 20% sodium chloride, once with 30% sodium hydroxide, and twice with water. After drying overnight with potassium carbonate the ether was removed through a short column and the residue distilled at reduced pressure. The distillate was then fractionated at atmospheric pressure through an 8 in. Dufton column.

For convenience the proportions of reagents used and their yield of tertiary carbinol are expressed in a tabular form. As a typical example of the fractionation of these reactions products that of Expt. 38 is given in full. The by-products from these reactions are dealt with on pp 222-226 .

Expt.	_iso_BuBr		Methyl Acetate		Me.CO._iso_Bu		Ratio of reactants	Refluxed hours	% Yield tert-OH	Source of _iso_BuBr
	gms	mols	gms	mols	gms.	mols				
34	80	0.6			40	0.4		1.5	27.0	HBr/H_2SO_4
35	137	1.0	19	0.25	-	-	4:1	1.5	33.0	HBr/H_2SO_4
36	210	1.53	40	0.54	-	-	3:1	1.5	26.5	HBr/H_2SO_4
37	230	1.68	31	0.42	-	-	4:1	6.0	25.0	HBr/H_2SO_4
38	420	3.06	58	0.78	-	-	4:1	2.0	22.5	HBr/H_2SO_4
39	411	3.0	57	0.77	-	-	4:1	1.5)	31.0	PBr_3
40	411	3.0	57	0.77	-	-	4:1	1.5)		
41	411	3.0	57	0.77	-	-	4:1	4.0)	25.0	PBr_3
42	411	3.0	57	0.77	-	-	4:1	4.0)		
43	274	2.0	50	0.67	-	-	3:1	4.0	27	PBr_3
44	411	3.0	76	1.0	-	-	3:1	6.0	20	HBr/H_2SO_4

These results are discussed on p 126 .

<u>Expt. 38</u> Fractionation gave:

No.	B.P.	gms	No.	B.P.	gms.
1	80-108	4.0	6	175 - 185	28.0
2	108-118	6.0	7	185 - 207	3.5
3	118-128	3.5	8	207 - 215	2.0
4	128-132	20.0	9	215 - 219	2.0
5	132-175	9.0	10	219 - 222	2.0

(45)

MethylMgBr and diisobutyl ketone.

A solution of methylMgBr was made in anhydrous ether by adding sufficient methyl bromide to 48.6 gms. magnesium (2 gm.atoms) to completely dissolve the magnesium. The solution was filtered through glass wool and 142 gms (1 gm mol) diisobutyl ketone were added slowly, the solution being stirred constantly by a mercury sealed stirrer. Reflux was carried out for 1 hour after addition of the ketone. The rest of the treatment was as in experiments (34) to (44).

The reaction product was fractionated at reduced pressure through a 12 inch column packed with single turn Fenske helices fitted with a total-reflux-variable-take off still head. The following results were obtained.

No.	B.P.	mm Hg	n_D^{22}	gms.
1	38.0-38.5	1.0	1.4297	4.0
2	38.0-38.5	1.0	1.4298	4.5
3	38.0-38.5	1.0	1.4298	7.0
4	38.0-38.5	1.0	1.4299	5.5.
5	38.5-39.0	1.0	1.4300	6.0
6	39.0-39.5	1.0	1.4302	7.0
7	39.0-39.0	1.0	1.4305	4.5
8	39.0-39.0	1.0	1.4307	7.0
9	39.0-39.5	1.0	1.4307	5.0
10	39.5-40.0	1.0	1.4307	8.5
11	39.5-40.0	1.0	1.4309	5.5.
12	33.0-33.5	0.75	1.4309	6.0
13	33.5-33.7	0.75	1.4309	5.0
14	33.5-33.7	0.75	1.4309	7.0
15	33.7-34.0	0.75	1.4309	9.0
16	33.7-34.0	0.75	1.4309	8.5
17	34.0-34.0	0.75	1.4309	10.0
18	34.0-34.5	0.75	1.4309	9.0
19	34.5-35.0	0.75	1.4309	3.0
20	32.5-33.0	0.50	1.4309	9.0
21	33.0-33.5	0.50	1.4309	7.5
22	33.5-34.0	0.75	1.4309	7.5
23	34.0-35.5	0.75	1.4309	3.5
24	Residue			1.5
25	Trap			15.0

(46) The azeotrope from Expt.45

(a) Part of the azeotrope was fractionated at atmospheric pressure through a 12 inch column packed with Fenske helices with the following result:

No.	B.P.	n_D^{23}
1	120-160	1.4261
2	160-166	1.4290
3	166-170	1.4296
4	170-170	1.4299
5	170-172	1.4299
6	172-173	1.4300
7	173-175	1.4302
8	175-179	1.4304
9	179-180	1.4304

(b) Some of fraction (2) was mixed with an equal volume of phenyl<u>iso</u>cyanate and heated at 100° for one hour, during which much solid formed. After cooling the solid was extracted with 100-120° petroleum ether and the filtrate was evaporated. The white crystalline solid so obtained was recrystallised from petroleum ether and had a M.P. 152-153°.

(c) Fraction (2) was also treated with 2:4-dinitrophenylhydrazone by Brady's method. Only the original phenylhydrazone was obtained.

(d) Dehydration of the azeotrope: part of the azeotrope was distilled over naphthalene-2-sulphonic acid, separated from the water in the distillate and re-distilled over fresh catalyst. The olefin obtained was washed with 10% sodium hydroxide and water, and was then dried over calcium chloride. It was then fractionated through a 12 inch column packed with Fenske helices and fitted with a total reflux variable take off still head.

No.	B.P.	gm	n_D^{23}
1	144.0-145.0	0.5	1.4205
2	144.5-145.0	1.0	1.4204
3	144.5-145.0	1.5	1.4204
4	145.0-145.5	2.0	1.4204
5	145.5-145.5	2.5	1.4204
6	Residue	1.0	1.4216

Fractions (1) to (5) were reduced in glacial acetic acid solution by PtO_2/H_2 at three atmospheres pressure. From the reduction was obtainedthe hydrocarbon B.P. 145-146° n_D^{23} 1.4075.

2:4:6-Trimethylheptanol-4, Fractionation & dehydration.

(47) The 2:4:6-trimethylheptanol-4 prepared in the previous experiments was bulked and fractionated through a 45 cm Vigreux column. The amount of carbinol bulked was 280 gm. Barometric pressure was 752 mm Hg.

The "tops" containing some water were set aside over anhydrous Na_2SO_4. The following fractions were then collected:

	B.P.	gms	n_D^{18}
(1)	178-179	29.0	1.4320
(2)	179-180	57.5	1.4327
(3)	180-181	47.5	1.4327
(4)	181-182	35.5	1.4330
(5)	182-183	19.5	1.4331
(6)	183-184	13.0	1.4334
(7)	184-185	-	1.4337

All distillates below 179 were dried over Na_2SO_4 for two days, filtered, and then fractionated giving:

	B.P.	gms.	n_D^{18}
(8(	175-176	2.0	1.4294
(9)	176-177	5.0	1.4305
(10)	177-178	4.5	1.4312
(11)	178-178	4.0	1.4319
(12)	178-179	3.5	1.4321
(13)	179-180	12.0	1.4324
(14)	180-181	11.0	1.4329
(15)	181-182	7.0	1.4330
(16)	182-183	2.0	1.4331

(48) Dehydration: The carbinol was dehydrated by distilling from a flask containing a small amount of naphthalene-2-sulphonic acid. The product was redistilled from naphthalene-2-sulphonic acid until no more water came over with the distillate. Fractions (2) to (6) and (13) to (16) were used. The crude heptene obtained was washed with three times 10% NaOH and three times H_2O to remove sulphur and acidic compounds, dried over $CaCl_2$, and fractionated through an 8 in. Dufton column. The amount of starting material was 142 gm. The distillate was collected in a small burette so that known volumes could be drawn off. The table A below shows the results:

TABLE A.

	B.P.	ml.	n_D^{20}
(1)	94.0-142.4	5	1.4154
(2)	142.4-142.5	5	1.4206
(3)	142.5-143.0	10	1.4208
(4)	143.0-143.5	10	1.4208
(5)	143.5-143.6	10	1.4209
(6)	143.6-143.9	10	1.4209
(7)	143.9-144.0	10	1.4210
(8)	144.0-144.2	10	1.4210
(9)	144.2-144.5	10	1.4211
(10)	144.5-144.7	10	1.4211
(11)	144.7-144.8	10	1.4211
(12)	144.8-145.0	10	1.4211
(13)	145.0-145.0	10	1.4210
(14)	145.0-145.1	10	1.4211
(15)	145.1-145.5	10	1.4211
(16)	145.5-145.6	10	1.4211
(17)	145.6-145.8	11	1.4212
(18)	145.8-146.0	10	1.4212
(19)	146.0-146.0	5	1.4212
(20)	146.0-146.7	5	1.4213
(21)	146.7-147.5	5	1.4219
(22)	147.5-149.0	3	1.4221

(49) Reduction of 2:4:6-trimethylheptene-2. The heptene was reduced in glacial acetic acid soln. with Adams PtO_2 catalyst and hydrogen under pressure. When no further fall in pressure was observed, the contents of the hydrogenation bottle were filtered and neutralized with 30% NaOH. The hydrocarbon layer was washed three times with H_2O and then dried over $CaCl_2$. This procedure was repeated until testing with a dilute soln. of bromine in carbontetrachloride showed no unsaturation present in the hydrocarbon. Fractions (3) to (19) were used.

Fractions (20) and (21) after hydrogenation had n_D^{22} 1.4185 and were therefore extracted three times with cold conc. H_2SO_4, washed three times with water, and dried over K_2CO_3. Much was lost by extraction and the product had n_D^{20}1.4375.

(50) Fractionation of 2:4:6-trimethylheptane. 107 gm of the hydro-carbon were fractionated through an 8 in. Dufton column. Barometric pressure was 753 mm. Table B shows the results obtained. Each fraction is of 5 ml.

TABLE B

No.	B.P.	n_D^{20}	No.	B.P.	n_D^{20}
(1)	142.1-144.1		(13)	145.5-145.5	
(2)	144.1-144.5	1.4092	(14)	145.5-145.6	
(3)	144.5-144.7		(15)	145.6-145.9	
(4)	144.7-144.8		(16)	145.9-146.0	
(5)	144.8-145.0		(17)	146.0-146.1	
(6)	145.0-145.1		(18)	146.1-146.2	
(7)	145.1-145.2		(19)	146.2-146.3	
(8)	145.2-145.3		(20)	146.3-146.4	1.4100
(9)	145.3-145.0		(21)	146.4-146.5	
(10)	145.0-145.0		(22)	146.5-146.7	
(11)	145.0-145.4	1.4097	(23)	146.7-146.8	
(12)	145.4-145.5		(24)	146.8-146.9	
			(25)	146.9-147.1	

Fractionation was stopped at fraction (26) since this fraction showed signs of unsaturation when tested with Br_2/CCl_4 solution. Extraction of fraction (26) with cold conc. H_2SO_4 gave a product which after washing and drying had n_D^{20} 1.4133.

Further reduction of the 13 gm. residue, n_D^{20} 1.4104, gave a product n_D^{20} 1.4080 showing no signs of unsaturation when tested. Re-reduction of fractions (1) to (25) gave a product of n_D^{20} 1.4073 still showing signs of unsaturation. A third reduction gave a product free from unsaturation n_D^{20} 1.4069.

The hydrocarbon was refractionated after refluxing over sodium, and was collected in 5 ml portions. Results are shown in Table C.

TABLE C

No.	B.P.	n_D^{16}	No.	B.P.	n_D^{16}
(1)	142.5-144.2	1.4082	(13)	146.2-146.2	1.4089
(2)	144.2-144.0	1.4081	(14)	146.2-146.4	1.4088
(3)	144.0-144.6	1.4081	(15)	146.4-146.6	1.4090
(4)	144.6-144.8	1.4084	(16)	146.6-146.6	1.4091
(5)	144.8-145.0	1.4084	(17)	146.6-146.8	1.4090
(6)	145.0-145.2	1.4084	(18)	146.8-146.9	1.4090
(7)	145.2-145.3	1.4087	(19)	146.9-146.9	1.4091
(8)	145.3-145.5	1.4087	(20)	146.9-147.0	1.4091
(9)	145.5-145.8	1.4087	(21)	147.0-147.1	1.4091
(10)	145.8-145.8	1.4088	(22)	147.1-147.4	1.4092
(11)	145.8-146.0	1.4088	(23)	147.4-147.8	1.4093
(12)	146.0-146.2	1.4089	(24)	147.8-148.2	1.4094

The hydrocarbon was redistilled after refluxing for 0.75 hour over sodium, the distillate being collected between 144.6° and 147.4°. After standing over sodium overnight the hydrocarbon was fractionated again, and collected in 5 ml portions. Results are shown in Table D.

TABLE D

No.	B.P.	$n_D^{17.25}$	No.	B.P.	$n_D^{17.25}$
(1)	144.4-144.7	1.4077	(11)	146.0-146.2	1.4081
(2)	144.7-145.0	1.4078	(12)	146.2-146.4	1.4082
(3)	145.0-145.2	1.4079	(13)	146.4-146.5	1.4082
(4)	145.2-145.4	1.4080	(14)	146.5-146.7	1.4083
(5)	145.4-145.5	1.4080	(15)	146.7-146.8	1.4083
(6)	145.5-145.6	1.4080	(16)	146.8-146.9	1.4083
(7)	145.6-145.7	1.4080	(17)	146.9-147.0	1.4083
(8)	145.7-145.9	1.4080	(18)	147.0-147.2	1.4084
(9)	145.9-146.1	1.4081	(19)	147.2-147.4	1.4084
(10)	146.1-146.0	1.4081	(20)	147.4-147.8	1.4087

Fractions (4) and (19) were sent for infra-red examination.

By-Products from Methyl Acetate Reactions

The low boiling liquids from Experiments (35) to (44) were bulked and fractionated through a 45 cm Vigreux column into (A) liquids below 119° (B) liquids between 119-140°.

(51) Fractionation of (A). An 8 in. Dufton column was used. Barometric pressure 751 mm Hg. Fractions of the following B.P.s were collected.

1)	77-78	5)	113-114
2)	82-92	6)	114-118
3)	92-102	7)	118-128
4)	102-113	8)	128-130

Fraction (6) smelled of methyl *iso*butyl ketone. The semicarbazone prepared from this fraction had M.P. 133° and a mixed M.P. with the semicarbazone of methyl *iso*butyl ketone of 133°. The B.P. of methyl *iso*butyl ketone is 115-116°.

Fd.	C 52.95	H. 9.33	N 25.8
Calc.	C 53.51	H. 9.38	N 26.75

(52) Fractionation of (B). A 45 cm Vigreux column was used. Distillates were collected at the following temperatures:

1)	89-115	5)	128-130
2)	115-118	6)	130-132
3)	118-127	7)	132-134
4)	127-128		

Fraction (6) was selected for preparation of derivatives.

The acid phthalate, purified by $NaHSO_3$ extraction, remained always as a viscous liquid. The *p*-toluene-sulphonate and 3:5-dinitrobenzoate were prepared.

METHYLISOBUTYLCARBINOL-p-TOLUENESULPHONATE

(53) A small amount of the carbinol was dissolved in dry pyridine and the equivalent amount of freshly crystallized *p*-toluenesulphonyl chloride was added in small portions, each portion dissolving with the evolution of heat. Long needles of pyridine hydrochloride separated after standing half an hour. The contents were poured into dilute HCl and shaken until there was no longer a smell of pyridine. A reddish oil separated at the surface, and colourless cube crystals appeared in the oil after standing overnight. The liquid was decanted from the crystals which were then dried on filter paper, and dissolved in dry 60-80° petroleum ether. This solution was allowed to crystallise at room temperature giving fine colourless crystals of methyl*iso*butylcarbinol-*p*-toluenesulphonate M.P. 39-40°.

Found	C 60.9	H 7.2	S 12.5
Req: for $C_{13}H_{20}O_3S$	C 60.96	H 7.79	S 13.09

METHYLISOBUTYLCARBINOL-3:5-DINITROBENZOATE

(54) Attempts to prepare this derivative from 3:5-dinitrobenzoyl-chloride in dry pyridine solution gave only 3:5-dinitrobenzoic acid.

The derivative was obtained by warming at 75-80° some of the carbinol added to less than the equivalent amount of 3:5-dinitrobenzoyl-chloride. The mixture solidified on standing overnight and was loosened with 60%

ethyl alcohol. The solid so obtained was recrystallized from 60% ethyl alcohol giving glistening scales of methyl*iso*butylcarbinol-3:5-dinitrobenzoate M.P. 60.5-61.5°.

Fd	C.52.47	H 5.4	N. 9.43
Req. for $C_{13}H_{16}O_6N_2$	C.52.7	H. 5.4	N. 9.46

Identification of Ketone $C_{12}H_{22}O$. (p.127)

Analysis

Analysis of some of the fractionated high boiling liquid obtained in Experiments (35) to(44) gave

	Found	C 79.30	H 12.08
$C_{12}H_{22}O$	Calc	C 79.14	H 12.28

Molecular weight

(55) As it was not possible for some while to make a derivative of this ketone its molecular weight was determined by cryoscopic method using benzene as solvent. After determining the cryoscopic constant for the benzene (the constant given by the usual authorities varies with the authority) and determining the M.wt for three concentrations of ketone, a M.wt. of 182.4 was obtained by extrapolation to zero concentration . The M.wt. of $C_{12}H_{22}O$ is 182.

Derivative

(56) Attempts to make a semicarbazone of this ketone were unsuccessful, and at first led to the belief that the by-product was not ketonic.

By using Brady's method, however, it was possible to prepare a 2:4-dinitrophenylhydrazone. This remained as an oil for several months but finally crystallised from 100-120° petroleum ether, giving deep crimson plates of 2:4:8-trimethyl-nonene-4-one-6,2:4-dinitrophenylhydrazone M.P. 126-127°.

Found	C 60.03	H 7.47	N 14.8
Req: for $C_{18}H_{26}O_4N_4$	C 59.68	H 7.18	N 15.47

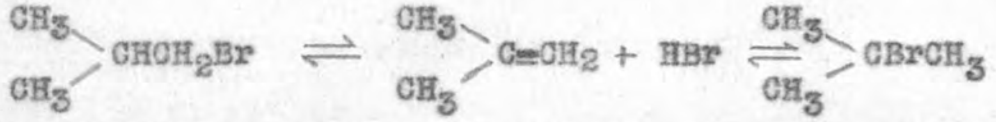
(56a) Reduction of $C_{12}H_{22}O$.

The ketone was reduced by shaking in glacial acetic acid solution with Adam's catalyst and hydrogen at 50 lbs sq. in for 12 hours. The product obtained after filtering, separating, washing with sodium hydroxide, and with water, was dried and fractionated under reduced pressure through a 12 inch column.

No.	B.P.	gm	n_D^{18}
1	78-81	0.5	1.4258
2	81-85	0.5	1.4290
3	85-86	3.0	1.4305
4	86-87	2.0	1.4305
5	86-87	3.0	1.4306
6	86-87	3.5	1.4307
7	86-87	3.5	1.4307
8	87-89	3.0	1.4308

ISOBUTYL BROMIDE

(57) A description of the difficulties experienced with the preparation of *iso*butyl bromide is included since, although the change of *iso*butyl bromide to its tertiary isomer



$$\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle CHCH_2Br \rightleftharpoons \left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle C{=}CH_2 + HBr \rightleftharpoons \left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle CBrCH_3$$

has long been known, it is felt that many research workers start with the use of *iso*butyl bromide in view without knowing the difficulties to be encountered; and that since this bromide presented such an obstacle in this work, there should be recorded a description of the attempts to overcome it.

The first intimation of these difficulties was given on attempting to distil a 500 gm. purchase of the bromide. Slow distillation gave a top distillate between 76.1° and 85.1°/ 760 mm., and when distillation was continued next day a product boiling between 85.1° and 93.1° was obtained.

The distillate boiling between 85.1° and 92.1° was therefore re-fractionated. The column used was of the Widmer type, lagged with cotton wool and carefully screened from draughts. A thermometer reading 0.2° divisions was used and viewed with a lens. The distillate was collected in 20 ml. portions except for the first 10 ml., and the following results were obtained:

No.	B.P.	No.	B.P.
1	84.5-84.6	8	87.1-81.1
2	84.6-84.6	9	81.1-88.8
3	84.6-85.1	10	88.8-90.1
4	85.1-85.5	11	90.1-90.7
5	85.5-85.5	12	90.7-91.3
6	85.5-86.3	13	91.3-91.7
7	86.3-87.1	14	91.7-92.2

indicating that in the steady rise of temperature the range of boiling point of each 20 mls. was decreasing as the boiling point increased, so that the distillation of the iso bromide was quicker than the change to the tertiary

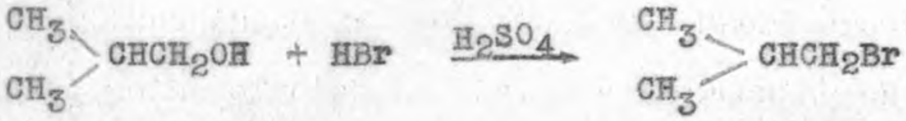
A quicker rate of distillation was therefore decided on. Fractions 11 12 13 14 were shaken twice with warm water to remove tertiary bromide, and dried with $Cacl_2$. 60 mls. of the bromide were used for fractionation in the same apparatus and within 15 mins. 50 mls. were collected with the following results:

Vol. of distillate	B.P.
5 mls	90.1
20 mls	91.1
30 mls	91.4
40 mls	91.7
50 mls	92.0

The distillate was returned to the flask and the distillation repeated:

Vol. of distillate	B.P.
5 mls	90.1
20 mls	91.1
35 mls	91.5
45 mls	91.8
53 mls	92.1

These figures showed that a fairly rapid distillation of the bromide gave a distillate which had undergone little, if any, isomerisation. It was decided therefore to prepare some isobutyl bromide by the quickest available method and compare its properties with those of commercially "pure" bromide. The method of preparation was as indicated by the scheme below.



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CHCH_2OH + HBr \xrightarrow{H_2SO_4} \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CHCH_2Br$$

using constant boiling hydrobromic acid (47-48%).

Preparations using Hydrobromic Acid

The reagents were mixed by adding the hydrobromic acid to the isobutyl alcohol, and then adding the sulphuric acid in a steady stream, the solution being kept cool under running water. The whole was then refluxed over a burner. Reflux was stopped each hour and the dark bromide which had separated was removed and steam distilled giving a colourless product. The steam distillate was then separated and extracted with conc. sulphuric acid, a procedure which was difficult owing to emulsion formation, and apparently never ending, since even after the fifth extraction the acid was still coloured brown and smelling of sulphur dioxide. The next two stages, washing with 10% sodium carbonate soln. and with water, were also made difficult by emulsification. After drying over $CaCl_2$ for 12 hours some of the bromide was fractionally distilled at 775 mm Hg through an 8 in. Dufton column, giving a small distillate between 89-90.5° and the major portion between 90.5° and 93°. No HBr was noticed during this second distillation.

It was apparent, therefore, that preparation of isobutyl bromide in this way would give a product which could reasonably be called usable. Treatment of 50 gm. portions of this bromide and similar treatment of the commercially "pure" bromide showed the former to be of a better condition. Some of this boiling between 91-93° was refluxed for 5 hours in a Cottrell pump and showed a constant boiling point of 92.3° the whole time.

On the strength of these observations it was decided that the higher boiling fraction of the bromide prepared by the HBr method was suitable for use in the Grignard reactions for the preparation of tertiary carbinols. The reasons for this were: (1) the only likely impurities were tertiary butyl bromide and unchanged alcohol. (2) Acid extraction should remove the alcohol as well as any olefins or unsaturated compounds formed, whilst steam distillation should remove the tertiary bromide.

Some more bromide was prepared as described, extracting the brown crude bromide with conc. sulphuric acid three times, steam distilling and then fractionating at ordinary pressure. 550 gm. of the bromide so prepared were shaken with 500 mls. water for 7 hours, after which the aqueous layer was titrated with standard alkali, and from the titration the amount of tertiary bromide in the product was calculated as 0.7%.

Preparations using PBr_3

These followed the method given in Organic Syntheses Coll. Vol.II, 358, but some slight modifications were made in the technique. The method given in Organic Syntheses is itself a modification of the method of preparing cyclopentyl bromide in which the bromide is liberated after reaction between the cyclopentyl alcohol and PBr_3 by pouring into water. Therefore in the first preparation of isobutyl bromide this procedure was adopted instead of vacuum distilling the bromide from the reaction mixture as directed in Organic Syntheses. Acid extraction of the bromide layer so obtained was very difficult since the strong emulsion formed could be separated only by using a large excess of sulphuric acid. The product however yielded very little low boiling liquid when fractionated through a 45 cm. Vigreux column, and gave a 30% yield of isobutyl bromide boiling between 90.5° and 93°.

At this stage it was decided to see whether a synthetic mixture of isobutyl and tert-butyl bromides could be separated by fractionation with the apparatus available. Some tert-butyl bromide was prepared from the pure crystallized alcohol and constant boiling hydrobromic acid, and after fractionation and drying over $CaCl_2$ for 24 hours, a mixture was made containing 18 gms. of the tertiary and 50 gms. of the iso bromides, the latter being some of that prepared with PBr_3. Fractionation through an 8 in. Dufton column showed that the separation of these bromides with this apparatus was not efficient, the following distillates being obtained:

(1)	76.0-82.0	3.0 gm.	discoloured
(2)	82.0-83.0	5.0 gm.	"
(3)	83.0-86.0	13.5 gm.	colourless
(4)	86.0-89.0	14.0 gm.	
(5)	89.0-90.5	13.0 gm.	
(6)	90.5-91.0	12.5 gm.	
(7)	Residue	4.0 gm.	

Fractions (2) and (3) were each shaken with 50 mls. water and estimation of the HBr in the water showed these fractions to contain 3.6% and 2.6% tertiary bromide respectively.

<u>Iso</u>butyl bromide was prepared in all eleven times by the PBr_3 method. Of six preparations in which the procedure given in Organic Syntheses was followed, yields between 28% and 41% were obtained of bromide boiling between 90° and 93°. It was noticed that very rapid stirring of the alcohol allowed a quick rate of addition of the PBr_3 without causing much rise in temperature, and therefore one preparation was tried in which PBr_3 was added in an almost continual stream whilst reactants were stirred very rapidly. Much more HBr came off during the vacuum distillation of the reaction mixture, but fractionation at atmospheric pressure gave a 45% yield of the bromide boiling between 90° and 93°. Since the method of cooling with ice and salt was messy and needed constant attention, another experiment was tried in which the refrigerant was ethyl alcohol/CO_2, and the temperature of the reaction mixture was maintained between -25° and -35°

An excess of PBr_3 was also used in this experiment amounting to 25% of that recommended by Organic Syntheses. The temperature of the reaction mixture rose to 35° some while after the addition of the PBr_3. The yield of isobutyl bromide from this experiment was 61% B.P. 89.9-93.0°.

In the course of these preparations the following points were noticeable. (1) the yield of isobutyl bromide is very variable. (2) very efficient cooling traps are necessary in the vacuum distillation to minimise losses. (3) a long period should be allowed for the sulphuric acid to drain from the last extraction of the vacuum distillate. It was noticed that a fine suspension of acid was usually formed which required at least a day to separate. (4) HBr was usually evolved during fractionation, more so in the later experiments than in the earlier.

Summary of Experimental work on 2:3:5-Trimethylhexane

(A) On the synthesis of 2:3:5-trimethylhexanol-3

Experiments (58) to (71) deal with the three syntheses used (i.e.)

(58) to(69) The interaction of methyl *iso*butyl ketone and *iso*propylmagnesium bromide.

(70) The interaction of methyl *iso*propyl ketone and *iso*butylmagnesium bromide.

(71) The interaction of *iso*propyl *iso*butyl ketone and methylmagnesium bromide.

(B) On the dehydration of 2:3:5-trimethylhexanol-3 and subsequent preparation of 2:3:5-trimethylhexane.

Experiments (72) to (74)

(C) On the use of cadmium dialkyls.

Experiments (75) to (79)

(D) On the preparation of methyl *iso*butyl ketone.

Experiments (80) to (88)

(E) Miscellaneous Intermediates (Notes)

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EXPERIMENTAL

2:3:5-trimethylhexanol-3

In the following experiments, unless otherwise stated, the Grignard solution was prepared and decanted from excess or undissolved magnesium through glass wool into a two litre flask fitted with a stirrer, two reflux condensers, and a dropping funnel. The requisite ketone was then added slowly with continuous stirring. After the addition was complete the solution was refluxed for a determined time. When cool the solution was poured onto crushed ice, dissolved out with concentrated HCl, and extracted twice with ether. The combined ether solutions were washed twice with 20% sodium chloride, twice with 30% sodium hydroxide, twice with water, and then dried over potassium carbonate. The ether was then removed through an 8 inch Dufton column, and the residue treated as described in the separate experiments.

IsopropylMgBr on Methylisobutyl ketone

(58)

Reagents used		Reflux
Isopropyl bromide	200 gm (1.63 mol)	1.0 hour
Magnesium	92 gm	
Ether	1000 ml	
Methyl isobutyl ketone	82 gm (0.82 mol)	

Addition of the ketone was accompanied by a brisk reaction which slowed down when about half the ketone had been added. The reaction product was distilled in vacuo between 26-148 °/59 mm Hg. Attempted fractionation of the distillate at atmospheric pressure was accompanied by much cracking, and the dried product was therefore distilled at a pressure of 24-27 mm. and collected in two parts

(a) below 100° colourless 25 gm n_D^{20} 1.4330
(b) between 100-140° pale yellow 30 gm n_D^{20} 1.4451

Fractionation of (a) at atmospheric pressure through an 8 inch Dufton column gave

No.	B.P.	ml.	n_D^{20}
1	132	5	-
2	132-165	4	1.4276
3	165-167	5	1.4318
4	167-168	5	1.4323
5	168-168	5	1.4321
6	168-185	4	1.4311

Fractionation of (b), same column, was accompanied by much cracking and gave:

No	B.P.	ml	n_D^{20}	
7	110-121	6		containing water; smell
8	116-119	2		MeCO*iso*Bu smelling of
9	119-165	2		Me.CO.*iso*Bu.
10	169-179	2		
11	179-199	2		
12	199-217	2		
13	217-218	4	1.4502	pale yellow
14	218-219	8	1.4512	pale yellow
15	219-220	4	1.4518	pale yellow
16	220-221	4	1.4520	pale yellow

(59) Reagents used		Reflux
*Iso*propyl bromide	492 gm (4 mol)	1.0 hour
Magnesium	98 gm (4 mol)	
Ether	2000 ml	
Methyl *iso*butyl ketone	100 gm (1 mol)	

Reaction was brisk throughout the addition. The first vacuum distillate came over mainly at 73-140°/24 mm Hg. The first atmospheric pressure distillation was accompanied by much cracking and was therefore stopped, and the liquids dried with sodium sulphate. The second vacuum distillation was at 54 mm Hg. and the distillates were collected at the following temperatures:

(a)	110	n_D^{21}	1.4318	colourless
(b)	110-120	n_D^{21}	1.4428	faintly yellow
(c)	118-140	n_D^{21}	1.4496	pale yellow

(60) Reagents used		Reflux
*Iso*propyl bromide	450 gm (3.66 mol)	2.0 hours
Magnesium	85 gm (3.5 mol)	
Ether	2000 ml	
Methyl *iso*butyl ketone	100 gm (1.0 mol)	

The reaction product was separated under reduced pressure into

(a) below 120°/35 mm Hg colourless
(b) between 100-150°/20 mm Hg pale yellow

Both fractions contained a small amount of water. Fraction (b) was dried with potassium carbonate and fractionated through an 8" Dufton column, giving after cracking:

No.	B.P.	n_D^{20}		
1	87-170	-		containing water
2	170-212			turbid, pale yellow
3	212-212	1.4469	(dried)	turbid, pale yellow
4	212-214	1.4475	(dried)	turbid, pale yellow
5	214-215	1.4483	(dried)	turbid, pale yellow
6	215-216	1.4492	(dried)	turbid, pale yellow
7	216-217	1.4501	(dried)	turbid, pale yellow
8	217-218	1.4509		pale yellow

(61) Reagents used		Reflux
*Iso*propyl bromide	193 gm (1.54 mol)	1.0 hour
Magnesium	28 gm (1.16 mol)	
Ether	800 ml	
Methyl *iso*butyl ketone	100 gm (1.0 mol)	

The reaction product weighed 119 gm and was separated at 26 mm Hg into

(a) below 103° 50 gm colourless
(b) between 103-146° 50 gm pale yellow

Fractionation of (a) at 757 mm Hg gave

No.	B.P.	gm.	n_D^{18}
1	88-124	2.0	
2	124-129	2.5	
3	129-131	3.0	
4	131-158	2.5	
5	158-163	5.0	
6	161-163	22.5	1.4312
7	163-219	4.5	

Fractionation of (b) at 757 mm Hg gave

No.	B.P.	gm	n_D^{18}	
8	109	-		containing water
9	109-110	13.0		containing water
10	110-212	3.0		containing water
11	212-216	2.0		
12	216-217	1.5		
13	217-219	3.5		
14	219-220	12.0	1.4525	

The semicarbazone prepared from fraction (9) had a M.P. 132.5°.

Found:	C 53.03	H 9.32	N 26.0
Req:	C 53.51	H 9.55	N 26.7

(62) <u>Reagents used</u> <u>Reflux</u>

<u>Iso</u>propyl bromide	316 gm (2.57 mol)	1 hour
Magnesium	56 gm (2.3 mol)	
Ether	1700 ml	
Methyl <u>iso</u>butyl ketone	100 gm (1.0 mol)	

The reaction product was separated under reduced pressure by Kontriangle distillation into (a) below 103 /25 mm Hg (b) 103-140 /25 mm Hg. Portion (b) was wet, and was dried by fitration through potassium carbonate.

<u>Fractionation of (a)</u> at 757 mm Hg

No.	B.P.	gm	n_D^{18}
1	79-120	2.0	
2	120-127	2.5	
3	127-127	3.0	
4	127-155	3.5	
5	155-158	2.0	
6	158-161	1.5	1.4208
7	161-164	25.0	1.4322
8	164-165	3.0	1.4322
9	164-166	1.0	
10	166-217	6.0	

<u>Fractionation of (b)</u> at 757 mm Hg

No.	B.P.	gm	n_D^{18}
11	87-89	5.0	
12	89-110	1.5	
13	88-110	2.5	
14	110-210	5.0	
15	210-217	7.0	
16	217-219	2.0	
17	218-219	3.0	1.4503
18	218-221	12.0	1.4517
19	219-220	4.0	1.4512

(63) Reagents used — Reflux

Reagents used		Reflux
Isopropyl bromide	316 gm (2.57 mol)	1.0 hour
Magnesium	56 gm (2.3 mol)	
Ether	1700 ml	
Methyl *iso*butyl ketone	100 gm (1.0 mol)	

The ketone was added as a 20% solution in anhydrous ether.

The reaction product weighed 120 gm and was separated under reduced pressure into

(a) below 105° 51 gm containing 1 ml water
(b) between 105-140° 53 gm containing 2 ml water

Both (a) and (b) were dried with potassium carbonate.

Fractionation of (a) at atmospheric pressure gave

No.	B.P.	gm	$n_D^{18.5}$	No.	B.P.	gm	$n_D^{18.5}$
1	74-126	5.0		6	160-161	1.0	1.4316
2	126-136	1.5		7	161-165	23.5	1.4322
3	136-146	2.0		8	161-162	2.0	1.4321
4	146-156	2.0		9	160-216	4.0	-
5	156-160	1.0	1.4309	10	216-218	3.0	1.4512

Fractionation of (b) at atmospheric pressure gave

11	86	4.0	(wet)	15	217-218	7.0	1.4486
12	86-210	3.0	(wet)	16	218-219	9.0	1.4493
13	210-215	3.5		17	218-219	7.0	1.4507
14	215-217	3.5	1.4482				

The semicarbazone prepared from (11) had a M.P. 132.5°

Found:	C	53.15	H	9.43	N	26.1
Req:		53.51	H	9.55	N	26.7

(64) Reagents used — Reflux

Reagents used		Reflux
*Iso*propyl bromide	173 gm (1.4 mol)	1.0 hour
Magnesium	28 gm (1.16 mol)	
Ether	1000 ml	
Methyl *iso*butyl ketone	50 gm (0.5 mol)	

The Grignard solution was decanted into a dropping funnel fitted with a soda lime tube and the solution was run slowly into a solution of the ketone in 500 ml ether. Reaction appeared to cease after half the Grignard had been added. The reaction product weighed 68 gm and was separated under reduced pressure into

(a)	below 105°	23 gm
(b)	above 105°	23 gm

Both (a) and (b) contained a small amount of water and were dried with potassium carbonate. Distillation of (a) gave

1	159°	5.0 gm
2	159-167°	12.5 gm

(65) Reagents used — Reflux

Reagents used		Reflux
*Iso*propyl bromide	310 gm (2.5 mol)	6 hours
Magnesium	56 gm (2.3 mol)	
Ether	1000 ml	
Methyl *iso*butyl ketone	100 gm (1.0 mol)	

The reaction product was separated under reduced pressure into

(a)	below 105°	45 gm
(b)	above 105°	38 gm

Fractionation of (a) at 762 mm Hg gave with some cracking

No.	B.P.	gm	
1	82-150	8.0	containing a little water
2	150-158	4.0	
3	158-161	2.0	
4	161-165	22.0	
5	161-166	1.0	
6	166-210	4.5	pale yellow
7	Residue	2.0	

Fractionation of (b) at 762 mm Hg gave

8	110-111	10.5	turbid
9	111-111	7.5	clear
10	111-218	4.0	pale yellow
11	218-221	3.5	pale yellow
12	220-222	8.5	pale yellow
13	Residue	2.0	

Semicarbazones prepared from (8) and (9) had each a M.P. 131-132°

Found:	C	53.51	H	9.58	N	26.6
Found:	C	53.51	H	9.63	N	26.5
Req:	C	53.51	H	9.55	N	26.7

(66)

Reagents used		Reflux
Isopropyl bromide	175 gm (1.34 mol)	8 hours
Magnesium	31 gm (1.23 mol)	
Ether	1000 ml	
Methyl isobutyl ketone	100 gm (1.0 mol)	

The reaction product was separated under reduced pressure into

(a) below 105° (b) above 105°

Fractionation of (a) at 760 mm Hg gave

No.	B.P.	gm	n_D^{20}
1	90-120	6.0	
2	120-161	5.0	
3	161-165	7.5	1.4319
4	161-166	18.0	1.4325
5	166-210	3.0	
6	210-215	3.5	
7	217-218	4.5	

Fractionation of (b) at 759 mm Hg gave

8	110	1.0	
9	110-214	4.5	
10	213-214	3.0	
11	211-215	3.0	
12	215-217	4.0	1.4483
13	217-219	11.0	1.4494
14	217-219	3.0	1.4508

(67)

Reagents used		Reflux
Isopropyl bromide	800 gm (6.5 mol)	2 hours
Magnesium	146 gm (6.0 mol)	
Ether	2000 ml	
Methyl isobutyl ketone	300 gm (3.0 mol)	

The reaction product was fractionated at reduced pressure through a 2 ft. column packed with Fenske helices, fitted with an electrically heated jacket and a total-reflux-variable-take-off still head.

Fractionation at 4 mm Hg.

No.	B.P.	gm	$n_D^{20.5}$	
1	40-55	24	1.4222	colourless
2	55-60	45	1.4304	colourless
3	60-65	27	1.4349	colourless
4	65-70	38	1.4368	colourless
5	70-75	10	1.4392	colourless
6	75-80	5	1.4437	colourless
7	80-85	12	1.4468	pale yellow
8	85-90	92	1.4503	pale yellow, very wet
9	85-90	10	1.4499	pale yellow, turbid
10	90-95	8	1.4504	pale yellow, turbid
11	95-130	15	1.4522	pale yellow, clear

The refractive indices were measured on the dried liquids.

(68) Reagents used Reflux

Isopropyl bromide	984 gm (8.5 mol)	2 hours
Magnesium	194 gm (8.0 mol)	
Ether	2250 ml	
Methyl isobutyl ketone	400 gm (4.0 mol)	

Fractionation at reduced pressure using same column as in Expt. (67).

No.	B.P.	mm	gm	n_D^{20}
1	40-43	3.0	24	1.4241
2	43-48	3.0	41	1.4309
3	38-53	3.0	40	1.4350
4	53-60	3.0	60	1.4382
5	60-65	3.0	25	1.4418
6	65-70	2.5	14	1.4453
7	70-75	2.0	40	1.4500
8	75-77	2.0	67	1.4518
9	77-82	2.0	18	1.4520
10	82-102	2.0	11	1.4520
11	102-132	2.0	22	1.4547

(69) Reagents used Reflux

Isopropyl bromide	984 gm (8.5 mol)	2 hours
Magnesium	194 gm (8.0 mol)	
Ether	2250 ml	
Methyl isobutyl ketone	400 gm (4.0 mol)	

The 450 gm product of this reaction was fractionated in two halves.

(A) 200 gm at 0.5 mm Hg

No.	B.P.	gm	n_D^{20}	
1	30-35	3.0	1.4080	colourless
2	35-40	3.0	1.4174	colourless
3	40-45	20.0	1.4273	colourless
4	45-50	24.0	1.4342	colourless
5	50-55	22.0	1.4368	colourless
6	55-60	15.0	1.4403	colourless
7	60-65	4.0	1.4412	colourless
8	65-70	0	-	-
9	70-75	8.0	-	colourless, turbid
10	75-80	39.0	1.4509	pale yellow, clear
11	80-85	11.0	1.4502	pale yellow, turbid
12	85-100	5.0	1.4480	pale yellow, turbid

(B) 250 gm at 30 mm Hg

1	30-60	3.0	1.4047	
2	60-70	8.0	1.4256	
3	70-75	8.0	1.4220	
4	75-79	4.0	1.4267	
5	79-84	8.0	1.4314	
6	84-89	28.0	1.4346	
7	89-90	16.0	1.4358	
8	90-95	6.0	1.4369	
9	95-100	8.0	1.4385	
10	100-105	7.0	1.4437	
11	105-110	5.0	-	
12	110-115	6.0	1.4470	
13	115-120	17.0	1.4498	
14	120-123	30.0	1.4514	
15	123-125	12.0	1.4512	
16	125-130	11.0	1.4508	
17	130-140	8.0	1.4500	turbid
18	140-150	4.0	1.4936	

The refractive indices of the fractions containing water were measured on dried specimens.

IsobutylMgBr on Methylisopropyl ketone

(70) **Reagents used** **Reflux**

Isobutyl bromide	304 gm	(2.22 mol)	2 hours
Magnesium	49 gm	(2.0 mol)	
Ether	1500 ml		
Methyl isopropyl ketone	86 gm	(1.0 mol)	

The reaction product was fractionated at 755 mm Hg

No.	B.P.	gm
1	39-60	-
2	60-90	7.5
3	90-100	4.5
4	100-110	31.5
5	110-115	22.0
6	115-159	3.5
7	159-167	25.0

MethylMgBr on isopropylisobutyl ketone

(71) A solution of methylmagnesium bromide was made from sufficient methyl bromide to dissolve 12.2 gm (0.5 mol) magnesium in 700 ml anhydrous ether. The solution was decanted through glass wool into a fresh flask, and to it were added slowly 43 gm (0.33 mol) *iso*propyl *iso*butyl ketone, followed by 1.5 hours reflux. The reaction product was distilled under reduced pressure and fractionated at atmospheric pressure, giving

(a) 105-162° 8.0 gm
(b) 162-167° 34.0 gm

Fractionation of (b) through a 6 inch column packed with Fenske helices gave

No.	B.P.	ml.	$n_D^{20.5}$	
1	157	3	1.4240	(Dried)
2	157-160	3	1.4294	"
3	162-163	4	1.4303	"
4	163-164	5	1.4308	"
5	164-165	10	1.4314	"
6	165-166	5	1.4318	"
7	166-166	1	1.4321	"
8	Residue	-	1.4323	

(72) Fractionation of 2:3:5-trimethylhexanol-4

The following fractions were bulked:

Expt.	Fractions
58	3,4,5
61	5,6
63	6,7,8
65	4
66	3,4
67	1,2,3,4,5
68	2,3,4,5
69A	3,4,5,6
69B	4,5,6,7,89

The carbinol was fractionated through a 2 ft. column packed with Fenske helices and fitted with a total-reflux-variable-take-off still head. After three preliminary fractionations to obtain a fairly pure starting material, the carbinol was collected as follows.

No.	B.P.	mm	n_D^{20}	gm
1	45.3	3	1.4321	50
2	45.3	3	1.4322	50
3	45.3	3	1.4322	50
4	45.3	3	1.4321	50
5	45.3	3	1.4320	10
6	45.3	3	1.4320	10
7	45.3	3	1.4320	10

(73) Dehydration of 2:3:5-trimethylhexanol-4

Most of the carbinol was dehydrated by distilling over naphthalene-2-sulphonic acid or by refluxing over anhydrous copper sulphate. The dried olefin from these dehydrations boiled between 126-136°.

An attempt was made to dehydrate 50 ml of the carbinol by refluxing with 75 ml acetic anhydride and 10 gm sodium acetate. After refluxing for 2 hours the product was distilled to dryness, the sodium acetate residue dissolved in a small amount of water, and again distilled to dryness. The combined distillates were separated from water, washed with sodium hydroxide and water, and dried with potassium carbonate. The product smelled strongly of unchanged carbinol, and was therefore refluxed for a further two hours with 50 ml acetic anhydride and 10 gm sodium acetate. After working up as before the product still smelled of tertiary carbinol, and had n_D^{20} 1.4258.

Dehydration of the same quantity of carbinol by naphthalene-2-sulphonic acid and copper sulphate gave respectively n_D^{20} 1.4237 and n_D^{20} 1.4246.

(74) Fractionation of 2:3:5-trimethylhexane

The 2:3:5-trimethylhexene from (73) was distilled and reduced in glacial acetic acid solution with PtO_2 and H_2 at three atmospheres pressure. After several distillations over sodium the product boiling over 1° range was fractionated through a 12 inch column packed with single and multi-turn Fenske helices, and fitted with a small total-reflux-variable-take- off still head.

No.	B.P.	ml	n_D^{20}
1	129.9-130.0	0.5	-
2	130.0-130.3	0.5	1.4061
3	130.3-130.4	1.0	1.4060
4	130.4-130.5	1.0	1.4060
5	130.5-130.5	5.0	1.4060
6	130.5-130.6	5.0	1.4060
7	130.6-130.6	5.0	1.4060
8	130.6-130.6	5.0	1.4060
9	130.6-130.6	5.0	1.4060
10	130.6-130.7	5.0	1.4060
11	130.7-130.6	5.0	1.4060
12	130.6-130.5	5.0	1.4060
13	130.5-130.7	5.0	1.4060
14	130.7-130.7	5.0	1.4060
15	130.7-130.7	5.0	1.4060
16	130.7-130.7	8.0	1.4060
17	130.7-130.7	5.0	1.4061
18	130.7-130.7	8.0	1.4060
19	130.7-130.7	5.0	1.4061
20	130.7-130.7	4.0	1.4061
21	130.7-130.7	3.0	1.4061
22	130.7-130.7	1.5	1.4061

Fractions (4) and (22) were sent to be examined in the Infra-red region of the spectrum.

Cadmium dialkyl syntheses: Experimental

(75) Methyl*iso*butyl ketone (1)

A solution of *iso*butylMgBr was made from 157 gm (1.14 mol) *iso*butyl bromide and 24.3 gm (1 mol) magnesium in 1000 ml anhydrous ether. This was decanted into a second dry flask fitted with a stirrer, reflux condensers, dropping funnel, and nitrogen inlet. A very slow stream of nitrogen was passed through the apparatus during reaction. The flask was surrounded by crushed ice, and to the solution were added 91.2 gm (0.5 mol) anhydrous cadmium chloride in small portions, and with continuous stirring. The addition of the dadmium chloride was accompanied for the most part by a brisk reaction. The contents of the flask were then heated under reflux for half an hour, allowed to cool, and then 78.5 gm (1 mol) acetyl chloride were slowly added with continuous stirring. After the addition of the chloride the flask contents were refluxed for 1 hour. The thick sludge formed during reaction was allowed to cool and was decomposed by pouring onto ice slurry and dilute HCl. A large amount of water was needed to dissolve the solid matter. The ether solution and extracts were washed with 30% sodium hydroxide and water, and were then dried over potassium carbonate. The aqueous liquors were distilled to a quarter bulk to see if any ketone remained in solution. None was obtained.

The ether solution was distilled through an 8 inch Dufton column, giving

(a) 50-100° 25 gm (b) 100-112° 6 gm (c) 112-116° 20 gm. Portion (a) was fractionated through a six inch column packed with Fenske helices:

No.	B.P.	ml	$n_D^{19.5}$
1	65-70	1.5	1.[illegible]
2	70-77	4.0	1.3800
3	77-78	4.0	1.3819
4	80-82	4.0	1.3839
5	82-84	4.0	1.3862
6	84-86	1.0	
7	86-88	1.0	
8	88-92	1.0	
9	92-100	1.0	
10	100-110	1.5	

Fraction 4 was refluxed with 30% sodium hydroxide and the aqueous layer was distilled to dryness. The residue was heated with dilute sulphuric acid, and gave a strong smell of acetic acid. The distillate was shaken with some benzoyl chloride and sodium hydroxide. A few globules separated out smelling of ethyl benzoate.

(76) Methyl isobutyl ketone (2)

The same procedure was used as in (75), except that the acetyl chloride was added as a 50% solution in dry ether, and that reflux was continued for 1.5 hours after the addition of the acetyl chloride. It was found better, too, to add water to the reaction flask for decomposition, using only a little dilute HCl. Distillation through an 8 inch Dufton column gave

(a) 70-85° 24gm (b) 85-112° 8 gm (c) 112-116° 20 gm

(77) Ethylisobutyl ketone

The same procedure was adopted as in (75). The propionyl chloride used was prepared from propionic acid and thionyl chloride (p.265). The reagents used were

*iso*butyl bromide	206.0 gm	(1.5 mol)
Magnesium	36.4 gm	(1.5 mol)
Ether	1000 ml	
Cadmium chloride	136.8 gm	(0.75mol)
Propionyl chloride	92.5 gm	(1.0 mol)

Fractionation of the reaction product was accompanied in the early part by fuming and an onion-like odour.

No.	B.P.	gm	
1	99-103	-	Pale yellow, fuming
2	103-130	18.0	yellow, fuming
3	130-133	6.5	colourless, no fumes, sweet smell
4	133-136	49.0	colourless, no fumes, sweet smell
5	136-137	10.0	colourless, no fumes, sweet smell
6	137-140	2.0	colourless, no fumes, sweet smell
7	140-186	6.0	heavy yellow liquid, repulsive odour

Fractions (3), (4), and (5) were bulked and re-fractionated, giving 60 gm ethyl *iso*butyl ketone B.P. 134-137°, this being a yeild of 26%.

(78) isopropylisobutyl ketone (1)

The same procedure was used as in (75). The reagents used were

Isobutyl bromide	206.0 gm	(1.5 mol)
Magnesium	36.5 gm	(1.5 mol)
Ether	1500 ml	
Cadmium chloride	136.8 gm	(0.75mol)
Isobutyryl chloride	106.5 gm	(1.0 mol)

The decomposition by adding water to the reaction flask was very vigorous. Fractionation was accompanied by fuming and an onion-like odour.

No.	B.P.	gm	
1	95-108	10	yellow, sweet smell
2	108-140	9	yellow, fuming
3	140-144	5	pale yellow
4	144-148	35	colourless
5	148-150	4	pale yellow
6	150-265	8	orange, repulsive odour

(79) isopropylisobutyl ketone (2)

The reagents used were

isobutyl bromide	113.0 gm	(0. 75 mol)
Magnesium	18.2 gm	(0.75 mol)
Ether	1500 ml	
Cadmium chloride	68.4 gm	(0.375 mol)
isobutyryl chloride	40.8 gm	(0.375 mol)

There were a few alterations in procedure in this experiment. (1) no ice bath was used, (2) the isobutyryl chloride was added in one quick stream, since vibration of the stirrer caused the tap of the dropping funnel to work loose, and (3) reflux was continued for 4.0 hours after adding the isobutyryl chloride. Fractionation was similar to (78), and gave 20 gm isopropyl isobutyl ketone B.P. 143-147°.

Methyl isobutyl ketone (Acetoacetic ester method)

(80) Following the directions given in Org. Synth. (Col. Vol. II, 248) two experiments were tried in which the following amounts of reagents were used:

	(a)	(b)	
EtOH	250 ml.	250 ml.	
Na	12 g.	12 g.	(0.5 mol)
Ester	65 g.	65 g.	(0.5 mol)
*iso*PrBr	70 g.	70 g.	(0.55 mol)
KI	-	2 g.	(0.1 mol)

The EtOH was dried by refluxing several hours with Na and ethyl phthalate, and distilled into the reaction flask. The mixed reagents were refluxed 13.5 hours and then 10 g. *iso*propyl bromide were added to each, and refluxed a further 6 hours. Yields of substituted ester were:

(a) between 195-201° 34 g; refractionated 196-201° 32 g.
(b) between 195-200° 40 g; refractionated 197-201° 36 g.

being 37% and 40% theory respectively.

(81) The following reagents were refluxed together for 36 hours.

EtOH	750 ml.	
Na	48 g.	(2 mols.)
Ester	260 g.	(2 mols.)
*iso*PrBr	270 g.	(2 mols 10%).

The yield of substituted ester B.P. 196-201° was 98 gms., this being 28.5% theory.

Alkylation of Acetone

(82) 40g (1 mol) sodamide were added in 5g portions to 450g (9 mol) A.R.acetone previously dried for one week over K_2CO_3. The addition was accompanied by a vigorous reaction and a greyish black sediment was formed. The soln. was refluxed for 1.5 hours and then 123g (1 mol) isopropyl bromide were added in small portions from a dropping funnel, refluxing being continuous. There was no sign of reaction on adding the bromide. After a few hours reflux the soln. was filtered at the pump. Fractionation of the amber soln. gave:

mesityl oxide	B.P.	126-130°
pale yellow liquid	B.P.	215-220°

but no methyl isobutyl ketone 115-118° and no diisopropyl ketone 164-165°.

(83) Repeat of (82) but cooled acetone in ice slurry first. Discarded since reaction with sodamide would not start at lower temp.

(84) 290g (5 mol) acetone were mixed with 290g dry benzene and to the mixture were added quickly 39g (1 mol) sodamide. A brisk reaction followed and the contents of the flask became very thick. 150 g more benzene were added and the whole refluxed for 1.5 hours, after which 123g (1 mol) isopropyl bromide were added slowly, reflux being continuous. After refluxing 45 min. the experiment was stopped and left overnight, refluxing being contimued for 45 min. next day. The contents

of the flask were semi-solid after standing overnight. Water was added to the flask and the upper layer separated, dried over K_2CO_3 and fractionated, giving:

a small amount of mesityl oxide
a larger amount of yellow liquid B.P. $213-220^\circ$.

No substitution products were obtained.

(85) Fractionation of the yellow distillate from (84):

	B.P.	mls.		B.P.	mls.
(a)	207-211	5	(e)	217-220	4
(b)	211-213	13	(f)	220-233	6
(c)	213-215	11	(g)	240-243	1.5
(d)	215-217	5	(h)	243-244	3.5

(86) The semicarbazone of fraction (b) was prepared, crystallization occurring only after the reactants had been kept in glacial acetic acid solution overnight. Three crystallizations from water gave shining plates M.P. 188°. The M.P. of the semicarbazone of isophorone is 188°.

Fd.	C 61.4	H 8.6	N 22.6
Calc.	C 61.5	H 8.7	N 21.5

Analysis of fraction (b)

Fd.	C 78.2	H 10.1
Calc.	C 77.7	H 10.1

(87) The semicarbazone of fraction (h) was prepared from a solution of 0.9g semicarbHCl, 0.6g NaOH, 0.5g fract. (h) in 1.4g glacial acetic acid. Crystals appeared after three days. After standing 10 weeks, the whole had become dry, there being yellow crystals around the sides of the flask. These were dissolved in EtOH and pptd. by adding water and scratching.

Repeating this several times gave a flocculent solid M.P. 142-150° (decomp.). Two recryst. from aqueous alcohol gave white shining scales M.P. 157-158° (decomp.). There was insufficient for analysis.

Reduction of Mesityl Oxide

(88) The mesityl oxide used in these reductions boiled between 127-129°. Unless otherwise mentioned the initial H_2 pressure was 42 lb. sq. in. After reduction the bottle contents were filtered by suction into a separating funnel, the bottle washed with acetic acid and the washings filtered. The acid soln. was neutralized with 30% NaOH soln., and the ketone layer was then washed with water three times, and dried with $CaCl_2$, and fradtionated through a 45 cm. Vigreux column.

(i)

Reagents		Rate of Fall of H_2 press.	
Mesityl Ox.	25.0 g.	2.0 lb. in	5 min.
Glac.Ac.Ac.	25.0 ml.	4.0	15
PtO_2 catalyst	0.05g.	5.0	25
		5.75	60

Reduction was stopped after 60 min. The theoretical fall in press. for 25g. mesityl oxide was 8.5 lb.

(ii) Mesityl Ox. 50 g. Glac.Ac.Ac. 25 ml. PtO_2 0.10 g.

lb.	min	lb.	min.	lb	min.	lb.	min.
1		5	7.0	9	12.75	13	22.5
2	3.25	6	8.25	10	14.75	14	26.25
3	4.5	7	9.5	11	16.75	15	35.0
4	5.75	8	11.0	12	19.75	16	60.0

Reduction was stopped after 70 min.

(iii) Mesityl Ox. 50 g. Glac.Ac.Ac. 25 ml. PtO_2 0.15 g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	1.5	5	4.25	9	7.5	13	12.25
2	2.5	6	5.0	10	8.25	14	13.75
3	3.25	7	6.0	11	9.5	15	15.75
4	3.75	8	6.75	12	11.5	16	19.25
						17	38.0

There was no further pressure after 50 min.

(iv) Mesityl Ox. 100 g. Glac. Ac.Ac. 50 ml. PtO_2 0.3 g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	0.8	10	5.85	19	9.6	28	13.2
2	1.75	11	6.35	20	9.9	29	13.75
3	2.4	12	6.9	21	10.3	30	14.3
4	3.0	13	7.35	22	10.6	31	14.95
5	3.5	14	7.7	23	11.0	32	15.8
6	4.0	15	8.15	24	11.4	33	16.9
7	4.5	16	8.45	25	11.8	34	16.2
8	5.0	17	8.85	26	12.2	35	23.5
9	5.45	18	9.25	27	12.65		

There was no further fall in pressure after 38 min. The pressure was raised to 15 lb. and no further fall was observed within a further 30 min.

(v) Mesityl Ox. 100 g. Glac. Ac.Ac. 50 ml. PtO_2 0.25 g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	0.9	10	5.85	19	10.15	28	16.65
2	1.65	11	6.3	20	10.65	29	17.7
3	2.35	12	6.9	21	11.15	30	18.8
4	3.0	13	7.35	22	11.8	31	20.05
5	3.5	14	7.75	23	12.5	32	-
6	4.0	15	8.2	24	13.15	33	23.65
7	4.45	16	8.6	25	13.8	34	25.5
8	4.95	17	9.1	26	14.6	35	28.3
9	5.45	18	9.6	27	15.5	36	31.7
						37	38.5

The pressure was then raised to 15 lb. and no fall occurred within a further 45 min.

(vi) Mesityl Ox. 100 g. Glac. Ac.Ac. 50 ml. PtO_2 0.25 g.

lb.	min.	lb.	min.	lb.	min.
10	4.0	26	12.75	34	22.25
17	6.05	31	17.9	37	28.2
22	9.9	33	20.2	38	31.0

The pressure was then raised to 15 lb. and fell 2 lb within the next 120 min.

(vii) Mesityl Ox. 100g. Glac. Ac.Ac. 50 ml. PtO_2 cat.0.25g

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	0.8	10	6.15	19	11.9	28	20.2
2	1.65	11	6.65	20	12.6	29	21.4
3	2.35	12	7.25	21	13.25	30	22.95
4	3.05	13	7.9	22	14.3	31	24.2
5	3.65	14	8.45	23	15.05	32	25.9
6	4.25	15	9.05	24	15.75	33	27.75
7	4.65	16	9.65	25	16.85	34	29.75
8	5.15	17	10.4	26	17.85	35	31.95
9	5.7	18	11.05	27	18.95	36	-
						37	38.55

(viii) Mesityl Ox. 100g. Glac. Ac.Ac. 50 ml. PtO_2 0.25g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	1.5	10	7.4	19	13.15	28	20.5
2	2.2	11	7.95	20	13.7	29	21.55
3	3.0	12	8.6	21	14.4	30	22.7
4	3.8	13	9.2	22	15.1	31	24.1
5	4.5	14	9.75	23	15.9	32	25.85
6	5.05	15	10.4	24	16.65	33	27.8
7	5.65	16	11.05	25	17.5	34	30.0
8	6.25	17	11.75	26	18.4	35	-
9	6.85	18	12.4	27	19.4	36	27.0
						37	60.0

The pressure was raised to 15 lb. and no fall was observed within a further 45 min.

(ix) Mesityl Ox. 100g. Glac. Ac.Ac. 50 ml. PtO$_2$ 0.25g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	-	10	3.75	19	8.05	28	14.45
2	1.25	11	4.15	20	8.6	29	15.4
3	1.65	12	4.6	21	9.2	30	16.5
4	1.95	13	5.05	22	9.85	31	17.6
5	2.25	14	5.05	23	10.45	32	19.0
6	2.55	15	5.95	24	11.05	33	20.4
7	2.8	16	6.45	25	11.9	34	22.1
8	3.1	17	6.9	26	12.6	35	24.1
9	3.4	18	7.5	27	13.5	36	26.1
						38	31.5

The pressure was then raised to 15 lb. and fell 1.5 lb. within a further 120 min.

(x) Mesityl Ox. 100g. Glac.Ac.Ac. 50 ml. PtO$_2$ 0.25g.

lb.	min.	lb.	min.	lb.	min.	lb.	min.
1	1.0	10	7.45	19	14.4	28	-
2	1.9	11	8.0	20	15.2	29	25.2
3	2.85	12	8.8	21	-	30	-
4	3.6	13	9.55	22	-	31	-
5	4.2	14	10.25	23	18.0	32	30.8
6	4.85	15	11.0	24	-	33	33.0
7	5.5	16	11.8	25	19.9	34	35.8
8	6.2	17	12.6	26	-	35	39.8
9	6.8	18	13.5	27	22.3	36	44.0
						37	54.0
						38	74.0

The pressure was then raised to 15 lb. and fell 0.25 lb. within the next 75 min.

(xi) Mesityl Ox. 100g. Glac.Ac.Ac. 50 ml. PtO_2 0.25g.

lb.	min.	lb	min.	lb.	min.	lb.	min.
1	0.75	10	3.9	19	-	28	-
2	1.2	11	4.35	20	-	29	20.4
3	1.6	12	4.9	21	11.0	30	-
4	-	13	5.5	22	-	31	23.8
5	2.2	14	6.05	23	12.8	32	-
6	2.5	15	6.6	24	-	33	28.5
7	2.8	16	-	25	15.0	34	31.4
8	3.15	17	7.9	26	-	35	35.0
9	3.5	18	8.65	27	17.3	36	40.0

The pressure was then raised to 15 lb. and fell 3 lb. within the next 75 min.

(xii) Mesityl Ox. 25g. Ethyl alcohol 50 ml. PtO_2 0.05g. Pressure fell 2 lb. in 10 min. and 3.5 lb. in 90 mins. This experiment was therefore discarded.

Miscellaneous Intermediates

Isobutyramide

This was prepared by the method of Aschan (1898)[77], but with some modifications. The use of $EtOH/CO_2$ as refrigerant facilitates the addition of the acid chloride to the ammonia, and it is better to add the chloride in a stream with rapid and continuous stirring. It was also found better to crystallise the _iso_butyramide instead of distilling it. The solvent used was 100-120° petroleum ether, and although _iso_butyramide is not very soluble in this it is possible to filter hot 1.3% solutions at the pump and allow them to crystallise.

It was found that crystallisation gave two forms, needles and plates. Needles were formed from dilute filtered solutions, while plates were formed from concentrated decanted solutions. A similar behaviour has been noticed with pivalamide by Jamison and Davidson[78], who, by X-ray analysis, found that the pivalamide needles contained traces of ammonium chloride, to which they attributed the control of crystal shape. Since the likelihood of ammonium chloride contamination in the _iso_butyramide is greater in crystals from concentrated decanted solutions than from dilute filtered solutions, it seems possible that the crystal shape is a question of concentration rather than the borrowing of crystal form.

Propionyl chloride

Some difficulty was experienced with the preparation of this reagent. This can be understood from the following boiling points:

Propionyl chloride	77-78°
Thionyl chloride	77-78°
Phosphorus trichloride	76-77°

Michael (1898)[79] prepared propionyl chloride from propionic acid and phosphorus trichloride, and removed excess phosphorus trichloride from the product by refluxing for several hours over sodium propionate. The present author found that it was not possible to remove phosphorus trichloride from the product even after twelve hours reflux.

It was possible to obtain a product free from thionyl chloride by refluxing the propionyl chloride over a small amount of propionic acid. More propionic anhydride is formed in this way, but the propionyl chloride obtained is pure. The reaction between propionic acid and thionyl chloride is very endothermic.

Isobutyryl chloride

This was prepared in 81% yield from isobutyric acid and thionyl chloride.

ADDENDUM

Four New Hydrocarbons

Four of the tertiary carbinols listed on pp. 66 and 67 were dehydrated by distilling over naphthalene-2-sulphonic acid, and the olefins thus obtained were reduced until the corresponding saturated hydrocarbons showed no sign of unsaturation. The hydrocarbons obtained were

(1) 3:4-dimethyloctane from 3:4-dimethyloctanol-4

B.P. 58·0-58·4°/20 mm Hg n_D^{18} 1·4190

Francis* gives 165°/760 mm Hg n_D^{20} 1·4190

(2) 3:4-dimethylnonane from 3:4-dimethylnonanol-4

B.P. 75·0-75·2°/18 mm Hg $n_D^{17\cdot5}$ 1·4233

Francis* gives 187°/760 mm Hg n_D^{20} 1·4241

(3) 2:4:5-trimethylheptane from 2:4:5-trimethylheptanol-4

B.P. 49·5°/18 mm Hg $n_D^{17\cdot5}$ 1·4170

Francis* gives 156·6°/760 mm Hg n_D^{20} 1·4162

(4) 2:6-dimethyl-4-isobutylheptane from 2:6-dimethyl-4-isobutylheptanol-4

B.P. 81·9-82·5°/20 mm Hg $n_D^{16\cdot5}$ 1·4252

The olefins from which the first three of these hydrocarbons were obtained appear to have consisted of isomeric mixtures, as shown by the experimental data on pp.

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* These values are given as calculated values by Francis (Ind.Eng.Chem., 1943, 35, 442-448)

That is, these olefins had a small boiling range and a small range of refractive index:-

(1) 3:4-dimethyloctene

B.P. 60·5-62·0°/25 mm Hg n_D^{20} 1.4310-1.4327

(2) 3:4-dimethylnonene

B.P. 76·0-78°/18 mm Hg $n_D^{18.5}$ 1.4345-1.4361

(3) 2:4:5-trimethylheptene

B.P. 51·0-53·0°/20 mm Hg n_D^{19} 1.4270-1.4342

In the case of 2:6-dimethyl-4-*iso*butylheptene, the range of B.P. and n was not so large

(4) 2:6-dimethyl-4-*iso*butylheptene-4

B.P. 80·5-81·7°/18 mm Hg n_D^{17} 1.4338-4343

EXPERIMENTAL

In each case in the preparation of the following four hydrocarbons, the requisite tertiary carbinol was distilled over naphthalene-2-sulphonic acid, and the distillate, after separation of the water and drying with calcuim chloride, was distilled again over fresh catalyst. The product was dried with calcuim chloride, and fractionated at reduced pressure through a 12 inch column packed with Fenske helices and fitted with a total-reflux-variable-take-off still head. The fractionated olefin was then reduced with hydrogen at 3 atmospheres pressure and Adam's PtO_2 catalyst in the presence of glacial acetic acid. Only in the case of 3:4-dimethyloctane was the olefin soluble in glacial acetic acid. Reduction was repeated until the hydrocarbon showed no sign of unsaturation, when, after washing with sodium hydroxide solution and water and drying with calcuim chloride, it was tested with a solution of bromine in carbontetrachloride. The hydrocarbon was then fractionated in a similar manner to the olefin.

3:4-dimethyloctane

Amount of 3:4-dimethyloctanol-4 used: 13 gm.

Fractionation of 3:4-dimethyloctene.

No.	B.P.	mm.Hg	gm	n_D^{20}
1	60·5–60·8	25	1·5	1.4310
2	60·8–61·0	25	2·0	1·4312
3	61·0–61·3	25	2·0	1·4318
4	61·3–61·3	25	2·0	1·4321
5	61·3–62·0	25	1·5	1·4327

Fractionation of 3:4-dimethyloctane

No.	B.P.	mm.Hg	gm	n_D^{18}
1	58·0–58·5	20	1·5	1·4190
2	58·0–58·0	20	1·5	1·4190
3	58·0–58·4	20	1·5	1·4190
4	58·4–58·4	20	1·5	1·4191
5	58·4–58·4	20	0·5	1·4191

3:4-dimethylnonane

Amount of 3:4-dimethylnonanol-4 used: 15 gm.

Fractionation of 3:4-dimethylnonene.

No.	B.P.	mm.Hg	gm	$n_D^{18\cdot5}$
1	76·0-76·0	18	2·0	1·4345
2	76·5-77·0	18	2·5	1·4350
3	76·5-77·0	18	2·5	1·4352
4	77·0-77·5	18	2·0	1·4357
5	77·5-78·0	18	1·5	1·4361
6	Residue	-	1·0	-

Fractionation of 3:4-dimethylnonane

No.	B.P.	mm.Hg	gm	$n_D^{17\cdot5}$
1	75·2-75·5	19	1·0	1·4233
2	75·0-75·2	18	1·5	1·4233
3	75·0-75·2	18	1·5	1·4233
4	75·0-75·2	18	1·5	1·4235
5	75·0-75·2	18	1·5	1·4237

2:4:5-trimethylheptane

Amount of 2:4:5-trimethylheptanol-4 used: 14 gm.

Fractionation of 2:4:5-trimethylheptene

No.	B.P.	mm.Hg	gm	n_D^{19}
1	51·0-51·3	20	1·0	1·4270
2	51·3-51·5	20	1·5	1·4271
3	51·5-52·0	20	1·5	1·4277
4	52·0-52·3	20	1·5	1·4293
5	52·3-52·6	20	1·5	1·4318
6	52·6-53·0	20	0·5	1·4342

Fractionation of 2:4:5-trimethylheptane

No.	B.P.	mm.Hg	gm	$n_D^{17.5}$
1	49·5	18	1·0	1·4174
2	49·5	18	1·5	1·4171
3	49·5	18	1·5	1·4170
4	49·5	18	1·5	1·4170
5	49·5	18	1·0	1·4170

2:6-dimethyl-4-isobutylheptane

Amount of 2:6-dimethyl-4-isobutylheptanol-4 used: 15 gm.

Fractionation of 2:6-dimethyl-4-isobutylheptene-4

No.	B.P.	mm.Hg	gm	n_D^{17}
1	78·5-81·0	19	1·0	1·4330
2	80·5-81·5	18	1·5	1·4338
3	80·5-81·0	18	1·5	1·4338
4	80·5-81·0	18	1·5	1·4338
5	81·0-81·5	18	1·5	1·4338
6	81·0-81·5	18	1·5	1·4340
7	81·5-81·7	18	1·5	1·4342
8	81·7-81·7	18	1·0	1·4343

Fractionation of 2:6-dimethyl-4-isobutylheptane

No.	B.P.	mm.Hg	gm	$n_D^{16\cdot5}$
1	81·3-81·5	18	1·0	1·4258
2	81·5-81·7	18	1·5	1·4257
3	81·7-81·9	19	1·5	1·4252
4	81·9-82·0	20	1·5	1·4252
5	82·0-82·5	20	1·5	1·4252
6	82·5-81·5	20	1·5	1·4252
7	82·5-83·0	20	1·0	1·4251

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