DISCUSSION
Chalcones constitute an interesting group of flavonoids as they are the intermediates from which most, if not all, the classes of flavonoids derive in vivo and also, they serve as starting materials for the synthesis of various classes of flavonoids in vitro. An examination of the structural features of chalcone would reveal that it possesses aromatic nuclei, a relatively less active olefin, a deactivated carbonyl and an \( \alpha,\beta \)-unsaturated carbonyl functionalities. The presence of enone function in the chalcone molecule confers antibiotic activity (Bacteriostatic/Bactericidal) upon it. Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties, which are detrimental to the growth of microbes, tubercle bacilli and acrus. The structural characteristics, some interesting therapeutic properties, such as hypotensive, antitumour, antipeptic ulcer activities and potential use of some of the chalcones and their derivatives as artificial sweeteners, stabilisers against heat and light have indeed for decades stimulated intensive research in this area.

One of the main objectives of the present studies was to develop synthetic strategies to assist in the synthesis and absolute stereochemistry of biflavonoids. Besides, the reactions of flavonoids and flavonoid precursors with various reagents have been explored in an attempt to synthesise medicinally interesting compounds. Furthermore, these reactions were taken in hand to
obtain an insight into the mechanism of the reactions. This part of
the thesis describes the results of the reactions of the chalcones
and flavonoid precursors with various reagents.

Fodar et al.^{68} have recently reported that L-ascorbic
acid (XXI) undergoes stereoselective addition to acrolein (XXII)
to give tricyclic hemiacetal lactone (XXIV) in a novel Michael type
reaction. Methyl vinyl ketone (XXV) reacts with L-ascorbic acid in
a similar fashion to give diketolactone derivative (XXVI). Upon the
action of methanolic hydrogen chloride on XXVI, the tricyclic methyl
ketal lactone (XXVII) forms.

The Michael addition takes place at pH 4 of ascorbic acid
and no basic catalyst is needed. Moreover, the use of water as a
solvent promoted the dissociation of ascorbic acid to produce
L-ascorbate-3-anion, an ambient nucleophile with two potentially
reactive sites O-3 and C-2. However, the π-electron density around
C-2 was sufficiently enhanced to make C-2 the nucleophile which can
attack the conjugated double bond of α,β-unsaturated carbonyl
compounds.

The precedent nucleophilic behaviour of C-2 in L-ascor-
bate-3-anion and the mechanistic realisation (Scheme-II) prompted
us to explore the extensive synthetic potential of this reaction
with chalcones which are reported to undergo Michael type
addition^{69,70}. 
As a model substrate, chalcone (XXVIII) was added slowly to a stirred aqueous solution of L-ascorbic acid under nitrogen atmosphere and the stirring was continued for 4 hours. The solid was filtered, washed and dried. T.l.c. examination of the solid showed that no reaction had taken place, probably, due to insolubility of chalcone in water.
In another experiment, chalcone dissolved in methanol/dimethylsulphoxide was treated with aqueous solution of ascorbic acid. The reaction, however, did not take place. The reaction did not produce any results even in the presence of a basic catalyst.

Our efforts to prepare compounds (XXIX–XXXI) were unsuccessful, presumably, due to steric hindrance, otherwise the anticipated products, XXIX resulting from Michael addition, XXX from subsequent hemiketal formation between O-6 and C-3 carbonyl and XXXI from the hemiketal formation by the attack of O-3 at the chalcone carbonyl group, would have been useful intermediates for further synthetic exploitations.

\[
\begin{align*}
(XXIX) & \\
(XXX) & \\
(XXXI) & 
\end{align*}
\]
Recently the first synthesis of thietan-2,4-dithiones (XXXIIIa-c)\(^7\) has been achieved by the reaction of alkyl p-tolyl sulphones (XXXIIa-c) with carbon disulphide in the presence of sodium 1,1-dimethylpropanolate. Also, p-cyanotoluene (XXXIIId) and t-butyl acetate (XXXIV) were shown to undergo this reaction, though 3-t-butoxycarbonylthietan-2,4-dithione (XXXV) was obtained in poor yield.

![Diagram](attachment:image.png)

(a) \( R = \text{SO}_2\text{Me} \)
(b) \( R = \text{SO}_2\text{Et} \)
(c) \( R = \text{SO}_2\text{NMe}_2 \)
(d) \( R = \text{CN} \)

![Diagram](attachment:image2.png)
The above reaction appears to involve active methyl or methylene group. This synthesis of thietan-2,4-dithiones, the first example of this class of compounds, fascinated us and we desired to extend this reaction to some simple acetophenones and flavanones. We carried out the reactions of acetophenone (XXXVI) and flavanone (XLI), in separate experiments, with carbon disulphide in the presence of sodium 1,1-dimethylpropanolate in N, N-dimethylformamide in the hope of getting compounds (XXXIX, XL, XLIII, XLIV) through plausible mechanisms (Scheme-III). However, these attempts did not produce any results worthy of note. A change of base from sodium 1,1-dimethylpropanolate to potassium t-butoxide, sodium methoxide and even to sodium hydroxide also did not prove helpful.

The failure of our efforts led us to presume that thietan-2,4-dithione formation requires methyl group of particular reactivity which is not, probably, suitably met in the substrates, XXXVI and XLI.
\[ \text{Ph-C-CH}_3 \xrightarrow{\text{CS}_2, t-C_5H_{11} ONa} \text{Ph-C-CH-C} \xrightleftharpoons{\text{DMF, 45°C}} \text{Ph-C-CH-C} \]

\[ \text{(XXXVI)} \quad \text{(XXXVII)} \]

\[ \text{Ph-C-CH-C} \xrightarrow{\text{DMF, 45°C}} \text{Ph-C-CH-C} \]

\[ \text{(XXXVIII)} \quad \text{(XL)} \]

\[ \text{Ph-C-CH-C} \xrightarrow{\text{DMF, 45°C}} \text{Ph-C-CH-C} \]

\[ \text{(XXXIX)} \]

\[ \text{(XL)} \]

\[ \text{CS}_2, t-C_5H_{11} ONa \xrightarrow{\text{DMF, 45°C}} \text{CS}_2, t-C_5H_{11} ONa \]

\[ \text{(XLIII)} \]

\[ \text{CS}_2, t-C_5H_{11} ONa \xrightarrow{\text{DMF, 45°C}} \text{CS}_2, t-C_5H_{11} ONa \]

\[ \text{(XLII)} \]

\[ \text{(XLIV)} \]

\[ \text{Scheme-III} \]
REACTION OF 2-HYDROXYACETOPHENONES WITH THIONYL CHLORIDE IN THE PRESENCE OF CATALYTIC AMOUNT OF PYRIDINE

Thionyl chloride is routinely used as a chlorinating agent for many different substrate types\textsuperscript{72,73}. However, unexpected reactions, in many cases, have been reported often without further detailed investigations. The reactions of thionyl chloride with various active methylene compounds have given rise to so-called abnormal products\textsuperscript{74}. The course of the reactions of thionyl chloride with active methylene compounds seems to be variable. Thus, it is difficult to predict the course of the reaction for a particular substrate.

Reactions of carbonyl compounds with thionyl chloride can proceed via O-sulphinylation or C-sulphinylation. The course of the reaction depends on factors such as the nature of the substrate, the amount and concentration of the reagent used, the order of addition, the solvent and the reaction temperature.

O-Sulphinylation of carbonyl compounds by thionyl chloride can lead to gem-dichlorides via an addition reaction at the carbonyl group (Reaction-1)\textsuperscript{75,76} and to $\alpha$-monochloroketones (Reaction-2) via enol sulphinylation.

C-Sulphinylation gives rise to $\alpha$-chlorosulphinyl ketones (Reaction-3) via the Hell-Volhard-Zelinsky reaction. These products may then undergo further transformations in the respective reaction mixtures, to give variety of products.
Reactions of thionyl chloride with active methylene compounds in the presence of a catalytic amount of pyridine have also been studied\textsuperscript{77-80}. Active methylene compounds which contain no hydrogen atoms on the $\alpha'$-carbon give $\alpha$-chlorosulphenyl chloride when treated with an excess of thionyl chloride in the presence of catalytic amount of pyridine or triethyl amine. Thus, treatment of 4-nitro-2,6-dimethoxyphenylacetic acid (XLV) with thionyl chloride and pyridine affords sulphenyl chloride (XLVI)\textsuperscript{77}.
Thionyl chloride containing pyridine converts adipic acid (XLVII) to the thiophene derivative (LI)\textsuperscript{78}. The reaction may be considered basically in terms of a cyclic sulphonylation, Pummerer rearrangement\textsuperscript{73} and subsequent dehydrochlorination.

\begin{align*}
\text{HOOC-CH}_2-\text{CH}_2-\text{COOH} & \xrightarrow{\text{SOCl}_2/\text{Py}} \begin{array}{c}
\text{Cl} \\
\text{C} \\
\text{S} \\
\text{C} \\
\text{C}
\end{array} \\
\text{Cl} & \rightarrow \\
\text{Cl} & \rightarrow \\
\text{Cl} & \rightarrow \\
\text{(XLIX)} & \rightarrow \\
\text{(L)} & \rightarrow \\
\text{(LI)}
\end{align*}

Reaction of acetophenone (XXXVI) with an excess of thionyl chloride in the presence of a catalytic amount of pyridine has been reported to give a mixture of α-chlorosulphonyl chloride (LII) and the tetrachloro-trisulphide (LIII)\textsuperscript{79-80}. The conversion of LII to LIII in hot thionyl chloride has been observed by n.m.r. spectroscopy\textsuperscript{79}. Thioacyl chloride (LIV) may be a possible intermediate, because sulphur dioxide produced \textit{in situ} during C-sulphonylation is in equilibrium, in the presence of excess thionyl chloride, with sulphur dichloride\textsuperscript{81}, which can be inserted between two molecules of thioacyl chloride (LIV) leading to tetrachloro-trisulphide (LIII).
Ph-C-CHg ^ Ph-C-CH-Cl + Ph-C-C-(S)3-C—C-Ph

(XXXVI)  (LII)  

o . / -^sci^  

Ph-d-c-ci 

(LIV)

(LIII)


g-Cl

79 80 Literature reveals that there is controversy over the existence of α-oxothioacyl chloride and that very little is known about the chemistry of related compounds with adjacent C=O and C=S groups. There are only a few α-oxothionic esters described but the cyclic α-oxothionic esters have hitherto not been described. Synthetic potential of α-chlorosulphenyl chlorides and tetrachlorotrisulphides have extensively been explored. However, because of the limited synthetic approach to thioacyl chlorides, their synthetic applications have not appeared in the literature.

We have investigated the reaction of some 2-hydroxyacetophenones with excess thionyl chloride in the presence of a catalytic amount of pyridine in an attempt to synthesise cyclic α-oxothionic esters (LV) and to subject them to photochemical and thermal decomposition studies with the aim to further the available informations on the reaction intermediates such as LVI, LVII and LVIII and also to explore the synthetic potential of the decomposition reaction.
The reaction of 2-hydroxyacetophenone (LIX) with thionyl chloride in the presence of catalytic amount of pyridine was performed in the following manner. A mixture of 2-hydroxyacetophenone, thionyl chloride and pyridine was stirred at room temperature for three hours. Excess thionyl chloride was then removed at room temperature under reduced pressure to give a red gummy mass which was chromatographed over a silica gel column. Elution of the column with a mixture of petrol:benzene (1:1) afforded a light pink coloured solid which was crystallised from chloroform-petrol mixture as white solid and characterised by spectral methods as the thiirane (LX). Further elution of the column with benzene yielded a complex mixture which could not be resolved even on repeated column chromatography.
CHARACTERISATION OF THIIRANE (LX)

The compound melting at 160-2°C analysed for C₁₆H₁₆Cl₂O₄S. It gave positive Beilstein test indicating the presence of halogen. The infra-red spectrum showed carbonyl (5-membered cyclic) and C-Cl bands at 1725 and 690 cm⁻¹, respectively. The u.v. spectrum displayed bands at 240 and 290 nm. The mass spectrum (Fig.-16) did not exhibit the molecular ion peak expected at m/z 364. However, the peak with the highest mass to charge ratio was seen at m/z 332 along-with two isotopic peaks at m/z 334 and 336. The relative intensities of these peaks were in the ratio of 3:2:1 which suggested the presence of two chlorine atoms in this ion. The formation of fragment at m/z 332 can be explained by the desulphurisation of molecular ion. The presence of the chlorine atoms in the aromatic rings was supported by the peaks at m/z 138 and 110. N.m.r. spectrum (Fig.-17) exhibited no signal other than the signals for the aromatic protons which appeared as a multiplet in the region δ 7.0-8.0 supporting the 1,2,3-trisubstituted nature of the two aromatic ring. It can be said on the basis of above data that compound is either a 1,3-oxathiole (LXI) or a thiirane (LX).
The C=C and enol ether bands, characteristic bands in the infra-red spectrum of 1,3-oxathiole derivatives, were however absent. The compound was, therefore, characterised as thiirane (LX). The structure was further supported by the mass spectrum (Chart-IV). The base peak was at m/z 166 with an isotopic peak at m/z 168 (33%). Another structurally diagnostic fragment was at m/z 198 accompanied by an isotopic peak at m/z 200. The peaks at m/z 103, 91 and 75 were also present.

Though the mechanism of the formation of thiirane (LX) is not fully clear, a plausible mechanism can be outlined as in Scheme-IV. O-Sulphinylation of the hydroxy as well as carbonyl groups followed by CI migration and loss of sulphur monoxide will give compound (LXIII) which will subsequently loss HCl to give benzofuran derivative (LXIV). C-Sulphinylation of compound (LXIV) and subsequent loss of HCl will give sulphine (LXVI). Dimerisation of the sulphine (LXVI) accompanied by the loss of SO₂ will give thiirane (LX).
Chart-IV

- Cl

\[ \text{m/z 332} \]

- Cl

\[ \text{m/z 297} \]

\[ \text{m/z 92} \]

\[ \text{m/z 110} \]

\[ \text{m/z 75} \]

\[ \text{m/z 138} \]

\[ \text{m/z 103} \]

\[ \text{m/z 163} \]

\[ \text{m/z 198} \]

\[ \text{m/z 166} \]

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Scheme-IV

(LIX) + SOCl₂/Py → (LXII)

(LXIV) → (LXIII)

SOCl₂ → C-Sulphonylation

(LXV) → (LXVI)

(LX) → (LXVII)

Dimerisation

-2SO₂

-2SO
The reaction of 2-hydroxy-4-methoxyacetophenone (LXVIII) with thionyl chloride in the presence of catalytic amount of pyridine was carried out in the previously described manner. Thus, a mixture of 2-hydroxy-4-methoxyacetophenone, thionyl chloride and pyridine was stirred at room temperature for three hours. Excess thionyl chloride was removed under reduced pressure at room temperature to give a sulphur smelling red tarry mass. T.l.c. examination revealed it to be a complex mixture. The crude mass was subjected to column chromatography. Elution of the column with petrol:benzene (4:1) afforded a dimeric product (LXIX). Further elution of the column with more polar solvents such as benzene, benzene-ethyl acetate mixture and ethyl acetate yielded a complex mixture which could not be separated on repeated column chromatography.
CHARACTERISATION OF LXIX

The product melting at 129-30°C analysed for $C_{18}H_{11}Cl_3O_5S_2$. It gave positive Beilstein test suggesting the presence of halogen. Molecular ion peak expected at m/z 476 was not observed in the mass spectrum (Fig.-18). The peak with the highest mass to charge ratio was seen at m/z 441 along with two isotopic peaks at m/z 443 and 445. The presence of two chlorine atoms in the ion at m/z 441 was evident from the relative intensities of the isotopic peaks. The fragment at m/z 441 may be formed by the loss of a chlorine atom from the molecular ion. Infra-red spectrum confirmed the absence of hydroxyl and carbonyl groups. It showed C=C, enol ether and C-Cl bands at 1610, 1230 and 690 cm$^{-1}$, respectively. N.m.r. spectrum (Fig.-19) displayed two ortho coupled doublets at $\delta$ 7.44 and 7.80 (J=9 Hz) which were assigned to the protons on the C-6 and C-6', respectively. A multiplet centred at $\delta$ 6.90 for three protons was attributed to the remaining aromatic protons on the rings A and B. A singlet at $\delta$ 3.80 for six protons was assigned to two methoxy groups. The structure was further elucidated with the help of mass spectometry (Chart-V). The base peak was at m/z 213 accompanied by an isotopic peak at m/z 215 (42.15%) indicating the presence of one chlorine atom in the ion. The ions at m/z 228 and 196 supported the presence of chlorine in ring B. The compound can be assigned any of the structures, LXIX or LXX.
Fig. 18
Chart-V
The loss of sulphur monoxide can not be accounted from LXX. The compound was, therefore, characterised as LXIX. The formation of ion at m/z 393 can be explained by the loss of a Cl and sulphur monoxide from the molecular ion. Subsequent loss of chlorine from this ion gave ions at m/z 358 and 323.

The mechanism for the formation of LXIX is also not fully understood. However, a plausible mechanism, in the light of available literature, can be written as in Scheme-V. The formation of LXIX can be explained in terms of either the coupling of α-oxothionic esters, (LXXIII) and (LXXVI), followed by conversion of carbonyl group into dichloride (Route-1) or by the conversion of >C=O group to >CCl₂ in α-oxothionic ester (LXXV) followed by coupling with the α-oxothionic ester (LXXIII) (Route-2).

As is evident from the mechanisms outlined in Schemes-IV and V, the behaviour of two acetophenones towards SOCl₂ in the presence of catalytic amount of pyridine is quite different. While
the initial step in the case of 2-hydroxyacetophenone (LIX) is O-sulphinylation of both the phenolic as well as carbonyl groups, C-sulphinylation is favoured in the case of 2-hydroxy-4-methoxyacetophenone (LXVIII).
Scheme V

(LXVIII) + (LXXVI) → (LXIX)
Dimethyl sulfoxide (DMSO) possesses unique capabilities and is one of the most studied solvents and reagents in organic synthesis. Its chemistry constitutes a topic of continuing interest to organic chemists, offering a rich and fruitful area of study and synthetic applications. The reactivity of DMSO like that of other sulphur compounds derives principally from the presence of vacant 3 'd' orbital on the sulphur atom and it undergoes reactions in which nucleophilic attack occurs on the sulphur atom. The lone pair of electrons on sulphur, however, cannot be expected to favour the approach of a nucleophile, in spite of the presence of a partial positive charge and vacant 'd' orbitals on the sulphur. Therefore, it is not surprising that most reactions in which nucleophilic attack takes place readily on sulphur are aided by prior electrophilic attack on the oxygen atom to give LXXVII. A nucleophile can now perform a facile displacement on sulphur with the departure of leaving group as shown in Scheme-VI. The formation of the sulphonium species (LXXVIII) is usually followed by further reactions.

\[
\begin{align*}
\text{CH}_3 \quad &\text{S} - \text{O} + \text{E} \quad \rightarrow \quad \text{CH}_3 \quad &\text{S} - \text{O} - \text{E} \\
\text{CH}_3 \quad &\downarrow \quad \text{LXXVII} \\
\text{CH}_3 \quad &\text{S} - \text{O} - \text{E} + \text{Nu} \quad \rightarrow \quad \text{Nu} - \text{S} \quad \left< \text{CH}_3 \right> + \text{OE} \\
\text{CH}_3 \quad &\text{Scheme-VI} \quad \text{LXXVIII}
\end{align*}
\]
Activated DMSO reagents have been widely explored for the preparation of sulphilimines $^{83-85}$ and sulphonimines $^{86-88}$, and in the oxidation of a wide variety of structurally diverse alcohols to carbonyl compounds $^{89-91}$. Various electrophilic reagents that have been used to activate dimethyl sulfoxide include trifluoroacetic anhydride $^{89}$, thionyl chloride $^{92}$, oxalyl chloride $^{92}$, dicyclohexyl-carbodiimide $^{93}$, phosphorus pentoxide $^{94}$ and sulphur trioxide-pyridine $^{95}$ etc. The use of acetic anhydride as an activator was first made by Albright and Goldmann $^{96}$ who achieved oxidation of hindered alcohols with DMSO/AC$_2$O. Most such oxidations were confined to comparatively simple alcohols but in a novel variation, Wikholm and Moore $^{97}$ applied the reaction to 2,5-dihydroxy-3,6-diphenyl-1,4-benzoquinone (LXXIX) and realised in this way a neat biogenetic type synthesis of pulvic acid lactone (LXXXII). As may be seen from the adduced mechanism (Scheme-VII), the rearrangement leading to the lactone is initiated by decomposition of the sulphonium salt with the involvement of the enolic double bond.
Oxidation of alcohol is not the only use to which DMSO/\(\text{Ac}_2\text{O}\) reagent has been put. The methyl thiomethyl ethers, formation of which was initially regarded as a nuisance, have become important as protecting groups for alcohols during reactions where dehydration is feared. The reagent has also been employed for the preparation of thiomethyl derivatives (LXXXIII) and (LXXXIV) of phenols and its reaction with \(\beta\)-dicarbonyl compounds, which lead to the stable ylides (LXXXV), has been investigated.
Realising the potential, Zaman et al.\textsuperscript{101} carried out detailed study on the reaction of 4-hydroxycoumarin and its 3-substituted derivatives with DMSO/Ac\textsubscript{2}O. Dimethyl sulphoxide and acetic anhydride converted 4-hydroxycoumarin (LXXXVI) into acetate (LXXXVII) at room temperature but at 120°C this was further transformed into the ylide 3-dimethylsulphoniochroman-2,4-dionate (LXXXVIII). At 160°C the reaction afforded dicoumarol (LXXXIX) and other products derived from this by further reaction.
Literature does not record any further instance of this type of oxidation reactions and it appeared therefore of interest to explore more fully the scope of this reaction. The DMSO/\text{Ac}_2\text{O} oxidation of 2-hydroxydibenzoylmethanes was taken up to check if dimerisations, according to the mechanisms outlined in Scheme-VIII, could be realised through this reaction.
[3,3]-Biflavone

Scheme-VIII
The reaction of 2'-hydroxydibenzoylmethane with dimethyl sulfoxide and acetic anhydride was conducted in the following manner. 2'-Hydroxydibenzoylmethane (XC) was dissolved in dimethyl sulfoxide and acetic anhydride was added. The reaction mixture was heated at 160°C for 4 hours. The usual work up of the reaction and chromatographic purification afforded 3-benzoyl-2-methylbenzo-4-pyrone (XCI) in 33% yield.

![Reaction Scheme](attachment:reaction_scheme.png)

**CHARACTERISATION OF 3-BENZOYL-2-METHYLBENZO-4-PYRONE (XCI)**

The compound melting at 117-8°C gave negative alc. FeCl₃ test indicating the absence of phenolic group. The absence of hydroxy group was further confirmed by its i.r. spectrum. Mass spectrum (Fig.-20) exhibited the molecular ion peak as the base peak at m/z 264. The i.r. spectrum displayed bands at 1670 and 1650 cm⁻¹ indicative of the presence of two carbonyl groups. N.m.r. spectrum (Fig.-21) of this compound showed a singlet for 3 protons at δ 2.40 and a multiplet, integrating for nine protons, in the region δ 7.4-8.15. Two possible structures can be written, keeping
in view the mechanistic considerations, on the basis of its i.r. and n.m.r. spectra in conjunction with the molecular ion peak at m/z 264. Two possible structures are 3-acetylflavone (XCII) and 3-benzoyl-2-methylbenzo-4-pyrone (XCI). The structure was further elucidated with the help of u.v. and mass spectra.

![Structure](xcii.png)

(XCII)

The compound exhibited in its u.v. spectrum a strong band for benzoyl moiety at 250 nm and a weak band at 292 nm. The most diagnostic peak in the mass spectrum of this compound (Chart-VI) was at m/z 187 due to the ion resulting from molecular ion by the loss of phenyl ring. The peak at m/z 121 may be attributed to the fragment resulting from the retro-Diels-Alder (RDA) fission. Other RDA fragment at m/z 144 was not present but two ions, probably derived from this fragment, at m/z 77 and 67 were prominent. Few other prominent peaks in the spectrum were at m/z 159, (M-PhCO)^+; 236, (M-CO)^+; 235, (M-CHO)^+ and 105, PhCO^+.

The ion derived from molecular ion by the loss of ring B is not observed in the mass spectrum of flavones. Furthermore, the
Chart-VI
band at longer wave length in generally strong in the u.v. spectra of flavones. The compound was, thus, characterised as 3-benzoyl-2-methylbenzo-4-pyrone (XCI).

Similarly, when the reaction of 2',4'-dihydroxydibenzoylmethane (XCIII) was performed with dimethyl sulphoxide and acetic anhydride under identical conditions for 4 hours, the reaction on usual work up and column chromatography over silica gel afforded 3-benzoyl-7-hydroxy-2-methylbenzo-4-pyrone (XCIV) in 25% yield.

![Chemical structures](image)

**CHARACTERISATION OF 3-BENZOYL-7-HYDROXY-2-METHYLBENZ0-4-PYRONE (XCIV)**

The compound melting at 230-2°C gave positive alc. FeCl₃ test. The mass spectrum (Fig.-22) exhibited molecular ion peak at m/z 280. The presence of phenolic group was further substantiated by its i.r. spectrum. i.r. spectrum exhibited bands at 3400 (OH), 1670 and 1660 cm⁻¹ (C=O). The u.v. spectrum displayed a strong band at 252 nm and a weak band at 291 nm. N.m.r. spectrum (Fig.-23) of this compound showed a singlet at δ 2.40 for three protons ascribable to C-2 methyl group. Aromatic region of the spectrum
displayed a multiplet for three protons in the region \( \delta 6.70-7.00 \) assignable to C-6,8 and C-7 hydroxyl protons. Two more multiplets, each for 3 protons, were seen in the region \( \delta 7.32-7.55 \) and \( \delta 7.70-8.00 \). These signals were attributed to the remaining 6 aromatic protons. Mass spectrum of this compound (Chart-VII) exhibited base peak at \( m/z 43 \). Two peaks resulting from the molecular ion by the loss of carbon monoxide and CHO, were present at \( m/z 252 \) and 251, respectively. The most diagnostic peak in the spectrum was at \( m/z 203 \) due to the ion derived from the \( M^+ \) by the loss of phenyl ring. RDA fragments were seen at \( m/z 136 \) and 137. Other peaks in the mass spectrum were at \( m/z 147, [M-(Ph+2CO)]^+; 175, [M-PhCO]^+; 109, 108, 77 \) and 67. The compound was thus characterised as 3-benzoyl-7-hydroxy-2-methylbenzo-4-pyrene (XCV).  

The formation of 3-benzoyl-2-methylbenzo-4-pyrones by the reaction of 2-hydroxydibenzoylmethanes with dimethyl sulphoxide and acetic anhydride can be explained in terms of conversion of 2-hydroxydibenzoylmethanes to enol acetates (XCV) followed by Fries rearrangement to give triketones (XCVI). The attack of 2-hydroxy group on the acetyl carbonyl group would have then resulted in the formation of 2-hydroxybenzo-4-pyranone derivatives (XCVII) followed by dehydration to give 3-benzoyl-2-methylbenzo-4-pyrone derivatives (Scheme-IX).
Chart-VII
The reaction of 2'-hydroxydibenzoylmethanes with dimethyl sulphoxide and acetic anhydride did not yield any of the expected products (Scheme-VIII). Furthermore, no thiomethylated product could be isolated. The absence of these products in this reaction
points to the existence of a particularly favourable mechanism, perhaps the one in Scheme-IX. It can be said that the species (XCIX), probably, did not form. It can be envisaged that CH$_2$=S-CH$_3$ species either was not present or the enol acetates (XCV) could not trap it to give (XCIX) as shown in Scheme-X. On the other hand, the Fries rearrangement was favoured.

\[
\begin{align*}
\text{R} & = \text{H, OH} \\
\text{(XCV)} & \xrightarrow{+ \text{CH}_2=\text{S}-\text{CH}_3} \text{(XCVIII)} \\
\text{(XCIX)}
\end{align*}
\]

Scheme-X
REACTION OF 2'-HYDROXYCHALCONES WITH IODINE MONOCHLORIDE UNDER BASIC CONDITION

The development of synthetic chemistry of biflavonoids, apart from flavonoids, requires additional impetus. To substantiate the structure, the synthesis of biflavonoids has attracted as much attention as the associated work of their isolation and structure elucidation. The efforts, however, remain restricted mainly to the synthesis of members of a few biflavone families, where Ullmann reaction comprises the major route. The reported synthetic approaches to biflavones employ the Ullmann coupling reaction in two ways. The one involves Ullmann coupling of the two iodinated flavone nuclei, whereas the other is based on the synthesis of suitably substituted biphenyls by Ullmann reaction followed by their hetero-annulation to biflavones. The synthesis of biflavonoids with reduced heterocyclic rings seems to be intricate by virtue of their stereochemical complexities. One of the main objectives of the present studies was to develop synthetic strategies to assist in the synthesis and absolute stereochemistry of reduced biflavonoids by the Ullmann type coupling of preannulated iodophenyl derivatives i.e. iodinated chalcones, which have hitherto not been employed in the synthesis of biflavonoids. Synthetic approach along this line may possibly provide a stereocontrolled route to the reduced biflavonoids. Hence, at the intermediate strategic level our initial studies were directed towards search for methodologies for selective and high yield syntheses of iodo-chalcones.
Aromatic ring iodinated derivatives are generally preferred for the better yields of the coupled products. Interaction of chalcones with various halogens and interhalogens has been reported, and although the preparation and properties of chalcone dihalides are well documented, only sporadic reports are available in the literature on the aromatic halogenation of chalcones. Moreover, the only reported method to bring about nuclear iodination of chalcone exploits iodine in the presence of an oxidising agent, iodic acid, and is not of general applicability. In the event of lack of a general, selective and convenient method for the synthesis of ring iodinated chalcones, we made a systematic attempt to develop convenient and high yielding methodology for the synthesis of iodochalcones and at subsequent instance to couple them en route to bichalcones. We have studied the reaction of various 2'-hydroxychalcones, having oxygenation pattern most abundant in natural flavonoids, with iodine monochloride under basic conditions.

Our choice of iodine monochloride was prompted by the fact that iodine monochloride is known to be a better iodinating agent than iodine, where an oxidising agent has to be present to oxidise iodine to a better electrophile. Although, the reaction of chalcones with iodine monochloride in acidic as well as neutral medium have extensively been studied, the behaviour of iodine monochloride towards chalcones in strong alkaline medium has, however, not been explored.
Interaction of iodine monochloride with chalcones in acidic or neutral medium results, generally, in the formation of $\alpha,\beta$-addition products$^{108}$. 3-Iodoflavanones have also been reported to be formed$^{109}$. The possibility of ring iodination of chalcones with iodine monochloride was indicated in Weber's studies$^{105}$, but the method seems limited as applicable only to chalcones possessing phloroglucinol derived ring A. Moreover, the possibility of the cyclisation of chalcones to the corresponding 8-iodoflavanones also limits product selectivity.

As a model substrate, the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone with iodine monochloride was conducted in the following manner. To a mixture of 2'-hydroxy-4,4',6'-trimethoxychalcone in alcohol and sodium hydroxide in water, iodine monochloride was added dropwise at room temperature with stirring. After continued stirring for additional 15 minutes at room temperature, the reaction was worked up to give 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (CI) in 93% yield.

![Chemical structure of 2'-hydroxy-4,4',6'-trimethoxychalcone and 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone](image)
CHARACTERISATION OF 2'-HYDROXY-3'-IODO-4,4',6'-TRIMETHOXYCHALCONE (CI)

The compound melting at 178°C gave positive Beilstein and alcoholic FeCl$_3$ tests. The presence of hydroxy group was further confirmed by its i.r. spectrum. The i.r. spectrum displayed OH stretching band at 3400 cm$^{-1}$ and carbonyl stretching band at 1620 cm$^{-1}$. Preliminary tests and the infra-red spectroscopy, although, provided valuable informations for the structure elucidation of the compound, the exact structure was elucidated on the basis of mass and n.m.r. spectroscopy. The molecular ion peak at m/z 440, in the mass spectrum of the compound (Chart-VIII), confirmed the presence of iodine in the molecule. The fragments at m/z 439 (M-H)$^+$ and at 333 (M-B ring)$^+$, characteristic ions in the mass spectrum of a 2'-hydroxychalcones, confirmed the absence of iodine in the ring B. The most diagnostic fragments which confirmed the presence of iodine in the ring A were retro-Diels-Alder fragments at m/z 306 and 134. Another fragment at m/z 307 which probably resulted by the fission of $\text{C} = \text{C}_\alpha$ bond, also confirmed the presence of iodine in ring A. The ion at m/z 161 is formed by the fission on other side of carbonyl group. An intense peak at m/z 121 is due to the characteristic benzyl cation. It is obvious, from the Chart-VIII, that the ions are derived both from the chalcone and its corresponding flavanone. These observations are indicative of the chalcone-flavanone isomerisation either thermally or on electron impact. The position of the iodine in the molecule was located with the help of n.m.r. spectro-
scopy. N.m.r. spectrum displayed a singlet at $\delta$ 7.82 integrating for two protons ascribable to the C-α and C-β protons. Three singlets at $\delta$ 3.88, 3.90 and 4.00, each integrating for three protons, were due to the three methoxyl protons. Aromatic region of the spectrum exhibited a pair of doublet at $\delta$ 6.96 and 7.58 ($J$=9 Hz), each for two protons and showing $A_2B_2$ pattern, which was assigned to the C-3,5 and C-2,6 protons, respectively. A singlet at $\delta$ 6.10 integrating for one proton was assigned to the C-5' proton. A downfield singlet for one proton at $\delta$ 13.20 was ascribed to 2'-OH group. The compound was, thus, characterised as 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (CI). The structure was further substantiated by comparison with an authentic sample of CI (co-t.l.c., m.m.p. and n.m.r.) prepared by Chen's procedure\textsuperscript{106}.

The position of iodine in the molecule was further confirmed by the oxidative cyclisation of compound (CI) to 8-iodo-5,7,4'-trimethoxyflavone (CII) with selenium dioxide in dioxane.
Chart-VIII
In the light of the available literature on the mechanism of electrophilic substitution, it can be speculated that under strong basic conditions the presence of the 2'-hydroxy group in the ring A, probably by the formation of phenoxide ion, facilitates electrophilic substitution. This gives a selective nuclear iodination product (CI) in competition with the electrophilic addition product (CIII). The high regio-selectivity of the reaction may be attributed to the steric factors. Two methoxy groups on either side of the carbon-5', probably, hinder the attack of iodonium ion at the 5'-position, and the iodonium ion goes to, comparatively less hindered, carbon-3' of the ring A. The mechanism of the reaction is outlined in Scheme-XI.

\[\text{Scheme-XI}\]
The above method of nuclear iodination was also found to work effectively in the case of chalcones whose ring A derives from resorcinol. Thus, the reaction of iodine monochloride with alcoholic solution of 2'-hydroxy-4,4'-dimethoxychalcone (CIV) in alkaline medium resulted in the formation of 2'-hydroxy-5'-iodo-4,4'-dimethoxychalcone (CV).

CHARACTERISATION OF 2'-HYDROXY-5'-IODO-4,4'-DIMETHOXYCHALCONE (CV)

The compound melting at 182-184°C exhibited, in its mass spectrum (Fig. 24), $M^+$ peak at m/z 410 showing the presence of iodine in the molecule. The presence of halogen was also indicated by the positive Beilstein test. The compound exhibited, in the infra-red spectrum, the bands at 3430 cm$^{-1}$ (OH) and 1625 cm$^{-1}$ (C=O). The structure of the compound was easily elucidated with the help of n.m.r. spectroscopy and mass spectrometry. The fragmentation pattern of the compound (Chart IX) clearly showed the presence of iodine in the ring A. The most diagnostic peaks in the spectrum were at m/z 277 and 276, derived from molecular ion by either the
Chart-IX
retro-Diels-Alder fission or fission of $\beta$-C$_\alpha$ bond. These fragments suggested the presence of iodine in ring A. The ring B fragments were seen at m/z 135, 133 and 121. The loss of ring B from molecule ion afforded an ion at m/z 303. The position of the iodine was located with the help of n.m.r. spectrum. Two singlets at $\delta$ 6.47 and 8.27 in the aromatic region of n.m.r. spectrum (Fig.-25) were assigned to two uncoupled aromatic ring A protons in the positions 3' and 6', respectively. The presence of iodine in the 3' position should have given two ortho-coupled doublets. Two singlets at $\delta$ 3.9 and 3.95, each integrating for three protons, were ascribable to methoxyl protons on the C-4 and C-4', respectively. Ring B protons were seen as two doublets at $\delta$ 6.95 and 7.65 (J=9 Hz), each for two protons, assignable to C-3,5 and 2,6 protons, respectively. A pair of doublets at $\delta$ 7.37 and 7.94 (J=17 Hz), each integrating for one proton, was due to the C$_\alpha$ and C$_\beta$ protons, respectively. The signal for hydroxy group was observed at $\delta$ 13.30 as a singlet for one proton. The compound was thus characterised as 2'-hydroxy-5'-iodo-4,4'-dimethoxychalcone (CV). In order to demonstrate the generality of the reaction, 2'-hydroxy-3',4',4'-trimethoxychalcone (CVI) was subjected to the above reaction under similar conditions. The reaction was worked up after 15 minutes to afford 2'-hydroxy-5'-iodo-3,4,4'-trimethoxychalcone (CVII) in 94% yield.
CHARACTERISATION OF 2'-HYDROXY-5'-IODO-3,4,4'-TRIMETHOXYCHALCONE (CVII)

The compound melting at 197-8°C showed in its mass spectrum, $M^+$ peak at m/z 440. It gave positive Beilstein and alc. FeCl₃ tests. The i.r. spectrum displayed bands at 3430 and 1620 cm⁻¹ for OH and C=O stretching frequencies, respectively. The structure of this compound was elucidated with the help of its n.m.r. and mass spectra. The mass spectrum (Fig.-26) showed molecular ion peak at m/z 440 accompanied by an $(M+H)^+$ ion. An ion at m/z 303, [M-B ring]$^+$, revealed the absence of iodine in ring B. RDA fragments at m/z 276 and 164 confirmed the presence of iodine in the ring A (Chart-X).

N.m.r. spectrum (Fig.-27) exhibited three singlets at δ 3.80, 3.88 and 3.90, each for three protons, assignable to the three methoxy groups. Aromatic region of the spectrum showed a shielded singlet for one proton at δ 6.45 ascribed to the C-3' proton. Another singlet for one proton at δ 8.26 was due the C-6'
proton. Ring B protons were seen as, a doublet at δ 6.80 (J=9 Hz) for C-5 proton and a multiplet centred at δ 7.16, for two protons, assignable to C-2,6 protons. A pair of doublet at δ 7.30 and 7.80 (J=17 Hz), each integrating for one proton, was due to the Cα and Cβ protons, respectively. A one proton singlet at δ 13.28 was attributed to the phenolic proton. The compound was thus, characterised as 2'-hydroxy-5'-iodo-3,4,4'-trimethoxychalcone (CVII). The mechanisms of the formation of 5'-iodochalcones (CV, CVII) are probably similar to that outlined in Scheme-XI. However, in these cases, electrophilic substitution occurred at C-5' as it is sterically less hindered compared to C-3'.

Subsequently, we intended to utilise iodochalcones in coupling reaction for the synthesis of bichalcones. The desire was two fold: the coupling of iodo-derivatives through an Ullmann type reaction and/or coupling through phenolic oxidation. It should be mentioned that the aromatic rings of phenols are very susceptible to oxidation by one-electron oxidants and indeed several one electron oxidants have been used in the oxidative coupling of hydroxyflavones. The conventional Ullmann coupling reaction of aromatic halides, which utilises Cu-bronze, is generally associated with low yield of the coupling product and moreover, the reaction has limit in its use with iodophenols\textsuperscript{110}. We therefore required a mild and more effective coupling reagent which could possibly entertain our motive of phenol oxidative coupling and we entrusted the domain of in-situ generated organometalllic reagents.
Chart-X
REACTION OF HALOCHALCONES WITH NiCl$_2$-Zn-KI REAGENT SYSTEM

Developments in organometallic chemistry through the decades have come with exponential growth. Organic synthesis has now attained an unprecedented sophistication which is due in large measures to the influx of rapidly evolving organometallic methodologies. New reactions based on organometallic species have not only expanded the capability of fundamental transforms, but also imparted significant latitude to the strategic levels of synthesis. Furthermore, developments in certain areas of organometallic chemistry, especially homogeneous catalysis, hold great promise in revolutionising the chemical industry.

Organic chemistry of nickel has emerged as the most heralded and widely used among the transition metals in organic synthesis. Great potential exists for the synthetic applications of the inter and intramolecular couplings of aryl and alkyl halides in the synthesis of complex molecules when mild conditions and selectivity are demanded by an array of sensitive functional groups. Zerovalent nickel reagents offer prolific new areas of synthetic organic methodology. It has been shown recently that some nickel complexes such as bis-(cycloocta-1,5-diene) nickel$^{111}$, tris-(triphenylphosphine) nickel$^{112}$ and bis-(triphenylphosphine) nickel (II) dichloride along with excess zinc powder and triphenylphosphine$^{113}$ can efficiently couple aryl and alkenyl halides under mild
conditions. However, the fact that these complexes are air sensi-
tive or are conventionally prepared by cumbersome techniques, involv­
ing trialkyl or dialkylalkoxyaluminum species as reducing
agents under vacuum line or dry box conditions, has limited their
synthetic usefulness\(^{114}\). The catalytic properties of elemental
nickel species have been the subject of much attention for exploit-
ation in organic synthesis. In-situ generated nickel (0) species, in
particular, have recently found potential applications in the
synthesis of biaryls\(^{115}\). The appeal derives from the simplicity of
reagent formation, their increased reactivity relative to traditional
complexes and in most circumstances predictable regio- and stereo-
chemistry. Quite often, in-situ generated nickel (0) species have
had the opportunity to demonstrate their potential only after more
customary nickel (0) complexes failed to give satisfactory results.

Takagi et al.\(^{116}\) have recently reported that the reduction
of nickel (II) salts, like nickel (II) chloride or bromide, with
zinc powder in the presence of potassium iodide and/or thiourea in
hexamethylphosphoric triamide (HMPA) yield a dispersed metallic
nickel species. They found that in-situ generated nickel species,
presumably atomic nickel, was an effective catalyst for the Ullmann-
type coupling reaction of aryl iodides with zinc powder to give
biaryls in excellent yields under mild conditions.

\[
2\text{ArI} + \text{Zn} \xrightarrow{\text{Ni(O)}} \text{Ar}_2 + \text{ZnI}_2
\]
Biaryls have also been prepared from aryl bromides, in high yields, applying the conditions used in the coupling of aryl iodides. The formation of biaryls from aryl bromides was found to be due to the rapid formation of aryl iodide by the Finkelstein-type halogen exchange reaction of aryl bromides with potassium iodide catalysed by the \textit{in-situ} generated nickel (0) species. In the reaction of aryl bromides with NiCl$_2$-Zn-KI reagent system, the Finkelstein-type halogen exchange and Ullmann-type coupling reactions compete, thus diminishing the selectivity. Detailed investigations on the selectivity of the reaction suggested that the selectivity depends on the amount of zinc powder used; a decreased amount of zinc powder favours the formation of aryl iodide, but it simultaneously reduces the conversion. A stoichiometric amount of zinc powder sufficed for the Ullmann-type coupling reaction, but the use of excess of zinc powder was desirable.

Aryl iodides containing an electron-withdrawing substituent in the ortho position afforded large quantities of dehalo-protonated products which probably arose from organozinc compounds, formed by the interaction of aryl iodides and zinc powder, which were fairly inert under these conditions. However, the use of excess of nickel (II) salt, in these cases, afforded biaryls in good yields presumably via the well known transfer of organo group from Zn (II) to Ni (II) even at ambient temperature.
With the precedent success, the methodology of Takagi et al.\textsuperscript{116} is exceptionally versatile, mild, convenient and high yielding compared with the several other methodologies for the Ullmann-type coupling of aryl and alkyl halides, and hence, the NiCl$_2$–Zn–KI appeared as a fascinating and promising reagent system to pursue our interests. With the use of NiCl$_2$–Zn–KI reagent system we might have several facilities. The dispersed metallic nickel, a reactive nickel species, which is easily produced by the reduction of NiCl$_2$ with zinc powder in the presence of potassium iodide might serve as an effective catalyst in the reaction of iodohydroxychalcones with zinc powder to yield bichalcones. Otherwise, if this Ullmann-type coupling is prohibited by some factors, in the light of known oxidative\textsuperscript{120} and Lewis acid type catalysing properties of zinc (II) chloride, the possible phenol oxidative coupling induced formation of bichalcones and chalcone–flavanone isomerisation was expected. The possibility of simultaneous occurrence of these reactions was also borne in mind.

When the iodoxchalones (C, CV, CVII) were subjected to the Takagi's reaction, no bichalcone was obtained. In a further attempt to achieve our target of synthesising bichalcones, the use of N,N-dimethylformamide (DMF) instead of HMPA was made, as it has been shown to be a good solvent for the coupling reactions\textsuperscript{121}. The results yet did not prove successful in bichalcone synthesis, however, cyclic dehalogeno-protonated products were obtained. Apart from the
synthetic significance, formation of these products has important implications in the understanding of flavonoid biogenesis.

As a model substrate, 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychloralcone (CI) was heated at reflux temperature in N,N-dimethylformamide in the presence of nickel chloride, zinc powder and potassium iodide for 3 hours. T.l.c. examination of the reaction mixture revealed almost total conversion. The reaction was worked up to yield 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) in 80% yield and a trace of 5-hydroxy-7,4'-dimethoxyflavone (CIX).
CHARACTERISATION OF 5-HYDROXY-7,4'-DIMETHOXYFLAVANONE (CVIII)

This compound melting at 115-6°C exhibited the molecular ion peak, in its mass spectrum, at m/z 300. It gave positive alcoholic FeCl₃ and Shinoda tests. Infra-red spectrum showed bands at 3440 and 1640 cm⁻¹ for hydroxyl and carbonyl stretchings, respectively. The u.v. spectrum showed maxima at 225, 286 and 320 nm indicating thereby the flavanone nature of the compound.

The n.m.r. spectrum exhibited a complex multiplet centred at δ 2.82 for two protons ascribed to C-3 protons. A singlet integrating for six protons at δ 3.70 was attributed to the C-7 and C-4' methoxy protons. A one proton doublet of doublet (J_{trans}=11 Hz, J_{cis}=5 Hz) resonating at δ 5.25 was unmistakably due to the C-2 proton. In the aromatic region, a shielded singlet at δ 5.94 integrating for two protons was assigned to C-6 and C-8 protons. The signals for the ring B protons appeared as a couple of doublets at δ 6.85 and 7.28 (J=9 Hz), each for two protons and showing A₂B₂ pattern. These signals were imputed to C-3,5 and C-2,6 protons, respectively. A singlet for one proton at δ 16.00 was ascribed to the C-5 hydroxyl proton. The compound was, thus, characterised as 5-hydroxy-7,4'-dimethoxyflavanone (CVIII).

The mass spectrum showed an intense molecular ion peak at m/z 300 accompanied by an (M+1)⁺ ion at m/z 301. The most diagnostic fragments in the spectrum were observed at m/z 166 and at m/z 134 resulting from the retro-Diels-Alder fission of the molecule.
The presence of the hydroxy group in the ring A was confirmed by these ions. Other characteristic fragments in the spectrum were at m/z 299, (M-H)^+; 193, (M-B ring)^+ and 121, benzyl cation (Chart-XI).

In the event of the failure of the Ullmann-type and phenol oxidative coupling reactions of 3'-iodochalcone (CI) to furnish bichalcone, 3'-bromo-2'-hydroxy-4,4',6'-trimethoxychalcone (CXa) was subjected to the same reaction. The reaction on usual work up too yielded the same dehalogenoprotonated cyclic products, 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) in 72% yield and a trace of 5-hydroxy-7,4'-dimethoxyflavone (CIX). It was then reasoned that the presence of free 2'-hydroxy group in these compounds might be responsible for the failure of Ullmann-type coupling reaction. However, when the reaction of 3'-bromo-2',4',4,6'-tetramethoxychalcone (CXb) was conducted with NiCl₂-Zn-KI reagent system in DMF under similar conditions, mainly 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) was obtained. It was, therefore, envisaged that this reagent system effected fast dehalogenoprotonation at C-3' and 2'-hydroxy-4,4',6'-trimethoxychalcone (C) and 2',4',4,6'-tetramethoxychalcone (CXc), having no halogen at C-3', when subjected to the above reaction yielded, expectedly, the same products (CVIII) (major) and (CIX) (minor).
Chart XI
It is evident from these studies that under the employed conditions the reaction did not follow the expected path (Scheme-XII). On the other hand, the major course of action of NiCl$_2$-Zn-KI on 2'-oxygenated chalcones is to induce cyclisation to the corresponding flavanones and to some extent oxidative cyclisation to flavone. Moreover, the process is accompanied, in respective cases, with the dehaloprotonation and selective demethylation of C-5 methoxy group.

It can be, therefore, envisaged that halochalcones could not trap the in-situ generated atomic nickel, but undergo fast dehaloprotonation. Dehaloprotonation might be effected either with Ni (O)$_2$ or ZnCl$_2$ in the presence of DMF. The cyclisation of chalcones to the corresponding flavanones may reasonably be explained in terms of catalysis by co-generated ZnCl$_2$ followed by
demethylation of the 2' and/or 6' methoxy group/s. It is quite probable that zinc chloride might effect demethylation of 2' and/or 6' methoxy group/s followed by simultaneous cyclisation. It is worthwhile to mention here that chalcones with free hydroxyls in the 2' and 6' positions cyclise themselves to the corresponding flavanones.\textsuperscript{125}
Flavanones, which are important intermediates for the synthesis of flavonoids and biflavonoids, are generally obtained by acid- or base-catalysed ring closure of chalcones; however, the reported methods are not high yielding and convenient. Also, the development of novel reagents which could mimic the role of chalcone-flavanone isomerase is extremely important in the study of flavonoid biosynthesis. Partially methylated polyhydroxyflavonoid compounds frequently occur in plants and the corresponding flavanones are often required for comparison and transformations. The methods available for partial demethylation are limited in their application to flavanones and chalcones containing phloroglucinol structure. Hence, the high yield chalcone-flavanone conversion accompanied by selective demethylation of the 5-OCH₃ group seemed interesting and prompted us to explore further synthetic potential of the reaction.

In extension, to define the scope of the reaction two chalcones with resorcinol derived ring A were subjected to the above reaction. Thus, 2'-hydroxy-4,4'-dimethoxychalcone (CIV) and 2'-hydroxy-3,4,4'-trimethoxychalcone (CVII) were refluxed, in separate experiments, in DMF in the presence of nickel chloride, zinc powder and potassium iodide for one week. The reactions on usual work up revealed no change and starting materials were recovered almost quantitatively.
It can be inferred from the above results that the presence of an oxygen function at the 6' position is the basic requirement for the cyclisation of chalcones to the corresponding flavanones with NiCl$_2$-Zn-KI in DMF.

The formation of a trace of 5-hydroxy-7,4'-dimethoxy-flavone (CIX), in the above reactions, fascinated us to further explore the potential of this reaction. Thus, a mixture of 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (CI), nickel chloride, zinc powder and potassium iodide in the molar ratio (1:1.1:1:1.25) was heated at reflux temperature in N,N-dimethylformamide for one week. The reaction on work up yielded 5-hydroxy-7,4'-dimethoxy-flavone (CIX), in 72% yield. The reactions of chalcones (CXa-c, C) with NiCl$_2$-Zn-KI reagent system were also studied under identical conditions and, in all the cases, the only product that could be obtained was 5-hydroxy-7,4'-dimethoxyflavone (CIX).
CHARACTERISATION OF 5-HYDROXY-7,4'-DIMETHOXYFLAVONE (CIX)

The compound, m.p. 170-171°C, gave positive alcoholic ferric chloride and Zn-HCl tests indicating it to be a hydroxyflavone. Its infra-red spectrum displayed bands at 3400 (OH) and 1620 cm\(^{-1}\) (C=O). The product exhibited maxima at 270 and 328 nm in the u.v. spectrum, characteristic of 5-hydroxy-7,4'-dimethoxyflavone (CIX).

The n.m.r. spectrum exhibited a singlet at \(\delta\) 3.85 integrating for six protons assignable to the methoxyls at C-4' and C-7. The protons on the ring A appeared as two meta-coupled doublets (J=3 Hz), each integrating for one proton, at \(\delta\) 6.27 and 6.36 ascribed to C-6 and C-8 protons, respectively. A sharp singlet at \(\delta\) 6.45 integrating for one proton was due to C-3 proton. Two
doublets, each integrating for two protons and indicating the $A_2B_2$ pattern, at $\delta$ 6.90 and 7.72 were assigned to the ring B protons in the positions 3',5' and 2',6', respectively. The signal for the C-5 hydroxy group proton was observed as a singlet at $\delta$ 16.50.

The mass spectrum exhibited the molecular ion peak as the base peak at m/z 298. The fragments resulting from the RDA fission of the molecular ion were observed at m/z 166 and 132. An ion at m/z 135 is characteristic ring B fragment formed by the retro-Diels-Alder fragmentation of the molecular ion by pathway II. Other prominent peaks in the spectrum were at m/z 297, (M-H)$^+$ and 269, (M-CHO)$^+$ (Chart-XII).

The synthesis of 5-hydroxy-7,4'-dimethoxyflavone (CIX) can be envisaged as a chalcone-flavanone-flavone conversion since the chalcone-flavanone conversion accompanied by selective demethylation is quite facile under these conditions.

Moreover, in a separate experiment, when 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) was heated at reflux temperature in DMF in the presence of NiCl$_2$-Zn-KI reagent system for one week, the conversion into 5-hydroxy-7,4'-dimethoxyflavone (CIX) was almost quantitative.
Chart-XII
The transformation of flavanone (CVIII) to flavone (CIX) may be explained in terms of catalysis by the *in-situ* generated atomic nickel. It is quite probable that the flavone (CIX) may be formed from metal enolate (CXI), which may be formed by the reaction of flavanone (CVIII) with ZnCl₂, by the oxidative loss of metal species. The possible intermediacy of metal enolate (CXI) in the flavanone-flavone conversion seems of immense biogenetic importance, since it offers an explanation for the biogenesis of flavones, having no substituent or without a free hydroxy group in the ring B, which is not yet fully understood.
Many special hypotheses, based on good chemical analogies, have been proposed to explain the genesis of flavones, having no substituent or without a free hydroxy group in ring B. Proposals for the formation of flavones have included direct oxidation of a flavanone to give a flavanone C-3 cation which could be transformed to flavone or enolisation of the flavanone followed by attack by the equivalent of OH and dehydration (Scheme-XIII). However, the mechanisms proposed for these oxidation reactions are doubtfully feasible in-vitro.

Scheme-XIII
Birch\textsuperscript{127} has suggested that the metal assisted enolisation of flavanone followed by an oxidative loss of the metal species would also yield the flavone. This hypothesis was, however, neglected in the event of lack of a chemical analogy for this reaction and the recent evidence suggesting that the chalcones rather than flavanone are the more direct precursors of flavones.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=0.3\textwidth]{diagram.png}};
\end{tikzpicture}
\end{center}

Pelter \textit{et al.}\textsuperscript{29} have proposed, on the basis of their studies on the oxidation experiments with flavonoids, that phenolic oxidation of a 4-(2)-hydroxychalcone or [4'-(2')-hydroxyflavanone] serves to initiate the transformation to flavone. The noteworthy point of their studies was the lack of oxidation of those compounds in which the hydroxy group on the ring B was methylated.

The production of flavones not bearing a hydroxy group on the B-ring is, thus, not explained by Pelter's hypothesis. Pelter \textit{et al.} have suggested that such compounds are made in a totally different fashion from other flavones, but if it be assumed that
the general mode of biosynthesis is the same, either a 4'-hydroxy group is lost after flavone formation or the oxidation proceeds by a different pathway. They have envisaged that these compounds are probably formed directly from chalcones by a modification of Birch's proposal (Scheme-XIV). Cyclisation of the 2'-hydroxychalcone is initiated by a metal ion to yield metal enolate (CXII) directly. The proposal differs from previous suggestion in that (CXII) does not arise from ketone by initial enolisation of flavanone.

![Scheme-XIV](image)

The possible intermediacy of zinc enolate (CXI) in the transformation of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) to 5-hydroxy-7,4'-dimethoxyflavone (CIX) stimulated interest in the mechanism of this reaction. Thus, in order to obtain an insight into the mechanism of this reaction, the reactions of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with zinc chloride and nickel chloride, in separate experiments, have been studied.
REACTION OF 2'-HYDROXY-4,4',6'-TRIMETHoxyCHALCONE (C) WITH ZINC CLORIDE

The reaction was performed by refluxing 2'-hydroxy-4,4',6'-trimethoxychalcone in N,N-dimethylformamide in the presence of zinc chloride. The reaction was terminated after one week and worked up to get a crude mass which was subjected to column chromatography over silica gel. Elution of the column with different solvent systems afforded four products which were identified as 5-hydroxy-7,4'-dimethoxyflavanone (CVIII), 5,5''-dihydroxy-7,7'', 4',4''-tetramethoxy-[8,8'']-biflavanone (CXII), 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[6,8'']-biflavanone (CXIII) and 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[6,6'']-biflavanone (CXIV).
(C) reflux, 1 week

ZnCl$_2$, DMF

(CVIII) +

(CXII) +

(CXIII) +

(CXIV)
CHARACTERISATION OF 5,5''-DIHYDROXY-7,7'',4',4''-TETRAMETHOXY-[8,8'']-
BIFLAVANONE (CXII)

The compound melting at 170-2°C gave positive alcoholic FeCl₃ and Shinoda tests. The infra-red spectrum showed bands at 3440 (OH) and 1635 cm⁻¹ (5-hydroxyflavanone C=O). Ultra-violet spectrum was almost identical to that of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) exhibiting bands at 228, 290 and 320 nm. The structure was further elucidated with the help of n.m.r. and mass spectra.

N.m.r. spectrum (Fig.-28), in particular the aromatic region, proved very helpful in the structure elucidation. A striking degree of symmetry in the molecule was clearly evident from even a cursory examination of the n.m.r. spectrum which, being remarkably similar to that of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) and showing only two equivalent high field phloroglucinol ring protons, at once suggested either a C-6/C-6'' or a C-8/C-8'' interflavonoidic linkage. The aromatic region of the spectrum displayed a pair of doublets, showing typical A₂B₂ pattern, at δ 6.91 and 7.37 (J=9 Hz) which were assignable to eight protons on the two p-substituted B-rings. A shielded singlet in the aromatic region at δ 6.05, with an integration one fourth to that of signals for rings B protons, was ascribed to the two equivalent protons on C-6 and C-6''. A multiplet centred at δ 3.00, integrating for four protons was ascribable to the C-3 and C-3'' methylene protons. Another multiplet centred
at δ 5.33 for 2 protons was assigned to the C-2 and C-2'' protons. Two singlets, each integrating for six protons, observed at δ 3.76 and 3.82 were due to the protons of the four methoxy groups on C-7,7'',4' and 4''. A singlet for two protons at δ 12.12 was due to the phenolic protons in the position 2' and 2'''. Of the two possible linkages, the compound was assigned C-8/C-8'' linkage since the n.m.r. data and melting point of this compound are different from that of 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[6,6'']-biflavanone (CXIV)128. The compound was thus characterised as 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[8,8'']-biflavanone (CXII), which was further supported by its mass spectrum (Fig.-29).

The pattern of the mass spectral fragmentation of the compound (Chart-XIII) provides clear evidence in favour of the high symmetry in the molecule. The mass spectrum is dominated by the doubly charged ions. The molecular ion peak expected at m/z 598 was not observed. However, the appearance of the ion at m/z 299 can be attributed either to the formation of doubly charged molecular ion, M''', or to the fission at the diaryl linkage giving two fragments with identical mass to charge ratios, or to the contributions from both. The loss of one hydrogen atom or ring B from each flavanone unit of the doubly charged molecular ion, M'''', gave doubly charged ions at m/z 298 and 192. The RDA fragmentation of the each flavanone unit yielded ring B fragment at m/z 134 and a doubly charged ion at m/z 165. RDA fragmentation by the alternate pathway
afforded another doubly charged ion at m/z 166. The formation of an ion at m/z 444 may be explained in terms of loss of CH₃ and OCH₃, loss of one hydrogen atom from one unit and ring B from the other unit. The ion at m/z 311 resulted from the RDA fission of one unit, loss of ring B from the other unit and loss of (CH₃+OCH₃). The formation of an ion at m/z 338 may be explained by the loss of two B-rings, one as a radical and the other as a cation, from the doubly charged molecular ion, M⁺⁺.

The linkage was further confirmed by comparing the product, obtained by the dehydrogenation followed by methylation, with an authentic sample of cupressuflavone hexamethyl ether (co-t.l.c., m.m.p. and u.v. shade).

CHARACTERISATION OF 5,5''-DIHYDROXY-7,7'',4',4''-TETRAMETHOXY-[6,8'']-BIFLAVANONE (CXIII)

The compound melting at 172-4°C exhibited, in its mass spectrum, the molecular ion peak at m/z 598. It gave positive alc. FeCl₃ test and red colour with conc. H₂SO₄ suggesting it to be a chalcone or flavanone. The i.r. spectrum exhibited bands at 3450 (OH) and 1630 cm⁻¹ (5-OH-flavanone C=O) besides usual aromatic bands. U.v. spectrum of this compound displayed maxima at 228, 289 and 320 nm. The i.r. and u.v. spectra in conjunction with the molecular ion peak revealed it to be a dehydrodimer of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII). The linkage of the two units was established with the help of n.m.r. and mass spectra.
The n.m.r. spectrum clearly indicated the unsymmetrical nature of linkage between the two flavanone units, and thus the possibility of I-8/II-8' and I-6/II-6'' was ruled out. Two singlets observed at δ 12.52 and 12.35, each for one proton were imputed to two phenolic protons. Signals for the protons of four methoxy groups were observed as a compact group of singlets in the region δ 3.77-3.90. Three doublets (J=9 Hz) at δ 7.00, 7.32 and 7.49 integrating for four, two and two protons, respectively, were ascribed to the protons on the two p-substituted B-rings. Two shielded singlets, in the aromatic region, each integrating for one proton, at δ 6.22 and 6.30 were ascribed to C-8 and C-6'' protons, respectively. Ring C protons appeared as two multiplets centred at δ 3.02 for 4 protons and δ 5.46 for two protons ascribable to C-3,3" and C-2,2" protons, respectively. The mass spectrum exhibited structurally diagnostic RDA fragments at m/z 134, 165 and 166 (Chart-XIV). A peak at m/z 192 is due to the doubly charged ion formed by the loss of ring B from each unit. The base peak in the spectrum was seen at m/z 121 due to the p-methoxybenzyl cation. Other structurally diagnostic peaks were present at m/z 465, resulting from the RDA fission of one unit, and at m/z 436 due to the ion formed by the loss of cinnamoyl cation from one unit and the hydrogen from the other unit. The peak at m/z 161 may be attributed to the p-methoxycinnamoyl cation. The structure was further confirmed by comparing the product, resulting from the dehydrogenation and methylation, with an authentic sample of agathisflavone hexamethyl ether\textsuperscript{128} (co-t.l.c., m.p. and m.m.p.).
CHARACTERISATION OF 5,5'¬DIHYDROXY-7,7',4',4''-TETRAMETHOXY-[6,6']-
BIFLAVANONE (CXIV)

This product melting at 291-4°C gave positive alc. FeCl₃ and Shinoda tests. The ultra-violet spectrum of the compound showed it to be a flavanone by exhibiting maxima at 229, 289 and 322 nm. The presence of hydroxy group was confirmed by the band at 3440 cm⁻¹ in its infra-red spectrum. The carbonyl band was observed at 1640 cm⁻¹. The i.r. and u.v. spectra in conjunction with the molecular ion peak gave an idea that the compound is a dimer of a flavanone. The structure was further elucidated with the help of n.m.r. and mass spectra.

The n.m.r. spectrum was clearly indicative of the symmetrical nature of the linkage between the two flavanone units. Signals for the four methoxyls were observed as singlets at δ 3.76 and 3.85 each integrating for six protons. A singlet at δ 12.00 for two protons was ascribed to C-5,5' hydroxy groups. The aromatic region of the n.m.r. spectrum exhibited two doublets (J=9 Hz) at δ 6.86 and 7.64 each for 4 protons and showing A₂B₂ pattern. These signals were attributed to the eight protons on the two p-substituted B-rings. A shielded singlet in the aromatic region at δ 6.40 for two protons could only be assigned to protons on the two electron-rich phloroglucinol rings. This signal was assigned to the C-8 and C-8'' protons of the A-rings. Ring C protons were seen as two multiplets centred at δ 2.98 and 5.75. The multiplet centred at δ 2.98 for
four protons was attributed to the C-3 and C-3” protons, while the protons at δ 5.75 for two protons was assigned to C-2 and C-2” protons of two flavanone units. The compound was, thus, characterised as 5,5”-dihydroxy-7,7”,4’,4”-tetramethoxy-[6,6”]-biflavanone (CXIV).

The structure was further substantiated by its mass spectrum (Chart-XV). The peak at m/z 299 can be attributed to either the doubly charged molecular ion or to the ion resulting from the fission of the diaryl linkage or to both. The peak at m/z 464 arose from the RDA fragmentation of one unit, while the RDA fragmentation of both the units yielded a doubly charged ion at m/z 165. The fragment at m/z 165 provided evidence in favour of the linkage of the two units through A-rings. Another doubly charged ion at m/z 192 may be attributed to the loss of B-rings from the doubly charged molecular ion. The base peak in the spectrum was observed at m/z 121 due to the p-methoxybenzyl cation.

An unequivocal evidence in support of the structure was provided by comparison of the compound, formed by the dehydrogenation and methylation, with an authentic sample of succedaneaflavone hexamethyl ether\textsuperscript{129} (co-t.l.c., m.p. and m.m.p.).

The formation of biflavanones (CXII-CXIV) can be explained either in terms of the oxidative coupling of 2’-hydroxy-4,4’,6’-trimethoxychalcone (C) followed by cyclisation accompanied by selective demethylation of C-5 and C-5” methoxy groups or by the conversion of
chalcone (C) to 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) followed by phenol oxidative coupling.

To obtain an insight into the mechanism, the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with ZnCl₂ was further studied. Thus, a mixture of chalcone (C) and ZnCl₂ was refluxed in DMF for 2 hours. The reaction on usual work up revealed almost quantitative formation of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII). It can be envisaged, thus, that the chalcone is first transformed to 5-hydroxy-7,4'-dimethoxyflavanone. A radical at 5-OH is then generated and delocalised on the carbons 6 and 8 to give radicals (CXVI) and (CXVII), respectively. The appropriate coupling of these mesomeric radicals or electrophilic substitution of these radicals on an intact molecule of 5-hydroxy-7,4'-dimethoxyflavanone may afford biflavanones (CXII-CXIV). A plausible mechanism for the formation biflavanones can be written as in Scheme-XV.
Scheme-XV

2 x (CXVII)  \rightarrow  (CXII)
(CXVII) + (CXVI)  \rightarrow  (CXIII)
2 x (CXVI)  \rightarrow  (CXIV)
REACTION OF 2'-HYDROXY-4,4',6'-TRIMETHOXYCHALCONE (C) WITH NICKEL CHLORIDE

The reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone has also been studied with nickel chloride in N,N-dimethylformamide to check the role of NiCl₂ in the NiCl₂-Zn-KI reagent system. The reaction was performed by refluxing a mixture of 2'-hydroxy-4,4',6'-trimethoxychalcone and nickel chloride in DMF for one week. After usual work up and chromatographic purification over silica gel column, four products, besides unreacted chalcone, were obtained which were characterised as 2'-hydroxy-4,4',6'-trimethoxydihydrochalcone (CXVIII), 5-hydroxy-7,4'-dimethoxyflavanone (CVIII), 5,5''-dihydroxy-7,7'',4',4'''-tetramethoxy-[8,8'']-biflavanone (CXII) and 2'''-hydroxy-5,7,4',4'',4''',6'''-hexamethoxy-[8,5'']-flavanonylchalcone (CXIX).
CHARACTERISATION OF 2'-HYDROXY-4,4',6'-TRIMETHOXYDIHYDROCHALCONE (CXVIII)

The compound melting at 138-40°C gave positive alc. FeCl₃ test and exhibited molecular ion peak, in its mass spectrum (Fig.-30) at m/z 316. The i.r. spectrum displayed stretching frequencies for OH and C=O groups at 3440 and 1620 cm⁻¹. Ultra-violet spectrum proved helpful in predicting the nature of the C₃-unit. The u.v. spectrum exhibited maxima at 220 and 282 nm. It was further evidenced by its n.m.r. spectrum (Fig.-31) which did not show the singlet for the protons on the α and β carbon atoms. Instead, a multiplet for four protons in the region δ 2.80-3.35 was observed which was attributed to the methylene protons on the C-α and C-β. Signal for the protons of the three methoxy groups was observed as a singlet at δ 3.81. Two meta-coupled doublets (J=3 Hz), each for one proton, at δ 5.91 and 6.03 were due to the protons on the C-3' and C-5' of electron-rich phloroglucinol ring A. A pair of doublets (J=9 Hz), showing A₂B₂ pattern and each integrating for two protons, at δ 6.82 and 7.15 was ascribed to C-3,5 and C-2,6 protons, respectively. A singlet integrating for one proton at δ 13.96 was due to the phenolic proton on the C-2'. The compound was, therefore, characterised as 2'-hydroxy-4,4',6'-trimethoxydihydrochalcone (CXVIII). Mass spectrum of this compound was in good agreement to the assigned structure (Chart-XVI). It exhibited an intense molecular ion peak at m/z 316 accompanied by an (M+H) ion at m/z 317.
The base peak was found at m/z 181, resulting from the molecular ion by the fission of the $C-C_\alpha$ bond. An ion at m/z 135 resulted from the fission by alternate pathway. Other structurally diagnostic peaks in the spectrum were at m/z 154, 134 and 121.

**CHARACTERISATION OF 2'''-HYDROXY-5,7,4',4'',4''',6'''-HEXAMETHOXY-[8,5'']-FLAVANONYL-CHALCONE (CXIX)**

The compound, m.p.169-71°C, showed the molecular ion peak, in its mass spectrum (Fig.-32) at m/z 626 suggesting it to be a dimer product. It gave positive alc. FeCl$_3$ test, dark red colour with conc. H$_2$SO$_4$. Its infra-red spectrum displayed stretching frequencies for hydroxy group at 3400 cm$^{-1}$ and two carbonyl stretching bands at 1640 and 1620 cm$^{-1}$. Ultra-violet spectrum displayed maxima at 225, 238, 280, 322 and 365 nm. The bands at 238 and 365 nm suggested the presence of chalcone moiety while those at 280 and 322 nm were indicative of flavanone structure. The molecular ion in conjunction with i.r. and u.v. spectra led us to conclude that the compound is a flavanonyl-chalcone. The position of the linkage was established with the help of n.m.r. spectroscopy.

The n.m.r. spectrum (Fig.-33) showed methoxyl signals as a compact group within the range $\delta$ 3.75-3.92. Two multiplets centred at $\delta$ 2.82, integrating for two protons, and $\delta$ 5.34 for one proton were ascribable to C-3 and C-2 protons of flavanone unit.
These signals confirmed the nature of one unit as flavanone. A singlet at δ 7.74 for two protons was assigned to the two olefinic protons of the chalcone unit, as seen in the model compound 2'-hydroxy-4,4',6'-trimethoxychalcone (C)\textsuperscript{102}. A singlet at δ 12.10 for one proton was ascribed to hydrogen bonded hydroxy group on C-2''. These signals confirmed the second unit as the chalcone. We then required to establish the points of linkage. A doublet at δ 6.92 (J=9 Hz) for four protons, due to the two superimposed doublets, was imputed to C-3',5',3'',5'' protons. Two more doublets at δ 7.37 and 7.54 (J=9 Hz), each for two protons and showing coupling to the companion doublet at δ 6.92 were assigned to the C-2',6' and C-2'',6'' protons, respectively. These signals suggested that neither of the B-rings was involved in the linkage. Furthermore, the presence of signals for C-ring protons of flavanone and olefinic protons of chalcone unit in the spectrum confirmed the linkage of the two units through rings A. The presence of two shielded singlets at δ 5.95 and 6.02, each for one proton, which could only be assigned to the electron-rich phloroglucinol rings, also confirmed the involvement of two rings A in the linkage. The signal for proton on the C-6 generally appears slightly high field compared to that on C-8 in the n.m.r. spectrum of 5,7-dioxygenated flavanones, while the C-3' proton signal resonates at slightly higher field compared to that at C-5' in the n.m.r. spectrum of chalcones whose ring A derives from phloroglucinol\textsuperscript{43}. These observations are of great importance in locating the position of linkage. The singlet
at δ 5.95 was, thus, assigned to C-3' proton of the chalcone unit and that at δ 6.02 to the C-6 proton of the flavanone unit. The compound was, therefore, characterised as 2'-hydroxy-5,7,4',4'',4''',6'''-hexamethoxy-[8,5''']-flavanonyl-chalcone (CIX).

The structure of the compound was further supported by its mass spectrum (Chart-XVII). Mass spectrum displayed molecular ion peak at m/z 626 and an (M+H)^+ ion at m/z 627. The base peak in the spectrum was at m/z 313 which can be attributed either to the fission at the diaryl linkage giving two fragments with identical mass to charge ratio, or to the formation of a doubly charged molecular ion, M^{2+}, or to contribution from both. An ion at m/z 121 was due to the p-methoxybenzyl cation, a characteristic flavanone and chalcone fragment. The structurally diagnostic fragment in the mass spectrum was the doubly charged ion at m/z 179 formed by the RDA fragmentation of the two units. Another important doubly charged ion at m/z 193 can be obtained by RDA fission of one unit and loss of ring B from other unit. RDA fragmentation of flavanone unit and loss of a methyl provided an ion at m/z 432. The peak at m/z 312 can be attributed to the doubly charged ion formed by the loss of one proton from each unit. An ion at m/z 327 also supports the linkage through rings A.

It is obvious from a cursory examination of the products obtained in the reaction of chalcone (C) with NiCl_2 that both the oxidative and reductive processes have taken place. The formation
Chart-XVII
of the 2'-hydroxy-4,4',6'-trimethoxydihydrochalcone (CXVIII) can be explained in terms of selective reduction of the olefinic bond, either by the Ni (0) or by Ni (II) complexes with DMF. The complexes of both the Ni (0) and Ni (II) species have been reported to effect reduction of the olefinic bond.

The formation of 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[8,8'']-biflavanone (CXII) can be explained, either in terms of phenol oxidative coupling of 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) or by the oxidative coupling of two 2'-hydroxy-4,4',6'-trimethoxychalcone (C) units followed by cyclisation of both the units and selective demethylation of the C-5 and C-5'' methoxy groups. A plausible mechanisms is outlined in Scheme-XVI.

The formation of flavanonyl-chalcone (CXIX) seems to result by the oxidative coupling of 2'-hydroxy-4,4',6'-trimethoxy-chalcone (C) followed by cyclisation of one unit. It is quite probable that the radical generated at 2'-hydroxy group of chalcone (C) and delocalised on the C-5' attacks electrophilically at the C-8 of an intact molecule of 5,7,4'-trimethoxyflavanone (CXXIV). The plausible mechanism for the formation of flavanonyl-chalcone (CXIX) is outlined in the Scheme-XVII.
(i) = Cyclisation
(ii) = Selective demethylation

Scheme - XVI
Scheme-XVII

(CXXI) \begin{align} \rightarrow \quad \text{(CXXII)} \end{align}

(CXXI) + (CXXII) 

(i) Coupling

(ii) Enolisation

\begin{align} \rightarrow \quad \text{Cyclisation} \end{align}

(CXIX)

\begin{align} \rightarrow \quad \text{Scheme-XVII} \end{align}
It can be said on the basis of the results of the reactions of 2-hydroxy-4,4',6'-trimethoxychalcone (C) with ZnCl₂ and with NiCl₂ that these salts are effective reagents for the chalcone-flavanone conversion accompanied by selective demethylation, and that NiCl₂ is not as much effective as ZnCl₂.

Since NiCl₂ reacts with zinc powder in the presence of KI to generate presumably atomic nickel and zinc chloride, the transformation of chalcones (C, CXc) to 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) with NiCl₂-Zn-KI reagent system can be speculated to be simply a ZnCl₂ mediated conversion. Furthermore, since 5-hydroxy-7,4'-dimethoxyflavone (CIX) was not obtained, even in trace, in the reactions of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with NiCl₂ and ZnCl₂, the possible intermediacy of zinc enolate (CXI) in the flavanone-flavone conversion was ruled out. The formation of 5-hydroxy-7,4'-dimethoxyflavone (CIX) in the reactions of chalcones or 5-hydroxy-7,4'-dimethoxyflavanone (CVIII) with NiCl₂-Zn-KI system can, thus, be explained in terms of dehydrogenation of 5-hydroxy-7,4'-dimethoxyflavanone with in-situ generated atomic nickel. Hydrogenation catalysts such as platinum, palladium and nickel etc. have been reported to effect dehydrogenation. The reaction, in this case, is reverse of the double bond hydrogenation and probably the mechanism is also the reverse of that one, though much is not known.
It is worthwhile to mention here that the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with zinc chloride produced 5-hydroxy-7,4'-dimethoxyflavanone and three isomeric biflavanones (CXII-CXIV) formed probably from CVIII by the phenol oxidative coupling. The reaction of 5-hydroxy-7,4'-dimethoxyflavanone with NiCl$_2$-Zn-KI, when conducted for one week, however, did not give any of these biflavanones. This can be attributed to the presence of iodide ion. It is envisaged that the coordination of iodide ion to the Zn (II) species, probably, increases the electron density of the Zn (II) species$^{117}$, thus, inhibiting it from abstracting electron from the electron rich ring A.

The dimeric products obtained in the reactions of 2'-hydroxy-4,4',6'-trimethoxychalcone with ZnCl$_2$ and with NiCl$_2$, which arise probably by the phenol oxidative coupling, are interesting both from synthetic as well as biogenetic point of views. The oxidative coupling of free radical species, derived from phenolic substrates is now widely accepted as the pathway by which many natural products are biosynthesised.$^{131}$ Such a route has also been suggested as being involved in the biogenesis of biflavonoids. Baker, Ollis and co-workers$^{41}$ were the forerunners of several who suggested that the concept of phenol oxidative coupling might offer an explanation for the biogenesis of biflavonoids.
Waiss and co-workers\textsuperscript{132} investigated the oxidative coupling of apigenin (CXXV) using alkaline potassium ferricyanide and isolated two biflavones with I-3/II-3' (CXXVI) and I-3/II-3 (CXXVII) interflavone linkages, which arose presumably by appropriate spin pairing of mesomeric radicals (CXXIX) and (CXXX).
Electron spin resonance (ESR)\textsuperscript{133} studies have shown that delocalisation of an unpaired electron initially generated at the C-4' hydroxy group in apigenin (CXXV) occurs only in rings B and C no hyperfine splitting has been observed at the carbon atoms of ring A. The self coupling of the mesomeric radicals (CXXIX) and (CXXX), therefore, can not explain the formation of natural biflavones which possess an interflavone linkage at C-6 or C-8 of ring A. Thus, in order to explain an interflavone linkage to ring A in naturally occurring biflavones Waiss and co-workers believed that a radical, initially generated at C-4' in apigenin and delocalised, attacks electrophilically the electron rich C-6 or C-8 position of an intact apigenin molecule.

Radical substitution, however, fails to offer an explanation for the formation of cupressuflavone, agathisflavone and succedaneaflavone (Fig.-4), in which the two units are linked through ring A, if it is accepted that no free radical can exist on ring A. However, if a free radical were to be generated at either of the hydroxy groups in ring A of apigenin, delocalisation of the electron in this ring would enable pairing between the independently generated radicals (CXXXII) and (CXXXIII) (Scheme-XVIII) to give biflavones involving rings A in linkage. The formation of these biflavones can also be explained by radical substitution if radical were to be generated on ring A, since ring A will be more susceptible to an electrophilic attack. Radical substitution, however, fails to explain the formation of taiwaniaflavone (CXXVI).
There is, however, no evidence in favour of generation of a radical on ring A of flavonoids. Synthesis of I-6/II-6 dimer of apigenin-7,4'-dimethyl ether (CXXXIV) by the oxidative dimerisation of apigenin-7,4'-dimethyl ether (CIX) with FeCl₃ in boiling dioxane has been reported, in 6% yield. However, Murti et al. when reinvestigated the reaction of apigenin-7,4'-dimethyl ether (CIX) with FeCl₃ in dioxane, isolated unexpectedly three isomeric biapigeninylmethane derivatives on methylation, named as hexamethyl ethers of homocupressuflavone (CXXXV), homosuccedaneaflavone (CXXXVI) and homoagathisflavone (CXXXVII).
Jackson and co-workers\textsuperscript{136} have reported the isolation of four biflavanones (CXXXVIIIa-d), involving I-3/II-8 linkage, from \textit{Garcinia buchananii} Baker and \textit{G. eugeniifolia} Wall. The biogenesis of these biflavanones is envisaged as involving either radical pairing or radical substitution of two complete or embryonic flavanone units (Scheme-XIX).

\begin{equation}
\text{(CXXXVIII)}
\end{equation}

(a) GB-1; \( R_1 = \text{OH}, R_2 = \text{H} \\
(b) GB-1a; \ R_1 = R_2 = \text{H} \\
(c) GB-2 ; \ R_1 = R_2 = \text{OH} \\
(d) GB-2a; \ R_1 = \text{H}, R_2 = \text{OH}
$X=\text{COOH}; \ 2,4,6$-trihydroxybenzoyl etc.

Route 1 (i) hydrogen abstraction, (ii) radical pairing, (iii) enolisation, and (iv) further extension of flavanone synthesis of applicable.

Route 2 (v) hydrogen abstraction, (vi) radical substitution, (vii) loss of H atom, (viii) enolisation.

Scheme-XIX

The genesis of various natural biflavones and biflavanones can be explained by the phenol oxidative coupling of hydroxyflavones and/or hydroxyflavanones either by the radical pairing or by radical substitution, but there are many biflavonoids the formation of which in plants can only be explained in terms of oxidative coupling at the chalcone stage followed by modification of the $C_3$-
unit. There is, however, no report, to the best of our knowledge, on the oxidative dimerisation of chalcones. Pelter and co-workers have investigated the oxidation of 2'-hydroxychalcones, derived from resorcinol, with alkaline potassium ferricyanide in detail. The noteworthy point of their studies is the lack of oxidation of any compound in which the hydroxy group on the ring B was methylated, although in every case a free phenolic group was available on C-2' of ring A. In no case could oxidation on ring A be observed, although the recovery of the starting material was excellent. The products of oxidation of 2-hydroxy- and 4-hydroxy-chalcones were either flavones or aurones.

The formation of biflavanones (CXII-CXIV) in the reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with zinc chloride, probably through the intermediacy of 5-hydroxy-7,4'-dimethoxyflavane none (CVIII), provide an experimental evidence in favour of generation of a radical on ring A of flavonoids, a serious limitation of the previous studies. Also, the transformation is an experimental evidence in favour of the idea that coupling can also take place at the flavanone level. Another evidence in favour of generation of a radical on ring A of flavonoids is provided by the transformation of chalcone (C) to flavanonyl-chalcone (CXIX). Oxidation on ring A of 2'-hydroxychalcones has not earlier been reported. The conversion of C to CXIX provides an experimental analogy to the hypothesis for the biosynthesis of biflavonoids from chalcones.
The transformation of chalcone (C) to flavanonyl-chalcone (CXIX) prompted us to study the oxidation of 2'-hydroxychalcones with known one electron oxidant, in alkaline medium to avoid cyclisation, in order to provide further support to the proposal for the biosynthesis of biflavonoids from chalcones. We selected iodine in the presence of potassium hydroxide as the reagent for this purpose.
REACTION OF 2'-HYDROXYCHALCONES WITH IODINE IN THE PRESENCE OF POTASSIUM HYDROXIDE

Iodine under basic condition is a known reagent for oxidation of phenols. The reagent has occasionally been reported to bring about oxidative coupling of certain phenolic substrates under appropriate conditions. Omura has recently investigated the oxidation of phenols with iodine in alkaline methanol in detail. The reaction of phenols with iodine in methanol containing alkali such as potassium hydroxide and sodium hydroxide has been carried out and, depending on the nature of the substituents and the amount of iodine used, leads to iodination, oxidation to give phenoxy radical, oxidative dimerisation or benzylic oxidation.

The reaction of 2'-hydroxy-4,4',6'-trimethoxychalcone (C) with iodine in the presence of potassium hydroxide afforded a red solid which was characterised as 2',2'''-dihydroxy-4,4',4'',4''',6',6'''-hexamethoxy-[5',5'']-bichalcone (CXXXIX).
CHARACTERISATION OF 2',2''-DIHYDROXY-4,4',4''',6',6''-HEXAMETHOXY-
[5',5'']-BICHALCOME (CXXXIX)

The compound melting at 189-91°C showed the molecular ion peak at m/z 626 in its mass spectrum. It gave brown colour with alc. FeCl₃ and red colour with conc. H₂SO₄ and aqueous NaOH showing the presence of chalcone moiety. I.r. spectrum displayed stretching bands at 3440 cm⁻¹ (OH) and 1625 cm⁻¹ (2'-OH-chalcone C=O). The u.v. spectrum showed maxima at 228, 350 and 370 nm. I.r. and u.v. spectra in conjunction with the M⁺⁺ at m/z 626 revealed it to be a bichalcone. The linkage was easily established with the help of n.m.r. spectrum. A cursory examination of the n.m.r. spectrum indicated high symmetry in the molecule. N.m.r. spectrum was very much similar to that of the starting chalcone and varied only in the signals for ring A protons. Signals for the protons of the six methoxy groups were observed as a compact group in the region δ 3.80-4.00. At the lowest field, in the n.m.r. spectrum, was present a singlet at δ 14.35 for two protons which was assigned to the protons of the two hydroxy groups on C-2' and C-2'''. Aromatic region of the spectrum displayed a couple of doublets (J=9 Hz) at δ 6.90 and 7.50, each for four protons and exhibiting the A₂B₂ pattern, which was ascribed to the protons on the two p-substituted B-rings. A singlet at δ 7.65 for four protons was assignable to the olefinic protons of the two units. It is evident now that ring and C₃-portion of the two chalcone units are not involved in the
linkage and two units are linked through ring A. The possibility of C-3'\slash C-5'' linkage was ruled out on the basis of high symmetry in the n.m.r. spectrum. A high shielded singlet at δ 5.62 for two protons was ascribed to the C-3' protons of the two units. The linkage was further supported by its mass spectrum (Chart-XVIII). The fragmentation pattern is typical as that for the 2'-hydroxy-chalcones. The structurally diagnostic fragments supporting the linkage of the two units through ring A were at m/z 358, 194 and 179.

The linkage was unequivocally confirmed by oxidation of bichalcone (CXXXIX) with selenium dioxide in isoamyl alcohol yielding a biflavone which was found identical in all respects to an authentic sample of succedaneaflavone hexamethyl ether\textsuperscript{129}. Further evidence in favour of the linkage was obtained by converting the bichalcone (CXXXIX) to 5,5''-dihydroxy-7,7'',4',4''-tetramethoxy-[6,6'']-biflavanone (CXIV) with zinc chloride.

As an extention, when the reaction of 2'-hydroxy-4,4'-dimethoxychalcone (CIV) was carried out with iodine in the presence of potassium hydroxide under identical conditions, the usual work up of the reaction afforded a crude dark yellow solid which was crystallised from methanol to give crystals of 2',2''-dihydroxy-4,4',4'',4'''-tetramethoxy-[3',5'']-bichalcone (CXL).
Chart-XVIII
CHARACTERISATION OF $2',2''$-DIHYDROXY-$4,4',4'',4'''$-TETRAMETHOXO-$[3',5'']$-bichalcone (CXL)

The compound melting at $180-1^\circ C$ exhibited, in its mass spectrum (Fig.-34), the molecular ion peak at m/z 566 indicating it to be a dimeric product. It gave positive alcoholic ferric chloride test showing the presence of phenolic group. It gave dark red colour with conc. $H_2SO_4$ and aq. NaOH solution indicative of the presence of chalcone or flavanone moiety. Infra-red spectrum displayed bands at 3440 (OH) and 1620 cm$^{-1}$ (C=O). The nature of the compound was evident from the u.v. spectrum which showed bands at 210, 230, 330 and 380 nm. These bands suggested it to be a bichalcone. The position of the interchalcone linkage was deter-
mined with the help of n.m.r. spectrum. N.m.r. spectrum (Fig.-35) displayed methoxyl protons as a compact group of four singlets in the region δ 3.70-4.10. The linkage of one unit through C-5" was confirmed by the presence of two singlets at δ 6.65 and 8.30 each integrating for one proton. These signals were imputed to C-3" and C-6" protons, respectively. The presence of a doublet (J=9 Hz) at δ 6.75 for one proton confirmed the linkage of other unit at C-3'. This signal was assigned to C-5' proton. Signals for the remaining aromatic protons as well as four olefinic protons were seen as two complex multiplets in the region δ 6.85-7.20 and 7.40-8.10 integrating for six and seven protons, respectively. Two downfield singlets at δ 13.60 and 14.00 were ascribed to two phenolic protons. The structure was further supported by the mass spectrometry (Chart-XIX). The fragmentation pattern was typical as that for the 2'-hydroxy-chalcones. Ring B fragments were seen at m/z 121, 133, 134, 135 and 161. Most structurally diagnostic fragments were at m/z 326, 325, 299, 271, 150 and 149.

The plausible mechanism\textsuperscript{139} for the formation of bichalcones (CXXXIX, CXL) can be outlined as in Scheme-XX. The phenolate anion (CXLII), formed from chalcones in the presence of potassium hydroxide, react with iodine to produce radicals (CXLII) and iodide ion. Delocalisation of the electron in the ring A will give radicals (CXLIII) and (CXLIV). The appropriate pairing of these radicals or the electrophilic attack on an intact molecule of chalcone will give bichalcones (CXXXIX, CXL).
(C) $R = \text{OCH}_3$

(CIV) $R = \text{H}$

(CXLIII)
(a) $R = \text{OCH}_3$; (b) $R = \text{H}$

(CXLII)
(a) $R = \text{OCH}_3$; (b) $R = \text{H}$

(CXLIV)
(a) $R = \text{OCH}_3$; (b) $R = \text{H}$

$2 \times (\text{CXLIIIa}) \rightarrow (\text{CXXXIX})$

$(\text{CXLIIb}) + (\text{CXLIVb}) \rightarrow (\text{CXL})$

Scheme-XX
The dimerisation of chalcones provide first experimental evidence in favour of proposal for the biogenesis of biflavonoids by the phenol oxidative coupling at the chalcone stage. Oxidation of 2'-hydroxy group of chalcones has not earlier been observed. The synthesis of these bichalcones also provide an explanation to the fact that most natural biflavonoids involve ring A in the linkage. The formation of biflavonoids involving either ring B or C₃-unit in the linkage can be explained by the generation of a radical at C-4 of chalcone.