PART IV

ACTION OF METAL ALKYLs ON CHROMANONE AND DERIVATIVES - DISCOVERY OF A NOVEL RING-OPENING REACTION
CHAPTER 4.1

ACTION OF METAL ALKYLS ON CHROMANONE AND DERIVATIVES - DISCOVERY OF A NOVEL RING-OPENING REACTION

Introduction

The benzopyrone and benzopyrene ring systems occur extensively in several natural products and biologically active compounds. Some representative examples are given below:

5-Hydroxy-4',7-dimethoxy flavone

Micromelin

Peucenin

Blancoic acid

R = H, Precocene I

R = OMe, Precocene II
The author wanted to construct an iso-oxazole ring fused chroman ring systems in order to study the chemistry of these compounds as well as to evaluate their biological properties. The author envisaged that such a ring-system could be constructed by using the Olofson-Barber reaction\(^1\) which is outlined below:

\[
\begin{align*}
\text{NOH} & \quad \text{Bu}^+\text{Li (2 moles)} \\
& \quad \text{THF, 0°} \\
& \quad \text{DMF} \\
\end{align*}
\]

The expected product from 4-chromanone\(^2\) (I) would be (II). Work-up of the reaction failed to give any of the desired iso-oxazole but gave a white solid, mp 88-90° as the major product. The characterisation of this product, obtained by a novel-ring cleavage, is described in the sequel.

The discovery of this new reaction, led the present investigator to examine the scope of this and related processes. The work done is described in the next sections.
When 4-chromanone oxime \(^3,4\) (III) was treated with an excess of \(\text{n-butyl-lithium}\) in hexane \((15\%)\) in dry tetrahydrofuran at \(0^\circ\), a mixture of products was obtained, from which only the major product (Chart 4.1), a white crystalline solid, mp 88-90\(^\circ\) (yield 15\%) was isolated. The structure of this compound was established to be \(\alpha\)-hydroxyphenyl-\(n\)-hexyl ketoxime (IV) from spectroscopical data. TLC of the reaction mixture on silica gel chromatoplates using benzene-ethylacetate \((4:1)\) as the developing system revealed the presence of the 4-chromanone oxime \((R_f = 0.39)\) and the product \((R_f = 0.53)\), among other polar products of lower \(R_f\) which could not be isolated even by PTLC. The product (IV) was separated from the substrate by column chromatography over silica gel.

**Chart 4.1 : Reaction of 4-chromanone oxime with \(\text{Bu}^n\text{Li}\)**

\[
\begin{align*}
\text{NOH} & \quad \xrightarrow{15\% \text{ Bu}^n\text{Li in hexane}} \quad \text{NOH} \\ 
\text{(III)} & \quad \text{THF, } 0^\circ \quad \text{(IV)}
\end{align*}
\]

**Structure of (IV)**

The structure of (IV) was established from its detailed spectroscopic analysis. The compound analysed for \(\text{C}_{13}\text{H}_{19}\text{NO}_2\) with a molecular-ion peak at \(m/z\) 221. The compound showed the expected IR absorption bands at 3400 (\(-\text{OH}\)) and 1608 (\(\text{C}=\text{N}\)) cm\(^{-1}\) in KBr disc (Fig.4.1, Table 4.1) and at 3560 (phenolic \(-\text{OH}\)), 3270-3330 (\(=\text{N}-\text{OH}\)) and 1602 (\(\text{C}=\text{N}\)) cm\(^{-1}\) (Fig.4.2, Table 4.2) when recorded in chloroform.
FIG. 4.1: IR SPECTRUM OF 2-HYDROXY PHENYL-n-HEXYL KETOXIME (IV) IN KBr DISC

FIG. 4.2: IR SPECTRUM OF 2-HYDROXY PHENYL-n-HEXYL KETOXIME (IV) IN CHLOROFORM
Table 4.1: IR spectrum of o-hydroxyphenyl-n-hexyl ketoxime (IV) in KBr disc

<table>
<thead>
<tr>
<th>Characteristic absorption band</th>
<th></th>
<th>Intensity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \nu ) in cm(^{-1} )</td>
<td>( \lambda ) in ( \mu )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3400</td>
<td>2.94</td>
<td>Strong (br)</td>
<td>-OH</td>
</tr>
<tr>
<td>1625</td>
<td>6.15</td>
<td>Medium</td>
<td>&gt;C=N-</td>
</tr>
<tr>
<td>1580</td>
<td>6.22</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>740</td>
<td>13.51</td>
<td>Strong</td>
<td>Disubstituted phenyl nucleus</td>
</tr>
</tbody>
</table>

Table 4.2: IR spectrum of o-hydroxyphenyl-n-hexyl ketoxime (IV) in chloroform

<table>
<thead>
<tr>
<th>Characteristic absorption band</th>
<th></th>
<th>Intensity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \nu ) in cm(^{-1} )</td>
<td>( \lambda ) in ( \mu )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3560</td>
<td>2.81</td>
<td>Medium</td>
<td>Phenolic -OH</td>
</tr>
<tr>
<td>3270-3330</td>
<td>3.06-3.00</td>
<td>Broad</td>
<td>=N-OH</td>
</tr>
<tr>
<td>1602</td>
<td>6.24</td>
<td>Medium</td>
<td>&gt;C=N-</td>
</tr>
</tbody>
</table>

The absence of two characteristic triplets of \( C_2 \) and \( C_3 \) of the chromanone ring at \( \delta \approx 3.09 \) and \( \delta \approx 4.32 \) in the 200 MHz \(^1\)H-NMR spectrum of (IV) in CDCl\(_3\) (Fig. 4.3, Table 4.3) suggested that ring-opening had occurred. The triplet at \( \delta \approx 0.90 \) (\( J = 7 \) Hz) and the multiplets at \( \delta \approx 1.60, \delta \approx 1.44 \) and \( \delta \approx 1.33 \) were due to one methyl and four methylene protons, indicated the attachment of n-butyl group in the compound.
(IV). The C₂⁻protons were deshielded since they are adjacent to the carbon atom of the oximino group. The NMR spectrum revealed the presence of =N-OH proton at δ 11.32. Of the four protons of the benzene ring, the most downfield double doublet at δ 7.43 (J = 7.9, 1.5 Hz) could be ascribed to the C₆⁻proton as it is deshielded by the oxime function in the ortho- position. The comparatively upfield triplet with fine splitting was attributed to the C₅⁻proton as this was para- to the electron-releasing hydroxyl group.

**Table 4.3 : 200 MHz ¹H-NMR spectrum of o-hydroxyphenyl-n-hexyl ketoxime (IV) in CDCl$_{3}$**

<table>
<thead>
<tr>
<th>Chemical shift δ</th>
<th>τ</th>
<th>No. of protons</th>
<th>Multiplicity (J in Hz)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>9.10</td>
<td>3</td>
<td>t (7)</td>
<td>-CH$_3$</td>
</tr>
<tr>
<td>1.60</td>
<td>8.40</td>
<td>8</td>
<td>m</td>
<td>-C$_3$⁻, C$_4$⁻, C$_5$⁻</td>
</tr>
<tr>
<td>1.33</td>
<td>8.56</td>
<td>8</td>
<td>m</td>
<td>C$_6$⁻, protons</td>
</tr>
<tr>
<td>2.86</td>
<td>7.14</td>
<td>2</td>
<td>t (8.1)</td>
<td>C$_2$⁻, H</td>
</tr>
<tr>
<td>6.91</td>
<td>3.09</td>
<td>1</td>
<td>t with f.s. (~8)</td>
<td>C$_5$⁻, H</td>
</tr>
<tr>
<td>6.97</td>
<td>3.03</td>
<td>1</td>
<td>dd (8.2, 0.9)</td>
<td>C$_3$⁻, H</td>
</tr>
<tr>
<td>7.26</td>
<td>2.74</td>
<td>1</td>
<td>t with f.s. (~8)</td>
<td>C$_4$⁻, H</td>
</tr>
<tr>
<td>7.43</td>
<td>2.57</td>
<td>1</td>
<td>dd (7.9, 1.5)</td>
<td>C$_6$⁻, H</td>
</tr>
<tr>
<td>11.32</td>
<td>-1.32</td>
<td>1</td>
<td>s</td>
<td>=N-OH</td>
</tr>
</tbody>
</table>

The high-resolution mass spectrum of the compound showed M$^+$ at m/z 221 corresponding to C$_{13}$H$_{19}$NO$_2$ (Fig. 4.4). The base peak
FIG. 4.3: RELEVANT PORTIONS OF 200 MHz $^1H$-NMR SPECTRUM OF $\alpha$-HYDROXY-PHENYL-$n$-HEXYL KETOXIME (IV) IN CDCl$_3$
FIG. 4.4: MASS SPECTRUM OF o-HYDROXYPHENYL-n-HEXYL KETOXIME (IV)
appeared at m/z 151 with loss of C_5H_{10} fragment from M^+ by the McLafferty rearrangement. The other characteristic peaks were obtained at m/z 204 (M-OH), 174 (M-NOH), 164 (M-C_4H_9), 148, 146, 134 (M-C_5H_{10}-OH), 133 (M-OH-C_5H_{11}), 120, 119, 107, 105, 91, 69, 65, 55, 43 and 29. The MS fragmentation pattern is depicted in Scheme 4.1.

Scheme 4.1: Mass spectral fragmentation of (IV)
Further evidence in favour of the structure (IV) was accumulated from its 20 MHz $^{13}$C-NMR spectrum in CDCl$_3$ (Fig. 4.5). The spectrum showed signals for thirteen carbons that the compound possessed. The carbon-13 chemical shift values were assigned as follows (Table 4.4). This showed a 6-carbon linear alkyl side-chain. The low-field signal at $\delta$ 163.4 was commensurate with the presence of an oxime carbon.

**Table 4.4: 20 MHz $^{13}$C-NMR spectrum of o-hydroxyphenyl-n-hexyl ketoxime (IV) in CDCl$_3$**

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>Chemical shift ($\delta$)</th>
<th>Multiplicity in SFORD spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117.6</td>
<td>s</td>
</tr>
<tr>
<td>2</td>
<td>157.9</td>
<td>s</td>
</tr>
<tr>
<td>3</td>
<td>117.4</td>
<td>d</td>
</tr>
<tr>
<td>4</td>
<td>127.4</td>
<td>d</td>
</tr>
<tr>
<td>5</td>
<td>119.1</td>
<td>d</td>
</tr>
<tr>
<td>6</td>
<td>130.6</td>
<td>d</td>
</tr>
<tr>
<td>1'</td>
<td>163.4</td>
<td>s</td>
</tr>
<tr>
<td>2'</td>
<td>24.6</td>
<td>t</td>
</tr>
<tr>
<td>3'</td>
<td>26.7</td>
<td>t</td>
</tr>
<tr>
<td>4'</td>
<td>29.4</td>
<td>t</td>
</tr>
<tr>
<td>5'</td>
<td>31.4 (32.40)*</td>
<td>t</td>
</tr>
<tr>
<td>6'</td>
<td>22.4 (22.65)*</td>
<td>t</td>
</tr>
<tr>
<td>7'</td>
<td>13.9 (13.86)*</td>
<td>t</td>
</tr>
</tbody>
</table>

* Chemical shift values calculated on the basis of Lindemann-Adams equation. This equation will not hold for carbons 2', 3', 4'.

The formation of (IV) has been rationalised mechanistically in Chart 4.2. There are *a priori* three possibilities:
FIG. 4-5: 20MHz $^{13}$C-NMR SPECTRUM OF $\omega$-HYDROXYPHENYL-$\pi$-HEXYL KETOXIME(IV) IN CDCl$_3$
(i) Direct SN$^2$ displacement at C$_2$ of the chromanone oxime would furnish the anionic species (IIIb).

(ii) Abstraction of a proton from the 3-position gives an anion (IIIA') which undergoes ring-opening to (IIIC'). Nucleophilic attack of Bu$^+$ on the olefinic double bond of (IIIC') would then generate an anionic species (IIId) corresponding to (IV).

(iii) In the third mechanism, ring-opening occurs via the formation of a cyclic intermediate (IIIC). Nucleophilic attack of Bu$^+$ on this cyclopropane ring would then give the anionic species (IIIB) as before.

Finally, protonation of the anionic species (IIIB) and (IIId) respectively resulted the compound (IV). Further comments on the mechanism have been given later.

Reaction of 4-chromanone with butyl-lithium

The reaction of 4-chromanone$^2$ (I) with an excess of n-butyl-lithium in tetrahydrofuran, followed by the usual workup was found to yield three different products, the separation of which were made by chromatography. The spectral studies of all these three compounds were made in detail leading to their structure elucidation.

Isolation of the products

(a) The major product, $R_f$ 0.68 [silica gel, benzene-ethyl acetate (4:1)] was isolated as a white crystalline solid, mp 55° (18.7%) from the petroleum ether–benzene (1:1) eluate. This compound, after spectral characterisation has been identified as 4-hydroxy-4-n-butyl chroman, C$_{13}$H$_{18}$O$_2$ (V).
Chart 4.2: Probable mechanism for the formation of (IV)

(III) \[\text{NOH} \rightarrow \text{Bu}^+\text{Li}^- \text{THF} \]

(IIIA) \[\text{N} \equiv \text{O} \text{Li}^+ \]

(i) Direct SN2

(IIIB) \[\text{N} \equiv \text{O} \text{Li}^+ \text{Bu}^+\text{Li}^-\]

(IIIA') \[\text{N} \equiv \text{O} \text{Li}^+ \text{Li}^- \]

(IIIC') \[\text{N} \equiv \text{O} \text{Li}^+ \text{Bu}^+\text{Li}^-\]

(IIIC) \[\text{N} \equiv \text{O} \text{Li}^+ \]

(IIID) \[\text{N} \equiv \text{O} \text{Li}^+ \text{CH}_3\]

(IIIb) Protonation

(IV) \[\text{NOH} \rightarrow \text{OH} \text{CH}_3\text{CH}_3\]
Spectral studies

The IR spectrum (Fig 4.6, Table 4.5) of the compound (V) is clearly marked by the absence of a carbonyl function whereas the broad band at 3340 cm$^{-1}$ indicated the presence of a hydroxyl function. This observation indicated the nucleophilic addition at the carbonyl carbon atom.

From the appearance of two triplets at $\delta$ 4.25 ($J = 6.5$ Hz) and at $\delta$ 1.97 ($J = 6.2$ Hz) due to the characteristic $C_2$- and $C_3$-methylene protons of the chroman ring in the 80 MHz $^1$H-NMR spectrum of (V) in CDCl$_3$ (Fig 4.7), it was evident that the heterocyclic ring remains intact. The methyl protons appeared as a triplet at $\delta$ 0.90 ($J = 6.2$ Hz) and the region between $\delta$ 1.60 and $\delta$ 1.10 accommodated all the three methylene protons of $C_1'$, $C_2'$, and $C_3'$. The double doublet at $\delta$ 7.47 ($J_o = 7.9$ Hz, $J_m = 1.85$ Hz) was due to the $C_5$-proton. The $^1$H-NMR data are collected in Table 4.6.
FIG. 1: IR SPECTRUM OF 4-HYDROXY-4-n-BUTYL CHROMAN(V) IN KBr DISC

FIG. 4: IR SPECTRUM OF 4-HYDROXY-4-n-BUTYL CHROMAN(V) IN KBr DISC

FIG. 5: IR SPECTRUM OF β-HYDROXY PHENYL-n-HEXYL KETONE (VI) IN THIN LIQUID FILM
FIG. 4.7: 80MHz $^1$H-NMR SPECTRUM OF 4-HYDROXY-4-n-BUTYL CHROMAN(V) IN CDCl$_3$. 
Table 4.5: IR spectrum of 4-hydroxy-4-n-butyl chroman (V) in KBr disc

<table>
<thead>
<tr>
<th>Characteristic absorption band</th>
<th>Intensity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu$ in cm$^{-1}$</td>
<td>$\lambda$ in $\mu$</td>
<td></td>
</tr>
<tr>
<td>3340</td>
<td>2.99</td>
<td>Broad</td>
</tr>
<tr>
<td>1130</td>
<td>8.85</td>
<td>Medium</td>
</tr>
<tr>
<td>1120</td>
<td>8.93</td>
<td>Medium</td>
</tr>
<tr>
<td>1100</td>
<td>9.09</td>
<td>Medium</td>
</tr>
<tr>
<td>808</td>
<td>12.37</td>
<td>Strong</td>
</tr>
<tr>
<td>750</td>
<td>13.33</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Table 4.6: 80 MHz $^1$H-NMR spectrum of 4-hydroxy-4-n-butyl chroman (V) in CDC$\text{Cl}_3$

<table>
<thead>
<tr>
<th>Chemical shift $\delta$</th>
<th>No. of protons</th>
<th>Multiplicity (J in Hz)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>9.10</td>
<td>3</td>
<td>t (6.2)</td>
</tr>
<tr>
<td>1.60-1.10</td>
<td>8.40-8.90</td>
<td>6</td>
<td>m</td>
</tr>
<tr>
<td>1.97</td>
<td>8.03</td>
<td>2</td>
<td>t (6.2)</td>
</tr>
<tr>
<td>4.25</td>
<td>5.75</td>
<td>2</td>
<td>t (6.5)</td>
</tr>
<tr>
<td>6.85</td>
<td>3.15</td>
<td>1</td>
<td>dd (9.5,2.1)</td>
</tr>
<tr>
<td>6.99-7.19</td>
<td>3.01-2.81</td>
<td>2</td>
<td>complex m</td>
</tr>
<tr>
<td>7.47</td>
<td>2.53</td>
<td>1</td>
<td>dd (7.9,1.85)</td>
</tr>
</tbody>
</table>
Structural characterisation of (V) also owes to its mass spectral fragmentation pattern (Fig. 4.8, Scheme 4.2). The molecular ion peak was observed at m/z 206 corresponding to the molecular formula C_{13}H_{18}O_{2}. The base peak at m/z 149 was generated by the loss of C_4H_9 fragment from M^+. The m/z 149 fragment loses CO to give the peak at m/z 121 which in turn loses a water molecule to give the peak at m/z 103. The other significant peaks were at m/z 131 (M-C_4H_9H_2O), 107 (M-C_4H_9-CH_2CO), 91, 77, 65, 55, 51, 39 and 29.

**Scheme 4.2: Mass spectral fragmentation of (V)**

\[
\begin{align*}
\text{CH}_3\text{CH} &= \text{CH}_2 & \text{m/z 39 (7\%)} \\
\text{C}_4\text{H}_7^+ & & \text{m/z 55 (6.4\%)} \\
\text{m/z 65} & (8.8\%) \\
\text{C}_6\text{H}_5^+ & & \text{m/z 77 (12.7\%)} \\
\text{C}_4\text{H}_3^+ & & \text{m/z 51 (3.5\%)} \\
\text{C}_2\text{H}_2 &= \text{CH}_2\text{CO} & \text{m/z 107 (16.4\%)} \\
\text{CH}_3\text{CH}_2^+ & & \text{m/z 29 (10.5\%)} \\
\text{m/z 121} & (5.5\%) \\
\text{-CO} & \text{-H}_2\text{O} & \text{m/z 103 (5.5\%)}
\end{align*}
\]
FIG. 4.8: MASS SPECTRUM OF 4-HYDROXY-4-n-BUTYL CHROMAN(V)
The formation of the compound (V) is a simple Grignard-type addition (Chart 4.3). Nucleophilic attack of Bu<sup>n</sup> at the carbonyl carbon results in an anionic species (Ia) which picks up a proton from the solvent generating the compound (V).

**Chart 4.3 : Mechanism for the formation of (V).**

\[ \text{(I)} \xrightarrow{\text{Bu Li} \text{ THF}} \text{(Ia)} \xrightarrow{\text{Protonation}} \text{(V)} \]

(b) The product, R<sub>f</sub> 0.55 [silica gel, benzene-ethylacetate (1:4)] isolated in poor yield from the petroleum ether-benzene (1:4) eluates was identified as the ring-opening product (VI) corresponding to chromanone oxime.

\[ \text{(VI)} \]

**Spectral studies**

The IR spectrum of (VI) revealed the presence of both the hydroxyl and carbonyl moieties by the appearance of a broad band at 3540-3160 cm<sup>-1</sup> and a medium band at 1725 cm<sup>-1</sup> (Fig 4.9, Table 4.7) respectively.
The presence of the n-butyl group was envisaged from its 80 MHz $^1$H NMR spectrum (Fig. 4.10, Table 4.8) which also could explain the structure (VI). The methylene protons adjacent to the carbonyl group came as a triplet at $\delta$ 2.12 ($J = 4.5$ Hz) while the other four methylene protons appeared in the upfield region $\delta$ 1.96-1.02. Of the four aromatic protons, the C$_6$-proton was deshielded by the presence of carbonyl group in the ortho-position and the region $\delta$ 7.55-6.60 accommodated all the others.

Table 4.7: IR spectrum of o-hydroxyphenyl-n-hexyl ketone (VI) in thin liquid film

<table>
<thead>
<tr>
<th>Characteristic absorption band</th>
<th>$\nu$ in cm$^{-1}$</th>
<th>$\lambda$ in $\mu$</th>
<th>Intensity</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3540-3160</td>
<td>2.82-3.16</td>
<td>Broad</td>
<td>-OH</td>
<td></td>
</tr>
<tr>
<td>1725</td>
<td>5.80</td>
<td>Medium</td>
<td>$&gt;\text{C}=\text{O}$</td>
<td></td>
</tr>
<tr>
<td>1610</td>
<td>6.21</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1580</td>
<td>6.33</td>
<td>Medium</td>
<td>Aromatic</td>
<td></td>
</tr>
<tr>
<td>1490</td>
<td>6.71</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>12.50</td>
<td>Medium</td>
<td>Disubstituted phenyl nucleus</td>
<td></td>
</tr>
<tr>
<td>755</td>
<td>13.24</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The product (VI) can be obtained either by the direct SN$^2$ displacement at C$_2$ of the chromanone or via the formation of the anion (Ib) initially, which undergoes ring-opening in the same way as described in the formation of the former ring opening product from chromanone oxime (Chart 4.2).
FIG. 4.10: 80MHz 1H-NMR SPECTRUM OF o-HYDROXYPHENYL-n-HEXYL KETONE (VI) IN CDCl₃ (D₂O-EXCHANGE)
Table 4.8: 80 MHz $^1$H-NMR spectrum of o-hydroxyphenyl n-hexyl ketone (VI) in CDC$_3$

<table>
<thead>
<tr>
<th>Chemical shift (δ)</th>
<th>No. of protons</th>
<th>Multiplicity (J in Hz)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.82</td>
<td>9.18</td>
<td>t (~5)</td>
<td>-CH$_3$</td>
</tr>
<tr>
<td>1.96-1.02</td>
<td>8.04-8.98</td>
<td>m</td>
<td>C$_3$, C$_4$, C$_5$ , C$_6$-protons</td>
</tr>
<tr>
<td>2.12</td>
<td>7.88</td>
<td>t (4.5)</td>
<td>C$_2$-H</td>
</tr>
<tr>
<td>7.55-6.60</td>
<td>2.45-3.40</td>
<td>m</td>
<td>C$_3$, C$_4$, C$_5$-protons</td>
</tr>
<tr>
<td>7.72</td>
<td>2.28</td>
<td>d (8)</td>
<td>C$_6$-H</td>
</tr>
</tbody>
</table>

(c) The third product, $R_f$ 0.58 [silica gel, benzene-ethyl acetate (4:1)] was isolated from the petroleum ether - benzene (1:4) eluates as an yellow gummy mass. In the IR spectrum of the compound no absorption was observed for carbonyl function, instead it exhibited a broad band in the region 3600-3200 cm$^{-1}$ for hydroxyl grouping and a strong band at 1640 cm$^{-1}$ for the olefinic double bond.

From the $^1$H-NMR spectrum (100 MHz, CDC$_3$) of the compound presence of the n-butyl group was indicated. The spectrum showed
the appearance of two phenolic -OH at $\delta$ 12.15 and at $\delta$ 12.52 from which it was implied that the compound might be a heterocyclic ring-cleaved product. The $^1$H-NMR spectrum of the compound also revealed the presence of olefinic proton, centered around at $\delta$ 4.15, a multiplet in the region at $\delta$ 6.56-7.76 for the aromatic protons, two triplets at $\delta$ 3.56 ($J = 3.6$ Hz) and $\delta$ 2.88 ($J = 3.8$ Hz) and a quartet at $\delta$ 3.20 ($J = 4$ Hz).

From these spectral records, it was assumed that the third product may be a $E$ and $Z$ isomeric mixture of the unsaturated ring-cleaved product (VII).

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{OH} \\
\text{H} \\
\text{CH}_3
\end{align*}
\]

(VII)

The formation of the product (VII) can be rationalised by the attack of a second molecule of butyl-lithium on either of the product (V) or (VI), followed by elimination of water.

**Grignard reaction of 4-chromanone oxime**

The attempted ring-opening by the Grignard reaction of 4-chromanone oxime with phenyl magnesium bromide in presence of dry tetrahydrofuran at 0-5° followed by the usual work up was found to gave back the starting material, 4-chromanone oxime(III).
Comparison in Reactivity between 4-Chromanone and 4-Chromanone oxime and comments on the probable mechanism

The major reaction for the ketone (I) is a Grignard-type nucleophilic attack on the carbonyl group, while the oxime (III) gives a ring-cleaved product exclusively. The nucleophilic attack by butyl-lithium is more facilitated in (I) as the carbonyl group is more polarised than the oximino-group in (III). This lack of reactivity on part of the oxime is confirmed by its inability to react with a Grignard reagent. Hence the ring-cleavage becomes more energetically favourable. Mechanism (ii) is preferred on the following grounds -

(1) The anion derived from (III) will be comparatively unstable and therefore more susceptible to fragmentation than the anion derived from (I). Hence the ring-fragmentation will be much more favored for the oxime.

(2) The selectivities for the $\text{SN}_2$ displacement [mechanism (i)] should not be significantly different, but would be somewhat more facile for the ketone. The large difference in yields of the ring-cleaved product for the two compounds would therefore rather difficult to explain.

(3) The cyclopropane mechanism [mechanism (iii)] cannot be operable for the ketone. In the oxime, this mechanism would involve $\text{SN}_2$
displacement by $C_4$ on $C_2$. This seems improbable from stereo-electronic considerations.

(4) The Olofson-Barber procedure with (VIII) gave the iso-oxazole (IX) in 74% yield. Had the SN$^2$ displacement been the major pathway for the ring-cleavage of the chromanone oxime, then the reaction with (VIII) would also have led mainly to the ring-cleaved product (X). Since this was not the case, it follows that the carbanion (IIIa') is involved in the ring-cleavage process and mechanism (ii) is the correct one.

\[
\begin{align*}
\text{(VIII)} & \xrightarrow{\text{(i) Bu}^n\text{Li (2 moles)/ DMF}} \text{(IX)} \\
\text{(X)} & \xrightarrow{\text{H}_3\text{O}^+} \text{(IIIa')} 
\end{align*}
\]
CHAPTER 4.2

EXPERIMENTAL

General

Melting points were recorded on an electrically heated Köfler block apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Models 782 and 582. $^1$H-NMR spectra, using CDCl$_3$ as solvent and TMS as the internal standard were recorded on a Varian-Associates 80 MHz CFT-20, 200 MHz XL-200 and Jeol FX-100 NMR instruments, $^{13}$C-NMR at 20 MHz on the Varian CFT-20 spectrometer.

Analytical samples were routinely dried over P$_2$O$_5$ in vacuo at room temperature. Anhydrous sodium sulphate was normally used for drying organic solvents and solutions. Silica gel (BDH, 60-120 mesh) was used for column chromatography and silica gel G (BDH) for thin layer chromatography. Spots on TLC were detected with iodine vapour.

The starting materials prepared were identified by comparison of their melting point and boiling points with the literature values and also by elemental analysis.

Preparation of the starting materials

(1) 4-Chromanone$_2$ (I)

PPA cyclisation of β-phenoxypropionic acid, obtained from β-chloropropanoic acid yielded 4-chromanone.
(a) **β-Chloropropionic acid** : Dry HCl gas was passed through a solution of acrylic acid (40 ml, 0.55 mol) in dry chloroform (150 ml), with stirring at 10-20° for 15 hr. The hydrogen chloride gas, generated by the dropwise addition of conc. HCl (100 ml) to conc. H$_2$SO$_4$ (150 ml) was dried by passing over conc. sulphuric acid. The reaction was monitored by the study of IR spectra of the reaction mixture from time to time. After completion of the reaction, the solvent was removed to give β-chloropropionic acid, bp 202-3° (Lit. 204°). Yield 48.5 g (80%). (Found : C, 33.02; H, 4.53; C$_3$H$_5$O$_2$Cl requires C, 33.18; H, 4.61%).

(b) **β-Phenoxypropionic acid** : β-Chloropropionic acid (46 g; 0.42 mol) was added dropwise to a solution of phenol (40 g; 0.42 mol) in 15% aqueous sodium hydroxide (200 ml) with stirring at room temperature. After the addition was completed, the reaction mixture was refluxed for 24 hr. in an oil bath and then cooled with stirring to room temperature. The reaction mixture was concentrated to half of its bulk under reduced pressure. The concentrated mixture was then extracted with ether, acidified with HCl (1:1) when the β-phenoxypropionic acid separated as an yellow oil which partially solidified on cooling. The oily mass was dissolved in ether and the ether solution extracted with 5% NaOH solution. The alkaline extract was acidified with HCl (1:1) when the phenoxypropionic acid separated in shiny, needle-like crystals. After cooling, the acid was filtered off and recrystallised from hot water from which it separated as long needles (35 g; 50%) melting at 96-97° (Lit. 98°).

(c) **PPA cyclisation of 3-phenoxypropionic acid** : β-Phenoxypropionic acid was cyclised to 4-chromanone with polyphosphoric acid (PPA)/xylene at ∼95° by the method of Fontaine.$^2$
85% Phosphoric acid (23 ml) and phosphorous pentoxide (37 g) and 200 ml dry xylene were stirred at 95-100° for 2 hr. A solution of β-phenoxypropionic acid (4.6 g; 0.03 mol) in dry xylene (100 ml) was added dropwise over 2 hr with stirring, the temperature being maintained at 95-98°. After the addition was completed, the reaction mixture was stirred for a further 3 hr at this temperature and then cooled (over 1½ hr) with stirring to room temperature. The viscous mass was poured onto crushed ice. The xylene layer was separated and the aqueous layer extracted with xylene (2x50 ml) and then with ether (4x50 ml). The combined organic extracts were dried over anhydrous Na₂SO₄ and the solvent removed under reduced pressure. The residue was distilled under reduced pressure to give 4-chromanone, bp 125-26°/13 mm (Lit.³ 128°/13 mm), yield 3.8 g (93%).

(2) 4-Chromanone oxime³,⁴ (III)

4-Chromanone oxime was prepared according to the method of Powell³,⁴.

Chromanone (2.0 g; 0.014 mol) and hydroxylamine hydrochloride (2.0 g; 0.03 mol) was dissolved in 35 ml of 85% ethanol. Anhydrous potassium carbonate (4.0 g; 0.03 mol) was added and the reaction mixture refluxed for 8 hours. The reaction mixture was then filtered and concentrated to ~ 10 ml. The concentrate was poured into water and the oxime precipitating out was filtered off. Solids from the first filtration was dissolved in the aqueous filtrate (from the second filtration) which was acidified and extracted with methylene chloride (2x25 ml). The methylene chloride extract was evaporated and the residue taken up in 5 ml ethanol. The latter was poured into water to obtain a second crop of the oxime. Total yield of the
Reactions of 4-Chromanone and its oxime derivative with n-butyl-lithium

Reactions were carried out in dry apparatus under an atmosphere of dry nitrogen.

(i) Reaction of 4-Chromanone oxime (III) with Bu^nLi

4-Chromanone oxime (0.5 g, 0.003 mol) in dry THF (10 ml) was cooled to 0°C (ice-bath). n-Butyl-lithium in hexane (2.5 ml of 1.6 M solution - 0.256 mol) was added with rapid stirring over 20 min. The resulting deep reddish yellow solution was stirred for an additional 4 hr at 0°C. Then the reaction mixture was allowed to warm up to room temperature and kept overnight. The reaction mixture condensed to a white semi-solid mass which was decomposed by the addition of a few drops of water, then acidified with HCl (1:1). After separation of the organic layer, the aqueous layer was extracted with chloroform (3x25 ml). The combined organic extracts were washed successively with NaHCO₃ solution and water, dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude mixture revealed the presence of the unreacted oxime and the ring-cleaved product (IV), as well as very polar components, which could not be isolated even by PTLC. The residue was then subjected to column chromatography. The petroleum ether – benzene (1:8) eluate afforded the reaction product as a yellow liquid from which white crystalline solid, mp 88-90°C, Rₛ = 0.53 [benzene – ethyl acetate (4:1)] was separated out. The pure product (IV), 100 mg (15%) was obtained by repeated crystallisation. Unreacted substrate was also recovered from petroleum ether – benzene (1:8) eluate in the latter fraction.
(Found : C, 70.48; H, 8.54; N, 6.21; C_{13}H_{19}NO_{2} requires C, 70.56; H, 8.65; N, 6.33%).

(ii) Reaction of 4-chromanone (I) with Bu"Li

The reaction was performed by the same process as described for 4-chromanone oxime, using the substrates and solvent in the proportion given below.

4-Chromanone : 0.5 g (0.003 mol)
Tetrahydrofuran : 10 ml
n-Butyl-lithium in hexane : 4.6 ml (1.6 M solution - 0.471 mol)

The reaction mixture was worked up in the usual manner. The products were separated by column chromatography (silica gel). One of the products (V) was the chroman derivative, mp 55°, obtained by rechromatography from the petroleum ether-benzene (1:1) eluates as white crystals (yield 130 mg; 18.7%), \( R_f \) 0.68 [benzene-ethylacetate (1:1)].

(Found : C, 77.09; H, 6.85; C_{13}H_{18}O_{2} requires C, 77.20; H, 6.98%).

The product (VI), \( R_f \) 0.55 [benzene-ethylacetate (4:1)] was obtained from the petroleum ether-benzene (1:4) eluates as yellow semi-solid mass in very poor yield. The third product, a mixture of E/Z isomers, \( [R_f \) 0.58, benzene-ethylacetate (4:1)] was also obtained from the petroleum ether-benzene (1:4) eluates as an yellow gummy mass.

Grignard reaction of 4-chromanone oxime

0.25 g (0.01 mol) of clean, dry magnesium turnings in 10 ml of dry tetrahydrofuran and a small crystal of iodine were taken in a 50 ml three necked R.B. flask. To this mixture 1.45 g (1 ml, 0.01 mol) of bromobenzene in ~ 5 ml of dry tetrahydrofuran was
added dropwise with stirring under nitrogen atmosphere at 0-5°. Stirring was continued for 2 hr after completion of addition. Next 0.5 g (0.003 mol) of chromanone oxime in 10 ml of dry THF was added dropwise to the vigorously stirred phenyl magnesium bromide solution over a period of 30 min. After addition was completed, the reaction mixture was stirred for another 4 hr at 0-5°. Then the reaction mixture was poured into crushed ice, acidified with HCl (1:1), extracted with ether, washed with NaHCO₃ solution and water and dried over anhydrous Na₂SO₄. Removal of the solvent gave back the starting oxime only.