CHAPTER I

SYNTHESIS OF ANTI-JUVENILE HORMONES: PRECOCENES & THEIR ANALOGUES
INTRODUCTION

For over 300 million years the insects have consistently been the world’s foremost opportunists. Yet virtually there are no effective means to control them. Records show that as long as 1000 B.C. insecticides were used though without much deep information about them. For the last 200 years chemicals have been used more effectively as insecticides. These traditional insecticides are divided into four classes depending upon their mode of action as,

1) Stomach poisons eg. BHC, DDT.
2) Contact poisons eg. Aldrin, Lindane.
3) Fumigants eg. CCl₄, CS₂.

Use of any of these brought about direct killing of the insects. Over the years these insecticides were found to have two major limitations, a) toxicity to mammals especially human and b) resistance to these chemicals developed by the insects.

Despite the use of millions of tons of insecticides, the crop destruction is not circumvented appreciably. There is a continuous persual for new and more efficient insecticides all over the world. The outcome of which was the discovery of insect juvenile hormones which opened a new avenue of hormonal insecticides.

In general any insect shows four major stages of development namely 1) egg, 2) larva, 3) pupa, and 4) adult. The juvenile
hormones are the chemicals which prevent the insect from maturing. They are secreted by the corpus allatum of an insect, a part of the CNS (brain) of the insect. Thus for moulting from one developmental stage to another, absence of juvenile hormone is essential.

Attempts were made to control the insect population by varying the juvenile hormone level in insects. This led to a limited success mainly due to,

1) Instability of the synthetic juvenile hormones and
2) Very short developmental period within which the absence of juvenile hormones works.

So a search started in a modified direction to find out compounds which would act as juvenile hormone antagonists or antijuvenile hormones (AJH). As an outcome of this Bowers et al 1 have isolated 2,2-dimethyl-7-methoxy-2H-1-benzopyran from Ageratum houstonianum in 1976 which was shown to be an effective AJH. Then onwards several chromene analogues were found to possess AJH activity. The main effects caused by chromenes in insects are summarized below.

1) Alteration of the course of metamorphosis and in some cases the external morphology of the insect.
2) Sterility induction in females.
3) Lethal effects.

The changed course of metamorphosis of the insect by chromenes is termed as "precocious metamorphosis" and hence
the chromenes causing this effect were called as "precocenes". Besides the effect on insects chromenes also show photochromic properties and act as nonsteroidal antifertility agents for humans. Thus chromenes constitute an important class of oxygen heterocycles and as such many synthetic approaches for them are reported in the literature. An overview of some naturally occurring chromenes is presented in TABLE 1. Also some selected syntheses of various chromenes are presented in TABLE 2. These have been classified into two groups viz.

a) 2H-1-benzopyrans,

b) benzodipyrans : linear and angular.
<table>
<thead>
<tr>
<th>NO.</th>
<th>STRUCTURE</th>
<th>REF.</th>
</tr>
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<tbody>
<tr>
<td>A)</td>
<td><img src="image" alt="Structure I" /></td>
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<td><img src="image" alt="Structure II" /></td>
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<td><img src="image" alt="Structure III" /></td>
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<td></td>
<td><img src="image" alt="Structure IV" /></td>
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<td></td>
<td><img src="image" alt="Structure V" /></td>
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<td></td>
<td><img src="image" alt="Structure VI" /></td>
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<td></td>
<td><img src="image" alt="Structure VII" /></td>
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<td>TABLE-1</td>
<td></td>
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<tr>
<td>VIII</td>
<td><img src="image" alt="Molecule VIII" /></td>
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<td>IX</td>
<td><img src="image" alt="Molecule IX" /></td>
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<tr>
<td>X</td>
<td><img src="image" alt="Molecule X" /></td>
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</tr>
<tr>
<td>XI</td>
<td><img src="image" alt="Molecule XI" /></td>
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</tr>
<tr>
<td>B)</td>
<td><img src="image" alt="Molecule XII" /></td>
<td>7</td>
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<tr>
<td>XII</td>
<td><img src="image" alt="Molecule XIII" /></td>
<td>8</td>
</tr>
<tr>
<td>XIII</td>
<td><img src="image" alt="Molecule XIV" /></td>
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</tr>
<tr>
<td>XV</td>
<td><img src="image1.png" alt="Image" /></td>
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<td>----------------------</td>
<td>---------</td>
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<tr>
<td>C)</td>
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<td>XVI</td>
<td><img src="image3.png" alt="Image" /></td>
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<td>XVIII</td>
<td><img src="image5.png" alt="Image" /></td>
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<tr>
<td>XIV</td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td>XX</td>
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<tr>
<td>GROUP-I</td>
<td>2H-1-benzopyrans</td>
<td></td>
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</tbody>
</table>

| I | \[
\begin{align*}
&R_1 \quad \text{OH} \\
&\text{R}_2
\end{align*}
\] + \[
\begin{align*}
&\text{COOH}
\end{align*}
\] \rightarrow 9 |

| II | \[
\begin{align*}
&\text{R}_1 \quad \text{OM} \\
&\text{R}_2 \\
&\text{R}_3 \\
&\text{R}_4
\end{align*}
\] + \[
\begin{align*}
&\text{R}_6 \\
&\text{R}_7
\end{align*}
\] \rightarrow 10 |

|M = Ti IV, Mg|

| III | \[
\begin{align*}
&\text{R}_1 \quad \text{OH} \\
&\text{R}_2
\end{align*}
\] + \[
\begin{align*}
&\text{COOH}
\end{align*}
\] \rightarrow 11 |

i) \(\text{Ph}_3\text{P}, \text{(cyclo-5-octadienyl)}\text{tris imidazolatotri rhodium, benzene, 140°, 6 hours.}\)

ii) DDQ
IV

\[
\begin{align*}
\text{IV} & \quad \text{HCO}_3 \quad \text{HCO}_3 \\
& \quad \text{HCO}_3 \\
\end{align*}
\]

i) \( \text{CH}_3\text{MgI} \)

\( \text{ii) } \text{H}_3\text{O}^+ \)

V

\[
\begin{align*}
\text{V} \quad \text{R} & \text{OH} + \quad \text{CH}_3 \quad \text{R} \\
& + \quad \text{CH}_3\quad \text{R} \\
& + \quad \text{CH}_3\quad \text{R} \\
& + \quad \text{CH}_3\quad \text{R} \\
\end{align*}
\]

\( \text{i), ii) } \)

\( \text{iii), iv) } \)

i) \( \text{N} \quad \text{toluene, reflux} \)

\( \text{ii) } \text{H}_2\text{O}^+ \)

\( \text{iii) } \text{LAH/ether} \)

\( \text{iv) } \text{H}_2\text{O}^+ \)

VI

\[
\begin{align*}
\text{VI} & \quad \text{R} \quad \text{OH} \\
& \quad \text{CH}_3 \\
& \quad \text{R} \\
& \quad \text{R} \\
\end{align*}
\]

\( \text{i), ii) } \)

\( \text{iii), iv) } \)

i) \( \text{LDA, ultrasonic radiations} \)

\( \text{ii) hexamethylenephosphoroustriamide/} \Delta \)

\( \text{iii) LAH/ether,} \)

\( \text{iv) PTSA} \)
VII

\[
\begin{align*}
\text{VII} & \quad \text{OH} \\
& \quad \text{R} \\
& \quad \text{R}^1 \\
\end{align*}
\]

\[+ \text{mCPBA}\]

\[
\begin{align*}
\text{i) cyclisation} \\
\text{ii) dehydration (PhO)}_3^\text{PMeI} \\
\end{align*}
\]

VIII

\[
\begin{align*}
\text{VIII} & \quad \text{MeO} \\
& \quad \text{OH} \\
& \quad \text{HO} \\
\text{HCO} & \quad \text{OH} \\
\text{HCO} & \quad \text{OH} \\
\end{align*}
\]

\[+ \text{Ethyl-3-triethyl-2-butenoate}
\]

IX

\[
\begin{align*}
\text{IX} & \quad \text{CHO} \\
\text{OH} & \quad \text{Ethyl-3-methyl-2-butenoate} \\
\text{CHO} & \quad \text{Ethyl-\(\alpha\)-bromo-isobutyrate} \\
\text{OH} & \quad \text{or} \\
\end{align*}
\]

\[+ \text{Ethyl-3-methyl-2-butenoate}
\]
XI

John's reagent

NaH, PhH

XII

i) \text{hv, } K_2CO_3, H_2CO
\text{ACETONE, ii)}

(\text{photoFries})

\text{aq. NaOH/ hexane}
**GROUP-II Linear benzodipyrans**

**XIII**

\[
\text{XIII} \quad \begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O}
\end{array}
\end{array}
\quad +
\begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array}
\quad \text{PPA}
\end{array}
\]

**XIV**

\[
\text{XIV} \quad \begin{array}{c}
\begin{array}{c}
\text{RO} \\
\text{OH}
\end{array}
\end{array}
\quad +
\begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array}
\quad \text{HOCMeCH=CH}_2
\end{array}
\]

**XV**

\[
\text{XV} \quad \begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{R}_1 \quad \text{Cl}
\end{array}
\end{array}
\quad +
\begin{array}{c}
\begin{array}{c}
\text{Cl}
\end{array}
\end{array}
\quad \text{Acetone}
\end{array}
\]

**XVI**

\[
\text{XVI} \quad \begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{Cl}
\end{array}
\end{array}
\quad +
\begin{array}{c}
\begin{array}{c}
\text{Cl}
\end{array}
\end{array}
\quad \text{CH}_3\text{SO}_3\text{H}
\end{array}
\]

\[
\quad \begin{array}{c}
\text{OH} \\
\text{Cl}
\end{array}
\quad +
\begin{array}{c}
\begin{array}{c}
\text{Cl}
\end{array}
\end{array}
\quad \text{CH}_3\text{SO}_3\text{H}
\end{array}
\]
a + \begin{align*}
\text{b} \quad & \xrightarrow{i) \text{LAH}_{\text{Et}_2\text{O}}} \\
& \xrightarrow{\text{ii) } \text{H}_3\text{O}^+} \\
1:4
\end{align*}

\text{XVII}

\begin{align*}
\text{a} \quad & \xrightarrow{\text{K}_2\text{CO}_3, \text{hexane}} \\
& \xrightarrow{\text{photoFries}} \\
\text{a} \quad & \xrightarrow{\text{aq. NaOH, hexane}} \\
& \xrightarrow{i) \text{LAH}_{\text{ether}}} \\
& \xrightarrow{\text{ii) } \text{H}_3\text{O}^+}
\end{align*}

\text{XVIII}

\begin{align*}
\text{a} \quad & \xrightarrow{i) 2 \text{ mol }, \text{ ultrasonic radiations}} \\
& \xrightarrow{\text{ii) HMPT/\Delta}} \\
\text{a} \quad & \xrightarrow{i) \text{LAH}_{\text{ether}}} \\
& \xrightarrow{\text{ii) } \text{H}_3\text{O}^+}
\end{align*}
GROUP—III Angular benzodipyrans

<table>
<thead>
<tr>
<th></th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( \text{HO-CH-CH₂-CO-Et} \xrightarrow{H₂SO₄} \text{HO-CH₃} )</td>
</tr>
<tr>
<td>II</td>
<td>( \text{HO-CH₂-CH₂-CH₃} + \text{C₆H₄-CH₃} \xrightarrow{PPA} \text{DDQ} )</td>
</tr>
<tr>
<td>III</td>
<td>( \text{HO-CH₂-CH₂-CH₃} + 2 \text{CH₂-COCl} \xrightarrow{AlI₃} )</td>
</tr>
</tbody>
</table>
PART I : SYNTHESIS OF 2H-1-BENZOPYRANS

STRUCTURE ACTIVITY RELATIONSHIP : For 2,2-dimethyl-6,7-dialkoxy-2H-benzo[b]pyran:

Bowers\textsuperscript{21a} in his structure-activity studies has pointed out that presence of C\textsubscript{7}- alkoxy substitution in benzopyran is the most important feature for AJH activity. Further an additional alkoxy substituent at C\textsubscript{6}- enhances the activity of the chromenes. Surprisingly presence of alkyl substituents instead of alkoxy at C\textsubscript{6}- and C\textsubscript{7}- positions were found to produce inactive chromenes. Moreover alkoxy substituents at C\textsubscript{5}- or C\textsubscript{8}- positions were also found to be ineffective. Further Soderlund et al\textsuperscript{27} have shown that alkyl groups bulkier than methyl on the C\textsubscript{2}- carbon atom decrease the activity of the compound and any substitution on C\textsubscript{3}- or C\textsubscript{4}-carbon also renders the compound inactive. Inactivity is also caused by the absence of the 3,4- double bond. A detailed discussion on this subject is provided by Matolcsy et al\textsuperscript{28}. As an outcome of these studies 2,2-dimethyl-6-methoxy-7-ethoxy-2H-benzo[b]pyran was found to possess highest AJH activity\textsuperscript{21a} for the insects like bugs. The effects caused by several precocenes on different insects some times resemble those caused by surgical removal of corpus allatum or those of antifeedants. At times they
are lethal. Due to this important structure-activity relationship it was decided to develop a convenient method for the synthesis of 2,2-dimethyl-6,7-dialkoxy chromenes which could also furnish the required chromenes with any desired alkoxy substituent at $C_6^-$ and $C_7^-$ positions.

**RETROSYNTHETIC ANALYSIS**

Retrosynthetic analysis of this benzopyran would suggest four pathways. These are given below.

A)  

B)  

C)  

D)  

PATHS A, B AND C.

First three pathways require either a presubstituted phenol, O-hydroxy benzaldehyde or cinnamic acid derivative as the starting compounds. Now to synthesize such presubstituted phenols is somewhat difficult. Same is the case for the presubstituted salicylaldehyde and the cinnamic acid derivatives which are generally synthesized from these aldehydes and malonic acid. So pathways A, B and C face the limitation of using a presubstituted starting compound. From the TABLE-2 it is clear that except in reaction X all other syntheses of the 2,2-dimethyl benzopyrans use presubstituted phenols as the starting compounds. These are therefore invariably low yielding reactions.

PATH D

This path suggests the introduction of the desired alkoxy substituents on the 2,2-dimethyl benzopyran system. Reaction sequence XIII (TABLE-2) represents the only attempt done in this direction. In this sequence the desired alkoxy substitution at C7- is achieved through a nucleophilic substitution on a benzopyrone.

Alternatively it was felt easier to achieve any desired alkoxy substitution at the C7- position using resorcinol as the starting compound. After this the substituent at C6- could be introduced directly or through transformation of any other suitable group. Direct introduction of oxygen on the benzenoid part could be achieved through lithiation followed by treatment of
the lithio derivative with oxygen\textsuperscript{29}. But the limitation in the present case was possibility of formation of 8-lithio derivative. Therefore it was decided to try the later option. For this purpose two groups were considered as the candidates, nitro and formyl. Conversion of aromatic nitro compound to a phenol via amine involves critical procedures. So conversion of aromatic aldehyde to phenol appeared to be the feasible route.

Based on the above discussion a route was planned leading to the required 2,2-dimethyl benzodipyran as depicted in \textbf{SCHEME-1}.

\begin{center}
\textbf{SCHEME-1}
\end{center}
**Synthesis of 2,2-dimethyl-7-alkoxy-2H-1-benzo[b]pyrans 4a and 4b**

To use the strategy of introducing alkoxy substituents regioselectively on a preformed chromene system the appropriate intermediate required was the corresponding 2,2-dimethyl chromene having desired alkoxy substituent at C7- which is known to be easily obtained from the corresponding chroman-4-one. This ketone in turn can be synthesized by various methods. Out of these methods, one reported by Kabbe et al.\(^\text{13}\) and the other reported by Shah et al.\(^\text{30}\) were found to be especially convenient due to,

1) easily accessible starting materials,
2) simple reaction conditions,
3) high yields.

These conversions are outlined in **SCHEME 2**. Conversion of chroman-4-one 3a to chromene 4a further involves O-alkylation followed by reduction by LAH and finally dehydration.

**SCHEME 2**
By following the above route the 7-alkoxy chromenes 4a and 4b were obtained in fairly good yields.

**PRESENT WORK**

**Formylation of the 2,2-dimethyl-7-alkoxy-2H-benzo[b]pyrans 4a, b**

Chromene 4a was converted to the corresponding 6-formyl derivative exclusively by the well known Vilsmeier-Haack reaction\(^3\). The melting point and spectral properties of the compound thus obtained matched perfectly with that of 5a. The elemental analysis of the compound was also consistent with the structure 5a. Based on the structure 5a the yield of the product was found to be 82%.

\[
\begin{align*}
\text{HCO} & \quad \text{DMF-POCl}_3 \\
\text{OH} & \quad \text{HCO} \\
\text{OHC} & \quad \text{OHC}
\end{align*}
\]

Similarly 4b was reacted under the Vilsmeier-Haack conditions. Work-up provided a dark brown liquid as the only product which after purification by column chromatography using n-hexane as the eluent was characterized as follows.
Characterization of the dark brown liquid:

IR : 1690

PMR :

<table>
<thead>
<tr>
<th>1.24</th>
<th>bs</th>
<th>6H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.68</td>
<td>t  (J=8)</td>
<td>3H</td>
</tr>
<tr>
<td>4.43</td>
<td>q  (J=8)</td>
<td>2H</td>
</tr>
<tr>
<td>6.04</td>
<td>d  (J=11)</td>
<td>1H</td>
</tr>
<tr>
<td>6.77</td>
<td>d  (J=11)</td>
<td>1H</td>
</tr>
<tr>
<td>6.91</td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>8.13</td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>11.20</td>
<td>s</td>
<td>1H</td>
</tr>
</tbody>
</table>

Thus the spectral data indicated the structure of the product to be 5b which was further supported by the elemental analysis.

For C_{14}H_{16}O_{3}:

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated: 72.39</td>
<td>6.94</td>
</tr>
<tr>
<td>observed:  72.10</td>
<td>6.81</td>
</tr>
</tbody>
</table>

Based on the structure 5b the yield of the product was found to be 79%.

Conversion of 2,2-dimethyl-7-alkoxy-6-formyl-benzo[b]pyran 5a, b into 2,2-dimethyl-7-alkoxy-6-hydroxy-2H-benzo[b]pyran 6c, d respectively

Aromatic aldehydes are known to undergo Baeyer-Villiger
oxidation with H$_2$O$_2$/^/-OH providing the corresponding formate esters which are very prone to hydrolysis.

\[
\text{R-CHO} \xrightarrow{} \text{R-OCHO} \xrightarrow{} \text{R-OH}
\]

This important synthetic route to convert aromatic aldehydes to phenols faces two limitations namely,

a) Activated double bonds carrying electron withdrawing substituents efficiently undergo epoxidation with H$_2$O$_2$/^/-OH combination and

b) Low yields of the phenolic products.

These factors reducing the utility of this approach were to a great extent overcome by Syper$^{32}$. In his modification hydrogen peroxide is reacted with the aromatic aldehyde dissolved in methylene chloride forming a neutral two phase system and containing a catalytic amount of SeO$_2$. Dichloromethane is used as the organic phase and 30% aq.H$_2$O$_2$ forms the aqueous phase. The role of selenium dioxide is to polarize the carbonyl group.

It was then decided to use Syper's method to convert the 6-formyl group in chromenes to a phenolic hydroxyl group because 1) the reaction is done at room temperature thus avoiding dimerisation$^{33}$ of the chromene and 2) high reported yields of the corresponding formates and the respective phenols.
Reaction of 5a with H₂O₂/CH₂Cl₂/SeO₂ proceeded smoothly and the completion of the conversion on TLC (hexane-ethyl acetate, 80:20) was observed after 36 hours. Usual work-up of the reaction mixture provided a dark yellow viscous liquid which was further subjected to hydrolysis and alkylation in situ. To this dark yellow residue slight excess of 5% aq. KOH was then added and the resulting mixture was heated on water bath for 20 minutes and dimethyl sulphate was added under stirring and heating was further continued. The conversion was monitored by TLC. The reaction went to completion within 45 minutes. Work-up provided a dark red oil. It was purified by column chromatography which provided a pale yellow liquid whose GLC analysis indicated it to be a single component. It was characterized as follows.

**Characterization of the pale yellow oil**

<table>
<thead>
<tr>
<th>PMR</th>
<th>1.40</th>
<th>s</th>
<th>6H</th>
<th>-C(CH₃)₂</th>
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<tbody>
<tr>
<td></td>
<td>3.78</td>
<td>s</td>
<td>6H</td>
<td>2 x -OCH₃</td>
</tr>
<tr>
<td></td>
<td>5.50</td>
<td>d (J=9)</td>
<td>1H</td>
<td>C₃-H</td>
</tr>
<tr>
<td></td>
<td>6.20</td>
<td>d (J=9)</td>
<td>1H</td>
<td>C₄-H</td>
</tr>
<tr>
<td></td>
<td>6.40</td>
<td>s</td>
<td>1H</td>
<td>C₈-H</td>
</tr>
<tr>
<td></td>
<td>6.50</td>
<td>s</td>
<td>1H</td>
<td>C₅-H</td>
</tr>
</tbody>
</table>

The PMR clearly supported structure 7a for the product and the elemental analysis further confirmed it.
Same reaction sequence was again followed using 5a with the only change that diethyl sulphate was used for O-alkylation instead of dimethyl sulphate. Work-up and purification furnished a nearly colourless oil. Its GLC analysis also exhibited one single peak. This was further characterized as follows.

Characterization of the colourless oil:

<table>
<thead>
<tr>
<th>PMR</th>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>t (J=7)</td>
<td>1.30</td>
<td>3H</td>
<td>-CH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s</td>
<td>1.42</td>
<td>6H</td>
<td>-C(CH₃)₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>s</td>
<td>3.92</td>
<td>3H</td>
<td>-OCH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q (J=7)</td>
<td>4.15</td>
<td>2H</td>
<td>-CH₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d (J=10)</td>
<td>5.60</td>
<td>1H</td>
<td>C₃-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d (J=10)</td>
<td>6.38</td>
<td>1H</td>
<td>C₄-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s</td>
<td>6.52</td>
<td>1H</td>
<td>C₈-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s</td>
<td>6.72</td>
<td>1H</td>
<td>C₅-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Again the structure suggested by the PMR as 7b was further confirmed by the elemental analysis.

For C₁₄H₁₈O₃ :

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated:</td>
<td>71.77</td>
<td>7.74</td>
<td></td>
</tr>
<tr>
<td>observed :</td>
<td>71.50</td>
<td>7.52</td>
<td>7b</td>
</tr>
</tbody>
</table>
Next the aldehyde 5b was reacted in the same way with H$_2$O$_2$/CH$_2$Cl$_2$/SeO$_2$ combination. This reaction also took 36 hours for completion. The corresponding formate ester so obtained was again hydrolysed and alkylated in situ using dimethyl sulphate and diethyl sulphate to obtain two different oils. One of which was a pale yellow liquid while the other one was yellowish brown. These liquid products were characterised as follows.

**Characterization of the pale yellow liquid product**

<table>
<thead>
<tr>
<th>PMR</th>
<th>1.45</th>
<th>bs</th>
<th>9H</th>
<th>-C(CH$_3$)$_2$, -CH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.90</td>
<td>s</td>
<td>3H</td>
<td>-OCH$_3$</td>
</tr>
<tr>
<td></td>
<td>4.17</td>
<td>q (J=7)</td>
<td>2H</td>
<td>-CH$_2$</td>
</tr>
<tr>
<td></td>
<td>5.62</td>
<td>d (J=10)</td>
<td>1H</td>
<td>C$_3$-H</td>
</tr>
<tr>
<td></td>
<td>6.40</td>
<td>d (J=10)</td>
<td>1H</td>
<td>C$_4$-H</td>
</tr>
<tr>
<td></td>
<td>6.51</td>
<td>s</td>
<td>1H</td>
<td>C$_5$-H</td>
</tr>
<tr>
<td></td>
<td>6.74</td>
<td>s</td>
<td>1H</td>
<td>C$_6$-H</td>
</tr>
</tbody>
</table>

The structure suggested by the PMR as $7c$ was further confirmed by the analysis.

For C$_{14}$H$_{18}$O$_3$ :

<table>
<thead>
<tr>
<th></th>
<th>71.77</th>
<th>7.74</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated :</td>
<td></td>
<td></td>
</tr>
<tr>
<td>observed :</td>
<td>71.61</td>
<td>7.63</td>
</tr>
</tbody>
</table>

![Chemical structure of 7c]
Characterization of the yellowish-brown liquid product

PMR : 

| 1.42  | bs | 12H -C(CH₃)₂, 2 x -CH₃ |
| 4.10  | m  | 4H 2 x -CH₂ |
| 5.57  | d (J=10) | 1H C₃-H |
| 6.34  | d (J=10) | 1H C₄-H |
| 6.50  | s  | 1H C₈-H |
| 6.68  | s  | 1H C₅-H |

The structure assigned to the above product based on its PMR was 7d which was further supported by its elemental analysis.

For C₁₅H₂₀O₃

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated : 72.55</td>
<td>8.12</td>
</tr>
<tr>
<td>observed  : 72.42</td>
<td>8.16</td>
</tr>
</tbody>
</table>

Alternate approach I : All the four chromenes 7a-d were also obtained by a slightly modified route wherein the starting compounds chosen were 3,4-dihydro-2,2-dimethyl-7-alkoxy-2H-1-benzo[b]pyrans 8b and 8c.

These chromans under the Vilsmeier-Haack conditions furnished the corresponding 6-formyl chromans 9a and 9b in good yields. These aldehydes 9a and 9b on treatment with the H₂O₂/CH₂Cl₂/SeO₂ combination, underwent smooth conversion to the corresponding formate esters 10a and 10b.
The hydrolysis of these formates provided the phenols 10c & 10d. These phenols were then converted to the respective 6-alkyl ethers 11a-d and in the last step into chromenes 7a-d using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). All these conversions worked equally efficiently compared with the earlier route. The reaction sequence along with the reagents and reaction conditions is presented in SCHEME-3. One of the intermediate phenols viz. 3,4-dihydro-2,2-dimethyl-6-hydroxy-7-methoxy-2H-benzo[b]pyran 10c was characterized as follows.

M.P. : 80°C

IR : 3295

PMR :  

| 1.33   | s   | 6H -C(CH₃)₂  |
| 1.80   | t (J=6) | 2H -CH₂  |
| 2.71   | t (J=6) | 2H -CH₂Ar  |
| 3.90   | s   | 3H -OCH₃  |
| 5.21   | bs  | 1H -OH(exchangeable) |
| 6.48   | s   | 1H C₈-H/C₅-H  |
| 6.74   | s   | 1H C₅-H/C₈-H  |

Thus the spectral data supported the structure 10c. This was further confirmed by its elemental analysis.

For C₁₂H₁₆O₃ :  

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated : 69.20</td>
<td>7.74</td>
</tr>
<tr>
<td>observed   : 69.08</td>
<td>7.52</td>
</tr>
</tbody>
</table>
Reagents:  i) Zn-Hg/HCl, ii) DMF-POCl₃, iii) H₂O₂/SeO₂/CH₂Cl₂, iv) DMS or DES/KOH, v) DDQ, vi) LAH/ether.

SCHEME-3
**Alternate approach II**: The combination of $\text{H}_2\text{O}_2/\text{CH}_2\text{Cl}_2/\text{SeO}_2$ used to convert aromatic aldehydes to formates also works on aromatic ketones$^{32}$. Bearing this fact in mind, another modification was thought of. Starting compound $9a$ was first oxidized using ceric ammonium nitrate (CAN) in a two phase system of diethyl ether, water and acetic acid. These conditions are known to bring about oxidation of the benzylic carbons efficiently$^{34}$. In the present case the reaction was complete within 20 minutes as indicated by TLC. Work up provided a pale yellow solid which was purified by column chromatography using hexane-ethyl acetate (10:1) as eluent. Crystallization from the same solvent system provided pale yellow crystals having m.p. $145^0$.

**Characterization of the yellow crystalline compound:**

**IR**: 2720, 1682, 1690

**PMR**:

<table>
<thead>
<tr>
<th>Chemical Group</th>
<th>Multiplicity</th>
<th>Integration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\text{C(CH}_3\text{)}_2$</td>
<td>s</td>
<td>6H</td>
<td>1.61</td>
</tr>
<tr>
<td>$-\text{CH}_2$</td>
<td>s</td>
<td>2H</td>
<td>2.83</td>
</tr>
<tr>
<td>$-\text{OCH}_3$</td>
<td>s</td>
<td>3H</td>
<td>4.15</td>
</tr>
<tr>
<td>$\text{C}_8\text{-H}$</td>
<td>s</td>
<td>1H</td>
<td>6.60</td>
</tr>
<tr>
<td>$\text{C}_5\text{-H}$</td>
<td>s</td>
<td>1H</td>
<td>8.52</td>
</tr>
<tr>
<td>$-\text{CHO}$</td>
<td>s</td>
<td>1H</td>
<td>10.54</td>
</tr>
</tbody>
</table>

The IR and PMR supported the structure $12$ which was further confirmed by its elemental analysis.
For C\textsubscript{13}H\textsubscript{14}O\textsubscript{4}:

\[
\begin{array}{cc}
\text{calculated} & 66.65 & 6.02 \\
\text{observed} & 66.53 & 5.90 \\
\end{array}
\]

Compound 1\textsubscript{2} thus obtained is so far unreported in the literature. So this constitutes the first synthesis of the same. It was then subjected to react with H\textsubscript{2}O\textsubscript{2}/CH\textsubscript{2}Cl\textsubscript{2}/SeO\textsubscript{2} combination first and then 5\% methanolic KOH respectively. Work-up and crystallization in hexane-ethyl acetate furnished an off-white crystalline compound having m.p. 136\textdegree as the exclusive product.

**Characterization of the compound having m.p. 136\textdegree**

**IR**: 3290, 1688

**PMR**: 1.46 \text{s} 6H -C(CH\textsubscript{3})\textsubscript{2}

2.66 \text{s} 2H -CH\textsubscript{2}

3.97 \text{s} 3H -OCH\textsubscript{3}

5.49 \text{s} 1H -OH (exchangeable)

6.37 \text{s} 1H C\textsubscript{8}-H

7.46 \text{s} 1H C\textsubscript{5}-H

The PMR of the compound revealed that the peak at 10.54 in the starting compound 1\textsubscript{2} was absent and an exchangeable peak appeared at 5.49. Further the methylene signal at 2.83 in compound 1\textsubscript{2} observed a high field shift at 2.66 in the product. Also the upfield shift of C\textsubscript{5}-H from 8.52 to 7.46 and appearance of only one carbonyl in the IR spectrum clearly indicated that the formyl
group underwent oxidation exclusively. Structure 13 was therefore assigned to the compound. Melting point of this compound also matched exactly with the reported one. The elemental analysis was also in accordance with the structure 13.

Literature survey revealed that only one synthesis has so far been reported for 13. The known approach involves a nucleophilic attack of alkoxide ion on 2,2-dimethyl-6,7-methylenedioxy-4H-benzopyran-4-one 14 as represented in the SCHEME-4

Conversion of 13 into precocenes has already been reported by the same authors.

The reaction sequence followed is as in SCHEME-5

i) CAN, Et₂O, AcOH, H₂O   ii) SeO₂/CH₂Cl₂/ H₂O₂
PART II: SYNTHESIS OF BENZODIPYRANS: THE PREOCENE ANALOGUES

After achieving successfully the synthesis of 2,2-dimethyl-6,7-dialkoxy-2H-benzo[b]pyrans with good yields attention was then focused mainly on the compounds which could be viewed as the analogues of the above synthesized benzopyrans. One of the reasons for the persual of different derivatives of chromenes is the species specific mechanism in insects as far as the AJH activity is concerned. This means that one chromene acting as a perfect AJH for a specific species of insect might prove to be completely inactive in the case of another species.

As discussed earlier in the structure activity relationship for the 2,2-dimethyl-6,7-dialkoxy-2H-1-benzo[b]pyrans presence of a 7-alkoxy substituent in the 2H-chromene skeleton is an important requirement to exhibit AJH activity. But it has been observed that the substituent undergoes dealkylation during a process termed as detoxification. Now to avoid this detoxification it was necessary to prevent the dealkylation of the substituent at the C7-position. This resulted in increasing the steric bulk at C7 which was best served by building another pyran ring involving the C7- and either C6- or C8. The benzodipyrrans thus obtained were classified into linear and angular benzodipyrrans. Some important members of these classes are depicted below. From the TABLE 2 it is quite clear that there are very few methods reported for the syntheses of the above mentioned benzodipyran systems having many limitations. Hence it was felt necessary to develop methods which could lead to
exclusive synthesis of linear or angular benzodipyrans systems 15-19.

**Linear benzodipyrans**

15

16

17

**Angular benzodipyrans**

18

19

**RETROSYNTHETIC ANALYSIS : LINEAR BENZODIPYRANS**

Three different disconnections could be shown for the linear benzodipyrans 15-17 which constitute three different synthetic pathways. These disconnections are as follows.

A) 

B)
A) In the first approach resorcinol is the starting material which is condensed with excess of isoprene when the linear tetrahydro benzodipyran is obtained as one of the products. The yields are not promising. In another approach resorcinol is first reacted with 3,3-dimethyl acrylic acid chloride to give the corresponding diester. PhotoFries followed by internal Michael addition gave the linear benzodipyran-dione in low yield along with the formation of other products also [TABLE 2].

B) The second approach makes use of resdiacetophenone. Acetone is condensed with it in presence of LDA under ultrasonic radiations. The condensate is treated with hexamethylene-phosphoroustriamide (HMPT) for dehydration yielding the dichromanone. It is then easily converted into the required dichromene via reduction and dehydration. Critical reaction conditions is the limiting factor in this approach.
C) The last approach involves building up of second pyran ring on a preformed benzopyran system regioselectively which has been explored as discussed below.

**PRESENT WORK**

**Linear benzodipyrans**: Starting material was easily accessible resdiacetophenone 22 which was then reacted with excess of acetone in the presence of pyrrolidine and benzene. The reaction mixture was refluxed using a Dean-Stark assembly. The reaction showed complete consumption of the starting material within four hours as indicated by the TLC. Work up provided a white crystalline product which was found to be a phenolic compound instead of being neutral one according to expectation. It showed melting point of 119\(^0\)C as against the literature\(^23\) m. p. 179\(^0\)C for compound 21.

**Characterization of the compound having m.p. 119\(^0\).**

**IR** : 1692

**PMR** :

<table>
<thead>
<tr>
<th>Value</th>
<th>s</th>
<th>6H</th>
<th>-C(CH(_3))(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.47</td>
<td>s</td>
<td>3H</td>
<td>-CH(_3)</td>
</tr>
<tr>
<td>2.70</td>
<td>s</td>
<td>2H</td>
<td>-CH(_2)</td>
</tr>
<tr>
<td>6.71</td>
<td>s</td>
<td>1H</td>
<td>CH(_8)-H</td>
</tr>
<tr>
<td>8.58</td>
<td>s</td>
<td>1H</td>
<td>CH(_5)-H</td>
</tr>
<tr>
<td>12.0</td>
<td>s</td>
<td>1H</td>
<td>-OH (exchangeable)</td>
</tr>
</tbody>
</table>
The PMR indicated presence of only one geminal dimethyl grouping. A singlet at 2.47 corresponding to three protons indicated presence of an acetyl group. A singlet at 2.70 was attributed to a methylene adjacent to carbonyl. A singlet at 12.0 indicated presence of a bonded hydroxyl group which confirmed that only one condensation had occurred. Thus the PMR supported the structure 23 instead of expected 21. This was further confirmed by its elemental analysis.

For C_{13}H_{14}O_{4} :

<table>
<thead>
<tr>
<th></th>
<th>calculated</th>
<th>observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>66.65</td>
<td>66.49</td>
</tr>
<tr>
<td>H</td>
<td>6.02</td>
<td>5.85</td>
</tr>
</tbody>
</table>

Changes in the quantities of acetone, pyrrolidine or in the reaction time proved to be unfruitful. It was then felt necessary to go for the third approach i.e. to build a pyran system on a preformed dihydrobenzopyran system.

It is well established fact that almost all electrophilic substitutions proceed at C_6 in 8a. So when this was reacted with 3,3-dimethyl acrylic acid in the presence of ZnCl_2/POCl_3, work up provided a low melting solid which was purified by column chromatography using n-hexane, crystallization from the same solvent furnished pale yellow needles having m.p. 86°.

**Characterization of the pale yellow product m.p. 86°**

IR : 1682
The PMR data revealed presence of two geminal dimethyl groupings and presence of two uncoupled aromatic protons. Based on this PMR structure 24 was assigned to the compound having m.p. 86°C. Literature survey revealed that this compound has been obtained by Camps et al.\textsuperscript{22} [TABLE 2, XVI] which had the same m.p. and PMR as above.

For C\textsubscript{16}H\textsubscript{20}O\textsubscript{3}:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated</td>
<td>73.84</td>
<td>7.64</td>
</tr>
<tr>
<td>observed</td>
<td>74.13</td>
<td>8.01</td>
</tr>
</tbody>
</table>

Thus 2,3,6,7-tetrahydro-2,2,8,8-tetramethyl-4H,8H-benzo[1,2-b:5,4-b'] dipyran-4-one 24 was obtained as the exclusive product of this reaction and it was further planned to react in three different ways leading to three different precocene analogues.

1) Reaction with DDQ: Reaction of compound 24 with DDQ using 1,4-dioxane as solvent furnished a yellow compound which was purified by vacuum sublimation. The pale yellow needles so
obtained were found to have m.p. 106\(^{\circ}\).

**Characterization of the yellow compound showing m.p. 106\(^{\circ}\).**

**PMR**:

- 1.43 \(\text{bs}\) \(12\text{H} \times -\text{C(CH}_3\text{)}_2\)
- 2.66 \(\text{s}\) \(2\text{H} \times -\text{CH}_2\)
- 5.66 \(\text{d (J=10)}\) \(1\text{H} \times C_3-\text{H}\)
- 6.35 \(\text{s}\) \(1\text{H} \times C_{10}-\text{H}\)
- 6.42 \(\text{d (J=10)}\) \(1\text{H} \times C_4-\text{H}\)
- 7.60 \(\text{s}\) \(1\text{H} \times C_5-\text{H}\)

For \(\text{C}_{16}\text{H}_{18}\text{O}_3\):

<table>
<thead>
<tr>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>74.39</td>
<td>7.02</td>
</tr>
<tr>
<td>74.44</td>
<td>7.12</td>
</tr>
</tbody>
</table>

Hence the structure 17 was assigned to the compound as indicated by the PMR and analysis.

This constitutes the first report of the synthesis of this benzodipyran system. The compound is so far unknown and is under investigations for the estimation of its biological activity.

**2) Reduction and dehydration of compound 24**

Standard procedure\(^{22}\) was used to reduce and dehydrate the chromanone 24. This furnished a semisolid which was column chromatographed using n-hexane as the eluent. An off-white semisolid was obtained which solidified on standing. It was recrystallized from n-hexane-ethyl acetate and had melting point
55° (lit. m. p. 56°). Its spectral and elemental analysis was in perfect agreement with the structure 15.

Dehydrogenation of the above chromene 15 using DDQ to provide the dichromene 16 is already reported. 25

3) Reaction of 24 with cetric ammonium nitrate (CAN)

To synthesize the dipyran 16 from compound 24, oxidation was thought to be a useful route in which formation of the dipyrandione 21 was anticipated. Various oxidizing reagents like SeO₂, CrO₃, KMnO₄ were tried but results were unsatisfactory. Compound 24 was finally reacted with CAN vide supra. Work up provided a yellow solid which was purified by column chromatography and crystallization from hexane-ethyl acetate. The pure compound showed m.p. 176°.

Characterization of the compound having m.p. 176°C

IR :  1690

PMR :  

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>1.50 s 12H</th>
<th>2.73 s 4H</th>
<th>6.47 s 1H</th>
<th>8.61 s 1H</th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>2xC(CH₃)₂</td>
<td>2 x -CH₂</td>
<td>C₁₀-H</td>
<td>C₅-H</td>
</tr>
</tbody>
</table>
The spectral data thus suggested structure 21 which was further supported by the elemental analysis and its literature\(^1\) m.p.179-180\(^0\)

For \(\text{C}_{16}\text{H}_{18}\text{O}_4\) :

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>calculated</td>
<td>70.05</td>
<td>6.70</td>
</tr>
<tr>
<td>observed</td>
<td>69.85</td>
<td>6.44</td>
</tr>
</tbody>
</table>

Thus the compound 2,3,7,8-tetrahydro-2,2,8,8-tetramethyl-4H,6H-benzo[1,2-b:5,4-b']dipyran-4,6-dione 21 was obtained in fairly good yield.

**Reduction and dehydration of 21**

To obtain the target compound 16 from the dione 21, it was reacted with LAH and the resultant diol was dehydrated during work up which provided a pale yellow liquid. This liquid solidified on standing. The solid had m.p. 77\(^0\). Its spectral and analytical data matched perfectly with the reported data\(^1\) for 2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b: 5,4-b']dipyran 16 (vide infra).

Thus the synthesis of linear tricyclic benzodipyrans along with their dihydro analogues and benzodipyrandiones was achieved successfully in fairly good yields.
PART III

SYNTHESIS OF ANGULAR BENZODYPYRANS

After completing the synthesis of the linear tricyclic benzodipyrans, their angular analogues 18 and 19 were the next targets. Very few syntheses of 18 and 19 are reported and in majority of them the desired precursors 25, 26 and 27 have been obtained as the side products in low yields.

In the reported syntheses either excess of isoprene\textsuperscript{25, 37} or 3,3-dimethyl acrylic acid\textsuperscript{26} was used as the condensing agent with resorcinol. In another case 1,3-dichloro-3-methyl-butane had also been used\textsuperscript{22}. Although most of these reported methods provide mixtures of compounds there is only one report\textsuperscript{24} where in compound 25 was exclusively obtained. All the known approaches could be classified into three categories from the retrosynthetic point of view. The disconnections principally are same as they are in the case of linear tricyclic precocenes and are listed below.
In the first retrosynthetic approach along with linear tricyclic benzodipyrans, angular benzodipyrans are also obtained in low yields when resorcinol is reacted with excess of prenylating agent.\textsuperscript{25,37}. For the second type of disconnection the synthon required would be 2,4-diacetyl resorcinol which in turn can be obtained by lithiation reaction. So the third approach was felt more suitable which involves construction of the pyran or pyrone on a preformed benzopyran ring system.
Initially, two alternatives were considered as shown in **SCHEME 6**. Either to use the organolithiation reaction to obtain the required 2-substituted resorcinol or to block the more reactive 6-position of the 3,4-dihydro-2,2-dimethyl-7-hydroxy-2H-benzo[b]pyran prior to conversion of the same into the target molecule and which would pose minimum problems in its removal afterwards. This strategy is represented in the **SCHEME 7**. The organolithiation approach was discarded due to the poor yields. So it was then decided to try the second approach. The most convenient blocking group was thought to be bromine.

**SCHEME 6**

**SCHEME 7**
PRESENT WORK

Thus the required synthon for the aforesaid approach was 3,4-dihydro-2,2-dimethyl-6-bromo-7-hydroxy-2H-benzo[b]pyran 29. To obtain this compound 3,4-dihydro-2,2-dimethyl-7-hydroxy-2H-benzo [b]pyran was then subjected to bromination using different conditions. Initially dioxane-dibromide was tried but the results were not encouraging. Finally acetic acid, bromine combination at 7-10° provided a single product as indicated by the TLC. The reaction was worked-up and the product obtained as a dark brown semisolid was purified by column chromatography. The residue solidified into pale yellow needles on standing. The product was then characterized as given below.

Characterization of the pale yellow needles:

M. P. 116°

PMR:

<table>
<thead>
<tr>
<th>Chemical Group</th>
<th>δ ppm</th>
<th>J (Hz)</th>
<th>Multiplicity</th>
<th>Number of protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>-C(CH₃)₂</td>
<td>1.31</td>
<td>s</td>
<td>6H</td>
<td>-C(CH₃)₂</td>
</tr>
<tr>
<td>-CH₂</td>
<td>1.76</td>
<td>t (J=6)</td>
<td>2H</td>
<td>-CH₂</td>
</tr>
<tr>
<td>-CH₂-Ar</td>
<td>2.69</td>
<td>t (J=6)</td>
<td>2H</td>
<td>-CH₂-Ar</td>
</tr>
<tr>
<td>-OH</td>
<td>5.36</td>
<td>s</td>
<td>1H</td>
<td>-OH (exchangeable)</td>
</tr>
<tr>
<td>C₈-H</td>
<td>6.56</td>
<td>s</td>
<td>1H</td>
<td>C₈-H</td>
</tr>
<tr>
<td>C₅-H</td>
<td>7.24</td>
<td>s</td>
<td>1H</td>
<td>C₅-H</td>
</tr>
</tbody>
</table>

The PMR thus indicated the formation of 29. Two singlets in the aromatic region clearly suggested that bromination has proceeded at C₆- position only and ruled out the possibility of 8-
bromo compound.

The elemental analysis also was in accordance with the anticipated molecular formula.

For C_{11}H_{13}O_{2}Br :

\[ \begin{array}{cc}
\text{C} & \text{H} \\
\text{calculated} & 51.36 & 5.09 \\
\text{observed} & 51.40 & 4.86 \\
\end{array} \]

After obtaining the chroman 29 it was reacted with 3,3-dimethyl acrylic acid in the presence of ZnCl\textsubscript{2} and POCl\textsubscript{3} at room temperature for 24 hours, the work up of which furnished a brown low melting solid. The solid was purified by column chromatography which gave a yellow crystalline solid characterized as follows.

Characterization of the yellow crystalline solid

M. P. \( 95-96^\circ \)

IR : 1685

PMR :

\[ \begin{array}{cccc}
1.36 & \text{s} & 6H & \text{C(CH}_3)_2 \\
1.89 & \text{s} & 6H & \text{C(CH}_3)_2 \\
2.20 & \text{t (J=6)} & 2H & \text{CH}_2 \\
2.86 & \text{t (J=6)} & 2H & \text{CH}_2\text{Ar} \\
3.26 & \text{s} & 2H & \text{CH}_2\text{CO}^- \\
7.40 & \text{s} & 1H & \text{C}_9\text{-H} \\
\end{array} \]
The compound thus was proved to be the required \(2,3,7,8\)-tetrahydro-2,2,6,6-tetramethyl-10-bromo-4H,6H-benzo \([1,2-b:3,4-b']\) dipyran-4-one \(30\).

After getting successfully \(30\), it was decided to get rid of bromine using LAH. Accordingly when the compound was reacted with LAH in ether the results were not encouraging. The product showed a positive test for presence of bromine even after complete reduction of the carbonyl group of the chromanone into a methylene. Instead of trying other conditions for the removal of bromine this route was discontinued.

So in the next attempt it was decided to use \(3,4\)-dihydro-2,2-dimethyl-5-hydroxy-2H-benzo[b]pyran \(35\) as the starting compound which could be obtained easily from the corresponding chroman-4-one \(28\). Compound \(35\) on condensation with 3,3-dimethyl acrylic acid is known\(^{24}\) to furnish \(2,3,9,10\)-tetrahydro-2,2,8,8-tetramethyl-4H,8H-benzo\([1,2-b:3,4-b']\)dipyran-4-one \(25\) which could be easily transformed into the desired benzodypyranes \(18\) and \(19\) respectively. The key intermediate required for this sequence was 2-acetyl resorcinol \(34\) which was obtained using a known procedure\(^{38a}\). The reaction sequence is depicted below (Scheme 8).
Following this method the dipyran' \textsuperscript{25} was obtained in good yield and was reacted in two different ways.

\textbf{1) Reduction and dehydration of 25}

This was done using LAH in ether. Work-up provided a brown liquid which on purification by column chromatography provided a TLC pure thick yellow liquid.

\textbf{Characterization of the yellow liquid}

\begin{verbatim}
PMR : 
1.37  s  6H  -C(CH\textsubscript{3})\textsubscript{2}
1.54  s  6H  -C(CH\textsubscript{3})\textsubscript{2}
2.19  t (J=6)  2H  -CH\textsubscript{2}
2.83  t (J=6)  2H  -CH\textsubscript{2}Ar
5.83  d (J=10)  1H  C\textsubscript{3}-H
6.74  d (J=10)  1H  C\textsubscript{4}H
6.86  d (J=9)  1H  C\textsubscript{6}H
7.30  d (J=9)  1H  C\textsubscript{5}-H
\end{verbatim}

For C\textsubscript{16}H\textsubscript{20}O\textsubscript{2}:

\begin{align*}
\text{C} & \quad \text{H} \\
\text{calculated} : & \quad 78.65 \quad 8.25 \\
\text{observed} : & \quad 78.62 \quad 8.60
\end{align*}

Based on this spectral and elemental analysis the structure \textsuperscript{18} was assigned to this compound.

Further as the last part of synthesis in this section it was
decided to convert compound 25 into the corresponding dichromene 19. For this conversion again oxidation was thought to be the convenient route, based on the earlier observation.

2) Oxidation of 2,3,9,10-tetrahydro-2,2,8,8-tetramethyl-4H,8H-benzo[1,2-b;3,4-b’]dipyran-4-one

Same procedure, used for the oxidation of 24 when applied for the oxidation of 25 provided a yellow solid. It was purified by column chromatography and crystallization from hexane-ethyl acetate. Pale yellow crystalline compound was obtained.

Characterization of the yellow solid

M. P. 161° (lit26. 161°).

IR : 1688

PMR :

<table>
<thead>
<tr>
<th>1.58</th>
<th>s</th>
<th>6H</th>
<th>-C(CH₃)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.62</td>
<td>s</td>
<td>6H</td>
<td>-C(CH₃)₂</td>
</tr>
<tr>
<td>2.85</td>
<td>s</td>
<td>4H</td>
<td>2 x -CH₂</td>
</tr>
<tr>
<td>7.00</td>
<td>d</td>
<td>(J=9)</td>
<td>1H</td>
</tr>
<tr>
<td>8.55</td>
<td>d</td>
<td>(J=9)</td>
<td>1H</td>
</tr>
</tbody>
</table>

For C₁₆H₁₈O₄ :

calculated : 70.05 6.70
observed : 69.92 6.54
Appearance of four protons as a singlet in the methylene region clearly indicated that the benzylic carbon exclusively underwent oxidation. Therefore structure 27 was assigned to the oxidation product.

**Reduction and dehydration of dipyrandione 27**

Compound 27 was subjected to reduction using LAH in order to obtain the last target the dipyran 19. Standard procedure furnished a liquid residue which was purified by column chromatography. A pale yellow liquid residue was obtained which was characterized as described below.

**Characterization of the pale yellow liquid:**

<table>
<thead>
<tr>
<th>PMR</th>
<th>1.35</th>
<th>bs</th>
<th>12H</th>
<th>2 x -C(CH₃)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.85</td>
<td>d (J=8)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
<tr>
<td>4.85</td>
<td>d (J=8)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
<tr>
<td>5.54</td>
<td>d (J=10)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
<tr>
<td>6.37</td>
<td>d (J=10)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
<tr>
<td>6.48</td>
<td>d (J=9)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
<tr>
<td>7.00</td>
<td>d (J=9)</td>
<td>1H</td>
<td>=CH</td>
<td></td>
</tr>
</tbody>
</table>

**PMR** spectrum of the product showed presence of six doublets each having coupling constant indicative of the cis or ortho coupled protons. Out of these two extremely shielded doublets were observed in the PMR. They were counterparts of each others as indicated by their coupling constants (J=8). The reason for this shielding is not clear enough. Structure 19 is assigned to this pale yellow liquid based on the PMR.
CONCLUSION

1) Synthesis of 2,2-dimethyl-2H-benzo[b]pyrans having any desired alkoxy substitution at C₆⁻ and C₇⁻ was achieved under mild conditions and in high yields by three different approaches.

2) Procedures were also developed to obtain linear and angular benzodipyrans as the exclusive products in high yields.
EXPERIMENTAL
EXPERIMENTAL

EXPERIMENT NO 1: 2',4'-Dihydroxy acetophenone 2

\[
\begin{align*}
\text{1} & \xrightarrow{\text{ZnCl}_2/\text{AcOH}} \text{2} \\
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

Resorcinol 1 (50 g, 0.455 mol) was dissolved in glacial acetic acid (100.0 ml, 1.73 mol). To this clear solution freshly fused powdered zinc chloride (50.0 g, 0.55 mol) was added and the reaction mixture was heated at 150° to reflux gently for 15 minutes. The resultant dark red solution was cooled and then poured in 1:1 HCl (400 ml). A dark yellow solid separated which was filtered, dried and crystallized from dilute ethanol.

YIELD: 41.2 g (60%).

M.P.: 145° (lit\textsuperscript{38b} m. p. 145-7°).

EXPERIMENT NO 2: 2,3-Dihydro-2,2-dimethyl-7-hydroxy-4H-benzo-pyran-4-one 3a

\[
\begin{align*}
\text{2} & \xrightarrow{i) \text{acetone, pyrroloidine, benzene, } ii) \text{H}_3\text{O}^+} \text{3a} \\
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \\
\text{CH}_3 & \\
\text{2} & \quad \text{3a}
\end{align*}
\]
2,4-Dihydroxyacetophenone 2 (35.0 g, 0.23 mol) was dissolved in dry benzene (500 ml). To this solution pyrrolidine (9.61 ml, 8.18 g, 0.115 mol) and dry acetone (16.87 ml, 13.35 g, 0.23 mol) were added and the reaction mixture was allowed to stand for 15 minutes at room temperature. It was then refluxed with a Dean Stark separator for 36 hours. The completion of the reaction was monitored by TLC. The reaction mixture was then allowed to attain room temperature. It was then filtered, washed with 5% aq. HCl when a colour change from dark red to pale yellow was observed. Finally it was washed with water, dried using anhydrous Na₂SO₄. Removal of the solvent provided a pale yellow solid which was recrystalized from dilute ethanol which furnished 3a as white needles.

**YIELD**: 30 g, (68%).


**PMR**:

| 1.43 | s | 6H -C(CH₃)₂ |
| 2.61 | s | 2H -CH₂ |
| 5.50 | bs | 1H -OH (exchangeable) |
| 6.30-6.49 | m | 2H C₆-H, C₈-H |
| 7.65 | d (J=8) | 1H C₅-H |
EXPERIMENT NO 3 : 2,3-Dihydro-2,2-dimethyl-7-hydroxy-4H-benzo-pyran-4-one 3a

Resorcinol 1 (30.0 g, 0.272 mol) was mixed with 3,3-dimethyl acrylic acid (27.3 g, 0.272 mol). Further freshly fused powdered zinc chloride (30.0 g, 0.22 mol) was added to it and the mixture was powdered finely. To this mixture phosphorous oxychloride (150 ml, 246.75 g, 1.6 mol) was added under mechanical stirring. The reaction mixture was further stirred at room temperature for another 90 minutes. The homogeneous deep red solution was left overnight at room temperature. The resultant viscous dark liquid was then decomposed over crushed ice (2.00Kg). A dark red solid was obtained which was filtered, dried, decolourised using activated charcoal and recrystallized from dilute ethanol.

**YIELD :** 37.25 g, (71%)  

**M.P. :** 168-170\(^{\circ}\)C. (lit\(^{30}\) m. p. 173\(^{\circ}\)).
EXPERIMENT NO 4: 2,3-Dihydro-2,2-dimethyl-7-methoxy-4H-benzo-pyran-4-one 3b

2,3-Dihydro-2,2-dimethyl-7-hydroxy-4H-benzopyran-4-one 3a (20.0 g, 0.104 mol) was added to a mixture of dry acetone (200.0 ml), dry K₂CO₃ (21.56 g, 0.156 mol) and freshly distilled dimethyl sulphate (11.85 ml, 15.75 g, 0.125 mol) and the mixture was refluxed for 12 hours. It was then cooled and filtered. Removal of acetone provided a dark red oil. It was purified by column chromatography using n-hexane as the eluent. A pale yellow residue was obtained which solidified into a white crystalline solid 3b.

M.P.: 81°C (lit19 81°)
YIELD: 19.7 g, (92%).

PMR:
1.5 s 6H -C(CH₃)₂
2.71 s 2H -CH₂
3.94 s 3H -OCH₃
6.47-6.84 m 2H C₆-H, C₈-H
8.02 d (J=9) 1H C₅-H
EXPERIMENT NO 5 : 2,2-Dimethyl-7-methoxy-2H-benzo[b]pyran 4a

![Chemical structure of 3b and 4a]

2,3-Dihydro-2,2-dimethyl-7-methoxy-4H-benzopyran-4-one 3b (15.0 g, 0.072 mol) was dissolved in dry diethyl ether (50.0 ml) and the resultant solution was added dropwise under nitrogen atmosphere at room temperature to a well stirred slurry of LAH (2.77 g, 0.072 mol) and dry diethyl ether (100.0 ml). This reaction mixture was then stirred at room temperature for 1 hour. As soon as the TLC indicated the completion of the reaction moist ether (10 ml) was added to it followed by a dropwise addition of water (50 ml) and HCl (4N, 100.0 ml) respectively. The resultant heterogeneous mixture was then heated on water bath at 50-55°C with continuous TLC monitoring. The dehydration completed within 15 minutes. A dark red residue lighter than the aqueous part was obtained which was extracted by ether. After removal of ether the residual oil was purified by column chromatography (neutral alumina and n-hexane) which furnished 4a as a pale yellow liquid. Alternatively the purification was also done by vacuum distillation.

**YIELD :** 11.20 g, (81%).
EXPERIMENT NO 6: 2,2-Dimethyl-6-formyl-7-methoxy-2H-benzo[b]pyran

2,2-Dimethyl-7-methoxy-2H-benzo[b]pyran \(4a\) (10.0 g, 0.052 mol) was added dropwise under stirring to an ice cold complex prepared from \(N,N\)-dimethyl formamide (4.0 ml, 3.84 g, 0.052 mol) and phosphorous oxychloride (4.92 ml, 8.07 g, 0.052 mol). The mixture was allowed to attain room temperature after the completion of addition. It was then heated on water bath at 80-85\(^\circ\)C for three hours. Then the reaction mixture was cooled to room temperature and the viscous dark red complex was added into a saturated solution of sodium acetate (150.0 ml). Compound \(5a\) separated out as a yellow solid was filtered, dried and recrystallized from n-hexane, ethyl acetate mixture.

**YIELD**: 9.500 g, (82%).

**PMR**:
- 1.40 s 6H \(-C(CH_3)_2\)
- 3.78 s 3H \(-OCH_3\)
- 5.51 d \((J=10)\) 1H \(C_3-H\)
- 6.28 s 1H \(C_8-H\)
- 6.47 m 2H \(C_4-H, C_6-H\)
- 6.97 d \((J=9)\) 1H \(C_5-H\)
M.P. : 74° (lit. 74°).

PMR :

1.50 s 6H -C(CH$_3$)$_2$
3.92 s 3H -OCH$_3$
5.62 d (J=9) 1H C$_3$-H
6.40 d (J=9) 1H C$_4$-H
6.47 s 1H C$_8$-H
7.60 s 1H C$_5$-H
10.42 s 1H CHO

EXPERIMENT NO. 7 : 2,2-Dimethyl-6-oxyformyl-7-methoxy-2H-benzo[b]pyran 6a

2,2-Dimethyl-6-formyl-7-methoxy-2H-benzo[b]pyran 5a (5.0 g, 0.022 mol) was added to a well stirred mixture of dichloromethene (50.0 ml), hydrogen peroxide (6.0 ml, aqueous 30%) and SeO$_2$ (0.2 g, 0.002 mol, freshly sublimed). This biphasic mixture was stirred at room temperature for 36 hours. It was then filtered, washed with water, saturated NaHCO$_3$ solution and again with water. Removal of the solvent provided a dark yellow viscous liquid. This liquid residue 6a which showed a distinctly different appearance on the TLC was used directly for the further conversion.

YIELD : 4.51 g (89%).
EXPERIMENT NO 8: 2,2-Dimethyl-6,7-dimethoxy-2H-benzo[b]pyran 7a

2,2-Dimethyl-6-oxyformyl-7-methoxy-2H-benzo[b]pyran 6a (1.5 g, 0.0064 mol) was dissolved in aqueous KOH (20 ml, 10.0%). To this reaction mixture dimethyl sulphate (0.9 ml, 1.2 g, 0.0095 mol) was added dropwise under stirring at 65-70°C. The mixture was stirred for 30 minutes at the same temperature. It was then cooled to room temperature and extracted with diethyl ether. Removal of ether left a dark red residue. This was purified by column chromatography using n-hexane as the eluent. This furnished Precocene II 7a as a pale yellow liquid which was found to be neutral (insoluble in dil. aq. NaOH).

YIELD: 1.20 g, (82%).

EXPERIMENT NO 9: 2,2-Dimethyl-6-ethoxy-7-methoxy-2H-benzo[b]pyran 7b

2,2-Dimethyl-6-ethoxy-7-methoxy-2H-benzo[b]pyran 6a (1.5 g, 0.0064 mol) was dissolved in aqueous KOH (20 ml, 10.0%). To this reaction mixture diethyl sulphate (0.9 ml, 1.2 g, 0.0095 mol) was added dropwise under stirring at 65-70°C. The mixture was stirred for 30 minutes at the same temperature. It was then cooled to room temperature and extracted with diethyl ether. Removal of ether left a dark red residue. This was purified by column chromatography using n-hexane as the eluent. This furnished Precocene II 7b as a pale yellow liquid which was found to be neutral (insoluble in dil. aq. NaOH).
2,2-Dimethyl-6-oxyformyl-7-methoxy-2H-benzo[b]pyran 6a (1.5 g, 0.0064 mol) was dissolved in aqueous KOH (20 ml, 10%). To this reaction mixture freshly distilled diethyl sulphate (1.30 ml, 1.48 g, 0.0096 mol) was added dropwise under stirring at 65-70°C. The reaction mixture was further stirred at the same temperature for 30 minutes. When the TLC indicated the completion of the conversion the mixture was allowed to attain room temperature and was extracted with ether. The extract was washed with water. Removal of the solvent provided a brownish-black liquid residue. It was purified by column chromatography using n-hexane as the eluent to furnish 7b as a colourless oil.

**YIELD:** 1.21 g (79%).

**EXPERIMENT NO 10:** 2,3-Dihydro-2,2-dimethyl-7-ethoxy-4H-benzopyran-4-one 3c

2,2-Dimethyl-7-hydroxy-4H-benzopyran-4-one 3a (20 g, 0.00104 mol) was dissolved in dry acetone (200 ml). To this solution freshly distilled diethyl-sulphate (16.40 ml, 19.3 g, 0.065 mol) was added and following the procedure described in experiment no. 4 a pale yellow semisolid was obtained. It solidified on standing.
M.P. : 58°

YIELD : 19.69 g, (86%)

EXPERIMENT NO 11 : 2,2-Dimethyl-7-ethoxy-2H-benzo[b]pyran 4b

Chromanone 3c (15 g, 0.068 mol) was dissolved in dry ether (50 ml) and the resultant solution was added dropwise under nitrogen atmosphere to a well stirred slurry of LAH (2.60 g, 0.068 mol) and dry ether (100 ml). Following the procedure of experiment no. 5, a pale yellow oil was obtained.

YIELD : 10.81 g, (78%).

EXPERIMENT NO 12 : 2,2-Dimethyl-6-formyl-7-ethoxy-2H-benzo[b]pyran 5b
2,2-Dimethyl-7-ethoxy-2H-benzo[b]pyran 4b (8.00 g, 0.039 mol) was added slowly, dropwise into an ice cold complex prepared from N,N-dimethylformamide (3.00 ml, 2.85 g, 0.039 mol) and phosphorous oxychloride (3.60 ml, 5.96 g, 0.039 mol) under stirring. The reaction mixture was then allowed to attain room temperature. It was then heated at 80-85°C on water bath for 3 hours. The dark red mixture was then cooled to room temperature and then was poured into a saturated solution of sodium acetate (150 ml). A red oil separated which was extracted using ether and washed with water. Removal of ether provided a dark red liquid residue which was purified by column chromatography using n-hexane as the eluent. Thus 5b was obtained as a dark brown liquid.

**YIELD:** 7.190 g, (79%).

**EXPERIMENT NO 13 : 2,2-Dimethyl-6-oxyformyl-7-ethoxy-2H-benzo[b]pyran 6b**

![Chemical Structure]

2,2-Dimethyl-6-formyl-7-ethoxy-2H-benzo[b]pyran 5b (5.00 g, 0.02 mol) was added to a well stirred mixture of dichloromethane (50 ml), hydrogen peroxide (6.00 ml, aq. 30%) and freshly sublimed SeO₂ (0.19 g, 0.0017 mol) at room temperature. This reaction mixture was then stirred at room temperature for 36 hours. The progress of the reaction was monitored by TLC. The mixture was then washed with water, saturated aq. NaHCO₃ and again
with water. Removal of the solvent furnished a brown residue. It was used directly for the further conversion.

**YIELD :** 4.60 g, (85%).

**EXPERIMENT NO 14: 2,2-Dimethyl-6-methoxy-7-ethoxy-2H-benzo[b]pyran 7c**

![Chemical structure](image)

2,2-Dimethyl-6-oxoformyl-7-ethoxy-benzo[b]pyran 6b (1.50 g, 0.006 mol) was dissolved in aq. KOH (20 ml, 10%). To this solution freshly distilled dimethyl sulphate (1.20 ml, 1.38 g, 0.0089 mol) was added dropwise under stirring at 65-70°C. Following the procedure and work up described in experiment no. 8 a pale yellow oil of 7c was obtained.

**YIELD :** 1.10 g, (76%).

**EXPERIMENT NO. 15 : 2,2-Dimethyl-6,7-diethoxy-2H-benzo[b]pyran 7d**

![Chemical structure](image)
2,2-Dimethyl-6-oxoformyl-7-ethoxy-2H-benzo[b]pyran 6b (1.50 g, 0.006 mol) was dissolved in aq. KOH (20 ml, 10%). To this reaction mixture freshly distilled diethyl sulphate (1.20 ml, 1.38 g, 0.0089 mol) was added dropwise under stirring at 65-70\(^{\circ}\)C. A brownish yellow oil was obtained using the procedure described in experiment no. 9.

YIELD: 1.12 g, (72%)

EXPERIMENT NO 16: 3,4-Dihydro-2,2-dimethyl-7-hydroxy-2H-benzopyran 8a

\[
\begin{align*}
\text{HO} & \quad \text{Zn-Hg/HCl} \quad \text{HO} \\
3a & \rightarrow 8a
\end{align*}
\]

2,3-Dihydro-2,2-dimethyl-7-hydroxy-benzopyran-4-one 3a (20.0 g, 0.104 mol) was added to an amalgum prepared from activated zinc powder (60.0 g), HgCl\(_2\) (1.8 g, 0.0062 mol) and 100 ml 5% HCl. To this mixture HCl (250 ml, 1:1) was added and the mixture was heated to reflux for 4 hours. Additional HCl (70 ml, 1:1) was then added and the mixture was further refluxed for 2 hours. A colour change was noticed from dark yellow to colourless in the initial 15 minutes of heating. The course of the reaction was monitored by TLC. The reaction mixture was then cooled, extracted with diethyl ether and washed with water. It was dried using
anhydrous Na$_2$SO$_4$. Removal of the solvent gave a thick pale yellow liquid which gradually solidified on standing. This pale yellow solid was further purified by column chromatography using n-hexane as the eluent. A white solid was obtained which was crystallized from the eluent itself to provide 8a.

**YIELD:** 15.20 g, (82%)

**M.P.:** 71° (lit$^{39}$ m.p. 68-70°)

**PMR:**

- 1.31 s 6H $-\text{C(CH}_3\text{)}_2$
- 1.76 t (J=6) 2H $-\text{CH}_2$
- 2.69 t (J=6) 2H $-\text{CH}_2\text{Ar}$
- 5.03 s 1H $-\text{OH}$ (exchangeable)
- 6.27-6.35 m 2H $-\text{C}_6\text{-H, C}_8\text{-H}$
- 6.88 d (J=7) 1H $-\text{C}_5\text{-H}$

**EXPERIMENT NO 17:** 3,4-Dihydro-2,2-dimethyl-7-methoxy-benzo[b]-pyran 8b

Compound 8a (12.0 g, 0.067 mol) was dissolved in 10% aq.KOH (80 ml). To this solution dimethyl sulphate (11.70 ml, 15.60 g, 0.12 mol) was simultaneously added with KOH (40 ml, 10%) dropwise
under stirring at 80°. The reaction mixture was further heated at 80° for 3 hours. It was then cooled and extracted with ether. The ether layer was successively washed with water, 2% NaOH and again water. Then it was dried over anhydrous Na₂SO₄ and concentrated. A yellow liquid was obtained which after purification by distillation furnished 8b as a pale yellow liquid.

**YIELD**: 11.65 g, (90%).

**B. P.**: 131° (8 mm of Hg).

**PMR**:

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**EXPERIMENT NO. 18**: 3,4-Dihydro-2,2-dimethyl-6-formyl-7-methoxy-benzo[b]pyran 9a

Compound 8b (5.0 g, 0.026 mol) was formylated using N,N-dimethyl-formamide (1.90 g, 2.01 ml, 0.026 mol) and phosphorous oxychloride (4.0 g, 2.43 ml, 0.026 mol) by following the procedure described in **Experiment No. 6**. The reaction was
complete within 3 hours. Work up provided 9a as a pale yellow solid which was crystallized from hexane-ethyl acetate.

YIELD : 4.20 g, (74%).

M. P. : 74° (lit39 m. p. 76-77°)

EXPERIMENT NO. 19 : 3,4-Dihydro-2,2-dimethyl-6-oxyformyl-7-

methoxy-benzo[b]pyran 10a

Aldehyde 9a (3.00 g, 0.014 mol) was dissolved in CH₂Cl₂ (50.00 ml). To this mixture H₂O₂ (3.50 ml, 30%) was added along with freshly sublimed SeO₂ (0.120 g, 0.001 mol). Following the procedure described in experiment no 7, the formate ester 10a was obtained as brown oil. It was directly used for further reaction.

YIELD : 2.81 g, (87%).
EXPERIMENT NO 20: 3,4-Dihydro-2,2-dimethyl-6-hydroxy-7-methoxy-benzo[b]pyran 10c

Compound 10a (2.00 g, 0.008 mol) was dissolved in methanolic KOH (30.00 ml, 5%). The clear solution so obtained was refluxed for 20 minutes. Methanol was then removed and the residue was acidified. A brown oil separated which was extracted using ether and purified by column chromatography. This provided 10c as a pale yellow solid.

M.P. : 80°

YIELD : 1.55 g (88%).

EXPERIMENT NO 21: 3,4-Dihydro-2,2-dimethyl-6,7-dimethoxy-benzo[b]pyran 11a.
Phenol 10c (0.50 g, 0.0024 mol) was dissolved in KOH (aq. 10%, 5.00 ml). To this solution DMS (0.34 ml, 0.45 g, 0.0036 mol) was added and the mixture was stirred at room temperature. The reaction was complete within 45 minutes as indicated by the TLC. The product was extracted using ether. Finally following the usual procedure the chroman 11a was obtained as a pale yellow oil after column chromatography using hexane.

M. P. : 55° (lit m. p. 57.5-58°)

YIELD : 0.37 g, (69% based on structure 11a).

EXPERIMENT NO 22 : 2,2-Dimethyl-6,7-dimethoxy-benzo[b]pyran 7a.

Chroman 11a (0.20 g, 0.0009 mol) was dissolved in 1,4-dioxane (10.00 ml). To the resulting solution DDQ (0.20 g, 0.0009 mol) was added and the mixture was refluxed for 6 hours. Solvent was then removed and the yellow residue was column chromatographed. Pale yellow oil 7a was obtained.

YIELD : 0.12 g, (61%).
EXPERIMENT NO 23: 3,4-Dihydro-2,2-dimethyl-6-ethoxy-7-methoxy-benzo[b]pyran 11b

Phenol 10c (0.50 g, 0.0024 mol) was subjected to etherification using KOH (aq. 5.00 ml, 10%) and diethyl sulphate (0.47 ml, 0.56 g, 0.0036 mol). Procedure described earlier in experiment no 21 was followed to obtain 11b as a pale yellow liquid.

YIELD: 0.41 g (72%).

PMR:

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EXPERIMENT NO 24 : 2,2-Dimethyl-6-ethoxy-7-methoxy-benzo[b]pyran

\[ 7b \]

Chroman \(11b\) (0.5 g, 0.0021 mol) was reacted with DDQ (0.48 g, 0.0021 mol) using 1,4-dioxane (10 ml) as the solvent by following the procedure as described in experiment no 22. Purification by column chromatography provided the chromene \(7b\) as colourless oil.

YIELD : 0.350 (65%).

EXPERIMENT NO 25 : 3,4-Dihydro-2,2-dimethyl-7-ethoxy-benzo[b]pyran

\[ 8c \]

Phenol \(8a\) (10 g, 0.056 mol) was subjected to etherification following the procedure described in experiment no 17 using KOH (aq. 150 ml, 10%) and diethyl sulphate (11.00 ml, 12.97 g, 0.084 mol). Work up provided a yellow liquid \(8c\) which was purified by
column chromatography.

YIELD : 9.60 g (83% based on the structure 8c).

EXPERIMENT NO 26 : 3,4-Dihydro-2,2-dimethyl-6-formyl-7-ethoxy-
benzo[b]pyran 9b

Chroman 8c (7.00 g, 0.034 mol) was reacted with a complex of
DMF (2.61 ml, 2.48 g, 0.034 mol) and POCI3 (3.20 ml, 5.20 g, 0.034
mol) using the procedure of experiment no 6. Usual work up
provided 9b as a brown liquid. It was purified by column
chromatography.

YIELD : 5.65 g (71%).

EXPERIMENT NO 27 : 3,4-Dimethyl-6-oxyformyl-7-ethoxy-
benzo[b]pyran 10b

Aldehyde 9b (5.00 g, 0.021 mol) was reacted under the
conditions described in experiment no 7 using CH2Cl2 (50 ml), H2O2
(5.50 ml, 30%) and SeO2 (0.19 g, 0.0017 mol). Usual work up
afforded 10b as a brown liquid.

**YIELD**: 4.20 g (79%).

**EXPERIMENT NO 28** : 3,4-Dihydro-2,2-dimethyl-6-methoxy-7-ethoxy-benzo[b]pyran 11c

Chroman 10b (1.50 g, 0.006 mol) was added to a warm KOH solution (50°, 5%, 20 ml). After 20 minutes DMS (0.85 ml, 1.10 g, 0.0087 mol) was added to the same reaction mixture. It was then stirred (45 minutes) and allowed to attain the room temperature. Product was extracted using ether and purified by column chromatography which furnished 11c as a pale yellow oil.

**YIELD**: 0.86 g, (61%).

**PMR**:

| 1.31-1.50  | m  | 9H  | -C(CH₃)₂, -CH₃ |
| 1.77       | t   | 2H  | -CH₂         |
| 2.70       | t   | 2H  | -CH₂-Ar     |
| 3.85       | s   | 3H  | -OCH₃        |
| 4.10       | q   | 2H  | -O-CH₂-CH₃  |
| 6.49       | s   | 1H  | -C₈-H       |
| 6.69       | s   | 1H  | -C₅-H       |
EXPERIMENT NO 29: 2,2-Dimethyl-7-ethoxy-6-methoxy-benzo[b]pyran

Chroman 11c (0.5 g, 0.0021 mol) was dehydrogenated using DDQ (0.480 g, 0.0021 mol) and 1,4-dioxane (10 ml) by following the conditions as described in experiment no 22. The product was purified by column chromatography using n-hexane as the eluent. Chromene 7c was thus obtained as a pale yellow liquid.

YIELD: 0.320 g (65%).

EXPERIMENT NO 30: 3,4-Dihydro-2,2-dimethyl-6,7-diethoxy-benzo[b]pyran 11d

Compound 10b (0.500 g, 0.0021 mol) was etherified by using aq. KOH (10 ml, 5%) and diethyl sulphate (0.46 g, 0.4 ml, 0.003 mol) under the conditions as described in experiment no 28. Chroman 11d was obtained as a pale yellow liquid.

YIELD: 0.440 g (82%).
EXPERIMENT NO 31: 2,2-Dimethyl-6,7-diethoxy-benzo[b]pyran 7d

Chroman 11d (0.2 g, 0.0008 mol) was dehydrogenated using DDQ (0.180 g, 0.0008 mol) in 1,4-dioxane (10 ml) by the conditions as described in experiment no 22. Usual work up and purification by column provided the chromene 7d as a colourless oil.

YIELD: 0.120 g (60.6%) 

EXPERIMENT NO 32: 2,3-Dihydro-2,2-dimethyl-6-formyl-7-methoxy-4H-benzopyran-4-one 12

Compound 9a (0.5 g, 0.0027 mol) was dissolved in a well stirred mixture of diethyl ether (50 ml), acetic acid (50 ml) and water (50 ml). Ammonium Cerium (IV) Nitrate (7.124 g, 0.013 mol) was added portionwise to this mixture. The reaction mixture was heated on water bath till the colour changed from orange to yellow
(20 minutes). The mixture was cooled and diluted with water (150 ml). The solid thus obtained was extracted with ethyl acetate. The ether layer was successively washed with water, sat. bicarbonate solution (60 ml) and again water (75 ml). The ether layer was dried over anhydrous Na₂SO₄, filtered and concentrated. A pale yellow solid was obtained which was purified by column chromatography using hexane-ethyl acetate and then was recrystallized from the same solvent system. Chromanone 12 was obtained in the form of pale yellow crystals whose structure was confirmed by spectral analysis as described earlier.

M. P. : 145°.

YIELD : 0.430 g (82%).

EXPERIMENT NO. 33 : 2,3-Dihydro-2,2-dimethyl-6-hydroxy-7-methoxy-4H-benzopyran-4-one 13

\[
\begin{align*}
\text{12} & \xrightarrow{i) H_2O_2/CH_2Cl_2} \text{13} \\
& \xrightarrow{ii) \text{alc. KOH}} \text{13} \\
& \xrightarrow{iii) H_3O^+} 
\end{align*}
\]

Compound 12 (0.3 g, 0.0013 mol) was added to a well stirred mixture of dichloromethane (5 ml), hydrogen peroxide (0.3 ml, 30%) and SeO₂ (0.011 g, 0.0001 mol, freshly sublimed). This biphasic system was stirred at room temperature for 36 hours. It was then filtered, washed with water, saturated NaHCO₃ and again with water. Drying of the organic layer and removal of the solvent
provided a brown residue was obtained. To this residue 5% alcoholic KOH (5 ml) was added and the mixture was warmed on water bath for 5 minutes. Alcohol was removed and water was added to the residue. This was acidified using (1:1) HCl. This provided a yellow solid which was recrystallized from hexane-ethyl acetate to give compound 13 as an off-white solid. Its structure was confirmed by spectral and elemental analysis as described earlier.

**YIELD**: 0.250 g (88%)

**M. P.**: 136° (lit^20 m. p. 136°).

**EXPERIMENT NO 34 : 2,4-Dihydroxy-5-acetyl-acetophenone 22**

Resorcinol 1 (3.00 g, 0.027 mol) was dissolved in acetic anhydride (10 ml, freshly distilled). To this solution freshly fused powdered ZnCl₂ (3.0 g, 0.022 mol) was added and the reaction mixture was heated at 142°. The heating was continued for 20 minutes and then the resultant dark red solution was allowed to attain room temperature. It was slowly poured into cold 1:1 HCl (50 ml). A dark red solid was obtained which was recrystallized from dilute ethanol to furnish dark yellow rediacetophenone 22.
M. P.: 178° (lit 178° m.p. 178°)

YIELD: 2.70 g (51%).

EXPERIMENT NO 35: 2,3-Dihydro-2,2-dimethyl-6-acetyl-7-hydroxy-4H-benzopyran-4-one 23

Resdiacetophenone 22 (1.0 g, 0.005 mol), acetone (0.01 mol, 1.00 ml) and pyrrolidine (0.0025 mol) were refluxed using benzene (50 ml) as a solvent in a Dean Stark separator. The completion of the reaction was monitored by TLC. The conversion was complete within 40 hours. Usual work up as described in experiment no 2 provided a pale yellow solid which after column chromatography and recrystallization from dilute ethanol gave the chromanone 23 as a shining white solid.

M. P.: 119°.

YIELD: 0.880 g (73%).
EXPERIMENT NO 36 : 2,3,6,7-Tetrahydro-2,2,8,8-tetramethyl-4H,8H-benzo[1,2-b:5,4-b']dipyran-4-one 24

A mixture of 7-hydroxy chroman 8a (2.0 g, 0.0112 mol), β,β-dimethyl acrylic acid (1.12 g, 0.0112 mol) and freshly fused powdered ZnCl₂ (2.0 g, 0.0146 mol) was dissolved in phosphorous oxychloride (20 ml) under stirring. The reaction mixture was kept overnight at room temperature. The resultant dark red viscous liquid was poured over crushed ice (200 g). A yellow solid was obtained which was further purified by column chromatography and recrystallization from the eluent itself n-hexane-ethyl acetate to furnish pale yellow needles of 24.

M. P. : 86° (lit²² 86-87°).

YIELD : 1.860 g (64%).

EXPERIMENT NO 37 : 2,3-Dihydro-2,2,8,8-tetramethyl-4H,8H-benzo[1,2-b:5,4-b']dipyran-4-one 17
Compound 24 (0.400 g, 0.0015 mol) was added to a mixture of DDQ (0.420 g, 0.0018 mol) and 1,4-dioxane (70 ml). The mixture was refluxed for 7 hours. The solvent was removed and the dark brown solid residue was purified by vacuum sublimation. The chromene 17 was obtained in the form of pale yellow needles.

M. P. : 106°.

YIELD : 0.250 g (62%).

EXPERIMENT NO 38 : 6,7-Dihydro-2,2,8,8-tetramethyl-2H-8H-benzo[1,2-b:5,4-b']dipyran 15

\[ \begin{array}{c}
\text{i) LAH/ether} \\
\text{ii) H}_2\text{O}^+ \\
\end{array} \]

Compound 24 (0.500 g, 0.0019 mol) was reduced by LAH (0.110 g, 0.0028 mol) in dry ether (50 ml) under the conditions as described in experiment no 5. The reaction was complete within 1.5 hours. The alcohol thus formed was dehydrated in situ by 4N HCl. Work up followed by purification by column chromatography provided the chromene 15 as a pale yellow liquid which further solidified on standing and was recrystallized using hexane-ethyl acetate.

M. P. : 56°. (lit. 22 m.p. 55-56°).

YIELD : 0.420 g (89%).
EXPERIMENT NO 39 : 2,3,7,8-Tetrahydro-2,2,8,8-tetramethyl-4H,6H-benzo[1,2-b:5,4-b']dipyran-4,6-dione 21

Compound 24 (0.3 g, 0.00115 mol) was added to a mixture of ether (30 ml), water (30 ml) and acetic acid (30 ml). To this solution CAN (3.790 g, 0.0069 mol) was added portionwise and under stirring. The resulting dark orange solution was heated on water bath for 30 minutes. The completion of the reaction was indicated by the colour change from orange to pale yellow. The solution was diluted with water (100 ml) and then extracted with ethyl acetate. The organic layer was successively washed with water, saturated NaHCO₃ and again water. The ethyl acetate layer was dried over anhydrous Na₂SO₄ and concentrated. The dark yellow solid thus obtained was purified by column chromatography and recrystallized from hexane-ethyl acetate which furnished compound 21 as a white
crystalline solid.

**M. P. :** 176° (lit²⁹ 179°)

**YIELD :** 0.250 g (75%).

**EXPERIMENT NO 40 :** 2,2,8,8-Tetramethyl-2H,8H-benzo[1,2-b:5,4-b']

**dipyran 16**

The dipyran dione 21 (0.200 g, 0.00073 mol) was reduced and dehydrated under N₂ atmosphere using LAH (0.100 g, 0.0026 mol) in dry ether (10 ml) by following the procedure as described in experiment no 5. Usual work up and purification by column chromatography provided the product 16 as a pale yellow solid which was further recrystallized from hexane-ethyl acetate.

**M. P. :** 77° (lit.¹⁹ m.p. 77°)

**YIELD :** 0.140 g (78%).
EXPERIMENT NO 41 : 3,4-Dihydro-2,2-dimethyl-6-bromo-7-hydroxy-benzo[b]pyran 29

7-Hydroxy chroman 8a (0.5 g, 0.0028 mol) was dissolved in glacial acetic acid (10 ml) and to this solution a solution of bromine (0.448 g, 0.14 ml, 0.0028 mol) in glacial acetic acid (5 ml) was added dropwise under stirring within 15 minutes and at 5-10°C. The contents were stirred further while the course of the reaction was followed by TLC. The reaction was complete after 20 minutes. The reaction mixture was poured into ice cold water (100 ml). A dark brown solid was obtained which was purified by column chromatography using n-hexane as the eluent. The pale yellow solid obtained was recrystallized from hexane-ethyl acetate.

M. P. : 116°C

YIELD : 0.430 g (60%).
EXPERIMENT NO 42 : 2,3,7,8-Tetrahydro-2,2,6,6-tetramethyl-10-bromo-2H,6H-benzo[1,2-b:3,4-b']dipyran-4-one 30

![Chemical Structure of Compounds 29 and 30]

Compound 29 (0.4 g, 0.0015 mol) was reacted with β,β-dimethyl acrylic acid (0.150 g, 0.0015 mol) in presence of freshly fused ZnCl₂ (0.4 g, 0.0029 mol) and POCl₃ (10 ml) under the conditions as described in experiment no 36. Usual work up provided a solid which on purification by column chromatography furnished compound 30 as a pale yellow solid.

M. P. : 95-96°C

YIELD : 0.280 g (53%).

EXPERIMENT NO 43 : 4-Methyl-7-hydroxy coumarin 31

![Chemical Structure of Compounds 1 and 31]

Resorcinol (20 g, 0.182 mol) was mixed with ethyl acetoacetate (23.66 g, 23.2 ml, 0.182 mol) and this slurry was added dropwise to concentrated H₂SO₄ (200 ml) kept at 5°C. The temperature was maintained at 5-10°C during the addition. After
the completion of the addition the reaction mixture was kept overnight at room temperature. Then it was poured over crushed ice under stirring. The pale yellow product was filtered, washed twice with water and dried. When recrystallized from 95% ethanol, 4-methyl-7-hydroxy-coumarin was obtained as colourless needles.

M. P. : 182°C (lit38a m.p. 183°C)  
YIELD : 28.0 g (87%)

EXPERIMENT NO 44 : 7-Acetoxy-4-methyl-coumarin 32

7-Hydroxy-4-methyl-coumarin (25 g, 0.142 mol) was added portionwise to freshly distilled acetic anhydride (125 ml) with vigorous stirring and at room temperature. The reaction was highly exothermic and as soon as the addition was complete the temperature of the reaction mixture started dropping and a white solid separated out. The reaction mixture was diluted with cold water and the product was filtered out, washed with water and then dried. It was recrystallized from 95% ethanol in the form of white crystalline solid.

M. P. : 152°C (lit38a m.p. 150-1°C)  
YIELD : 28.8 g (93%).
EXPERIMENT NO 45 : 8-Acetyl-7-hydroxy-4-methyl-coumarin 33

7-Acetoxy-4-methyl-coumarin (22.0 g, 0.101 mol) was thoroughly mixed with powdered anhydrous AlCl₃ (66.0 g, 0.496 mol) and the mixture was heated at 150°C for one hour. The resulting reaction mixture was slowly decomposed over cold dilute HCl (10%, 400 ml). A pale yellow solid separated out. It was filtered, washed with water and dried. It was crystallized from hexane-ethanol to furnish the desired 8-acetyl coumarin as cream colored crystalline compound.

M. P. : 162°C (lit 38a m.p. 162-3°C)

YIELD : 15.850 g (72%).

EXPERIMENT NO 46 : 2,6-Dihydroxy acetophenone 34

To a suspension of 8-acetyl-7-hydroxy-4-methyl-coumarin (14.80 g, 0.0680 mol) in distilled water (50 ml) was added a solution of NaOH (12.90 g, 0.323 mol) in distilled water (50 ml) dropwise through a dropping funnel and under N₂ atmosphere. After
heating the reaction mixture on steam bath for 5 hours it was cooled and then acidified by 1:1 dilute HCl. Atmosphere of N₂ was maintained throughout the reaction. Pale brown product precipitated out on acidification was filtered, washed with cold water and dried. It was crystallized from dilute ethanol.

M. P. : 154° (lit\(^{38a}\) 154-5°)

YIELD : 7.600 g (74%).

EXPERIMENT NO 47 : 2,3-Dihydro-2,2-dimethyl-5-hydroxy-4H-benzopyran-4-one 28

A mixture of 2-acetyl resorcinol 34 (2.0 g, 0.013 mol), acetone (0.760 g, 1.00 ml) and freshly distilled pyrrolidine (0.467 g, 0.5 ml, 0.0065 mol) in dry benzene (50 ml) was refluxed using Dean Stark separator for 4 hours. The reaction mixture was filtered and washed with dilute HCl. The solvent was dried over Na₂SO₄, filtered, removed and the residue was column chromatographed. 5-hydroxy chromanone 28 was obtained as a white solid.

M. P. : 79° (lit\(^{26}\) m.p.79°)

YIELD : 2.0 g (79%).
EXPERIMENT NO 48: 3,4-Dihydro-2,2-dimethyl-5-hydroxy-2H-benzo[b]pyran 35

5-Hydroxy chromanone 28 (1.0 g, 0.0052 mol) was reduced using activated zinc powder (5.0 g), HgCl₂ (0.150 g, 0.005 mol) and 1:1 HCl (30 ml) under Clemmenson conditions as described in experiment no 16. Usual work up provided 5-hydroxy chroman 35 as a dense yellow liquid.

YIELD: 0.700 g (76%).

PMR:

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Zn-Hg/HCl, Δ
EXPERIMENT NO 49 : 2,3,9,10-Tetrahydro-2,2,8,8-tetramethyl-4H,8H-
benzo[1,2-b:3,4-b']dipyran-4-one 25

5-Hydroxy chroman 35 (0.5 g, 0.0028 mol) was reacted with 8,8-acrylic acid (0.280 g, 0.0028 mol) in presence of freshly fused ZnCl₂ (0.5 g, 0.0036 mol) and PCl₃ (7.0 ml) by the procedure followed in experiment no 36. A brown semi-solid was obtained which on purification by column chromatography using hexane as the eluent provided 25 as a pale yellow solid.

M. P. : 117°C (lit m.p. 117-118°C)

YIELD : 0.5 g (69%).

IR : 1682

PMR

| 1.35  | s    | 6H   | -C(CH₃)₂       |
| 1.61  | s    | 6H   | -C(CH₃)₂       |
| 1.90  | t (J=7) | 2H  | -CH₂           |
| 2.83  | m    | 4H   | 2 x -CH₂       |
| 6.80  | d (J=10) | 1H  | -C₆-H          |
| 8.13  | d (J=10) | 1H  | -C₅-H          |
EXPERIMENT NO 50 : 9,10-Dihydro-2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b:3,4-b']dipyran 18

Chromanone 25 (0.20 g, 0.00076 mol) was dissolved in dry ether (5.00 ml) and the solution was added dropwise to a well stirred mixture of ether (50.00 ml) and LAH (0.100 g, 0.0026 mol). Following the procedure of experiment 5 a pale yellow liquid was obtained after column chromatography.

YIELD : 0.15 g (79%).

EXPERIMENT NO 51 : 2,3,6,7-Tetrahydro-2,2,6,6-tetramethyl-4H,8H-benzo[1,2-b:3,4-b']dipyran-4,8-dione 27

Compound 25 (0.200 g, 0.00076 mol) was dissolved in a mixture of ether, acetic acid and water (20 ml each) and CAN (2.5 g, 0.0046 mol) was added to this solution. The reaction was carried out under the conditions as described in experiment no 39. Work up provided a yellow solid which was recrystallized from hexane-ethyl acetate.
M. P. : 161° (lit 161°).

YIELD : 0.170 (78%)

EXPERIMENT NO 52 : 2,2,6,6-Tetramethyl-2H,6H-benzo[1,2-b:3,4-b'] dipyran 19

Benzodipyrandione 27 (0.10 g, 0.00073 mol) was reduced with LAH (0.10 g, 0.026 mol) using the procedure described in experiment no 5. Work up followed by column chromatography using hexane provided compound 19 as a pale yellow liquid.

YIELD : 0.06 g (72%).
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