SECTION III

INTRODUCTION AND DISCUSSION TO

THE PREPARATION OF OPTICALLY ACTIVE ESTERS FROM

(+) 1-METHYL BUTYRIC ACID BY ACYLATION OF ALCOHOLS AND PHENOLS
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(+) 1-METHYL BUTYRIC ACID BY ACYLATION OF ALCOHOLS AND PHENOLS

The replacement of hydrogen of the hydroxy group by acyl groups to yield esters can generally be effected by means of an acid anhydride or acyl chloride under suitable conditions. The free carboxylic acids can also be used but their application is determined by the nature of the hydroxy compound. Primary and secondary alcohols in general yield esters comparatively easily.

ACYLATION BY REACTION WITH ACIDS

Carboxylic groups are able to react directly with the hydroxyl group to yield acyl derivatives:

\[ \text{R.COON} + \text{HOR'} \rightarrow \text{R.COOR'} + \text{H}_2\text{O} \]

The reaction is one of equilibrium, the position of equilibrium being determined by character of the acid, the alcohol used and the relative proportion of each, in accordance with the law of mass action:

\[ \frac{[\text{R.COON}]}{[\text{R.COOR'}]} \times \frac{[\text{R'OH}]}{[\text{H}_2\text{O}]} = K \]

Mineral acids exert an accelerating influence on esterification. The effect is in proportion to their
strength and concentration. When sulphuric acid is added to a mixture of the acid (R.COOH) and alcohol (R OH), there is first of all established the usual acid base equilibria, in which the proton is shared between all the various basic species in the solution, with the formation of the acids R OH, R.COOH in equilibria with the base R OH, RCOOH, HSO (and after the reaction has proceeded with the formation of water, H O and H O will participate).

Since it is the acid and the alcohol that are concerned with, the state in which these are present is of first importance. The acid can be protonated in two ways to give (a) or (b):

In (a) and (b) the positive charge on oxygen will further withdraw electrons towards oxygen and will create a greater disymmetry in the C - O bond. Thus, protonation of the acid has increased its ability to accept nucleophilic attack by the alcohol.
The reaction then leads to ester (g) is:

\[
\begin{align*}
R - C^+OH & \rightleftharpoons R - C - OH & \rightleftharpoons R - C^+O^-H \\
\text{(c)} & \quad \text{(d)} & \quad \text{(e)}
\end{align*}
\]

\[
\begin{align*}
R - C^+OH & \rightleftharpoons A^- + R - C^+O^-H \\
\text{(f)} & \quad \text{(g)}
\end{align*}
\]

After the initial attack (c), the succeeding stages (d), (e), (f) are simply proton exchange reactions, in which the proton is shared between the basic oxygen atoms of the intermediate and the base (which can be any base present); \(A^-\), step (f) \(\rightarrow\) (e) is the exact analogy of the step leading to (d), but in (f) \(\rightarrow\) (e) the nucleophilic water attacks the protonated ester (f).

**ACYLATION BY REACTION WITH ACID HALIDES**

Primary and secondary alcohols may be readily esterified with aliphatic acid chlorides in organic solvents, under Schotten-Baumann\(^{125}\) conditions.

\[
\begin{align*}
R.COCl & \rightarrow R OH & \rightarrow R.COO^+R^- + HCl
\end{align*}
\]
The reaction is quite rapid, somewhat exothermic and proceeds well at low temperature, but the rate of esterification is less rapid than for esterification with the corresponding aliphatic acid bromide with methanol and ethanol. Acetyl chloride produces less ester than either benzene sulphonyl chloride in the Schotten-Baumann technique (loc. cit.), owing to its greater tendency to hydrolyse under these conditions. Esterifications have been carried out in ether\textsuperscript{126}, dioxane\textsuperscript{127}, carbontetrachloride\textsuperscript{128}, in the presence of excess alcohol, or in the absence of solvent.

The removal of the hydrogen chloride produced in the reaction is not always required, with a primary alcohol, there is no formation of alkyl chloride or olefin with the hydrogen chloride. However, the ester may be hydrolysed back to the alcohol and the acid if the hydrogen chloride is permitted to accurate and remain in the solvent, particularly at higher temperatures for aqueous or alcoholic solutions and, infact, may react in other ways, so that excellent yields are achieved only when it is removed. Frequently pyridine\textsuperscript{129} has been applied as an efficient hydrogen chloride acceptor.

Secondary alcohols generally require removal of the hydrogen chloride produced for satisfactory acylation. With tertiary alcohols, however, acylation does not normally
occur; the reaction affords instead tertiary chlorides or olefins.

\[ \text{CH}_3\text{COCl} + \text{R}_3\text{COH} \rightarrow \text{R}_3\text{CCl} + \text{CH}_3\text{COOH} \]

\[ \text{CH}_3\text{COCl} + (\text{CH}_3)_3\text{C.OH} \xrightarrow{\text{C}_6\text{H}_5\text{N}} (\text{CH}_3)_3\text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{N.HCl} \]

The yield of ester is uniformly greater with the lowering of the temperature, as hydrolysis of acid chloride is inhibited. The acid chloride should be added in small portions to prevent local overheating. Potassium hydroxide has been found better as the hydrogen chloride acceptor. Acylation of aqueous methanol and ethanol solutions by this technique are ineffective but the substitution of higher homologous of acid chlorides reduces the importance of the competing hydrolysis reaction. The use of acetone as a solvent for acylations with the lower acid chloride is efficient. The esterification of bifunctional compounds such as amino alcohols, which are usually prone to react preferentially at the amino group can be accomplished by conducting the reaction in acid solution, under which conditions, the salt of the amine is inert and hydroxyl group is readily acylated.

\[ \text{R.COCl} + \text{C}_2\text{H}_4\text{NH}_3\text{OH} \rightarrow \text{R.COOC}_2\text{H}_4\text{NH}_3\text{Cl} \]

\[ \text{R.COCl} + \text{C}_2\text{H}_4\text{NH}_2(\text{C}_2\text{H}_4\text{OH})_2 \rightarrow \left[ \text{R.COOC}_2\text{H}_4\text{NH}_2\text{C}_2\text{H}_4 \right] \text{Cl} \]
The data obtained by several workers\textsuperscript{131-135} indicate that the rate of reaction for a given alcohol decreases with the increase of chain length of acid chloride. Further acetyl chloride and other homologous acyl chlorides react much more rapidly with a given alcohol than benzoyl chloride or substituted benzoyl chlorides but less rapidly than the chloro substituted acetyl chloride. This has been usually explained on the basis that the positive potential of the carbonyl carbon atom in benzoyl chloride is lowered considerably by the adjacent phenyl group through the contributions of resonance from I to III (or I' to III'), whereas in acetyl chloride the carbonyl unsaturation has no aromatic nucleus in conjugation with which to promote strong resonance.
\[
\begin{align*}
\text{CH}_3\text{COC}_1 & \iff \text{CH}_3 - \text{C} - \text{Cl} \iff \text{HCH}_2 = \text{C} - \text{Cl} \\
\text{CH}_3\text{COC}_1 & \iff \text{Cl} \iff \text{CH}_2 = \text{C} = \text{O}
\end{align*}
\]
Branching of the chain in an aliphatic acid chloride has been observed to lower the velocity of the acylation, probably as a consequence of steric hinderance. The kinetics of alcoholysis of both aromatic and aliphatic acid chloride confirm to a first order reaction and in dilute solution the reaction has shown the characteristic of both a unimolecular, and a pseudo-unimolecular reactions.

(i) $\text{RCOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH} \xrightarrow{k_1} \text{RCOC}_2\text{H}_5 \xrightarrow{k_2} \text{RCOOC}_2\text{H}_5 + \text{H} + \text{Cl}$

(ii) $\text{RCOC}_2\text{H}_5 \xrightarrow{k'_1} (\text{RC} = 0) + \text{Cl}$

When the esterification of secondary and tertiary alcohols with aliphatic acid chloride is conducted in ether in the presence of certain metal, good yields of the corresponding esters are produced. Magnesium, aluminium, zinc and the alkali metals have been studied for this purpose under various conditions. It has been inferred that the metal functions in this reaction as a hydrogen chloride acceptor. The possibility that esterification occurs through the metal alkoxide, formed directly
from the alcohol and the metal and is more probable, at least with sodium metal. It is in agreement with the general observation that acid chlorides react very rapidly with metal alkoxide to give esters.

$$2R'OH + 2M \rightarrow 2R'OM + H_2$$

$$R'OM + RCOCl \rightarrow R'COOR' + MCl$$

The acylation of phenols with aliphatic acid chloride is only one of the modes in which these compounds may react (I), in the presence of suitable acidic catalyst, or solvents. The acid chloride may condense in Friedel-Crafts type acylation (II) to give phenolic ketones:

$$RCOCl + C_6H_5OH \rightarrow RCOOC_6H_5 + HCl \quad (I)$$

$$RCOCl + C_6H_5OH \xrightarrow{AlCl_3} OH.C_6H_4.CO_R (o/p) + HCl \quad (II)$$

In a few instances the hydrogen chloride eliminated in the esterification may function as the acid catalyst to induce a Friedel-Crafts acylation of the phenol. This is particularly true when the phenolic aromatic ring is poly-functional, the reaction usually occurring in the absence of added catalyst.

The Schotten-Baumann (loc.cit.,) techniques of acylation is not applicable to the esterification of phenols, since phenols are solubilized by sodium hydroxide into the
aqueous phase to phenoxide ions. The stronger hydroxyl ions undergo selective reactions with the acid chloride instead (III) to afford a soap, and desired esterification (reaction I) is thereby minimised.

\[
R\text{.COCl} + \text{NaOH} \rightarrow R\text{.COONa} + \text{NaCl} \quad \text{(III)}
\]

In the presence of suitable hydrogen chloride acceptor, such as magnesium\textsuperscript{141} or in the absence of the solvent, the maximum conversion to ester can usually be realised.

Einhorn and Hollandt\textsuperscript{142} have suggested a very useful method of acylating both alcoholic and phenolic hydroxy groups, which consists in the reaction of the hydroxy compounds with the appropriate acid chloride in presence of pyridine, quinoline or less rarely some other tertiary amine.
DISCUSSION

Few optically active acylated derivatives like methyl, ethyl, propyl esters of (+) l-methyl butyric acid \([\alpha_c]_{D}^{35} + 12.3\) (1,1) have been reported in the literature. In order to collect more information, regarding the optically active esters, the acylation of aliphatic and aromatic hydroxy compounds have been carried out.

As it is shown in the introduction that primary alcohols react more readily with the acid than the corresponding secondary alcohols, while tertiary alcohols and phenols do not react to any serious extent. For this reason the first two primary alcohols, methanol and ethanol are directly esterified with (+) l-methyl butyric acid whereas the other alcohols like n- and iso-propanol, n-, iso-, sec- and tert-butanol, 2-methyl butan-1-ol, n-benzyl alcohol, n-octyl alcohol and the phenols like phenol, o-, m- and p-cresols, o-, m- and p-chloro phenols, o-, m- and p-nitrophenols and 2:4 dichloro phenol were condensed with the (+) l-methyl butyryl chloride \([\alpha_c]_{D}^{35} + 4.5\) (1,1) in presence of pyridine.
The optical rotations of these acylated derivatives of alcohols and phenols have been recorded in Tables I and II.

It was observed that in the case of normal aliphatic series the optical rotations decreases with increase of -CH$_2$- group in the alcoholic portion of the optically active esters. The maximum optical rotation $[\alpha]_D^{22} + 3.9$ (1,1) was observed in case of (+) methyl 1-methyl butyrate, whereas minimum optical rotation $[\alpha]_D^{22} + 2.6$ (1,1) was observed in case of (+) n-octyl 1-methyl butyrate.

In the case of optically active esters having aromatic substitution the optical rotation was observed as follows: p-substituents $>$ m-substituents $>$ o-substituents.

The results are tabulated as under:

<table>
<thead>
<tr>
<th>Substituent Group</th>
<th>para Position</th>
<th>meta Position</th>
<th>ortho Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH$_3$</td>
<td>+ 3.2</td>
<td>+ 2.9</td>
<td>+ 2.6</td>
</tr>
<tr>
<td>-Cl</td>
<td>+ 3.3</td>
<td>+ 3.3</td>
<td>+ 2.7</td>
</tr>
<tr>
<td>-NO$_2$</td>
<td>+ 2.9</td>
<td>+ 2.5</td>
<td>+ 2.3</td>
</tr>
</tbody>
</table>

Over and above this, these optically active acylated derivatives from various phenols have been subjected to Fries migration in presence of anhydrous aluminium chloride under suitable experimental condition (Section IV).
### TABLE I

**OPTICALLY ACTIVE ESTERS OF THE TYPE (+) CH<sub>3</sub>·CH<sub>2</sub>·CH·COOR**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of the Ester</th>
<th>b.p. °C</th>
<th>Yield %</th>
<th>Density d&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Refractive Index n&lt;sub&gt;32&lt;/sub&gt;</th>
<th>Specific Rotation [α]&lt;sup&gt;32&lt;/sup&gt; D&lt;sub&gt;1,1&lt;/sub&gt;</th>
<th>Molecular Rotation [M]&lt;sup&gt;32&lt;/sup&gt; D&lt;sub&gt;1,1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(+) Methyl 1-methyl butyrate*</td>
<td>115</td>
<td>70</td>
<td>0.8632</td>
<td>1.404</td>
<td>+3.90</td>
<td>+4.5</td>
</tr>
<tr>
<td>2.</td>
<td>(+) Ethyl 1-methyl butyrate*</td>
<td>130</td>
<td>60</td>
<td>0.8594</td>
<td>1.399</td>
<td>+3.80</td>
<td>+5.0</td>
</tr>
<tr>
<td>3.</td>
<td>(+) n-Propyl 1-methyl butyrate</td>
<td>145</td>
<td>63</td>
<td>0.8542</td>
<td>1.405</td>
<td>+3.60</td>
<td>+5.2</td>
</tr>
<tr>
<td>4.</td>
<td>(+) n-Butyl 1-methyl butyrate</td>
<td>100</td>
<td>68</td>
<td>0.8531</td>
<td>1.403</td>
<td>+3.40</td>
<td>+5.4</td>
</tr>
<tr>
<td>5.</td>
<td>(+) n-Hexyl 1-methyl butyrate</td>
<td>120</td>
<td>69</td>
<td>0.8468</td>
<td>1.413</td>
<td>+2.90</td>
<td>+5.4</td>
</tr>
<tr>
<td>6.</td>
<td>(+) n-Octyl 1-methyl butyrate</td>
<td>170</td>
<td>67</td>
<td>0.8491</td>
<td>1.414</td>
<td>+2.60</td>
<td>+5.6</td>
</tr>
<tr>
<td>7.</td>
<td>(+) iso-Propyl 1-methyl butyrate</td>
<td>125</td>
<td>51</td>
<td>0.8531</td>
<td>1.394</td>
<td>+3.80</td>
<td>+5.2</td>
</tr>
<tr>
<td>8.</td>
<td>(+) iso-Butyl 1-methyl butyrate</td>
<td>80</td>
<td>60</td>
<td>0.8502</td>
<td>1.406</td>
<td>+3.50</td>
<td>+5.5</td>
</tr>
<tr>
<td>9.</td>
<td>(+) (2-Methyl)-butyl 1-methyl butyrate</td>
<td>185</td>
<td>47</td>
<td>0.8468</td>
<td>1.407</td>
<td>+5.70</td>
<td>+9.9</td>
</tr>
<tr>
<td>10.</td>
<td>(+) sec-Butyl 1-methyl butyrate</td>
<td>110</td>
<td>50</td>
<td>0.8493</td>
<td>1.478</td>
<td>+3.50</td>
<td>+5.5</td>
</tr>
<tr>
<td>11.</td>
<td>(+) tert-Butyl 1-methyl butyrate</td>
<td>125</td>
<td>40</td>
<td>0.8550</td>
<td>1.413</td>
<td>+3.30</td>
<td>+5.2</td>
</tr>
<tr>
<td>12.</td>
<td>(+) Benzyl 1-methyl butyrate</td>
<td>175</td>
<td>59</td>
<td>0.9983</td>
<td>1.492</td>
<td>+2.80</td>
<td>+5.4</td>
</tr>
</tbody>
</table>

* Prepared by direct esterification, rest are prepared from (+) 1-methyl butyryl chloride.

\[
[\text{M}]_{D}^{32} = \frac{[\alpha]_{D}^{32} \times M}{100}
\]
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of the Ketone</th>
<th>b.p. °C/15 mm</th>
<th>Density d₂⁰²</th>
<th>Refractive Index n₂²</th>
<th>Specific Rotation [α]D³₂</th>
<th>Molecular Rotation [M]D³₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(+) Phenyl 1-methyl butyrate</td>
<td>105</td>
<td>71</td>
<td>0.9785</td>
<td>1.487</td>
<td>+ 3.6</td>
</tr>
<tr>
<td>2.</td>
<td>(+) o-Cresyl 1-methyl butyrate</td>
<td>110</td>
<td>70</td>
<td>0.9718</td>
<td>1.492</td>
<td>+ 2.6</td>
</tr>
<tr>
<td>3.</td>
<td>(+) m-Cresyl 1-methyl butyrate</td>
<td>115</td>
<td>68</td>
<td>0.9650</td>
<td>1.489</td>
<td>+ 2.9</td>
</tr>
<tr>
<td>4.</td>
<td>(+) p-Cresyl 1-methyl butyrate</td>
<td>125</td>
<td>72</td>
<td>0.9682</td>
<td>1.490</td>
<td>+ 3.2</td>
</tr>
<tr>
<td>5.</td>
<td>(+) o-Chloro phenyl 1-methyl butyrate</td>
<td>130</td>
<td>50</td>
<td>1.0964</td>
<td>1.504</td>
<td>+ 2.7</td>
</tr>
<tr>
<td>6.</td>
<td>(+) m-Chloro phenyl 1-methyl butyrate</td>
<td>120</td>
<td>48</td>
<td>1.0952</td>
<td>1.501</td>
<td>+ 3.3</td>
</tr>
<tr>
<td>7.</td>
<td>(+) p-Chloro phenyl 1-methyl butyrate</td>
<td>140</td>
<td>61</td>
<td>1.0903</td>
<td>1.502</td>
<td>+ 3.8</td>
</tr>
<tr>
<td>8.</td>
<td>(+) o-Nitro phenyl 1-methyl butyrate</td>
<td>175</td>
<td>40</td>
<td>1.1262</td>
<td>1.510</td>
<td>+ 2.3</td>
</tr>
<tr>
<td>9.</td>
<td>(+) m-Nitro phenyl 1-methyl butyrate</td>
<td>160</td>
<td>48</td>
<td>1.1266</td>
<td>1.513</td>
<td>+ 2.5</td>
</tr>
<tr>
<td>10.</td>
<td>(+) p-Nitro phenyl 1-methyl butyrate</td>
<td>180</td>
<td>51</td>
<td>1.1252</td>
<td>1.502</td>
<td>+ 2.9</td>
</tr>
<tr>
<td>11.</td>
<td>(+) 2:4 dichloro phenyl 1-methyl butyrate</td>
<td>130</td>
<td>41</td>
<td>1.2160</td>
<td>1.522</td>
<td>+ 2.1</td>
</tr>
</tbody>
</table>

\[
\frac{[\alpha]D^{32}}{100} = \frac{[\alpha]D^{32} \times M}{M}
\]
ACYLATION OF ALCOHOLS

(A) Acylation of Condensation of Alcohols with (+) 1-Methyl Butyric Acid
\[
(+) \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COOH} + R - \text{OH} \xrightarrow{H_2SO_4} \text{CH}_3\quad (+) \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COOR}
\]

(1) R = -Methyl
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COOC}_3 \quad \text{CH}_3
\]
(+ Methyl 1-methyl butyrate

(2) R = -Ethyl
\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COOC}_3 \cdot\text{CH}_3 \quad \text{CH}_3
\]
(+ Ethyl 1-methyl butyrate

(B) Acylation by Condensation of Alcohols with (+) 1-Methyl Butyryl Chloride
\[
(+ \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COCl} + R - \text{OH} \xrightarrow{C_5H_5N} \text{CH}_3\quad (+) \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}\cdot\text{COOR}
\]
(1) $R = \text{n-Propyl}$
\[
\text{CH}_3\cdot\text{CH}_2\cdot*\cdot\text{CH}\cdot\text{COOCH}_2\cdot\text{CH}_2\cdot\text{CH}_3
\]
\[
\text{CH}_3
\]

(+) n-Propyl 1-methyl butyrate

(2) $R = \text{n-Butyl}$
\[
\text{CH}_3\cdot\text{CH}_2\cdot*\cdot\text{CH}\cdot\text{COOCH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3
\]
\[
\text{CH}_3
\]

(+) n-Butyl 1-methyl butyrate

(3) $R = \text{n-Hexyl}$
\[
\text{CH}_3\cdot\text{CH}_2\cdot*\cdot\text{CH}\cdot\text{COOCH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3
\]
\[
\text{CH}_3
\]

(+) n-Hexyl 1-methyl butyrate

(4) $R = \text{n-Octyl}$
\[
\text{CH}_3\cdot\text{CH}_2\cdot*\cdot\text{CH}\cdot\text{COOCH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3
\]
\[
\text{CH}_3
\]

(+) n-Octyl 1-methyl butyrate

(5) $R = \text{iso-Propyl}$
\[
\text{CH}_3\cdot\text{CH}_2\cdot*\cdot\text{CH}\cdot\text{COOCH}_2\cdot\text{CH}_3
\]
\[
\text{CH}_3\cdot\text{CH}_3\cdot\text{CH}_3
\]

(+) iso-Propyl 1-methyl butyrate
(6) \( R = \text{iso-Butyl} \)

\[
\begin{align*}
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH} \cdot \text{COOCH} \cdot \text{CH} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

(+ ) iso-Butyl 1-methyl butyrate

(7) \( R = \text{2-Methyl butyl} \)

\[
\begin{align*}
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH} \cdot \text{COOCH}_2 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

(+ ) 2-Methyl butyl 1-methyl butyrate

(8) \( R = \text{sec-Butyl} \)

\[
\begin{align*}
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH} \cdot \text{COOCH} \cdot \text{CH}_2 \cdot \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

(+ ) sec-Butyl 1-methyl butyrate

(9) \( R = \text{tert-Butyl} \)

\[
\begin{align*}
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH} \cdot \text{COOCH}_2 \cdot \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

(+ ) tert-Butyl 1-methyl butyrate

(10) \( R = \text{Benzyl} \)

\[
\begin{align*}
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH} \cdot \text{COOCH}_2 \\
\text{CH}_3
\end{align*}
\]

(+ ) Benzyl 1-Methyl butyrate
ACYLATION OF PHENOLS

(C) Acylation of Condensation of Phenols with (+) 1-Methyl Butyryl Chloride

\[ (+) \text{CH}_3\text{CH}_2\text{CH}^*\text{COCl} + \text{ArOH} \xrightarrow{\text{CH}_3\text{C}_5\text{H}_5\text{N}} \]

\[ (+) \text{CH}_3\text{CH}_2\text{CH}^*\text{COOAr} \]

(1) \( \text{Ar} = -\text{C}_6\text{H}_5 \)

\[ \text{CH}_3\text{CH}_2\text{CH}^*\text{COO} \]

(+) Phenyl 1-methyl butyrate

(2) \( \text{Ar} = -\text{C}_6\text{H}_4\text{CH}_3 \) (o)

\[ \text{H}_3\text{C} \]

\[ \text{CH}_3\text{CH}_2\text{CH}^*\text{COO} \]

(+) o-Cresyl 1-methyl butyrate

(3) \( \text{Ar} = -\text{C}_6\text{H}_4\text{CH}_3 \) (m)

\[ \text{CH}_3 \]

\[ \text{CH}_3\text{CH}_2\text{CH}^*\text{COO} \]

(+) m-Cresyl 1-methyl butyrate
(4) $Ar = \text{-C}_6\text{H}_4\text{CH}_3$ (p)

$$\text{CH}_3\text{-CH}2\text{-CH}_2\text{-COO} - \text{C}_6\text{H}_4\text{-CH}_3$$

(+) p-Cresyl 1-methyl butyrate

(5) $Ar = \text{-C}_6\text{H}_4\text{Cl}$ (o)

$$\text{CH}_3\text{-CH}2\text{-CH}_2\text{-COO} - \text{C}_6\text{H}_4\text{Cl}$$

(+) o-Chloro phenyl 1-methyl butyrate

(6) $Ar = \text{-C}_6\text{H}_4\text{Cl}$ (m)

$$\text{CH}_3\text{-CH}2\text{-CH}_2\text{-COO} - \text{C}_6\text{H}_4\text{Cl}$$

(+) m-Chloro phenyl 1-methyl butyrate

(7) $Ar = \text{-C}_6\text{H}_4\text{Cl}$ (p)

$$\text{CH}_3\text{-CH}2\text{-CH}_2\text{-COO} - \text{C}_6\text{H}_4\text{Cl}$$

(+) p-Chloro phenyl 1-methyl butyrate
(8) $\text{Ar} = -\text{C}_6\text{H}_4\text{NO}_2$ (o)

(+) CH$_3$.CH$_2$.CH.COO

$\begin{array}{c}
\text{CH}_3 \\
\text{\_}\text{\_} \\
\text{\_}\text{\_} \\
\text{\_}\text{\_}
\end{array}$

(+) o-Nitro phenyl 1-methyl butyrate

(9) $\text{Ar} = -\text{C}_6\text{H}_4\text{NO}_2$ (m)

(+) CH$_3$.CH$_2$.CH.COO

$\begin{array}{c}
\text{CH}_3 \\
\text{\_}\text{\_} \\
\text{\_}\text{\_} \\
\text{\_}\text{\_}
\end{array}$

(+) m-Nitro phenyl 1-methyl butyrate

(10) $\text{Ar} = -\text{C}_6\text{H}_4\text{NO}_2$ (p)

(+) CH$_3$.CH$_2$.CH.COO

$\begin{array}{c}
\text{CH}_3 \\
\text{\_}\text{\_} \\
\text{\_}\text{\_} \\
\text{\_}\text{\_}
\end{array}$

(+) p-Nitro phenyl 1-methyl butyrate

(11) $\text{Ar} = -\text{C}_6\text{H}_3\text{Cl}_2$ (2:4)

(+) CH$_3$.CH$_2$.CH.COO

$\begin{array}{c}
\text{Cl} \\
\text{\_}\text{\_} \\
\text{\_}\text{\_} \\
\text{\_}\text{\_}
\end{array}$

(+ 2:4 Dichloro phenyl 1-methyl butyrate
EXPERIMENTAL
EXPERIMENTAL

PREPARATION OF OPTICALLY ACTIVE ESTERS
BY ACYLATION OF ALCOHOLS AND PHENOLS

Acylation by Condensation of Alcohol with
(+ 1-Methyl Butyric Acid

Preparation of (+) Methyl 1-Methyl Butyrate

A mixture of (+) 1-methyl butyric acid (20.4 g.,
0.2 mole), methanol (40 cc.) and concentrated sulphuric
acid (4 cc.) were refluxed on water bath for 6 to 8 hours.
The excess of methanol was distilled off and the residual
product was extracted with ether. The ethereal layer was
washed with sodium carbonate solution (50 cc., 10 %) and
finally with water, and dried (magnesium sulphate). After
removal of ether the residue on distillation gave
(+ methyl 1-methyl butyrate, b.p. 115°, yield 70 %,
$\text{d}_4^{32} 0.8632$, $n^{32} 1.404$, $[\alpha]_D^{32} + 3.9$ (1,1).

Found : C, 62.13; H, 10.12 %
$C_6H_{12}O_2$ required : C, 62.05; H, 10.35 %

Preparation of (+) Ethyl 1-Methyl Butyrate

(+ 1-Methyl butyric acid (20.4 g., 0.2 mole) was
esterified by absolute ethanol (50 cc.) in presence of
concentrated sulphuric acid (3 cc.) as described in the
previous process. The residue, on distillation gave
(+)-ethyl 1-methyl butyrate, b.p. 130°, yield 60 %,
$\delta^2_4$ 0.8594, $n^2_3$ 1.399, $[\alpha]_D^2 + 3.8$ (l,l).

Found : C, 64.38; H, 10.56 %
C$_7$H$_{14}$O$_2$ required : C, 64.63; H, 10.76 %

Acylation by Condensation of Alcohols with
(+)-1-Methyl Butyryl Chloride

Preparation of (+)-n-Propyl 1-Methyl Butyrate

Into a 500 cc. round bottomed flask were placed
n-propanol (20 g.) and pyridine (100 cc.). To this
(+)-1-methyl butyryl chloride (18 g., 0.15 mole) was
added at room temperature during 15 to 29 minutes. The
contents were refluxed for 1¾ hour. The contents were
cooled, treated with hydrochloric acid (3 N) to remove
excess of pyridine, and extracted with ether. The ethereal
layer was washed with sodium carbonate solution (100 cc.,
10 %), water and dried (sodium sulphate). After removal
of the ether the residue on distillation gave (+)-n-propyl
1-methyl butyrate, b.p. 145°, yield 63 %, $\delta^2_4$ 0.8542,
$n^2_3$ 1.405, $[\alpha]_D^2 + 3.6$ (l,l).

Found : C, 66.36; H, 11.28 %
C$_8$H$_{16}$O$_2$ required : C, 66.67; H, 11.11 %
Preparation of (+) n-Butyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with n-butanol (11.1 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) n-butyl 1-methyl butyrate, b.p. 100°/15 mm., yield 68%, $d_4^{32} 0.8542$, $n_2^{32} 1.405$, $[\alpha]^D_{2} + 3.4$ (1,1).

Found: C, 68.21; H, 11.22%
$C_9H_{18}O_2$ required: C, 68.34; H, 11.40%

Preparation of (+) n-Hexyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with n-hexanol (21 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) n-hexyl 1-methyl butyrate, b.p. 120°/15 mm., yield 69%, $d_4^{32} 0.8468$, $n_2^{32} 1.413$, $[\alpha]^D_{2} + 2.9$ (1,1).

Found: C, 70.78; H, 11.69%
$C_{11}H_{22}O_2$ required: C, 70.98; H, 11.82%

Preparation of (+) n-Octyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with n-octanol (25 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) n-octyl 1-methyl butyrate, b.p. 170°/15 mm., yield 67%, $d_4^{32} 0.8491$, $n_2^{32} 1.413$, $[\alpha]^D_{2} + 2.6$ (1,1).
Preparation of (+) iso-Propyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with iso-propanol (20 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) iso-propyl 1-methyl butyrate, b.p. 125°, yield 51 %, 4 0.8513, n 32 1.394, [α] D 32 + 3.8 (1,1).

Found : C, 66.31; H, 11.19 %
C 13H 26O 2 required : C, 66.67; H, 11.11 %

Preparation of (+) iso-Butyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with iso-butanol (11.1 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) iso-butyl 1-methyl butyrate, b.p. 80°/15 mm., yield 60 %, 4 0.8502, n 32 1.403, [α] D 32 + 3.5 (1,1).

Found : C, 68.03; H, 11.42 %
C 9H 18O 2 required : C, 68.34; H, 11.40 %
Preparation of (+) 2-Methyl Butyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with (-)-2-methyl butan-1-ol $\left[\alpha\right]_D^{32} 4.7$ (1,1) (17 g.) in presence of pyridine (80 cc.). The reaction was completed to get (+) 2-methyl butyl 1-methyl butyrate, b.p. 85°/15 mm., yield 47 %, $d_4^{32} 0.8468$, $n_2^{32} 1.407$, $\left[\alpha\right]_D^{32} + 5.7$ (1,1).

Found: C, 69.36; H, 11.75 %
C$_{10}$H$_{20}$O$_2$ required: C, 69.77; H, 11.62 %

Preparation of (+) sec-Butyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with sec-butanol (11.1 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) sec-butyl 1-methyl butyrate, b.p. 110°/15 mm., yield 50 %, $d_4^{32} 0.8493$, $n_2^{32} 1.478$, $\left[\alpha\right]_D^{32} + 3.6$ (1,1).

Found: C, 68.48; H, 11.51 %
C$_9$H$_{18}$O$_2$ required: C, 68.34; H, 11.40 %

Preparation of (+) tert-Butyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with tert-butanol (11.1 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) tert-butyl 1-methyl butyrate, b.p. 105°/15 mm., yield 40 %, $d_4^{32} 0.8550$, $n_2^{32} 1.403$, $\left[\alpha\right]_D^{32} + 3.3$ (1,1).
Preparation of (+) Benzyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (18 g., 0.15 mole) was condensed with benzyl alcohol (26 g.) in presence of pyridine (80 cc.). The reaction was completed as earlier to get (+) benzyl 1-methyl butyrate, b.p. 175°/15 mm., yield 59%, \( d_4^{32} 0.9983 \), \( n_2^{32} 1.492 \), \([\alpha]_D^{32} + 2.8 \) (1,1).

Found : C, 76.22; H, 7.42 %
C_{12}H_{16}O_{2} required : C, 76.47; H, 7.84 %
Acylation by Condensation of Phenols with (+) 1-Methyl Butyryl Chloride

Preparation of (+) Phenyl 1-Methyl Butyrate

Into a 500 cc. round-bottomed flask were placed (+) 1-methyl butyryl chloride (24.1 g., 0.2 mole) and pyridine (100 cc.). To this phenol (18.2 g.) was slowly added during 15 to 20 minutes at room temperature. The reaction mixture was refluxed for 2 hours. The contents were cooled and treated with hydrochloric acid (3 N) to remove excess of pyridine and extracted with ether. The ethereal layer was successively washed with sodium hydroxide (50 cc., 2 N), water and dried (sodium sulphate). The ether was removed by distillation and the residue on distillation under reduced pressure gave (+) phenyl 1-methyl butyrate, b.p. 105°/15 mm., yield 71%, $d_4^2$ 0.9785, $n_32^2$ 1.487, $[\alpha]_D^{32} + 3.6$ (1,1).

Found: C, 78.31; H, 8.12%

$\text{C}_{11}\text{H}_{14}\text{O}_2$ required: C, 78.57; H, 8.33%

Preparation of (+) o-Cresyl 1-Methyl Butyrate

(+1 1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with o-cresol (21.6 g.) in presence of pyridine (100 cc.). The reaction was completed as before to get (+) o-cresyl 1-methyl butyrate, b.p. 110°/15 mm., yield 70%, $d_4^2$ 0.9718, $n_32^2$ 1.492, $[\alpha]_D^{32} + 2.6$ (1,1).
Preparation of (+) m-Cresyl 1-Methyl Butyrate

(+1 Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with m-cresol (21.6 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) m-cresyl 1-methyl butyrate, b.p. 116°/15 mm., yield 68%, \(d_4^{32} 0.9718\), \(n_3^{32} 1.492\), \([\alpha]_D^{32} + 2.9\) (1,1).

Preparation of (+) p-Cresyl 1-Methyl Butyrate

(+1 Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with p-cresol (21.6 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) p-cresyl 1-methyl butyrate, b.p. 125°/15 mm., yield 72%, \(d_4^{32} 0.9682\), \(n_3^{32} 1.490\), \([\alpha]_D^{32} + 3.2\) (1,1).

Preparation of (+) o-Chloro Phenyl 1-Methyl Butyrate

(+1 Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with o-chloro phenol (26 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get o-chloro phenyl 1-methyl butyrate, b.p. 130°/15 mm., yield 50%, \(d_4^{32} 1.096\), \(n_3^{32} 1.504\), \([\alpha]_D^{32} + 2.7\) (1,1).
Preparation of (+) m-Chloro Phenyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with m-chloro phenol (26 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) m-chloro phenyl 1-methyl butyrate, b.p. 120°/15 mm., yield 48%, $d_4^{32} 1.0952$, $n^2 1.501$, $[\alpha]_D^{22} + 3.3$ (l,l).

Found : Cl, 16.60 %
$C_{11}H_{13}O_2Cl$ required : Cl, 16.74 %

Preparation of (+) p-Chloro Phenyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with p-chloro phenol (26 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) p-chloro phenyl 1-methyl butyrate, b.p. 140°/15 mm., yield 61%, $d_4^{32} 1.0903$, $n^2 1.502$, $[\alpha]_D^{22} + 3.8$ (l,l).

Found : Cl, 16.32 %
$C_{11}H_{13}O_2Cl$ required : Cl, 16.74 %.
Preparation of (+) o-Nitro Phenyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with o-nitro phenol (28 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) o-nitro phenyl 1-methyl butyrate, b.p. 175°/15 mm., yield 40%, d₄ 1.126, n₃₂ 1.510, [α]D₃₂ + 2.3 (l,l).

Found: N, 6.41%
C₁₁H₁₃O₄N required: N, 6.28%

Preparation of (+) m-Nitro Phenyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with m-nitro phenol (28 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) m-nitro phenyl 1-methyl butyrate, b.p. 160°/15 mm., yield 48%, d₄ 1.1266, n₃₂ 1.513, [α]D₃₂ + 2.5 (l,l).

Found: N, 6.46%
C₁₁H₁₃O₄N required: N, 6.28%

Preparation of (+) p-Nitro Phenyl 1-Methyl Butyrate

(+1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with p-nitro phenol (28 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) p-nitro phenyl 1-methyl butyrate, b.p. 180°/15 mm.,
yields 51%, $d_4^{32} 1.1252$, $n_32^{32} 1.502$, $[\alpha]_D^{32} + 2.9$ (1,1).

Found: N, 6.41%

C$_{11}$H$_{13}$O$_4$N required: N, 6.28%

Preparation of (+) 2:4 Dichloro Phenyl 1-Methyl Butyrate

(+)-1-Methyl butyryl chloride (24.1 g., 0.2 mole) was condensed with 2:4 dichloro phenol (33 g.) in presence of pyridine (100 cc.). The reaction was completed as earlier to get (+) 2:4 dichloro phenyl 1-methyl butyrate, b.p. 137°/15 mm., yield 41%, $d_4^{32} 1.2162$, $n_32^{32} 1.522$, $[\alpha]_D^{32} + 2.1$ (1,1).

Found: Cl, 28.41%

C$_{11}$H$_{12}$O$_2$Cl$_2$ required: Cl, 28.75%