Chapter 1
CHAPTER - 1

1.1. General Introduction

There are innumerable groups of organic compounds in nature. Of all the groups heterocyclic system plays the most vital role in the lives of animals and plants. Nearly one half of the organic compounds have heterocyclic rings in their structure, which play a significant role in the metabolic activities of all living cells. Mechanistic investigations have enhanced our understanding of these compounds. Heterocyclic compounds are made use of in medicine, agriculture and genetics. They possess properties like brilliant colouring as found in flowers and fruits and poisonous or herbal properties as found in plants and herbs. These properties have attracted many inquiring minds, leading to indepth research studies which have yielded interesting findings.

Oxygen containing heterocyclic compounds constitute one of the most important and fascinating groups of substances among heterocyclic compounds. Some of the structural patterns of these compounds are chromones, coumarins, chalcones, flavones, xanthones, rotenoids and pterocarpens¹ (Chart 1.1, Page.No.2). In fact, the biological relationship of these compounds have drawn the attention of organic chemists for a long time. Adoption of new analytical techniques in organic chemistry such as chromatography, UV, IR, NMR and mass spectrometry has resulted in achieving remarkable progress in establishing their structures and arriving at their synthesis. Physiological activity exhibited by some of those structures has given added significance to their chemistry (discussed in section 1.3). One of the extensions of this pattern is those heterocyclic compounds which have a 2,2-dimethyl -2H-pyran ring embedded in their structure.
CHART 1.1

1. Chalcone

2. Flavone

3. Flavanone

4. Coumarin

5. Chromone

6. Xanthone

7. Isoflavone

8. Flavonol

9. Xanthyletin
1.2. **Structural Determination and Synthesis of Chromones and Flavonoids**

The structural elucidation of chromones and flavonoids has been determined by chemical and by physical methods.

**i) Chemical method**

(a) **Chromones**

When chromones (1) are heated with aqueous alkali \(^2\) or sodium ethoxide \(^3\), the pyrone ring opens and a 2-hydroxyphenyl alkylketone (2) is formed. This method has been employed frequently for characterising a chromone and distinguishing it from a coumarin. The other examples \(^4\)\(^5\)\(^6\) for the degradation process of chromone is as given in Chart 1.2 (Page No.4).

(b) **Flavonoids**

Flavones

The chemical method \(^7\) employed for structural determination for flavones (6) is alkaline hydrolysis. The reaction proceeds via an intermediate β-dicarbonyl compound (7) which can break down in a number of ways (Chart 1.2).

Flavonols

3-Methoxylated flavones on treatment with hydrogen bromide give α-hydroxy ketones which reduce Tollen’s and Fehling’s reagents and form osazones. Once a compound is thus recognised as a flavonol, it is usually submitted to alkaline degradation (Chart 1.3, Page No.5).

3-Alkoxyflavone (8) on degradation with alkali cleaves into 2-alkoxy -2′-hydroxy-acetophenone (9) and benzoic acid \(^8\) (10). Isorhamnetin on oxidative cleavage \((O_2+\) alkaline solution) gives phloroglucinol and vanillic acid \(^9\). Europtin (11) on reductive cleavage (using Na-Hg) gives a mono methylether of phloroglucinol (12), 3,4,5 - trihydroxyphenyl propionic acid (13) and 3,4,5-trihydroxyphenyl propanol \(^10\) (14) (Chart 1.3).
Structural determination of chromones and flavonoids

(a) Chromones

\[
\begin{align*}
R_3 & \quad R_1 \quad \text{(i)} \text{OH}^- \quad \text{(ii)} \text{H}^+ \quad R_3 \quad R_1 \text{COOH} \\
& \quad \quad \quad \quad \quad \quad \text{OH} \quad \text{COCH}_2R_2 \\
1 & \quad \quad \quad \quad \quad \quad 2 \\
\end{align*}
\]

(b) Flavonoids

Flavones

\[
\begin{align*}
\text{HO} & \quad \text{O} \quad \text{CH}_3 \\
\text{Br} & \quad \text{Br} \\
3 & \quad \quad \quad \quad \quad \quad 4 \\
\text{(i)} \text{OH}^- \quad \text{(ii)} \text{H}^+ \\
& \quad \quad \quad \quad \quad \quad \text{Br} \quad \text{Ac} \\
& \quad \quad \quad \quad \quad \quad \text{HO} \quad \text{OH} \\
& \quad \quad \quad \quad \quad \quad \text{5} \\
\end{align*}
\]
CHART 1.3

Flavonols

Alkaline degradation

[Chemical reactions and structural formulas are shown, depicting the degradation process of flavonols under alkaline conditions.]

ArCOOH

O2 + alkaline

solution

ArCOOH

10

+
Needles to say, there has been a considerable effort to replace these tedious degradation studies of structure determination by physical methods (spectroscopy).

ii) Physical methods

UV spectroscopy

(a) Chromones

The ultraviolet spectra of most of the substituted chromones are similar to that of chromones \(^{11,12}\). The absorption band showed peaks at 285, 290, 296 and 301 nm (in cyclo hexane).

(b) Flavonoids

The ultraviolet spectra \(^{13,14}\) of most flavonoids, consist of two major absorption bands, the one at 300 - 400 nm (band I) is considered to arise from the cinnamoyl system (ring B), whilst the maximum in the region 240-245 nm (band II) is associated with ring A, the benzoyl moiety.

It is often possible to distinguish the various types of flavonoids by examination, particularly of the band I absorption. Thus, flavone (15) absorbs at 300-350 nm, whilst in flavonol (16) this peak occurs in the region 350-385 nm as shown below,
IR spectroscopy

(a) Chromones

2-Methylchromones show absorption of infrared radiation at 1665 cm⁻¹ for 2-methyl, 1658 cm⁻¹ for 3-methyl and 1670 cm⁻¹ for chromone part. But in solid state the frequencies of radiation appeared at low values. In potassium bromide disk or as a nujol mull, chromone absorbs at 1617 cm⁻¹, 2-methyl at 1643 cm⁻¹, 3-methyl at 1640 cm⁻¹.

(b) Flavonoids

Unfortunately IR spectroscopy has not proved useful because the carbonyl stretching frequency in flavones and isoflavones almost occur near 1650 cm⁻¹ and its position is not sensitive to the substitution pattern, except that when a hydroxyl group is present at C-3, peak is sometimes found at a lower frequency of 1616 cm⁻¹.

In flavonols a medium to strong band centered between 3350 and 3250 cm⁻¹ for the hydroxyl group absorption.

'\text{H-NMR spectroscopy}

(a) Chromones

The presence of an alkyl group provides additional signals to those of chromone and if one or more of the alkyl groups are attached to the benzene ring, the complex ABCD-type multiplet is simplified. The alkyl group protons resonate at 2.36 δ for 2-methylchromone, at 2.05 δ for 3-methylchromone and at 2.84 δ (CH) and 1.33 δ (CH₃) for 2-isopropylchromone, C₃ - olefinic proton resonated at 5.62 δ to 6.40 δ as a singlet.
(b) **Flavonoids**

The $^1$H-NMR spectra of flavonoids were hindered by their lack of solubility in CDCl$_3$ and CCl$_4$; progress was made following the introduction of DMSO-d$_6$ but the most of significant advance arose from the conversion of flavonoids into their more soluble trimethylsilyl ethers. Proton magnetic resonance in trimethylsilylated flavonoids normally occurs between 0 and 9 ppm, and within this range, signals may be assigned tentatively to structural features.

Two aromatic rings exert little or no influence on the spectral characteristics of each other. Ring A protons, C$_6$-H and C$_8$-H, in 5,7-dihydroxyflavonoids appear separately as doublets with coupling constant $J=2.5$ Hz in the range 5.70 - 6.70 ppm. The H-6 doublet consistently occurs at higher field than the H-8. The C$_5$ protons in the case of 7-hydroxyflavonoids are strongly deshielded by the 4-keto group and appear near 8.00 ppm, as a doublet ($J=9$Hz) due to ortho coupling with H-6. Signals for H-6 (quartet, $J=9$ and 2.5 Hz) and H-8 (doublet, $J=2.5$ Hz) occur at a lower field than that in the 5,7-dihydroxyflavonoids. The substitution pattern for ring B is rather more variable but the usual aromatic couplings are observed. In the case of 4'-oxygenated flavonoids, protons at C-2', 3', 5', and 6', due to free rotation of the B-ring, appear as two pairs of ortho coupled doublets with coupling $J=8.50$ Hz, in the range 6.50 - 7.90 ppm. The H-3',5' doublet always occurs upfield from the H-2', 6' doublet due to the shielding effect of oxygen substituent and to the deshielding influence of C-ring function on H-2' and 6'.

Flavonoids are mainly differentiated by the signal of C-3 proton of C-ring. The appearance of the signals of ring - C proton varies both with the location of the aryl ring B and with the oxidation state of the flavonoid. In flavones C-3 proton usually appears as a sharp singlet around 6.30 ppm.

In flavanones, the C$_2$ - proton appears as a quartet centered at about 5.20 ppm. The two C$_3$-protons, each gives rise to quartets due to spin-spin interaction with each other and with C$_2$-H. The quartets appear at about 2.80 ppm; however they overlap and are generally not well differentiated. In the chalcones, H$_\alpha$ and H$_\beta$ appear as
doublets (J=17 Hz) in the range 6.70 - 7.40 and 7.30 - 7.70 ppm respectively. The benzylic proton in aurones appear as a singlet in the range 6.50 - 6.70 ppm. In DMSO-d₆ aurones exhibit this signal in the range 6.30 - 6.90 ppm, the exact position being a function of the hydroxylation pattern. In the spectrum of 3,5,7-trihydroxy flavone (5,7-dihydroxyflavonol)¹⁴, hydroxyl proton resonances occur at 12.40 ppm (5-OH), 10.93 ppm (7-OH) and 9.70 ppm (3-OH). The disappearance, on addition of D₂O, of the signals observed, confirms their identity as hydroxyl proton resonances. The other proton signals of flavonol resonate more or less at the same ppm as like that of flavone.

**Mass spectroscopy**

(a) Chromones

Mass spectral fragmentation pattern of a simple chromone i.e. 2-methylchromone (17)²⁰ on bombardment with electron, gives molecular ion peak at m/e 160 and other ions of m/e 132, 131, 120, 92 and 64. The fragmentation pattern of the compound 17 is as given in Chart 1.4 (Page No.10).

(b) Flavonoids

Flavone ²¹ gives the molecular ion as the base peak with other major peaks corresponding to [M-H]⁺, [M-CO]⁺, A₁⁺, [A₁-CO]⁺, and B₁⁺. The mass fragmentation pattern of simple flavone and 5,7-dihydroxyflavone (18) is as shown in Chart 1.4. In most of the flavonol ²² aglycones molecular ion peak is the base peak. The other ions are [M-H]⁺, [M-H₂O]⁺, [M-CH₃]⁺, [M-CH₃CO]⁺ and [M-CO-H]⁺. An example 19 of this type of fragmentation pattern is explained in the Chart 1.5. (Page No.11).

1.3. Pharmacological Properties of Chromones and Flavonoids

(a) Chromones

The lack of 2,2-dialkylchromans - tocopherols (vitamin E)¹ is known to prevent the normal completion of pregnancy in rats and induce resorption of the foetus. The diprenyl substituted phenolic compounds known as the cannabinoids are the active constituents of hashish and marijuana. They are known for their
a) Mass fragmentation pattern of 2-methyl chromone

\[
\text{CHART 1.4}
\]

\[
\text{CHART 1.4}
\]

b) Mass fragmentation pattern of Flavone
CHART 1.5

(C) Mass fragmentation pattern of Flavonols

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{C}_8\text{H}_7\text{O}_3 \quad \text{m/e} 151(100\%) \\
\text{HO} & \quad \text{C}_8\text{H}_7\text{O}_3 \quad \text{m/e} 329 (5\%) \\
\text{C}=0^+ & \\
\text{C}_8\text{H}_7\text{O}_3 & \\
\text{[M-CH}_3]^+ & \quad \text{m/e 329 (5\%)} \\
\text{[M-CH}_3\text{]+} & \quad \text{m/e 326 (12\%)} \\
\text{[CO-H]} & \\
\text{[M-CO-H]} & \quad \text{m/e 315 (16\%)} \\
\text{[M-CH}_3\text{CO]} & \quad \text{m/e 301(6\%)} \\
\end{align*}
\]
medicinal as well as psychotomimetic properties. 2,2-Dimethylpyranocoumarin derivatives such as suksdorfin, dihydrosamidin and visnadin possess vasodilating properties. Rotenoids androttelerin are known for their poisonous and marked insecticidal properties. Methylallopateroxylin, 2,2-dimethylpyranochromone, showed anti-depressant properties. 2,2-Dimethylpyranocarbazole derivatives such as girinimbine have antifungal and antibiotic properties. 2,2-Dimethylpyran-acridones like acronycine, are reported to inhibit the growth of tumors. Precocenes are natural pro-allatocidins. These are known inhibitors of juvenile hormone biosynthesis in susceptible insects.

Toxicity exhibited by precocenes, particularly in vertebrates has toned down the potential interest of these compounds for insect control. But due to bioactivation and reactivity, these chromene structures are valuable models for toxicological studies. Some simple chromones are among the few non-nitrogenous compounds to show spasmolytic activity. Modern pharmacologic work has confirmed the bronchodilating and antispasmodic activity of khelin, a 2-methylchromone derivative, which was used in ancient times as a folk remedy. One of the most effective agents currently available for the treatment of the bronchial spasms attendant to asthma is a synthetic agent that incorporates the chromone moiety.

(b) **Flavonoids**

Flavonoids have been shown to be important factors in capillary resistance. They are also reported to be the anti-inflammatories and synergists of ascorbic acid. Srinivasan et al. have presented with evidence that flavonoids play an important role in the circulatory system by acting on the aggregation of erythrocytes. Flavonoids with multiple methoxy and ethoxy groups are effective inhibitors of blood cell aggregation. This aggregation of erythrocytes promote a variety of pathological effects. According to Swain and Bate-Smith, majority of the flavonoids are completely innocuous in the diet. They play a vital role in the area of plant-insect relationships. The extensive screening programmes of plant products for anticancer drugs claim that flavonoids may contribute to, or be effective in
combatting certain types of cancer. Besides all these, flavonoids are found to be active against micro-organisms; and are found to be highly specific in their activity as antimicrobials, hence may be alternatives to conventional fungicides. Unsubstituted flavone and flavanone were highly active while the hydroxylated flavonoids possess only weak activity.

Biogenesis of oxygen heterocycles is another aspect of considerable interest. They may be metabolic by-products or may be essential for the vital processes of existence and growth. Biogenetic studies have brought to lime-light, the natures pathways to synthesise these compounds. Studies with modern tools like radioactive tracers have led to a resonably clear understanding of these mechanisms.

1.4. Biosynthesis of Chromones and Flavonoids

Although the terms 'biogenesis' and 'biosynthesis' are often used without distinction, it is customery to use the former term for a hypothesis and the latter for an experimentally proven route.

The pioneering work by a number of research groups has established that benzenoid ring systems arise by two pathways: One from shikimic acid and the other from acetic acid.

(a) Shikimic Acid pathway

The shikimic acid pathway starts with the aldol condensation of phosphoenol pyruvate with a tetrose sugar. The formation of the key compound, shikimic acid, then occurs as shown in Chart 1.6. Shikimic acid formed is then transformed into aromatic compounds through prephenic acid. Usually, the aromatic rings derived from shikimic acid have the 4-, 3,4- and 3,4,5-oxygenation patterns (Chart 1.6, Page.No.14).

(b) Acetic Acid Pathway

Biologically activated acetic acid units are involved in the acetic acid pathway. These form poly-ß-ketomethylene acids, by formal elimination of water in head-to-tail linkage with each other or with naturally occurring carboxylic
(a) Shikimic acid pathway

1. Shikimic acid
2. Dehydroquinic acid
3. Dehydroshikimic acid
4. Prephenic acid
5. Phenyl pyruvic acid
6. p-Hydroxy phenyl-cinnamic acid
7. p-Hydroxy phenyl-lactic acid

CHART 1.6
acids. Ring closure by aldol condensation or C-acylation would then produce phenolic natural products. Compounds thus derived are referred to as acetogenins (29,30). The schematic pathway is as shown in Chart 1.7 (Page No. 16).

Among the oxygen heterocycles, chromones and xanthones are considered to arise from the acetogenin pathway.

1.4.1. Biosynthesis of chromones

According to Devon and Scott 44, the biogenesis of chromones (33,34) involves the formation of the main skeleton from five acetate units (31). The biogenesis of chromones in higher plants may involve a side chain of five carbon atoms, of which some may become part of the heterocyclic ring.

Numerous C-methylated chromones are known in nature. Whether the introduction of the C-methyl group takes place after the chromone system has been formed or at the earlier stage of the hypothetical polyketomethylene precursor, or at the state just prior to the closure of the heterocyclic ring cannot be stated with assurance. The co-occurrence of [A] and [B] made Schmid and Bolleter 45 to suggest [C] as a precursor which can undergo ring closure in two ways to give [A] and [B]. O-Methylation also is frequently observed.

Allport and Bu'Lock 46 demonstrated the biogenesis of 5-hydroxy-2-methylchromone (36) from the respective chromanone by the use of C-1 labelled sodium acetate (35) (Chart 1.7, Page No. 17).

From Dianella revolute and Styandra grandis, a series of 2-alkyl-5, 7-dihydroxy-6-methylchromones have been isolated 47. The alkyl groups in them are saturated C-27, C-29 and C-31 chains, thus removing the limitation that all naturally occurring chromones possess a 2-methyl or a 2-hydroxymethyl group 47. It supports the idea of the polyacetate origin of these compounds as against the incorporation of a mevalonate unit postulated by Dean. The mechanism of the pathway is shown in Chart 1.7.
b. Acetic acid Pathway

\[
\text{CH}_3\text{COOH} + 3\text{CH}_3\text{COOH} \rightarrow \text{27}
\]

\[
\text{Aldol Condensation} \quad \rightarrow \quad \text{28}
\]

\[
\text{C - acylation} \quad \rightarrow \quad \text{30}
\]

Orsellinic acid

\[
\begin{align*}
\text{HO} & \quad \text{COOH} \\
\text{HO} & \quad \text{CH} - \text{CH} - \text{C} - \text{OH} \\
\text{HO} & \quad \text{I} \\
\text{CHR} & \quad 2
\end{align*}
\]

Phloroacetophenone

\[
\begin{align*}
\text{HO} & \quad \text{CO} - \text{CH} - \text{CO} - \text{CH}_2 - \text{R} \\
\text{OH} & \quad \text{CO} - \text{CH}_2 - \text{CO} - \text{CH}_2 - \text{R}
\end{align*}
\]

c. Biosynthesis of chromones

\[
\begin{align*}
\text{31} \\
\text{5 - Acetate Units}
\end{align*}
\]
CHART 1.7 Contd..

Eugenitin [A]

Isoeugenitin [B]

CH₃COONa

33

34

35

36
1.4.2. Biosynthesis of flavonoids

Biogenesis and biosynthesis of flavonoids have been well studied and extensively reviewed. In the past few years, the enzymology of flavonoid biosynthesis has made particularly rapid progress. It became firmly established that all classes of flavonoids derive their carbon skeleton from compounds of intermediary cell metabolism through the cation of two consecutive (General phenylpropanoid and flavonoid glycoside) path ways. Phenylpropanoid units derived from the shikimate pathway are common structural elements of all flavonoid compounds and of various other classes of phenylpropanoids, such as lignin, stilbenes and cinnamate esters.

Earlier feeding experiments with radioactively labelled precursors have established that the carbon skeleton of flavonoid (39) is derived from acetate (37) and phenylalanine (38); ring A is formed by a head-to-tail condensation of three acetate units and ring B as well as carbon atoms 2,3 and 4 of the heterocyclic ring C arise from phenylalanine. The three oxygen functions of ring A come from the carbonyl group of acetate, the oxygen functions of ring B are introduced by oxidation at the expense of molecular oxygen.

More recent investigations at the enzymic level have largely confirmed the hypothetic steps which had been deduced from incorporation experiments. The condensation of the acyl residues from one molecule of 4-coumaroyl-CoA (40 a-d) and three molecules of malonyl-CoA forming chalcone (41), the first common
intermediate, in the synthesis of all class of flavonoids 42-47 are illustrated in Chart 1.8 (Page No.20). The enzymes catalysing individual steps are phenylalanine ammonia-lyase, cinnamate 4-hydroxylase and 4-coumarate-CoA ligase. The sequence of reactions converting phenylalanine into CoA ester derivatives of substituted cinnamic acids was therefore termed "general phenylpropanoid metabolism". 

The frequent co-occurrence of chalcones, flavanones, flavones and flavonols suggests that their biosynthetic pathways are closely related. In vivo, chalcones with a phloroglucinal type substitution in ring A are exclusive intermediates in the formation of 5,7-dihydroxyflavonoids, while chalcones with a resorcinol type substitution in ring A are selectively converted into 7-hydroxyflavonoids. However, an enzyme catalysing the synthesis of a chalcone with a resorcinol structure in ring A has not been reported. Further, the actual mechanisms through which flavanones are converted into flavones, flavonols and other flavonoids are in most cases not well understood. Only a few studies with cell-free extracts have demonstrated the oxidation of flavanones to the corresponding flavones and the hydroxylation of flavanones in the 3-position to yield the corresponding dihydroflavonols.

The flavonoid glycoside path way consists of about 13 enzymes which catalyse several consecutive steps of flavone and flavonol biosynthesis studied in cultured parsley cells. The first step is the conversion of acetyl-CoA to malonyl-CoA, which serves as substrates for three enzymes chalcone-synthase and two malonyl transferases. In the second step, the chalcone is formed from 4-coumaroyl-CoA and malonyl-CoA. The chalcone is isomerised to the corresponding flavanone, which is further converted into the basic flavone and flavonol structures. The subsequent steps are substitution of ring B of the aglycones by hydroxylation and O-methylation. The final steps are glycosylation of the aglycones and acylation of the resulting glycosides.
Biosynthesis of flavonoids

1. From COOH to 40b
2. From 40a to 40b
3. From 3 HOOC - CH₂ CO - SCoA to 3 CH₃ CO - SCoA
4. From 40b to 40c
5. From 40c to 40d
6. From 40d to Chalcone
7. From Chalcone to Flavanone
8. From Flavanone to Anthocyanidin
9. From Anthocyanidin to Flavone
10. From Flavone to Aurone
11. From Flavone to Isoflavone
12. From Isoflavone to Flavonol
1.5. Isoprenoid Substituents in Oxygen Heterocycles

The widespread occurrence in plants and other organisms of compounds that contain, as both C- and O-linked substituents, the typical isoprenoid residue (48), strongly suggests that there exists in many living organisms a source of this grouping in a biological form that permits its introduction by alkylation or acylation.

Aneja et al. 52 suggested mevalonic acid (49) (via acetate) to be the ultimate source of these isoprenoid units which eventually gives rise to the active synthetic fragment, isopentenyl pyrophosphate(50).

\[
\begin{align*}
\text{Mevalonic acid} & \quad \text{Isopentenyl-pyrophosphate} \\
49 & \quad 50
\end{align*}
\]

The availability of isopentenyl-pyrophosphate or its isomeric 3-methyl-2-butene fragment as an alkylating agent provides a ready solution to the question of the biosynthesis of such isoprenoid compounds. Numerous derived forms of the prenyl residue occur in nature. Ollis and Sutherland 39 have reviewed in detail the occurrence, structure and synthesis of such compounds (Table 1.1, Page No's.22&23).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-(\rightarrow)-(\rightarrow)- Dimethylallyl derivatives</td>
<td></td>
</tr>
<tr>
<td>1. Preremirol</td>
<td>53</td>
</tr>
<tr>
<td>2. Bavachin (R=H)</td>
<td>54</td>
</tr>
<tr>
<td>3. Bavachinin (R=CH(_3))</td>
<td>54</td>
</tr>
<tr>
<td>4. Suberosin</td>
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<tr>
<td>O-Dimethylallyl derivative</td>
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<td>5. Brayleyanin</td>
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<tr>
<td>C-(\alpha,\beta)- Dimethylallyl derivative</td>
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<td>6. Cudraniaxanthone</td>
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<td>2,2 - Dimethylchromene derivatives</td>
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<td>7. Pomiferin</td>
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<tr>
<td>8. Lapachenol</td>
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<td>9. Xantheletin</td>
<td>55</td>
</tr>
<tr>
<td>10. Medicosimine</td>
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<td>Table 1.1</td>
<td>2,2-Dimethyl chroman derivatives</td>
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<tr>
<td>-----------</td>
<td>--------------------------------</td>
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<tr>
<td>11. Fuscin</td>
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<tr>
<td>12. Bischromanoisoflavone</td>
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<td>13. Gammandol</td>
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</tr>
<tr>
<td>14. Phellamuretin</td>
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<tr>
<td>Isopropyl benzofuran derivative</td>
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</tr>
<tr>
<td>15. Munetone</td>
<td><img src="image5" alt="Munetone" /></td>
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<tr>
<td>Structurally modified C-5 units</td>
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</tr>
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<td>16. Osthol</td>
<td><img src="image6" alt="Osthol" /></td>
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<tr>
<td>17. Visamminol</td>
<td><img src="image7" alt="Visamminol" /></td>
</tr>
<tr>
<td>18. Amurensin</td>
<td><img src="image8" alt="Amurensin" /></td>
</tr>
<tr>
<td>19. Byakangelicol</td>
<td><img src="image9" alt="Byakangelicol" /></td>
</tr>
<tr>
<td>20. Cannabi-chromene</td>
<td><img src="image10" alt="Cannabi-chromene" /></td>
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</tbody>
</table>
O-Alkylation occurs at a latter stage in the biosynthesis of these compounds. C-Alkylation also occurs at a latter stage for those aromatic rings which have the shikimic origin. For compounds of acetic acid origin, the C-alkylation occurs on a preformed phenol or alternatively on the activated methylene group of the polyketide intermediate.

The senecioyl residue as in the C-acylated glabralactone (51) and the O-acylated samicidin (52) appears frequently in natural compounds.

![Glabralactone and Samicidin](image)

Senecioic acid (53), (β,β-dimethylacrylic acid) is of natural occurrence and its availability as an acylating agent, perhaps as the CoA ester is a plausible supposition.

1.5.1. Natural 2,2-dimethylchromenes and their derivatives

The five-carbon unit in aromatic natural products exists very commonly in the form of a 2,2-dimethylchromene system. According to Ollis and Sutherland the photochemical formation of a 2,2-dimethylchromene (56) occurs from C-dimethylallylphenol (54) precursor. The reaction is initiated by the oxidation of the phenolic anion, followed by the loss of the benzylic proton to give a quinonemethide.
intermediate which then cyclises to a 2,2-dimethylchromene. However, the mechanistic ease of oxidation of the allylic methylene group coupled with the frequent occurrence of the \(-\text{COCH}=\text{CMe}_2\) and \(-\text{COCH}_2\text{CHMe}_2\) residues makes feasible the mechanism - B\textsuperscript{39}.

Polonsky and her coworkers\textsuperscript{66} have postulated another route to the formation of 2,2-dimethyl chromene system, based on their studies on allylic photo sensitized oxidation of several natural products. This involves the oxidation of methylbutenyl unit (55) to a cis-allylic alcohol which can yield the 2,2-dimethylchromene on cyclodehydration.

However, Taylor et al\textsuperscript{67} have pointed out that the allylic alcohol (55) from the hydroperoxide obtained by oxidation with singlet oxygen was probably trans and not cis as assumed. Trans isomers are formed in similar cases\textsuperscript{68,69}. Hence, another possibility has been envisaged for the formation of the chromene ring, in which the trans allylic alcohol is transformed into the o-quinone-allylide which then cyclises to the chromene (56).

The phenolic derivatives, so formed, can undergo secondary transformations including oxidative coupling reactions to give rise to more complex heterocyclic compounds which incorporate 2,2-dimethylchromene (56) unit in their structure (Chart 1.9, Page No.26).

1.6. Objective

**Synthesis of 2,2-dimethylchromene derivatives**

The synthetic routes for 2,2-dimethylchromene derivatives can be broadly classified into two types. The \(C_5\)-isoprene unit for forming the pyran ring is introduced in one step possibly with subsequent minor modification by reacting suitably substituted phenolic compounds with a reactant which provides the \(C_5\)-unit. In the second method, a \(C_5\)-unit is introduced either in a ring form or in a chain form into a simple phenolic starting material and further structure is built up by reacting it with appropriate substrates.

A convenient synthetic route for 2,2-dimethylchromene derivatives is to start with the easily accessible 2,2-dimethylchromanones. These can be readily converted
Synthesis of Natural 2,2-dimethyl chromenes and their derivatives

A. 

\[
\begin{align*}
\text{54} & \xrightarrow{-2e} \text{55} \\
\text{55} & \xrightarrow{\text{H}^+} \text{56}
\end{align*}
\]

B. 

\[
\begin{align*}
\text{55} & \xrightarrow{\text{H}^+} \text{56} \\
\text{56} & \xrightarrow{-\text{H}^+} \text{56}
\end{align*}
\]

C. 

\[
\begin{align*}
\text{55} & \xrightarrow{\text{H}^+} \text{56}
\end{align*}
\]

D. 

\[
\begin{align*}
\text{55} & \xrightarrow{\text{H}^+} \text{56}
\end{align*}
\]
into the chromans or chromenes and further structural features can be built on them. This forms the basis for the synthesis of several 2,2-dimethyl-2H-pyranochromones and 2,2-dimethylpyranoflavonoids described in this thesis.

**Present Work**

2,2-Dimethylchromans are readily and conveniently accessible compounds and hence serve as intermediates for the synthesis of 2,2-dimethyl-2H-pyranochromones and 2,2-dimethylpyranoflavonoids. The present work is therefore based on the second approach mentioned above and is described in Chapters II to V. The aim was to develop convenient general routes for the synthesis of pyranochromones and pyranoflavonoids using the readily available 2,2-dimethylchromans as intermediates.

In Chapter II after a brief survey of the relevant literature, the synthesis and characterisation of 3,4-dihydro-2,2-dimethyl-2H-pyranochromones and 3,4-dihydro-2,2-dimethyl-2H-pyranocoumarins from hydroxy-2,2-dimethylchromans are described. Hydroxychromans on condensation with ethyl acetoacetate in the presence of anhydrous AICl₃ and phosphorous oxychloride gave 6,7-dihydro-4,8,8-trimethylpyrano (2,3-g) chrom-2-ones. When 7-hydroxy-2,2-dimethylchroman (57) was heated with ethyl acetoacetate in the absence of any condensing agent to give a mixture of two products. These two compounds were characterised as 6,7-dihydro-4,8,8-trimethylpyrano (2,3-g) chrom-2-one (58) and 6,7-dihydro-2,8,8-trimethylpyrano (2,3-g) chrom-4-one (59). Extension of this reaction to 61 and 66 led to a mixture 62+63 and 67+68 respectively. Demethylation of dihydropyranochromones 59,63 and 68 were dehydrogenated using DDQ to give the pyranochromones 60,65 and 70. The pyranochromone was also obtained from 7-hydroxy-2-methyl-6-C-prenylchromone by cyclodehydrogenation with DDQ.
In Chapter III the synthesis and characterisation of some new acetylhydroxyflavones (71 & 72), 3,4-dihydro-2,2-dimethyl-2H-pyranoflavones and related flavones are discussed. The new acetyl-hydroxyflavones are obtained from β-diketones, synthesised by the way of Baker-Venkataraman rearrangement of 5-acetyl-2,4-diaroyldioxy acetophenone. This Chapter also deals with the synthesis and characterisation of 3,4-dihydro-2,2-dimethyl-2H-pyranoflavone 73,74 from 2-benzylidene derivatives. The literature survey pertinent to this work is reviewed in the beginning of the Chapter.

In Chapter IV after a brief review of the relevant literature, the syntheses of the key intermediates required for further building up the pyranoflanavanone and pyranoflavone moieties are described. This is followed by the work carried out in the synthesis and characterisation of some model analogue of 3,4-dihydro-2,2-dimethyl-2H-pyranoflanavanones. The key intermediates used in the present study are the acetyl derivatives of hydroxychromans 75,76,77 and these were obtained by the Thermal-Fries rearrangement of acetyloxychromans. In the present study, 7-acetyloxy-, 5-acetyloxy-7-methoxy-, 7-acetyloxy-5-methoxy-and 5,7-diacetyldioxychromans obtained from the corresponding hydroxy chromans by acetylation, were subjected to Thermal-Fries rearrangement with anhydrous aluminium chloride in carbon disulphide. In each case, the acetyl hydroxychroman was purified by chromatography over silica gel and characterised. Suitably substituted acetyl hydroxychromans were then subjected to condensation with aryl aldehydes in the presence of 50% aqueous ethanolic potassium hydroxide to give the corresponding dihydropyranochalcones in minor yield and dihydropyranoflanavanones 78, 79 & 80 in major yield. The dihydropyranoflanavanones afforded are the derivatives of natural products such as racemoflavone, atalantoflavone and mixtecacin.

In Chapter V after a brief survey of the relevant literature, the synthesis and characterisation of 3,4-dihydro-2,2-dimethyl-2H-pyranoflanonols (84,85) and their 2,2-dimethyl-2H-pyano derivatives are discussed. Suitably substituted ω-chloroacetyl hydroxychromans (81-83) required for the building up to these
structures were obtained from the Hoesch reaction of 7-hydroxy- and 5-hydroxy-7-methoxy, -2,2-dimethylchromans with chloroacetonitrile and dry hydrogen chloride. A mixture of the products was obtained in first case and these were separated by column chromatography over silica gel. Appropriate ω-chloroacetyl hydroxychroman was subjected to condensation with arylaldehydes in cold ethanolic alkali to give the 3,4-dihydro-2,2-dimethyl-2H-pyranoflavonols. The aromatic aldehydes used in the present study are 4-methoxy-, 3,4-methylenedioxy- and 3,4-dimethoxy-benzaldehydes. Methylation of these flavonols followed by dehydrogenation with NBS/pyridine gave the corresponding 2,2-dimethyl-2H-pyran derivatives. One of these is the linear isomer of the natural product, pongachromene.

The Chapter VI deals with the phytochemical investigation of a medicinal plant. The isolation and characterisation of pentacyclic triterpenoids, Lupeol (87) and Oleanonic acid (88) from Oberonia iridifolia (fam. Orchidaceae) have been described.

Structures of some typical compounds synthesised and described in Chapters II to VI, are shown in Chart 1.10 (Page No's. 30,31 & 32).

As is evident from the work described, in this thesis, very general and convenient methods for the synthesis of pyranochromones, pyranocoumarins and pyranoflavonoids have been developed using acetyl hydroxychromans and ω-chloroacetyl hydroxychromans as the key intermediates. The application of these methods has been well illustrated by synthesising some naturally occurring pyranochromones and pyranoflavonoids.

All compounds are characterised by chemical and spectral methods.
CHAPTER 2

57 R = H
61 R = OCH₃
58 R = H
62 R = OCH₃
65 R = OCH₃
63 R = OCH₃
64 R = OH
66

(i) EAA / diphenyl ether
(ii) AlCl₃/CH₃CN

CHAPTER 3

71
a: R₁ = R₂ = OCH₃,
b: R₁ = OCH₃, R₂ = H
72
a: R₁ = R₂ = OCH₃,
b: R₁ = OCH₃, R₂ = H
Chapter 4

75 \( R_1 = R_4 = H, R_2 = COCH_3, R_3 = OH \)

76 \( R_1 = OH, R_2 = COCH_3, R_3 = OCH_3, R_4 = H \)

77 \( R_1 = OCH_3, R_2 = H, R_3 = OH, R_4 = COCH_3 \)

\( a: R_1 = OCH_3, R_2 = H \)  
\( b: R_1 = R_2 = OCH_3 \)  
\( c: R_1, R_2 = -O- \)  
\( d: R_1 = R_2 = H \)
CHAPTER 5

81 $R_1 = R_4 = H, R_2 = \text{COCH}_2\text{Cl}, R_3 = \text{OH}$
82 $R_1 = H, R_2 = \text{COCH}_2\text{Cl}, R_3 = \text{OH}, R_4 = \text{COCH}_2\text{Cl}$
83 $R_1 = \text{OH}, R_2 = \text{COCH}_2\text{Cl}, R_3 = \text{OCH}_3, R_4 = H$

a: $R_1 = \text{OCH}_3, R_2 = H$
b: $R_1 = R_2 = \text{OCH}_3$
c: $R_1, R_2 = -$ 

CHAPTER 6

87
88