PART B

CHEMISTRY OF COUMARINS
INTRODUCTION:

Coumarins are a class of naturally occuring lactones which are indexed in the current chemical abstracts as 2H[1]-benzopyran-2-ones. The parent coumarin molecule (I) can be looked upon as arising out of the fusion of benzene ring with the C(5)-C(6) bonds of pyran-2-one (IA). In the numbering adopted for this molecule, the ring oxygen receives position (1), carbonyl carbon (2) and goes around the ring as shown in (I)\(^1\).

\[
\begin{align*}
(\text{IA}) & \quad (\text{I}) \\
\end{align*}
\]

Anantkrishnan\(^2\) discussed the "Mills-Nixon effect", in which the reactivity of coumarin was rationalised based on the comparative studies of bromination, nitration of coumarin, naphthalene and benzene. Considering the possible electron displacements in the coumarin molecule, Thakur and Shah\(^3\) predicted C(6) and C(8) as the most reactive centres.

The greater electron densities can be seen on C(6) and C(8) from the resonating structures (B) and (C). Out of these two, C(6) seems to be
more reactive because of its proximity to the oxygen atom, similar to the reactivity of the para position of phenol. Structure (A) though imparts more electron density to the C(3) position, the electrophilic substitution at C(3) is less probable due to its nearness to the electron withdrawing carbonyl group. Infact, the π-electron densities calculated by Song and Gordon⁴ are quite close to the resonance picture of the molecule given above. The values of π-electron densities for the ground state of coumarin are given below.

\[
\begin{array}{c}
\text{C(1)} & \text{C(2)} & \text{C(3)} & \text{C(4)} & \text{C(5)} & \text{C(6)} \\
0.982 & 0.940 & 1.017 & 0.770 & 1.455 & 1.028 & 1.801
\end{array}
\]

Considering the structures (B), (C) and (D), Bassignana and Cogrossi⁵ have proposed structure (E) which according to them represents the hybrid or resonating state of the molecule.

\[
\text{(E)}
\]

However, contributing structures of the type (D), do not have strong spectral evidences, the position of the carbonyl frequency in the IR spectrum (1710 cm⁻¹) is more in accordance with an enol lactone⁶. Hence, the contribution from such type of structures is negligible and the resonating state (E) appears to be less probable.

The ability of coumarin and its derivatives to induce drug metabolizing enzymes has been subjected to a quantum chemical analysis by Wald and Feuer⁷. The net atomic charge distribution at various positions of the coumarin ring are given below.
Coumarin has been used as a useful model in elucidating the electronic structure and photoreaction of psoralenes. The configurational analysis of coumarin by Song et. al in the ground state indicates some charge transfer delocalization extending to the ethylenic region. The dipole moment of coumarin (4.51X10^{-18} e.s.u) determined earlier by Rau also indicates similar delocalisation.

Aromaticity:

It is difficult to explain the disputable aromatic character of coumarin molecule. In some respects the heterocyclic ring behaves as an aromatic system, in others as though it is aliphatic.

In the PMR spectrum of coumarin, the signals from the protons at C(3) and C(4) appear in the region for olefinic and aromatic protons at 6.45 and 7.80 δppm respectively with a coupling constant of 9.8Hz. These values are typical of a cis alkene rather than an aryl ring. Finally, the 13C-NMR spectra of coumarins are consistant with an essentially aliphatic heterocyclic ring, the chemical shifts of C(2), C(3) and C(4) in coumarin are remarkably close to the values for the corresponding carbons in α-pyrone given below.
\[ \text{\(^{13}\)C-NMR data (δ ppm)} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>C(2)</th>
<th>C(3)</th>
<th>C(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Pyrone</td>
<td>162.0</td>
<td>116.7</td>
<td>144.3</td>
</tr>
<tr>
<td>Coumarin</td>
<td>160.4</td>
<td>116.4</td>
<td>143.4</td>
</tr>
</tbody>
</table>

Nevertheless, coumarin does show some aromatic character in its pattern of reactivity. Examples;

1. The carbonyl oxygen can be alkylated by powerful alkylating agents to give stable pyrilm salts:\(^{16}\)

\[ \text{\(\text{Et}_3\text{OBF}_4^+\)} \]

2. The coumarin nucleus is susceptible to electrophilic substitution\(^{16}\). Sulphonation takes place initially in the carbacylic ring at C(6), under more forcing condition one -SO\(_3\)H group can be introduced at C(3) also.

As in the case of simple pyrones, the properties of the heterocyclic ring of coumarin are greatly influenced by the presence of substituents.
Spectroscopic properties:

Ultraviolet Spectroscopy:

Ganguly and Bagchi\textsuperscript{13} have studied the ultraviolet spectra of coumarin and its methyl derivatives. The introduction of methyl group in various positions does not enhance the nature of the spectrum to a great extent. The bands observed in the case of coumarin derivatives are given below.

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ (\textit{e})\textmu (Solvent Ethanol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coumarin</td>
<td>273.5 (4,0368), 307, 309 (3,7449)</td>
</tr>
<tr>
<td>2</td>
<td>4-Methyl coumarin</td>
<td>271.0 (3,9975), 307 (3,7559)</td>
</tr>
<tr>
<td>3</td>
<td>4-Phenoxy methyl coumarin\textsuperscript{15}</td>
<td>208.0 (4,39), 268 (4,05), 308 (3,77)</td>
</tr>
</tbody>
</table>

Infrared Spectroscopy:

In the year 1938, Murti and Sheshadri\textsuperscript{15} reported the IR spectrum of the parent coumarin. Later Cogrossi and Bassignana\textsuperscript{5} studied the IR spectra of 3-acyl coumarins. For parent coumarin they have assigned the following bands with \( \nu (\text{cm}^{-1}) \) values.

<table>
<thead>
<tr>
<th>( \nu (\text{cm}^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C=O (( \delta )-lactone)</td>
</tr>
<tr>
<td>C=C</td>
</tr>
<tr>
<td>C-O</td>
</tr>
<tr>
<td>C-H deformations</td>
</tr>
</tbody>
</table>
For the compounds that we have synthesised during the present investigation, the carbonyl group of coumarin appears at around 1700-1720 cm\(^{-1}\). The carbonyl groups linked at 3-position of the coumarin ring usually appear around 1660-1680 cm\(^{-1}\), unless linked to a strong electronegative group\(^5\).

**Proton Magnetic Resonance Spectroscopy:**

The PMR spectra of coumarin and its derivatives were studied by Dharmatti et al\(^{11}\). They analysed the spectrum of the parent coumarin as follows. C(3)-H, C(4)-H as AB type and the four [C(5), C(6), C(7) and C(8)] protons of the phenyl part as ABCD type. They have expressed the chemical shift similar to that of cyclohexane. Pirkle and Dines\(^{16}\) studied the PMR spectra of some 2-pyrones and related compounds. Some of the chemical shift data for C(3) and C(4) protons of pyrones and coumarins are given below.

**Chemical shift (\(\delta\)ppm)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>C(3)-H</th>
<th>C(4)-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-pyrone</td>
<td>6.38</td>
<td>7.56</td>
</tr>
<tr>
<td>2</td>
<td>4-methyl-2-pyrone</td>
<td>6.10</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Coumarin(^{10})</td>
<td>6.45</td>
<td>7.80</td>
</tr>
<tr>
<td>4</td>
<td>5,6,7,8-tetrahydro coumarin</td>
<td>6.10</td>
<td>7.15</td>
</tr>
<tr>
<td>5</td>
<td>3-Nitro-5,6,7,8-tetrahydro coumarin</td>
<td>--</td>
<td>8.25</td>
</tr>
</tbody>
</table>
Mass Spectroscopy:

Barnes et.al\textsuperscript{17} studied the electron impact on coumarin molecule. Coumarin exhibits a fairly intense molecular ion peak and shows (M-CO) ion peak indicating the transient formation of benzofuran.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{\textsuperscript{146}m/e} \text{ coumarin} \text{+ CO} \rightarrow \text{\textsuperscript{118}m/e} \text{ benzofuran}};
\end{tikzpicture}
\end{center}

Ring synthesis:

1. Perkin synthesis:

The history of coumarin synthesis began in the mid nineteenth century with its discovery by Perkin which bears his name\textsuperscript{18}. The parent compound was obtained by heating salicylaldehyde and acetic anhydride in presence of sodium acetate and established its relation with o-hydroxy cinnamic acid which on elimination of a molecule of water forms the lactone ring.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{\textsuperscript{146}m/e} \text{ coumarin} \text{+ COONa} \rightarrow \text{\textsuperscript{118}m/e} \text{ benzofuran}};
\end{tikzpicture}
\end{center}

Thus, coumarins are a group of lactones derived from o-hydroxycinnamic acids. In other words, a coumarin ring system is formed by the fusion of a benzene and 1:2 or \(\alpha\)-pyrone ring. Later, M.Crawford and J.A.M.Shaw\textsuperscript{19} reported that the condensation of salicylaldehyde and its derivatives with acid anhydrides and the corresponding sodium salts can take place both intramolecularly and intermolecularly to give the same coumarin, where as in the latter case it is frequently accompanied by the corresponding o-coumaric acid.
2. Pechmann synthesis\textsuperscript{20}:

Von Pechmann reported his alternative method of coumarin synthesis which involves the reaction of $\beta$-ketoester and phenols in presence of strong acid.

\[
\text{R = H, halo, alkyl, alkoxy ; R}^1 \text{ = H, alkyl, aryl, halomethyl etc.}
\]

3. Knoevenagel synthesis\textsuperscript{31}:

3-substituted coumarins can be obtained in good yield by the application of Knoevenagel reaction, by condensing o-hydroxy aldehydes with ethyl acetoacetate in presence of piperidine.

4. Kostanecki-Robinson synthesis\textsuperscript{1}:

This reaction can be used to prepare 3 and 4 substituted coumarins. This is rather uncertain method because chromones are equally likely to be formed here. The reaction is as shown below.

\[
\text{R}^1 = \text{R}^2 = \text{H or alkyl.}
\]
5. The synthesis of 4-hydroxy coumarins deserves a special mention on the grounds that this type of substitution pattern is found in several important coumarins. The most widely used method is Pechmann\textsuperscript{22} reaction, carried out in presence of anhydrous zinc chloride and phosphoryl chloride.

![Chemical Structure](image1)

6. I.C. Badhawar and coworkers\textsuperscript{23} have synthesised differently substituted coumarins by the action of $\alpha$-formyl phenylacetonitriles on various phenols in presence of zinc chloride or hydrogen chloride.

![Chemical Structure](image2)

7. J. Kagan\textsuperscript{24} described a photochemical method for the synthesis of Esculetin. Irradiation of 3, 4-dihydroxycinnamic acid in presence of oxygen gives esculetin.

![Chemical Structure](image3)

8. Ahluwalia and Kumar\textsuperscript{25} have synthesised 4-methyl coumarins by the action of 2-methoxy-benzoylacetonitrile and hydrobromic acid in presence of acetic anhydride.

![Chemical Structure](image4)

$R =$ alkyl and alkoxy.
9. R. Arad-Yelli et al.\textsuperscript{26} described a photochemical method for the synthesis of 5-chlorocoumarin. UV irradiation of 2, 6-dichloro cinnamic acid and its esters give 5-chlorocoumarin.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{COOR} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{COOR} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{COOR} \\
\text{hv} & \rightarrow & \text{Cl} & \quad \text{Cl} & \quad \text{CO} & \quad \text{O} \\
R = \text{H, Me}
\end{align*}
\]

10. Otto S. Wolfbeis et al.\textsuperscript{27} have synthesised 3-cyano-5, 6-benzocoumarin (II) by heating \(\beta\)-naphthol, aniline and triethyl orthoformate at reflux under anhydrous condition to get an enamine (I), which on heating with ethylcyanoacetate in presence of piperidine gave 3-cyano-5,6-benzo coumarin (II).

\[
\begin{align*}
\text{ArNH}_2 & \quad \text{Triethylorthoformate} & \quad \text{CNCH}_2\text{COOEt} & \quad \text{Piperidine} \\
\text{H} & \quad \text{N} & \quad \text{O} & \quad \text{CNCH}_2\text{COOEt} & \quad \text{Piperidine} \\
\text{II} & \quad \text{HN} & \quad \text{OH} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
\text{I} & \quad \text{HN} & \quad \text{OH} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN}
\end{align*}
\]

11. Hans Junek et al.\textsuperscript{28} synthesised methyl \(\alpha\)-cyano-\(\beta\)-amino-\(\beta\)-(coumarin-3-yl)acrylate by condensing salicylaldehyde with \(\alpha\)-cyano-\(\beta\)-amino-\(\gamma\)-carbomethoxymethylcrotonate.

\[
\begin{align*}
\text{CHO} & \quad \text{NH}_2 & \quad \text{MeOOC} & \quad \text{C} & \quad \text{CN} & \quad \text{COOCH}_3 \\
\text{OH} & \quad \text{H}_2\text{C} & \quad \text{C} & \quad \text{CN} & \quad \text{COOCH}_3 & \quad \text{Amide}
\end{align*}
\]

12. A number of polycyclic derivatives of coumarin have been synthesised from methoxymethyl phenolic ethers, using directed metallation.
to introduce the o-formyl group\textsuperscript{30}. The same o-lithiated species undergoes conjugate addition to protected \(-\)thiounsaturated acids. Deprotonation results in cyclisation to the dihydrocoumarin and subsequent dehydrosulphonylation gives 3,4-disubstituted coumarins\textsuperscript{31}.

\begin{align*}
\text{R} & \quad \text{SPh} \quad \text{N} \\
\xrightarrow{\text{i, ii}} & \quad \text{PhS} \quad \text{Ph} \\
\xrightarrow{\text{iii-v}} & \quad \text{O} \\
\end{align*}

i) 2-methoxymethoxyphenyllithium ii) $E^+$ iii) $H^+$ iv) MCPBA v) $\Delta, CCl_4$

13. T.Harayama et al\textsuperscript{31} reported the convenient synthesis of simple coumarin by the reaction of salicylaldehyde ($R = 3-, 4-, 5-, 6-\text{Br}; 4-, 5-, 6-\text{CO}_2\text{Me}, 4-, 5-, 6-\text{OMe}$) with carboethoxymethylene triphenyl phosphorane in diethylamine under reflux.

14. Recently, A.Arcadi et al\textsuperscript{32} reported the synthesis of substituted coumarins through a sequential vinylic substitution/annelation process.
Crystal structure:

Crystal structure of coumarin was first reported by S. Ramaswamy in the year 1941. Coumarin crystals are usually in the orthorhombic system. It has space group $Pc2_1$ with $a$) 15.000, b) 5.664, c) 7.915Å and $Z = 4$. The structure consists of nearly planar molecules held together by Van der Waals forces. X-ray crystallographic structural data of some coumarins are tabulated below.

<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>Space group</th>
<th>Unit cell parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no. of molecules/unit cell</td>
<td>A°: deg</td>
</tr>
<tr>
<td>1</td>
<td>Coumarin$^{37}$</td>
<td>orthorhombic $Pc2_1$; $Z=4$</td>
<td>$a = 15.466$, $b = 5.676$, $c = 7.917$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\alpha = \beta = \gamma = 90$</td>
</tr>
<tr>
<td>2</td>
<td>4-hydroxy coumarin$^{39}$</td>
<td>orthorhombic $P2_12_22$; $Z=4$</td>
<td>$a = 10.11$, $b = 12.18$, $c = 6.95$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\alpha = \beta = \gamma = 90$</td>
</tr>
<tr>
<td>3</td>
<td>4-methyl-7-chloro coumarin</td>
<td>monoclinic $P2_1/c$; $Z=4$</td>
<td>$a = 4.039$, $b = 9.728$, $c = 10.870$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\beta = 90.91$</td>
</tr>
<tr>
<td>4</td>
<td>8-methoxy coumarin</td>
<td>monoclinic $P2_1/c$; $Z=8$</td>
<td>$a = 7.529$, $b = 13.803$, $c = 16.176$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\beta = 102.07$</td>
</tr>
<tr>
<td>5</td>
<td>7-acetoxy coumarin</td>
<td>monoclinic $P2_1/c$; $Z=4$</td>
<td>$a = 3.833$, $b = 22.665$, $c = 10.975$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\beta = 96.27$</td>
</tr>
</tbody>
</table>

In a collaborative research programme, crystal structure of some coumarin derivatives have also been reported from our laboratory. During the present investigation, we have studied the crystal structure of newly synthesised 3-bromo-7-ethoxy-4-methylcoumarin and 8-methoxy-
In the recent years, crystal structure determination has played an important role in solving the problems of solid state photochemical dimerisation of coumarins. On irradiation, coumarin gets dimerized into four possible forms. Direct irradiation in polar solvents, results head-to-head syn dimer\textsuperscript{42}, in presence of a sensitizer, it gets dimerized to head-to-head anti dimer\textsuperscript{43} and in non-polar solvents affords neither dimeric products\textsuperscript{44}. All these dimerized products were mainly characterised by their crystal structure study.

**Biological activity:**

The parent coumarin was first isolated in 1820 from Tonka bean by Vogel\textsuperscript{45}. The importance and interest of naturally occuring coumarins were mainly because of the famous anticoagulant dicoumarol. Groth\textsuperscript{46} screened dicoumarol against fourteen bacterial species and found that menadione failed to antagonise the growth inhibition of S.aureus caused by the former. Paulo de Lacereda\textsuperscript{47} found that dicoumarol at a dilution of 1-50000 stopped the growth of S.pyrogenes, S.aureus and S.albus.

Coumarin is present in many plants\textsuperscript{48} occurs in roots, barks, leaves and fruits. It has also been isolated from microorganisms\textsuperscript{49} and animals\textsuperscript{50}. Due to its pleasant fragrant odour, it was frequently used as a flavouring substance until the discovery of its heptotoxic action.

Ron and Mayer\textsuperscript{50} observed its toxic action on algae and found that coumarin prevented the growth of Chlorella vulgaris cultures in $1.4 \times 10^{-3}\text{mol}^{-1}$ concentration. Coumarin inhibits the germination growth of subsequent roots of the plants. Its effect on wheat, potato tubers and tomato are well known and have been reviewed.\textsuperscript{52,53}
Russian workers during their study on the effects of coumarin in high plants have found that its growth has stimulated the action at lower concentrations and growth inhibition action at higher concentrations. This action indicates that, in lower concentration coumarin exerts a hormonal action, while in higher concentration it has an anti-auxin effect.

Coumarin has got a wide range of effects in animals also. The depression of smooth muscle and dilation of peripheral blood vessels by coumarin, in frogs, rabbits, and mice was noticed by Rai.

Buckle et.al have synthesised various aryloxy, alkoxy 4-hydroxy-3-nitro-coumarins which inhibits histamine release in rats and also antagonise the effects of a slow reactive substance of anaphylaxis. The most active compound was (I).

Metabolism of coumarin in animal body is as shown below.
Coumarin (II) is degraded in animal body by hydroxylation\textsuperscript{45} in both rabbit and rat, the major products are 3-hydroxycoumarins (III) and 7-hydroxy coumarins (IV). The hydroxylation of (III) is followed by the opening of the \(\alpha\)-pyrone ring via o-hydroxy-phenylpyruvic acid to yield finally, o-hydroxyphenylacetic acid (V) and o-hydroxyphenylacetic acid (VI) respectively\textsuperscript{45}.

Coumarin and some of its derivatives possessing melting points lower than 100°C have been found to have strong antihelmintic action\textsuperscript{58}. Coumarin itself has low antibacterial activity, but some natural derivatives possess a greater effect. Coumarin structure also occurs in novobiocin\textsuperscript{59} and in anti-biotics like coumermycin\textsuperscript{60} and chartreusin\textsuperscript{61}.

During the course of total synthesis of natural products like 6,7-benzomorphans, D.L.Boger and M.Patel\textsuperscript{62} investigated the preparative scope of the inverse electron demand Diels-Alder reaction utilising coumarin derivative (a) as diene. Compound (a) undergoes [4+2] cycloaddition with 1,1-dimethoxy ethylene and 1,1,2-trimethoxyethylene to provide benzomorphans (b) and (c).

\[\text{CO}_2\text{CH}_3\]
\[\text{CH}_3\text{O}\]
\[\text{CH}_3\text{O}\]
\[\text{CH}_3\text{O}\]
\[\text{CO}_2\text{CH}_3\]

\[\text{CO}_2\text{CH}_3\]
\[\text{CH}_3\text{O}\]
\[\text{CH}_3\text{O}\]
\[\text{CH}_3\text{O}\]
\[\text{CO}_2\text{CH}_3\]
In view of the vital role played by coumarin in nature and the utility of its innumerable derivatives in the fields of medicine, industry and agriculture, synthesis of a number of coumarin derivatives have been undertaken during the present work and many of them have been studied for their effects on bacterial and fungal species. The structures of all the compounds have been confirmed by analytical and spectral data and is being presented in different parts of the thesis.