--- SECTION VI ---

INTRODUCTION & DISCUSSION
TO
THE PREPARATION
OF
OPTICALLY ACTIVE UNSATURATED ESTERS
THROUGH CLAISEN CONDENSATION
Preparations of Optically Active Unsaturated Esters

Through Claisen Condensation:

The Claisen condensation usually refers to the condensations in the presence of the basic catalysts between esters and esters or ketones and esters or to the condensation of arylaldehydes and acylphenones with esters to form $\beta$-keto esters or $\beta$-diketones or the unsaturated esters respectively.

The Claisen condensation between the esters consists in the reaction, in the presence of certain bases, of an ester having hydrogen on the $\omega$-carbon atom with a second molecule of the same ester or with another ester (which may or may not have hydrogen on the $\omega$-carbon atom) to form a $\beta$-keto ester. The base capable of effecting such reactions includes sodium alkoxides, triphenyl methyl sodium, sodium amide and certain Grignard reagents such as mesitylmagnesium bromide and isopropyl magnesium bromide; also, metallic sodium effects certain condensations, the sodium alkoxide which is formed in the reaction mixture probably serving as the active condensing agent.\textsuperscript{115}

The classical example of this reaction is the preparation of acetoacetic ester condensation. The ester is obtained from ethyl acetate by means of sodium ethoxide, for
which the following mechanism of the reaction may be written

\[
\text{CH}_3\text{C}O\text{OC}_2\text{H}_5 + \text{CH}_3\text{C}O\text{OC}_2\text{H}_5 + \text{NaOC}_2\text{H}_5 \rightarrow \\
\text{CH}_3\text{C}(\text{ONa})\text{=CHCOOC}_2\text{H}_5 + 2\text{C}_2\text{H}_5\text{OH}.
\]

The reaction probably involves an ionic mechanism, the first step of which is an acid-base exchange; in the presence of the ethoxide ion the hydrogen on the \(\alpha\)-carbon atom is ionized as a proton to form the ester anion (enolate anion) which is probably a resonance hybrid of the two structures: \(-\text{CH}_2-\text{C}=\text{O}(\text{C}_2\text{H}_5)\) and \(\text{CH}_2=\text{C}-\text{O}^-(\text{OC}_2\text{H}_5)\).

(1) \[
\text{CH}_3\text{C}O\text{OC}_2\text{H}_5 + \text{CH}_2\text{C}O\text{OC}_2\text{H}_5 \rightarrow (\text{CH}_2\text{COOC}_2\text{H}_5)^- + \text{C}_2\text{H}_5\text{OH}
\]

The second step involves the condensation of the ester anion with the carbonyl group of a molecule of unchanged ester, presumably forming an intermediate anion (with the charge on the oxygen) which, on release of the ethoxide ion, forms acetoacetic ester.

(2) \[
\text{CH}_3\text{C}=\text{O}^-(\text{OC}_2\text{H}_5) + (\text{CH}_2\text{COOC}_2\text{H}_5)^- \rightarrow \\
\text{CH}_3\text{C}=\text{CH}_2\text{C}O\text{OC}_2\text{H}_5 + \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{OC}_2\text{H}_5
\]

Acetoacetic ester is then converted into its anion by the action of the ethoxide ion; this third step involves an acid-base reaction in which a hydrogen on the \(\alpha\)-carbon atom of
The Claisen condensation also consists in the condensation between the aryl aldehydes and the esters of the type \( R'CHgCOOR'' \) — having hydrogen of the \( \alpha \)-carbon atom — in the presence of metallic sodium or sodium ethylate to form unsaturated esters of the type \( RCH=C(R')COOR'' \).

The mechanism of the reaction parallels that of acetoacetonic ester condensation. An addition compound of the ester and sodium ethylate is first formed which is transformed into an unsaturated sodio ether; an addition compound between this ether and the aldehyde forms next, and through a molecular rearrangement and cleavage of sodium hydroxide, changes to the unsaturated ester.

\[
\begin{align*}
\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 & \overset{\text{NaOC}_2\text{H}_5}{\longrightarrow} \text{CH}_3\text{O(ONa)(OC}_2\text{H}_5)_2 \longrightarrow \\
\text{CH}_2=\text{C(ONa)OC}_2\text{H}_5 & \overset{\text{RCHO}}{\longrightarrow} \text{RCHCH}_2\text{C(0)(ONa)OC}_2\text{H}_5 \longrightarrow \\
\text{RCH=CHC(OH)(ONa)OC}_2\text{H}_5 & \longrightarrow \text{RCH=CHCOOC}_2\text{H}_5 + \text{NaOH}
\end{align*}
\]

Claisen's reaction often proceeds quite smoothly, giving unsaturated ester in fairly good yield and the final product can be readily obtained in a pure form.

The usual procedure is to dissolve the aldehyde in
the ester and a little alcohol and metallic sodium cut in small pieces. The mixture is cooled in the neighbourhood of 0° and agitated during the reaction. If the sodium sand is used the aldehyde is added on it dropwise at 0° C.

Certain aromatic and heterocyclic unsaturated esters are best prepared by condensation of ethyl acetate and aromatic aldehydes by sodium sand. Benzaldehyde in this reaction gives ethyl cinnamate, p-methyl benzaldehyde, furfural, furyl acrolein and 2-thiophene carboxy aldehyde have been condensed in a similar way.

In Claisen condensation not only sodium or sodium ethoxide has been used as the condensing agent, but also amide of alkali metals can be used and they are excellent catalysts for this reaction, but the difficulty is that they form some amide as by-products.

The Claisen reaction proceeds readily with succinic esters. Ketones as well as aldehydes may be condensed with these esters. One or both methylene groups may be made to react. The compounds obtained by the condensation of two aldehyde molecules \( \text{HOCOC}(-\text{CHR})\text{C}(-\text{CHR})\text{COOH} \) are known as fulginic acids.

The condensation of aldehydes and ketones with \( \alpha \)-chloro esters in the presence of alkaline substances results in the formation of glycid carboxylic acids.
Sodium amide is the best catalyst for this Claisen condensation. Very little work has been carried out for the preparation of optically active unsaturated esters through Claisen condensation.

In the present investigation the optically active unsaturated esters through the Claisen reaction have been prepared and the study of their optical activity has been undertaken.
DISCUSSION

When the Claisen condensation is carried out between the aldehydes and an ester of the type $R'\text{CHO}$ — having hydrogen on the $\alpha$-carbon atom — in the presence of a basic catalyst such as sodium sand or metallic sodium and a trace of alcohol or sodium ethoxide, it forms unsaturated esters of the type $R'\text{CH=C(R')COOR''}$.

Here the condensation was carried out between the aryl aldehydes ($R'\text{CHO}$) — simple or substituted — and the $(+)$2-methyl butyl acetate ($\text{CH}_3\cdot\text{COO.CH}_2\cdot\text{CH(CH}_3)\cdot\text{CH}_2\cdot\text{CH}_3$) in the presence of sodium ethoxide to form the optically active unsaturated ester of the type

$$R\cdot\text{CH=CH.CO.}\text{CH}_2\cdot\text{CH(CH}_3)\cdot\text{CH}_2\cdot\text{CH}_3 .$$

This condensation was tried in the presence of sodium sand.

By the action of sodium sand on 2-methyl butyl acetate immediate reaction is set up and a dark yellow viscous mass is formed. The product may possibly be acyloin or diketone or high boiling products $^{127-30}$.

The condensation was also tried with the metallic sodium and a trace of alcohol, when it took a very long time to dissolve the sodium and practically the condensation
could not be effected.

However, when the condensation was carried out by sodium ethoxide, the yield of the optically active unsaturated esters was comparatively better and the esters could be readily obtained in a pure form.

The optically active unsaturated esters of the type

$$\text{R.CH=CH.CO0.CH}_2\cdot\text{CH(CH}_3\cdot\text{CH}_2\cdot\text{CH}_3$$

are obtained by the action of (+)-2-methyl butyl acetate and the different aryl aldehydes. The aldehydes used are: benzaldehyde, o-chlorobenzaldehyde, p-chlorobenzaldehyde, p-tolyl aldehyde, anisaldehyde (p-methoxy benzaldehyde) and cinnamic aldehyde and the unsaturated esters are:

- 2-methyl butyl cinnamate, $\alpha_D^{35} + 2.9840$ (1, 0.5);
- 2-methyl butyl o-chloro cinnamate, $\alpha_D^{35} + 1.1750$ (1, 0.5);
- 2-methyl butyl p-chloro cinnamate, $\alpha_D^{35} + 1.1420$ (1, 0.5);
- 2-methyl butyl p-methyl cinnamate, $\alpha_D^{35} + 1.1768$ (1, 0.5);
- 2-methyl butyl p-methoxy cinnamate, $\alpha_D^{35} + 2.760$ (1, 0.5); and
- 2-methyl butyl cinnamyl cinnamate, $\alpha_D^{35} + 0.2091$ (1, 0.5) respectively.

The condensation was tried with furfural but it could not be effected. When the condensation was tried with p-nitrobenzaldehyde, the condensation product was dark coloured viscous liquid and difficult to distil.
(1) RCHO = Benzaldehyde,
(2) $RCHO = \text{o-Chloro benaldehyde,}$

\[
\begin{array}{c}
\text{CH}=\text{CH}.\text{COO}.\text{CH}_2-^*\text{CH} \\
\text{CH}_3
\end{array}
\]

(+)-2-Methyl butyl o-chloro cinnamate

(3) $RCHO = \text{p-Chloro benaldehyde,}$

\[
\begin{array}{c}
\text{Cl} \\
\text{CH}=\text{CH}.\text{COO}.\text{CH}_2-^*\text{CH} \\
\text{CH}_3
\end{array}
\]

(+)-2-Methyl butyl p-chloro cinnamate

(4) $RCHO = \text{p-Tolylaldehyde,}$

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{CH}=\text{CH}.\text{COO}.\text{CH}_2-^*\text{CH} \\
\text{CH}_3
\end{array}
\]

(+)-2-Methyl butyl p-methyl cinnamate

(5) $RCHO = \text{p-Methoxy benaldehyde,}$

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{CH}=\text{CH}.\text{COO}.\text{CH}_2-^*\text{CH} \\
\text{CH}_3
\end{array}
\]

(+)-2-Methyl butyl p-methoxy cinnamate
(6) $RCHO = \text{Cinnamic aldehyde,}$

$$\text{CH}_2\text{CH}_3$$

$\text{CH=CH.CH=CH.CO}_2\text{CH}_2*$

$\text{CH}_3$

\[\text{2-Methyl butyl cinnamyl cinnamate}\]

\[\text{or}\]

(\(\beta\)-Methyl butyl 5-phenyl 2:4-pentadiene carboxylate)

Detailed data of the unsaturated esters so prepared is given in table on the following page.
<table>
<thead>
<tr>
<th>No.</th>
<th>Unsaturated esters</th>
<th>Yield per cent</th>
<th>B.P. °C</th>
<th>d$_{40}$</th>
<th>n$_{D}$</th>
<th>α$_{35}$ ($l$, 0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2-Methyl butyl cinnamate</td>
<td>28.7</td>
<td>138-40°</td>
<td>0.9019</td>
<td>1.464</td>
<td>+ 2.9840</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>2-Methyl butyl o-chloro cinnamate</td>
<td>14.1</td>
<td>260-70°</td>
<td>1.3219</td>
<td>1.538</td>
<td>+ 1.1750</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>2-Methyl butyl p-chloro cinnamate</td>
<td>22.2</td>
<td>265/</td>
<td>1.3237</td>
<td>1.546</td>
<td>+ 1.1420</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>2-Methyl butyl p-methyl cinnamate</td>
<td>32.6</td>
<td>230/</td>
<td>1.1827</td>
<td>1.541</td>
<td>+ 1.1768</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>2-Methyl butyl p-methoxy cinnamate</td>
<td>28.1</td>
<td>275/</td>
<td>1.2553</td>
<td>1.566</td>
<td>+ 2.760</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>2-Methyl butyl cinnamyl cinnamate</td>
<td>13.6</td>
<td>243/</td>
<td>1.1473</td>
<td>1.569</td>
<td>+ 0.2091</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
These unsaturated esters show the unsaturation tests viz., rapid decolourisation of bromine water and also the rapid decolourisation of alkaline potassium permanganate solution (Baeyer's test).

The ester is characterised by the fact that when (+)-2-methyl butyl cinnamate on hydrolysis by alkali and acidification it gave the cinnamic acid.

Reduction of these optically unsaturated esters, however, was not possible.
Preparation of Optically Active Unsaturated Esters:

Unsaturated Ester from Benzaldehyde:

The flask fitted with a mechanical stirrer, containing the mixture of freshly distilled benzaldehyde (35.0 g. : 0.33 mole) and (+)-2-methyl butyl acetate (120 c.c., b.p. 139°, $\alpha_D^{35} + 2.078$; $d_4^{35} 1.009$; $n_34^{35} 1.396$) was cooled in a freezing mixture. To this stirred and cooled mixture was gradually added a cooled solution of sodium ethoxide—prepared from sodium (7.82 g. : 0.34 mole) and absolute alcohol (120 c.c.)—during 2 hours at 0° C.

After the addition was complete, the viscous mixture was stirred for one hour in ice bath, then two more hours at room temperature and then decomposed by glacial acetic acid and ice cold water. The layer of ester which separated was washed, dried (sodium sulphate) and distilled in vacuum and after the removal of unreacted (+)-2-methyl butyl acetate and benzaldehyde, the (+)-2-methyl butyl cinnamate collected at 138-40°/10 mm. Yield: 28.7 per cent.

$\alpha_D^{35} 0.8019$; $n_34^{35} 1.1464$; $\alpha_D^{35} + 2.9840$.

Found: C, 76.61; H, 7.95 per cent.

$C_{14}H_{18}O_2$ requires: C, 77.05; H, 8.25 per cent.
Preparation of Cinnamic acid from (+)-2-Methyl Butyl Cinnamate:

In a flask (fitted with a reflux condenser, a dropping funnel and a stirrer) containing a hot aqueous alkali solution (potassium hydroxide 50%: 20 c.c.) was added dropwise, the (+)-2-methyl butyl cinnamate (10.0 g.). The mixture was boiled under reflux for four to five hours. It was then extracted with ether to remove the unchanged ester and remove (+)-2-methyl butane-1-ol. The aqueous portion was acidified with sulphuric acid (1:1). The crude cinnamic acid thus obtained was crystallised from water, m.p. 132.4°; no depression in mixed melting point with the pure specimen of authentic cinnamic acid.
Unsaturated Ester from o-Chlorobenzaldehyde:

The mixture of o-chlorobenzaldehyde (92.7 g.: 0.66 mole) and (+)-2-methyl butyl acetate (240 g.) was cooled in a freezing bath and stirred. To this mixture, was added a cooled solution of sodium ethoxide (sodium 15.64 g.: 0.68 mole in absolute alcohol 240 c.c.) at 0° C. After the addition was complete, the viscous mixture was stirred in ice bath for one hour and then at room temperature for two more hours. The contents were decomposed by glacial acetic acid and ice water. The layer of ester thus separated was washed, dried (sodium sulphate) and distilled in vacuum and after the removal of unreacted (+)-2-methyl butyl acetate and o-chlorobenzaldehyde, the (+)-2-methyl butyl o-chlorocinnamate collected at 260-70°/10 mm. Yield: 14.1 per cent.

\[ d_4^{35} = 1.3219; \quad n_34^{24} = 1.538; \quad \alpha_c^{35} + 1.175. \]

Found: Cl, 13.57 per cent.

\[ C_{14}H_{17}OCl \] requires: Cl, 14.06 per cent.

Unsaturated Ester from p-Chlorobenzaldehyde:

A cooled solution of sodium ethoxide (sodium 7.82 g.: 0.34 mole in absolute alcohol 120 c.c.) was added to a stirred mixture of p-chlorobenzaldehyde (46.4 g.: 0.33 mole) and (+)-2-methyl butyl acetate (220 g.) during 2 hours at 0° C. After the addition was complete, the mixture.
was stirred for one hour in ice bath and then two more hours at room temperature. Then the contents were decomposed by glacial acetic acid and ice water. The layer of the ester was separated, washed, dried (sodium sulphate) and distilled in vacuum and after removal of the unreacted products, the (+)-2-methyl butyl p-chloro cinnamate was collected at 265°/10 mm. Yield: 22.2 per cent.

$$d_4^{35} = 1.3237; \quad n^\text{D} = 1.546; \quad \alpha_D^{35} = 1.1420.$$  
Found: Cl, 13.81 per cent.

$C_{14}H_{17}O_2Cl$ requires: Cl, 14.06 per cent.

**Unsaturated Ester from p-tolylaldehyde:**

A cooled solution of sodium ethoxide (sodium 7.82 g.; 0.34 mole in absolute alcohol 120 c.c.) was added to a stirred mixture of p-tolylaldehyde (40.0 g.; 0.33 mole) and (+) 2-methyl butyl acetate (220 g.) at 0°C during 2 hours.

The (+)-2-methyl butyl p-methyl cinnamate was collected at 230°/10 mm. Yield: 32.6 per cent.

$$d_4^{35} = 1.1827; \quad n^\text{D} = 1.541; \quad \alpha_D^{35} = 1.1768.$$  
Found: C, 77.28; H, 8.32 per cent.

$C_{15}H_{20}O_2$ requires: C, 77.59; H, 8.62 per cent.
Unsaturated Ester from p-Methoxy Benzaldehyde:

The mixture of p-methoxy benzaldehyde (anisaldehyde 44.9 g. : 0.33 mole) and (+)-2-methyl butyl acetate (220 g.) was cooled in a freezing bath and stirred. To this mixture, was added a cooled solution of sodium ethoxide (sodium 7.82 g. : 0.34 mole in absolute alcohol 120 c.c.) at 0° C during 2 hours.

The (+)-2-methyl butyl p-methoxy cinnamate was collected at 275°/10 mm. Yield: 28.1 per cent.

$\delta^3_{4}$ 1.2553; $\eta^3_{4}$ 1.566; $\alpha^3_{D}$ + 2.760.

Found: C, 72.24; H, 7.73 per cent.

$C_{15}H_{20}O_3$ requires: C, 72.57; H, 8.06 per cent.

Unsaturated Ester from Cinnamyl Aldehyde:

A cooled solution of sodium ethoxide (sodium 7.82 g. : 0.34 mole in absolute alcohol 120 c.c.) was added to a stirred mixture of cinnamic aldehyde (80.5 g. : 0.33 mole) and (+)-2-methyl butyl acetate (220 g.) at 0° C during 2 hours.

The optically active ester was collected at 243°/10 mm. Yield: 13.6 per cent.

$\delta^3_{4}$ 1.1473; $\eta^3_{4}$ 1.569; $\alpha^3_{D}$ + 0.2091.
Found: C, 78.36; H, 12.87 per cent.

C$_{16}$H$_{20}$O$_2$ requires: C, 78.68; H, 13.11 per cent.