MODES OF ADDITION OF SIMPLE
ORGANOMAGNESIUM REAGENTS TO COUMARIN
AND 4-SUBSTITUTED COUMARINS

R. W. TICKLE
The reaction of an ethyl Grignard reagent with a 4-(4-pyridyl) coumarin was found to yield a 4-ethyl-4-(4-pyridyl)-3,4-dihydrocoumarin as well as the expected 2,2-diethyl-4-(4-pyridyl)-2H-chromene. A series of substituted coumarins was prepared to investigate the mode of addition of Grignard reagents. The novel 1,4-addition reaction to give a dihydrocoumarin was found to be enhanced when the 4-substituent of the coumarin was strongly electron-withdrawing, and depressed when the substituent was electron-donating.

The Grignard reagent itself was found to affect the type of products obtained. Since the reactions of dialkylmagnesiums with coumarins were found to give high yields of the 1,2-addition products almost exclusively, it was concluded that this was the reactive species present in a Grignard reagent in those reactions which led to 1,2-addition. Conversely, alkylmagnesium halides were thought to be the reactive species from a Grignard reagent when 1,4-addition products were obtained.

The difference in mode of addition of the two forms of the reagent suggested that the dialkylmagnesiums reacted with a coumarin via a cyclic intermediate to give the 1,2-addition product, whilst alkylmagnesium halides effectively provided the carbanion $\overset{2}{\ominus}$, nucleophilic attack by this leading to 1,4-addition.

The reaction of a phenyl Grignard reagent with a 4-methylcoumarin yielded a phenylbutenone by the novel single 1,2-addition of a Grignard reagent to a 4-substituted coumarin. Attempts to purify this butenone by crystallisation afforded the isomeric 2-hydroxychromene.

Some of the 3,4-dihydrocoumarins have been treated further with Grignard reagents to give products dependent upon the reaction conditions. Chromanols, formed by the novel single 1,2-addition of Grignard reagents,
and carbinols derived from double 1,2-addition could be isolated. In some instances the double addition reaction could be carried out as two separate stages, with isolation of the intermediate chromanols.
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</tbody>
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C. THE REACTION OF GRIGNARD REAGENTS WITH 3,4-DIHYDROCOUMARINS

PART 4 - REFERENCES
INTRODUCTION

The reactions of Grignard reagents with coumarins are reported to proceed by initial 1,2-addition. In a few cases, where a 3-carboxy group activates the 4-position of the coumarin, 1,4-addition occurs.

In the course of synthesising substituted 2H-chromenes of type (2) for biological screening purposes, the coumarin (1) was treated with ethyl-magnesium bromide. The reaction yielded the 2H-chromene (2) by 1,2-addition, and the 3,4-dihydrocoumarin (3) by 1,4-addition.

The corresponding 1,4-addition of Grignard reagents to α,β-unsaturated esters is reported to occur readily, and can be promoted with catalysts.

The subject of this thesis is an investigation of the mode of addition of Grignard reagents to coumarin and 4-substituted coumarins. The effects on the reaction of altering the 4-substituent of the coumarin, of using a catalyst and of using different solvents have all been studied. The composition of the Grignard reagent was found to be the most important factor in determining the mode of addition.

The reaction of Grignard reagents with several substituted 3,4-dihydrocoumarins has also been studied.

A. Methods for the preparation of Coumarins

a) The Pechmann Reaction.

The Pechmann reaction is the most convenient method of preparing coumarins and involves the condensation of a phenol with a β-ketoester.
in the presence of a condensing agent\(^1\), as shown below:

\[
\begin{align*}
\text{R} & \quad \beta \text{C}=0 \\
\alpha \text{CH}_2 & \quad \text{CO}_2 \text{Et} \\
\end{align*}
\]

Several mechanisms for the reaction have been proposed. Peckmann and Diusberg\(^1\) suggested that the reactive hydrogen ortho to the hydroxyl group of the phenol added to the carbonyl group of the \(\beta\)-ketoester to give an intermediate ester. Sethna and Phadke\(^2\) suggested that the \(\beta\)-ketoester condensed in its enolic form. Thus, the reaction may be considered as an nucleophile attack of the enolic form of the \(\beta\)-ketoester on the position ortho to the hydroxyl group of the phenol, followed by dehydration of the resulting hydroxyester, and cyclisation with elimination of ethanol, as shown below:

Simonis and his co-workers\(^3,4,5\) used phosphorus pentoxide as the condensing agent in place of sulphuric acid and demonstrated that with the same reactants chromones (5) rather than coumarins resulted.
The mechanism of the reaction suggested by Robertson et al. involves formation of a phenoxy ester by the interaction of the enolic form of the ester and phenol with the removal of a molecule of water. The phenoxy intermediate then undergoes ring closure to a chromone.

The reactivity of the phenol in the Pechmann reaction was found to be enhanced when an electron-donating group, such as methyl, hydroxyl, methoxy, etc. was present as a meta-substituent, and depressed when an electron-withdrawing group, such as nitro, carboxy, etc. was present in the same position.

Thus, no reaction occurs between ethyl acetoacetate (4) and m-nitrophenol (6; X = NO₂) in the presence of sulphuric acid. With resorcinol (6; X = OH) however, a high yield of the 7-hydroxycoumarin (7; X = OH) is obtained.

It appears therefore, that activation of the ortho position of the phenol facilitates reaction.

Similarly, Sethna and Phadka suggested that ϕ-ketoesters with substituents likely to increase the enolisation, or stabilise the enolic form, were likely to be very reactive in the Pechmann condensation. However, they gave no evidence for this suggestion.

The role of the condensing agent in the Pechmann reaction is found to be important. Generally the agent is acidic, and concentrated or 80% sulphuric acid is most widely used. However, phosphorus oxychloride, aluminium chloride, zinc chloride and hydrogen chloride have all been
b) Other Reactions

The Perkin reaction\(^9\) has proved successful for synthesising a number of coumarins.

\[
\text{HCO} \quad \xrightarrow{\text{HOCO}} \quad \text{(9)} + \text{HOCO} \quad \text{CH}_3\text{COO} \quad \text{(10)}
\]

Thus, treatment of the salicylaldehyde (8) with sodium acetate in acetic anhydride at 140° yielded coumarin (9) and \(\alpha\)-acetylcoumaric acid (10).

Substituted acid anhydrides may be used in the reaction, to give 3-substituted coumarins\(^{10}\).

The Claisen condensation\(^{11}\) is also used for synthesising 3-substituted coumarins.

\[
\text{MeOCO} \quad \xrightarrow{\text{Na/240°}} \quad \text{(11)} \quad \xrightarrow{\text{RCH}_2\text{COO}} \quad \text{(12)}
\]

Thus, treatment of the methyl acylsalicylate (11) with sodium at 240° yielded the 3-alkylcoumarin (12). The hydroxy group can be removed by treatment with phosphorus pentachloride followed by zinc in alcohol.

4-Substituted coumarins can be prepared by application of the Reformatsky reaction\(^{12}\).

\[
\text{CH}_3\text{OCO} \quad \xrightarrow{\text{EtOOCO}} \quad \text{(13)} \quad \xrightarrow{\text{CH}_3\text{O}} \quad \text{(14)} \quad \xrightarrow{\text{R}} \quad \text{(15)}
\]

Thus, treatment of the \(\alpha\)-methoxyphenylketone (13) with the bromoester and zinc, followed by dehydration and demethylation affords the coumarin...
A 4-phenylcoumarin (17) has also been prepared by Woods and Holland\textsuperscript{13} utilising the Pechmann type condensation with a conjugated acetylenic ester.

\[
\begin{align*}
\text{Ph} & \quad \begin{array}{c}
\text{C} \\
\mid \\
\text{H} \\
\mid \\
\text{O} \\
\mid \\
\text{C} \quad \text{CO}_2\text{Et}
\end{array} + \begin{array}{c}
\text{C} \\
\mid \\
\text{H} \\
\mid \\
\text{X}
\end{array} \xrightarrow{\text{ZnCl}_2} \begin{array}{c}
\text{R} \\
\mid \\
\text{O} \\
\mid \\
\text{X}
\end{array}
\end{align*}
\]

(16) (6) (17)

The condensation of the acetylenic ester (16) with resorcinol (6; \(X = \text{OH}\)) in the presence of zinc chloride yielded the 4-phenylcoumarin (17).

The dehydrogenation of dihydrocoumarins (18) has been shown to give coumarins, but in most cases this is of little synthetic value, since dihydrocoumarins are often more difficult to prepare than the corresponding coumarins\textsuperscript{14}.

\[
\begin{array}{c}
\text{O} \\
\mid \\
\text{O}
\end{array}
\]

(18)

A review by Sethna and Phadka\textsuperscript{2} covers the general methods of preparation of coumarins. The review by Wauzonck\textsuperscript{15} in 'Heterocyclic Compounds' gives a comprehensive coverage of the literature on the Pechmann reaction, with tables of coumarins, condensing agents and yields.

B. The Composition of the Grignard Reagent

The composition of Grignard reagents has been the subject of several reviews\textsuperscript{16, 17, 18, 19} and many papers in recent years. The review by Ashby\textsuperscript{19} summarises the extensive literature on the subject up to 1967.

The most widely accepted theory is that put forward by Schlenk and Schlenk\textsuperscript{20} in 1929; they suggested the equilibria (1) and (2) to explain the composite nature of Grignard reagents.
Ashby\textsuperscript{21} studied the degree of association of several Grignard reagents in tetrahydrofuran by ebullioscopic methods. He found that over a wide concentration range the reagents were all monomeric. Following this report, other workers\textsuperscript{22, 23, 24} obtained the same results in diethyl ether at low concentrations (0.1M) for several Grignard reagents; as well as diethylmagnesium, and a mixture of diethylmagnesium and magnesium bromide. These results show that the Schlenk equilibrium (2) is incorrect, and the composition does not involve the dimeric \textit{R}_2\textit{Mg} \cdot \textit{MgX}_2' structure.

Some association occurred in ether at higher concentrations, for which Ashby\textsuperscript{23} postulated a symmetrical dimeric species involved in the following equilibrium (3).

\begin{equation}
(R\textit{MgX})_2 \rightleftharpoons 2R\textit{MgX} \rightleftharpoons \textit{R}_2\textit{Mg} + \textit{MgX}_2
\end{equation}

Since the Grignard reagent exists as an equilibrium mixture, kinetic experiments were carried out in an attempt to demonstrate which species takes part in the reaction with a carbonyl compound.

The reaction of dimethylmagnesium with a benzophenone in ether was found to proceed some ten times faster than the corresponding reaction of methylmagnesium bromide\textsuperscript{25, 26}. Only one of the two potentially reactive alkyl groups in dimethylmagnesium actually reacted. The reaction with methylmagnesium bromide was reported to follow a third-order law, and to be dependent on the concentration of carbonyl compound\textsuperscript{26}. Thus the rate-determining step involves the reaction with the Grignard reagent and not the dissociation of the Grignard reagent. Since the dissociation of the Grignard reagent must therefore be fast, it was concluded that dimethylmagnesium was not an intermediate reactive species in a solution of a Grignard reagent in ether.
In his review, Ashby suggested the following conclusions.

1) 'RMgX' species exists in diethyl ether and in tetrahydrofuran.

2) In diethyl ether at low concentrations (0.3 M) the reagent is mainly the monomeric 'RMgX' species. At higher concentrations association occurs, which may be represented as in the equilibrium (4).

\[ \text{etc. } \xrightarrow{\text{Trimer}} (\text{RMgX})_2 \xrightarrow{\text{2RMgX}} \text{R}_2 \text{Mg + MgX}_2 \xrightarrow{\text{(R}_2 \text{Mg)}_2 } \text{etc} \]

The bonding in e.g. the trimer, is represented as follows:

\[
\begin{array}{c}
\text{R} \\
\text{Mg} \\
\text{X} \\
\text{H}_2 \text{OEt} \\
\end{array}
\begin{array}{c}
\text{R} \\
\text{Mg} \\
\text{X} \\
\text{H}_2 \text{OEt} \\
\end{array}
\begin{array}{c}
\text{R} \\
\text{Mg} \\
\text{X} \\
\text{H}_2 \text{OEt} \\
\end{array}
\]

3) In tetrahydrofuran over a wide concentration range the reagent exists as a roughly equivalent mixture of 'RMgX', 'R_2 Mg' and 'MgX_2' in equilibrium.

Smith et al., from thermochemical experiments in ether and tetrahydrofuran, with solutions of dialkylmagnesium and magnesium halides, came to similar conclusions.

Salinger and Mosher compared the infrared spectra of solutions of Grignard reagents and the corresponding dialkylmagnesium reagent in ether and in tetrahydrofuran. In ether, the spectra of the two types of reagent were identical. In tetrahydrofuran, however, the spectra were noticeably different, and were interpreted in terms of the Schlenk equilibrium (1).

\[ 2\text{RMgX} \xrightarrow{\text{R}_2 \text{Mg + MgX}_2 } -1 \]

Infrared spectroscopy was used by Ashby et al. to demonstrate kinetically that dimethylmagnesium is a reactive species in a solution of methylmagnesium bromide. In the publication however no mention of solvent was made.
Several recent papers\textsuperscript{30, 31, 32, 33} have reported the use of low-temperature nuclear magnetic resonance spectroscopy for investigating the composition of Grignard reagents. At low temperatures, down to \(-105^\circ\), good resolution of the methyl protons of methylmagnesium bromide, and dimethylmagnesium in ether were reported. Ashby\textsuperscript{32} found that initially a time averaged signal from the two species was seen, which resolved into two signals as the temperature was decreased, with precipitation of magnesium bromide. They suggested that since the signals for dimethylmagnesium in ether only appeared slowly as magnesium bromide precipitated, the Schlenk equilibrium (1) lay mainly to the right.

\[
\text{Me}_2\text{Mg} + \text{MgBr}_2 \rightleftharpoons 2\text{MeMgBr} \quad -(1)
\]

It was reported that in tetrahydrofuran\textsuperscript{33} it was not possible to observe distinct signals for the two species, and at low temperature the equilibrium (1) had moved over completely to the left.

Investigations into tert-butylmagnesium halides in ether and tetrahydrofuran, proved to be more successful\textsuperscript{33}. The nmr spectra of tert-butylmagnesium chloride in ether at room temperature showed only a time averaged signal. At \(-26^\circ\) however, the signal was resolved for the two species. In tetrahydrofuran, two signals were observed at room temperature, which did not coalesce at \(+65^\circ\) (the boiling point of tetrahydrofuran). They concluded again, that in ether the equilibrium (1) was applicable, but was shifted to the right, and for the reagent in tetrahydrofuran the equilibrium (1) was roughly statistical.

Similar results have also been obtained with arylmagnesium halides\textsuperscript{30, 31}. The present theory on the composition of the Grignard reagent is therefore, that in tetrahydrofuran at most concentrations, an equilibrium with 'RMgX', 'R_2Mg' and 'MgX_2' exists. In diethyl ether however, the reagent is mainly 'RMgX' at low concentrations (0.3M) and becomes progressively more associated into (RMgX)_n at higher concentrations.
A further complicating factor in the composition of Grignard reagents is the degree to which they are solvated in solution. Stucky and Rundle\textsuperscript{34} found by X-ray studies that phenylmagnesium bromide crystals exist as \textit{PhMgBr} \cdot 2Et\textsubscript{2}O. In solution they have normally been represented as being the dietherate\textsuperscript{16, 17, 20}, but other molecules of solvent in both diethyl ether and tetrahydrofuran are likely to be loosely bound around the inner shell, and thus the actual number of solvent molecules involved is likely to be difficult to determine in such a changing environment.

C. The Reaction of Grignard Reagents with $\alpha, \beta$-Unsaturated Esters.

Grignard reagents may react with $\alpha, \beta$-unsaturated esters in the same manner as with saturated esters to give the corresponding ketone or alcohol.

$$
R'\text{COOR}'' \xrightarrow{\text{R''MgX}} R'\text{COR}''' \rightarrow R'\text{C(OH)}(R''')_2
$$

Conversely, Grignard reagents may react by 1,4-addition to unsaturated esters to give the corresponding saturated ester.

$$
R''-\text{CH}=\text{CH}-(R''')_2 \rightarrow R''-\text{CH}=\text{CH}-\text{COR}'
$$

The reaction may involve normal addition to the ester function, followed by conjugate addition (1,4-) to the resulting $\alpha, \beta$-unsaturated ketone.

$$
R''-\text{CH}=\text{CH}-(R''')_2 \rightarrow R''-\text{CH}=\text{CH}-(R''')_2 \rightarrow R''-\text{CH}-(R''')_2
$$

The most general method of representing the normal reaction, put forward by Grignard\textsuperscript{35} in 1901, involves the formation of an intermediate magnesium halide complex, as shown below:
It is now considered that the mechanism involves a six-membered intermediate. Similarly, the mechanism suggested for the conjugate addition of Grignard reagents to \( \alpha\beta \)-unsaturated esters involves a six-membered transition state with either the alkylmagnesium halide or dialkylmagnesium. A series of experiments were carried out by Kohler et al. in an attempt to correlate normal and conjugate addition modes with the nature of the substituent groups on the unsaturated ester. Thus, various \( \alpha \)-substitute cinnamic esters (19) were treated with both methyl and phenylmagnesium halides.
Generally, methylmagnesium iodide yielded mainly the 1,2-addition product (21), and phenylmagnesium bromide mainly the 1,4-product (20). However, both reagents gave the normal addition product (21) when the α-substituent was electron-donating (e.g., R = CH₃), and the conjugate addition product (20) was formed when the α-substituent was strongly electron-withdrawing (e.g., R = CN).

Many other results[^40]^[41]^[42]^[43] have been reported for the reaction of Grignard reagents with α,β-unsaturated esters. Generally, it has been found that moderate yields of conjugate addition products are obtained with Grignard reagents other than methylmagnesium halide. However, the steric and electronic contributions of the substituents can alter the mode of addition. Table I below shows how changing a substituent on an α,β-unsaturated ester affects the type of product obtained.

Several substituted cinnamic esters (22) have been treated with Grignard reagents, the corresponding type of product obtained, either saturated ester (23) or unsaturated carbinol (24) are shown in Table I below.

<table>
<thead>
<tr>
<th>R'</th>
<th>R''</th>
<th>R'''</th>
<th>Type of Grignard addition</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>1,2-</td>
<td>(24)</td>
<td>38, 39</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>1,4-</td>
<td>(23)</td>
<td>38, 39</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>1,2-</td>
<td>(24)</td>
<td>39</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>1,2-</td>
<td>(24')</td>
<td>39a</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>1,4-</td>
<td>(23)</td>
<td>38</td>
</tr>
</tbody>
</table>
The presence of iron and manganese impurities in the magnesium used for preparing the reagents, has resulted in reduced yields of conjugate addition product in some reactions. It was suggested that in these examples the impurity catalysed a secondary reaction leading to a product formed by the Michael addition of the conjugate addition product with the starting ester.

The presence of catalytic quantities of cuprous chloride in the reaction of methylmagnesium bromide with isophorone (25), was found to alter the mode of addition of the Grignard reagent from 1,2- to 1,4-.

Thus, treatment of isophorone (25) with methylmagnesium bromide yields the carbinol (26) and its dehydration product, the cyclohexadiene (27). In the presence of cuprous chloride however, the cyclic ketone (28) is obtained.

Following the report on this work, the effect of catalytic quantities (1 - 5%) of cuprous chloride on the reaction of Grignard reagents with \(\alpha,\beta\)-unsaturated esters was investigated. Generally, in the presence of cuprous chloride the yields of the 1,4-addition products were improved. Munch-Petersen found that the presence of cuprous chloride altered the mode of addition with several ethyl esters, from 1,2- to predominantly 1,4-.

Nielson et. al. investigated the effects
of inverse addition of the Grignard reagent either with or without cuprous chloride. Little difference in the yields of product was found with either the normal or the inverse methods of Grignard addition in the absence of catalyst. With cuprous chloride present, the yield of conjugate addition product was significantly larger when the inverse method of Grignard addition was used. Andersen and Munch-Petersen compared reactions at 0° and -10°, and found no difference in the yields of products.

The results of a series of experiments by Munch-Petersen and Andersen suggested that cuprous chloride had a limited life-time as a catalyst in a Grignard reagent solution. They found that cuprous chloride had little effect on the yields of product when it was added in one portion before ester addition was started. If however, it was added in small portions concurrently with ester solution, the yields of conjugate product were improved.

The reaction of Grignard reagents with \( \alpha,\beta \)-acetylenic esters gave exclusively the 1,2-addition product under normal conditions. In the presence of catalytic quantities of cuprous chloride, high yields of the 1,4-addition products were obtained.

The composite nature of a Grignard reagent in solution (c.f. the Schlenk equilibrium) affects the mode of addition of Grignard reagents to \( \alpha,\beta \)-unsaturated esters. Jacobsen et al. investigated the effects of various reagents with sec-butyl crotonate (29) in ether.

\[
\begin{align*}
\text{CH}_2\text{-CH} &= \text{CH-COOBu}^\text{sec} \\
\text{CH}_2\text{-CH} &= \text{CH-COOBu}^\text{sec}
\end{align*}
\]

Three types of reagent were used in the reactions.

1) An alkyl Grignard reagent (from magnesium and an alkylhalide).
2) A dialkylmagnesium reagent (prepared by adding dioxan to the Grignard solution and precipitating the halide).
3) An alkylmagnesium halide (from addition of magnesium halide to a Grignard reagent). The yields of the saturated ester (30) are shown in Table 2 below.
Table 2

<table>
<thead>
<tr>
<th>Reagent</th>
<th>% Yield of Ester (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_2$Mg</td>
<td>87</td>
</tr>
<tr>
<td>$R$MgBr + $R_2$Mg</td>
<td>77</td>
</tr>
<tr>
<td>RMgBr</td>
<td>50</td>
</tr>
</tbody>
</table>

These results show that the dialkylmagnesium reagent promotes 1,4-addition.

Riegel et al.\(^5\) compared the yields of conjugate addition product (32) from the reactions of $\alpha$-naphthylmethyl cadmium chloride and the corresponding magnesium reagent with several alkylidenemalonic esters (31).

\[
\begin{align*}
R-CH = O(COOEt)_2 & \rightarrow \\
\end{align*}
\]

(31)

The cadmium reagent in each case produced a higher yield of the malonic ester (32, R = Me, Et or Pr\(^i\)) than did the corresponding magnesium reagent.

The reaction of Grignard reagents, other than methylmagnesium halides, with $\alpha$, $\beta$-unsaturated esters tend to give the 1,4-addition products. Methylmagnesium halides normally yield the 1,2-addition products. The presence of cuprous chloride increases the yields of conjugate addition product, and in many instances alters the mode of addition from 1,2- to
1,4-addition. Similarly, examples of increased yields of 1,4-addition products with cadmium and with dialkylmagnesium reagents have been reported.

D. The Reaction of Grignard Reagents with Coumarins.

The reaction of Grignard reagents with coumarin, unlike \( \alpha, \beta \) -unsaturated esters, is reported to give mainly 1,2-addition products. There are three possible type of products which may be produced by 1,2-addition, as shown below:

\[
\begin{align*}
\text{O} & \xrightarrow{\text{R}-\text{RMgX}} \text{R} - \text{O} - \text{O} - \text{H} \\
\text{R} & \xrightarrow{\text{R}-\text{O}} \text{R} - \text{O} - \text{H} \\
\end{align*}
\]

The product produced by single 1,2-addition can exist in two forms, either of which with acid during work-up will afford another product, thus:

\[
\begin{align*}
\text{R} - \text{O} - \text{O} - \text{H} & \xrightleftharpoons{\text{HX}} \xrightarrow{\text{HX}} \left[ \begin{array}{c} \text{R} - \text{O} + \text{X}^- \\ \end{array} \right] \\
\end{align*}
\]

The product produced by double 1,2-addition will yield the corresponding dehydrated product, when treated with acid during the work-up procedure.
Similarly, the product produced by 1,2- plus 1,4-addition can exist in two forms, either of which with acid during work-up will yield the dehydrated product, as shown below:

The type of product produced in the reaction was thought to be dependent on the position and type of substituent on the coumarin ring, and the nature of the Grignard reagent.\textsuperscript{58}

Treatment of coumarin (9) itself with methyl or phenylmagnesium bromide was found by Decker and Fellenburg\textsuperscript{59} to give the corresponding benzopyrylium salt (33; \( R = \text{Me or Ph} \)).
They confirmed the structures by independent synthesis.

Similarly, Willstatter et al. synthesized benzopyrylium salts from methoxycoumarins and aryl Grignard reagents.

The reaction of an excess of Grignard reagent with coumarin yielded disubstituted 2H-chromenes (34).<ref>

$\text{(34)}$

With methyl or ethylmagnesium iodide the dialkylchromene (34; $R = \text{Me or Et}$) was obtained, plus an unidentifiable high boiling product. With isopropylmagnesium bromide, only the high boiling product was obtained. The reaction of phenylmagnesium bromide with coumarin (9) yielded a product thought to have the structure of the diol (35; $R = \text{Ph}$), but the compound could not be cyclised with acid to the chromene (34; $R = \text{Ph}$).

Lowenbein et al. repeated the reaction with phenylmagnesium bromide and claimed to have isolated the 2,2-diphenylchromene (34; $R = \text{Ph}$) and the 2,4-diphenylchroman-2-ol (36).

$\text{(36)}$

$\text{(37)}$

The latter compound they then treated with acetic acid to obtain the 2,4-diphenyl-4H-chromene (37).
Similarly, they obtained corresponding chromanols \((38; R^* = \text{Me or H})\) and 4H-chromenes \((39; R^* = \text{Me or H})\) from reaction of phenylmagnesium bromide with 5,7-dimethyl, 4,6-dimethyl and 4,7-dimethylcoumarins.

The reaction of phenylmagnesium bromide with coumarin was repeated by Barnes et al.\(^63\) and Holmberg et al.\(^64\). They were able, by using more modern methods of structure analysis, to determine that the diphenyldiol \((35; R = \text{Ph})\) and the diphenylketone \((40)\) were the main products of the reaction.

\[
\begin{align*}
&\text{Ph} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
\end{align*}
\rightarrow
\begin{align*}
&\text{Ph} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
\end{align*}
\]

Acid treatment of the two compounds gave respectively, 2,2-diphenyl-2H-chromene \((34; R = \text{Ph})\) and 2,4-diphenyl-4H-chromene \((37)\).

The products obtained from reaction of phenylmagnesium bromide with substituted coumarins depends on the position of substitution. Thus with 3-phenyl \(^65\) or 3-methyl-coumarin \(^66\), the corresponding 2,3,4-trisubstituted chroman-2-ol \((41; R = \text{Ph or Me})\) was obtained, which with acetic acid afforded the corresponding 4H-chromene \((42; R = \text{Ph or Me})\).

\[
\begin{align*}
&
\text{R} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
&\text{HO} & & \\
\end{align*}
\rightarrow
\begin{align*}
&
\text{R} & & \\
&\text{Ph} & & \\
&\text{Ph} & & \\
\end{align*}
\]

With 4-methyl or 4-methoxycoumarin \(^66\), the 2,2-diphenyl-2H-chromenes \((43; R = \text{Me or MeO})\) were obtained.
The mechanism suggested for the formation of the chroman-2-ols in involves initial attack of one molecule of reagent at the carbonyl carbon atom, followed by ring-opening and then conjugate addition to the resulting \( \alpha,\beta \)-unsaturated ketone. The reaction may be represented in the following manner:

\[ \text{RMgX} \quad \rightarrow \quad \text{R} \quad \text{MgX}^{-} \]

Attempts were made by several workers to prepare benzopyrylium salts from 4-substituted coumarins. The reactions of 3-methyl, 3-phenyl and 3-methoxycoumarins (44) with phenylmagnesium bromide in dilute solution proceeded smoothly to give good yields of the corresponding benzopyrylium salts (45; \( R = \text{Me, MeO or Ph} \)).

\[ (44) \quad \rightarrow \quad (45) \]

With 4-methyl or 4-phenylcoumarin however, little reaction occurred with phenylmagnesium bromide in dilute solution. In more concentrated solution, the corresponding 2,2-diaryl-2H-chromene (43; \( R = \text{Me or Ph} \)) was formed. Similar results were obtained on treatment of 4-methyl-7-methoxycoumarin with several aryl Grignard reagents.
Shriner and Sharp treated coumarin (9) itself with a series of n-alkyl Grignard reagents.

\[
\text{RMgX} \quad \text{C}^\text{R} \quad \text{O} \quad \text{O} \\
\text{(9)} \quad \rightarrow \quad \text{R} \quad \text{C}^\text{R} \quad \text{O} \quad \text{O} \\
\text{(34)}
\]

Table 3

<table>
<thead>
<tr>
<th>'RMgBr' (R=)</th>
<th>% Yield of Chromene (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>59</td>
</tr>
<tr>
<td>ethyl</td>
<td>64</td>
</tr>
<tr>
<td>n-propyl</td>
<td>68</td>
</tr>
<tr>
<td>n-butyl</td>
<td>70</td>
</tr>
<tr>
<td>n-amyl</td>
<td>77</td>
</tr>
<tr>
<td>n-hexyl</td>
<td>83</td>
</tr>
<tr>
<td>n-heptyl</td>
<td>91</td>
</tr>
</tbody>
</table>

They isolated only the corresponding 2H-chromenes (34) from the reactions, as is shown in Table 3 above. The mechanism they suggested for the reaction involved the addition of one molecule of reagent to the carbonyl group, followed by double decomposition with another molecule, without ring-opening of the lactone.

The mechanism above was shown to be incorrect by Smith and Ruoff, who obtained the corresponding carbinols (35; \(R = \text{Me or Et}\)) from the reaction of the Grignard reagents with coumarin (9). The structure of the carbinols (35) were verified by hydrogenation to the known saturated carbinols (46).
Treatment of the carbinols (35; R = Me, Et or Bu\(^2\)) will glacial acetic acid afforded the corresponding chromene (34; R = Me, Et or Bu\(^2\)).

From the above results, the reaction obviously does involve ring-opening. To remain consistent with the mechanism suggested for \((1,2 + 1,4)\)-addition, the reaction probably proceeds in the manner shown below:

The initial reaction of the Grignard reagent with the coumarin, involving one molecule of reagent in a four-membered intermediate as shown above, is only representative. The reaction is likely to involve two molecules of reagent in a six-membered intermediate.
Razdan et al. treated a pyridyl coumarin with a Grignard reagent at various temperatures.

\[
\begin{align*}
(47) & \quad \text{R=CH(CH}_2\text{)}_2\text{CH(CH}_3\text{)}_2\text{C}_5\text{H}_11. \\
(48) & \quad (49) \\
(50) & \quad (51)
\end{align*}
\]

They found that the reaction of the 4-pyridylcoumarin (47) with methylmagnesium bromide in an ether-anisole mixture at 50°, yielded the triol (48), which on treatment with glacial acetic acid afforded the 2H-chromene (49).

When the reaction was carried out at 100° however, a third molecule of reagent reacted with the coumarin (47) to give the 2,2,3-trimethyltriol (50), which again could be cyclised with acetic acid to the trimethylchroman (51). They attributed 1,3-addition to the electron withdrawing effect of the pyridyl group resulting in the Grignard reagent adding to the vinylpyridine (48).

A few examples of 1,4-addition of Grignard reagents to coumarins have been reported, the products being 3,4-dihydrocoumarins.
Holmberg treated ethyl 3-coumarin-carboxylate (52) with phenylmagnesium bromide to afford ethyl 4-phenyl-3,4-dihydro-3-coumarin-carboxylate (53). Treatment of the remaining material from the reaction with potassium hydroxide, yielded 3,4-dihydro-4-phenylcoumarin (54) and the propiophenone (40). The latter compound (40) was produced by 1,2- plus 1,4-additions, followed by hydrolysis and decarboxylation with potassium hydroxide. The dihydrocoumarin (54) was obtained by hydrolysis and decarboxylation of the ester (53).

The above results are expected if the coumarin (52) is regarded as a substituted methylenemalonic ester (55).

The 4-position of the coumarin, like the β-position of the methylenemalonic ester, is doubly activated for nucleophilic addition by having two electron withdrawing (ester) groups attached to the 3- or α-position.

Holmberg has also obtained ethyl 4-phenyl-3-coumarin-carboxylate (57) from the reaction of phenylmagnesium bromide with ethyl 4-methoxy-3-coumarin-carboxylate (56).
The mechanism suggested by Holmberg involved 1,4-addition of the Grignard reagent to the unsaturated ester group, followed by 1,4-elimination of methoxymagnesium bromide as shown below:

Other ethyl 4-aryl-3,4-dihydro-3-coumarin carboxylates (58; R = 3-methyl-2-methoxyphenyl, 2,5-dimethoxyphenyl, and 2-methoxyphenyl) have been obtained by the reaction of the corresponding arylmagnesium halide with ethyl 3-coumarin carboxylate (52)\(^{74b,74c}\).

No other examples of the 1,4-addition of organomagnesium reagents to coumarins could be found in the literature.

E. Methods for the Preparation of Dihydrocoumarins

The literature on the synthesis of 3,4-dihydrocoumarins is more limited than on the synthesis of coumarins. There are two general methods of preparing dihydrocoumarins; by hydrogenation of coumarins, and by the condensation of an activated olefin with a phenol in the presence of a condensing agent.

The hydrogenation of coumarin (9) to dihydrocoumarin (18) has been effected in the presence of both Raney nickel\(^{75,76,77}\) at between 40° and
100°, and copper chromite\(^76\) at 140° and 100 Ats. pressure.

Hydrogenation in the presence of 10\% palladium on charcoal was found by Spath et. al.\(^78\), to proceed at room temperature.

In a similar manner, substituted 3,4-dihydrocoumarins have been prepared by hydrogenation of the corresponding substituted coumarin\(^79\).

The condensation of a phenol with an \(\alpha,\beta\) -unsaturated nitrile or carboxylic acid to give a dihydrocoumarin may be considered as analogous to the Pechmann condensation, and proceeds by a similar mechanism.

Fischer and Nouri\(^80\) condensed phenylacrylonitrile (59) and phloroglucinol (60) using hydrogen chloride in the presence of zinc chloride, to yield 3,4-dihydro-5,7-dihydroxy-4-phenylcoumarin (61). They suggested the reaction proceeded via an intermediate, unstable imine, which was readily hydrolysed with water to the dihydrocoumarin (61).

Gupta and Paul\(^81\) have obtained several 3- and 4-aryldihydrocoumarins by this method.

Sato et. al.\(^82\) used aluminium chloride with hydrogen chloride as condensing agent, with various alkylacrylonitriles (62) and phenols (63) to obtain for example, 3,4-dihydro-4,7-dimethylcoumarin (64).
Similarly, with aluminium chloride and hydrogen chloride, Amakasu obtained various 4-methyl-3,4-dihydrocoumarins from allylnitrite and phenols.

Cinnamic acid and a phenol with concentrated sulphuric acid is reported by Simpson et al. to give on heating, a 4-phenyl-3,4-dihydrocoumarin (65).

The same product was obtained by heating the corresponding cinnamate ester (66) with concentrated sulphuric acid.

Hasebe compared the yields of product obtained with different condensing agents. He found that in the condensation of m-cresol (63) with 3-methylcinnamic acid (67), the highest yield of dihydrocoumarin (68) was obtained using polyphosphoric acid.

A new synthesis of 3,4-dihydrocoumarins is reported from purely alicyclic precursors by Ramani et al. They heated a solution of 2-methylcyclohexan-1,3-dione (69) and 1,1-bis-diethylaminomethyl acetone (70) in benzene, with pyridine. The resulting solution was then treated with dry hydrogen chloride to give 3,4-dihydro-5,6,8-trimethylcoumarin (71).
It is likely that the reaction can be adapted so that other substituted dihydrocoumarins may be synthesised by this route.

The only examples of the preparation of substituted dihydrocoumarins from Grignard reagent addition to a coumarin, have already been described.

F. The Reaction of Grignard Reagents with Dihydrocoumarins

The reaction of Grignard reagents with dihydrocoumarins are much simpler than the corresponding reaction with coumarins. Due to the absence of the conjugated double bond in dihydrocoumarins only 1,2-addition is possible. This can give rise to a chroman-2-ol (72) from addition of one molecule of reagent to dihydrocoumarin (18), and to a ring-opened carbinol (46) from the addition of two molecules:
The chromanol (72) may exist in either the enolic (72) or ketonic (73) form, and treatment of either with acid during work-up gives the 4H-chromene (74). Similarly the carbinol (46) can be cyclised to the chroman (75) with acid.

Bridge et. al.\(^{37}\) in 1937 appear to be the first workers to report the reaction of a dihydrocoumarin with a Grignard reagent. They obtained 7-benzyloxy-2,2-dimethylchroman (77) from treatment of the dihydrocoumarin (76) with methylmagnesium bromide.

\[
\text{MeMgBr} \quad \text{MeMgI}
\]

Other authors\(^{88, 89, 90}\) have since obtained substituted chromans from the reaction of Grignard reagents with dihydrocoumarins.

Thus, treatment of the dihydrocoumarin (78) with methylmagnesium iodide yielded the chroman (79)\(^ {90}\). The reaction of a Grignard reagent with a dihydrocoumarin (18) is analogous to the reaction with a coumarin (page 15), and probably proceeds via the chromanol (72) or ketone (73), to give the carbinol (46).
In an attempt to verify this type of mechanism, Smith et al. treated dihydrocoumarin (18) with a series of alkyl Grignard reagents, under varied reaction conditions. In each case the carbinol (46; \( R = \text{alkyl} \)) was obtained, while none of the required chromanol (72) or ketone (73) could be isolated. The carbinols (46; \( R = \text{alkyl} \)) with acid, afforded the chromans (75; \( R = \text{alkyl} \)).

Geissman treated 3,4-dihydro-4-phenylcoumarin (54) with phenylmagnesium bromide in an attempt to prepare the chroman-2-ol (36) or the ketone (40) by single 1,2-addition.
The only product isolated from the reaction was the carbinol (80), by double 1,2-addition of the reagent. The same product was also isolated on treatment of the chroman-2-ol (36; or as its isomer 40) with phenylmagnesium bromide. Treatment of the carbinol (80) with acetic acid afforded the chroman (81).

From his results, Geisman suggested that the chroman-2-ol (36) or the isomeric ketone (40) is an intermediate in the reaction of phenylmagnesium bromide with the dihydrocoumarin (54) to give the carbinol (80).

A short review on the reaction of Grignard reagents with dihydrocoumarins is to be found in 'Heterocyclic Compounds, Vol. II'.

A. Preparation of Coumarins

For the work described in this thesis a series of substituted coumarins were required. Several of these coumarins were previously prepared by Razden et al.\textsuperscript{73}, who used the method of Pechmann.\textsuperscript{1} (The generally accepted method of numbering coumarins is shown below).

Thus, they treated ethyl isonicotinoylacetate (82) and the resorcinol (83; \( R = \text{alkyl} \)) with a mixture of concentrated sulphuric acid and phosphorus oxychloride, to obtain the corresponding coumarin (47; \( R = \text{alkyl} \)).

The procedure described by Razden et al. was used for preparing most of the coumarins, as indicated in Table 1:

In each case the \( \beta \)-ketoester (84) and the phenol (85) were treated with a condensing agent to give the corresponding coumarin (86).
<table>
<thead>
<tr>
<th><strong>β</strong>-Ketoester (84)</th>
<th>Phenol (85)</th>
<th>Condensing Agent</th>
<th>Coumarin (86)</th>
<th>Yield, %</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl isonicotinoylacetae</td>
<td>5-n-heptylresorcinol</td>
<td>H$_2$SO$_4$/POCl$_3$</td>
<td>4-pyridyl</td>
<td>n-heptyl</td>
<td>CH</td>
</tr>
<tr>
<td>&quot;</td>
<td>5-(2-octyl)resorcinol</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2-octyl</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>orcinol monohydrate</td>
<td>&quot;</td>
<td>methyl</td>
<td>&quot;</td>
<td>36$^\circ$</td>
</tr>
<tr>
<td>&quot;</td>
<td>2-m-cresol</td>
<td>&quot;</td>
<td>&quot;</td>
<td>H</td>
<td>20</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>14$^a$</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
</tr>
<tr>
<td>Ethyl picolinoylacetae</td>
<td>5-(2-octyl)resorcinol</td>
<td>H$_2$SO$_4$/POCl$_3$</td>
<td>2-pyridyl</td>
<td>2-octyl</td>
<td>OH</td>
</tr>
<tr>
<td>&quot;</td>
<td>orcinol monohydrate</td>
<td>&quot;</td>
<td>methyl</td>
<td>&quot;</td>
<td>50</td>
</tr>
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<td>&quot;</td>
<td>3-pyridyl</td>
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<td>OH</td>
</tr>
<tr>
<td>&quot;</td>
<td>2-m-cresol</td>
<td>&quot;</td>
<td>&quot;</td>
<td>H</td>
<td>5</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
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<td>&quot;</td>
<td>19$^a$</td>
</tr>
<tr>
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<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
</tr>
<tr>
<td>Ethyl benzoylacetae</td>
<td>5-(2-octyl)resorcinol</td>
<td>H$_2$SO$_4$/POCl$_3$</td>
<td>phenyl</td>
<td>2-octyl</td>
<td>OH</td>
</tr>
<tr>
<td>&quot;</td>
<td>orcinol monohydrate</td>
<td>&quot;</td>
<td>methyl</td>
<td>&quot;</td>
<td>15</td>
</tr>
<tr>
<td>ω-Ketoester (84)</td>
<td>Phenol (85)</td>
<td>Condensing Agent</td>
<td>Coumarin (86)</td>
<td>Yield %</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------</td>
<td>--------------------------------</td>
<td>----------------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>Ethyl ω-anisoylacate</td>
<td>orcinol monohydrate</td>
<td>H₂SO₄/POCl₃</td>
<td>ω-methoxy methyl OH 0</td>
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<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>ω-methoxy phenyl &quot; &quot; 0^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl ω-anisoylacate</td>
<td>&quot;</td>
<td>&quot;</td>
<td>ω-methoxy phenyl &quot; &quot; 0</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>90% H₂SO₄</td>
<td>ω-methoxy phenyl &quot; &quot; 8^a</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>HCl/EtOH</td>
<td>ω-methoxy phenyl &quot; &quot; 0</td>
<td>95</td>
<td></td>
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<tr>
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<td>&quot;</td>
<td>POCl₃/benzene</td>
<td>ω-methoxy phenyl &quot; &quot; 60</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Ethyl acetoacetate</td>
<td>&quot;</td>
<td>90% H₂SO₄</td>
<td>methyl &quot; &quot; &quot; 77</td>
<td>96</td>
<td></td>
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<td>&quot;</td>
<td>m-cresol</td>
<td>&quot;</td>
<td>&quot; &quot; R 40</td>
<td>97</td>
<td></td>
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<tr>
<td>Ethyl trifluoro-3-oxobutrate</td>
<td>&quot;</td>
<td>H₂SO₄</td>
<td>trifluoromethyl &quot; &quot; 28^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl ω-nitrobenzoylacate</td>
<td>orcinol monohydrate</td>
<td>H₂SO₄/POCl₃</td>
<td>ω-nitro-phenyl &quot; &quot; OH 59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) The reaction mixture was heated in these examples.  b) Isolated as the monohydrate.  c) This coumarin has previously been isolated as the hemihydrate.
Most of the reactions afforded good yields of the required substituted coumarins (86), however in a few cases alternative condensing agents had to be used.

It can be seen from Table I that the reaction of ethyl isonicotinoylacetate (82) with m-cresol (63) was tried with several condensing agents, and the highest yield of the coumarin (87) was obtained with 90% sulphuric acid.

Attempts to prepare the o-methoxyphenylcoumarin (86; \( \text{R}' = \text{o-MeOPh} \), \( \text{R}'' = \text{Me} \)) by the usual procedure was unsuccessful the starting ketoacetate (83) being recovered in high yield.
A possible explanation for this lack of reaction is that since the ketoacetate (88) has an electron donating methoxy group in the \( \alpha \)-position of the phenyl ring, there may be resonance as indicated (88) and (88a), such that nucleophilic attack at the carbonyl carbon atom is prevented. Alternatively, steric hindrance by the \( \alpha \)-methoxy group may prevent nucleophilic attack.

Attempts were then made to prepare the \( p \)-methoxyphenylcoumarin (89), where again, the starting ketoacetate (90) might be considered to be unreactive for reasons analogous to that proposed for the \( \alpha \)-methoxy isomer. However, a high yield of the coumarin (89) was obtained using phosphorus oxychloride in benzene. It appears from this result that steric hindrance was responsible for the lack of reaction with the \( \alpha \)-methoxy isomer.

Interestingly, the attempt to prepare the \( p \)-methoxyphenylcoumarin (89) using hydrogen chloride in ethanol, yielded a quantity of \( p \)-methoxyacetophenone. This compound arose presumably by acid hydrolysis followed by decarboxylation of the ketoacetate (90).

It can be seen from Table I that several trends are apparent in the yield of products from the reactions. Thus, the highest yields of the coumarins (86) were obtained from phenols (85) with a long alkyl side-chain.
Conversely, the yields of coumarins obtained from the reactions with $\mu$-cresol (65) are generally found to be lower than those obtained with orcinol (91). Similar results have been reported previously.

One further compound, the $p$-aminophenylcoumarin (93), was prepared by reduction of the corresponding $p$-nitrophenoxybenzoesulfonic acid (92) with tin and hydrochloric acid.

Most of the above coumarins (Table I) are stable, yellow crystalline solids, fairly insoluble in most solvents. They all give characteristic infrared spectra, with a band at $\nu_{\text{max}} 1680-1720 \text{ cm}^{-1}$ due to the 'C = O' group of the ester.
B. The Reaction of Grignard Reagents with Coumarins.

The reaction of Grignard reagents with 4-substituted coumarins (94; $R'$ = alkyl or aryl) is reported to yield only the carbinols (95; $R'$ = alkyl or aryl, $R''$ = alkyl or aryl), by 1,2-addition. Treatment of these carbinols with acid, during or after work-up, was found to yield the corresponding 2H-chromene (96; $R'$ = alkyl or aryl, $R''$ = alkyl or aryl). Razdan et al. used this reaction to prepare several 7-alkyl-2H-chromenes (49). (The generally accepted method of numbering chromenes is shown on structure (49) below.)

Thus, they treated a series of 7-alkylcoumarins (47) with an excess of a methyl Grignard reagent in an ether-anisole mixture at 50°C. In each case the corresponding alkylcarbinol (48) was obtained.
In some instances they isolated the pure carbinol (48; \( R = \text{alkyl} \)), but generally the crude product was treated directly with glacial acetic acid to yield the corresponding 2H-chromene (49; \( R = \text{alkyl} \)).

The series of 7-alkyl-2H-chromenes (49) were prepared by Rasdan et al. because of their structural similarities to the biologically active cannabinoids. Several of the 7-alkyl-2H-chromenes (49) have been found to possess interesting biological activity, and thus the work described in this thesis began as an attempt to prepare biologically active pyridyl-chromenes related to those previously prepared.

Initially, the 7-n-heptylcoumarin (47; \( R = C_7H_{15} \)) was treated with an ethyl Grignard reagent in ether, in place of ether-anisole, because of the difficulties in isolating products from anisole.

![Chemical structures](image)

A low yield (22%) of the intermediate carbinol (97) was obtained, and treatment of this with glacial acetic acid readily yielded the corresponding diethylchromene (2). (The carbinols have all been named as substituted prop-1-en-3-ols (c.f. structure 48), so that they can all easily be recognised as one type of product.) Preliminary efforts to isolate other products from the remaining gum from the reaction were unsuccessful. However, t.l.c. with ethyl acetate on a silica gel plate indicated that mainly one product was present.
The i.r. spectrum of the gum showed no band at \( \sim 1700 \text{ cm}^{-1} \), consistent with the absence of starting coumarin (47), but there was a band at 1760 cm\(^{-1}\) indicative of a carbonyl group, as in the dihydrocoumarin (3). The n.m.r. spectrum showed, amongst other signals, an 'AB' quartet near \( \gamma \) 7, as expected for the 3-methylene group in compound (3).

![Structure (3)](image)

It thus appeared that 1,4-addition of the Grignard reagent to the coumarin had occurred to yield the 4-ethyl-3,4-dihydrocoumarin (3).

Attempts to purify the dihydrocoumarin were unsuccessful, however it was finally isolated as the corresponding methiodide, and the structure confirmed by elemental analysis, n.m.r. and i.r. spectroscopy. (The numbering used for the dihydrocoumarins is shown on the structure (3)).

The reaction of the ethyl Grignard reagent with the coumarin (47; \( R = n\text{-heptyl} \)) was repeated, with a large excess of the Grignard reagent in an ether-benzene mixture, and in tetrahydrofuran, both under reflux. Table 2 shows the results of these two reactions, and the results of the previous reaction.
Table 2

<table>
<thead>
<tr>
<th>Holes of Grignard Reagent/mol of Coumarin</th>
<th>Solvent</th>
<th>% Yield of Carbinol (97)</th>
<th>% Yield of Dihydrocoumarin (3) as the methiodide</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ether</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>ether-benzene</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>tetrahydrofuran</td>
<td>0</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a. Allowing for recovered coumarin.)

In the last two experiments shown in Table 2, none of the carbinol (97) could be isolated, but an increased yield of the dihydrocoumarin (3) was obtained.

It appears from these results that 1,4-addition to a coumarin is promoted by the use of a more polar solvent. However, in all three experiments a high percentage of the starting coumarin is unaccounted for, possibly because of the difficulties encountered in isolation.

The reaction of an ethyl Grignard reagent with the 4-(4-pyridyl) coumarin (47; R = n-heptyl) to give the 4-ethyl-3,4-dihydrocoumarin (3), appears to be the first example of a Grignard reagent adding by the 1,4-mechanism to a 4-substituted coumarin. As it appeared that the alkyl part of the Grignard reagent had affected its mode of addition to the coumarin (47; R = n-heptyl), the reaction was repeated with the methyl and the n-propyl Grignard reagents.

![Molecules](image-url)
The reaction with the methyl reagent, as found by Razdan et. al.\textsuperscript{73}, readily afforded the carbinol (98), which with acid yielded the 2H-chromene (99). With the n-propyl reagent the only product obtained was the 4-(n-propyl)-3,4-dihydrocoumarin (100), isolated as the methiodide.

Since the 1,4-addition of Grignard reagents to coumarins appears to be a novel reaction, except for the examples with a 3-carboxy substituted coumarin, it was decided to investigate more fully the conditions under which 1,2- or 1,4-addition occurs. Because of the difficulties in isolating and purifying the products with a long 7-alkyl side-chain, the experiments were continued using the 7-methyl coumarin (101). It had been found that with the shorter side-chain, the products were more crystalline and easier to isolate, so that a higher percentage of the starting coumarin could be accounted for when treated with Grignard reagents.

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

Since the coumarins, especially those with a short side-chain, are fairly insoluble, most of the Grignard reactions were carried out in tetrahydrofuran. Hence, the coumarin (101) was treated with a series of Grignard reagents in tetrahydrofuran at room temperature. A large
excess of Grignard reagent (10 mol/mol of coumarin) was used; since for 1,2-addition to a coumarin, between three and five moles of reagent are required. From each reaction the carbinol (102; \( R = \text{alkyl or aryl} \)) or the dihydrocoumarin (104; \( R = \text{alkyl or aryl} \)), or a mixture of both was isolated, as recorded in Table 3 below. The carbinols (102; \( R = \text{alkyl or aryl} \)) were treated with acetic acid to yield the corresponding chromenes (103; \( R = \text{alkyl or aryl} \)).

![Diagram](image)

**Table 3**

<table>
<thead>
<tr>
<th>Grignard Reagent ( R = )</th>
<th>% Yield of Carbinol (102)</th>
<th>% Yield of Dihydrocoumarin (104)</th>
<th>% Yield of Chromene (103) from Carbinol (102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>75</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>ethyl</td>
<td>9</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>isopropyl</td>
<td>13</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>phenyl</td>
<td>76</td>
<td>0</td>
<td>80</td>
</tr>
</tbody>
</table>
From Table 3 it can be see that the reactions with the methyl and phenyl reagents afforded only the carbinols (102; \( R = \text{Me or Ph} \)), by 1,2-addition. With the ethyl and isopropyl reagents however, the main products were the corresponding dihydrocoumarins (104; \( R = \text{Et and Pr}^1 \)).

There are several possible contributing factors which will determine the mode of addition of a Grignard reagent to a coumarin. The initial reaction with the coumarin may be represented as follows:
The pyridyl substituent exerts a strongly electron withdrawing effect on the 4-position of the coumarin, due to a combination of a negative inductive and mesomeric effect.

The mode of addition of a Grignard reagent will therefore depend partly on the relative electron deficiencies at the 2- and 4-carbon atoms of the coumarin (105b and 105c). This is particularly important if the Grignard reagent is regarded as an ionic reagent, effectively reacting as $R^-$ and $^{+}\text{MgX}$. A further factor in deciding the mode of addition of the Grignard reagent is the relative hindrance at the 2- and 4-position of the coumarin ring. With a 4-substituted coumarin (c.f. 101) the 4-position may be more sterically hindered than the 2-position. However, due to co-ordination of the magnesium with the carbonyl group, for example as in (105a), the 2-position may become more hindered than the 4-position.

The reaction of a Grignard reagent with an $\alpha,\beta$-unsaturated ester is reported to proceed via a six-membered cyclic intermediate, to afford a 1,4-addition product, as follows:

![Chemical diagram](attachment:image.png)

This mechanism cannot apply to the corresponding reaction with a coumarin since the unsaturated ester part of the coumarin is in the fixed, trans-configuration. If then, the conjugate addition reaction is considered to be the nucleophilic addition of a carbanion $R^-$ to the 4-position of the coumarin ring, then the stability of the carbanion and the carbon-magnesium bond strength of the reagent will affect the reaction. For example, if the carbanion is not very stable (e.g. $\text{Me}^-$), then 1,2-addition may be promoted. This is likely to
occur by the cyclic mechanism (107a) $\rightarrow$ (107b) rather than as carbanion attack.

\[ \begin{array}{c}
\text{X} \\
\text{Ng} \\
\text{R} \\
\text{Ng} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{X} \\
\text{Ng} \\
\text{R} \\
\text{Ng} \\
\end{array} \]

\[ (107a) \quad \rightarrow \quad (107b) \]

a. Effect of 4-Substituents

The possible effects of the electron withdrawing properties of the 4-pyridyl group have already been noted. In an attempt to evaluate the contribution of these effects on the mode of addition of a Grignard reagent to a coumarin, a series of Grignard reactions have been carried out with the 4-(2-pyridyl)coumarin (108) and the 4-(3-pyridyl)coumarin (109).

\[ \begin{array}{c}
\text{R} \\
\text{Ng} \\
\text{OH} \\
\text{CH}_3 \\
\end{array} \quad \begin{array}{c}
\text{R} \\
\text{Ng} \\
\text{OH} \\
\text{CH}_3 \\
\end{array} \]

\[ (108) \quad (109) \]

The strength of the pyridyl substituent as an electron withdrawing group depends on the position of attachment on the pyridine ring and is in the order $2 > 4 > 3$. The 2-pyridyl group is the strongest, because of the proximity of the electron deficient nitrogen. The 3-pyridyl group is the weakest electron withdrawing substituent of the series, since there is no contributing mesomeric shift.
Table 4 below summarises the results obtained from treatment of the 4-substituted coumarins (108 and 109) with a series of Grignard reagents (10 mol excess) in tetrahydrofuran. The products of the reactions were either the 3,4-dihydrocoumarins of type (110) or the carbinols (111), or a mixture of both. Treatment of the carbinol (111) with acetic acid afforded the corresponding 2H-chromene (112).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>R'</th>
<th>R''</th>
<th>% Yield of Dihydrocoumarin (110)</th>
<th>% Yield of Carbinol (111)</th>
<th>% Yield of Chromene (112) from pure carbinol (111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-pyridyl</td>
<td>methyl</td>
<td>55</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ethyl</td>
<td>64</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>isopropyl</td>
<td>70</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>t-butyl</td>
<td>No product could be isolated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>phenyl</td>
<td>73</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3-pyridyl</td>
<td>methyl</td>
<td>0</td>
<td>51</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>ethyl</td>
<td>60</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>isopropyl</td>
<td>87</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>cyclohexyl</td>
<td>73</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>allyl</td>
<td>No reaction occurred</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>phenyl</td>
<td>7</td>
<td>71</td>
<td>90</td>
</tr>
</tbody>
</table>

(a. Isolated directly from the crude reaction as the corresponding chromene (24))
From the results in Table 4 it can be seen that, as expected, only the corresponding 3,4-dihydrocoumarins of type (110) were obtained from the reactions with the 4-(2-pyridyl)coumarin (108), even with the methyl and phenyl Grignard reagents.

With the intention of extending the number of Grignard reagents and investigating the effect of increased size of the alkyl part of the reagent on the mode of addition, the 4-(2-pyridyl)coumarin (108) was also treated with a tert-butyl Grignard reagent. However, a black gum was obtained from the reaction, and no single product could be isolated.

The reaction of Grignard reagents with the 4-(3-pyridyl)coumarin (109), as can be seen from Table 4, yielded the same type of products as were obtained from the 4-(4-pyridyl)coumarin (101). Thus, with the methyl and phenyl reagents mainly the 1,2-addition products were isolated, whilst with the ethyl and isopropyl reagents, the 1,4-addition products were obtained.

It has been reported previously that where 1,4-addition of Grignard reagents to an \( \alpha,\beta \)-unsaturated ester occurs, the methyl Grignard reagent often reacts differently to give the 1,2-addition product. However, the phenyl Grignard reagent is reported to yield 1,4-addition products as readily as other reagents. Thus, it is surprising that with the 4-(4-pyridyl)coumarin (101) and the 4-(3-pyridyl)coumarin (109), the phenyl reagent is similar to the methyl reagent in yielding the 1,2-addition product.
If the mechanism of the reaction with a phenyl reagent is determined by the size of the phenyl group, then the cyclohexyl reagent, being a similar size, should react by the same mechanism. Since the cyclohexyl Grignard reagent reacted to give the 1,4-addition product (113), then the phenyl reagent presumably must react with the coumarins (101 and 109) to give the 1,2-addition product because of the electronic character of the phenyl group.

Since the mode of addition of Grignard reagents to the 4(4-pyridyl) coumarin (101) and the 4-(3-pyridyl)coumarin (109) was similar, the effect of replacing the pyridyl group by a phenyl group was investigated. The electron withdrawing effect due to the phenyl group, will be far less than for the pyridyl group. Thus, it may be expected that 1,2-addition is more likely to occur.

Table 5 below summarises the results obtained from treatment of the 4-phenylcoumarin (114) with a series of Grignard reagents in tetrahydrofuran. In each experiment either the dihydrocoumarin (115) or the carbinol (116) or a mixture of both was obtained. Treatment of the carbinol (116) with glacial acetic acid afforded the corresponding chromene (117).
It can be seen from Table 5 that the type of products obtained are the same as were obtained in the corresponding reactions with the 4-(4-pyridyl)- and the 4-(3-pyridyl)-coumarins (c.f. Tables 3 and 4). Therefore, the inductive effect of the phenyl group must be large enough to make the 4-position of the coumarin ring more electron deficient than the 2-position.

A 4-phenylcoumarin with a long side-chain has also been treated with a methyl Grignard reagent.

Thus, treatment of the coumarin (118) in a benzene-ether mixture at room temperature yielded an oil, from which no product could be isolated until glacial acetic acid had been added. This procedure enabled the chromene (120) to be separated in high yield from the dihydrocoumarin (119), present in low yield. (The different solvent
Although some of the dihydro coumarin (119) was isolated from this reaction, the result is comparable with that obtained for the 7-methylcoumarin (114) in Table 5. In some examples it seems that only the major product was isolated. There was little chance of separating minor products from these reactions unless the yield was at least 10%.

All the 4-substituents of the coumarins used so far have been electron withdrawing to some extent, and so the effect of an electron donating 4-substituent on the mode of addition of a Grignard reagent to a coumarin was investigated. Thus, the p-aminophenylcoumarin (93) was treated with a methyl Grignard reagent in tetrahydrofuran.

![Chemical structure of compound 93]

A black gum was obtained after work-up of the reaction mixture, which from t.l.c. appeared to contain a mixture of products, and no separation of the mixture could be achieved. Although it was realised that the Grignard reagent would interact with the amino group, with the excess of reagent present it was hoped that the normal reaction would still occur.

It was therefore decided, because of the above unsuccessful results, to continue the investigation into the effect of an electron donating
substituent, with a coumarin containing a 4-substituent which would be unreactive towards a Grignard reagent. Initially, it was intended to use the o-methoxyphenylcoumarin (121), but because of difficulties in preparing this compound, the experiments were carried out with the p-methoxyphenylcoumarin (89).

Since the p-methoxyphenyl group is strongly electron donating, the 4-position of the coumarin ring will have a high electron density and thus 1,2-addition should occur. Table 6 summarises the results. The reaction with each Grignard reagent in tetrahydrofuran gave either the dihydrocoumarin (122) or the carbinol (123), or a mixture of both. Treatment of the carbinol (123) with glacial acetic acid afforded the 2H-chromene (124).
Table 6

<table>
<thead>
<tr>
<th>Grignard Reagent $R$</th>
<th>% Yield of Dihydrocoumarin (122)</th>
<th>% Yield of Carbinol (123)</th>
<th>% Yield of Chromene (124) from pure Carbinol (123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>0</td>
<td>77&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ethyl</td>
<td>63</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>isopropyl</td>
<td>69</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>79</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>phenyl</td>
<td>0</td>
<td>79&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a. Isolated directly as the 2H-chromene; b. Crude yield).

Table 6 indicates that the type of product obtained from Grignard reagent addition to the $p$-methoxyphenylcoumarin (89) is the same as previously obtained (c.f. Table 3, 4 and 5). If the mechanism of the reaction is studied more closely, the reason becomes clear—

![Chemical structures](image-url)
Due to the lone-pair of electrons on the oxygen of the methoxy group, formation of a magnesium complex is likely to involve an electron shift, as shown on the structure (89), to a charged species of type (125a) and contributing species (125b) and (125c). The second molecule of reagent will therefore add to the intermediate complex, represented by the structure (125b) or (125c), in the same manner as with a coumarin with an electron withdrawing 4-substituent. The intermediate complex for the latter reaction is represented in the structures (126a) and (126b).

Therefore, the mode of addition of a Grignard reagent to a coumarin appears to be affected little by the electron directing nature of the 4-substituent. In one instance however, with the strongly electron withdrawing 2-pyridyl group, 1,4-addition was promoted. Since all the 4-substituents of the coumarins investigated so far, have been aromatic, the effect of a non aromatic substituent was examined. The simplest substituted coumarin that fits the necessary requirements is the 4-methylcoumarin (127). The methyl group has a weakly positive inductive effect, and therefore with a 4-methylcoumarin (127) the 4-position will have a higher electron density than otherwise. This will ensure
that the carbonyl carbon is more electron deficient than the 4-position, so that 1,2-addition will be promoted.

\[
\begin{align*}
\text{I27} & \xrightarrow{\text{I.Mg/MeBr}} \text{I26} \\
\end{align*}
\]

Treatment of the 4-methylcoumarin (127) with a methyl Grignard reagent, followed by heating under reflux in acetic acid, afforded the tetramethyl-2H-chromene (128). Similar reactions with the ethyl, isopropyl and cyclohexyl reagents, under a variety of conditions, were unsuccessful, the coumarin (127) being recovered in each case. In each of these unsuccessful experiments, addition of the Grignard reagent precipitated a solid, very probably a magnesium complex of the coumarin (127).

The reaction of a phenyl reagent with the coumarin (127) was more successful, and yielded novel products.

\[
\begin{align*}
\text{I29} & \xleftrightarrow{\text{Ph}} \text{I30} \\
\end{align*}
\]

A mauve compound, first obtained, showed i.r. bands at \( \nu 3300 \) (OH) and 1691 \( (C = O) \text{cm}^{-1} \) indicative of the propenone structure (129). Crystallisation of the mauve solid then afforded colourless crystals of the chromen-2-ol (130), from which the carbonyl absorption at 1691 \text{cm}^{-1} was absent. On prolonged standing the colourless crystals slowly turned mauve. The n.m.r. spectrum of the chromen-2-ol (130) confirmed the structure. Attempts to obtain the n.m.r. spectrum of the propenone (129) however were unsuccessful, because of rapid transformation into
Single 1,2-addition of the phenyl Grignard reagent to the coumarin (127) is a completely new finding and probably occurred because of the insolubility of the magnesium complex of the propenone (129). Considerable efforts have been made by other workers previously to obtain the single 1,2-addition product from the reaction of a Grignard reagent with a 4-substituted coumarin, but without success.

Because of the high degree of insolubility of the coumarin (127), and the lack of reaction with some of the Grignard reagents, no conclusions could be reached on the effect of the 4-methyl substituent on the course of the Grignard reaction.

b. Promotion of 1,4-Addition.

Several substituted 3,4-dihydrocoumarins, some of which have already been described, were required for biological screening. In some cases the yield of dihydrocoumarins obtained by the action of a Grignard reagent upon the corresponding coumarin was inconveniently low, and in other cases, the required dihydrocoumarins were not obtained, only the corresponding 1,2-addition products. Therefore, some means of increasing the yield of dihydrocoumarins from these reactions was required, and in some cases a way of altering the reaction was needed, so that the 1,4-rather than 1,2-product was obtained.

Cuprous chloride had been advocated for promoting 1,4-addition of Grignard reagents to α,β-unsaturated ketones and esters, and so use of this catalyst was tried in the corresponding reaction with coumarins. With each coumarin, reactions were carried out in parallel, with and without the catalyst.

Thus, the reaction of a methyl Grignard reagent with the coumarin (131) in tetrahydrofuran, previously described by Razden et. al. 73, was carried out in the absence of catalyst at room temperature, and
then in the presence of cuprous chloride at $-20^\circ$. 

In both experiments, only the carbinol (132) was isolated. This could not readily be purified, but was identified with an authentic sample supplied by Dr. Razdan. 

Similarly, the reaction of the methyl reagent with the 4-(3-pyridyl)coumarin (109), reported earlier in this thesis, was repeated in the presence of cuprous chloride at $-20^\circ$. The reaction again yielded only the carbinol (133), and the yield was similar to that obtained before.
When the 4-(2-pyridyl)coumarin (134) was treated with an ethyl Grignard reagent in tetrahydrofuran, on its own at room temperature, and in the presence of cuprous chloride at -20°, the dihydrocoumarin (135; R = Et) was obtained, isolated as the hydrochloride. In the absence of catalyst the yield was 33% and in the presence of cuprous chloride it was 45%.

The coumarin (134) was also treated with a phenyl reagent in tetrahydrofuran at room temperature. Table 7 below summarises the reactions carried out, with the proportion of cuprous chloride present in each reaction, and the corresponding yield of dihydrocoumarin (135; R = Ph) obtained.

<table>
<thead>
<tr>
<th>Mol of Cu₂Cl₂ per 1 mol of phenyl Grignard reagent.</th>
<th>% Yield of Dihydrocoumarin (135; R = Ph).</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48 (Average from 3 expts.)</td>
</tr>
<tr>
<td>0.001</td>
<td>65</td>
</tr>
<tr>
<td>0.005</td>
<td>67.5 (Average from 2 expts.)</td>
</tr>
</tbody>
</table>
The only product isolated from the reactions of the phenyl reagent with the coumarin (134) was the corresponding 3,4-dihydrocoumarin (135; \( R = \text{Ph} \)). However, the yield of the 1,4-addition product was significantly increased in the presence of cuprous chloride, although little increase in yield was obtained on increasing the quantity of cuprous chloride from 0.001 to 0.005 mol.

\[ \text{(I09)} \quad \rightarrow \quad \text{(I36)} \]

The reaction of the 4-(3-pyridyl)coumarin (109) with an ethyl Grignard reagent in tetrahydrofuran was repeated, in the presence of cuprous chloride at room temperature. The yield of the ethyl-3,4-dihydrocoumarin (136) was found to be increased, from 60\% to 75\%. None of the corresponding 2H-chromene, as obtained in the previous reaction, could be isolated.

It has been reported that cuprous chloride has a limited lifetime in a Grignard reagent solution. The best yields resulted from portionwise addition of cuprous chloride, concurrently with the carbonyl compound, at a reaction temperature of -10 to -20°C. This procedure was followed for the reactions with the methyl- and ethyl- reagents, because the addition of cuprous chloride to solutions of the above at room temperature was found to be violently exothermic. In contrast,
cuprous chloride could safely be added in a single portion to solutions of the phenyl reagent at room temperature and the reactions proceeded satisfactorily.

From the results obtained so far, it appears that in the reactions where no 1,4-addition product is normally isolated, the presence of cuprous chloride in the reaction mixture has no affect. Thus, no 1,4-addition product was isolated in the reactions of a methyl reagent with either of the coumarins (109) and (131), with or without a catalyst.

The use of cuprous chloride as a catalyst however, does promote 1,4-addition in those reactions where 1,4-addition normally occurs.

c. The Effect of the 5-Hydroxy Group.

The mode of addition of Grignard reagents to esters, ketones and \(\alpha,\beta\)-unsaturated esters has been reported to proceed by a cyclic mechanism as follows:

\[
\begin{array}{c}
\text{\(\alpha,\beta\)-unsaturated ester} \\
\text{Grignard reagent} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Cyclic adduct} \\
\end{array}
\]

Although this type of mechanism cannot apply to the corresponding 1,4-addition of a Grignard reagent with a coumarin, because of the fixed trans-configuration of the \(\alpha,\beta\)-unsaturated lactone moiety, a cyclic mechanism involving the 5-hydroxy group can be proposed:
It is generally accepted that the reaction of a Grignard reagent with a ketone or ester involves the formation of an initial co-ordination complex. With a hydroxy group, the active proton may be displaced in a fast reaction by the reagent. With a hydroxy coumarin, the initial complex will therefore be of type (I38a) or (I38b). An electron shift represented by (139), will then yield the dihydrocoumarin (141) after hydrolysis of the magnesium complex (140).

The validity of the above mechanism can be examined by either protecting the hydroxy group as an ether, or by using the deshydroxy compound. Since a protected hydroxy group would still have a lone-pair of electrons to bond with the Grignard reagent, and may interfere in other ways because of its size, the latter method was used.

Thus, the coumarin (87) which lacks the 5-hydroxy group was treated
with a series of Grignard reagents in tetrahydrofuran. These reactions yielded the 3,4-dihydrocoumarin (142; $R = \text{alkyl}$) or the carbinol (143; $R = \text{Me}$ or Ph), as shown in Table 8. In one case, a product could not be isolated, but after treatment with glacial acetic acid, the chromene (144; $R = \text{Me}$) was obtained.
Table 8

<table>
<thead>
<tr>
<th>Grignard Reagent R=</th>
<th>% Yield of Dihydrocoumarin (142)</th>
<th>% Yield of Carbinol (143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>0</td>
<td>73a</td>
</tr>
<tr>
<td>ethyl</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>isopropyl</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>phenyl</td>
<td>0</td>
<td>51</td>
</tr>
</tbody>
</table>

(a. Isolated directly as the 2H-chromene (144; R = Me)).

Table 8 above shows that the 1,4-addition product is still obtained in the absence of the 5-hydroxyl group. These results are very similar to the results shown in Table 3, for the series of reactions with the related hydroxy coumarin (101).

It is clear from a comparison of the results in Tables (8) and (3) that the mechanism of conjugate addition of a Grignard reagent to a coumarin does not obviously involve the 5-hydroxy group. Consequently, it seems that the 1,4-addition takes place as follows:
As suggested previously, treatment of a coumarin (9) with a Grignard reagent affords a complex of type (145). An electromeric shift, accompanied by nucleophilic addition of the carbanion \( R^- \), as shown (146), will afford a complex (147) which on hydrolysis yields the dihydrocoumarin (148). The electromeric shift (146) may be accompanied by a concerted addition of the reagent \( R-\text{MgX} \) rather than carbanion attack.
Although the hydroxy group of the coumarin was found not to participate in the conjugate addition of a Grignard reagent, the deshydroxycoumarin (87) was found, as expected, to be more soluble than the corresponding hydroxycoumarin (101). This property was thought likely to be common to other compounds, and therefore the deshydroxy coumarin (149) was treated with a series of Grignard reagents. Some of the reactions with the corresponding 5-hydroxycoumarin (127) were unsuccessful due to the low solubility of this coumarin.

\[
\text{Table 9 shows the yields of dihydrocoumarin (150; } R = \text{ alkyl) or carbinol (151; } R = \text{ alkyl or phenyl) obtained from each reaction. Treatment of these carbinols (151; } R = \text{ alkyl or phenyl) with acetic acid afforded the corresponding 2H-chromenes (152; } R = \text{ alkyl or phenyl).}
\]
It can be seen from the results in Table 9 that the reactions afforded 1,2-addition products in all but one case. In this, the dihydrocoumarin (150) was isolated from the reaction of the isopropyl reagent with the coumarin (149). To verify these results, the reactions of the ethyl-, isopropyl- and cyclohexyl- Grignard reagents with the coumarin (149) were repeated under identical conditions. It can be seen from Table 9 that similar results were obtained.

The results reported in Table 9 are surprising, since it was expected that the isopropyl and cyclohexyl Grignard reagents would react with a coumarin in a similar manner, because of their similar spatial requirement at the reaction site. In an attempt to obtain further information, the coumarin (149) was treated with a cycloheptyl Grignard reagent.
The reaction afforded a mixture of products as indicated by t.l.c., but no single compound could be isolated. It appears from this result, and a previous result with the tert-butyl Grignard reagent, that reactions of bulky Grignard reagents with coumarins yield complicated mixtures of products. Therefore, no further reactions with these reagents were carried out at this stage.

The 4-methyl substituent (with its +I effect) encourages 1,2-addition of Grignard reagents to the coumarin (149, c.f. Table 9). To determine the effect of a -I alkyl substituent, the 4-trifluoromethylcoumarin (153) was next examined.

Only sufficient of the coumarin (153) was available for treatment with the ethyl Grignard reagent. The main product was the carbinol (154), accompanied by a low yield of the corresponding dihydrocoumarin (155). This result is similar to that obtained with the 4-methylcoumarin (149). Therefore, changing the 4-substituent from methyl (+I) to trifluoromethyl (-I) appears to make little difference to the mode of addition of a Grignard reagent. The possible significance of this is mentioned later.

In concluding this section of the thesis, it can be seen that some of the results shown in Table 9 differ from those found earlier, and these differences are collected together in Table 10.
<table>
<thead>
<tr>
<th>Coumarin</th>
<th>R= methyl</th>
<th>ethyl</th>
<th>isopropyl</th>
<th>cyclohexyl</th>
<th>phenyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>(149)</td>
<td>1,2-</td>
<td>1,2-</td>
<td>1,2-</td>
<td>1,2-</td>
<td>1,2-</td>
</tr>
<tr>
<td>(87)</td>
<td>1,2-</td>
<td>1,4-</td>
<td>1,4-</td>
<td>1,4-</td>
<td>1,2-</td>
</tr>
<tr>
<td>(101)</td>
<td>1,2-</td>
<td>1,4-</td>
<td>1,4-</td>
<td></td>
<td>1,2-</td>
</tr>
<tr>
<td>(106)</td>
<td>1,4-</td>
<td>1,4-</td>
<td>1,4-</td>
<td></td>
<td>1,4-</td>
</tr>
</tbody>
</table>

*Note: The table represents the mode of addition of reagents to Coumarins.*
These results show that the mode of addition of a Grignard reagent to a 4-substituted coumarin does depend on the 4-substituent. Thus, the same results are obtained in the presence or absence of the 5-hydroxy group (O1 and O7), and so in all the above experiments the only variables are the reagent and the 4-substituent. The 4-substituents may be classed electronically as strongly electron withdrawing (2-pyridyl), electron withdrawing (4-pyridyl) and weakly electron donating (methyl). From Table 10, it appears that 1,4-addition of a Grignard reagent is promoted when the 4-substituent of the coumarin is strongly electron withdrawing, and depressed when the substituent is electron donating.

Table 11

(Mode of addition of reagents to coumarins)

<table>
<thead>
<tr>
<th>Coumarin</th>
<th>Reagent</th>
<th>R=</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4-</td>
<td>methyl</td>
<td>1,2-</td>
</tr>
<tr>
<td>1,4-</td>
<td>ethyl</td>
<td>1,4-</td>
</tr>
<tr>
<td>1,4-</td>
<td>isopropyl</td>
<td>1,4-</td>
</tr>
<tr>
<td>-</td>
<td>cyclohexyl</td>
<td>1,4-</td>
</tr>
<tr>
<td>1,2-</td>
<td>phenyl</td>
<td>1,2-</td>
</tr>
</tbody>
</table>
From the conclusions on the effect of the 4-substituent on the mode of addition of Grignard reagent to a coumarin, the reactions indicated in Table 11 would be expected, in changing the 4-substituent from 4-pyridyl to 3-pyridyl to p-methoxyphenyl, to show a tendency towards the production of the 1,2-addition product. However, although the 4-substituents become progressively more electron donating, they all exert a -I effect on the coumarin ring. It would appear from the results, that the direction of the inductive effect of the 4-substituent is more important than the overall electron directing strength of the substituent.

It can be seen from Tables 10 and 11 that the mode of addition of a Grignard reagent to a coumarin depends on the reagent itself, as well as the 4-substituent. Thus, the methyl and phenyl reagents react in a similar manner, to generally give the 1,2-addition products, whilst the ethyl, isopropyl and cyclohexyl reagents generally yield the 1,4-addition products. No direct correlation appears to exist between the size of the alkyl or aryl part of the reagent and the mode of addition of the reagent, nor are there any obvious differences in the electronic nature of the reagents to explain the results.

d. Effect of Solvent and the Composition of the Grignard Reagent.

The reactions of Grignard reagents with coumarin (9) itself are reported to yield the corresponding carbinols (35; R = alkyl), and with acid, during or after work-up, the chromenes (34; R = alkyl).
Because of some of the conflicting results obtained from the reactions of Grignard reagents with 4-substituted coumarins, it was decided to repeat some of the reported reactions.

Coumarin (9) was treated with a series of Grignard reagents in ether following the procedure described by Shriner and Sharp. Table 12 shows the yield of dihydrocoumarin (94), carbinol (35) or ketone (156) obtained from each reaction.

![Chemical structures](image)

Table 12

<table>
<thead>
<tr>
<th>Grignard Reagent R</th>
<th>% Yield of Dihydrocoumarin (94)</th>
<th>% Yield of Carbinol (35)</th>
<th>% Yield of Ketone (156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>0</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>ethyl</td>
<td>35 (16)(^a)</td>
<td>36 (^b) (34)(^a)</td>
<td>0</td>
</tr>
<tr>
<td>isopropyl</td>
<td>78</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>0</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>phenyl</td>
<td>0</td>
<td>48</td>
<td>17</td>
</tr>
</tbody>
</table>

\(^a\) This reaction was repeated, \(^b\) Isolated as the corresponding 2H-chromene (34; R = Et).

Table 13 below shows the results of some of the same reactions carried out by other workers.
Table 13

<table>
<thead>
<tr>
<th>Grignard Reagent</th>
<th>% Yield of Carbinol (35)</th>
<th>% Yield of Ketone (156)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>59&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>ethyl</td>
<td>64&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>&quot;</td>
</tr>
<tr>
<td>phenyl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63</td>
</tr>
</tbody>
</table>

(a. This reaction was carried out in a benzene-ether mixture."

b. These products were isolated directly as the corresponding 2H-chromene (34; R = Me and Et).

c. Crude yield, A, Yield not quoted.)

A comparison of Tables 12 and 13 shows that the reactions of the methyl and phenyl Grignard reagents with coumarin have both proceeded in a similar manner to those previously reported. However, the reaction of the ethyl reagent with coumarin was found to proceed in a different manner, to yield some of the 1,4-addition product (94; R = Et).

Following the reported procedure, no products could be isolated from the crude reaction mixture.

\[
\begin{align*}
\text{Et} & \hspace{1cm} \text{Et} \\
\text{O} & \hspace{1cm} \text{O} \\
\text{Et} & \hspace{1cm} \text{Et} \\
\text{(I57)} & \hspace{1cm} \text{(I58)}
\end{align*}
\]

The crude mixture was therefore treated with acetic acid, and the 2H-chromene (I57) and the dihydrocoumarin (I58) were separated by column chromatography of the resulting crude oil. Higher yields of the products were obtained on repeating the reaction, because in the initial reaction mechanical losses had been incurred in attempting to follow the reported procedure.
Smith and Ruoff\textsuperscript{72} isolated by crystallisation only the carbinol (35; R = Et) from the reaction with the ethyl Grignard reagent. They appeared to make no attempts to isolate any other products from the reaction mixture.

(The reactions represented as single steps, may of course take place by concerted mechanisms.)
The reaction of the phenyl Grignard reagent with coumarin to give the carbinol (35; R = Ph) and the ketone (156; R = Ph), probably involves two competing reactions as represented above. Thus, the initial reaction of the reagent with the coumarin will probably give a complex of type (159), which with a second molecule of reagent will give via (160) the single 1,2-addition complex (161). This complex (161) with further reagent will then undergo ring-opening to the resonance hybrid cation (162), which will suffer nucleophilic attack by the reagent to give (after hydrolysis) the carbinol (35; R = Ph) and the ketone (156; R = Ph). The preferred mode of attack (162) → (35) or (162) → (156) will probably depend on the size and electronic nature of the alkyl part of the reagent. Thus, with the phenyl reagent both reaction courses are taken, so the products are the carbinol (35; R = Ph) and the ketone (156; R = Ph). With the cyclohexyl Grignard reagent however, the cyclohexyl group appears to be too large for a second molecule of reagent to attack the 2-position, and therefore only conjugate addition occurs to give the ketone (156; R = cyclohexyl). This type of competing reaction is similar to the reaction of a Grignard reagent with a 4-substituted coumarin, to give either the 1,2- or 1,4- addition product.

The formation of 1,4-addition products from the reaction of Grignard reagents with coumarin (9) is not so surprising after the results already obtained with the 4-methyl coumarin (149), but does represent a new finding.

<table>
<thead>
<tr>
<th>Coumarin</th>
<th>Grignard Reagent</th>
<th>% 1,2-Addition</th>
<th>% 1,4-Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,7-Dimethylcoumarin</td>
<td>ethyl</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>4,7-Dimethylcoumarin</td>
<td>isopropyl</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>Coumarin</td>
<td>ethyl</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>&quot;</td>
<td>isopropyl</td>
<td>0</td>
<td>78</td>
</tr>
</tbody>
</table>

Table 14
Table 14 summarises the results of the reaction of coumarin (9) and 4,7-dimethylcoumarin (149) with the ethyl and isopropyl Grignard reagents. It can be seen that coumarin with the ethyl Grignard reagent gives both 1,2- and 1,4- addition products, whereas the methylcoumarin (149) yielded only the 1,2-addition product. This latter result was explained by the +I effect of the 4-methyl group increasing the electron density at the 4-position such that 1,2-addition was more likely to occur. In the absence of the methyl substituent the electron density at the 4-position of the coumarin will be less, so that 1,4-addition is more likely to occur.

The differences in electronic nature of the two coumarins appears to have little effect on the corresponding reactions with the other Grignard reagents.

The results obtained so far indicate that the composition of the Grignard reagents may affect the mode of addition to a coumarin. Thus, the type of products obtained from the reactions of a series of Grignard reagents with a coumarin are dependent on the Grignard reagent.

There are several contributing factors which may account for the production of these products from the reactions with the different reagents.

The position of equilibrium of the Schlenk equations (1) and (4) may affect the course of reaction.

\[ R_2 Mg + MgX_2 \rightleftharpoons 2RMgX \quad \text{(In tetrahydrofuran)} \quad -(1) \]

\[ \frac{n}{2} R_2 Mg + \frac{n}{2} MgX_2 \rightleftharpoons nRMgX \rightleftharpoons \frac{n}{2} (RMgX)_2 \rightleftharpoons \frac{n}{3} (RMgX)_3 \rightleftharpoons \text{etc.} \quad \text{(In ether)} \quad -(4) \]

Grignard reagents, normally represented as 'RMgX', are reported to
exist as equilibrium mixtures, as shown in equations (1) and (4). It is possible that the position of equilibrium is markedly different for each reagent. Thus, one Grignard reagent may exist as mainly \( R_2Mg \), whilst another reagent exist as \( RMgX \). However, in the reported estimations of the position of equilibrium for several Grignard reagents, no mention of any significant differences between reagents has been made.

The relative-rates of reaction of \( R_2Mg \) and \( RMgX \) with coumarins however, may be such that one reaction predominates.

\[
\begin{align*}
R_2Mg + MgX_2 & \rightleftharpoons 2RMgX \quad (1) \\
\text{Coumarin} + \text{Reagent} & \rightleftharpoons \text{Initial Complex} \quad (5) \\
\text{Initial Complex} + \text{Reagent} & \rightleftharpoons \text{Product Complex} \quad (6) \\
\text{Product Complex} + H_2O & \rightleftharpoons \text{Product} + \text{Residue} \quad (7)
\end{align*}
\]

Aston and Bernhard reported that dimethylmagnesium reacted a lot faster than methylmagnesium bromide with a substituted bensophenone. A similar difference may be found between the two types of reagent on reaction with a coumarin.

The reaction of a Grignard reagent with a coumarin, analogous to the suggested mechanism for a ketone, may be represented by the above steps, (5), (6) and (7). The initial step (5) is thought to occur because in many instances Grignard reagents give evidence of co-ordinating with carbonyl compounds, as shown by a colour change and evolution of heat, and then regeneration of the starting carbonyl compound on hydrolysis. If the second step (6) is the rate determining step, then the type of addition product formed should be dependent on the nature of the reagent (1). The second step (6) can be shown as follows:

\[
\begin{align*}
\text{Initial Complex} + R_2Mg & \rightleftharpoons \text{Product Complex (A)} \quad (8) \\
or \quad \text{Initial Complex} + RMgX & \rightleftharpoons \text{Product Complex (B)} \quad (9)
\end{align*}
\]

Which of these steps occur depends on the relative rates of reaction of the two reagents. If, in addition, one species of reagent reacted by
the 1,2-mechanism, and the other by the 1,4-mechanism, then the formation of the two types of products is to be expected. The type of products obtained from the reaction of a Grignard reagent with a coumarin depends therefore on the relative rates of reaction of the two species of reagent with the coumarin.

The rates of reaction will be dependent on the solvent, and on the steric and electronic properties of both the coumarin and the reagent. Attempts were therefore made to investigate these solvent effects.

Coumarin (9) was treated again with a series of Grignard reagents, but in tetrahydrofuran, in order to compare the results with those for the same reactions in ether.

![Chemical structures](image)

**Table 15**

<table>
<thead>
<tr>
<th>Grignard Reagent R=</th>
<th>Yield of Products, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td></td>
<td>Dihydrocoumarin (94)</td>
</tr>
<tr>
<td>methyl</td>
<td>-</td>
</tr>
<tr>
<td>ethyl</td>
<td>53</td>
</tr>
<tr>
<td>isopropyl</td>
<td>94</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>65</td>
</tr>
<tr>
<td>phenyl</td>
<td>0</td>
</tr>
</tbody>
</table>

(a. Isolated directly as the 2H-chromene) (The products from repetitive reactions were in many instances not purified, but the structures were confirmed, and the yields calculated from comparative g.l.c.).
Table 15 shows the results of the reactions of the Grignard reagents with coumarin (9) in both ether and tetrahydrofuran. It can be seen that similar products were obtained from both reactions with the phenyl reagent. In a similar manner, only the 1,4-addition product (94; R = Pr\textsuperscript{iso}) was obtained from the reaction of the isopropyl Grignard reagent in ether and in tetrahydrofuran. However, the effect of using tetrahydrofuran in place of ether for the reaction of the ethyl Grignard reagent with coumarin (9), was to increase the proportion of 1,4- to 1,2-addition product. The effect on the reaction with the cyclohexyl reagent, was to completely change the mode of addition, from 1,2- in ether, to 1,4- in tetrahydrofuran.

\[
\text{R}_2\text{Mg} + \text{MgX}_2 \rightleftharpoons 2\text{RMgX} \quad -(1)
\]

On consideration of the composition of the different reagents, a possible explanation for these results can be deduced. In tetrahydrofuran the equilibrium (1) is reported to favour the dialkylmagnesium species more than it does in ether\textsuperscript{19}. Since, with coumarin (9) in tetrahydrofuran the 1,4-addition product is generally obtained, then it can be postulated that dialkylmagnesium reacts with a coumarin by the 1,4-mechanism. It then follows that alkyl- or aryl-magnesium halides react with a coumarin by the 1,2-mechanism. If this holds, it then also follows that the reaction of coumarin with the isopropyl Grignard reagent in tetrahydrofuran is really a reaction with diisopropylmagnesium, so that the dihydrocoumarin (94; R = Pr\textsuperscript{iso}) is obtained. On the other hand, because the phenyl Grignard reagent in tetrahydrofuran behaves as phenylmagnesium bromide, the interaction with coumarin (9) gives the carbinol (35; R = Ph) and the ketone (156; R = Ph). Either the phenyl Grignard reagent exists as such in tetrahydrofuran or, if it has a mixed composition, then the rate of reaction of PhMgBr with coumarin must be much faster than the rate for Ph\textsubscript{2}Mg,
as suggested previously.

Since the mode of addition of a Grignard reagent to coumarin (9) does appear to depend on the solvent, it was decided to repeat some of the reactions previously carried out, in other solvents.

Thus, the 4(4-pyridyl)coumarin (87) was treated with the ethyl Grignard reagent in ether, instead of in tetrahydrofuran as previously.

Thus, the 4(4-pyridyl)coumarin (87) was treated with the ethyl Grignard reagent in ether, instead of in tetrahydrofuran as previously.

**Table 16**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% Yield of Dihydrocoumarin (164)</th>
<th>% Yield of Carbinol (163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ether</td>
<td>59</td>
<td>11</td>
</tr>
<tr>
<td>tetrahydrofuran</td>
<td>79</td>
<td>0</td>
</tr>
</tbody>
</table>

It can be seen from Table 16 that the change of solvent has influenced the yield and type of product in a similar way to that observed with the reaction of the ethyl Grignard reagent with coumarin, Table 15. Thus, the ratio of 1,2 to 1,4-addition product is changed. When both products are obtained, this is either because the rates of
reaction of both types of reagent with the coumarin are about the same, or because the relative concentrations of the two types are such that the same overall result pertains, this requires the assumption that interconversion of the types is slow.

As a further example of a solvent effect, it was decided to treat a substituted 5-hydroxycoumarin with a Grignard reagent in a different solvent. Thus, the coumarin (101) was treated with the ethyl reagent in ether, to compare with the reaction carried out previously in tetrahydrofuran. Unfortunately, no reaction occurred, evidently because the coumarin remained undissolved even with heating under reflux. No attempts were made to treat other 5-hydroxy-7-methyl-coumarins with Grignard reagents in ether, because it is likely that they also will be insoluble, and so unreactive in ether.

Since it appears from the results of the reactions carried out in ether and in tetrahydrofuran, that the $R_2$Mg species reacts by 1,4-addition, and the $RMgX$ species reacts by 1,2-addition, several reactions were carried out to confirm this theory. Dialkyl and diarylmagnesiums can be prepared by the addition of dioxan to a solution of a Grignard reagent in ether, thus:

$$2RMgBr \xrightarrow{\text{DIOXAN}} R_2Mg + MgBr_2 \cdot \text{Dioxan} \downarrow$$  

\(\text{(10)}\)
Addition of dioxan causes a magnesium bromide-dioxan complex to precipitate out of solution (10), leaving only the dialkyl or diarylmagnesium in solution.

The above procedure was used to prepare several dialkylmagnesiums, which were then allowed to react with several coumarins. In each case, the precipitate was not removed, since any attempts at filtration would result in the decomposition of some of the reagent, and other workers have found that under the conditions used, the above reaction (10) does not appear to be reversible.

Thus, the 4-(4-pyridyl)coumarin (87) was treated with a solution of diethylmagnesium in ether. Only the diethylcarbinol (163) was obtained, apart from unchanged coumarin (87; 50%).

Table 17 shows the results of this reaction, and the corresponding results obtained previously for the reactions of the ethyl Grignard reagent with the coumarin (87).
Table 17

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>% Yield of Carbinol (163)</th>
<th>% Yield of Dihydrocoumarin (164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂Mg + EtMgBr</td>
<td>tetrahydrofuran</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Et₂Mg + EtMgBr</td>
<td>ether</td>
<td>7</td>
<td>59</td>
</tr>
<tr>
<td>Et₂Mg</td>
<td>ether-dioxan</td>
<td>82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
</tbody>
</table>

(a. Based on recovered coumarin).

These results further confirm that the type of products obtained from the reaction of a Grignard reagent with a coumarin depends on the relative rates of reaction of the different species comprising the reagent. Diethylmagnesium with the coumarin gave only the 1,2-addition product (163), whilst the normal Grignard reagent in tetrahydrofuran gave the 1,4-addition product (164). From these results it can be concluded that the reactive species of reagent that reacts with a coumarin to give a conjugate addition product is $R_{2}MgX$, rather than $R_{2}Mg$ which was suggested previously. It would appear from this, that the composition of the Grignard reagent (c.f. Schlenk equilibrium 1 and 4) does not necessarily affect the type of products obtained from reaction with a coumarin. Since, as was discussed earlier, if the reaction was dependent on composition of the Grignard reagents, the opposite of the above should occur.

Previous workers have obtained increased yields of conjugate addition product when a normal Grignard reagent was replaced by the corresponding dialkylmagnesium in reactions with $\alpha,\beta$-unsaturated esters. A possible reason for this difference between $\alpha,\beta$-unsaturated esters and coumarins, is that the mechanism of Grignard reagent addition is different. The cyclic intermediate versus carbanion mechanisms of Grignard addition have already been discussed.
The report that dimethylmagnesium reacts a lot faster than methylmagnesium bromide with a benzophenone has also been discussed. From the results obtained with coumarins, it would appear that dimethylmagnesium does not always react faster, the relative rates being dependent on the carbonyl compound.

Because of the results obtained from the reaction of diethylmagnesium with the 4-(4-pyridyl)cumarin (87; Table 17), it was decided to carry out some further reactions with dialkylmagnesiums. Thus, coumarin (9) was treated with diethylmagnesium and with di-isopropylmagnesium. The results of these two reactions, and the corresponding reactions of the Grignard reagents in ether and tetrahydrofuran are shown in Table 18.
Table 18

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>% Yield of Dihydrocoumarin (94)</th>
<th>% Yield of Carbinol (55)</th>
<th>% Yield of Ketone (156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtMgBr + Et₂Mg</td>
<td>tetrahydrofuran</td>
<td>53</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ether</td>
<td>35</td>
<td>36^a</td>
<td>0</td>
</tr>
<tr>
<td>Et₂Mg</td>
<td>ether-dioxan</td>
<td>0</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>PrMgBr + Pr₂Mg</td>
<td>tetrahydrofuran</td>
<td>94</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ether</td>
<td>78</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pr₂Mg</td>
<td>ether-dioxan</td>
<td>19</td>
<td>37</td>
<td>42</td>
</tr>
</tbody>
</table>

(a. Isolated directly as the corresponding 2H-chromene.)

The results shown in Table 18 confirm the previous findings (Table 17) regarding the reactive species. Dialkylmagnesium again yielded the 1,2-addition products (35; R = Et and Pr^i) and (156; R = Pr^i), from reaction with coumarin. Isopropylmagnesium bromide appears to be the reactive species in the reaction of the isopropyl Grignard reagent with coumarin in ether and tetrahydrofuran, whilst with the ethyl Grignard reagent, the rates of reaction of both species of reagent (RMgBr and R₂Mg) with coumarin (9) appear to be similar.

A possible complicating factor in the reactions of Grignard reagents with coumarins in tetrahydrofuran, is that Analar grade tetrahydrofuran has been used in these reactions, which contains quinol as a stabiliser. It is possible that the quinol interferes with the mode of addition of Grignard reagents. Two Grignard reactions have therefore been carried out using tetrahydrofuran distilled from lithium aluminium hydride.
Thus, coumarin (9) was treated with the phenyl and the cyclohexyl Grignard reagents in redistilled tetrahydrofuran. The results of these two reactions and the results of the corresponding reactions carried out previously, given in Table 19 below, show that the presence of quinol in the Analar tetrahydrofuran had been without effect.

<table>
<thead>
<tr>
<th>Grignard Reagent R=</th>
<th>Solvent</th>
<th>% Yield of Dihydrocoumarin (165)</th>
<th>% Yield of Carbinol (165a)</th>
<th>% Yield of Ketone (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexyl</td>
<td>tetrahydrofuran</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>redistilled &quot;</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>phenyl</td>
<td>&quot;</td>
<td>-</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>phenyl</td>
<td>ether</td>
<td>-</td>
<td>48</td>
<td>17</td>
</tr>
</tbody>
</table>
The following conclusions can be made from the findings in this section of the thesis. Dialkyl- or diaryl-magnesiums react with coumarins by the 1,2-addition mode, as is shown by the results in Table 20.

### Table 20

<table>
<thead>
<tr>
<th>Coumarin</th>
<th>$R_2\text{Mg}$</th>
<th>$%$ 1,2-Addition</th>
<th>$%$ 1,4-Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumarin</td>
<td>ethyl</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>Coumarin</td>
<td>isopropyl</td>
<td>79</td>
<td>19</td>
</tr>
<tr>
<td>7-methyl-4-$(4\text{-pyridyl})$ coumarin</td>
<td>ethyl</td>
<td>82</td>
<td>0</td>
</tr>
</tbody>
</table>

Since Grignard reagents are considered to consist of equilibria containing $R_2\text{Mg}$, $R\text{MgX}$ and $(R\text{MgX})_n$, it is reasonable to assume that the $R\text{MgX}$ species, or the associated $(R\text{MgX})_n$ species, reacts with a coumarin by the 1,4-mechanism. This is demonstrated by the results shown in Table 21, where it can be seen that as opposed to the reaction with di-isopropylmagnesium, the isopropyl Grignard reagent with coumarin yielded the 1,4-addition product. Thus it is likely that isopropylmagnesium bromide is the reactive species in the reaction of the isopropyl Grignard reagent with coumarin.

### Table 21

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>$%$ Yield from reaction with Coumarin (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Pr}_2\text{Mg} + \text{Pr}_2\text{MgBr}$</td>
<td>tetrahydrofuran</td>
<td>0 94</td>
</tr>
<tr>
<td>&quot;</td>
<td>ether</td>
<td>0 78</td>
</tr>
<tr>
<td>$\text{Pr}_2\text{Mg}$</td>
<td>ether-dioxan</td>
<td>79 19</td>
</tr>
</tbody>
</table>
Some of the results obtained from the reaction of Grignard reagents with coumarins have indicated a difference between the different reagents. Thus, the reactions of a series of Grignard reagents with a coumarin in a particular solvent, can yield different types of products with the different reagents, as shown in Table 22.

Table 22

<table>
<thead>
<tr>
<th>Grignard Reagent</th>
<th>% Yield from the reaction of Grignard reagents with Coumarin (9) in Ether</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2-Addition</td>
</tr>
<tr>
<td>methyl</td>
<td>81</td>
</tr>
<tr>
<td>ethyl</td>
<td>36</td>
</tr>
<tr>
<td>isopropyl</td>
<td>0</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>57</td>
</tr>
<tr>
<td>phenyl</td>
<td>65</td>
</tr>
</tbody>
</table>

These results indicate that with coumarin in ether, the methyl-, cyclohexyl- and phenyl- Grignard reagents react as the corresponding \( R_2\text{Mg} \) reagent, the isopropyl Grignard reagent reacts as the \( RMgX \) reagent, and the ethyl Grignard reagent as a mixture of both \( R_2\text{Mg} \) and \( RMgX \). Since each of the reagents will initially exist as a mixture of the two species \( (R_2\text{Mg} \) and \( RMgX \)), then the differences in the mode of addition of the Grignard reagents can only be explained as a difference in the relative rates of reaction of the two species with the coumarin. For example, the results in Table 22 indicate that with coumarin (9) in ether, the rates of reaction of the different reagents are such that; \( \text{Me}_2\text{Mg} > \text{MeMgBr}, \text{cyclohexyl}_2\text{Mg} > \text{cyclohexylMgBr}, \text{Ph}_2\text{Mg} > \text{PhMgBr}, \text{Pr}^{\text{iso}}\text{MgBr} > \text{Pr}^{\text{iso}}\text{Mg} \) and \( \text{Et}_2\text{Mg} \sim \text{EtMgBr} \).

The relative rates of reaction of the two species of reagent
with a coumarin are dependent on the solvent of reaction, as is shown in Table 23.

Table 23

<table>
<thead>
<tr>
<th>Grignard Reagent R=</th>
<th>% Yield of Products from reaction with Coumarin (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In Tetrahydrofuran</td>
</tr>
<tr>
<td></td>
<td>1,2-Addition</td>
</tr>
<tr>
<td>ethyl</td>
<td>13</td>
</tr>
<tr>
<td>isopropyl</td>
<td>0</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>0</td>
</tr>
</tbody>
</table>

Thus, the corresponding yields of 1,2- or 1,4-addition product are changed when the reactions are carried out in different solvents.

The reason for these differences in rates of reaction of the two types of reagent ($R_2Mg$ and $RMgX$) with a particular coumarin, must be due to some property of the alkyl or aryl part of the reagent. For a series of reagents in the same solvent, the steric size and electronic nature of the different 'R-' groups will not be the same. From the results obtained however, no explanation is apparent as to the properties of the alkyl or aryl part of the reagent which determine the mode of reaction with a coumarin.

The possible mechanisms for the two types of reaction have already been discussed, and it was suggested that 1,2-addition of a Grignard reagent to a coumarin occurred by an electromeric shift, whilst 1,4-addition occurred as nucleophilic attack of the carbanion $R^\ominus$. A possible explanation for the different mechanisms of addition of the two types of reagent, is that there is little tendency for the carbanion to be produced from $R_2Mg$, whilst $RMgX$ readily forms the carbanion $R^\ominus$. 
c. Properties of the Grignard reaction products

All of the products from the Grignard reactions showed characteristic n.m.r. and i.r. spectra for their class of compounds. The data is shown in the experimental section.

The n.m.r. spectra of the dihydrocoumarins showed, amongst other signals, a signal near 7 often as an 'AB' quartet, as expected for the 3-methylene group.

Several compounds from the reactions were isolated as hydrates. Correct elemental analysis were obtained for these hydrates, even after prolonged drying, and in some instances sharp peaks were obtained for the hydrate protons in the n.m.r. 4-Ethyl-5-hydroxy-7-methyl-4-(4-pyridyl)-3,4-dihydrocoumarin was isolated as a quarter hydrate, for which a correct elemental analysis was obtained. To verify the hydrate composition, a sample was recrystallised, and then re-analysed. The correct analysis for a quarter hydrate was again obtained.

C. The Reaction of Grignard Reagents with 3,4-Dihydrocoumarins

Several analogues of the 2H-chromenes reported in this thesis have interesting biological properties. It was therefore decided to prepare some structurally similar chromans for comparative screening.

One method of preparing chromans of type (75) is from the reaction of a Grignard reagent with a 3,4-dihydrocoumarin. The reaction is reported to proceed via the diol (46), which readily dehydrates to the chroman (75).

\[ (\text{I8}) \xrightarrow{\text{RMgX}} (\text{46}) \xrightarrow{\text{H}^+} (\text{75}) \]
Attempts have previously been made to isolate the chromanols (72) or ketones (73) from the reactions, but without success.

\[
\begin{array}{cc}
72 & 73 \\
\end{array}
\]

In the present work, the reaction of the methyl Grignard reagent with the 3,4-dihydrocoumarin (166) in ether was found surprisingly, to give the chroman-2-ol (167) as the only product.

\[
\begin{array}{cc}
(166) & (167) \\
\end{array}
\]

The same product was obtained in a higher yield on repeating the reaction in tetrahydrofuran at 0°C. This appears to be the first example of a chromanol being obtained from the reaction of a Grignard reagent with a dihydrocoumarin.

That the compound exists as the chromanol (167) and not as the isomeric ketone (168), is demonstrated by its physical properties.
Thus, there is no carbonyl band in the infrared spectrum. The signals in the n.m.r. spectrum, assigned to the protons of the 2-methyl group, are at a higher field than would be expected for a methyl group attached to a carbonyl group (< T 8). Moreover, there are two singlets from the protons of the 2-methyl group, at T 8.50 and 8.98 in the ratio 4:1, indicative of the two diastereoisomers of compound (167). Whereas the ketone (168) would give only one signal for the carbonyl methyl.

Thus, there is no carbonyl band in the infrared spectrum. The signals in the n.m.r. spectrum, assigned to the protons of the 2-methyl group, are at a higher field than would be expected for a methyl group attached to a carbonyl group (< T 8). Moreover, there are two singlets from the protons of the 2-methyl group, at T 8.50 and 8.98 in the ratio 4:1, indicative of the two diastereoisomers of compound (167). Whereas the ketone (168) would give only one signal for the carbonyl methyl.
The chroman-2-ol (167) is readily dehydrated with glacial acetic acid to the 4H-chromen (169). As expected, the n.m.r. spectrum of the latter shows only one signal from the 2-methyl group.

Treatment of the dihydrocoumarin (166) with a methyl Grignard reagent, in a tetrahydrofuran-ether, or benzene-ether mixture under reflux, afforded the carbinol (170). The same product was also obtained from the corresponding Grignard reaction with the chroman-2-ol (167).

The carbinol (170) was purified by crystallisation from ethyl acetate, to yield the compound as an ethyl acetate clathrate (ratio of host: guest, 3:1). The ethyl acetate was not removed by drying at 100°/0.1 mmHg for 2 h, so the compound was not a normal solvate. The presence of the ethyl acetate was confirmed by elemental analysis, n.m.r. and i.r. spectroscopy. By crystallisation of the ethyl acetate clathrate from chloroform and from ethanol, an analogous chloroform clathrate (ratio of host: guest; 3:1), and an ethanol clathrate (ratio of host: guest; 3:2) were obtained.
Compounds of related structure to the carbinol (170) have been reported by Baker et al. and Mac Nicol to form clathrates. Thus, chromans (171; \( X = 0 \) and \( X = 5 \)) do so with many common solvents, and the crystal structures of the corresponding ethanol and chloroform clathrates have been determined by the X-ray method.

Treatment of the carbinol (170), as the ethyl acetate clathrate, with glacial acetic acid afforded the chroman (172). This compound did not form clathrates.

The reaction of the 4-ethyl-3,4-dihydrocoumarin (173) with a methyl Grignard reagent has also been investigated, using the
same sets of reaction conditions as used with the phenyldihydrocoumarin (166).

\[
\text{MeMeI} \quad \begin{array}{c}
\text{(I73)} \\
\text{Et} \\
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{CH}_3 \\
\end{array} \rightarrow \begin{array}{c}
\text{(I74)} \\
\text{Et} \\
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{CH}_3 \\
\end{array}
\]

In each case a solid precipitated from the reaction mixture and the only product isolated was the chroman-2-ol (174). Again, the 2-methyl group gave two singlets in the n.m.r. spectrum at \( \delta 8.55 \) and 9.20, due to the presence of the two diastereoisomers. In contrast to the 4-phenylchroman-2-ol (167), no further substitution occurred on treatment of the 4-ethylchroman-2-ol (174) with a methyl Grignard reagent.

\[
\text{(I75)} \\
\text{Et} \\
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{CH}_3 \\
\]

Thus, attempts to prepare the carbinol (175) were unsuccessful, probably due to the formation of an insoluble magnesium complex of the chromanol (174).

The reaction of methyl Grignard reagents with the dihydrocoumarin (176) under varied conditions was investigated.

\[
\begin{align*}
\text{(I76)} & \xrightarrow{\text{MeMgX}} \text{(I77)} \\
\text{(I78)} & \xrightarrow{\text{H}^+} \text{(I79)}
\end{align*}
\]
Thus, treatment of the dihydrocoumarin (176) with the methyl Grignard reagent in tetrahydrofuran at 0°, afforded the chromanol (177). With the methyl reagent in a benzene-ether mixture under reflux, the carbinol (178) was isolated. These two products on treatment with glacial acetic acid, yielded the 4H-chromené (179) and the chroman (180) respectively.

In the n.m.r. spectrum of the carbinol (178), the protons of the two 3-methyl groups appeared at $\gamma$ 8.54 and 9.32. The latter figure is high for methyl protons attached to a carbinol group, and is probably due to the shielding effect of the aromatic rings.

From the results obtained in these experiments, the reaction of a Grignard reagent with a 3,4-dihydrocoumarin may be represented as follows:-
The type of product isolated in the reaction appears to be dependent on the solubility of the intermediate magnesium complex (182). Thus, the reaction with the 4-ethyl-3,4-dihydrocoumarin (181; R\(^{1}\) = Et and R\(^{2}\) = Me) proceeded, with precipitation of a solid, to give only the chromanol (184; R\(^{1}\) = Et and R\(^{2}\) = Me). With the 4-phenyl-3,4-dihydrocoumarin (181; R\(^{1}\) = Ph and R\(^{2}\) = Me) however, the reaction proceeded further with heating under reflux, to give the carbinol (185; R\(^{1}\) = Ph and R\(^{2}\) = Me).

The Grignard reagent from methyl iodide was generally used in these reactions, since it is so convenient to prepare. In tetrahydrofuran however, magnesium iodide precipitates out, and thus the corresponding bromide was used. In some experiments however, to avoid changing reagents, the reactions were carried out in a tetrahydrofuran-ether mixture.
The Grignard reagents in this section of the thesis have been referred to for convenience as the corresponding alkyl- or phenyl-
magnesium halide. However, the composition of the reagents is not known, and may contain, or be present as, the corresponding dialkyl-
or diarylmagnesium.

Most of the reactions were followed by thin-layer chromatography in ethyl acetate, chloroform or benzene. Column chromatography was carried out on Silica Gel MFC columns. Melting points are uncorrected. Infrared spectra were recorded with Unicam SP200 or Perkin Elmer 137 instruments. Nuclear magnetic resonance spectra recorded with Varian A60 or Perkin Elmer R10A instruments, with tetramethylsilane as internal reference.
A) Preparation of Substituted Coumarins.

General Procedure.

Concentrated sulphuric acid (50 ml) was added dropwise during 0.5h to a stirred mixture of the resorcinol or phenol (0.1 mol) and the \( \beta \)-ketoester (0.1 mol) at an external temperature of 0°C. Phosphoryl chloride (25 ml) was then added in one portion, and the mixture stirred at ambient temperature for 16 - 18h. The resultant oil was poured slowly into a solution of sodium hydrogen carbonate containing ice, and the coumarin then extracted into chloroform. The organic layer was dried (\( \text{Na}_2\text{SO}_4 \)) and the solvent removed on a rotary evaporator to leave a solid coumarin. The coumarins were then purified by crystallisation or extractive crystallisation.

7-n-Heptyl-5-hydroxy-4-(4-pyridyl)coumarin (66; \( R' = 4\)-pyridyl, \( R'' = n\)-heptyl, \( \text{X} = \text{OH} \)).

Treatment of 5-n-heptylresorcinol (41.6g) and ethyl isonicotinoylacetate (53.6g), following the general procedure, yielded on crystallisation of the crude product from ethanol, the 4-(4-pyridyl)coumarin (50.2g, 74%), m.p. 165-166°C (lit., 73 m.p. 164-165°C) (Found: C, 74.9; H, 6.9; N, 4.2. Calc. for \( \text{C}_{21}\text{H}_{25}\text{NO}_2: \text{C}, 74.8; \text{H}, 6.8; \text{N}, 4.2\% \)).

5-Hydroxy-7-methyl-4-(2-pyridyl)coumarin (66; \( R' = 2\)-pyridyl, \( R'' = \text{Me}, \text{X} = \text{OH} \)).

The reaction of 5-methylresorcinol monohydrate with ethyl picolinoylacetate gave the 4-(2-pyridyl)coumarin (50%), m.p. 179-180°C (from ethanol) (Found: C, 70.75; H, 4.4; N, 5.4. \( \text{C}_{15}\text{H}_{11}\text{NO}_3 \) requires C, 71.1; H, 4.3; N, 5.5%). 
\( \gamma \) max (Nujol) 1700 (C = 0), 1635, 1590, 1630 and 790 cm\(^{-1}\),
\( T \) (\( d^6\text{DMSO} \)) -1.75 (broad s, 0 - H), 1.33 (dt, 6'-H), 1.95 (td, 4'-H),
2.16 (dd, 3'-H), 2.45 (td, 5'-H), (J \( \text{H}_4\text{H}_5 \) = J \( \text{H}_4\text{H}_6 \) = J \( \text{H}_5\text{H}_6 \) = J \( \text{H}_4\text{H}_7 = 6 \), J \( \text{H}_4\text{H}_7 = 5 \), J \( \text{H}_4\text{H}_7 = 5 \), J \( \text{H}_4\text{H}_7 = 5 \).
J = 4.6, = 1.5 Hz), 3.28 and 3.38 (d, d, J = 1.0 Hz, 2xArH), 3.58 (s, 3-H) and 7.66 (s, 7-CH₃).

5-Hydroxy-7-methyl-4-(3-pyridyl)coumarin (86; R¹ = 3-pyridyl, R² = Me, X = OH).

5-Methylresorcinol monohydrate and ethyl nicotinoylacetate yielded an insoluble mixture which could not be crystallised. Purification was effected by continuous extraction of the mixture with ethanol for 16h, to give the 4-(3-pyridyl)coumarin (45%), m.p. 310-312° (Found: C, 70.8; H, 4.55; N, 5.4. C₁₅H₁₁NO₂ requires C, 71.1; H, 4.3; N, 5.5%), νmax (Nujol) 1720 (C = O), 1610 and 840 cm⁻¹.

5-Hydroxy-7-methyl-4-(4-pyridyl)coumarin (86; R¹ = 4-pyridyl, R² = Me, X = OH).

5-Methylresorcinol monohydrate and ethyl isonicotinoylacetate yielded a crude mixture which could not be crystallised. Continuous extraction of the crude product with ethanol for 16h, yielded the 4-(4-pyridyl)coumarin (36%), m.p. 320-321° (Found: C, 70.9; H, 4.3; N, 5.3. C₁₅H₁₁NO₂ requires C, 71.1; H, 4.3; N, 5.5%), νmax (Nujol) 1720 (C = O), 1610 and 840 cm⁻¹. (Razdan et al. isolated this coumarin as the hemihydrate (77%), m.p. 304-306°).

5-Hydroxy-7-methyl-4-phenylcoumarin (86; R¹ = Ph, R² = Me, X = OH).

The reaction of 5-methylresorcinol monohydrate and ethyl benzoyleacetate gave the 4-phenylcoumarin (15%), m.p. 217-218° (from acetone) (Lit., m.p. 226°) (Found: C, 76.4; H, 5.0. Calc. for C₁₆H₁₂O₂: C, 76.2; H, 4.6%), ν(CDC1₃) 0.5br (s, OH), 2.6 (s, 5x 4-ArH), 3.28 and 3.48 (s, s, 2x ArH), 4.04 (s, 3-H) and 7.7 (s, CH₃).
5-Hydroxy-7-(2-octyl)-4-(2-pyridyl)coumarin \( (86; R^1 = 2\text{-Pyridyl}; R^2 = 2\text{-Octyl}, X = \text{OH}) \).

The reaction of 5-(2-octyl)resorcinol with ethyl picolinoylacebate, followed by crystallisation of the resultant crude product from a mixture of ether and petroleum ether (b.p. 40-60°), yielded the 4-(2-pyridyl)coumarin \( (80\%) \), m.p. 69-70° (Found: C, 75.4; H, 7.2; N, 3.9. \( C_{22}H_{25}NO_2 \) requires C, 75.2; H, 7.1; N, 4.0%), \( \overline{\nu} \) (CDCl\(_3\)) - 0.4 (s, 0H), 1.3 (dd, 6'-H), 1.91 (td, 4'-H), 2.14 (dd, 3'-H), 2.43 (td, 5'-H), \( \beta \) (8.4 Hz), 2.22 and 3.30 (d, d, \( J = 1.5\) Hz, 2xArH), 3.55 (s, 3-H), 7.35 (m, \( J = 6.5\) Hz, chain 7-CH), 8.16-9.00 (m, chain \( \beta - \text{CH}_3 \)), \( (\text{CH}_2)_{5} \)) and 9.15 (t, \( J = 4.5\) Hz, terminal \( \text{CH}_3 \)).

5-Hydroxy-7-(2-octyl)-4-(4-pyridyl)coumarin \( (86; R^1 = 4\text{-Pyridyl}, R^2 = 2\text{-Octyl}, X = \text{OH}) \).

5-(2-Octyl)resorcinol and ethyl isonicotinoylacebate yielded, after crystallisation from ethanol, the pyridylecoumarin \( (90\%) \), m.p. 203-205° (Lit\(^7\), m.p. 203-205°), \( \overline{\nu} \) (CDCl\(_3\)) - 0.75br (OH), 1.31 (ca.d, 2'- and 6'-H), 2.56 (dd, \( J_{2,13} = J_{5,16} = 5 \), \( J_{2,16} = J_{3,15} = 1.0\) Hz, 3'-, 5'-H), 3.21 and 3.37 (d, d, \( J = 1.0\) Hz, 2xArH), 3.96 (s, 3-H), 7.35 (m, chain \( \alpha - \text{CH}_3 \)), 8.2-9.0 (m, chain \( \beta - \text{CH}_3 \)), \( (\text{CH}_2)_{5} \)) and 9.15 (t, \( J = 7\) Hz, terminal \( \text{CH}_3 \)).

5-Hydroxy-7-(2-octyl)-4-phenylcoumarin \( (86; R^1 = \text{Ph}, R^2 = 2\text{-Octyl}, X = \text{OH}) \).

5-(2-Octyl)resorcinol and ethyl benzoylacetate yielded, after crystallisation from a mixture of ethanol and water, the 4-phenylecoumarin \( (13\%) \), m.p. 146-147° (Found: C, 78.5, H, 7.5. \( C_{23}H_{26}O_3 \) requires C, 78.85; H, 7.4%), \( \overline{\nu} \) (CDCl\(_3\)) 2.48 (s, 5xArH), 3.17 and 3.46 (d, d, \( J = 1.5\) Hz, 6'-, 8-H), 3.94 (s, 3-H), 4.72 (s, HOD), 7.35 (m, 7-CH) and 8.3 - 9.3 (m, CH\(_2\) and \( C_6\)H\(_{13}\)).
Attempted preparation of 5-Hydroxy-4-((c-methoxyphenyl)-7-methylcoumarin
(86; R' = o-HoPh, R'' = Me, X = OH).

1) No products could be obtained from the reaction of 5-methylresorcinol
monohydrate with ethyl o-anisoylacacetate, a new quantitative yield of
starting acetate being recovered.

2) Similarly, no product was obtained on repeating the reaction with
heating at 50° for 24h. and then stirring at ambient temperature for 24h.

7-Methyl-4-((3-pyridyl)coumarin (86; R' = 3-Pyridyl, R'' = Me, X = H).

1) Treatment of m-cresol with ethyl nicotinoylacacetate, followed by
crystallisation of the crude product from ethyl acetate, yielded the
4-((3-pyridyl)coumarin (5%), m.p. 163-165° (Found: C, 75.55; H, 4.7; N, 5.9.
C_{15}H_{11}NO_{2} requires C, 75.9; H, 4.6; N, 5.9%), T (CDCl_{3}) 1.2 (dd, 6'-H),
1.25 (s, 2'-H), 2.16 (dt, 4'-H), 2.48 (td, 5'-H), (J_{4,5} = 7.5, J_{3,6,5} = J_{2,4}
= J_{4,16} = 1.5Hz), 2.7 (d, 5-H), 2.75 (d, 8-H), 2.94 (dd, 6-H), (J_{56} = J_{68}
1.5Hz), 3.65 (s, 3-H) and 7.52 (s, CH_{3}).

2) The reaction was repeated with heating at 50° for 16h, to give the
3-pyridylcoumarin (19%), m.p. and mixed m.p. 163-164°.

3) Phosphoryl chloride (6 ml) was added to a mixture of m-cresol (2.7g)
and ethyl nicotinoylacacetate (4.8g) in dry benzene (100 ml), and the mixture
heated under reflux; a) for 1h, and b) for 16h. The reaction mixture
in both cases yielded only the starting materials in near quantitative
yield.

5-Hydroxy-7-methyl-4-((p-nitrophenyl)coumarin (86; R' = p-NO_{2}Ph, R'' = Me,
X = OH).

5-Methylresorcinol monohydrate and ethyl p-nitrobenzoylacacetate yielded,
after crystallisation from ethanol, the 4-((p-nitrophenyl)coumarin (59%),
m.p. 292-293°c(Found: C, 64.5; H, 3.8; N, 4.5. C_{16}H_{11}NO_{2} requires C, 64.6;
H, 3.7; N, 4.7%), ν_{max} (Nujol) 1675 (γ = 0), 1620, 1590, 1090, 840 and
725 cm\(^{-1}\), \(\delta\) (d\(^6\)DMSO) 0.25 br (s, OH), 1.75 (d, 2\(\times\)ArH), 2.34 (d, J\(\text{Hz}\), 2\(\times\)-ArH), 3.25 and 3.48 (s, s, 6-\(\times\) (8-\(\times\), 6-)H), 3.92 (s, 3-H) and 7.70 (s, CH\(_3\)).

4-(p-Aminophenyl)-5-hydroxy-7-methylcoumarin (93).

Concentrated hydrochloric acid (40 ml) was added dropwise to a mixture of the p-nitrophenylcoumarin (14.8 g) and granulated tin (13.4 g) suspended in ethanol (20 ml), and the mixture heated on a steam-bath until all the tin had dissolved (3 h). After 3 h, the solution was cooled and poured into an excess of a saturated solution of sodium hydrogen carbonate. The precipitate was filtered off and continuously extracted with ethanol to give the p-aminophenylcoumarin as the monohydrate (9.47 g, 71%), m.p. 262-263\(^\circ\) (Found: C, 68.15; H, 4.7; N, 4.9. C\(_{16}\)H\(_{13}\)NO\(_3\). H\(_2\)O requires C, 67.8; H, 4.6; N, 4.9%), \(\delta\) (d\(^6\)DMSO) 0.0 br (s, OH), 2.90 (d, 2\(\times\)-ArH), 3.42 (d, \(\int_{2,1,3} = \int_{5,1,6} = 8.5\text{Hz}\), 2\(\times\) 2-ArH), 3.30 and 3.43 (s, s, 6-\(\times\), 8-\(\times\), (8-\(\times\), 6-)H) 4.10 (s, 3-H), 4.72 (s, NH\(_2\)) and 7.7 (s, CH\(_3\)).

7-Methyl-4-(4-pyridyl)coumarin (87)

1) m-Cresol and ethyl isonicotinoylacetate yielded, after crystallisation from ethyl acetate, the 4-(4-pyridyl)coumarin (20%), m.p. 149-150\(^\circ\) (Found: C, 75.7; H, 4.75; N, 5.65. C\(_{15}\)H\(_{11}\)NO\(_2\) requires C, 75.9; H, 4.6; N, 5.9%). \(\nu\)\(_{\text{max}}\) (Nujol) 1720 (C = 0), 1622, 1600, 1280, 1125 and 835 cm\(^{-1}\), \(\delta\) (CDCl\(_3\)) 1.18 (d, 2\(\times\) and 6\(\times\)-H), 2.60 (d, \(\int_{2,1,3} = \int_{5,1,6} = 4.5\text{Hz}\), 3\(\times\)- and 5\(\times\)-H), 2.69 (d, 5-H), 2.75 (s, 8-H), 2.93 (d, \(\int_{5,6} = 9\text{Hz}\), 6-H), 3.68 (s, 3-H) and 7.52 (s, CH\(_3\)).

2) The reaction was repeated with heating at 50\(^\circ\) for 50 h, to give the pyridylcoumarin (14%), m.p. 149-150\(^\circ\).

3) A solution of m-cresol (2.7 g) and ethyl isonicotinoylacetate (4.8 g) with phosphoryl chloride (6 ml) in dry benzene (100 ml) was heated under reflux for 16 h. An excess of sodium hydrogen carbonate solution (saturated) was added carefully to the cooled solution, and the aqueous layer was
extracted with chloroform. The organic extract was dried and the solvent evaporated to give the starting acetate (4.34g).

4) Sulphuric acid (10 ml; 90%) was added dropwise to a mixture of m-cresol (2.7g) and ethyl isonicotinoylacetate (4.8g) at an external temperature of 0°. The solution was then heated at 55° for 3 days. The cooled reaction mixture was poured into an excess of sodium hydrogen carbonate solution (saturated), this was extracted with chloroform, and the extract was dried and the solvent evaporated to give the pyridylcoumarin (3.5g, 60%), m.p. and mixed m.p. 149-150° (from ethyl acetate).

5-Hydroxy-4-(p-methoxyphenyl)-7-methylcumarin (89).

1) No product could be isolated from the reaction of orcinol monohydrate with ethyl p-anisoylacetate (prepared in 88% yield by the literature procedure), the starting acetate (94%) being recovered.

2) Sulphuric acid (10 ml; 90%) was added dropwise to a stirred mixture of orcinol monohydrate (3.5g) and ethyl p-anisoylacetate (5.5g) at an external temperature of 0°. The solution was stirred at ambient temperature for 48h and then heated at 55° for 6h. The cooled solution was poured into water and the aqueous layer decanted off. The remaining oil was washed with ether and continuously extracted with ethanol for 16h to give the p-methoxyphenylcumarin (0.55g, 8%), m.p. 261-262° (Found: C, 72.1; H, 5.05. C₁₇H₁₄O₄ requires C, 72.3; H, 4.95%). ν_max (Nujol) 1660 (C=O), 1600, 1245, 1080 and 830 cm⁻¹, τ (d⁶DMSO) 0-1.0 hr (OH), 2.66 (d, 2'-, 6'-H), 3.08 (d, J₂₁,₃₁= J₅₁,₆₁= 8.5Hz, 3'-, 5'-H), 3.28 and 3.49 (s, s, 6'-, 8'-, 8'-, 6'-H) 4.07 (s, 3'-H), 6.2 (s, OCH₃) and 7.71 (s, CH₃). (Pillon obtained a compound which he thought had the above structure, but he was unable to purify it.)

3) Hydrogen chloride was passed slowly into a solution of orcinol monohydrate (1.7g) and ethyl p-anisoylacetate (2.7g) in ethanol (15 ml) at an external temperature of 0° during 1h. The solution was kept at 0° for 24h and then heated under reflux for 12h. The cooled solution was
poured into water, neutralised with sodium hydrogen carbonate solution and then extracted with chloroform to yield a mixture of starting materials and p-methoxyacetophenone, as shown by n.m.r.

4) A solution of orcinol monohydrate (1.7g) and ethyl p-anisoylacetate (2.7g) with phosphoryl chloride (10 ml) in dry benzene (20 ml) was stirred at ambient temperature for 7 days, during this time a solid precipitated. The suspension was poured into water and the resultant solid purified by continuous ethanol extraction, to yield the methoxyphenylcoumarin (2.1g, 60%), m.p. and mixed m.p. 262-263°.

5-Hydroxy-4,7-dimethylcoumarin (86; R' = R'' = Me, X = OH).

Sulphuric acid (36 ml; 90%) was added dropwise to a stirred mixture of orcinol monohydrate (14.2g) and ethyl acetoacetate (13.0g) at an external temperature of 0°, and the solution then stirred at ambient temperature for 16h. The reaction mixture was poured into an excess of sodium hydrogen carbonate solution (saturated) and extracted with chloroform. The extract was dried and the solvent evaporated to give 5-hydroxy-4, 7-dimethylcoumarin (14.2g, 77%), m.p. 261-262° (from acetone) (Lit.96 m.p. 250°) (Found: C, 69.95; H, 5.2. Calc. for C_{11}H_{10}O_3: C, 69.5; H, 5.3%), \( \uparrow \) (d_{DMSO}^6) -0.4 (s, OH), 3.4 (s, 6-, 8-H), 4.0 (q, 3-H), 7.45 (d, J 1:0Hz, 4-CH_3) and 7.70 (s, 7-CH_3).

4,7-Dimethylcoumarin (86; R' = R'' = Me, X = H).

Concentrated sulphuric acid (80 ml) was added dropwise to a stirred mixture of m-cresol and ethyl acetoacetate (26.0g) at an external temperature of 0°, and the solution stirred at ambient temperature for 16h. The general procedure was then followed to give, after crystallisation from ethanol, the dimethylcoumarin (13.0g, 40%), m.p. 132-133° (Lit.97 m.p. 132°), \( \uparrow \) (CDCl_3) 2.56 (d, J8Hz, 5-H), 2.96 (ca.d, J8Hz, 6-H), 2.95 (ca.d, 8-H), 3.85 (q, J 1.0Hz, 3-H) and 7.60 (ca.d + s, 4-CH_3 and 7-CH_3).
4-Trifluoromethyl-7-methylcoumarin (66; \(R^1 = CF_3\), \(R^2 = Me\), \(X = H\)).

Concentrated sulphuric acid (4 ml) was added dropwise to a stirred mixture of \(m\)-cresol (1.08 g) and ethyl 4,4,4-trifluoro-3-oxobutyrate (1.84 g) at an external temperature of 0\(^\circ\)C, and the solution was then stirred at ambient temperature for 16h. The solution was poured into water (15 ml) and neutralised with solid sodium hydrogen carbonate, to give a solid precipitate. Crystallisation from petroleum ether (b.p. 60-80\(^\circ\)C) yielded the trifluoromethylcoumarin as the monohydrate (0.63 g, 28\%), m.p. 94-95\(^\circ\)C (Found: C, 53.4; H, 2.9. \(C_{11}H_{17}F_3O_2\) requires C, 53.65; H, 2.8%).

\(\delta (CDCl_3 + D_2O)\) 2.43 (d, 5-H), 2.9 (d, \(J = 7Hz\), 6-H), 2.82 (s, 8-H), 3.37 (s, 3-H), 5.18 (s, HOD) and 7.51 (s, 7-CH\(_3\)).

B. The Reaction of Grignard Reagents with Coumarins.

General Procedure.

1. Preparation of Grignard reagents.

A few drops of the alkyl or arylhalide were added to magnesium turnings (0.1 g atom) in tetrahydrofuran or dry diethyl ether (100 ml) containing a crystal or iodine. After a few minutes the solution changed colour and became warm. Stirring was commenced, and the remainder of the alkyl or arylhalide (total, 0.1 mol) in tetrahydrofuran or dry ether (10 ml) was added dropwise during 20 min. (In the preparation of methylmagnesium bromide, bromomethane was bubbled into the stirred suspension in a current of nitrogen gas.) Stirring was continued for a further 20 min. until the solution had cooled to room temperature.

2. The reaction of Grignard reagents with coumarins.

The coumarin (0.01 mol) as a slurry, or solution in tetrahydrofuran, dry ether, or dry benzene (50 ml), was added dropwise during 0.5 h, to a stirred solution of the Grignard reagent (0.1 mol). The reaction mixture was stirred at ambient temperature for 1h, and then poured
slowly into an excess of ammonium chloride solution (saturated). The aqueous solution was extracted with ether, the extract dried (MgSO₄) and the solvent evaporated. (Tetrahydrofuran extracts were evaporated nearly to dryness, re-extracted with ether, and then dried.) The resulting crude material, containing either the dihydrocoumarin or the carbinol, or a mixture of both, was then fractionally crystallised or purified by column chromatography. In some examples, no products could be isolated, and so the crude material was treated directly by the procedure described in 3 below.

3. Crystallisation with acetic acid.

The carbinol, or the crude material (1.0 g) from above, was heated under reflux in glacial acetic acid (5 ml) for 1 h. The cooled solution was poured into water (25 ml) to give the crude products. Solid products were isolated by filtration and purified by crystallisation. Oily products were extracted into ether, the extract washed with sodium hydrogen carbonate solution and water, and then dried (MgSO₄). The solvent was removed by evaporation under reduced pressure and the resultant material purified by crystallisation or column chromatography.

a. 7-α-Heptyl-5-hydroxy-4-(4-pyridyl)coumarin.

1. With methylmagnesium bromide.

The heptylcoumarin (20.22 g, 0.05 mol) in dry benzene (400 ml) was added during 1 h. to a stirred solution of methylmagnesium bromide (0.6 mol) in dry ether (400 ml), and the mixture heated under reflux for 2 h. Following the general procedure, an oil was obtained which was heated under reflux in glacial acetic acid for 1 h. The acid solution was poured into water and the resulting precipitate crystallised from acetonitrile to give 7-α-heptyl-2,2-dimethyl-4-(4-pyridyl)-2H-chromen-5-ol.
as the hemihydrate (99) \( (6.76 \text{ g}, 32\%) \), m.p. 154-155° (Found: C, 76.7; H, 8.3; N, 3.9. \( \text{C}_{25}\text{H}_{29}\text{NO}_{2} \cdot 0.5\text{H}_{2}\text{O} \) requires C, 76.7; H, 8.3; N, 3.9%).

2. With ethylmagnesium bromide

a) In diethyl ether

A suspension of the heptylcoumarin (6.74 g, 0.02 mol) in ether (50 ml) was added portionwise during 0.5 h to a solution of ethylmagnesium bromide (0.06 mol) in ether (120 ml), and the mixture heated under reflux for 2 h. Crystallisation of the resulting crude gum from carbon tetrachloride afforded 3,3-diethyl-1-(4-n-heptyl-2,6-dihydroxyphenyl)-1-(4-pyridyl)prop-1-en-3-ol as the monohydrate (97) \( (1.7 \text{ g}, 22\%) \), m.p. 161-162° (Found: C, 72.5; H, 8.6; N, 3.3. \( \text{C}_{25}\text{H}_{35}\text{NO}_{3} \cdot \text{H}_{2}\text{O} \) requires C, 72.3; H, 8.4; N, 3.3%).

\( \nu_{\text{max}} \) (Nujol) 3300 (O-H), 1602, 1280, 1050, 1020 and 830 cm\(^{-1}\).

\( \delta \) (CDCl\(_3\)) 1.68 (dd, 2', 6', H), 2.83 (dd, \( J_{2',3'} = 4.0 \), \( J_{3',5'} = 1.4 \text{Hz} \), 3'-, 5'-H), 3.48 (s, 2H), 3.64 (s, 2ArH), 6.0 br (2xOH), 7.54 (t, J 6.5 Hz, ArCH\(_2\)) and 8.1 - 9.3 (m, 2xC\(_2\)H\(_5\), C\(_6\)H\(_4\)).

The filtrate from the crystallisation was evaporated to dryness. T.l.c. of the residue showed the presence of mainly one product, whilst a band at 1760 cm\(^{-1}\) in the infrared and an 'AB' quartet at \( \nu 7.0 \) in the n.m.r. indicated a product other than the carbinol or coumarin. Unsuccessful attempts were made to isolate a product from the residue by crystallisation and by column chromatography. Finally, treatment with an excess of methyl iodide in acetone (10 ml) yielded 4-ethyl-7-n-heptyl-3,4-dihydro-5-hydroxy-4-(4-pyridyl)coumarin as the methiodide (3) \( (0.77 \text{ g}, 8\%) \), m.p. 247-249° (from ethanol) (Found: C, 56.3; H, 6.2; N, 2.7; I, 25.2. \( \text{C}_{24}\text{H}_{32}\text{I} \text{NO}_{3} \) requires C, 56.4; H, 6.3; N, 2.8; I, 25.0%).

\( \nu_{\text{max}} \) (Nujol), 1745 (C=O), 1650, 1622, 1580 and 1220 cm\(^{-1}\). \( \delta \) (d\(_6\)DMSO) 0.60 br (OH), 1.15 (d, 2', 6'-H), 2.04 (d, J 5Hz, 3'-, 5'-H).
3.47 (s, 6~, 8~H), 5.66 (s, N—^CH^), 6,89 (m, 3~E2 ) and 8.4-9.3 (m, CH_2CH_3 and C_H^15).

The diethylpropenol (0.3g) was heated under reflux in glacial acetic acid (5 ml) for 1 h. Crystallisation of the resulting solid from acetonitrile afforded 2,2-diethyl-7a-heptyl-4-(4-pyridyl)-2H-chromene-5-ol as the hemihydrate (2) (0.45g, 51%), m.p. 121-122° (Found: C, 76.9; H, 8.6; N, 3.6. C_{25}H_{35}NO_2 • \frac{1}{2}H_2O requires C, 77.3; H, 8.7; N, 3.6%).

\[ ^{\text{1H NMR}} \times 3 \times \text{H} \rightarrow ]

\[ \text{2.65 (dd, 2 \times 35 \times \text{H})}, \ 2.68 \ (\text{dd}, \text{J}_2 = 3.15, \ 3.15 \ 1.5 \text{Hz}, \ 3.15 \ 5.15 \text{H}), \ 3.60 \ (\text{dd}, \text{J}_2 = 3.15, \ 3.15 \ 1.5 \text{Hz}, \ 3.15 \ 5.15 \text{H}), \ 3.72 \ (s, 6-, 8- (s-, 6- H)), 4.45 (s, 3-H), 5.42 (s, NOD), 7.5 (m, 7-CH_2), 8.20 (q, \text{J} 7Hz, 2x2-CH_2), 8.70 (br 5 , (CH_2)_5) \text{and} 9.06 (m, 3 x terminal CH_3).

b) In a diethyl ether benzene mixture.

A solution of the heptylcoumarin (3.37 g, 0.01 mol) in benzene (150 ml) was added portionwise during 0.5h to a solution of ethylmagnesium bromide (0.1 mol) in ether (50 ml), and the solution heated under reflux for 1h. Treatment of the reaction mixture in the usual manner, followed by heating with an excess of methyl iodide yielded from ethanol, the 4-ethyl-3,4-dihydrocoumarin as the methiodide (2.1 g, 41%), m.p. and mixed m.p. 249-251°.

c) In tetrahydrofuran

The reaction was repeated as in b) above in tetrahydrofuran to give the dihydrocoumarin methiodide (l.85g, 36%), m.p. and mixed m.p. 248-250°.

3. With n-propylmagnesium bromide

The heptylcoumarin (3.37g, 0.01 mol) in ether (50 ml) was treated with n-propylmagnesium bromide (0.1 mol) in benzene (110 ml) as in 2. b) above to yield the 7-n-heptyl-3,4-dihydro-5-hydroxy-4-n-propyl-4-(4-pyridyl)coumarin as the methiodide hemihydrate (100) (2.2g, 36%), m.p. 277-279° (from aqueous ethanol) (Found: C, 56.5;
H, 6.4; N, 2.6; I., 25.2; C<sub>26</sub>H<sub>34</sub>IN<sub>3</sub> · ½H<sub>2</sub>O requires C, 56.4; H, 6.6; N, 2.6; 1., 23.9%; \( \nu_{\text{max}} \) (Nujol) 1750 (0 = 0), 1660, 1530, 1585, 1220 and 1070 cm<sup>-1</sup>, \( \nu \) (d<sub>6</sub> DMSO) 1.18 (eqd d, 2', 6', 6'-H), 2.05 (eqd d, J<sub>2,13</sub> = J<sub>5,16</sub> = 6 Hz, 5'-- 6'--H), 3.46 (s, 6-- 8--H), 5.67 (s, N<sup>--</sup>CH<sub>2</sub>), 6.29 with D<sub>2</sub>0(s, OH), 6.88 (m, 3-Hz) and 8.2 -- 9.3 (m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and C<sub>7</sub>H<sub>15</sub>).

b. 5-Hydroxy-7-Methyl-4-(4-Pyridyl)coumarin.

Treatment of the 4-(4-pyridyl)coumarin with methylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting gum from a mixture of acetonitrile and ethanol, yielded 1-(2,6-dihydroxy-4-methylphenyl)-3,3-dimethyl-1-(4-pyridyl)prop-1-en-3-ol (102; R = Me) (75%), m.p. 199-200° (Found: C, 71.8; H, 6.8; N, 5.0. C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub> requires C, 71.6; H, 6.7; N, 4.9%), \( \nu \) (d<sub>6</sub> DMSO) 1.25 br (s, 3xOH), 1.56 (dd, 2'--, 6'--H), 2.78 (dd, 3'--, 5'--H), (J<sub>2,13</sub> = J<sub>5,16</sub> = 4.5, J<sub>2,16</sub> = J<sub>5,15</sub> = 1.5Hz), 3.41 (s, 2-H), 3.72 (s, 2xArH), 7.80 (s, ArCH<sub>3</sub>) and 8.83 (s, 2xCH<sub>2</sub>).

The above pyridylpropenol (10g) was heated under reflux in glacial acetic acid, and the resulting gum crystallised from ethyl acetate, to give 2,2,7-trimethyl-4-(4-pyridyl)-2H-chromen-5-ol (103; R = Me) (0.8g, 90%), m.p. 259-260° (Found C, 76.3; H, 6.3; N, 5.0. C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> requires C, 76.4; H, 64; N, 5.2%), \( \nu \) (d<sub>6</sub> DMSO) 0.75 (s, OH), 1.55 (dd, 2'--, 6'--H), 2.83 (dd, 3'--, 5'--H), (J<sub>2,13</sub> = 4.5, J<sub>2,16</sub> = 2Hz, 3.76 (s, 2xArH), 4.33 (s, 3-H), 7.83 (s, 7-CH<sub>3</sub>) and 8.64 (s, gem-dich<sub>2</sub>CH<sub>3</sub>).

2) With ethylmagnesium bromide.

a) In tetrahydrofuran.

The reaction of ethylmagnesium bromide with the 4-(4-pyridyl)coumarin in tetrahydrofuran, followed by crystallisation of the resulting gum from ethyl acetate, yielded 4-ethyl-3,4-dihydro-
5-hydroxy-7-methyl-4-(4-pyridyl)coumarin as the quarter hydrate
(104; R=Et) (77%), m.p. 157-158° (Found: C, 70.8; H, 6.1; N, 4.8.
C₁₇H₁₇NO₃.·½H₂O requires C, 70.9; H, 6.1; N, 4.9%); ν(CDCl₃)
~1.0 br (OH), 1.64 (dd, 2', 6'-H), 2.70 (dd, 3', 5'-H),
(J₂,₃ = J₃,₅ = 4.5, J₂,₆ = J₅,₆ = 1.5 Hz), 3.51 (s, 6', 8-H),
7.11 (s, 3-H₂), 7.40 (m, 4-CH₂), 7.79 (s, 7-CH₃) and 9.05 (t, J
7Hz, CH₃). The product was re-crystallised from ethyl acetate and
re-analysed, to confirm that the compound was a quarter hydrate,
(Found: C, 71.0; H, 6.1; N, 4.8%).

The filtrates from the crystallisation were combined and
evaporated to a small bulk to yield 3,3-diethyl-1-(2,6-dihydroxy
-4-methylphenyl)-1-(4-pyridyl)prop-1-en-3-ol (102; R=Et) (9%),
m.p. 238-239° (Found: C, 73.1; H, 7.4; N, 4.5. C₁₉H₂₃NO₃ requires
C, 72.8; H, 7.3; N, 4.5%), ν(DMSO) 1.4 br (OH), 1.61 (dd, 2',-
6'-H), 2.83 (dd, 3', 5'-H), (J₂,₃ = J₃,₅ = 4.5, J₂,₆ = J₅,₆ =
1.5 Hz), 3.60 (s, 2-H), 3.76 (s, 2xArH), 5.5 br (2xOH), 7.83 (s,
ArCH₃), 8.58 (m, 6Hz, 2x3-CH₂) and 9.18 (t, 6Hz, 2xCH₃).

b. In Ether.

The reaction of ethylmagnesium bromide with the 4-(4-pyridyl)
coumarin was repeated, with diethyl ether as solvent. No reaction
occurred, the coumarin being recovered in quantitative yield.

3. With isopropylmagnesium bromide.

The reaction of isopropylmagnesium bromide with the 4-(4-
pyridyl)coumarin in tetrahydrofuran, followed by crystallisation of
the resulting gum from a mixture of ethyl acetate and ethanol, yielded
3,4-dihydro-5-hydroxy-7-methyl-4-isopropyl-4-(4-pyridyl)coumarin
(104; R=Pr) (60%), m.p. 313-314° (Found: C, 72.9; H, 6.5; N, 4.7.
C₁₈H₁₉NO₃ requires C, 72.7; H, 6.4; N, 4.7%); ν(DMSO) 0.5br
(OH), 1.50 (dd, 2', 6'-H), 2.58 (dd, J₂,₃ = J₃,₅ = 4.5, J₂,₆ =
J₅,₆ = 1.5Hz 3', 5'-H), 3.40 and 3.63 (s, s, 2xArH), 6.79 and
7.08 (AB quartet, J 16Hz, 3-H₂), 6.55 (m, 4-CH), 7.80 (s, 7-CH₃),
Evaporation of the filtrate from the crystallisation, yielded 1-(2,6-dihydroxy-4-methylphenyl)-3,3-di-isopropyl-1-(4-pyridyl)prop-1-en-3-ol (102; R=Fr') (13%; m.p. 223-225° (from ethyl acetate) (Found: C, 73.9; H, 8.1, N, 4.2. \( \text{C}_2\text{H}_{17}\text{NO}_3 \) requires C, 73.9; H, 7.9; N, 4.1%), \( \nu \) (CDCl\(_3\)) 1.65 (br.s, 2'-, 6'-H), 2.65 (br.s, 3', 5'-H), 3.50 (s, 2xArH), 3.66 (s, 2-H), 5.4br (3xOH), 7.55 (m, 2x3-GH), 7.71 (s, ArCl\(_2\)) and 8.95 (m, 4xOH)

**4. With phenylmagnesium bromide.**

Treatment of the 4'' (4-pyridyl)coumarin with phenylmagnesium bromide in tetrahydrofuran yielded 1-(2,6-dihydroxy-4-methylphenyl)-3,3-diphenyl-1-(4-pyridyl)prop-1-en-3-ol as a quarter hydrate (102; R=Ph) (76%), m.p. 240-241° (from ethanol) (Found: C, 78.4; H, 5.8; N, 3.3. \( \text{C}_{27}\text{H}_{23}\text{N}0_3 \cdot \frac{1}{4}\text{H}_2\text{O} \) requires C, 78.3; H, 5.7; N, 3.4%), \( \nu \) (d\(_6\)DMSO) 1.59 (dd, \( \text{J}_{2',5'} = \text{J}_{5',6'} = 4.5, \text{J}_{2',6'} = \text{J}_{3',5'} = 1.5 \) Hz, 2'-, 6'-H), 2.4 - 2.95 (m, 10xArH, 3', 5'-H) 3.03 (s, 2xArH), 4.03 (s, 2xArH), 6.27 (s, HOD) and 8.00 (s, ArOH).

The above pyridylpropenol (1.0g) was heated under reflux in glacial acetic acid to give, from a mixture of ethanol and acetone, 7-methyl-2,2-diphenyl-4-(4-pyridyl)-2H-chromen-5-ol (103; R=Ph) (0.74g, 60%), m.p. 275-276° (Found: C, 83.3; H, 5.5; N, 3.5. \( \text{C}_{27}\text{H}_{21}\text{NO}_2 \) requires C, 82.9; H, 5.4, N, 3.6%), \( \nu \) (d\(_6\)DMSO) 1.25br (OH), 1.50 (d, \( \text{J}_{2',3'} = \text{J}_{5',6'} = 4.5\) Hz, 2'-, 6'-H), 2.60 (m, 10xArH, 3', 5'-H), 3.49 and 3.76 (s, s, 6'-, 8'-(8-, 6-)H), 3.72 (s, 3'-H) and 7.84 (s, 7-CH\(_3\)).

**c. 5-Hydroxy-7-Methyl-4-(2-Pyridyl)coumarin.**

1. **With methylmagnesium bromide.**

Treatment of the 4-(2-pyridyl)coumarin with methylmagnesium bromide in tetrahydrofuran yielded 3,4-dihydro-5-hydroxy-4,7-dimethyl-4-(2-pyridyl)coumarin (110; R'=2-py; R"=Me) (55%), m.p.
161-162° (from ethyl acetate) (Found: C, 71.0; H, 5.7; N, 5.1.

\( C_{16}H_{15}NO_3 \) requires C, 71.4; H, 5.6; N, 5.2%, \( \nu_{\text{max}} \) (Nujol) 1765 (C=O), 1620, 1590 and 830 cm\(^{-1}\), \( \nu \) (CDCl\(_3\)) -1.3 br (s, OH), 1.48 (dt, 6'-H), 2.25 (td, 4'-H), 2.62 (d, 3'-H), 2.79 (m, 5'-H),
\( J_{3',4'} = J_{4',5'} = 7.5, J_{5',6'} = 5.0, J_{4',6'} = 1.5 \text{ Hz} \), 3.39 and 3.61 (s, s 6-8-(8-6-8)), 6.72 and 7.12 (AB quartet, \( J_{16\text{Hz}, 3-\text{Hz}} \)), 7.77 (s, 7-\text{CH}_{3}) and 8.02 (s, 4-\text{CH}_{2}).

2. With ethylmagnesium bromide

The reaction of the 4-(2-pyridyl)coumarin with ethylmagnesium bromide in tetrahydrofuran gave 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-(2-pyridyl)coumarin (110; \( R' = \text{2-Py, } R'' = \text{Et} \) (64%), m.p. 127-129° (from ethyl acetate) (Found: C, 71.9; H, 6.1; N, 4.9.

\( C_{17}H_{17}NO_3 \) requires C, 72.1; H, 6.0; N, 4.9%, \( \nu_{\text{max}} \) (Nujol) 1760 \( \nu \) (CDCl\(_3\)) -0.5 br (s, OH), 1.50 (c.a.dd, 6'-H), 2.24 (td, 4'-H), 2.60 (d, 3'-H), 2.78 (m, 5'-H),
\( J_{3',4'} = J_{4',5'} = 8, J_{5',6'} = 5.5, J_{3',5'} = J_{4',6'} = 1.5 \text{ Hz} \), 3.37 and 3.58 (s, s, 2xArH), 6.60 and 7.02 (AB quartet, \( J_{16\text{Hz}, 3-\text{Hz}} \)), 7.60 (m, \( J_{7.5\text{Hz}, 4-\text{CH}_{2}} \)), 7.76 (s, 7-\text{CH}_{3}) and 9.18 (t, \( J_{7.5\text{Hz}, \text{CH}_{3}} \)).

3. With isopropylmagnesium bromide

The 4-(2-pyridyl)coumarin with isopropylmagnesium bromide in tetrahydrofuran yielded, after crystallisation of the resulting crude gum from ethyl acetate, 3,4-dihydro-5-hydroxy-7-methyl-4-isopropyl-4-(2-pyridyl)coumarin (110; \( R' = \text{2-Py, } R'' = \text{Pr}^3 \) (70%), m.p. 200-202° (Found: C, 72.5; H, 6.6; N, 4.7. \( C_{18}H_{19}NO_3 \) requires C, 72.7; H, 6.4; N, 4.7%, \( \nu_{\text{max}} \) (Nujol) 1750 \( \nu \) (CDCl\(_3\)) -0.5 br (s, OH), 1.44 (at, 6'-H),
2.20 (td, 4'-H), 2.58 (dd, 3'-H), 2.75 (m, 5'-H),
\( J_{3',4'} = J_{4',5'} = 8, J_{5',6'} = 5, J_{3',5'} = J_{4',6'} = 1.5 \text{ Hz} \), 3.39 and 3.59 (d, d, \( J_{2\text{Hz}, 2xArH} \))
6.25 (m, \( J_{7\text{Hz}, 4-\text{CH}_{2}} \)), 6.82 and 7.12 (AB quartet, \( J_{16\text{Hz}, 3-\text{Hz}} \)).
4. With tert-butylmagnesium bromide.

The reaction of tert-butylmagnesium bromide with the 4-(2-pyridyl)coumarin in tetrahydrofuran yielded a mixture of products, as indicated by t.l.c. No separation of the mixture was achieved.

5. With phenylmagnesium bromide

Treatment of the 4-(2-pyridyl)coumarin with phenylmagnesium bromide in tetrahydrofuran yielded, after crystallisation of the resulting crude gum from ethyl acetate, 3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-4-(2-pyridyl)coumarin (110; \( R^1 = 2\text{-Py}, R^2 = \text{Ph} \)) (73%), m.p. 198-199° (Found: C, 76.5; H, 5.2; N, 4.2. \( \text{C}_{21}\text{H}_{17}\text{NO}_{3} \) requires C, 76.1; H, 5.2; N, 4.2%), \( \nu_{\max} \) (Nujol) 1760 (C = O), 1635, 1595, 1575 and 1260 cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 0.70 br (s, OH), 1.50 (d, 6'-H), 2.08 (td, 4'-H), 2.37 (d, 3'-H), (J - \( J_{3,4} \) = \( J_{4,5} \) = \( J_{3,5} \) = 8, \( J_{5,6} \) = 2.0 Hz), 2.72 br (m, 4x4- ArH), 3.08 (m, 4-ArH, 5'-H), 3.33 and 3.45 (s, s, 6-, 8- (6-, 6-) H), 6.57 and 6.97 (AB quartet, \( J_{16.5} \) Hz, 3-H') and 7.70 (s, 7-CH\(_3\)).

6. 5-Hydroxy-7-Methyl-4-(3-Pyridyl)coumarin

1. With methylmagnesium bromide

Treatment of the 4-(3-pyridyl)coumarin with methylmagnesium bromide in tetrahydrofuran followed by crystallisation of the resultant crude product from a mixture of acetonitrile and water, yielded 1-(2,6-dihydroxy-4-methylphenyl)-3,3-dimethyl-1-(3-pyridyl)-dihydro-1H-3-ol (111; \( R^1 = 3\text{-Py}, R^2 = \text{Me} \)) (51%), m.p. 205-206° (Found: C, 71.5; H, 6.7; N, 4.8. \( \text{C}_{17}\text{H}_{19}\text{NO}_{3} \) requires C, 71.6; H, 6.7; N, 4.9%), \( \delta \) (d\(_6\)DMSO) 1.65 (br.s, 2'-H, 6'-H), 2.2-2.9 (m, 4'-, 5'-H), 3.67 (s, 2-H), 3.75 (s, 3- and 5-ArH), 6.30 (s, HOD), 7.82 (s, ArCH\(_2\)) and 8.63 (s, gem-diCH\(_3\)).

The above pyridylpropanol (0.5g) in glacial acetic acid (2.5 ml)
was heated under reflux for 1 h, and then poured into water (12.5 ml).

The resulting precipitate was crystallised from acetonitrile to yield 2,2,7-trimethyl-4-(3-pyridyl)-2H-chromen-5-ol (112; R¹ = 3-F, R² = Me) (0.35g, 76%), m.p. 202-203° (Found: C, 76.1; H, 6.4; N, 5.4. C₁₁H₁₄NO₂ requires C, 76.4; H, 6.4; N, 5.2%).

In DMSO 0.75 (s, OH), 1.6 (dd, J₅₁₆: 5, J₄₁₅: 2Hz, 6H-H), 1.68 (d, J₂₇₁₄: 2Hz, 2H-H), 2.3-2.8 (m, 4', 5'-H), 3.74 (s, 6'-, 8-H), 4.38 (s, 3-H), 7.8 (s, 7-CH₃) and 8.61 (s, gem-diCH₂).

1a. With methylmagnesium bromide in the presence of cuprous chloride.

The 4-(3-pyridyl)coumarin (2.53g, 0.01 mol) in tetrahydrofuran (50 ml) was added dropwise to a solution of methylmagnesium bromide (0.1 mol) in tetrahydrofuran (110 ml) at -10° to -20° during 0.5h. During the addition at regular intervals, small portions of cuprous chloride (total of 0.2g, 0.001 mol) were added. The reaction mixture was allowed to warm to room temperature during 1h and then stirred for a further 1h. Treatment of the reaction mixture in the usual manner yielded the dimethylpropanol (1.51g, 53%), m.p. 205-206° (from acetonitrile-ethanol).

2. With ethylmagnesium bromide

Ethylmagnesium bromide with the 4-(3-pyridyl)-coumarin in tetrahydrofuran, followed by crystallisation of the resulting product from acetonitrile-water, yielded 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-(3-pyridyl)coumarin as the hemihydrate (110; R¹ = 3-F, R² = Et) (60%), m.p. 223-224° (Found: C, 70.3; H, 6.1; N, 4.8. C₁₇H₁₇NO₄: 0.5H₂O requires C, 69.9; H, 6.2; N, 4.8%).

In Nujol 1775 (C = 0), 1625, 1595, 1270, 835 and 715 cm⁻¹,

\( \nu_{\text{max}} \) (νmax) 0.6 br (s, OH), 1.62 (br.s, 2H-6H-H), 2.2-2.8 (m, 4'-, 5'-H), 3.44 and 3.54 (s, s, 6'-, 8-(8,-6')H), 6.92 (s, 3-H₂), 7.77 (s, 7-CH₃), 7.9 (m, 4-CH₂-) and 9.15 (t, J 7Hz, CH₂).
The filtrate from the crystallisation was evaporated to dryness, heated under reflux in glacial acetic acid (10 ml), and then poured into water. The resulting solid was crystallised from acetonitrile to yield 2,2-diethyl-7-methyl-4-(3-pyridyl)-2H-chromen-5-one as the hemihydrate (112; R' = 3-Py, R'' = Et) (5%), m.p. 168-169° (Found: C, 75.25; H, 7.15; N, 4.8. C_{19}H_{21}NO_2 \cdot \frac{1}{2}H_2O requires C, 75.0; H, 7.2; N, 4.6%). \( ^1H \) (CDCl_3) 1.68 (dd, 6'-H), 1.58 (d, 2'-H), 2.29 (dt, 4'-H), 2.76 (dd, 5'-H), \( J_{5',6'} = 1.7 \text{ Hz} \), 3.64 and 3.70 (as, 2xArH), 4.52 (s, 3-H), 5.46 (s, HOD), 7.18 (3,7-CH_3), 8.20 (q, \text{J}_7Hz, 2x2-CH_2) and 9.05 (t, \text{J}_7Hz, 2xCH_2).

2a. With ethyllmagnesium bromide in the presence of cuprous chloride.

The 4-(3-pyridyl)coumarin (2.53 g, 0.01 mol) in tetrahydrofuran (50 mol) was added dropwise to a solution of ethyllmagnesium bromide (0.1 mol) in tetrahydrofuran (110 ml) at \(-10^\circ\) to \(-20^\circ\) during 0.5 h. During the addition, at regular intervals, small portions of cuprous chloride (total of 0.2 g, 0.001 mol) were added. The reaction mixture was allowed to warm to room temperature during 1 h and stirred for a further 1 h. Treatment of the reaction mixture in the usual manner yielded 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-(3-pyridyl)coumarin (110; R' = 3-Py, R'' = Et) (2.07 g, 73%), m.p. 233-234° (from acetonitrile-ethanol) (Found: C, 72.4; H, 6.2; N, 5.0. C_{17}H_{17}NO_3 requires C, 72.1; H, 6.0; N, 5.0%).

3. With isopropylmagnesium bromide

Treatment of the 4-(3-pyridyl)coumarin with isopropylmagnesium bromide in tetrahydrofuran yielded the highly insoluble 3,4-dihydro-5-hydroxy-7-methyl-4-isopropyl-4-(3-pyridyl)coumarin (110; R' = 3-Py, R'' = Pr) (87%), m.p. 300-301° (after washing with hot acetone). Crystallisation was finally achieved with difficulty from a mixture of dimethyl sulphoxide and water to give the isopropylidihydrop-
Coumarin (45%), m.p. 300-301° (Found: C, 72.4; H, 6.4; N, 4.6.

C_{18}H_{19}NO_3 requires C, 72.7; H, 6.4; N, 4.7%). δ_{max} (Nujol)
1770 (C = O), 1620, 1585, 1285, 1140 and 830 cm⁻¹, T (d_{6}DMSO)
1.38 (d, 2'-H), 1.61 (c, a, dd, J_{5,16} = 4, J_{2,14} = J_{4,16} = 2, Hz,
6'-H), 2.18 (br, 4'-H), 2.65 (br, 5'-H), 3.39 and 3.62 (s, s, 2xArH),
6.30 (s, 6H), 6.75 and 7.03 (AB quartet, J_{17}Hz, 3-H_2), 6.9 (m,
4-CH), 7.80 (s, 7-CH_3), 9.00 (d, J5Hz, CH_2) and 9.31 (d, J6Hz,
CH_3).

4. With cyclohexylmagnesium bromide.

Treatment of the 4-(3-pyridyl)coumarin with cyclohexylmagnesium bromide in tetrahydrofuran yielded 4-cyclohexyl-3,4-dihydro-5-
hydroxy-7-methyl-4-(3-pyridyl)coumarin (110; R' = 3-Py, R" =
cyclohexyl) (73%), m.p. 306-307° (from ethanol) (Found: C, 74.5;
H, 6.9; N, 4.0.

C_{21}H_{25}NO_3 requires C, 74.7; H, 6.8; N, 4.1%).
T (d_{6}DMSO) -0.1 (s, 0H), 1.35 (d, 2'-H), 1.70 (dd, 6'-H), 2.21
(dt, 4'-H), 2.71 (dd, 5'-H), (J_{5,16} = 6.5, J_{4,16} = 1.5, J_{2,14} = 2Hz),
3.94 and 3.65 (s, s, 2xArH), 6.72 and 7.04 (AB quartet, J16Hz, 3-H_2), 7.80
(s, 7-CH_3) and 8.1-9.1 (brd, cyclohexyl)

5. With allylmagnesium bromide.

Treatment of the 4-(3-pyridyl)coumarin with allylmagnesium bromide in tetrahydrofuran yielded only the starting coumarin.

6. With phenylmagnesium bromide.

Treatment of the 4-(3-pyridyl)coumarin with phenylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the
resulting oil from a mixture of acetone and petroleum ether (b.p.
60-80°), yielded 1-(2,6-dihydroxy-4-methylphenyl)-3,3-diphenyl-1-
(3-pyridyl)-prop-1-en-3-ol as the hemihydrate (111; R' = 3-Py,
R" = Ph) (71%), m.p. 316-318° (Found: C, 77.4; H, 6.1; N, 3.3.
C_{27}H_{33}NO_3 · 0.5H_2O requires C, 77.5; H, 5.8; N, 3.3%).
T (d_{6}DMSO)
1.6 (s, 2'-, 6'-H), 2.2-3.0 (m, 10xArH, 4'-, 5'-H), 3.17 (s, 2-H),
4.00 (s, 3'-H), 5.18 (s, HOD) and 7.88 (s, 4'-ArCH).  

Evaporation of the acetone-petroleum ether filtrate yielded crude product, which was crystallised from ethyl acetate, to yield 3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-4-(3-pyridyl)coumarin as the quarter hydrate (110, R' = 3-Py, R'' = Ph), (7%), m.p. 272-273° (Found: C, 74.9; H, 5.3; N, 4.1).  
\[ \text{C}_{21}H_{17}NO_3 \cdot \frac{1}{2} \text{H}_2\text{O} \]
requires C, 75.1; H, 5.2; N, 4.2%. \( \gamma_{\text{max}} \) (Nujol) 1760 (\( \delta = 0 \)), 1620, 1585, 1252, 1060 and 838 cm\(^{-1} \), \( \delta \) (\( \text{d}^6\text{DMSO} \)) 0.40 (s, OH), 1.60 (dd, \( J_{2',6'} = 4.5 \), \( J_{4',6'} = 2.5 \), \( 2'-\text{H} \)), 2.67 (\( \text{d} \), 5xArH, \( 4', 5'\)-H), 3.51 (s, 4x, 8-H), 6.49 (s, 3-H) and 7.74 (s, 7-CH).  

The above pyridylpropenol (2.75g) was heated under reflux in glacial acetic acid (15 ml) to give, on pouring into water, the highly insoluble 7-methyl-2,2-diphenyl-4-(3-pyridyl)-2H-chromen-5-ol as the monohydrate (112; R' = 3-Py, R'' = Ph) (2.35 g, 90%), m.p. 313-315° (after washing with hot acetone) (Found: C, 79.7; H, 5.4; N, 3.4. \[ \text{C}_{27}H_{21}NO_2\text{H}_2\text{O} \]
requires C, 79.2; H, 5.3; N, 3.4%). \( \delta \) (\( \text{d}^6\text{DMSO} \)) 0.75 br (s, OH), 1.5br (m, 2'-, 6'-H), 2.2-2.8 br (m, 10xArH, 4'-, 5'-H), 3.52 and 3.80 (s, s, 6-, 8-(8-, 6-)H), 3.76 (s, 3-H) and 7.83 (s, 7-CH).  

e. 5-Hydroxy-7-methyl-4-phenylcoumarin  
1. With methylmagnesium bromide  

The reaction of methylmagnesium bromide with the 4-phenylcoumarin in tetrahydrofuran yielded a solid which could not be crystallised. T.L.C. of the material showed a single spot with both chloroform and ethyl acetate solvents. The absence of a carbonyl band in the infrared spectrum indicated 1,2-addition.  

The crude solid was heated under reflux in glacial acetic acid, and the resulting solid crystallised from petroleum ether (b.p. 60-80°) to yield, 2,2,7-trimethyl-4-phenyl-2H-chromen-5-ol.
With ethylmagnesium bromide.

Treatment of the 4-phenylcoumarin with ethylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting material from ethyl acetate, yielded 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-coumarin (115; R = Et) (80%), m.p. 183-184° (Found: C, 76.2; H, 6.4. C_{16}H_{18}O_3 requires C, 76.6; H, 6.4%).

\[ \gamma_{\text{max (Nujol)}} 3470 (\text{O-H}), 1740 (\text{C = O}), 1650, 1585, 1280, 1053 \text{ and 840 cm}^{-1}, \ \nu (\text{CDCl}_3) 2.66 (s, 5xArH), 3.46 and 3.57 (s, s, 6-, 8-(8-, 6-)H), 5.30 (s, OH), 7.04 and 7.2 (AB quartet, J=16Hz, 3-H_2), 7.73 (s, 7-CH_3), 7.75 (m, J=7Hz, 4-CH_2) and 9.06 (t, J=7Hz, CH_2).

3. With isopropylmagnesium bromide.

Treatment of the 4-phenylcoumarin with isopropylmagnesium bromide in tetrahydrofuran yielded 3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-4-isopropyl-coumarin (115; R = Pr) (73%), m.p. 154-155° (from benzene) (Found: C, 77.25; H, 6.7. C_{19}H_{20}O_3 requires C, 77.0; H, 6.75%). \[ \gamma_{\text{max (Nujol)}} 3250 (\text{OH}), 1720 (\text{C = O}), 1625, 1585, 1085 \text{ and 840 cm}^{-1}, \ \nu (d^6\text{DMSO}) 0.70 \text{ br (OH)}, 2.7 (m, 5xArH), 3.42 and 3.69 (s, s, 6-, 8-(8-, 6-)H), 6.55 (m, J=7Hz, 4-CH), 6.83 and 7.10 (AB quartet, J=16Hz, 3-H_2), 7.81 (s, 7-CH_3), 9.00 (d, J=7Hz, CH_2) and 9.37 (d, J=7Hz, CH_2).

4. With cyclohexylmagnesium bromide.

Treatment of the 4-phenylcoumarin with cyclohexylmagnesium bromide in tetrahydrofuran yielded 4-cyclohexyl-3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-coumarin (115; R = cyclohexyl) (83%), m.p. 204-205° (from benzene) (Found: C, 78.7; H, 7.3. C_{22}H_{24}O_3 requires C, 78.6; H, 7.1%). \[ \gamma_{\text{max (Nujol)}} 3300(\text{OH}), 1760 (\text{C = O}),
1620, 1595, 1090 and 830 cm\(^{-1}\), \(\nu\) (CDCl\(_3\)) 2.65 (s, 5\(\times\)ArH), 3.52 (s, 6–, 8–H), 4.67 (s, OH), 6.84 and 7.19 (AB quartet, \(J\) 16Hz, 3–H\(_2\)), 7.80 (s, 7–CH\(_3\)) and 8.0–9.1 (cyclohexyl).

5. With phenylmagnesium bromide

Treatment of the 4-phenylcoumarin with phenylmagnesium bromide in tetrahydrofuran yielded, after crystallisation of the resulting crude material from benzene, 1-(2,6-dihydroxy-4-methylphenyl)-1,3,3-triphenylprop-1-en-3-ol (116; \(R = Ph\)) (71%), m.p. 158–159\(^\circ\) (Found: C, 82.2; H, 6.0, \(C_{28}H_{24}O_3\) requires C, 82.3; H, 5.9%). \(\nu\) (CDCl\(_3\)) 2.70 (m, 15\(\times\)ArH and 2–H), 3.81 (s, 2\(\times\)ArH), 5.1 br (s, 3\(\times\)OH) and 7.84 (s, \(\text{ArCH}_3\)).

The above triphenylpropenol (0.4 g) was heated under reflux in glacial acetic acid for 1 h, the solution was poured into water and the resulting solid crystallised from diethyl ether to give 7-methyl-2,2,4-triphenyl-2H-chromen-5-ol (117; \(R = Ph\)) (0.3g, 77%), m.p. 170–171\(^\circ\) (Found: C, 86.2; H, 5.9. \(C_{28}H_{22}O_2\) requires C, 86.1; H, 5.6%).

f. 5-Hydroxy-7-(2-octyl)-4-Phenylcoumarin

With methylmagnesium bromide

The octylcoumarin (7.0g, 0.02 mol) in dry benzene (100 ml) was added during 0.5 h to a solution of methylmagnesium bromide (0.2 mol) in dry ether (100 ml), and the reaction mixture stirred at ambient temperature for 1 h. Treatment of the resulting oil with acetic acid, yielded 3,4-dihydro-5-hydroxy-4-methyl-7-(2-octyl)-4-phenylcoumarin (119) (1.2g, 16%), m.p. 136\(^\circ\) (from a mixture of petroleum ether (b.p. 60–80\(^\circ\)) and ethyl acetate) (Found: C, 78.5; H, 8.3. \(C_{24}H_{30}O_3\) requires C, 78.7; H, 8.2%), \(\nu\) max (Nujol) 3425 (0–H), 1745 (C = O), 1630, 1585, 1045, 840 and 700 cm\(^{-1}\), \(\nu\) (CDCl\(_3\)) 2.60 (s, 5\(\times\)ArH), 3.43 and 3.59 (d, d, \(J\) 1.5Hz, 6–, 8–, (6–, 6–)H), 5.46 (s, OH), 6.93 and 7.26 (AB quartet, \(J\) 16Hz, 3–H\(_2\)).
The filtrate from the crystallisation was chromatographed with petroleum ether (b.p. 60-80°) and benzene 5:1 to give 2,2-dimethyl-7-(2-octyl)-4-phenyl-2H-chromen-5-ol (120) (4.62 g, 63%) as a colourless oil, (7 > 99% by glc) (Found: C, 82.2; H, 9.0.

\[ C_{25}H_{32}O_2 \] requires C, 82.4; H, 8.8%), \( ^1H (CDCl_3) \) 2.57 (s, 5xArH), 3.57 and 3.71 (d, d, J 1.5Hz, 6-, 8- (8-, 6-)H), 4.50 (s, 3-H), 5.48 (s, OH), 7.45 (m, 7-CH), 8.54 (s, 2x2-0H), 8.72 (m, 7-chain /3-CH\_\_ and (CH\_\_\_) and 9.11 (t, J 4.5Hz, terminal chain-CH\_\_).

5-Hydroxy-4-(\(p\)-methoxyphenyl)-7-methylcoumarin

1. With methylmagnesium bromide

The reaction of methylmagnesium bromide with the 4-(\(p\)-methoxyphenyl)coumarin in tetrahydrofuran gave a crude gum which was treated with glacial acetic acid. The resulting oil was purified by chromatography with a mixture of benzene and petroleum ether (b.p. 60-80°) 1:1, to give 4-(\(p\)-methoxyphenyl)-2,2,7-trimethyl-2H-chromen-5-ol (124; R = Me), (77%), m.p. 127-128° (Found: C, 77.2; H, 7.0.

\[ C_{19}H_{20}O_2 \] requires C, 77.0; H, 6.8%), \( ^1H (CDCl_3) \) 2.68 (d, 2xArH), 3.08 (d, JCH\_\_H\_\_, 2xArH), 3.61 and 3.75 (s, s, 6-, 8- (8-, 6-)H), 4.57 (s, 3-H), 5.29 (s, OH), 6.20 (s, OCH\_\_), 7.80 (s, 7-CH\_\_ and 8.60 (s, gem-diCH\_\_).

2. With ethylmagnesium bromide

The reaction of ethylmagnesium bromide with the 4-(\(p\)-methoxyphenyl)coumarin in tetrahydrofuran yielded a gum. Purification of the gum by chromatography with benzene, followed by crystallisation from a mixture of petroleum ether (b.p. 60-80°) and ether, gave 4-ethyl-3,4-dihydro-5-hydroxy-4-(\(p\)-methoxyphenyl)-7-methylcoumarin (122; R = Et) (63%), m.p. 153-154° (Found: C, 72.95; H, 6.4. \[ C_{19}H_{20}O_4 \] requires C, 73.0; H, 6.4%), \( \gamma \max \) (Nujol) 3400 (OH), 1760 (C = O), 1620,
1585, 1245 and 835 cm$^{-1}$, $\nu$ (CDCl$_3$) 2.68 (d, 2xm-ArH), 5.12 (d, J$_{SH} = 20$Hz, 2xo-ArH), 3.47 and 3.56 (s, s, 6-, 8-(8-, 6-)H), 4.98 (s, OH), 6.22 (s, OCH$_3$), 7.08 and 7.20 (AB quartet, J$_{16}$Hz, 3-H$_2$), 7.73 (s, 7-CH$_3$), 7.85 (m, J 7.5Hz, 4-CH$_2$) and 9.08 (t, J 7.5Hz, CH$_3$).

3. With isopropylmagnesium bromide.

Treatment of the 4-($p$-methoxyphenyl)coumarin with isopropylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting crude product from a mixture of ethanol and water, yielded 3,4-dihydro-5-hydroxy-4-($p$-methoxyphenyl)-7-methyl-4-isopropylcoumarin (122; $R = Pr^3$), (69%), m.p. 158-159$^\circ$ (Found: C, 73.5; H, 7.0. C$_{20}$H$_{25}$O$_4$ requires C, 73.6; H, 7.75%). $\nu$ (CDCl$_3$) 2.59 (d, 2xm-ArH), 3.19 (d, J$_{SH} = 20$Hz, 2xo-ArH), 3.54 (s, 6-, 8-H), 4.60 (s, OH), 6.24 (s, OCH$_3$), 6.91 and 7.22 (AB quartet, J$_{16}$Hz, 3-H$_2$), 6.90 (m, 4-CH$_2$), 7.80 (s, 7-CH$_3$), 8.99 (d, J 7Hz, CH$_3$) and 9.20 (d, J 7Hz, CH$_3$).

4. With cyclohexylmagnesium bromide.

Treatment of the 4-($p$-methoxyphenyl)coumarin with cyclohexylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting solid from aqueous ethanol, yielded 4-cyclohexyl-3,4-dihydro-5-hydroxy-7-methyl-4-($p$-methoxyphenyl)coumarin as the hemihydrate (122; $R = cyclohexyl$) (79%), m.p. 148-149$^\circ$ (Found: C, 73.7; H, 7.7. C$_{25}$H$_{26}$O$_4$·$\frac{1}{2}$H$_2$O requires C, 73.6; H, 7.2%). $\nu$$_{max}$ (Nujol) 3430 (OH), 1735 (C = O), 1625, 1580, 1275 and 835 cm$^{-1}$, $\nu$ (CDCl$_3$) 2.60 (d, 2xm-ArH), 3.16 (d, J$_{SH} = 20$Hz, 2xo-ArH), 3.53 (s, 6-, 8-H), 4.60 (s, OH), 6.25 (s, OCH$_3$), 6.90 and 7.22 (AB quartet, J$_{17}$Hz, 3-H$_2$), 7.78 (s, 7-CH$_3$) and 8.0-9.1 (m, cyclohexyl).

5. With phenylmagnesium bromide.

The reaction of phenylmagnesium bromide with the 4-($p$-methoxyphenyl)coumarin in tetrahydrofuran yielded impure 1-(2,6-dihydroxy-4-methylphenyl)-1-($p$-methoxyphenyl)-3,3-diphenylprop-1-en-3-ol.
Treatment of the diphenylpropenol (0.7 g) with glacial acetic acid under reflux yielded 7-methyl-2,2-diphenyl-4-(p-methoxyphenyl)-2H-chromen-5-ol (124; R = Ph) (0.6 g, 83%), m.p. 152-153° (from petroleum ether (b.p. 60-80°)) (Found C, 82.5; H, 5.8. C_{29}H_{24}O_{3} requires C, 82.8; H, 5.7%).

\[ \text{\( ^{1}H\text{NMR (CDCl}_3\)} \text{ 2.62 (m, 10ArH and 2xArH), 3.04 (d, J8.5 Hz, 2xArH), 3.52 and 3.81 (s, 5x, 6x, 6H), 4.05 (s, 3-H), 5.31 (s, OH), 6.19 (s, OCH\textsubscript{3}) and 7.80 (s, 7-CH\textsubscript{3}).} \]

**h. 4-(p-Aminophenyl)-5-Hydroxy-7-Methylcoumarin**

**With methylmagnesium bromide**

Treatment of the 4-(p-aminophenyl)coumarin with methylmagnesium bromide in tetrahydrofuran gave a black gum containing a mixture of products, which could not be identified.

**i. 5-Hydroxy-4,7-Dimethylcoumarin**

1. **With methylmagnesium bromide**

Treatment of the 5-hydroxycoumarin with methylmagnesium bromide in tetrahydrofuran, followed by heating the resulting material under reflux in glacial acetic acid, gave 2,2,4,7-tetramethyl-2H-chromen-5-ol (128) (66%), m.p. 94-95° (from petroleum ether) (Found: C, 76.15; H, 8.0. C_{15}H_{16}O requires C, 76.5; H, 7.8%).

\[ \nu_{\text{max}} (\text{Nujol}) \text{ 3360 (OH), 1620, 1580, 1150, 1075 and 840 cm}^{-1} \text{, } \nu (\text{CDCl}_3) \text{ 3.72 and 3.91 (s, s, 2xArH), 4.73 (s, 3-H), 5.28 (s, OH), 7.80 (s, 4-H, 7-CH\textsubscript{3}) and 8.63 (s, 2-diCH\textsubscript{3})}. \]

2. **With ethylmagnesium bromide**

Treatment of the 5-hydroxycoumarin with ethylmagnesium bromide in tetrahydrofuran, at ambient temperature for 1 h or with heating under reflux for 24 h, yielded only the starting coumarin.
Similarly, the reaction in an ether-benzene solvent mixture with heating under reflux for 24 h was unsuccessful.

The initial reaction in either solvent system involved precipitation of a solid, which did not dissolve even with heating.

3. **With isopropylmagnesium bromide.**

Treatment of the hydroxycoumarin with isopropylmagnesium bromide in tetrahydrofuran resulted in the immediate precipitation of a solid. Work-up of the reaction mixture in the normal manner afforded only the starting coumarin.

4. **With cyclohexylmagnesium bromide.**

The reaction of cyclohexylmagnesium bromide with the hydroxycoumarin in tetrahydrofuran involved initial precipitation of a solid, to yield on work-up the starting coumarin.

5. **With phenylmagnesium bromide.**

Treatment of the 5-hydroxycoumarin with phenylmagnesium bromide in tetrahydrofuran gave, from column chromatography of the crude product in a mixture of benzene and chloroform 1:1, mauve crystals of 1(2,6-dihydroxy-4-methylphenyl)-1-methyl-3-phenylprop-1-en-3-one (129) (65%), m.p. 155-156°, νmax (Nujol) 3300 (O-H), 1691 (C = O), 1619, 1580, 825 and 700 cm⁻¹. The product was then crystallised from diethyl ether to give colourless crystals of 4,7-dimethyl-2-phenyl-2H-chromen-2, 5-diol (130) (59%), m.p. 155-156° (Found: C, 76.4; H, 6.2. C₁₇H₁₆O₃ requires C, 76.1; H, 6.0%), νmax (Nujol) 3320 (O-H), 1624, 1593, 1000, 828 and 700 cm⁻¹, δ (CDCl₃) 2.69 (m, 5xArH), 3.28 (q, J1.5Hz, 3-H), 3.82 (s, 6-, 8-H), 5.57 (s, HOD) and 7.82 (m, 4-, 7-CH₂).

The colourless crystals on exposure to air, slowly turned mauve.

j. **5-Hydroxy-7-(3-methyl-2-octyl)-4-(4-pyridyl)coumarin**

1. **With methylmagnesium bromide**
Treatment of the 7-(3-methyl-2-octyl)coumarin with methylmagnesium bromide in tetrahydrofuran yielded crude 1-(2, 6-dihydroxy-4-(3-methyl-2-octyl)phenyl)-3,3-dimethyl-1-(4-pyridyl)prop-1-en-3-ol (132) (86%), $\nu_{\text{max}}$ (Nujol) 3250 (OH), 2700 (OH), 1600, 1400, and 830 cm$^{-1}$. The sample was identical by t.l.c. (ethyl acetate) and infrared spectroscopy to an authentic sample of the propenol; and the characteristic band at $\nu$ 1760 cm$^{-1}$ due to the $C=O$ function of the dihydrocoumarin was not present.

1a. With methylmagnesium bromide in the presence of cuprous chloride.

The reaction of the 7-(3-methyl-2-octyl)coumarin with methylmagnesium bromide in tetrahydrofuran was repeated at -10° to -20°. Cuprous chloride (total 0.2g, 0.001 mol) was added portionwise during the coumarin addition. On completion of the addition the solution was allowed to warm to room temperature during 1 h and then stirred for a further 1 h. Treatment of the reaction mixture in the usual manner yielded the crude dimethylpropenol (132) (85%) as above, $\nu_{\text{max}}$ (Nujol) 3250 (OH), 2700 (OH), 1603, 1400 and 830 cm$^{-1}$. Identical by t.l.c. to the above sample, and an authentic sample of the propenol.

k. 5-Hydroxy-7-(2-octyl)-4-(2-pyridyl)coumarin

1. With ethylmagnesium bromide.

Treatment of the octylcoumarin with ethylmagnesium bromide in tetrahydrofuran yielded a crude gum. Treatment of the gum with an ethereal solution of hydrogen chloride, followed by crystallisation of the resulting solid from an ethanol-acetone mixture yielded, 4-ethyl-3,4-dihydro-5-hydroxy-7-(2-octyl)-4-(2-pyridyl)coumarin isolated as the hydrochloride (135;
N, 3*4 * C24H32N2O3. HCl requires C, 69.0; H, 7.7; Cl, 8.5; N, 3.4%. \( \nu (\text{CDCl}_3) 1.46 \) (dt, 6'-H), 2.20 (td, 4'-H), 2.58 (d, 3'-H), 2.75 (m, 5'-H), (J5,6, 4.5, J5,4, 7.5, J4,5, = J4,6, = 1.0Hz), 3.37 and 3.56 (d, d, 1.5Hz, 6-, 2-(8, 6)-H), 5.5 br (OH), 6.31 (d, 3-H2), 7.5 (m, 4-CH2 and 7-CH) and 8.3-9.35 (m, 4- \( \beta \)-CH2, 7- \( \beta \) CH2 and \( \beta \) H).  

1a. With ethylmagnesium bromide in the presence of cuprous chloride.

The octylcoumarin was treated with ethylmagnesium bromide in tetrahydrofuran at -10 to -20°. Cuprous chloride (total 0.2 g, 0.001 mol) was added portionwise at regular intervals during the addition of the coumarin, and the reaction mixture was then allowed to warm to room temperature during 1 h. The resulting crude gum was treated with an ethereal solution of hydrogen chloride to give a solid product. Crystallisation of this solid from an ethanol-acetone mixture afforded the 4-ethyl-3,4-dihydrocoumarin as the hydrochloride (135; \( R = \text{Et} \)) (47%), m.p. 217-218°.  

2. With phenylmagnesium bromide.

Treatment of the octylcoumarin with phenylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting material from aqueous ethanol yielded, 3,4-dihydro-5-hydroxy-7-(2-octyl)-4-phenyl-4-(2-pyrindyl)coumarin (135; \( R = \text{Ph} \)) (48%, average from three reactions), m.p. 123-124° (Found: C, 78.3; H, 7.3; N, 3.2. C26H31N2O3 requires C, 78.3; H, 7.2; N, 3.3%).  

\( \nu \) (Nujol) 1765 (C = 0), 1630, 1600, 1580, 1070 and 850 cm\(^{-1}\), \( \nu \) (CDCl3) 0.7 (s, 0-H), 1.50 (d, 6'-H), 2.13 (td, 4'-H), 2.40 (d, 3'-H), (J5,6, 4.5, J5,4, 7.0, J4,5, = J4,6, = J3,15, = 1.5Hz), 2.55-3.25 (m, 5x4-ArH and 5'-H), 3.34 and 3.48 (d, d, 1.5 Hz, 6- and 8-, (E-, 6-)H) 6.58 and 7.00 (AB quartet, J16Hz, 3-H2).
2a. With phenylmagnesium bromide in the presence of 1% cuprous chloride.

The octylcoumarin in tetrahydrofuran was added dropwise to a solution of phenylmagnesium bromide in tetrahydrofuran containing cuprous chloride (0.2 g, 0.001 mol), to give the phenyl-3,4-dihydrocoumarin (135; R = Ph) (65%), m.p. and mixed m.p. 123-124° (from aqueous ethanol).

2b. With phenylmagnesium bromide in the presence of 5% cuprous chloride.

The reaction of the octylcoumarin with phenylmagnesium bromide in tetrahydrofuran in the presence of cuprous chloride (1.0g, 0.005 mol) following the procedure described in a) above, yielded the phenyl-3,4-dihydrocoumarin (135; R = Ph) (67.5%; average yield from two experiments), m.p. and mixed m.p. 123-124° (from aqueous ethanol).

1. 7-Methyl-4-(4-Pyridyl)coumarin

1. With methylmagnesium bromide

The reaction of methylmagnesium bromide with the 4-(4-pyridyl)coumarin in tetrahydrofuran, followed by heating the resulting material under reflux in glacial acetic acid yielded 2,2,7-trimethyl-4-(4-pyridyl)-2H-chromene (144; R = Me) (73%), m.p. 119-120° (from acetonitrile) (Found: C, 81.3; H, 6.9; N, 5.6. 

\( \text{C}_{17} \text{H}_{17} \text{NO}\) requires C, 81.3; H, 6.8; N, 5.8%). \( \nu_{\text{max}} \) (Nujol), 1610, 1590, 1260, 1145, 995 and 825 cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 1.35 (dd, 2', 6'-H), 2.75 (d, d, 3', 5'-H), (J\(_{2,3'} = J_{5,6'} = 4.5, J_{2,6'} = J_{3',5'} = 1.5\) Hz), 3.16 (d, J\(_{5,6} = 7.5\) Hz, 5'-H), 3.28 (d, 8-H), 3.36 (dd, J\(_{5,6} = 7.5, J_{6,8} = 1.0\) Hz, 6'-H), 4.39 (s, 3-H), 7.70 (s, 7-CH\(_3\)) and 8.52 (s, gem-di-CH\(_3\)).
2. **With ethylmagnesium bromide.**

**a. In tetrahydrofuran**

Treatment of the pyridylcoumarin with ethylmagnesium bromide in tetrahydrofuran gave a gum which could not be crystallised. Chromatography of the gum in chloroform gave 4-ethyl-3,4-dihydro-7-methyl-4-(4-pyridyl)coumarin (142; R = Et) (79%), m.p. 174-175° (Found: C, 76.7; H, 6.6; N, 5.5; C₁₇H₁₇NO₂ requires C, 76.4; H, 6.8; N, 5.2%). νmax (Nujol) 1760 (C = O), 1596, 1204, 1160 and 820 cm⁻¹, ν (CDCl₃) 1.60 (d, 2'-, 6'-H), 2.74 (d, J₂₁₅₁ = J₅₁₆₁ = 6Hz, 3'-, 5'-H), 3.14 (d, 5'-H), 3.5 (d, J₂₃₆₁ = 10Hz, 6-H), 3.38 (s, 8-H), 7.70 (s, 3-H₂), 3.80 (s, 7-CH₃), 8.51 (m, 4-CH₂) and 9.07 (t, J7.5Hz, CH₃).

**b. In diethyl ether.**

The reaction was repeated in diethyl ether to give, on separation and purification by chromatography in chloroform a first fraction containing 3,3-diethyl-1-(2-hydroxy-4-methylphenyl)-1-(4-pyridyl)prop-1-en-3-ol (143; R = Et) (7%), m.p. 185-187° (from ethyl acetate (Found: C, 76.5; H, 7.8; N, 4.8; C₁₉H₂₂NO₂ requires C, 76.9; H, 7.7; N, 4.7%), ν (d⁶DMSO) 1.59 (d, 2'-, 6'-H), 2.90 (d, J₂₁₅₁ = J₅₁₆₁ = 6Hz, 3'-, 5'-H), 3.08 (d, 6-ArH), 3.30 (s, 3-ArH), 3.35 (J₅₁₆₁ = 6Hz, 5-ArH), 3.67 (s, 2-H), 6.18 br (s, HOD), 7.72 (s, ArCH₂), 8.59 (q, J7Hz, 2x3-CH₂) and 9.14 (t, J7Hz, 2xCH₂).

The second fraction from the column contained 4-ethyl-3,4-dihydro-7-methyl-4-(4-pyridyl)coumarin (142; R = Et) (59%), m.p. and mixed m.p. 174-175°.

**c. In diethyl ether with dioxan.**

Dried, distilled dioxan (0.15 mol) was added dropwise to a solution of ethylmagnesium bromide (0.10 mol) in diethyl ether.
during 0.5 h. The suspension was stirred at ambient temperature for 16 h and the coumarin (0.01 mol) was then added. The general procedure was then followed to give after chromatography in chloroform, the starting coumarin (50%), m.p. 149-150°, and the pyridyl-propenol (143; R = Et) (41%), m.p. 166-167° (from ethyl acetate).

3. **With isopropylmagnesium bromide.**

Treatment of the 4-(4-pyridyl)coumarin with isopropylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting gum from acetonitrile, yielded 3,4-dihydro-7-methyl-4-isopropyl-4-(4-pyridyl)coumarin (142; R = Pr\(^3\)) (64%), m.p. 165-166° (Found: C, 76.55; H, 6.5; N, 4.75. \(\text{C}_{18}\text{H}_{19}\text{NO}_2\) \(\text{C}, 76.8; \text{H}, 6.8; \text{N}, 5.0\%\), \(\nu\) (CDCl\(_3\)) 1.47 (dd, 2'-, 6'-H), 2.81 (dd, \(J_{2',1} = J_{5',6'} = 5.0, J_{2',6'} = J_{3',15'} = 1.5\text{Hz}, 3'-'- 5'-H), 2.55 (d, 5-H), 3.05 (dd, \(J_{5,6} = 8, J_{6,1} = 1.0\text{Hz}, 6'-H), 3.29 (d, 8-H), 6.72 and 7.19 (AB quartet, \(J_{16\text{Hz}, 3'-\text{H}}), 7.26 (m, \(J_{7\text{Hz}, 4'-\text{CH}}), 7.66 (s, 7'-\text{CH}_2), 8.98 (d, \(J_{7\text{Hz}, \text{CH}_2}) and 9.24 (d, \(J_{7\text{Hz}, \text{CH}_2})

4. **With cyclohexylmagnesium bromide.**

Treatment of the 4-(4-pyridyl)coumarin with cyclohexylmagnesium bromide in tetrahydrofuran yielded a crude oil. Chromatography of the oil in chloroform, gave 4-cyclohexyl-3,4-dihydro-7-methyl-4-(4-pyridyl)coumarin (142; R = cyclohexyl) (74%), m.p. 70-71° (Found: C, 78.1; H, 7.4; N, 4.1. \(\text{C}_{21}\text{H}_{25}\text{NO}_2\) requires C, 78.5; H, 7.2; N, 4.3%), \(\nu\) \(\text{max}\) (Nujol) 1760 (C = 0), 1620, 1594, 1210, 1160 and 831 cm\(^{-1}\), \(\nu\) (CDCl\(_3\)) 1.55 (d, 2'-, 6'-H), 2.89 (d, \(J_{2',1} = J_{5',6'} = 5\text{Hz}, 3'-'- 5'-H), 2.68 (d, 5-H), 3.15 (d, \(J_{5,6} = 9\text{Hz}, 6'-H), 3.17 (s, 8-H), 6.70 and 7.19 (AB quartet, \(J_{16\text{Hz}, 3'-\text{H}}), 7.66 (s, 7'-\text{CH}_2), 8.98 (d, \(J_{7\text{Hz}, \text{CH}_2}) and 8.0-9.2 (br, cyclohexyl).

5. **With phenylmagnesium bromide.**

The reaction of phenylmagnesium bromide with the 4-(4-pyridyl)coumarin in tetrahydrofuran, followed by crystallisation of the resulting gum from a mixture of acetonitrile and ether, yielded 1-(2-
hydroxy-4-methylphenyl)-3,3-dimethyl-1-(4-pyridyl)prop-1-en-2-ol as the monohydrate (143; R = Ph) (51%), m.p. 156-158° (Found: C, 78.7; H, 6.3; N, 3.15. C\textsubscript{27}H\textsubscript{23}NO\textsubscript{2}.H\textsubscript{2}O requires C, 79.0; H, 6.1; N, 3.4%). 

\( \nu_{\text{max}} ^{\text{Nujol}} \) 3360 (OH), 1600, 1240, 1020, 835 and 700 cm\(^{-1}\), \( \nu ^{\text{CDCl}_{3}} \) 1.66 (d, \( J_{2,1'5} = J_{5,16} = 5.5 \text{ Hz}, 2', 6'-H \)), 2.4-2.85 (m, 10x3-ArH; 3', 5', 8-ArH), 2.98 (d, \( J_{5,6} = 11 \text{ Hz}, 6\text{-ArH} \)), 3.45 (s, 2-H), 6.2 br (2xOH) and 7.78 (s, 7-CH\(_3\)).

m. **4,7-Dimethylcoumarin**

1. **With methylmagnesium bromide**

Treatment of 4,7-dimethylcoumarin with methylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting gum from diethyl ether, yielded 1-(2-hydroxy-4-methylphenyl)-1,3,3-trimethylprop-1-en-3-ol (151; R = Me) (87%), m.p. 105-106° (Found: C, 75.9; H, 8.65. C\(_{13}\)H\(_{18}\)O requires C, 75.8; H, 8.7%). 

\( \nu_{\text{max}} ^{\text{Nujol}} \) 3300 (OH), 1605, 1148, 970, 910 and 820 cm\(^{-1}\), \( \nu ^{\text{CDCl}_{3}} \) 3.10 (d, 6-ArH), 3.31 (d, \( J_{5,6} = 2\text{ Hz}, 5\text{-ArH} \)), 3.28 (s, 3-ArH), 4.20 (q, \( J = 1.5 \text{ Hz}, 2\text{-H} \)), 5.37 (s, 2xOH), 7.71 (s, 4-ArCH\(_3\)), 8.05 (d, \( J = 1.5 \text{ Hz}, 1\text{-CH}_{2} \)) and 8.78 (s, gem-diCH\(_3\)).

The trimethylpropenol (0.4g) was heated under reflux in glacial acetic acid for 1 h. Chromatography of the resulting crude product in petroleum ether (b.p. 60-80°) gave 2,2,4,7-tetramethyl-2H-chromene (152; R = Me) (0.3 g, 85%) as a colourless oil, (Found: C, 83.2; H, 8.6. C\(_{15}\)H\(_{16}\)O requires C, 83.0; H, 8.5%). 

\( \nu_{\text{max}} ^{\text{film}} \) 1610, 1386, 1305, 1155 and 825 cm\(^{-1}\), \( \nu ^{\text{CCL}_{4}} \) 3.10 (d, 5-H), 3.48 (dd, \( J_{5,6} = 9, J_{6,8} = 2 \text{ Hz}, 6\text{-H} \)), 3.49 (d, 8-H), 4.78 (q, \( J = 5.5 \text{ Hz}, 3\text{-H} \)), 7.76 (s, 7-CH\(_2\)), 8.07 (d, \( J = 1.5 \text{ Hz}, 4\text{-CH}_{2} \)) and 8.67 (s, gem-diCH\(_3\)). Irradiation of the signal \( \nu = 8.07 \) caused the quartet \( \nu = 4.78 \) to collapse to a singlet.

2. **With ethylmagnesium bromide**.

The reaction of ethylmagnesium bromide with 4,7-dimethyl-
coumarin in tetrahydrofuran, followed by crystallisation of the resulting oil from petroleum ether (b.p. 60-80°), yielded 3,3-
diethyl-1-(2-hydroxy-4-methylphenyl)-1-methylprop-1-en-3-ol (151; 
R = Et) (67%), m.p. 89-90° (Found: C, 77.15; H, 9.55. C_{15}H_{22}O_2 
requires C, 76.9; H, 9.8%). ν\text{max} (Nujol) 3400 (OH), 1651, 1623, 
1300, 1131 and 823 cm\(^{-1}\), T (CDCl\(_3\)) 3.08 (d, 6-ArH), 3.32 (d, 5-CH\(_3\), 
5-ArH), 3.26 (s, 3-ArH), 4.38 (q, J 1.5 Hz, 2-H), 5.38 (s, HOD), 7.71 
(s, 4-ArCH\(_3\)), 8.02 (d, J 1.5 Hz, 1-CH\(_3\)), 8.50 (q, J 8 Hz, 2x3-CH\(_2\)) 
and 9.13 (t, 2xCH\(_3\)).

Treatment of the above methylpropenol with glacial acetic acid, 
followed by chromatography of the resulting oil in petroleum ether 
(b.p. 60-80°), gave 2,2-diethyl-4,7-dimethyl-2H-chromene (152; 
R = Et) (90%) as a yellow oil. (Found: C, 83.6; H, 9.5. C_{15}H_{20}O 
requires C, 83.3; H, 9.3%), ν\text{max} (Film), 1622, 1261, 1180 and 
838 cm\(^{-1}\), T (CCl\(_4\)) 3.12 (d, 5-H), 3.52 (d, 2x5CH\(_3\), 6-H), 3.50 (s, 
8-H), 4.89 (q, J 1.0 Hz, 3-H), 7.76 (s, 7-CH\(_2\)), 8.02 (d, J 1.0 Hz, 
4-CH\(_3\)), 8.38 (q, 2x2-CH\(_2\)), and 9.10 (t, J 7.5 Hz, 2xCH\(_3\)). (See 
end of this section for a repeat of this reaction.

3. With isopropylmagnesium bromide.

Treatment of 4,7-dimethylcoumarin with isopropylmagnesium bromide in tetrahydrofuran, followed by purification of the resulting oil by chromatography in a solvent mixture of benzene and petroleum ether (b.p. 60-80°) 1:1, gave, as a colourless oil, 3,4-dihydro- 
4,7-dimethyl-4-isopropylcoumarin (150; R = Pr\(^t\)) (72%), (Found: 
C, 77.45; H, 8.6. C_{14}H_{18}O_2 requires C, 77.1; H, 8.2%), ν\text{max} 
(Film) 1770 (C=O), 1626, 1591, 1428, 1160 and 831 cm\(^{-1}\), T 
(CCl\(_4\)) 2.96 (d, 5-H), 3.20 (d, J 16 Hz, 6-H), 3.22 (s, 8-H), 7.27 
and 7.72 (AB quartet, J 16 Hz, 3-H\(_2\)), 7.7 (s, 7-CH\(_2\)), 
8.25 (m, J 16 Hz, 4-CH), 8.75 (s, 4-CH\(_3\)), 9.08 (d, J 7 Hz, CH\(_3\)) and 
9.19 (d, J 7 Hz, CH\(_3\)).
4. **With cyclohexylmagnesium bromide.**

Treatment of 4,7-dimethylcoumarin with cyclohexylmagnesium bromide in tetrahydrofuran, followed by chromatography of the resulting oil in a mixture of benzene and petroleum ether (b.p. 60-80°) 1:1, yielded 3,3-dicyclohexyl-1-(2-hydroxy-4-methylphenyl)-1-methylprop-1-en-3-ol (151; R = cyclohexyl) (72%). Crystallisation from petroleum ether (b.p. 60-80°) gave the propenol, m.p. 157-158° (Found: C, 80.6; H, 10.1. C\textsubscript{25}H\textsubscript{34}O requires C, 80.7; H, 9.9%). ν\textsubscript{max} (Nujol) 3250 (0-H), 1615, 1505, 1250, 945 and 820 cm\textsuperscript{-1}, τ (CCl\textsubscript{4}) 3.21 (d, 6-ArH), 3.42 (d, J\textsubscript{CH}5Hz, 5-ArH), 3.50 (s, 3-ArH), 4.58 (m, 2-H, and 2xOH), 7.75 (s, 4-ArCH\textsubscript{3}), 8.05 (d, J 1.0Hz, 1-CH\textsubscript{3}) and 8.1-9.0 (cyclohexyl).

Treatment of the dicyclohexylpropenol (0.4g) with glacial acetic acid yielded 2,2-dicyclohexyl-4,7-dimethyl-2H-chromene (152; R = cyclohexyl) (0.36g, 88%), m.p. 114-115° (from petroleum ether (b.p. 60-80°)) (Found: C, 85.2; H, 10.1. C\textsubscript{25}H\textsubscript{34}O requires C, 85.2; H, 9.9%), ν\textsubscript{max} (Nujol) 1605, 1504, 1305, 1160, 840 and 803 cm\textsuperscript{-1}, τ (CCl\textsubscript{4}) 3.18 (d, 5-H), 3.58 (d, J\textsubscript{CH}5Hz, 6-H), 3.57 (s, 8-H), 5.01 (q, J 1.0Hz, 3-H), 7.75 (s, 7-CH\textsubscript{3}), 7.99 (d, J 1.0 Hz, 4-CH\textsubscript{3}) and 8.1-9.0 (cyclohexyl).

5. **With cycloheptylmagnesium bromide**

Treatment of 4,7-dimethylcoumarin with cycloheptylmagnesium bromide in tetrahydrofuran yielded a black tar. T.l.c. of the tar indicated that several products were present, however no separation could be achieved.

6. **With phenylmagnesium bromide**

Treatment of 4,7-dimethylcoumarin with phenylmagnesium bromide in tetrahydrofuran, followed by crystallisation of the resulting solid from acetone, yielded 1-(2-hydroxy-4-methylphenyl)-3,3-diphenyl-1-methylprop-1-en-3-ol (151; R = Ph) (72%), m.p.
134-135° (Found: C, 83.3; H, 6.8. C_{23}H_{22}O_2 requires C, 83.6; H, 6.7%), ν_{\text{max}} (Nujol) 3380 (O-H), 1605, 1460, 1250, 1228, 760 and 702 cm⁻¹, T (CDCl₃) 2.73 (m, 10xArH, 6-ArH), 3.40 (d, J_56 8Hz, 5-ArH), 3.39 (s, 3-ArH), 3.54 (q, J 1.5Hz, 2-H), 7.2 br (2xOH), 7.78 (s, ArCH₃) and 7.95 (d, J 1.5Hz, 1-CH₃).

The methylpropenol with glacial acetic acid under reflux yielded an oil, which on chromatography in benzene gave 4,7-dimethyl-2,2-diphenyl-2H-chromene (152; R = Ph) (0.3g, 81%), m.p. 84-85°, (Found: C, 88.3; H, 6.7. C_{23}H_{20}O requires C, 88.5; H, 6.4%), ν_{\text{max}} (Nujol) 1620, 1160, 1020, 772 and 702 cm⁻¹, T (CCl₄) 2.76 (m, 10xArH), 3.09 (d, 5-H), 3.4 (s, 8-H), 3.47 (d, J_56 8Hz, 6-H), 4.27 (q, J 1.5Hz, 3-H), 7.82 (s, 7-CH₃) and 7.89 (d, J 1.5Hz, 4-CH₃).

The repeat reactions of 4,7-dimethylcoumarin with ethyl, isopropyl, and cyclohexylmagnesium bromides respectively.

4,7-Dimethylcoumarin (0.005 mol) was treated with ethyl, isopropyl and cyclohexylmagnesium bromide (0.05 mol) respectively, following the procedure described previously. The reactions were carried out simultaneously under as near the same conditions as possible; the same batch of reagents and solvents were used, and the times of addition and reaction were identical.

N.m.r. spectra for the crude products in each case indicated that the yields of products were similar to those obtained previously. The crude mixtures were purified as described previously to give the diethylpropenol (68%); the isopropyl-dihydrocoumarin (79%); and the dicyclohexylpropenol (70%).

n. 4-Trifluoromethyl-7-Methylcoumarin

With ethylmagnesium bromide.

The coumarin (0.005 mol) was treated with ethylmagnesium bromide (0.05 mol) in tetrahydrofuran to give 3,3-
diethyl-trifluoromethyl-1-(2-hydroxy-4-methylphenyl)prop-1-en-3-ol
(154) (59%), m.p. 112-114° (from petroleum ether (b.p. 60-80°))
(Found: C, 62.65; H, 6.7. C₁₅H₁₅F₃O₂ requires C, 62.5; H, 6.5%).

\[ \nu_{\text{max}} \text{ (Nujol)} 3370 (0-H), 3100, 1620, 1280, 1160 \text{ and } 1000 \text{ cm}^{-1}, \]
\[ \nu \text{ (CDCl₃) 2.90 (d, 6-\text{ArH}), 3.17 (d, J 56 Hz, 5-\text{ArH}), 3.2 (s, 3-\text{ArH}), 3.44 (q, J 2.0 Hz, 2-H), 4.32 br (sOH), 7.60 (s, ArCH₃), 8.30 (q, J 7Hz, 2x3-CH₂) and 8.94 (t, J 7Hz, 2x3-CH₂).} \]

The filtrate from the crystallisation was purified by chromatography in petroleum ether (b.p. 60-80°) to give 4-ethyl-4-
trifluoromethyl-3,4-dihydro-7-methylcoumarin (155) (15%), as a yellow oil, 89% pure by g.l.c. (2% Neopentyl Glycol Succinate),
\[ \nu \text{(CCl₄) 2.74 (d, 5-H), 3.03 (d, J 56 Hz, 6-H), 3.11 (s, 8-H), 7.18 (s, 3-H₂), 7.61 (s, 7-CH₃), 7.96 (m, J 7Hz, 4-CH₂) and 9.06 (t, J 7Hz, CH₃).} \]

**Coumarin**

1. **With methylmagnesium bromide**

Coumarin (7.35, 0.05 mol) in ether (100 ml) was added dropwise during 1 h to a stirred solution of methylmagnesium bromide (0.2 mol) in ether (74 ml). The general procedure was then followed to give on crystallisation from petroleum ether (b.p. 40-60°), 1-(-2-hydroxyphenyl)-3,3-dimethylprop-1-en-3-ol (35; R = Me) (7.23 g, 81%), m.p. 58-59° (Lit. 53-55°) (Found:
C, 74.5; H, 7.9. Calc. for C₁₁H₁₄O₂: C, 74.2; H, 7.9%).
\[ \nu \text{(CCl₄) 3.18 (m, 4xArH), 3.75 (d, 1-H), 4.10 br (2xOH), 4.25 (d, J 13Hz, 2-H) and 2.74 (s, gem-diCH₂).} \]

Treatment of the above dimethylpropanol with glacial acetic acid, followed by column chromatography with benzene, yielded 2,2-
dimethyl-2H-chromene (34; R = Me) (> 99% pure by g.l.c (2% S.E. 30 and 1% CDMS))
\[ \nu \text{(CCl₄) 3.20 (m, 4xArH) 3.78 (d, J 10Hz, 3-H), 4.50 (d, J 10Hz, 4-H) and 8.60 (s, gem-diCH₂).} \]
(Found: m/e, 160
Calc. for C_{11}H_{12}O \quad H, 160). A correct analysis could not be obtained for this compound (c.f. J. Houben\(^6\)).

2. With ethylmagnesium bromide. (Following the procedure of Shriner and Sharp\(^7\))
   
a. In ether
   
   Ethyl bromide (21.8 g, 0.2 mol) in diethyl ether (37 ml) was added during 1 h to magnesium turnings (5.04 g, 0.21 mol) in ether (37 ml). The solution was stirred at ambient temperature for 1 h and coumarin (7.3 g, 0.05 mol) in ether (100 ml) added dropwise during 1 h. The solution was stirred for a further 1 h at ambient temperature and the crude products isolated in the usual manner. Two products were indicated by t.l.c. of the crude mixture, and from the n.m.r. and i.r. spectra these were thought to be the corresponding dihydrocoumarin and the dimethyldiol.

   No separation of the products could be achieved by distillation (b.p. 105-118\(^0\)/0.3-0.5 mm) or by column chromatography in benzene.

   The crude mixture was then heated under reflux in glacial acetic acid (60 ml) to give an oil; t.l.c. and n.m.r. and i.r. spectroscopy indicated the presence of the dihydrocoumarin and the diethylchromene.

   The first fraction from column chromatography of the crude oil eluted by a mixture of benzene and petroleum ether (b.p. 60-80\(^0\)) 1:1, yielded 2,2-diethyl-2H-chromene (34; R = Et) (3.3 g, 34\%), as a colourless oil, (99\% by g.l.c. (3% X.E.60); n\(^D\) 1.5428, Lit \(n_D\) 1.5428), (Found: C, 82.7; H, 8.7. Calc. for C\(_{13}\) H\(_{16}\): C, 83.0; H, 8.5\%)

   \(\nu_{\text{max}}\) (Film) 2980, 1300, 1125, 982 \(\text{cm}^{-1}\), \(\nu\) (CCl\(_4\)) 3.26 (m, 4\(\times\)ArH), 3.7 (d, 3-H), 4.70 (d, J=9Hz, 4-H), 8.38 (q, 2\(\times\)2-CH\(_2\)) and 9.10 (t, J=7.5Hz, 2xCH\(_3\))

   The second fraction contained 4-ethyl-3,4-dihydrocoumarin (94; R = Et) (1.4 g, 16\%), as a red oil (99\% by g.l.c. (3% X.E.60))
(Found: C, 75.0; H, 7.1 · C₁₁H₁₂O₂ requires C, 75.0; H, 6.8%)

\[
\nu_{\text{max}} \text{ (Film) } 2950, 1775 (C = 0), 1470, 1220, 1165, 920 \text{ and } 765 \text{ cm}^{-1},
\]

\[
\nu \text{ (CCl₄) } 2.92 \text{ (m, 4xArH)}, 7.33 \text{ (s, 3-H₂)}, 7.00-7.45 \text{ (m, 4-CH)},
\]

8.44 \text{ (h, 4-CH₂)} \text{ and } 9.08 \text{ (t, J 7Hz, 4-CH₂)}.

b. Repeat reaction in ether.

The reaction of coumarin with ethylmagnesium bromide in ether was repeated following the procedure described in a) above. No attempt was made to isolate the initial crude products, which were treated directly with glacial acetic acid. Column chromatography as described under a) yielded 2,2-diethyl-2H-chromene (34; R = Et) (36%) and 4-ethyl-3,4-dihydrocoumarin (94; R = Et) (35%).

c. In tetrahydrofuran.

Treatment of coumarin with ethylmagnesium bromide in tetrahydrofuran, following the procedure in b., yielded 2,2-diethyl-2H-chromene (34; R = Et) (13%; g.l.c. (3% X.E. 60) > 99%), and 4-ethyl-3,4-dihydrocoumarin (94; R = Et) (53%; g.l.c. (3% X.E. 60) > 99%).

d. In an ether-dioxan mixture.

Dry redistilled dioxan (25.2g, 0.3 mol) was added during 1h to a solution of ethylmagnesium bromide (0.2 mol) in ether (74 ml), and the suspension then stirred at ambient temperature for 16h. Coumarin (7.3g, 0.05 mol) in ether (100 ml) was then added during 1h and the suspension stirred for a further 1h at ambient temperature. The procedure outlined in b. was then followed to give 2,2-diethyl-2H-chromene (34; R = Et) (7.3g, 83%).

3. With isopropylmagnesium bromide.

a) In tetrahydrofuran.

Treatment of coumarin with isopropylmagnesium bromide in tetrahydrofuran, followed by chromatography of the resulting oil in chloroform, yielded 3,4-dihydro-4-isopropylycoumarin (94; R = Pr) (94%; > 99% by g.l.c. (20% D.C. 550)) as a colourless
oil, (Found: C, 75.9; H, 7.4. C_{12}H_{14}O_{2} requires C, 75.8; H, 7.4%),

\( \gamma_{\text{max}} \) (Nujol) 1765 (C = 0), 1465, 1220, 1185, 1160, 925 and 766 cm\(^{-1}\),

\( \nu \) (CCl\(_4\)) 2.93 (m, 4xArH), 7.28 (m, 3-H[2, 4-H]), 8.15 br(4-CH),
8.99 (d, CH\(_3\)) and 9.10 (d, J 5Hz, CH\(_3\)).

b. In diethyl ether

Treatment of coumarin with isopropylmagnesium bromide in diethyl ether following the procedure described in a., yielded an oil containing 75\%, by g.l.c. (20\%, d.c. 550), of 3,4-dihydro-4-isopropylcoumarin (94; R = Pr\(^i\)) (73\%).

c. In an ether-dioxan mixture

Dry, redistilled dioxan (18.8g, 0.225 mol) was added during 1h to a solution of isopropylmagnesium bromide (0.15 mol) in ether (135 ml). The suspension was stirred at ambient temperature for 16h, and then coumarin (4.38g, 0.03 mol) in ether (100 ml) added during 0.5 h. The mixture was stirred for a further 1h and the reaction mixture then decomposed in the usual manner.

Crystallisation of the resulting gum from petroleum ether (b.p. 60-80\(^\circ\)) yielded 1-(2-hydroxyphenyl)-3,3-di-isopropylpropan-1-en-3-ol (95; R = Pr\(^i\)) (37\%), m.p. 123-124\(^\circ\) (Found: C, 76.9; H, 9.5 .

C\(_{15}\)H\(_{22}\)O\(_2\) requires C, 77.0; H, 9.4%), \(\nu\) (CDCl\(_3\)) 3.00 (m, 4xArH),
3.20br (2xOH), 3.50 (d, 1-H), 4.35(d, J12Hz, 2-H), 8.15 (m, 2x3-CH),
9.00 (d, 2xCH\(_3\)) and 9.10 (d, J5Hz, 2xCH\(_3\)).

Chromatography of the filtrate from the crystallisation in petroleum ether; ether 1:1, yielded a fraction containing 3,4-dihydro-4-isopropylcoumarin (94; R = Pr\(^i\)) (19\%; > 99\% by g.l.c.
(20\% . d.c. 550)). The second fraction contained 1-(2-hydroxyphenyl)-1,3-di-isopropylpropan-3-one (156;R=isopropyl)42%; > 99%
by g.l.c.) as a yellow oil, (Found: C, 76.65; H, 9.6 . C\(_{15}\)H\(_{22}\)O\(_2\)
requires C, 77.0; H, 9.4%), \(\gamma_{\text{max}} \) (Film) 3400 (OH), 1690 (0-0),
1460, 1225, 910 and 753 cm\(^{-1}\), \(\nu\) (CCl\(_4\)) 3.08 (m, 4xArH), 7.06
(m, 1-H and 2-H\(_2\)), 8.08 (m, 1-CH, 3-CH), 8.8 (d, J 6Hz, CH\(_3\)),
8.92 (d, J 6 Hz, CH\textsubscript{3}) and 8.97 (d, J 6 Hz, CH\textsubscript{3}).

4. With cyclohexylmagnesium bromide

a. In ether.

Coumarin (7.35 g, 0.05 mol) in ether (100 ml) was added during 1 h to a solution of cyclohexylmagnesium bromide (0.2 mol) in ether (74 ml), and the solution then stirred at ambient temperature for 1 h. Chromatography of the resulting crude product in petroleum ether (b.p. 60-80\textdegree C - benzene 1:4, yielded 1,3-dicyclohexyl-1-(2-hydroxyphenyl)propan-3-one (156; R = cyclohexyl) (9.1 g, 57\%), m.p. 94-95\degree C (Found: C, 80.3; H, 9.4 \( \text{C}_{21}\text{H}_{20}\text{O}_{2} \) requires C, 80.3; H, 9.55), \( \nu \)\textsubscript{max} (Nujol) 3450 (o-H), 1690 (o = 0), 1595, 1265, 1230 and 750 cm\textsuperscript{-1}, \( \tau \) (CCl\textsubscript{4}) 3.16 (m, 4xArH), 7.16 (m, 2-H\textsubscript{2}), 7.60 br (m, 1-H) and 7.9-9.1 (m, di-cyclohexyl).

b. In tetrahydrofuran.

The reaction described in a. above was repeated in tetrahydrofuran. Chromatography of the crude product in chloroform yielded 4-cyclohexyl-3,4-dihydrocoumarin (94; R = cyclohexyl) (85\%) (7 97\% by g.l.c. (2\% S.E. 30 + 1\% CDMS)) as a yellow oil, (Found: C, 78.3; H, 8.1 \( \text{C}_{15}\text{H}_{18}\text{O}_{2} \) requires C, 78.3; H, 7.8\%), \( \nu \)\textsubscript{max} (Film) 1775 (C = 0), 1615, 1595, 1365, 1225, 1170 and 770 cm\textsuperscript{-1}, \( \tau \) (CCl\textsubscript{4}) 2.95 (m, 4xArH), 7.28 (s, 2-H\textsubscript{2}, 3-H) and 8.0-9.1 (cyclohexyl).

c. In redistilled tetrahydrofuran.

Tetrahydrofuran was distilled from lithium aluminium hydride, and used immediately. The reaction outlined in b. was followed to give a crude oil containing 65\% by g.l.c. (2\% S.E. 30 + 1\% CDMS) of 4-cyclohexyl-3,4-dihydrocoumarin (94; R = cyclohexyl) (85\%).

5. With phenylmagnesium bromide.

a) In Ether.

Coumarin (7.35 g, 0.05 mol) in ether (100 ml) was
added during 1h to a solution of phenylmagnesium bromide (0.2 mol) in ether (74 ml) to yield a crude oil. Trituration of this oil with diethyl ether gave 1-(2-(hydroxyphenyl)-1,3-diphenylpropan-3-one (156; R = Ph) (2.6 g, 17%), m.p. 168-170° (from ether), $\nu_{\text{max}}$ (Nujol) 3360 (o-H) and 1665 (C = O) cm$^{-1}$, (Lit.$^{63}$, m.p. 168-169°, $\nu_{\text{max}}$ (Nujol) 3360 and 1670 cm$^{-1}$).

The ether soluble material was crystallised from carbon tetrachloride to give 1-(2-hydroxyphenyl)-3,3-diphenylprop-1-en-3-ol (35; R = Ph) (7.24 g, 48%), m.p. 99-100°, $\nu_{\text{max}}$ (Nujol) 3400 (O-H) and 3200 (O-H) cm$^{-1}$, (Lit.$^{63}$, m.p. 98-99°, $\nu_{\text{max}}$ (CHCl$_3$) 3600 and 3400 cm$^{-1}$).

b. In redistilled tetrahydrofuran.

Treatment of coumarin with phenylmagnesium bromide in re-distilled tetrahydrofuran, following the procedure outlined in a), yielded 1-(2-hydroxyphenyl)-1,3-diphenylpropan-3-one (156; R = Ph) (13%), m.p. 168-169° and 1-(2-hydroxyphenyl)-3,3-diphenyl-prop-1-en-3-ol (35; R = Ph) (48%), m.p. 99-100°.

C. The Reaction of Grignard Reagents with 3,4-Dihydrocoumarins

The procedure outlined on page 105 was followed for the preparation of the Grignard reagents, and for the corresponding reactions with the dihydrocoumarins.

2,7-Dimethyl-4-Phenyl-4-(2-Pyridyl)chroman-2,5-Diol (167)  

1) In ether.

3,4-Dihydro-5-hydroxy-7-methyl-4-phenyl-4-(2-pyridyl)coumarin (3.31 g, 0.01 mol) as a slurry in dry ether (50 ml) was added portionwise during 0.5h to a solution of methylmagnesium iodide (0.1 mol) in ether (110 ml) and the mixture heated under reflux for 2h. A crude product was obtained, which on trituration with ether yielded the pyridylchroman-2,5-diol (1.0 g, 26%).
m.p. 252-254° (from ethanol) (Found: C, 75.8; H, 6.2; N, 3.9.
C_{22}H_{21}NO_3 requires C, 76.1; H, 5.9; N, 3.9). ν_{max} (Nujol) 3250 (O-H), 1620, 1580, 1070 and 830 cm^{-1}, \nu (d_6,DMSO) 0.0 br(O-H), 1.35 (s, O-H), 1.60 (d, 4'-H), 2.35 (t, 4'-H), 2.5-3.2 (m, 5xArH, 3'-H and 5'-H), (J_{314} = J_{415} = 6.5, J_{315} = J_{516} = 4.5, J_{416} = 1.0Hz), 3.82 (s, 6'-H), 6.93 and 7.83 (d, d, J = 13Hz, 3-H_2), 7.82 (s, 7-CH_3), 8.50 (s) and 8.98 (s) (2-CH_3, isomers).

2. In tetrahydrofuran

The reaction was repeated in tetrahydrofuran at 0° with methylmagnesium bromide, to yield the pyridylchroman-2,5-diol (64%), m.p. and mixed m.p. 255-256° (from ethanol).

2,7-Dimethyl-4-Phenyl-4-(2-Pyridyl)-4H-Chromen-5-ol (169)

A sample of the above chromandiol was heated under reflux for 1h in glacial acetic acid to give, after crystallisation of the resulting gum from petroleum ether (b.p. 60-80°), the pyridyl-4H-chromenol, m.p. 201-202° (Found: C, 79.6; H, 5.6; N, 3.9. C_{22}H_{19}NO_2 requires C, 79.3; H, 5.9; N, 4.2%). ν (CDCl_3) 1.58 (d, 6'-H), 2.20 (dd, 4'-H), 2.82 (m, 5xArH), 3.21 (m, 3', 5'-H), (J_{314}, 7.5, J_{416}, 1.0, J_{516}, 5.0Hz), 3.51 and 3.58 (d, d, J = 1.0Hz, 6-, 8-(E, 6a) H), 5.26 (q, 3-H), 5.46 (s, exchangeable, OH), 7.77 (s, 7-CH_3) and 8.00 (d, J = 1.0Hz, 2-CH_3).

1-(2,6-Dihydroxy-4-Methylphenyl)-3,3-Dimethyl-1-Phenyl-1-(2-Pyridyl)propan-3-ol (170)

A. From the dihydrocoumarin

1. In a tetrahydrofuran-ether mixture

A solution of 3,4-dihydro-5-hydroxy-7-methyl-4-phenyl-4-(2-pyridyl)coumarin (3.31g, 0.01 mol) in tetrahydrofuran (50 ml) was added dropwise during 0.5h to a solution of methylmagnesium iodide (0.1 mol) in dry ether (110 ml), and the mixture was heated under reflux for 2h. The crude product from the reaction was
crystallised from ethyl acetate to give the pyridylpropanol as an ethyl acetate clathrate (ratio host:guest, 3:1) (1.6g, 41%), m.p. 211-212° (after drying at 100°/0.1 mmHg for 2h) (Found: C, 73.9; H, 7.3; N, 3.4 • C29H25NO3 • 3/4C4H10 requires C, 74.2; H, 7.1; N, 3.5%). V max (Nujol) 3300 (O-H), 1738 (C = O), 1620, 1270 and 1070 cm⁻¹, Δ (CDCl₃) 1.72 (dt, J = 16; 4.5, J = 0.5Hz, 6'-H), 2.3-3.2 (m, 5xArH, 3'-. 4'-. and 5'-H), 3.65 (s, 3-. 5-ArH), 4.4br (3xOH), 6.00 and 7.45 (d, d, 14Hz, 2-H₂), 7.75 (s, 4-ArCH₃), 8.53 (s, 3-CH₃) and 9.25 (s, 3-CH₃); ethyl acetate, 5.88 (q), 8.0 (s) and 8.76 (t).

Crystallisation of the ethyl acetate clathrate from chloroform yielded the pyridylpropanol as the chloroform clathrate (ratio host: guest, 3:1), m.p. 211-212° (Found: C, 69.1; H, 6.3; N, 3.4; Cl, 8.4 • C29H25NO3 • 3/4CHCl₃ requires C, 69.5; H, 6.3; N, 3.5; Cl, 8.6%). Δ (CD₃SO) 1.25 (s, 2xOH); 1.74 (dd, J = 516; 4.5, J = 1.5Hz, 6'-H), 2.3-3.2 (m, 5xArH, 3'-. 4'-. and 5'-H), 3.90 (s, 2x1-ArH), 4.50 (s, OH), 6.81 (m, 2-H₂), 7.88' (s, 4-ArCH₃), 9.03 (s, 3-CH₃).

Crystallisation of the ethyl acetate clathrate from ethanol yielded the pyridylpropanol as the ethanol clathrate (ratio host: guest, 3:2), m.p. 211-212° (Found: C, 74.1; H, 7.5; N, 3.4 • C29H25NO3 • 3/2C₂H₆O requires C, 74.1; H, 7.5; N, 3.5%). Δ (CDCl₃) 1.67 (dd, J = 516; 6.0, J = 1.5Hz, 6'-H), 2.3-3.2 (m, 5xArH, 3'-. 4'-. and 5'-H), 3.64 (s, 2x1-ArH), 4.0-5.5 (br, 3xOH), 5.98 (d, 2-H), 7.49 (d, J = 14Hz, 2-H), 7.75 (s, 4-ArCH₃), 8.52 (s, 3-CH₃) and 9.25 (s, 3-CH₃); ethanol, 6.29 (q) and 8.79 (t).

2. In a benzene-ether mixture

The reaction was repeated in a benzene-ether (1:1) mixture, to give from ethyl acetate, the pyridylpropanol-ethyl acetate clathrate (62%; in two experiments), m.p. and mixed m.p. 211-212°.
B. From the chromandiol

A solution of 2,7-dimethyl-4-phenyl-4-(2-pyridyl)chroman-2,5-diol (1.75 g, 0.005 mol) in dry benzene was added dropwise during 0.5 h to a solution of methylmagnesium iodide (0.05 mol) in dry ether (30 ml), and the mixture was heated under reflux for 2.5 h. Crystallisation of the resulting material from ethyl acetate afforded the pyridylpropanol-ethyl acetate clathrate (91%), m.p. and mixed m.p. 211-212°.

2,2,7-Trimethyl-4-Phenyl-4-(2-Pyridyl)chroman-5-ol (172)

The pyridylpropanol-ethyl acetate clathrate was treated with glacial acetic acid, and the resultant material crystallised from ethyl acetate, to yield the pyridylchroman-5-ol (85%), m.p. 225-226° (Found: C, 79.9; H, 6.9; N, 4.0. \( C_{25}H_{33}NO_2 \) requires C, 80.0; H, 6.7; N, 4.1%). \( ^1H \) (CDCl₃) - 1.40 (s, 3°H), 1.42 (di, 6'-H), 2.11 (td, 4'-H), 2.30 (dd, 3'-H), 3.28 (m, 5'-H), (J₁₄.₁₅ = J₁₅.₁₆ = 3.0, J₁₄.₁₆ = 4.5, J₁₅.₁₆ = 1.5 Hz), 2.8 (m, 4xArH), 3.3 (s, ArH), 3.55 and 3.65 (d, J = 1.5 Hz, 6-°, 8°- (8°-6°)H), 6.95 and 7.74 (d, d, J = 15 Hz, 3-H₂), 7.74 (s, 7-CH₃), 8.62 (s, 2-CH₃) and 8.95 (s, 2-CH₂).

4-Ethyl-2,7-Dimethyl-4-(2-Pyridyl)chroman-2,5-diol (174)

A solution of 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-(2-pyridyl)coumarin (3.03 g, 0.01 mol) in tetrahydrofuran (100 ml) was added during 20 min to a solution of methylmagnesium bromide (0.1 mol) in tetrahydrofuran (110 ml) at 0°. The solution was stirred at 0° for 0.5 h and then allowed to warm to room temperature during 0.5 h. The usual work-up, followed by crystallisation from ethyl acetate, yielded the pyridylchromandiol (2.15 g, 72%), m.p. 222-223° (Found: C, 72.3; H, 7.1; N, 4.6. \( C_{15}H_{21}NO_3 \) requires C, 72.2; H, 7.0; N, 4.7%). \( \nu_{max} \) (Nujol) 3200 (0-H), 1625, 1585, 1170 and 838 cm⁻¹, \( \overline{\nu} \) (d₆DMSO) 0.88 (s, OH), 1.57 (s, OH), 1.65
(d, 6',-H), 2.21 (td, 4'-H), 2.5 (a, 3'-H), 2.80 (t, 5'-H), (J3,4,  
=J4,5, =J5,6, 5Hz), 3.85 (s, 6'-H), 7.2-8.2 (includes  
solvent peaks) (m, 4-CH2, 3-H2 and 7-CH2), 8.55 (s) and 9.20 (s)  
(2-CH2, isomers), and 9.36 (t, J 7Hz, CH2 of ethyl).

Attempted Preparation of 1-Ethyl-1-(2,6-Dihydroxy-4-Methyl- 
phenyl)-3,5-Dimethyl-1-(2-Pyridyl)propen-3-ol (175)

A. From 4-ethyl-3,4-dihydro-5-hydroxy-7-methyl-4-(2-pyridyl) 
coumarin

1. In a benzene-ether mixture

A solution of the dihydrocoumarin (1.51 g, 0.005 mol) in benzene (100 ml) was added during 20 min to a stirred solution of methylmagnesium iodide (0.05 mol) in ether (30 ml) to give a solid precipitate, the mixture was heated under reflux for 2.5 h, and the resulting crude product crystallised from ethyl acetate to yield the pyridylchromandiol (1.05 g, 69%), m.p. and mixed m.p. 222-223°. None of the required carbinol was isolated. Similar results were obtained on repeating the reaction with heating under reflux for 16 h.

2. In a tetrahydrofuran-ether mixture.

The experiment was repeated in a tetrahydrofuran-ether mixture, with heating under reflux for 2.5 h. The pyridylchromandiol (71%), m.p. and mixed m.p. 222-223°, was again isolated.

B. From 4-ethyl-2,7-dimethyl-4-(2-pyridyl)chroman-2,5-diol.

A solution of the pyridylchromandiol (1.49 g, 0.005 mol) in benzene (50 ml) was added dropwise during 20 min to a solution of methylmagnesium iodide (0.05 mol) in dry ether (30 ml). A solid formed immediately, and did not appear to dissolve even after heating under reflux for 2.5 h. The usual work-up yielded the starting pyridylchromandiol (1.46 g, 97%), m.p. and mixed m.p. 222-223°.
A solution of 3,4-dihydro-5-hydroxy-7-(2-octyl)-4-phenyl-4-(2-pyridyl)coumarin (12.87 g, 0.05 mol) in tetrahydrofuran (200 ml) was added dropwise during 20 min to a solution of methylmagnesium bromide (0.3 mol) in tetrahydrofuran (250 ml) at 0°, and the mixture was stirred for 0.5 h at 0°. After allowing the solution to warm to room temperature during 0.5 h, the usual work up afforded the 7-(2-octyl)chromandiol (6.85 g, 51%), m.p. 168–169° (from ethyl acetate) (Found: C, 78.2; H, 8.0; N, 3.0. C_{29}H_{39}NO requires C, 78.2; H, 7.9; N, 3.1%). ν_{max} (Nujol) 3500 (O-H), 1620, 1600 1580, 1100 and 755 cm^{-1}, ν (CDCl₃) 0.20 br (O-H), 1.62 (d, δ_{516}, 5Hz, 6'-H), 2.25 (m, 3',-4',-H), 2.82 (m, 4xArH), 3.2 (m, 5-H and ArH), 3.58 and 3.66 (d, d, δ 1.5Hz, 6-, 8- (9-, 6'H)), 4.30 br (O-H), 6.91 and 7.76 (d, d, δ 14Hz, 3'-H), 7.5 (m, chain α-CH), 8.36 (s, 2-CH₃) 8.73 (m, chain β-CH₃, (CH₂)₂) and 9.12 (t, δ 4.5Hz, terminal CH₂).

2-Methyl-7-(2-octyl)-4-phenyl-4-(2-pyridyl)-4H-Chromen-5-ol (179)

The above 7-(2-octyl)chromandiol was treated with glacial acetic acid, and the resulting crude material crystallised from ethyl acetate to yield the pyridyl-4H-chromenol (50%), m.p. 171–172° (Found: C, 81.5; H, 7.9; N, 3.1. C_{29}H_{33}NO requires C, 81.5; H, 7.7; N, 3.2%). ν (CDCl₃) 1.54 (d, δ 516, 5Hz, 6'-H), 2.18 (m, 3',-4',-H), 2.80 (m, 4xArH), 3.18 (m, ArH, 5'-H), 3.49 and 3.58 (d, d, δ 1.5Hz, 6-, 8- (9-, 6'H)), 5.26 (q, 3-H), 7.4 br (m, chain α-CH), 8.00 (d, δ 1.0Hz, 2-CH₃), 8.74 (m, chain β-CH₃, (CH₂)₂) and 9.16 (t, δ 5Hz, terminal CH₂).

1-(2,6-Dihydroxy-4-(2-octylphenyl)-3,3-Dimethyl-1-Phenyl-1-(2-Pyridyl)propan-3-ol (178)

A solution of 3,4-dihydro-5-hydroxy-7-(2-octyl)-4-phenyl-4-
(2-pyridyl)coumarin (12.87g, 0.03 mol) in dry benzene (350 ml) was added dropwise during 0.5h to a solution of methylmagnesium iodide (0.3 mol) in dry ether (200 ml), and the mixture was heated under reflux for 2.5h. Crystallisation of the resulting crude material from a mixture of ether and petroleum ether (b.p. 60-80°) yielded the pyridylpropanol (8.46g, 61%), m.p. 146-147° (Found: C, 78.35; H, 8.5; N, 3.1. C_{30}H_{39}NO_2 requires C, 78.1; H, 8.45; N, 3.0%). T (CDCl_3) 1.66 (dt, J_5', 6', 1.0Hz, 6'-H), 2.3-3.2 (m, 5xArH, 3', 4', 5'-H), 3.62 (s, 2x1-ArH), 3.9 br (3xOH), 5.99 and 7.50 (d,d, J 14Hz, 2-H_2), 3.5 br (m, chain CH), 8.54 (s, 3-CH_3), 8.74 (m, chain β-CH_3, (CH_2)_5), 9.13 (t, J 4.5Hz, terminal CH_2) and 9.32 (s, 3-CH_3).

2,2-Dimethyl-7-(2-Octyl)-4-Phenyl-4-(2-Pyridyl)chroman-5-ol

Treatment of the above pyridylpropanol with glacial acetic acid, followed by crystallisation of the resulting gum from petroleum ether (b.p. 60-80°), yielded the pyridylchroman (69%), m.p. 140-141° (Found: C, 81.6; H, 8.5; N, 3.1. C_{30}H_{37}NO_2 requires C, 81.3; H, 8.4; N, 3.2%). T (CDCl_3) -1.5 (s, OH), 1.4 (d, 6'-H) 2.12 (td, 4'-H), 2.30 (dd, 3'-H), (J_3',4'=J_4',5'= 6.5, J_5'=16, 5.0, J_3'=J_4'= 1.5Hz), 2.82 (m, 4xArH), 3.33 (m, 5'-H and ArH), 3.58 and 3.67 (d,d, J 1.5Hz, 6-, 8- (8-, 6-)H), 6.96 and 7.78 (d,d, J 15Hz, 3-H_2), 7.5 (m, 7-CH), 8.63 (s, 2-CH_2), 8.76 (m, chain β-CH_3, (CH_2)_5), 8.95 (s, 2-CH_2) and 9.16 (t, J 7Hz, terminal CH_2).
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