SECTION II
INTRODUCTION AND DISCUSSION TO
THE PREPARATION OF OPTICALLY ACTIVE UNSYMMETRICAL KETONES FROM (+) ACID HALIDE BY
(A) GRIGNARDREACTION
(B) FRIEDEL-CRAFT'S REACTION
INTRODUCTION AND DISCUSSION TO
PREPARATION OF OPTICALLY ACTIVE UNSYMETRICAL KETONES
FROM (+) ACID HALIDE BY
(A) GRIGNARD REACTION

The synthesis of ketones from acid halides and organometallic compounds may be represented by the following equation, in which the halo atom of acid halide is replaced by the organic group of the organometallic compound.

\[ \text{R.COX} + \text{R}'\text{MX} \rightarrow \text{R.COR} + \text{MX} \]

MECHANISM OF THE REACTION

Courto"t suggested the following course of the reaction:

\[ \text{R.COC1} + \text{R'MX} \rightarrow \text{R.COR} + \text{MXCl} \]

or

\[ \text{R.COC1} + \text{R'MX} \rightarrow \text{R - C - R'} \]

\[ \text{OMX} \]

\[ \text{OMX} \]

\[ \text{R - C - R'} \]

\[ \text{H}_2\text{O} \]

\[ \text{R.COR} + \text{HCl} + \text{MXOH} \]

Both these courses involved formation of the Werner complexes which rearrange to form ketone and metallic halide.
In either case the reaction would be of second order and either the first step (complex formation) or the second step (rearrangement) might be rate determining. Kharash and Reinmuth have discarded the following possible rearrangement (i.e., a second order mechanism) put forth by Courtot by reasoning that the rearrangement of this type should certainly be followed by further rearrangement (either monomolecular or bimolecular) to form a keto-metallic halide complex. After studying the views of different authors they concluded that ion-exchange must be preceded by some sort of addition complex formation, though not necessarily by carbonyl double bond addition.
On the whole, it appears most probable that the normal reaction includes (1) aryl halide Grignard reagent Werner complex formation, and (2) a rate determining ionic rearrangement of the complex and that the reaction product is ketone-metallic halide Werner complex.

The abnormal reaction of acid chloride and Grignard reagent may proceed in one or more of several ways:

(i) Reduction of acid chloride to a primary alcohol,
(ii) Reduction to a secondary alcohol,
(iii) Reduction to an aldehyde
(iv) Ester formation,
(v) Coupling reaction.

Whitemor et al\textsuperscript{69} put down the following steps which are apparently involved in the reaction with Grignard reagent.

\[
\begin{align*}
R\text{COCl} & \xrightarrow{} R\text{CHO} & \xrightarrow{} R\text{CH}_2\text{OH} \\
& \quad \downarrow & \\
R\text{CO},R' & \quad R\text{CH}_2,R' & \quad R\text{CHO}
\end{align*}
\]

Gilman and Nelson\textsuperscript{70} indicated the reaction of acid halide with diethyl ether produced the ester, in presence of anhydrous magnesium halide in a very small quantity. Fuson and Corse\textsuperscript{71} have reported a coupling reaction.
In order to minimise above side reactions, and to increase the yield of ketones in the Grignard reaction, the following steps have been suggested:

(i) Low operating temperature,
(ii) Reverse addition, i.e., addition of Grignard reagent to the acid chloride solution,
(iii) The use of excess of the acid chloride.

However, in favourable cases and under optimum experimental conditions, the yields are 40-60%.

Generally organozinc and organocadmium compounds are used in order to obtain ketone in good yield.

Use of Organozinc Compounds

Bleaise and co-workers have prepared number of ketones and ketonic esters with the use of organozinc compounds in 80-95% yield. This method consists in the reaction of acid chlorides with dialkyl zinc compounds, prepared from alkyl iodides and zinc dust.

\[ 2RI + 2Zn \rightarrow \text{R}_2Zn + \text{ZnI}_2 \]

\[ \text{RCOCl } + \text{R}_2Zn \rightarrow \text{R.CO.R} + \text{R.ZnCl} \]
The superiority of organozinc compounds depends largely on their low order of reactivity towards ketone carbonyl groups with the result that the formation of tertiary alcohol is not an important side reaction. This low order of reactivity is illustrated by comparative experiments showing the time required for the development of a positive Gilman test with Mischler's ketone.

Suter and Weston studied the possibility of preparing aryl alkyl ketones (e.g., 3,5 dimethoxy phenyl alkyl ketones) from the action of zinc or cadmium alkyls on acid chloride.

Jones has prepared long chain ketonic acids in good yield e.g., octadecylzinc chloride was treated with a series of \( \alpha \)-carbethoxy acyl chlorides to produce ketonic acids in 75-90% yield. Brensch and Baykut prepared di-n-alkyl ketones containing 15-22 carbon atoms from alkyl zinc iodides and aliphatic acid halide.

**Use of Organocadmium Compounds**

The very hygroscopic nature and the tediousness of preparing anhydrous zinc chloride and the difficulties encountered in rapid weighing of the lumps of the solid zinc chloride led to much less hygroscopic, more effective cadmium chloride in the Grignard synthesis of ketones. These organocadmium compounds are generally superior and are more
widely used than the other organometallic compounds and so the synthesis with organocadmium compounds have been studied more systematically.

The preparation of ketones by the use of organocadmium compounds was first recommended by Gilman and Nelson (loc. cit.). The following reactions are involved in the preparation:

\[ \text{R.Br} + \text{Mg} \rightarrow \text{R.Mg.Br} \]
\[ 2\text{R.Mg.Br} + \text{CdCl}_2 \rightarrow \text{R.Cd.R} + \text{Mg.Br}_2 + \text{MgCl}_2 \]
\[ \text{R.Cd.R} + 2\text{R.COCl} \rightarrow 2\text{R.CO.R} + \text{CdCl}_2 \]

Cason\textsuperscript{78,79} has made an exhaustive study of the following:

(i) Nature of alkyl or aryl halide,
(ii) Cadmium halide,
(iii) Acid chloride,
(iv) Reaction of cadmium reagent with other groups,
(v) Side reactions and the use of proper solvent.

(i) **Nature of Alkyl or Aryl Halide**

In the reaction of organocadmium compounds with acid halides, it has been found that acid iodides are most reactive and acid fluorides least reactive. This is in the line with the reactivity of C - X bond in displacement reactions indicates that preliminary reaction of the organometallic
compound at the carbonyl group may not be involved. Cason\textsuperscript{80} has supported this view on experimental evidence and postulated on initial coordination of cadmium with the central oxygen atom followed by breaking bonds, the Cd - O bond being formed preferentially at the unhindered carbonyl group. Several investigators including Cason (loc.cit.), DeBenneville\textsuperscript{81}, Gilman and Nelson (loc.cit.) have noted that if the Grignard reagent in which the cadmium derivative is prepared from chloride, the yield of ketone is higher than from iodide, but less than from bromide. Cole and Julican\textsuperscript{82} reported the preparation of methyl ketone using dimethyl cadmium and obtained the same yield with methyl iodide or methyl bromide.

(ii) \textbf{Cadmium Halide}

Gilman and Nelson (loc.cit.) have shown that secondary and tertiary organocadmium compounds are thermally unstable in comparison with primary, but the tertiary compounds are stable than secondary. Cason (loc.cit.) recommended 0.8 mole of acid halide with one mole of alkyl bromide. He has pointed out that an excess of organocadmium compound will produce an improvement in the yield based on the acid halide. He also suggests the use of less hygroscopic and less expensive chloride instead of bromide.
(iii) The Nature of Acid Chloride

Cason (loc.cit.) reported that both aromatic and aliphatic acid chloride react smoothly; the aliphatic being more reactive. Sheck, Angur et al$^{82}$ found that an aliphatic acid chloride of high molecular weight such as stearyl chloride react satisfactorily. Bunnet and Tarbell$^{83}$ prepared $\alpha$-chloro ketones by reacting organocadmium compounds with $\alpha$-chloro acid chloride.

(iv) Reaction of Cadmium Reagent with Other Groups

Gilman and Nelson (loc.cit.) found that if the carbonyl group is activated by an adjacent group such as an ester group, the cadmium reagent may add to the activated carbonyl. Riegel et al$^{84}$ reported that cadmium reagent adds in 1-4 manner to alkylidene malonic esters.

In addition to this Gilman and Nelson (loc.cit.) investigated that -

(a) coupling with ter-butyl did not occur,
(b) reaction with phenyl isocyanate did not occur,
(c) reaction with amide, nitrile etc. did not occur.

(v) Side Reactions and the Use of Proper Solvent

Gilman and Nelson (loc.cit.) indicated that the reaction of acid halide with diethyl ether produced the ester, in presence of anhydrous magnesium halide in a very small
quantity. They have also suggested that if the latter part of the reaction is carried out in benzene (after distilling of ether) ester formation can greatly be reduced.

**Reaction with \( \alpha - \beta \) Unsaturated Carbonyl Halide**

The reaction between \( \alpha - \beta \) -unsaturated halides and Grignard reagent was found to resemble that of the corresponding \( \alpha - \beta \) -unsaturated esters. Kohler and Heritage\(^8\)\(^5\) studied the reaction between cinnamonyl chloride and phenyl magnesium bromide in ethereal solution. Ivanoff and Nicoloff\(^8\)\(^6\) also studied the reaction between cinnamonyl chloride and Grignard reagent derived from sodium phenyl acetate wherein ketone formation and 1:4 addition to the unsaturated ketone are reported.
Freund first observed the formation of ketones from acid chloride and dimethyl and diethyl zinc. Other organometallic compounds were also tried when organozinc, organocadmium and organomagnesium reagents have been found to be generally useful for such synthesis.

Cason (loc. cit.) found that the maximum useful ratio of acid chloride to bromide is about 1:0.8. Use of a larger ratio of acid chloride does not increase the yield. If methyl bromide or ethyl bromide is used, some loss of dialkyl cadmium occurs when the ether is distilled from the mixture; so it is advisable to use only 0.5 molar equivalent of the acid chloride.

Cason (loc. cit.) has also put the stress on the use of proper solvent. In the present work the preparation of the Grignard reagent and its reaction with cadmium chloride was carried out in ether, but the ether was replaced with benzene before the addition of acid chloride so that -

(i) The precipitate which forms in the reaction mixture after the addition of acid chloride, is less likely to become too thick for efficient stirring if benzene is used.
(ii) The side reaction between the organocadmium compound and the acid chloride or ketone formed to yield metallic enolate, does not occur so rapidly in benzene as in ether.

(iii) The use of benzene allows a higher reflux temperature and accordingly, the reaction requires a shorter time in benzene.

(iv) It was noted that smaller quantities of ethyl esters are produced as by-products, if the ether is largely replaced by benzene before the reaction with acid chloride.

Gilman and Nelson (loc. cit.) showed that reaction of cadmium reagent with the enol form of the ketone is always accompanied by potential side reaction. Kenyon and Campbell by using d-methyl phenyl acetyl chloride proved that no significant racemization occurred during this reaction. It may be assumed that the concentration of the enol form of the ketone was very small, and the reaction asymmetry in the ketone may have resulted from the fact that nearly all the enol formed during the reaction, was lost by condensation with another molecule of ketone.

The present work deals with the preparation of optically active ketones by the interaction of (+) 1-methyl butyryl chloride [\(\alpha\)]\(_D\)\(^{35} + 4.5\) (l,l), and organocadmium
compounds, prepared by the interaction of anhydrous cadmium chloride and Grignard reagent RMgX, where R is methyl, ethyl, n- and iso-propyl, n- and iso-butyl, and iso-amyl groups. The (+) 1-methyl butyryl chloride was obtained by treating (+) 1-methyl butyric acid $[\alpha]_D^{35} + 12.3$ with phosphorous trichloride. The acid was obtained by oxidizing (-) 2-methyl butane-1-ol $[\alpha]_D^{35} - 4.7$ with alkaline potassium permanganate.

Care was taken to see that there was no rearrangement or racemization occurred during the reaction (also noted by Campbell and Kenyon, loc.cit.) and very little loss by formation of dialkyl cadmium derivative had occurred. This is in agreement with the observation by Cason (loc.cit.).

Moreover recently Inove and Weborky reported the addition of phenyl magnesium bromide to (-) methyl crotonate resulting in the formation of (+) 3-phenyl butyric acid. Further when this reaction was catalyzed by cuprous chloride, the reaction product so obtained showed a change in the sign of optical rotation. In the present experiments, such a change in the sign of optical rotation has not been observed.

Cason (loc.cit.) reported that aliphatic acid chlorides react much more smoothly than aromatic acid halides. (+) 1-Methyl butyryl chloride being an aliphatic acid halide, reacts very conveniently, giving good yields of the resulting optically active ketones. All these ketones are colourless liquids with characteristic odour.
While carrying out the reaction, instead of the usual molar proportions, the best results were obtained by keeping the ratio of alkyl halide to acyl halide as 0.2 M and 0.16 M. It is also noted that with a slight excess of the organocadmium reagent, there is a considerable increase in the yield, which agrees with observation made by Cason and Prout (loc. cit.).

The specific rotations of optically active ketones of the type (±) R.CO.CH.CH₂.CH₃ have been taken in CH₃ homogeneous state and recorded in Table I. It has been found that with the increase of -CH₂ group in the constitution of the optically active ketones, there is an irregular change in the magnitude of optical rotation.
TABLE I

OPTICALLY ACTIVE UNSYMMETRIC KETONES OF THE TYPE (+) CH₃·CH₂·CH·CO·R

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of the Ketone</th>
<th>B.P.</th>
<th>Yield</th>
<th>Density 35°</th>
<th>Refractive Index n 35</th>
<th>Specific Rotation α 35°</th>
<th>Molecular Rotation M 35°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>°C/15 mm</td>
<td>%</td>
<td>d 4</td>
<td>35</td>
<td>(l,l)</td>
<td>(l,l)</td>
</tr>
<tr>
<td>1.</td>
<td>3-Methyl pentan-2-one</td>
<td>130</td>
<td>71</td>
<td>0.8193</td>
<td>1.423</td>
<td>+ 4.4</td>
<td>+ 4.5</td>
</tr>
<tr>
<td>2.</td>
<td>4-Methyl hexan-3-one</td>
<td>140</td>
<td>69</td>
<td>0.8110</td>
<td>1.421</td>
<td>+ 4.0</td>
<td>+ 4.6</td>
</tr>
<tr>
<td>3.</td>
<td>5-Methyl heptan-4-one</td>
<td>151</td>
<td>67</td>
<td>0.8210</td>
<td>1.428</td>
<td>+ 5.1</td>
<td>+ 6.5</td>
</tr>
<tr>
<td>4.</td>
<td>2,4-Dimethyl hexan-3-one</td>
<td>150</td>
<td>44</td>
<td>0.8097</td>
<td>1.420</td>
<td>+ 1.6</td>
<td>+ 2.1</td>
</tr>
<tr>
<td>5.</td>
<td>6-Methyl octan-5-one</td>
<td>165</td>
<td>73</td>
<td>0.8290</td>
<td>1.431</td>
<td>+ 5.2</td>
<td>+ 7.4</td>
</tr>
<tr>
<td>6.</td>
<td>2,5-Dimethyl heptan-4-one</td>
<td>160</td>
<td>40</td>
<td>0.8206</td>
<td>1.424</td>
<td>+ 3.9</td>
<td>+ 5.6</td>
</tr>
<tr>
<td>7.</td>
<td>7-Methyl nonan-6-one</td>
<td>185</td>
<td>68</td>
<td>0.8426</td>
<td>1.437</td>
<td>+ 2.6</td>
<td>+ 4.1</td>
</tr>
<tr>
<td>8.</td>
<td>3,6-Dimethyl octan-5-one</td>
<td>180</td>
<td>35</td>
<td>0.8226</td>
<td>1.429</td>
<td>+ 3.3</td>
<td>+ 5.3</td>
</tr>
<tr>
<td>9.</td>
<td>10-Methyl dodecan-9-one</td>
<td>205</td>
<td>65</td>
<td>0.8426</td>
<td>1.439</td>
<td>+ 1.8</td>
<td>+ 5.1</td>
</tr>
</tbody>
</table>

\[
[M]^{35}_D = \frac{[\alpha]^{35}_D \times M}{100}
\]
REACTIONS

\[
\text{(+)} \quad \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCL} + R\cdot\text{MgX} \xrightarrow{\text{CdCl}_2} \text{(+)} \quad \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{CH}_2\cdot\text{COR} \\
\text{CH}_3
\]

(1) \( R = \text{Methyl} \)
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCH}_3 \\
\text{CH}_3
\]

(+) 3-methyl pentan-2-one

(2) \( R = \text{Ethyl} \)
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCH}_2\cdot\text{CH}_3 \\
\text{CH}_3
\]

(+) 4-methyl hexan-3-one

(3) \( R = \text{n-propyl} \)
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCH}_2\cdot\text{CH}_2\cdot\text{CH}_3 \\
\text{CH}_3
\]

(+) 5-methyl heptan-4-one

(4) \( R = \text{iso-propyl} \)
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCH}_2\cdot\text{CH}_3 \\
\text{CH}_3 \quad \text{CH}_3
\]

(+) 2:4 dimethyl hexan-3-one

(5) \( R = \text{n-butyl} \)
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}^*\cdot\text{COCH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3 \\
\text{CH}_3
\]

(+) 6-methyl octan-5-one
(6) \( R = \text{iso-butyl} \)
\[
\begin{align*}
\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} & \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_3 \\
\text{CH}_3 & \text{ CH}_3
\end{align*}
\]

\((+)\) 2:5-dimethyl heptan-4-one

(7) \( R = \text{n-amyl} \)
\[
\begin{align*}
\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} & \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\
\text{CH}_3
\end{align*}
\]

\((+)\) 7-methyl nonan-6-one

(8) \( R = \text{iso-amyl} \)
\[
\begin{align*}
\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} & \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\
\text{CH}_3 & \text{ CH}_3
\end{align*}
\]

\((+)\) 3:6 dimethyl octan-5-one

(9) \( R = \text{n-octyl} \)
\[
\begin{align*}
\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} & \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\
\text{CH}_3
\end{align*}
\]

\((+)\) 10-methyl-dodecan-9-one.
APPARATUS FOR GRIGNARD REACTION
EXPERIMENTAL
EXPERIMENTAL

PREPARATION OF (–) 2-METHYL BUTAN-1-OL

The fusel oil b.p. 80–132°, containing 18–20% of the optically active (–) 2-methyl butan-1-ol was fractionally distilled using a column of 16" long and the distillate b.p. 127–128.5° was collected. The active (–) 2-methyl butan-1-ol had, \( d_4^{35} 0.8279, n_3^{34} 1.407, [\alpha]_D^{35} - 4.7 \) (l, l).

PREPARATION OF (+) 1-METHYL BUTYRIC ACID

(–) 2-Methyl butan-1-ol (88 g.) and sodium carbonate (17 g. in 100 cc. water) were placed in a 3-litre beaker equipped with a mechanical stirrer. To this stirred mixture potassium permanganate solution (125 g. in 1500 cc. water) was added during four hours at room temperature. The mixture was further stirred for four hours, kept overnight and filtered. The filtrate was concentrated on water bath and acidified by sulphuric acid (50%). The acidified solution was extracted with chloroform (55 cc. x 2). The chloroform layer was dried (magnesium sulphate), and chloroform was distilled off. The residue on distillation under reduced pressure gave (+) 1-methyl butyric acid, b.p. 135°/15 mm., yield 57%, \( d_4^{35} 0.9179, n_3^{35} 1.442, [\alpha]_D^{35} + 12.3 \) (l, l).

Found by titration with sodium hydroxide \( M 101.4, \) \( C_7H_{14}O_2 \) required \( M 102.0. \)
PREPARATION OF (+) 1-METHYL BUTYRYL CHLORIDE

(+)-1-Methyl butyric acid (51 g.) and phosphorous trichloride (44.6 g.) were placed in a 250 cc. round bottomed flask fitted with a refluxed condenser. The contents were refluxed for two hours at 80-90°. The upper colourless layer was decanted from the syrupy residue. The upper layer on distillation gave (+)-1-methyl butyryl chloride, b.p. 115-120°, yield 89%, d₄⁰ 0.8219, n₃⁰ 1.427, [α]₃⁰D + 4.5 (1,1).

PREPARATION OF OPTICALLY ACTIVE UNSYMETRICAL KETONES FROM (+) 1-METHYL BUTYRYL CHLORIDE

Preparation of 3-Methyl Pentan-2-One

In a 500 cc. three necked round bottomed flask fitted with a mercury sealed Hershberg stirrer, reflux condenser and a dropping funnel were placed magnesium turnings (4.8 g., 0.2 mole) and anhydrous ether (100 cc.). To this, methyl iodide (28.4 g., 0.2 mole) in anhydrous ether (100 cc.) was slowly added from the dropping funnel during one hour. After completion of the addition, the contents were refluxed on water bath for one hour.

The Grignard complex so formed was cooled to 0° and anhydrous cadmium chloride (20.1 g., 0.11 mole) was added during 10-15 minutes at room temperature and refluxed the
contents for 45 minutes on water bath. On distillation of ether a dark viscous residue remained in the flask. Benzene (100 cc.) free from thiophene was added to the residue and the distillation continued until an addition distillate (25 to 30 cc.) has been collected. A second portion of the dry benzene (100 cc.) was added and the mixture was refluxed with stirring for one hour. (+) 1-methyl butyryl chloride (19.28 g., 0.16 mole) in dry benzene (100 cc.) was added to the contents during 30 minutes. Due to the formation of heavy precipitate stirring become difficult, and was stopped. The mixture was refluxed on water bath for an hour, and kept overnight. The contents of the flask were cooled and decomposed by the careful addition of ice and water, followed by sufficient sulphuric acid (20 %). The aqueous portion was separated, extracted with benzene (2 x 50 cc.). The benzene extract was successively washed with water (100 cc.), sodium carbonate solution (100 cc., 5 %), water (100 cc.) and saturated sodium chloride solution (50 cc.), and dried (sodium sulphate). On evaporation of benzene, the residual oil on distillation under reduced pressure gave (+) 3-methyl pentan-2-one, b.p. 130°/15 mm., yield 71%, $d_4^{25}$ 0.8192, $n_3^{25}$ 1.423, $[\alpha]_D^{25} + 4.4$ (1,1).

Found : C, 71.76; H, 11.61%

C$_6$H$_{12}$O required : C, 72.00; H, 12.00 %
Preparation of (+) 4-Methyl Hexan-3-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), ethyl iodide (31.2 g., 0.2 mole) and anhydrous ether (200 cc.). The reaction was carried out by employing anhydrous cadmium chloride (20.1 g., 0.1 mole) and (+) 1-methyl butyryl chloride (19.28 g., 0.16 mole) as before. On completion of the reaction the residue on distillation under reduced pressure gave (+) 4-methyl hexan-3-one, b.p. 140°/15 mm., yield 68%, d₄ 0.8110, n₃₅ 1.421, [α]D 35 + 4.0 (1,1).

Found : C, 72.90; H, 12.77 %
C₇H₁₄O required : C, 73.69; H, 12.28 %

Preparation of (+) 5-Methyl Heptan-4-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), n-propyl bromide (24.6 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.1 mole) and (+) 1-methyl butyryl chloride (19.28 g., 0.16 mole) as before. On completion of the reaction the residue, on distillation under reduced pressure gave (+) 5-methyl heptan-4-one, b.p. 151°/15 mm., yield 67%, d₄ 0.8210, n₃₅ 1.428, [α]D 35 + 5.1 (1,1).

Found : C, 74.71; H, 12.13 %
C₈H₁₆O required : C, 75.00; H, 12.53 %
Preparation of (+) 2:4 Dimethyl Hexan-3-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), iso-propyl bromide (24.6 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.11 mole) and (+) 1-methyl butyryl chloride (19.28 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 2:4 dimethyl hexan-3-one, b.p. 150°/15 mm., yield 44%, d_5^35 0.8097, n_35^35 1.420, [\alpha]_D^35 + 1.6 (l,l).

Found : C, 75.30; H, 12.14%

C_8H_{16}O required : C, 75.00; H, 12.53%

Preparation of (+) 6-Methyl-Octan-5-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), n-butyl bromide (27.4 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.11 mole) and (+) 1-methyl butyryl chloride (19.28 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 6-methyl octan-5-one, b.p. 165°/15 mm., yield 73%, d_4^35 0.8296, n_35^35 1.431, [\alpha]_D^35 + 5.2 (l,l).

Found : C, 76.35; H, 12.79%

C_9H_{18}O required : C, 76.05; H, 12.68%
Preparation of (+) 2;5 Dimethyl Heptan-4-one

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), iso-butyl bromide (27.4 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.1 mole) and (+) 1-methyl butyryl chloride (19.2 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 2:5 dimethyl heptan-4-one, b.p. 160°/15 mm., yield 40%, d₄ 0.8206, n₃₅ 1.424, [α]₃₅ + 3.9 (1,1).

Found : C, 76.46; H, 12.96 %
C₉H₁₈O required : C, 76.05; H, 12.68 %

Preparation of (+) 7-Methyl Nonan-6-one

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), n-amyl bromide (30.2 g., 0.2 mole), and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.11 mole) and (+) 1-methyl butyryl chloride (19.2 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 7-methyl nonan-6-one, b.p. 185°/15 mm., yield 68%, d₄ 0.8426, n₃₅ 1.437, [α]₃₅ + 2.6 (1,1).

Found : C, 76.72; H, 12.99 %
C₁₀H₂₀O required : C, 76.93; H, 12.82 %
Preparation of (+) 3:6 Dimethyl Octan-5-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), iso-amyl bromide (30.2 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed by using anhydrous cadmium chloride (20.1 g., 0.1 mole) and (+) 1-methyl butyryl chloride (19.2 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 3:6 dimethyl octan-5-one, b.p. 180°/15 mm., yield 35%, 
\[ \delta^\text{D}_{4} \] 0.8226, \( n^\text{D}_{5} \) 1.429, \( [\alpha]_{\text{D}}^\text{35} \) + 3.3 (1,1).

Found : C, 76.69; H, 12.68 %
C\textsubscript{10}H\textsubscript{20}O required : C, 76.93; H, 12.82 %

Preparation of (+) 10-Methyl Dodecan-9-One

The Grignard reagent was prepared from magnesium turnings (4.8 g., 0.2 mole), n-octyl bromide (38.6 g., 0.2 mole) and anhydrous ether (100 cc.). The reaction was completed as before by using anhydrous cadmium chloride (20.1 g., 0.1 mole) and (+) 1-methyl butyryl chloride (19.2 g., 0.16 mole) as above. On completion of the reaction the residue on distillation under reduced pressure gave (+) 10-methyl dodecan-9-one, b.p. 205°/15 mm., yield 65%,
\[ \delta^\text{D}_{4} \] 0.8426, \( n^\text{D}_{5} \) 1.439, \( [\alpha]_{\text{D}}^\text{35} \) + 1.8 (1,1).

Found : C, 79.06; H, 13.72 %
C\textsubscript{13}H\textsubscript{26}O required : C, 78.77; H, 13.13 %
INTRODUCTION AND DISCUSSION TO THE PREPARATION OF OPTICALLY ACTIVE UNSYMMETRICAL KETONES FROM (+) ACID HALIDE BY

(B) FRIEDEL-CRAFTS REACTION

The acid halides react with aromatic hydrocarbons in presence of anhydrous aluminium chloride to yield ketones:

\[ \text{Ar}.H + R.CCCl \xrightarrow{\text{AlCl}_3} \text{Ar} \text{C} = 0 + \text{HCl} \]

The reaction is quite general and a large variety of acyl halides may be condensed with aromatic compounds, such as halides of aliphatic and aromatic acids, carbonyl chloride, thiophosgene and sulphonyl chloride. The order of reactivity for acyl halides in the Friedel-Crafts ketone synthesis has been found by Calloway\textsuperscript{90} to be acyl iodide > acyl bromide > acyl chloride > acyl flouride. This is just opposite to the order determined in case of alkyl halides in Friedel-Crafts alkylation.

FRIEDEL-CRAFTS REACTION MECHANISM

The Friedel-Crafts acylation reaction involves three reactants a hydrocarbon, an acyl component and a catalyst. The overall reaction can be expressed as follows:
Ar.H + R.COCl $\xrightarrow{\text{AlCl}_3}$ Ar.CO.R.AlCl$_3$ + HCl

It is generally agreed that the complex $\text{R.CO.} \cdot (X) \cdot \text{AlCl}_3$ is formed$^{91}$ between the acyl halide and AlCl$_3$, or it dissociates into $[\text{R.CO}]^+ [\text{AlCl}_4^-]$ as suggested by Eitel and Barbalk$^{92}$. The addition compound $\text{R.CO.} \cdot (X) \cdot \text{AlCl}_3$ is considered to be a real potential acylating agent or alternatively it is also considered to be an oxonium complex$^{93}$

$$\text{R} - \text{C(X)} = 0 - \text{AlCl}_3$$

or

$$[\text{R} - \text{C(X)} = 0 - \text{AlCl}_3 - 0 = \text{C(X)} - \text{R}]^+ \text{AlCl}_4^-$$

This may be expected to ionize to produce the acetylium salt.

$$\text{R} - \text{C} = 0 \left[\begin{array}{c} \text{Cl} \\ - \text{AlCl}_3 \end{array}\right]^{(-)} \text{ i.e.,}$

$$\text{R.CO} \cdot \text{Cl} + \text{AlCl}_3 \xrightarrow{\text{(+)}} \text{R.CO} \text{AlCl}_4$$

The degree of ionization has been established experimentally by number of authors$^{94}$. The acyl cation so produced has been accepted by many authors$^{95}$ (Eitel and Barbalk, loc.cit.) as the actual acylating agent in the Friedel-Crafts reaction. Burton and Prail$^{96}$ suggested that this electrophilic acetylium ion reacts in the following manner with Benzene to give acetophenone:
Fairbrother has shown experimentally by the use of radioactive aluminium chloride that an interchange of chlorine atoms takes place between acetyl chloride and aluminium chloride.

\[
\text{CH}_3\text{COCl} + \text{AlCl}_3 \rightarrow (\text{CH}_3\text{CO})^+ + (\text{AlCl}_4)^- \]

The interchange, however, does not prove that acyl halide complex actually undergoes ionization. Wertyporsch and Firla have shown by conductivity measurements that the addition of aluminium chloride to acetyl chloride results in proportionate lowering of the molecular conductivity of this acid halide. The fact that alkyl halides undergo rearrangements in Friedel-Crafts reactions whereas no branching occurs with acyl halides may thus be explained by the differences in ionization of aluminium chloride complexes formed.

Baddeley and Voss (loc.cit.) gave the evidence recently that the cation is present in traces in a particular system and the addition compound was consequently represented as

\[
\text{R.C(X)} = \text{C}^+ - \text{AlCl}_3 \rightleftharpoons \text{R.CO}^+ + \text{AlCl}_4^- \]

They showed the
fact that 2:4:6 tribromo benzoyl halide reacts with such hydrocarbons as m-xylene and benzene in presence of aluminium halide was considered to provide evidence that the acylating agent is here not the sterically hindered oxonium complex but the acylium ion.

This vision has been recently challenged by Brown and Bonner. They argued that when acylation of toluene results in the practically exclusive formation of para isomer, some intermediate must be involved in the substitution stage of larger steric requirements than the acylium ion, which would be expected to yield some ortho isomer as well. Brown and Greyson, Brown, Pearsall and Greyson concluded that substitution proceeds rather by a bimolecular nucleophilic attack ($S_{N2}$ type) of the aromatic component on the acyl-halide aluminium.

The explanation by Tedder suggests that acylation by means of acyl chloride and aluminium chloride may take place by either of the two mechanisms, the ionic (I) and the nucleophilic substitution ($S$), depending on the reactivity of the aromatic substrate.

**Ionic Mechanism : (I)**

\[
\begin{align*}
\text{Ar} + R - \text{CO}^+ + \text{AlCl}_4^- & \rightarrow [\text{Ar} - \text{COR}]^+ [\text{AlCl}_4^-]^- \\
& \text{transition state} \\
& \rightarrow \text{Ar} + R - \text{CO}^- + \text{AlCl}_3 + \text{HCl} \\
& \text{Stable intermediate}
\end{align*}
\]
Substitution Mechanism: (S)

Quite a different type of mechanism has also been proposed in which initial step is the formation of an enol derivative e.g., with acetyl chloride \( \text{CH}_2 = \text{C} \cdot \text{Cl} - \text{OAlCl}_2 \). Since this formation takes four days, such an intermediate cannot be of significance in normal Friedel-Crafts reactions.

Summarizing, the reactions with acyl halides may be written as

(a) \( \text{R.COCl} + \text{AlCl}_3 \rightleftharpoons \left[ \text{R.CO} \right]^{(+) \text{AlCl}_4}^{(-)} \)

(b) \( \text{C}_6\text{H}_6 + \left[ \text{R.CO} \right]^{(+) \text{AlCl}_4}^{(-)} \rightarrow \text{C}_6\text{H}_5\text{CO.R} + \text{H}^{(+) \text{AlCl}_4}^{(-)} \)

(c) \( \text{H}^{(+) \text{AlCl}_4}^{(-)} \rightarrow \text{AlCl}_3 + \text{HCl} \)

Actually, the initially formed complex in (a) combines with benzene to give a complex \( \text{C}_6\text{H}_6 \left[ \text{R.CO} \right]^{(+) \text{AlCl}_4}^{(-)} \). Combining (b) and (c) we have;
but the ketone produced, combines with an equivalent of aluminium chloride with the production of an inactive complex. The following conclusions can be drawn:

(1) Normal Friedel-Crafts acylation reactions with aromatic substances of a wide range of reactivity, probably proceed primarily by a novel type of substitution mechanism (S).

(2) Ionic substitution becomes important only under special circumstances when (a) a sterically hindered acyl halide is used, or (b) a sterically hindered position, e.g., the 9-anthryl position, is being substituted.

The latest brief interpretation of the Friedel-Crafts acylation mechanism has been considered by Gore to occur through one or more mechanisms involving (a) an unsolvated acyl halide catalyst complex, (b) an acylium ion and (c) a solvated complex. The contributions of three mechanisms depend upon the solvent the steric requirements of acyl halide and the hydrocarbon and the amount of acyl halide.
GENERAL FEATURES OF THE FRIEDEL-CRAFTS ACYLATION REACTION

Catalyst

Aluminium chloride is most generally used, because it is undoubtedly the cheapest of the most efficient catalyst in this reaction. The purity of aluminium chloride itself has a considerable influence on the yield of product. In practice a ratio of 1.1 mole of the catalyst has been found optimum for the reaction. Since one mole of ketone produced, the catalyst is in effect being continuously removed from the reaction mixture.

The Acyl Component

For the introduction of the acyl group (R.C0-) into an aromatic nucleus, the chloride R.C0Cl is most frequently used. $\infty$-R-Unsaturated acid chloride generally cannot be used as they polymerize. The reactivity of acyl halides has been shown to decrease in the expected order of decreasing atomic weight of the halogens, $I<Br<Cl<F$. Ketones have been recently employed$^{106}$ as the successful acylating agent.

The Solvent

A variety of solvents has been used in the Friedel-Crafts acylation reaction, the most commonly used ones being carbon disulfide and nitrobenzene. In non-polar solvents,
such as carbon disulphide, light petroleum or carbon tetrachloride, neither aluminium chloride nor its complex with acyl halides is appreciably soluble; the reaction is heterogeneous throughout its course. A polar solvent such as nitrobenzene dissolves not only aluminium chloride, but also the acyl-chloride-aluminium-chloride complex and usually the aluminium chloride complex of the resulting ketone.

Bassilios, Maker and Salem\textsuperscript{107} in acetylation experiments with a set of non-polar solvents observed that cyclohexane, n-hexane and carbon disulphide were somewhat faster than carbon tetrachloride. It was further noted that the rate of acylation is much higher with solvents of high dipole moment. Carbon disulphide has been recommended for most purposes and particularly when alkyl migrations are to be avoided\textsuperscript{108}.

**Addition Sequence**

In a systematic investigation of the different addition procedures, it was found\textsuperscript{109} best yields and purest isomers are obtained by Perrier's sequence, which involves final addition of hydrocarbon to the performed acylchloride catalyst adduct.
Reaction of Halogenated Benzene with Acid Halide

The reaction of chlorobenzene with acetyl chloride was first reported by Collet\textsuperscript{110}. Thereafter number of workers including Gautier, Strauss and Ackermann\textsuperscript{111}, carried different experimental conditions and claimed to have secured more than 80% yield of the p-chloro acetophenone. Similarly, Schweitzer, Schoff, Hale and Thorp\textsuperscript{112} reacted acetyl chloride with bromo-benzene in carbon disulphide in presence of aluminium chloride and obtained p-bromo acetophenone in varying yields. Schweitzer, Klages et al\textsuperscript{113} also prepared p-iodoacetophenone by Friedel-Crafts acylation method.

Reaction of Alkyl Benzene with Acid Chloride

Acylation of alkyl benzene in presence of anhydrous aluminium chloride involves no migration of the alkyl group present. Attempts to enforce diacylation by raising the temperature causes\textsuperscript{114} (a) decomposition of acylating agent, (b) dehydrogenation of alkyl substituent.

Verely\textsuperscript{115} secured an 80% yield of corresponding ketones by acetylating toluene, xylene and cymene.
Reaction of Phenolic Ethers and Acyl Chloride

Alkyl ethers of phenol react with acid chlorides in presence of aluminium chloride to give p-acyl substitution. The reaction of anisole with acetyl chloride has been much studied. Klages (loc.cit.) using petroleum ether as the solvent and keeping the temperature less than 5° obtained 80% yield of p-propionyl phenetole and p-butyryl phenetole from the corresponding acyl chlorides and phenetole.

Various substituted ethers have been reacted with acyl chlorides in the presence of anhydrous aluminium chloride. Whereas with unsubstituted ethers, the entering acyl groups generally goes para to the ether linkage. In general, it can be put that with o-alkyl substituted ethers, the entering acyl groups goes para to the ether linkage, with meta and para alkyl substituted ethers, it enters ortho to the ether linkage.

Acylation with Different Compounds

As a general rule, the electronegative groups present in the hydrocarbon component have an inhibiting effect on the reaction. The effect is most marked with benzene, monoalkyl benzene etc. so that acylation of nitrobenzene, benzoic acid or benzophenone for example is impossible. The
extent of the reaction of monohalo toluenes with acyl chlorides depends upon the position of the halogen in the ring; p-chloro toluene fails to react with o-bromo ethyl benzoyl bromide. Aromatic nitriles in which the cyano group is joined to a nuclear carbon atom fail to undergo Friedel-Crafts reaction. Such nitriles are partially converted to triazines under the influence of aluminium chloride and aliphatic acid chlorides\textsuperscript{118}. 
DISCUSSION

The only record of an attempted preparation of an optically active ketones from optically active acid halides is that of McKenzie and Widdows\textsuperscript{119} who condensed (+) phenyl p-tolyl acetyl chloride with benzene. They failed to obtain optically active ketone; and a mixture largely consisting of diphenyl and triphenyl methanol was isolated. They believed that the formation of the inactive ketone (in small amount) was due to the presence of $\alpha$-hydrogen atom.

Thereafter the same optical instability of secondary diaryl acetyl chloride has been confirmed by Bleazard and Rothstein\textsuperscript{120} in the case of (+) phenyl p-tolyl acetyl chloride and (+) $\alpha$-p-chloro phenyl $\alpha$-phenyl acetyl chloride, both of which yield inactive ketones when condensed with anisole. But this was explained as racemization due to the potential keto-enol system. These workers then established the first case of an asymmetric synthesis using the Friedel-Crafts reaction. They prepared (-) p-methoxy phenyl 1-phenyl 1-p-tolyl propyl ketone from (-) $\alpha$-phenyl $\alpha$-p-tolyl propionyl chloride with anisole.
They suggested that the retention of optical activity in this case demonstrated that the catalyst itself had no direct effect on carbon skeleton. Further, the above ketone in order to remain optically active, must remain in the planar form. This planar configuration results from the sufficiently free carbonium ion, formed by the elimination of carbon monoxide. However, they could not isolate active ketone from (+) 2:2:3:5:5,-pentamethyl hexane 3-carbonyl chloride, because of the elimination of carbon monoxide. Instead, a mixture was obtained possibly 3-methoxy phenyl 2:2:3:5:5, pentamethyl hexane and 1-ter-butyl 1:3:3, trimethyl butyl methoxy phenyl ketone. To throw further light on this mechanism we undertook the Friedel-Crafts acylation reaction by interacting optically active (+) 1-methyl butyroyl chloride with aromatic compounds such as benzene, toluene, m-xylene, ethyl benzene, p-cymene, chlorobenzene, bromobenzene, anisole and pheptole in presence of anhydrous aluminium chloride to get optically active unsymmetrical ketones. The (+) 1-methyl
butyryl chloride was obtained by treating (+) 1-methyl butyric acid $[\alpha]_D^{35} + 12.3$ with phosphorous trichloride obtained by oxidising (-) 2-methyl butane-1-ol $[\alpha]_D^{35} - 4.7 \ (1,1)$ with alkaline potassium permanganate.

The Catalyst

The insufficient amount of catalyst lowers the yield$^{121}$. Using excess of aluminium chloride with optically active higher alkyl halide Austin$^{122}$ obtained racemized product. In the present Friedel-Crafts acylation reaction, the optically active (+) 1-methyl butyryl chloride yields optically active unsymmetrical ketones with the above mentioned aromatic compounds in presence of anhydrous aluminium chloride without the slightest rearrangement. This is also noted by Bleazared and Rothstein (loc.cit.) in case of (+) phenyl p-tolyl acetyl chloride.

The addition sequence adopted by Lock et al and Bouvault (loc.cit.) was adopted in which the mixture of the hydrocarbon, i.e., aromatic part and the catalyst was reacted by the optically active (+) 1-methyl butyryl chloride.

The optical rotation of the ketones of the type $\text{(+)} \text{Ar.CO.CH.CH}_2\text{CH}_3$ have been taken in homogeneous solution. Looking to the table of the specific rotations,
it is found that in case of Ar from benzene, toluene, ethyl benzene, the optical rotation decreases with the increase of the side chain, halo substituted ketones. Optical rotation of bromo ketone is higher than the chloro ketone. Ketones containing ethereal linkage in the side chain optical rotation of ethoxy ketone is higher than the methoxy ketone.
<table>
<thead>
<tr>
<th>No.</th>
<th>Name of the Ketone</th>
<th>B.P. °C/15 mm</th>
<th>Yield %</th>
<th>Density d 4°C 15 mm</th>
<th>Refractive Index n D 35</th>
<th>Specific Molecular Rotation [α] D 35</th>
<th>[M] D 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>α-Methyl butyrophenone</td>
<td>135</td>
<td>65</td>
<td>1.098</td>
<td>1.447</td>
<td>+5.1</td>
<td>+8.3</td>
</tr>
<tr>
<td>2.</td>
<td>4-Methyl α-methyl butyrophenone</td>
<td>165</td>
<td>55</td>
<td>1.101</td>
<td>1.478</td>
<td>+4.4</td>
<td>+7.7</td>
</tr>
<tr>
<td>3.</td>
<td>4-Ethyl α-methyl butyrophenone</td>
<td>180</td>
<td>50</td>
<td>1.159</td>
<td>1.495</td>
<td>+0.9</td>
<td>+1.4</td>
</tr>
<tr>
<td>4.</td>
<td>2:4-Dimethyl α-methyl butyrophenone</td>
<td>198</td>
<td>50</td>
<td>1.159</td>
<td>1.496</td>
<td>+1.3</td>
<td>+2.5</td>
</tr>
<tr>
<td>5.</td>
<td>4-Chloro α-methyl butyrophenone</td>
<td>175</td>
<td>58</td>
<td>1.147</td>
<td>1.488</td>
<td>+3.9</td>
<td>+7.7</td>
</tr>
<tr>
<td>6.</td>
<td>4-Bromo α-methyl butyrophenone</td>
<td>130</td>
<td>60</td>
<td>1.159</td>
<td>1.498</td>
<td>+3.7</td>
<td>+8.9</td>
</tr>
<tr>
<td>7.</td>
<td>4-Methoxy α-methyl butyrophenone</td>
<td>160</td>
<td>55</td>
<td>1.179</td>
<td>1.518</td>
<td>+3.2</td>
<td>+6.1</td>
</tr>
<tr>
<td>8.</td>
<td>4-Ethoxy α-methyl butyrophenone</td>
<td>175</td>
<td>58</td>
<td>1.159</td>
<td>1.498</td>
<td>+7.1</td>
<td>+14.6</td>
</tr>
</tbody>
</table>

\[
[M]_{D}^{35} = \frac{[\alpha]_{D}^{35} \times M}{100}
\]
REACTIONS

TYPE (A): IN CASE OF MONOSUBSTITUTED

\[ X - \text{Ph} + (+)\text{ClCO.CH.CH}_2\text{CH}_3 \xrightarrow{\text{AlCl}_3} \text{PhCO.CH.CH}_2\text{CH}_3 \]

\[ (+) X - \text{PhCO.CH.CH}_2\text{CH}_3 \]

TYPE (B): IN CASE OF DISUBSTITUTED

\[ Y - \text{Ph} + (+)\text{ClCO.CH.CH}_2\text{CH}_3 \xrightarrow{\text{AlCl}_3} \text{PhCO.CH.CH}_2\text{CH}_3 \]

\[ (+) Y - \text{PhCO.CH.CH}_2\text{CH}_3 \]

TYPE (A)

(1) When \( X = \text{H} \)

\[ \text{CO.CH.CH}_2\text{CH}_3 \]

\( (+) \alpha\text{-methyl butyrophenone} \)

(2) When \( X = \text{-CH}_3 \)

\[ \text{CH}_3 \text{CO.CH.CH}_2\text{CH}_3 \]

\( (+) 4\text{-methyl \alpha\text{-methyl butyrophenone}} \)
(3) When $X = \text{C}_2\text{H}_5$

$\text{C}_2\text{H}_5 \quad \text{CO.} \quad \text{CH}_2.\text{CH}_3$

(+) 4-ethyl $\alpha$-methyl butyrophenone

(4) When $X = -\text{Cl}$

$\text{Cl} \quad \text{CO.} \quad \text{CH}_2.\text{CH}_3$

(+) 4-chloro $\alpha$-methyl butyrophenone

(5) When $X = -\text{Br}$

$\text{Br} \quad \text{CO.} \quad \text{CH}_2.\text{CH}_3$

(+) 4-bromo $\alpha$-methyl butyrophenone

(6) When $X = -\text{OCH}_3$

$\text{CH}_3.\text{O} \quad \text{CO.} \quad \text{CH}_2.\text{CH}_3$

(+) 4-methoxy $\alpha$-methyl butyrophenone

(7) When $X = -\text{OC}_2\text{H}_5$

$\text{C}_2\text{H}_5.\text{O} \quad \text{CO.} \quad \text{CH}_2.\text{CH}_3$

(+) 4-ethoxy $\alpha$-methyl butyrophenone
TYPE (B)

(1) When $X = -\text{CH}_3$ and $Y = -\text{CH}_3$

\[
\begin{array}{c}
\text{CH}_3 \\
\text{H}_3\text{C} \quad \text{--} \quad \text{CO.}\text{CH.}\text{CH}_2.\text{CH}_3 \\
\text{CH}_3
\end{array}
\]

(+) 2:4 dimethyl \text{\textalpha}-methyl butyrophenone.
EXPERIMENTAL
EXPERIMENTAL
PREPARATION OF OPTICALLY ACTIVE UNSYMMETRICAL KETONES
FROM (+) ACID HALIDE BY
(B) FRIEDEL-CRAFTS REACTION

Preparation of (+) α-Methyl Butyrophenone

In a 500 cc. three necked round bottomed flask fitted with a separating funnel, a mercury sealed stirrer and a double surface refluxed condensor carrying a calcium chloride guard tube were placed finely powdered anhydrous aluminium chloride (20 g., 0.15 mole) and dry benzene (44 g., 0.55 mole). To this (+) 1-methyl butyryl chloride (18.0 g., 0.15 mole) was slowly added during 40-45 minutes at a temperature below 10°.

The mixture was then heated on a water bath at 50-60° till all the hydrogen chloride gas has evolved (one hour). The mixture was then slowly poured on to a mixture of crushed ice and concentrated hydrochloric acid (15-20 cc.) with vigorous stirring to dissolve aluminium salt. The dark coloured benzene layer was separated, washed with water, sodium hydroxide solution (2 N), again with water and dried (magnesium sulphate). Benzene was removed by distillation and the residue on distillation under reduced pressure gave (+) α-methyl butyrophenone, b.p. 135°/15 mm.,
Preparation of (+) 4-Methyl α-Methyl Butyrophenone

In 500 cc. three necked round bottomed flask as described above, were placed finely powdered anhydrous aluminium chloride (20 g., 0.15 mole) and sodium dried toluene (50.6 g., 0.55 mole). To this (+) 1-methyl butyryl chloride (18.0 g., 0.15 mole) was slowly added and the reaction was completed as before. The residual oil on distillation under reduced pressure gave (+) 4-methyl α-methyl butyrophenone, b.p. 165°/15 mm., yield 55%, d₄ 1.101, n₃5 1.478, $[\alpha]_{D}^{35}$ + 4.4 (1,1).

Found : C, 81.28; H, 8.83%
C₁₂H₁₆O required : C, 81.83; H, 9.09%

Preparation of (+) 4-Ethyl α-Methyl Butyrophenone

A mixture of finely powdered anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.) and ethyl benzene (15.9 g., 0.15 mole) was taken in a 1000 cc. three necked round bottomed flask arranged as described before. (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was allowed to react slowly during 50-60 minutes, the contents were refluxed for 30 minutes.
The carbon disulphide was distilled off and the contents were poured with stirring onto a mixture of crushed ice and hydrochloric acid (60 cc.), and extracted with ether. The ethereal layer was washed with water and dried (magnesium sulphate). Ether was evaporated, the residue on distillation under diminished pressure gave (+) 4-ethyl α-methyl butyrophenone, b.p. 180°/15 mm., yield 50%,

\[ d_{4}^{35} 1.159, n_{35}^{35} 1.495, [\alpha]_{D}^{35} + 0.9 \] (1,1).

Found: C, 81.65; H, 9.21%

C\(_{13}\)H\(_{18}\)O required: C, 82.10; H, 9.47%

**Preparation of (+) 2:4 Dimethyl α-Methyl Butyrophenone**

In a 1000 cc. three necked flask arranged as before, were placed anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.), and m-xylene (15.9 g., 0.15 mole). (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was added during 50-60 minutes. The reaction was completed as before. (+) 2:4 Dimethyl α-methyl butyrophenone was obtained at b.p. 198°/15 mm., yield 50%,

\[ d_{4}^{35} 1.159, n_{35}^{35} 1.496, [\alpha]_{D}^{35} + 1.3 \] (1,1).

Found: C, 81.86; H, 9.28%

C\(_{13}\)H\(_{18}\)O required: C, 82.10; H, 9.47%.
Preparation of (+) 4-Chloro \( \alpha \)-Methyl Butyrophenone

In a 1000 cc. three necked flask arranged as before, were placed anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.), and pure chlorobenzene (16.9 g., 0.15 mole). (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was added during 50-60 minutes. The reaction was completed as before. (+) 4-Chloro \( \alpha \)-methyl butyrophenone was obtained at, b.p. 175°/15 mm., yield 58\%, \( d_4^{35} 1.147 \), \( n_4^{35} 1.488 \), \( [\alpha]_D^{35} + 3.9 \) (\( l, l \)).

Found : C, 67.73; H, 6.45 %

\( C_{11}H_{13}Cl \) required : C, 67.17; H, 6.62 %

Preparation of (+) 4-Bromo \( \alpha \)-Methyl Butyrophenone

In a 1000 cc. three necked flask arranged as before, were placed anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.), and pure bromobenzene (23.5 g., 0.15 mole). (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was added during 50-60 minutes. The reaction was completed as before. (+) 4-Bromo \( \alpha \)-methyl butyrophenone was obtained at, b.p. 130°/15 mm., yield 60\%, \( d_4^{35} 1.159 \), \( n_4^{35} 1.498 \), \( [\alpha]_D^{35} + 3.7 \) (\( l,l \)).

Found : C, 54.32; H, 5.28 %

\( C_{11}H_{13}Br \) required : C, 54.78; H, 5.39 %
Preparation of (+) 4-Methoxy α-Methyl Butyrophenone

In a 1000 cc. three necked flask arranged as before, were placed anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.) and distilled anisole (16.2 g., 0.15 mole). (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was added during 45-50 minutes. The reaction was completed as before. The residue on distillation under diminished pressure gave (+) 4-methoxy α-methyl butyrophenone, b.p. 160°C/15 mm., yield 55%, \( d_4^{35} \) 1.179, \( n_35 \) 1.518, \( [\alpha]_D^{35} + 3.2 \) (1,1).

Found: C, 74.63; H, 8.19%

\( C_{12}H_{16}O \) required: C, 75.01; H, 8.33%

Preparation of (+) 4-Ethoxy α-Methyl Butyrophenone

In a 1000 cc. three necked flask arranged as before, were placed anhydrous aluminium chloride (42.7 g., 0.32 mole), dry carbon disulphide (50 cc.) and distilled phenetole (18.3 g., 0.15 mole). (+) 1-Methyl butyryl chloride (18.0 g., 0.15 mole) was added during 45-50 minutes. The reaction was completed as before. The residue on distillation under diminished pressure gave (+) 4-ethoxy α-methyl butyrophenone, b.p. 175°C/15 mm., yield 58%, \( d_4^{35} \) 1.159, \( n_35 \) 1.498, \( [\alpha]_D^{35} + 7.1 \) (1,1).

Found: C, 75.23; H, 8.65%

\( C_{15}H_{18}O \) required: C, 75.71; H, 8.74%.