CHAPTER III

Synthesis of Furocoumarins
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Furocoumarins is an important class of compounds having furan ring fused with benzenoid part of the coumarin ring system. Depending on the nature of fusion, the furocoumarins are classified into various ring systems like psoralen 1, pseudopsoralen 2, angelicin 3, allopsoralen 4.

Psoralen : 7H-furo [3,2-g] [1] benzopyran-7-one

Pseudopsoralen : 6H-furo [2,3-g] [1] benzopyran-6-one
Angelicin: 5H-furo [2,3-b] [1] benzopyran-5-one

Alloporsalen: 7H-furo [2,3-f] [1] benzopyran-7-one

The linear isomer is extracted from the seeds of Indian plant *Psoralea corylifolia*¹, while some of its derivatives are extracted from bark of *Swietenia*².

Psoralen, alloporsalen and many of their derivatives are used against psoriasis³⁴⁸ and against cancer⁹⁻¹⁸. Some of these derivatives show hypotensive¹⁹ and antiveratrinic⁵ activities.
Known methods of synthesis of psoralens

The synthetic methods for psoralen and its derivatives can be classified into two groups involving building up of coumarin ring on suitably substituted preformed benzofuran skeleton or vice versa.

Group I

In this group the most widely used method includes condensation of β-ketoesters with 6-hydroxy-2,3-dihydrobenzofuran. In some cases malic acid or malonic acid are also used as condensing agents. Use of malonic acid requires decarboxylation of the carboxylic acid. Both the above paths furnish the dihyropsoralen derivative. Dehydrogenation of using Pd-C gives the target molecule.
Use of dihydrobenzofuran is required to avoid the cyclisation at 7-position leading to angular furocoumarin. The critical step in the above pathway is the dehydrogenation of the dihydro derivative 7.

Das Gupta et al.\textsuperscript{25} have reported the condensation of α,β-unsaturated ester 8 with 5 to yield tetrahydro derivative 2 which on dehydrogenation gives 6-methyl psoralen.

In some cases, a blocking group at 7-position of 6-hydroxy-benzofuran 10 is used to prevent the formation of angular furocoumarins\textsuperscript{26,27}. 

\begin{center}
\includegraphics[width=0.8\textwidth]{chemical_formula.png}
\end{center}
In a novel approach Worden et al. prepared 5-formyl-6-methoxy-benzofuran through lithiation of corresponding bromo derivative. This was followed by demethylation and cyclisation with diethylmalonate leading to carbethoxy derivative, which on hydrolysis and decarboxylation gave psoralen.
Essence of this method is the synthesis of \( 12 \) which although in low yield, is achieved as follows.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{CHO} & \quad \text{CHO} \\
\text{CHO} & \quad \text{CHO} \\
\text{Br} & \quad \text{Br} \\
\end{align*}
\]

\[\begin{align*}
\text{CH}_3\text{I} & \quad \text{BrCH}_2\text{COOEt} \\
\text{gla AcOH} & \quad \text{NaOH, EtOH} \\
\text{Ac}_2\text{O}, \text{AcONa} & \quad \text{H}_3\text{CO} \]

**Group II**

The second group of methods available for the synthesis of psoralens, constitutes building-up of the furan ring on suitably substituted preformed coumarin ring system.

The electrophilic substitution reactions on 7-hydroxycoumarin ring directs the entry of the electrophile mainly at the 8-position leading to formation of angular furocoumarins rather than the target psoralen. Hence the 8-position has to be blocked to facilitate the entry of the electrophile at 6-position furnishing the required precursor.
The blocking group generally used is a halogen viz. bromine\textsuperscript{28} and iodine\textsuperscript{29, 30} which is then easily removed.

\[
\text{Claisen rearrangement in PhNMe}_2 \quad \xrightarrow{i)} \quad \text{Oxidation} \quad \xrightarrow{ii)} \quad \text{Cyclodehydration}
\]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\end{align*}
\]

The methyl, methoxy and hydroxy groups are also used as blocking group\textsuperscript{23, 31}. Thus the substitution takes place at the 6-position thereby facilitating the formation of linear furocoumarin.
3-Methyl\textsuperscript{32} and 3-ethyl\textsuperscript{33} derivatives are prepared starting from the hydroxycoumarin \textsuperscript{14} by a direct acylation or Fries rearrangement of the acyloxy derivative to give \textsuperscript{15}. It is then treated with ethyl bromoacetate and hydrolysed to get the acid \textsuperscript{16} which on cyclisation using sodium acetate and acetic anhydride yields the psoralen derivative.
Claisen rearrangement of the allyl ether 17 yielding the allyl derivative 18 followed by ozonolysis and cyclo-dehydration is used by Pardanani et al.\textsuperscript{34} and Kaufman\textsuperscript{35} to synthesise 5-phenyl-9-methyl and 9-methyl derivatives.
A somewhat different approach is reported by Maki. The 7-hydroxy-7-hydroxycoumarin 19 is treated with diethyl acetal of bromoacetaldehyde to give diethoxyethyl ether 20 which on acidic hydrolysis yields the formyl derivative 21. Base catalysed cyclisation of 21 gives psoralens. In this reaction the coumarin ring opens up making the 6-position more active. This results in the formation of the desired linear product.

![Chemical structure](image)

A similar method used for the synthesis of 3-phenyl derivatives involves condensation of 7-hydroxy-7-hydroxycoumarin 22 with O'-bromoacetophenone to yield ether 23 which on cyclisation in the presence of sodium ethoxide or potassium hydroxide furnishes the psoralen derivatives.
In an altogether different approach, a mixture of linear and angular isomers is obtained when 7-hydroxy-coumarin 24 is reacted with 25.
Kaufman\textsuperscript{40} reported the synthesis of dimethyl psoralen using condensation with chloroacetone followed by cyclisation in basic medium.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{psoralen.png}};
\end{tikzpicture}
\end{center}

Ozonolysis followed by orthophosphoric acid cyclisation of naturally occurring coumarin \textsuperscript{26} to furnish psoralen is also reported\textsuperscript{41}.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{coumarin.png}};
\end{tikzpicture}
\end{center}

Simultaneous building up of both lactone ring and furan ring is reported\textsuperscript{42} in the reaction of the isopropyl ester \textsuperscript{27} with chloroacetonitrile giving the ether \textsuperscript{28}. It is
cyclised to 29 which is then further transformed into the psoralen.
Present work

Our approach for the synthesis of linear furcoumarins is totally different from those reported so far in the literature. Our approach utilizes the fact that ring contraction takes place when 3-bromocoumarin 30 are treated with a base giving respective coumarilic acids 31 which can be easily decarboxylated to the furan derivative 32.

\[
\begin{align*}
\text{30} & \xrightarrow{\text{aq. KOH}} \text{31} \\
\text{R}_1 = \text{H}, \text{CH}_3 & \quad \text{R}_2 = \text{OH}, \text{OCH}_3 \\
\text{R}_3 = \text{H}, \text{COCH}_3
\end{align*}
\]

Interestingly in case of 3-bromocoumarins 33 having acyl substituents at 6- and 8-position, direct formation of benzofuran derivative 34 is reported. The acid 35 (Scheme 1) is a minor product.
Based on this reasoning the synthesis of linear furocoumarins (such as 36) would require the monobromo dicoumarin 37 as a precursor. This in turn could be obtained by controlled bromination of dicoumarin 38. (Scheme 2).
Known methods of synthesis for linear dicoumarins

1. Common method \(^{49-56}\)

\[
\begin{align*}
\text{R}_{1} &= \text{H}, \text{CH}_{3} ; \\
\text{R}_{2} &= \text{H}, \text{CH}_{3}, \text{Ph} \\
\text{R}_{3} &= \text{H}, \text{CH} ; \\
\text{R}_{4} &= \text{H}, \text{OH}, \text{X} \\
\text{R}_{5} &= \text{CH}_{3}, \text{Ph} ; \\
\text{R}_{6} &= \text{H}, \text{CH}_{3}
\end{align*}
\]

2. Edwards method \(^{57}\)

\[
\begin{align*}
\text{R}_{1} &= \text{H} \\
\text{R}_{2} &= \text{CH}_{2} \text{OH}
\end{align*}
\]
3. Kostanecki Robinson method\textsuperscript{58-61}

\[
\begin{align*}
&\text{HO} \quad \text{OH} \\
&\quad \quad \text{R}_2 \quad \text{R}_1 \\
&\xrightarrow{\text{Ac}_2\text{O}, \text{AcONa}} \\
&\quad \quad \text{-OR-} \\
&\quad \quad \text{Ac}_2\text{O}, \text{PhCH}_2\text{COONa} \\
&\quad \quad \text{R}_2 \quad \text{R}_1 \\
&\xrightarrow{\text{R}_1=\text{H}, \text{COCH}_3, \text{COPh}} \\
&\quad \quad \text{HO} \quad \text{O} \\
&\quad \quad \text{Ph} \quad \text{C} \\
&\quad \quad \text{R}_1 \\
&\xrightarrow{\text{Ac}_2\text{O}, \text{AcONa}} \\
&\quad \quad \text{R}_2 \quad \text{R}_1 \\
&\xrightarrow{\text{R}_1=\text{H}, \text{Ph}} \\
&\quad \quad \text{R}_2 \quad \text{R}_1 \\
&\xrightarrow{\text{R}_1=\text{H}, \text{COCH}_3, \text{COPh}} \\
\end{align*}
\]

4. Worden et al.\textsuperscript{62} method

\[
\begin{align*}
&\text{H}_3\text{CO} \quad \text{R}_1 \quad \text{OCH}_3 \\
&\quad \quad \text{Br} \quad \text{Br} \\
&\xrightarrow{i) \text{n-BuLi}} \\
&\quad \quad \text{DMF} \\
&\quad \quad \text{iii) AlCl}_3 \\
&\quad \quad \text{Ac}_2\text{O}, \text{K}_2\text{CO}_3 \\
&\quad \quad \text{-OR-} \\
&\quad \quad \text{CH}_2(\text{COOEt})_2, \text{Piperidine, EtOH} \\
&\quad \quad \text{R}_1 \quad \text{R}_2 \\
&\quad \quad \text{R}_3 \quad \text{R}_2 \\
&\quad \quad \text{R}_1=\text{H}, \text{CH}_3 \\
&\quad \quad \text{R}_2, \text{R}_3=\text{H}, \text{COOEt}
\end{align*}
\]
5. Shaikh et al. method

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OHC} & \quad \text{OHC} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{ACNHCH}_2\text{COOH}, & \quad \text{Ac}_2\text{O}, \text{AcONa} \\
i) \quad & \quad \quad \text{ii) Hydrolysis} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OHC} & \quad \text{OHC} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

6. Shaikh et al. method

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{R}_1 & = \text{CH}_3, \text{Et} \\
\text{(EtO)}_2\text{CO} & \quad \text{Na} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{OH} & \quad \text{OH} \\
\text{R}_1 & = \text{H}, \text{CH}_3 \\
\end{align*}
\]
7. Deshpande et al.\textsuperscript{65} method

Since the dicoumarins were to be converted into the monobromo derivative, the method used for dicoumarin synthesis should have no substituent at the 3-position. Methods 5 and 7 were therefore unsatisfactory. Methods 1, 6 and 8 start...
with a preformed coumarin and initially it was felt that such a method should be avoided as it would be a multistep process. Methods 2 and 4 are also unsatisfactory since both C-3 and C-4 positions in each of the coumarin ring are unsubstituted, such coumarins generally afford 3,4-dibromo derivatives on bromination and these have to be subsequently converted to 3-bromocoumarins. Method 3 suffers from the drawback that the yields of the dicoumarin are low.

The most reasonable approach, thus appears to be the double Wittig reaction on a substrate similar to that used in method 3. This also looked attractive since in our laboratory the conversion of 39 to 38 had been achieved by the route (method 8). It may be pointed out that 39 itself is obtained in very low yield.

**Synthesis of 3,5-dimethyl psoralen 40**

The first step in our approach for the synthesis of psoralen 36 (Scheme 2) was achieved through Wittig reaction using 2,4-dihydroxy-5-acetyl acetophenone 40. Compound 40 was refluxed with two moles of Wittig reagent in dry toluene for 12 hours, which gave dicoumarin 38, m.p. 316° (lit. 318°) in good yield (80%). Thus the present method represents a very convenient synthesis of the linear dicoumarin.
The next step was bromination of 38. Unfortunately all our attempts to brominate 38 were unsuccessful because of its extremely low solubility in all solvents used for bromination.

The failure to brominate the dicoumarin prompted us to modify the reaction sequence in our approach for the synthesis of psoralen 36 (Scheme 2). Hence it was considered feasible to prepare a benzofuran, obviously through hydrolysis of a 3-bromocoumarin as envisaged (Scheme 1). The benzofuran could then be used as the foundation to construct the coumarin. This is outlined below (Scheme 3). The crucial
part of this strategy involves the transformation of 40 to 39 using one mole of Wittig reagent. In order that this strategy should be practicable, the yield of 39 should be good.
Thus a Wittig reaction on \(^4\) was carried out, this time, using one mole of the Wittig reagent to furnish 4-methyl-6-acetyl-7-hydroxycoumarin \(^2\), m.p. 208° (lit.\(^4\) m.p. 210°), in 80% yield. Its bromination using bromine in glacial acetic acid gave 3-bromo-4-methyl-6-acetyl-7-hydroxycoumarin \(^1\), m.p. 215° (lit.\(^4\) m.p. 216°) in good yield (92%). The bromo compound \(^1\) was then refluxed with aqueous sodium carbonate solution for 3 hours when a yellow crystalline 3-methyl-5-acetyl-6-hydroxybenzofuran \(^2\), m.p. 136° (lit.\(^4\) m.p. 138°) in 70% yield was obtained. This compound was further characterised by its IR and \(^1\)H-NMR spectrum (CDCl\(_3\)) (Fig. 1). Wittig reaction of \(^4\) in toluene furnished the psoralen \(^3\), m.p. 223° (lit.\(^3\) m.p. 224-5°) in 82% yield. Its \(^1\)H-NMR spectrum (CDCl\(_3\)) was in complete agreement with the reported data\(^3\) (Fig. 2). Thus a new five step synthesis of psoralen \(^3\) has been achieved. The overall yield of this synthesis is 42% starting with resorcinol.

\(^1\)H-NMR of \(^3\)

| 2.30 | d   | J=2 Hz | 3H | -CH\(_3\) |
| 2.52 | d   | J=2 Hz | 3H | -CH\(_3\) |
| 6.21 | bs  | J=2 Hz | 1H | 3-H     |
| 7.27 | s   |       | 1H | 9-H     |
| 7.42 | d   | J=2 Hz | 1H | 7-H     |
| 7.86 | s   |       | 1H | 5-H     |
An interesting feature of this synthesis is the reaction of 3-bromocoumarin with aqueous sodium carbonate directly furnishing benzofuran, rather than the acid. This is in agreement with earlier reports in which conversion of 3-bromocoumarins having acyl substituent at 6- or 8-position to the benzofurans is given. No significant amount of acid is obtained in our reaction.

Approach for synthesis of psoralen

The synthon for the synthesis of psoralen according to above strategy would be. This is obtained by a lithiation reaction which involves a cumbersome procedure. Due to limitations in the laboratory, a novel and simple approach was designed on the following retrosynthetic analysis (Scheme 4).
The synthone \(^4\) would be considered as a protected coumarin. The advantage would be that \(^4\) being an open chain equivalent of coumarin, the electrophilic substitution reaction should take place at 5-position and not at 3-position.

Wittig reaction on \(2,4\)-dimethoxybenzaldehyde \(^4\) yielded the E-ester \(^4\) in 70% and was characterised from its \(^1\)H-NMR spectrum.

\[^1\text{H-NMR of } 4 \text{ (CDCl}_3\text{)}\]

| 1.24 | t | \(J=7\) Hz | 3H | -\(\text{CH}_2\text{-CH}_3\) |
| 3.74 | s | 3H | -\(\text{OCH}_3\) |
| 3.78 | s | 3H | -\(\text{OCH}_3\) |
| 4.21 | q | \(J=7\) Hz | 2H | -\(\text{CH}_2\text{-CH}_3\) |
| 6.37 | d | \(J=16\) Hz | 1H | \(\text{H} \underset{\text{C=CCOEt}}{\text{C=C<}}\) |
| 6.38 | bs | 1H | 3-H |
| 7.35 | d | \(J=9\) Hz | 1H | 5-H |
| 7.86 | d | \(J=16\) Hz | 1H | \(\text{H} \underset{\text{C=CCOEt}}{\text{C=C<}}\) |
| 7.87 | d | \(J=9\) Hz | 1H | 6-H |

Since the olefinic protons at 6.37 and 7.86 appeared as doublets with \(J=16\) Hz, it was obvious that the ester had the expected E-geometry.
The Vilsmeier-Haack reaction of 46 has not been reported so far. Usually such reactions are successful only on electron rich aromatic substrates. It was then felt that as 46 has two strong electron donating substituent and only one electron withdrawing substituent, this reaction may work out with careful experimentation. It was also felt that the double bond may undergo formylation, hence it was realized that this may be the bottleneck in the present synthesis.

Now the formylation of 46 using dimethylformamide and phosphorous oxychloride yielded a mixture of products. Chromatographic separation gave a product, m.p. 120°, in poor yield (10%). This was characterised from its $^1$H-NMR (CDCl$_3$) (Fig. 3) and elemental analysis to be the desired aldehyde 48.

$^1$H-NMR of 48

| 1.41 | t | J=7 Hz | 3H | -CH$_2$-CH$_3$ |
| 3.98 | s |  | 6H | -OCH$_3$ |
| 4.26 | q | J=7 Hz | 2H | -CH$_2$-CH$_3$ |
| 6.42 | s |  | 1H | 3-H |
| 6.47 | d | J=16 Hz | 1H | COOEt |
| 7.79 | d | J=16 Hz | 1H | COOEt |
| 7.98 | s |  | 1H | 6-H |
| 10.24 | s |  | 1H | CHO |
Elemental analysis: Agreed with the composition C_{14}H_{15}O_{5}.

Changing the reaction conditions failed to improve the yield of 48, hence this synthesis of psoralen 44 was abandoned.

**Synthesis of 2-methyl psoralen**

A similar retrosynthesis was planned for 2-methyl psoralen 49 involving the formylation of 50 as the key step, as follows:

![Chemical diagram](image)
2,4-Dimethoxybenzaldehyde \(51\) was converted into the nitrostyrene \(52\) m.p. 70° (lit. m.p. 72°) in 62% yield. Since the conversion of \(53a\) to the benzyl ketone \(54\) is reported using iron and hydrochloric acid, it was decided to use these reagents for the conversion of \(52\) to \(53\).

\[
\begin{align*}
\text{OCH}_3 & \quad \text{Fe-HCl} \quad \text{OCH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Thus compound \(52\) on reduction with the reagent afforded a gummy product in 79% yield. The spectral properties coupled with the mode of formation indicated that the product should be represented by structure \(53\).
Formylation of 53 using dimethylformamide gave a very complex mixture. But use of N-methyl formanilide in the formylation reaction, after chromatographic separation, afforded a thick oil in low yield (10%). This product was characterised from its spectral properties as the desired aldehyde 55.
\[ ^1H-\text{NMR of 55 (CDCl}_3\text{)} (\text{Fig. 4}) : \]

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Signal</th>
<th>Protons</th>
<th>Assignments</th>
</tr>
</thead>
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<tr>
<td>2.10</td>
<td>s</td>
<td>3H</td>
<td>-CH\textsubscript{3}</td>
</tr>
<tr>
<td>3.76</td>
<td>s</td>
<td>2H</td>
<td>-CH\textsubscript{2}-</td>
</tr>
<tr>
<td>3.84</td>
<td>s</td>
<td>3H</td>
<td>-OCH\textsubscript{3}</td>
</tr>
<tr>
<td>3.90</td>
<td>s</td>
<td>3H</td>
<td>-OCH\textsubscript{3}</td>
</tr>
<tr>
<td>6.40</td>
<td>s</td>
<td>1H</td>
<td>3-H</td>
</tr>
<tr>
<td>7.54</td>
<td>s</td>
<td>1H</td>
<td>6-H</td>
</tr>
<tr>
<td>10.20</td>
<td>s</td>
<td>1H</td>
<td>-CHO</td>
</tr>
</tbody>
</table>

All our attempts to increase the yield of 55 by changing various parameters of the reaction, failed.

It was then decided to first formylate 52 and to convert the resulting aldehyde 56, to the benzyl ketone 55, which can be easily modified into the 2-methyl-5-formyl-6-hydroxy benzofuran derivative 57 which in turn, through Wittig reaction or Perkin reaction could be easily converted into the desired 2-methyl derivative 59.

Reaction of 52 with N-methyl formanilide and POCl\textsubscript{3} immediately resulted in colour change and the formation of a single new product as indicated by tlc. The spectral data showed the absence of both -CHO and nitro olefin groups and indicated the formation of a nitrile (IR band at 2240 cm\textsuperscript{-1}). The \[ ^1H-\text{NMR} \] was also consistent with the nitrile structure 58.
Fig. 4: $^1$H NMR Spectrum of compound S5.
The m.p. 95° was also similar to that reported for 58 (lit. 69 m.p. 96°). The identity was further confirmed with the direct comparison (tlc, mmp and IR) with an authentic sample. Since one step conversion of aldehyde to nitrile using nitroethane and sodium acetate has been reported by Wadia and coworkers 71, this reaction was not investigated.

Thus the difficulty in obtaining 55, in appreciable quantities made us to abandon this approach.

**Synthesis of allopsoralen**

Our next target was allopsoralens 59 and 60.

![Chemical structure](image)

59  R = CH₃
60  R = H

**Known methods of synthesis of allopsoralen**

The known methods for the synthesis of allopsoralens can be summarized as shown below.
1. Chudgar et al.\textsuperscript{72}, Jesthi et al.\textsuperscript{73} method

\[
\begin{align*}
R = \text{CH}_3, \text{Pr}, \text{iso-Bu}, \text{Ph} 
\end{align*}
\]

2. Salvi et al.\textsuperscript{74}

\[
\begin{align*}
R = \text{CH}_3, \text{Et} 
\end{align*}
\]

3. Giuseppe et al.\textsuperscript{75}

\[
\begin{align*}
R = \text{H}, \text{CH}_3 
\end{align*}
\]
Our approach

Our approach for the synthesis of allopsoralen was similar to that used for synthesis of psoralen (Scheme 3). By choosing a suitable benzofuran as a synthone, allopsoralen could be obtained by building up of the coumarin ring using the Wittig reaction.
Synthesis of 3,9-dimethyl allopsoralen 59

4-Methyl-7-hydroxycoumarin 61 was converted to the acetate 62. This compound on Fries-migration furnished 4-methyl-7-hydroxy-8-acetylcoumarin 63, m.p. 166° (lit. 78 m.p. 168°) in good yield (80%).

Bromination of 63 by the known method exclusively gave the expected 3-bromo-4-methyl-7-hydroxy-8-acetylcoumarin 65, m.p. 218° (lit. 44 m.p. 218°) in 84% yield. As reported, ring contraction was achieved by refluxing 65 in aqueous lithium carbonate instead of sodium carbonate for 6 hours to give pure 3-methyl-6-hydroxy-7-acetyl benzofuran 66, m.p. 110° (lit. 44 m.p. 112°) in 75% yield. The 1H-NMR spectrum supported its structure.

1H-NMR of 66 (CDCl₃) (Fig. 5)

| 2.22 | d | J=2 Hz | 3H | -CH₃ |
| 2.89 | s |       | 3H | -CO-CH₃ |
| 6.80 | d | J=9 Hz | 1H | 5-H |
| 7.36 | q | J=2 Hz | 1H | 2-H |
| 7.54 | d | J=9 Hz | 1H | 4-H |
| 12.74| s |       | 1H | -OH (exchanged with D₂O) |
Wittig reaction on 66 in refluxing toluene yielded target allopsoralen 59, m.p. 197-8° (lit.69 m.p. 198°). Its $^1$H-NMR and elemental analysis further confirmed its structure.
$^1$H-NMR of 59 (CDCl$_3$) (Fig. 6):

<table>
<thead>
<tr>
<th>H</th>
<th>J</th>
<th>J</th>
<th>Value</th>
<th>Assignments</th>
</tr>
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<tbody>
<tr>
<td>2.30</td>
<td>d</td>
<td>J=2 Hz</td>
<td>3H</td>
<td>-CH$_3$</td>
</tr>
<tr>
<td>2.78</td>
<td>d</td>
<td>J=2 Hz</td>
<td>3H</td>
<td>-CH$_3$</td>
</tr>
<tr>
<td>6.25</td>
<td>d</td>
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<td>1H</td>
<td>8-H</td>
</tr>
<tr>
<td>7.22</td>
<td>d</td>
<td>J=9 Hz</td>
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<td>5-H</td>
</tr>
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<td>7.49</td>
<td>d</td>
<td>J=2 Hz</td>
<td>1H</td>
<td>2-H</td>
</tr>
<tr>
<td>7.58</td>
<td>d</td>
<td>J=9 Hz</td>
<td>1H</td>
<td>4-H</td>
</tr>
</tbody>
</table>

Synthesis of 9-methyl allopsoralen 60

A similar strategy was also employed for the synthesis of 9-methyl allopsoralen 60.

7-Hydroxycoumarin 62 was prepared from resorcinol through condensation with malic acid. Acetylation of 62 gave 67, m.p. 140$^\circ$ (lit. 79 m.p. 142$^\circ$) which on Fries-migration yielded 7-hydroxy-8-acetylcoumarin 68, m.p. 166$^\circ$ (lit. 80 m.p. 167$^\circ$). Bromination of 68 with bromine in glacial acetic acid gave a compound, m.p. 182$^\circ$, in 88% yield. This compound was characterised as the desired bromo compound 69 from its spectral and analytical data. Compound 69 was then treated with 10% aqueous sodium carbonate to furnish a compound, m.p. 117$^\circ$, in 94% yield. Its structure was confirmed by its $^1$H-NMR spectrum (CDCl$_3$)(Fig. 7), IR data and elemental analysis to be 70.
Fig 6: $^1$H NMR Spectrum of compound 59
Fig. 7. $^1$H NMR Spectrum of compound 20.
The construction of the coumarin ring was achieved by Wittig reaction furnishing the hitherto unreported allopsoralen 60, m.p. 182° in 88% yield. The structure of 60 was supported by its spectral and analytical data.

### $^1$H-NMR of 70

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
<th>Quantity</th>
<th>Proton</th>
<th>Coupling Constant</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.90</td>
<td>s</td>
<td></td>
<td>3H</td>
<td>-COCH$_3$</td>
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<tr>
<td>6.72</td>
<td>d</td>
<td></td>
<td>1H</td>
<td>3-H</td>
<td></td>
</tr>
<tr>
<td>6.87</td>
<td>d</td>
<td></td>
<td>1H</td>
<td>5-H</td>
<td></td>
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<tr>
<td>7.59</td>
<td>d</td>
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<td>1H</td>
<td>2-H</td>
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<td>7.64</td>
<td>d</td>
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<td>4-H</td>
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<td>12.80</td>
<td>s</td>
<td></td>
<td>1H</td>
<td>-OH (exchanged with D$_2$O)</td>
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</tr>
</tbody>
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### $^1$H-NMR of 60 (CDCl$_3$)(Fig. 8)

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
<th>Quantity</th>
<th>Proton</th>
<th>Coupling Constant</th>
<th>Assignment</th>
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<tr>
<td>2.74</td>
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<td>-CH$_3$</td>
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<td>6.16</td>
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<td>6.75</td>
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<td>7.14</td>
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<td>1H</td>
<td>5-H</td>
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<td>7.50-7.70</td>
<td>m</td>
<td></td>
<td>2H</td>
<td>2-H, 4-H</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 8: $^1$H NMR Spectrum of compound 50.
\[
\begin{align*}
\text{HO-CH}_2\text{OH} & \xrightarrow{\text{Malic acid, } \text{Conc. } \text{H}_2\text{SO}_4} \quad \text{HO-CH}_2\text{O} \quad \text{Ac}_2\text{O} \\
\text{AcO-} & \quad \xrightarrow{\text{AlCl}_3, \Delta} \quad \text{H}_3\text{C-} \quad \text{Br}_2, \quad \text{gla } \text{AcOH} \\
\text{H}_3\text{C-} & \quad \xrightarrow{10\% \text{aq. } \text{Na}_2\text{CO}_3} \quad \text{H}_3\text{C-} \\
\text{Ph}_3\text{P} = \text{CH-} & \quad \xrightarrow{\text{Ph}_3\text{P} = \text{CH-}}, \quad \text{toluene} \\
\end{align*}
\]
Conclusions

1. The Wittig approach has been used for the synthesis of dicoumarins, psoralen and allopsoralens.

2. The linear dicoumarin has been synthesised by a double Wittig reaction on the diketone. Such a double Wittig reaction has so far not been reported for the synthesis of dicoumarins. This synthesis represents a simple two step high yield synthesis of the dicoumarin starting with resorcinol.

3. A five step synthesis of linear furocoumarin; psoralen, starting with resorcinol has been accomplished. The yield in each step is above 70%.

4. Two allopsoralens have been synthesised. Both syntheses involve a six step synthesis starting with resorcinol. The yields of each step in both syntheses are greater than 75%.
Expt. 3.1: 2,4-Dihydroxy-5-acetyl acetophenone

A mixture of finely powdered resorcinol (2 g), powdered anhydrous zinc chloride (2 g) and acetic anhydride (2.8 ml) was heated at 142° for 15 minutes. The reaction mixture was cooled and poured into dil. HCl (1:1) when a yellow solid separated. It was filtered and dried (3 g, 85%), m.p. 177° (MeOH) (lit. m.p. 178-80°).

IR: 1650 cm⁻¹ (carbonyl).

¹H-NMR (CDCl₃):

<table>
<thead>
<tr>
<th>δ</th>
<th>s</th>
<th>6H</th>
<th>-CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.60</td>
<td>s</td>
<td>6H</td>
<td>-CH₃</td>
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<td>6.39</td>
<td>s</td>
<td>1H</td>
<td>3-H</td>
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<tr>
<td>8.15</td>
<td>s</td>
<td>1H</td>
<td>6-H</td>
</tr>
<tr>
<td>12.80</td>
<td>s</td>
<td>2H</td>
<td>-OH  (exchanged with D₂O)</td>
</tr>
</tbody>
</table>
Expt. 3.2: 4,6-Dimethyl-2H,8H-benzo[1,2-b: 5,4-b']-dipyran-2,8-dione 38

A mixture of 2,4-dihydroxy-5-acetyl acetophenone (0.8 g), Wittig reagent (3.5 g) and dry toluene (14 ml) was refluxed for 12 hours. Toluene was removed in vacuo. The residue was treated with aq. EtOH (50%) to get the dicoumarin (0.8 g, 80%), m.p. 316° (lit. m.p. 318°).

IR: 1735 cm⁻¹ (carbonyl).

Mass: m/z 242 (M⁺).

Expt. 3.3: 4-Methyl-6-acetyl-7-hydroxycoumarin 39
A mixture of 2,4-dihydroxy-5-acetyl acetophenone (1.6 g), Wittig reagent (3.5 g) and dry toluene (20 ml) was refluxed for 15 hours. Toluene was removed in vacuo and the residue obtained was treated with aq. EtOH (50%) to get a yellow solid which was filtered and dried to get 4-methyl-6-acetyl-7-hydroxy coumarin (1.44 g, 80%), m.p. 208° (hexane-ethyl acetate) (lit. m.p. 210°).

Expt. 3.4 : 3-Bromo-4-methyl-6-acetyl-7-hydroxycoumarin

A solution of bromine (0.32 g) in glacial acetic acid (1 ml) was added dropwise under stirring to a solution of 4-methyl-6-acetyl-7-hydroxycoumarin (0.436 g) in glacial acetic acid (9.5 ml) during 30 minutes. The reaction mixture was poured in water and treated with aq. saturated sodium hydrogen sulphite solution. The solid obtained was filtered and dried to furnish 3-bromo-4-methyl-6-acetyl-7-hydroxycoumarin (0.55 g, 93%), m.p. 215° (lit. m.p. 216°).
Expt. 3.5: 3-Methyl-5-acetyl-6-hydroxy benzofuran 42

\[ \text{HO} \quad \text{aq} \quad \text{Na}_2\text{CO}_3 \quad \text{CH}_3 \quad \text{O} \]

A mixture of 3-bromo-4-methyl-6-acetyl-7-hydroxy-coumarin (0.5 g), sodium carbonate (0.53 g) and water (6.5 ml) was refluxed for 3 hours. The product, being steam volatile, got accumulated in the reflux condenser in pure form (0.225 g, 70%), m.p. 136° (lit. m.p. 138°).

Expt. 3.6: 3,5-Dimethyl-7H-furo [3,2-g] [11 benzopyran-7-one 36

\[ \text{HO} \quad \text{Ph}_3\text{P}=\text{CH} \cdot \text{COOEt} \quad \text{Toluene} \quad \text{CH}_3 \quad \text{O} \]

A mixture of 3-methyl-5-acetyl-6-hydroxy benzofuran (0.27 g), Wittig reagent (0.85 g) and dry toluene (10 ml) was
refluxed for 7 hours. Toluene was removed in vacuo and the residue was treated with aq. EtOH (50%) and the solid thus separated was filtered and dried to furnish the furocoumarin (0.25 g, 82%), m.p. 225° (CHCl₃) (lit. 224-5°).

Expt. 3.7: 2,4-Dimethoxy benzaldehyde

\[
\text{H}_3\text{CO} - \text{OCH}_3 \quad \xrightarrow{\text{DMF, POCl}_3} \quad \text{H}_3\text{CO} - \text{OCH}_3 \quad \text{CHO}
\]

Vilsmeier-Haack complex was prepared by dropwise addition of dry dimethylformamide (11 ml) to phosphorous oxychloride (15 ml) maintained at 0-5°. To this complex, resorcinol dimethyl ether (15 ml) was added in portions and the resulting mixture was heated on water bath for 6 hours with occasional stirring. The reaction mixture was cooled, poured in water (100 ml) and left overnight when the product separated out as a crystalline solid. This solid was filtered, washed with cold water and dried to yield the 2,4-dimethoxy benzaldehyde (14 g, 78%), m.p. 70° (lit. m.p. 68-70°).
$^1$H-NMR (CDCl$_3$):

<table>
<thead>
<tr>
<th>Signal</th>
<th>s</th>
<th>3H</th>
<th>-OCH$_3$</th>
</tr>
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<tr>
<td>3.89</td>
<td></td>
<td>3H</td>
<td>-OCH$_3$</td>
</tr>
<tr>
<td>3.91</td>
<td></td>
<td>3H</td>
<td></td>
</tr>
<tr>
<td>6.40-6.65</td>
<td>m</td>
<td>2H</td>
<td>3-H, 5-H</td>
</tr>
<tr>
<td>7.80</td>
<td>d</td>
<td>1H</td>
<td>6-H</td>
</tr>
<tr>
<td>10.30</td>
<td>s</td>
<td>1H</td>
<td>-CHO</td>
</tr>
</tbody>
</table>

Expt. 3.8: Ethyl-2,4-dimethoxy cinnamate

A mixture of 2,4-dimethoxy benzaldehyde (5 g), Wittig reagent (12.5 g) and dry toluene (25 ml) was refluxed for 12 hours. Toluene was removed in vacuo. The residue was treated with hot hexane under stirring and filtered. The filtrate was evaporated when an oily product separated out. Slow cooling of this gave ethyl-2,4-dimethoxy cinnamate (4.8 g, 70%), m.p. 61° (hexane).

Elemental analysis:

<table>
<thead>
<tr>
<th>Found</th>
<th>Calculated</th>
</tr>
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<tbody>
<tr>
<td>C, 66.35%</td>
<td>C, 66.10%</td>
</tr>
<tr>
<td>H, 6.82%</td>
<td>H, 6.78%</td>
</tr>
</tbody>
</table>
Vilsmeier-Haack complex was prepared by addition of dry dimethylformamide (0.8 ml) to phosphorous oxychloride (1 ml) maintaining the temperature between 0-5°. Ethyl-2,4-dimethoxy cinnamate (1 g) was added to it and the reaction mixture was heated on water bath for 6 hours, poured in water and the sticky mass thus obtained was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Removal of ether furnished a thick oil which on column chromatography over silica gel using ethyl acetate-hexane (1:4) furnished 48 (0.11 g, 10%), m.p. 120°.

Elemental analysis:

Found: C, 63.48%; H, 6.19%
Calculated: C, 63.63%; H, 6.06%.
Expt. 3.10: 2,4-Dimethoxy-α-methyl nitrostyrene 52

A mixture of 2,4-dimethoxy benzaldehyde (1 g), nitroethane (1 ml), ammonium acetate (0.7 g) and glacial acetic acid (20 ml) was refluxed for 1.5 hours. The reaction mixture was cooled and poured in cold water to get sticky solid. It was then extracted with ether, washed with water and dried over anhydrous sodium sulphate. Removal of ether furnished an oil which solidified on keeping to give 2,4-dimethoxy nitrostyrene (0.84 g, 62%), m.p. 70° (lit. 68 m.p. 72°).

$^1$H-NMR (CDCl$_3$):

- 2.32 s 3H -CH$_3$
- 3.80 s 6H -OCH$_3$
- 6.40-6.55 m 2H 3-H, 5-H
- 7.23 d J=9 Hz 1H 6-H
- 8.20 bs 1H $\text{H} \text{C} \Rightarrow \text{C} \text{CH}_3$ $\text{NO}_2$
Expt. 3.11: (2,4-Dimethoxy) benzyl methyl ketone 53

A mixture of 2,4-dimethoxy nitrostyrene (1.3 g), iron powder (1.6 g), ferric chloride (0.032 g), toluene (10 ml) and water (4 ml) was heated and maintained at 75°. To it conc. HCl (2 ml) was added dropwise, under stirring during 30 minutes. Heating and stirring was continued further for 30 minutes, cooled and filtered. Filtrate was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Removal of solvent furnished an oil which was purified by column chromatography over silica gel using ethylacetate-hexane (1:4) as eluent to yield 2,4-dimethoxybenzyl methyl ketone as a thick oil (0.9 g, 79%).
\[ ^1H\text{-NMR (CCl}_4) \]:

- 1.90 s 3H -CH\textsubscript{3}
- 3.39 s 2H -CH\textsubscript{2}\textsuperscript{-}
- 3.68 s 3H -OCH\textsubscript{3}
- 3.70 s 3H -OCH\textsubscript{3}
- 6.20-6.40 m 2H 3-H, 5-H
- 6.83 d \( J = 9 \text{ Hz} \) 1H 6-H

Expt. 3.12: 2,4-Dimethoxy-5-formyl benzyl methyl ketone 55

Vilsmeier-Haack complex was prepared by addition of N-methyl formanilide (0.5 ml) to phosphorous oxychloride (0.6 ml) maintaining the temperature between 0-5\degree. A solution of (2,4-dimethoxy) benzyl methyl ketone (0.7 g) in dry methylene chloride (3 ml) was added to it under stirring. The reaction mixture was left at room temperature for 24 hours, concentrated and poured in water. The sticky mass obtained was extracted with ethyl acetate, washed with dil. HCl (1:1) and dried over
anhydrous sodium sulphate. Removal of ethyl acetate yielded an oil which on column chromatography over silica gel using ethylacetate-hexane (1:4) as eluent furnished the expected formyl derivative as a thick oil (0.08 g, 10%).

Expt. 3.13 : 2,4-Dimethoxy benzonitrile 58

Vilsmeier-Haack complex was prepared by addition of N-methyl formanilide (0.2 ml) to phosphorous oxychloride (0.3 ml) maintaining the temperature between 0-5\(^\circ\). 2,4-Dimethoxy nitrostyrene (0.2 g) was added to it under stirring. After 5 minutes it was poured in cold water when a yellow solid separated. It was filtered, washed with water and dried to furnish 2,4-dimethoxy benzonitrile (0.12 g, 89\%), m.p. 95\(^\circ\) (lit.\(^{69}\) m.p. 96\(^\circ\)).

IR : 2240 cm\(^{-1}\) (C≡N).
$^1$H-NMR (CDCl$_3$) :

3.85  s  3H  -OCH$_3$
3.90  s  3H  -OCH$_3$
6.42-6.55  m  2H  3-H, 5-H
7.44  d  J=9 Hz  1H  6-H

Expt. 3.14 : 4-Methyl-7-hydroxycoumarin

Refer to Chapter I, Expt. 1.8.

Expt. 3.15 : 4-Methyl-7-acetoxycoumarin 63

A mixture of 4-methyl-7-hydroxycoumarin (1 g) and acetic anhydride (2 ml) was refluxed for 1.5 hours. Reaction mixture was cooled and poured into water to get a white solid. It was filtered, washed with cold aq. NaOH (10%) and dried to yield 4-methyl-7-acetoxycoumarin (1.2 g, 97%), m.p. 152° (lit. 82 m.p. 152-3°).
Expt. 3.16: 4-Methyl-7-hydroxy-8-acetylcoumarin 64

A homogeneous mixture of 4-methyl-7-acetoxycoumarin (1 g) and anhydrous aluminium chloride (3 g) was heated at 160° for 1.5 hours. It was then cooled and decomposed with cold dil. HCl (1:1). The solid obtained was dissolved in cold aq. NaOH (10%), filtered and the clear filtrate was acidified with conc. HCl to yield 4-methyl-7-hydroxy-8-acetylcoumarin (0.8 g, 80%), m.p. 166° (hexane-ethanol) (lit. 78 m.p. 168°).

Expt. 3.17: 3-Bromo-4-methyl-7-hydroxy-8-acetylcoumarin 65
A solution of bromine (0.65 g) in glacial acetic acid (2.2 ml) was added dropwise, under stirring to a solution of 4-methyl-7-hydroxy-8-acetylcoumarin (0.372 g) in glacial acetic acid (19 ml). Stirring was continued further for 5 hours. The reaction mixture was poured in cold water, treated with aq. saturated sodium hydrogen sulphite and the solid formed was filtered, washed with water and dried to yield 3-bromo-4-methyl-7-hydroxy-8-acetylcoumarin (1 g, 84%), m.p. 218° (hexane-ethanol) (lit. m.p. 218°).

Expt. 3.18: 3-Methyl-6-hydroxy-7-acetyl benzofuran 66

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CO}_2 \quad \text{Br} \\
\text{HO} & \\
\text{CH}_3 & \quad \text{Li}_2\text{CO}_3 \\
\end{align*}
\]

A mixture of 3-bromo-4-methyl-7-hydroxy-8-acetylcoumarin (0.5 g), lithium carbonate (0.34 g) and water (25 ml) was refluxed for 6 hours. The product being steam volatile, accumulated in the reflux condenser. Removal of it gave pure product (0.24 g, 75%), m.p. 110° (lit. m.p. 112°).
Expt. 3.19: 3,9-Dimethyl-7H-furo[2,3-f] [11] benzopyran-7-one 59

A mixture of 3-methyl-6-hydroxy-7-acetyl benzofuran (0.48 g), Wittig reagent (1.5 g) and dry toluene (21 ml) was refluxed for 10 hours. Toluene was removed in vacuo and the residue obtained was treated with aq. EtOH (50%). The solid separated was filtered and dried to yield the furocoumarin (0.45 g, 83%), m.p. 197-80° (hexane-ethanol) (lit. 69 m.p. 198°).

Expt. 3.20: 7-Hydroxycoumarin 62
To an intimate powdered mixture of resorcinol (22 g) and malic acid (26.8 g) was added conc. $\text{H}_2\text{SO}_4$ (54 ml) and the mixture was stirred when it solidified. It was then carefully heated on a wire gauze when it first melted and then started frothing. Heating was continued till the evolution of gases ceased and a dark red solution resulted. This was cooled, poured under stirring over crushed ice when a solid separated out. It was filtered and washed with water. The moist cake was suspended in aq. sodium bicarbonate (10%), stirred, filtered, washed with water and dried to yield 7-hydroxycoumarin (13.8 g, 43%), m.p. 219° (aq. ethanol) (lit. m.p. 223-240°).

Expt. 3.21: 7-Acetoxycoumarin 67

A mixture of 7-hydroxycoumarin (2.2 g) and acetic anhydride (4.4 ml) was refluxed for 1.5 hours. Reaction mixture was cooled and poured in cold water when a white solid
formed. The solid was triturated with cold aq. NaOH (10\%), filtered and dried to yield 7-acetoxycoumarin (2.6 g, 90\%), m.p. 140° (lit.\textsuperscript{79} m.p. 142°).

\textbf{Expt. 3.22 : 7-Hydroxy-8-acetylcoumarin 68}

A homogeneous mixture of 7-acetoxycoumarin (2 g) and anhydrous aluminium chloride (6 g) was heated at 170° for 2 hours. The complex was decomposed with dil. HCl (1:1) to get a brown solid. This solid was dissolved in cold aq. NaOH (10\%), filtered and the clear filtrate was acidified with conc. HCl to get a yellow solid. It was filtered, washed with water and dried to obtain 7-hydroxy-8-acetylcoumarin (1.8 g, 90\%), m.p. 166° (lit.\textsuperscript{80} m.p. 167°).
Expt. 3.23 : 3-Bromo-7-hydroxy-8-acetylcoumarin 69

A solution of bromine (0.3 g) in glacial acetic acid (1 ml) was added dropwise, under stirring, to the solution of 7-hydroxy-8-acetylcoumarin (0.4 g) in glacial acetic acid (9.5 ml) during 10 minutes. Stirring was continued further for 1.5 hours. The reaction mixture was poured in water, treated with aq. saturated sodium hydrogen sulphite solution and the solid formed was filtered, washed with water and dried to yield 3-bromo-7-hydroxy-8-acetylcoumarin (0.5 g, 88%), m.p. 182°.

Elemental analysis:

Found: C, 46.85%; H, 2.51%
Calculated: C, 46.64%; H, 2.47%.
Expt. 3.24: 6-Hydroxy-7-acetyl benzofuran 70

A mixture of 3-bromo-7-hydroxy-3-acetylcoumarin (0.600 g), sodium carbonate (0.650 g) and water (8.0 ml) was refluxed for 3 hours. The product being steam volatile, accumulated in the reflux condenser. Removal of it gave yellow needles of 6-hydroxy-7-acetyl benzofuran (0.350 g, 91\%\), m.p. 117°.

**Elemental analysis:**

Found: C, 68.01\%; H, 4.47\%

Calculated: C, 68.18\%; H, 4.54\%.
Expt. 3.25 : 9-Methyl-7H-furo [2,3-f] [1] benzopyran-7-one 60

A mixture of 6-hydroxy-7-acetyl benzofuran (0.5 g), Wittig reagent (1.1 g) and dry toluene (15 ml) was refluxed for 16 hours. Toluene was removed in vacuo and the residue formed was treated with aq. EtOH (50%) to yield the furo-coumarin (0.5 g, 88%), m.p. 182° (hexane-ethyl acetate). IR : 1740 cm⁻¹.
Elemental analysis :
Found : C, 72.14%; H, 4.09%
Calculated : C, 72.00%; H, 4.00%.
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