Theoretical
During the last few years there has been a revival of interest in the chemistry, biosynthesis and physiological properties of flavones, isoflavones and other flavanoids. The term flavanoid covers a large group of naturally occurring compounds in which two benzene rings are linked in a propane bridge \((C_6-C_3-C_6)\) except in the isoflavone in which the arrangement is \((C_6-C-C-C_6)\). The flavanoids include chalcones, dihydro chalcones, aurones, flavanones, flavones and isoflavones, 2,3-dihydro flavanols, flavan-3,4-diols-(leucoauthocyanidines) anthocyanidines and catechins. Sheshadri\(^1\) has discussed the biochemistry of flavanoids and related plant pigments. Geissman\(^2\) has given a detailed account of their distribution in plants and possible mechanism of the biogenesis.

The flavanoids vary from two (in catechin) to five (in flavanols) in the state of oxidation of the propane chain calculated as the number of hydroxyl groups attached to the three carbon atoms including the hydroxyls obtained by hydration of the double bond and by hydrolytic fission of the pyran ring. Many interconversions of the flavanoids are possible in the laboratory as shown in (Chart-I) where there is no evidence that they represent biosynthetic pathway, although two or more flavanoid types
(flavanols and flavanols for instance) often occur together in the same plant.

Chart-I
Some of the reactions by which chalcone and the isomeric flavanones can be converted to flavones and flavanols can take an alternative course leading to aurones (2 benzylidene coumaranones) which are isomeric with flavones and have been found to accompany chalcones and flavanones in few plants.

Naturally occurring flavanoids are at same or a higher oxidation level than flavanones and many hypothesis have been proposed to explain the genesis of each series. In general such postulates are based on satisfactory chemical analogies, particularly the Algar-Flynn-Oyamada (A.F.O.) reaction. This A.F.O. reaction involved the direct manipulation of the C-3 position of the flavone molecule. Proposals for the formation of flavone have included direct oxidation of a flavanone to give a cation at C-3 position which could be transformed to a flavone, flavanol or isoflavone. Enolization of the flavanone followed by attack by the equivalent of (OH+ ) and dehydration or metal assisted enolization followed by an oxidative loss of the metal could also yield the flavone (Chart-II).
2'-hydroxy chalcone is oxidized in one step to the corresponding flavanol with hydrogen peroxide in alkaline medium. A.F.O. reaction proceeds via a chalcone epoxide and a trans-2,3-dihydroxy flavanol but according to Dean and Podimuang, that reaction is depending on the substitution of the chalcone and reaction conditions. This reaction can also result
in the formation of benzyl coumaranones (aurones) as well as 2-benzyl-2-hydroxy-dihydrobenzofuran-3-one and 2-aryl-benzofuran-3-carboxylic acid either as the main product or as by product.

In contrast to the earlier confusion about the influence of substituents and temperature on the A.F.O. reaction, it is now established that chalcones with an hydroxyl group in position 2 or 4 and lacking a 6'-methoxy group yield primarily flavanols whereas chalcones with a 6'-methoxy group and lacking a 2- or 4-hydroxyl group are also able to form aurones, in addition to flavanols. The formation of aurones is favoured by oxidation in the cold whereas high temperature favour the formation of flavanols.

The best yields of flavanols are obtained by a modified A.F.O. reaction. The polyhydroxy chalcones completely protected except for the 2'-hydroxyl group are oxidized for up to 15 mts. with a solution containing 5-30% hydrogen peroxide and 10-20% sodium hydroxide or the corresponding amount of sodiumperoxide. Most of the naturally occurring flavanols that have been synthesized by modified A.F.O. oxidation from 2'-hydroxy chalcones, the simultaneous and preferential formation of aurones is avoided if the A.F.O. oxidation is carried out on 2'-hydroxy-α-methoxy chalcones. However, this rule is again limited by the
effect of substitution, for example, oxidation of 2'-hydroxy-
α-methoxy chalcones possessing a methoxy group at position
6', the main product is a [2-(α-hydroxy benzyl)-2-methoxy
coumaran-3-one] whereas the same chalcone lacking a substi-
tuent at position 6' yielded the flavanol\textsuperscript{11}. This oxidation
mostly proceeds with partial demethylation to the 3-hydroxy
flavone. Isoflavones have been thought to arise from chal-
cones through chalcone epoxide\textsuperscript{12,13} or by an analogy with
the facile rearrangement of tetra-O-methyl catechin by
phosphorous pentachloride\textsuperscript{14}. Isoflavones could be formed
by rearrangement of derivatives of flavananol\textsuperscript{13} also.

A different approach has looked at the probable
results of the oxidative manipulation of the ubiquitous 4'-
(or 2')-hydroxy group of ring B of various flavanoids of
different oxidation levels. This approach is based on analo-
gies to the production of lignans and lignins\textsuperscript{15} and treat
chalcone simply as a modified (C\textsubscript{6}-C\textsubscript{3}) lignin unit. The
isolation of such products as thiaflavin\textsuperscript{16} amentoflavone\textsuperscript{17}
and silybin\textsuperscript{18} etc. affirms the ability of plants to oxida-
tively manipulate the ring B of flavanoids. Conversion of
kaemferol to quercetin and dihydro kaemferol to dihydro-
quercetin is also a different mode of oxidation reactions
with flavanoids\textsuperscript{19}. Experiments on the enzymic oxidation of
myscytrin show that oxidative dimerizations involving ring
B can occur at the flavanol stage also\textsuperscript{20}.
1.2. **Photochemical reactions**

The importance of light in the regulation of flavanoid biosynthesis in higher plants has been established\(^2\). In the terminal buds of etiolated pea seedlings, for example, very short irradiations with red light are sufficient to cause significant changes in flavanoid contents. These changes being reversible by far red light, indicating involvement of photochrome\(^2\),\(^2\)\(^3\). In several other species investigated, short irradiations with red light have little effect, whereas continuous illumination with light of various spectral region elicits considerable long term increase in the level of flavanoids or other phenolic compounds\(^2\)\(^4\)-\(^2\)\(^6\). There are two different hypotheses developed concerning the manner in which these responses are mediated (a) continuous illumination acts solely through the phytochrome systems\(^2\)\(^7\) and (b) photo receptors rather than phytochromes are involved\(^2\)\(^8\). It has been shown that irradiation of dark alaska pea seedlings leads to complex changes in the flavanoids\(^1\)\(^9\),\(^2\)\(^2\),\(^2\)\(^9\),\(^3\)\(^0\), these changes can be resolved into two photo systems, one mediated through phytochrome and leading to rapid but small increase in K.G.C. (Kaempferol-3-p-coumaroyl tri-glucoside) and Q.G.C. (Quercetin-3-p-coumaroyl tri-glucoside) levels while the other requiring continuous illumination and
resulting in much larger changes in flavanoid levels occurring after about 18 hrs\textsuperscript{19}. In several other species in which continuous illumination leads to increase in flavanoid or phenol contents, changes in the extractable activity of phenyl alamine ammonia-lyase (PAL) have been observed\textsuperscript{31,32}.

It could be argued that labelled chalcone/flavanone intermediate administered to a plant are first degraded to cinnamic acids and subsequently enter the pool of the precursors of flavanoid synthesis. The labelled flavanone into cyanidin and biochanin have been studied by feeding experiment with seedling of \textit{Brassica oleraceae} and \textit{Cicer arietinum}. Since 5,7,4'-tri hydroxy flavanone was shown to be the more efficient precursor of cyanidin, quercetin and biochanin than the enantiomer. It was assumed that only the flavanone serves as substrate for the reverse reaction of the chalcone flavanone isomerase, which would supply a chalcone concentration sufficiently high for other enzymes to act on this substrate. Kinetic studies\textsuperscript{34} on the conversion of the pair (4-\textsuperscript{14}C)-2',4',4'-trihydroxy chalcone/(3',5'-H)-7,4'-dihydroxy flavanone to the corresponding dihydro flavanol, flavone, flavanol and 4'-methoxy isoflavone\textsuperscript{35} were interpreted as favouring a chalcone as the more immediate precursor.
Other possible products of chalcones are dihydroaurones intermediate in the biosynthesis of aurones. Wong et al.\textsuperscript{36-38} reported the conversion of 4',2',4-trihydroxy chalcone (I) to the corresponding dihydroxy aurone hispidol (II) by cell free extracts from Soya bean seedlings and isolated two diastereo isomers of 4',6-dihydroxy-2-(α-hydroxy benzyl) coumaranone (II) which were proposed as intermediate for biosynthesis of aurones. Since the chalcone was also converted to both dihydroflavananol (IV) and flavanol (V) by cell free extracts of chick pea and Soya bean seedlings\textsuperscript{39,40}. It is possible that these reactions are generally catalyzed by peroxidases via free radical as intermediate, similar results have been drawn by Pelter et al.\textsuperscript{41} from studies on the oxidation of a chalcone by potassium ferricyanide to the corresponding aurone, flavone, dihydroflavanol and isoflavone.
Photochemical reactions also play an important role in oxidation of flavanoids. Photocyclization of 2'-hydroxy chalcone VI in benzene has been reported as a new method for flavanone VII synthesis$^{42}$. This type of photo cyclization on irradiation with light of $\lambda \approx 365$ nm, parent and methoxy substituted chalcones undergo facile cyclization to give
corresponding flavanones in deoxygenated solution.

\[ \text{corresponding flavanones}^{43} \]

This method of 2'-hydroxy chalcones is apparently a reverse reaction of the photochemical ring opening of flavanone. It has previously been reported that the photolysis of substituted flavanone undergo ring opening to give 2'-hydroxy chalcone or hydrogen abstraction to give dimeric product. Padwa et al. have shown that the photochemical rearrangement of 3-chromanone derivatives take place via enolization. Similar mechanism has also been proposed for the photochemical ring opening reaction of the substituted flavanone VIII in benzene. It is noted that photo cyclization of the 2'-hydroxy chalcones to the flava-
nones is apparently the reverse reaction of the photochemical ring opening of the flavanones and that both reactions can indeed be reversible under suitable conditions.
It seems, therefore, reasonable to assume a similar mechanism (involving enolization) for the photo cyclization. Photo chemical excitation of chalcone would lead to enolization, to give X which, however, undergo cis-trans isomerization to XI for the subsequent cyclization.

This reaction may be exothermic or less endothermic due to the recovery of aromatic stability, and proceed effectively via a thermal 6π electro cyclic process.
Chalcone oxides also play an important role in photochemical transformation. The rearrangement of epoxide of chalcone have received extensive study and have been the subject of several reviews. These compounds generally display two type of photo behaviour (a) photo isomerization of aryl cyclo-pentanone oxide to pyrylium oxide and (b) photo isomerization of \( \alpha,\beta \)-epoxy ketone to \( \beta \)-diketone. Although \( \text{C}_\alpha-\text{O} \) bond cleavage is the predominant mode of photo fragmentation of \( \alpha,\beta \)-epoxy ketone, Muzart et al. have demonstrated that \( \text{C}_\alpha-\text{C}_\beta \) bond cleavage can also occur in certain optically active derivatives. Irradiation of trans-chalcone oxide XIII in acetonitrile with 313 nm radiation led to the formation of dibenzoyl methane (XIV) as the major product. The formation of XIV from XIII was first described by Bodforss in 1918 and is assumed to arise from the cleavage of \( \text{C}_\alpha-\text{O} \) bond of the oxirane followed by a 1,2 shift of \( \alpha \)-hydrogen to the \( \alpha \)-position.

\[
\begin{align*}
\text{XIII} & \xrightarrow{hv} \text{XIV} \\
& \text{(III)} \\
& \text{(XIV)}
\end{align*}
\]
Ground state molecular oxygen can be energetized to excited singlet state by energy transfer from a suitable energy sensitizer. This activated state of molecular oxygen can take part in the chemical reaction with substrate containing activated double bond even in aromatic oxygen heterocycles. Since plants containing well known photo sensitizer such as chlorophyll, molecular oxygen is expected to play an important role in the biogenesis of natural products.

Yokoe et al. have studied the photo oxidation and rearrangement of flavones and flavanols. In case of flavones two
isomers of 2,2-linked dimerized products were obtained in which one is $\alpha$-Ph dimer XIX and the other is $\beta$-Ph dimer XX

\[ \text{(XVII) } R = \text{Me} \quad \text{(XIX) } R = \text{Me}, R' = \alpha\text{-Ph} \]
\[ \text{(XVIII) } R = \text{H} \quad \text{(XX) } R = \text{H}, R' = \beta\text{-Ph} \]

where as in case of flavanols (XXI) some new photo rearranged products XXII, XXIII and XXIV were obtained.
Irradiation of 4'-methoxy flavanone with high pressure mercury lamp in benzene and in 2-propanol gave 4-methoxy-2'-hydroxy chalcone and a mixture of pinacol, similarly to the other flavanones, in both the solvents the remaining part of the product was interactable polymer. The formation of 4-methoxy-2'-hydroxy chalcone may be recognized as a 6π electrocyclic reaction of the enolic form of 4'-methoxy-flavanone. A similar type of photo chemical electrocyclic reaction has been observed for 2H-pyran. Under similar photo chemical reactions 5,7,4'-trimethoxy flavone was largely recovered under the formation of some resinous material in benzene while in 2-propanol it undergo faster photo decomposition and gives a complex mixture of atleast six products. 5,7-dimethyl-4'-methoxy flavanone which is photo chemically rather unreactive in 2-propanol undergoes oxidative coupling by irradiation in benzene to give XXVII. On larger irradiation, XXVII suffered further photo decomposition to give a resinous material. It may be reasonable to assume that the formation of XXVII involves an intra-

\[
\begin{array}{ccc}
  X & Y & Z \\
  (a) & H & H & H \\
  (c) & H & OCH_3 & H \\
  (e) & CH_3 & H & H \\
  (g) & CH_3 & OCH_3 & H \\
  (b) & H & CH_3 & H \\
  (d) & H & O-CH_2 - O \\
  (f) & CH_3 & CH_3 & H \\
  (h) & CH_3 & O-CH_2 - O \\
\end{array}
\]
molecular hydrogen abstraction of the excited 5,7-dimethyl-4'-methoxy flavanone, similar to that of O-alkyl phenyl ketone.\textsuperscript{60b}

But in the case of 2-styryl-4H-chromen-4-ones (XXV)\textsuperscript{60} on irradiation with high pressure mercury lamp at room temperature gave benzo[a] xanthones (XXVI). Here the cyclization of methoxy substituted styryl chromones occurred at
the para position relative to the other group on the styryl ring, whereas 2-[
\[\beta-(2\text{-naphthyl})\text{vinyl}\] chromone was cyclized at the \(\alpha\)-position of the naphthalene ring.

A

(b)

(c)

(d)

(e)

(f)

(g)

(h)

(i)

H

CH\(_3\)

H

CH\(_3\)

H

H

OCH\(_3\)

CH\(_3\)

H

H

OCH\(_3\)

H

H

CH\(_3\)

OCH\(_3\)

H

H

OCH\(_3\)

H

H

H

Br
1.3. Biological oxygenation

Biological oxygenation catalysed by oxygenase in the metabolism of natural substances is also an interesting problem in this field. Many model reactions have been investigated so as to give a clue to the mechanism of biological oxygenation. Oxygenation of 3-hydroxy flavone catalyzed by quercetinase is an interesting example of this oxygenation reaction. It leads to the oxidative cleavage of the heterocyclic ring to give the corresponding depsides and carbon monoxide. Nishinaga et al. have reported that the base catalyzed oxygenation of 3-hydroxy flavone where, there is no hydroxy group at 7-position gave the same product as obtained in the quercetinase reaction, providing basic information for understanding the enzyme reaction from the standpoint of the reactivity of the substrate towards molecular oxygen. On the other hand 3-hydroxy flavone having 7-OH group gives the oxidation products different from that of the enzymic reaction. The oxidation of 7,3,4'-trihydroxy flavone (XXVII) in aqueous alkaline solution at room temperature gave 2,4-dihydroxy benzoic acid (XXVIII), 4-hydroxy phenyl glyoxylic acid (XXIX) and 4-hydroxy benzoic acid (XXX). Oxygenation in absolute methanol containing sodium methoxide gave XXVIIIalb; XXIXalb and XXX.
The oxygenation of 3-hydroxy flavone (XXXI) by superoxide anion in tetrahydrofuran also results in the oxidative cleavage of the heterocyclic ring to give the 2-benzyl oxyphenylglyoxylic acid (XXXII) in good yield without the loss of carbon monoxide. No reaction was observed, however with XXXIh. KO₂ and 18-crown-6-ether were treated with a solution of XXXI with tetrahydrofuran at ambient temperature, product XXXII was obtained. The sodium salt of 3-hydroxy flavone (XXXIa) did not react with KO₂ and Na₂O₂.
(with added 18-crown-6-ether), however its reaction with oxygen in tetrahydrofuran proceeded rapidly and yielded the corresponding depsides XXXIIIa and carbon monoxide.

(a) \( R_1 = R_2 = R_3 = H \)

(b) \( R_1 = R_3 = H, R_2 = OH \)

(c) \( R_1 = R_3 = H, R_2 = OMe \)

(d) \( R_1 = H, R_2 = R_3 = OH \)

(e) \( R_1 = OMe, R_2 = R_3 = H \)

(f) \( R_1 = R_2 = H, R_3 = OMe \)

(g) \( R_1 = H, R_2 = R_3 = OMe \)

(h) \( R_1 = OH, R_2 = R_3 = H \)
Oxygenation of quercetin (XXXVIa) to XXXVIIa and the ene reaction of singlet oxygen to an olefin having allylic hydrogens, Matsuura et al. have investigated the reaction of 3-hydroxy flavones XXXVIa-c with singlet oxygen which is generated by dye-sensitized photooxygenation. Under the conditions XXXVIa-c gave the corresponding depsides XXXVIIa detected by TLC only and XXXVIIb,c isolated as the methyl ethers respectively in addition to carbon dioxide and carbon monoxide. From the fact that carbon monoxide is stable under the reaction conditions and that photo-sensitized oxygenation of p-methoxy phenyl glyoxylic acid gives p-anisic acid and carbon dioxide in good yield. The formation of carbon dioxide has been explained by the oxidative decarboxylation of XLI via path (B) in a competition with path (A). The formation of keto hydroxy peroxide XXXVIII can alternatively be ascribed to a radical intermediate XLII which results from photosensitized oxygenation, possibly involving hydrogen abstraction of the 3-OH group by the triplet excited sensitizer. This possibility has been excluded by the following experiments.
(XXXVI) \[ \xrightarrow{\text{Path-A}} \]

(XXXVIII)

(XL)

(XLI)

(XXXVII) $\xrightarrow{\text{Path-B}}$

CO

(XXXXIX)

a. $X = \text{OH}$
b. $X = \text{OMe}$
c. $X = \text{H}$
On oxidation with MnO$_2$ which is known to oxidize phenols into phenoxy radical XXXVi c gives only a dihydrodimer XLIII in nitrogen or oxygen atmosphere.

\[
\text{(XXXVIc)} \xrightarrow{\text{MnO}_2} \text{XLII}
\]

\[
\text{XLIII}
\]

\[X = H\]

These above experiments indicate that the XLII even under oxygen easily dimerizes to XLIII rather than reacting with the ground state oxygen.
The singlet oxygen reaction of the 3-OH flavone was thought to be a good mimic for the quercetinase catalyzed reaction and to be a possibility that the enzymic reaction might involve singlet oxygen. However, this was not conclusive since other oxygenation methods have been found effective for the depside formation from 3-hydroxy flavone.

Nishinaga et al. \(^{68}\) have found that auto-oxidation of 3,4'-dihydroxy flavone (XLIV) in dimethyl formamide in presence of potassium t-butoxide resulted in the formation of the corresponding depside XLVa and carbon monoxide in almost quantitative yield. This reaction also proceeds rapidly in dimethyl sulfoxide containing the same base but rate of the reaction becomes slow in sodium methoxide-methenol or sodium hydroxide-water. 3-hydroxy flavone itself undergo auto-oxidation even in potassium t-butoxide-dimethyl formamide. No oxygen uptake is apparently observed because of the liberation of the same volume of carbon monoxide. However, when the oxygenation is carried out with 3,4',7-trihydroxy flavone (XLIVb) in potassium t-butoxide-dimethyl formamide, oxygen absorption increases at the expense of carbon monoxide.
(XLIV) → (XLVII)

(XLV) + CO → (XLVIII)

(a) X = Y = H
(b) X = OH, Y = H
(c) X = Y = OH
In a series of biochemical studies by Simpson et al. 69,70, it was found that quercetinase is a copper enzyme, a mechanism was proposed involving a ternary complex of substrate, copper, and oxygen which undergo a sequence of intramolecular reactions to form depside XXXVIIa. If the mechanism is applicable to non-enzymatic model system, a copper-3-hydroxy flavone complex L might undergo a similar cleavage reaction in the presence of oxygen.
When copper(III) or cobalt(II) chelate (L1) of 3-hydroxy flavone (XXXVIa) was treated with oxygen in various organic solvents (DMF, DMSO, pyridine or CH₂Cl₂) no reaction takes place. However, addition of XXXVIc in the system causes oxygenation to give the corresponding depside XXXVIIc indicating that in the non-enzymatic reaction such a ternary complex L1 may be capable of catalyzing the oxygenation of 3-hydroxy flavone.

Apart from the quercetinase problem the photo-oxygenation of 3-methoxy flavone seems interesting in view of the biogenesis of certain flavanoids. Photolysis of quercetin penta methyl ether (LII) under nitrogen has been found to yield LIII as one of the photoproduct. Unsensitized photo-oxygenation of simple 3-methoxy flavone (LIIb) gave further oxidation product LIV in addition to LIII. The results represent possible mimics for the biogenesis of uncommon flavanoids such as peltogynol (LV) and distimonanthin (LVI) which are supposed to be derived from a 3-methoxy flavone precursor in vivo. An intramolecular hydrogen abstraction of the excited 3-methoxy flavone followed by dehydrogenation to give LIII which may be photo oxidized by a free radical chain mechanism to form LIV.
\[ \text{OCH}_3 \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{H}_3\text{CO} \]

\[ \text{H} \]

\[ \text{X} = \text{OMe} \]

\[ \text{X} = \text{H} \]
1.4. Per-iodic Acid Oxidation

It has been shown that flavanol (XXXVIc) is oxidized by periodic acid in aqueous dioxan to give 3-(2H-benzo-furanones) (LVII)\(^7^4\), a ring chain tautomer of the hydroxy propantrione (LVIII) and the flavandione (LIX). When oxidation of flavanol is carried out in methanol, the product formed is a 3-hemiketal of the 3,4-flavandione (LXI)\(^7^5\). The formation of such a product is readily accommodated by the Alder oxidation mechanism.
When methanol is present it attacks the cation C-2 forming LXI a ketal which unlike the hemiketal LIX can not undergo ring chain tautomerism. The actual product is colourless methyl-3-hemiketal (LXII). Sublimation of methyl-3-hemiketal (LXII) changes into flavandione (LXI) and recrystallization of LXII from dilute acetic acid gives the hydrated product LXIII. Similar reaction of 4'-methoxy flavanol (LXIXa), 7-methoxy flavanol (LXIXb) and 4',7-dimethoxy flavanol (LXIXc) with periodic acid in methanol gave compounds LXXa, LXXIa, LXXIIa, LXXb, LXXIb, LXXIIb and LXXc, LXXIc, LXXIIc respectively.

\[
\text{(LXIX)} \\
\text{(LXX)} \\
\text{(LXXI)} \\
\text{(LXXII)}
\]

a. \( R_1 = H, \; R_2 = \text{OMe} \)
b. \( R_1 = \text{OMe}, \; R_2 = H \)
c. \( R_1 = R_2 = \text{OMe} \)
The methyl 3-hemiketal of 2-methoxy 3,4-flavandiones (LXVI) react readily with ylides ethyl (triphenyl-phosphoranylidene) acetate to form (ethyl-2-methoxy-3-(carboxymethylene) flavanone (LXV) which is readily reduced by Zn/acetic acid to form 3-carbethoxy methyl flavone (LXVI). Conjugate addition of bromide and cyanide to enone system converts LXVI to the substituted carbethoxy methyl flavone (LXVIII).
1.5. **Metal Ion Oxidation**

Lead (IV) acetate and manganese (III) acetate oxidation in flavanoids have also been reported to give cyclic products. It could be expected that the reaction of 2'-hydroxy, 2-methyl isoflavone with metal salts might give a dehydrorotenoid by the removal of hydrogen from the hydroxyl group or methyl group. This dehydrorotenoid can be transformed into rotenoid which is known as fish poison. It is also expected that the reaction of 2'-hydroxy isoflavone with metal salts could give benzofuro-[2,3-b][1] benzopyran-11-one which has been found in natural source as Lisctin. The oxidation of 2'-hydroxy-4',7-dimethoxy isoflavone (LXXIIIe) in the lead (IV) acetate yielded two products LXXIV and LXXV when the reaction was conducted at room temperature, LXXIVe was the major product, at reflux temperature, however, LXXV was the major product. In conclusion, the reaction of 2'-hydroxy 2-methyl isoflavones (LXXIIIa-d) with lead (IV) acetate and Manganese (III) acetate did not yield the expected dehydrorotenoid, but gave a new dihydro-benzofuro-[2,3-b][1] benzopyran-11-one (LXXIVa-d) while the reaction of 2'-hydroxy isoflavone gave benzofuro-[2,3-b][1]-benzopyran-11-one (LXXV).
(a) $R_1 = \text{CH}_3$, $R_2 = R_4 = \text{H}$, $R_3 = \text{OMe}$
(b) $R_1 = \text{CH}_3$, $R_2 = \text{H}$, $R_3 = R_4 = \text{OMe}$
(c) $R_1 = \text{CH}_3$, $R_2 = R_3 = \text{OMe}$, $R_4 = \text{H}$
(d) $R_1 = \text{CH}_3$, $R_2 = R_3 = R_4 = \text{OMe}$
(e) $R_1 = \text{H}$, $R_2 = \text{H}$, $R_3 = R_4 = \text{OMe}$

Lead (IV) acetate and manganese (III) acetate have also been used in oxidation of 3-hydroxyflavones. When 4',7-dimethoxy-3-hydroxy flavone (LXXVIc) was treated
with lead (IV) acetate in acetic acid, five different compounds LXXVII, LXXVIII, LXXIX, LXXX and LXXXI were obtained,

\[(LXXVI)\]

\[(LXXVII)\]

\[(LXXVIII)\]

\[(LXXIX)\]

\[(LXXX)\]

\[(LXXXI)\]

(a) \(R_1 = \text{OMe}, R_2 = R_3 = H\)

(b) \(R_1 = R_2 = \text{OMe}, R_3 = H\)

(c) \(R_1 = R_3 = \text{OMe}, R_2 = H\)

(d) \(R_1 = R_2 = R_3 = \text{OMe}\)
but when 4',7-dimethoxy flavone (LXXVIc) was treated with manganese (III) acetate, five different compounds, were obtained LXXVII, LXXX, LXXXI, LXXXII, LXXXIII in which two compounds LXXXII and LXXXIII are quite different from that of LTA oxidation.

\[
\text{MeO-} \quad \begin{array}{c}
\text{O-C} \\
\text{Me}
\end{array} \\
\text{MeO-} \quad \begin{array}{c}
\text{O-C} \\
\text{Me}
\end{array}
\]

( LXXXII)

\[
\text{HO} \quad \begin{array}{c}
\text{•OH} \\
\text{OCH3}
\end{array}
\]

( LXXXIII)

oxidation of flavanone with lead (IV) acetate \(^{85}\) gave a complex mixture of flavanoids. When flavanone oxidized with lead (IV) acetate in acetic acid at 80 - 90°C the corresponding flavone, isoflavone, and 3-acetoxy flavone have been isolated. Same results were obtained in case of 7-methoxy flavanone (LXXXIVa) and 7,4'-dimethoxy flavanone (LXXXIVb), but in case of 7,3',4'-trimethoxy flavanone (LXXXIVc), 3-acetoxy flavone derivative has not been isolated. 7-methoxy flavanone (LXXXIVa) and 7,4'-dimethoxy flavanone (LXXXIVb) gave the corresponding flavone (LXXVa,b), isoflavone (LXXXVIa,b) and 3-acetoxy flavone (LXXXVIIa,b),
where as in case of 7,3',4'-trimethoxy flavanone (LXXXIVc) only corresponding flavone (LXXXVc) and isoflavone (LXXXVIc) were obtained. The mechanism for conversion of flavanone to isoflavone has been explained by the acetylation at 3-position of flavanone by Wagner Meerwin rearrangement.

\[ \text{(LXXXIV)} \]

\[ \text{(LXXXV)} \]

\[ \text{(LXXXVI)} \]

(a) \( R_1 = \text{OMe}, R_2 = R_3 = \text{H} \)

(b) \( R_1 = R_3 = \text{OMe}, R_2 = \text{H} \)

(c) \( R_1 = R_2 = R_3 = \text{OMe} \)
Under the similar reaction conditions 7-methoxy 2:2 dimethyl chromanone (LXXXVIII) gave only single racemic 3-acetoxy derivative LXXXIX whereas 7-methoxy 2-methyl chromanone (XC) gave trans and cis recimats XCI and XCII.

Chalcones are normally oxidized with thallium (III) nitrate (TTN) with rearrangement providing easy access to a variety of compounds. In the reaction of 2'-benzyloxy-4,4'-dimethoxy
chalcone (XClIII) with TTN\textsuperscript{86} 1-(2-benzyloxy-4-methoxyphenyl)-2-(4-methoxy phenyl) ethanedione (XClIV) was formed which on debenzylation gave LXXVIIc.

\[
\text{(XClIII)} \quad \text{(XClIV)}
\]

In addition, the Thallium (III) nitrate is useful for oxidative rearrangement of chalcones in acidic methanol\textsuperscript{87}. In this reaction aryl migration takes place which is the key intermediate XCV for the synthesis of isoflavone XCVI.

\[
\text{(XCV)}
\]

\[
\text{(XCVI)}
\]
Nitro substituted chalcones on oxidation with Thallium(III) nitrate do not give the rearranged products but oxidative cyclization has been observed\(^8\). 2'-hydroxy,3'-nitro-chalcones (XCVII) on oxidation with TTN gave aurone derivatives XCVIII and a nitro derivative XCIX as a minor product\(^9\).

\[\text{(XCVII)}\]

\[\text{(XCVII)}\]

\[\text{(XCIX)}\]

(a) \(R_1 = R_2 = R_3 = R_4 = H\)

(b) \(R_1 = H, R_2 = R_3 = OMe, R_4 = NO_2\)

(c) \(R_1 = R_3 = CH_3, R_2 = R_4 = H\)
Oxidation of flavanone hydrazones with active manganese dioxide has been reported to produce the azines in addition to the parent flavanones. In view of the interesting results observed on oxidation of 4-oximino flavan with selenium dioxide, a novel type of oxidation of flavanone hydrazones (C) with SeO₂ in aqueous dioxane gave flavones (CI) as the major product and two other dimerized products have been isolated, one is 3,3-linked biflavanone CII and the other is 3,3-linked biflavone CIII.

(a) \( R = R' = H \)  
(b) \( R = H, R' = OMe \)  
(c) \( R = Me, R' = H \)  
(d) \( R = Me, R' = OMe \)
1.6. Oxidative coupling of phenols

Oxidation of phenolic compounds as a mode of formation of a diversity of biological important structure has been investigated for a long time. Phenol oxidation with modified metal complex have received considerable attention during last few years.

Although the role of copper ions in enzymic phenol oxidation has been recognized relatively little attention has been paid to the use of copper complexes in phenol oxidation, either as a synthetic method or in a biomimetic type synthesis of natural products. Oxidation of phenols using copper complexes under aerobic conditions yielded quinones, polyether.

Kögic and co-workers recently shows that oxidation of phenol using an excess of the pyridine-copper complex (PyCuClOMe) as oxidant gave cis-cis muconic acid via an intermediate of O-benzo-quinone when an oxygen substituent is already present in the ortho position of phenol. Furthermore the formation of polyethers from the cupric pyridine complex, catalysed oxidation of 2,6-dimethyl phenol (CIV) in which O-quinone formation is blocked under aerobic conditions is a well described process. Exclusion of oxygen in the oxidation of phenol could lead to the elimination of pathways A and B possibly giving coupled phenolic products. According to the above observations using cupric amine
complexes under anaerobic conditions in molar quantities is a general reaction for intramolecular and intermolecular coupling of phenols.

\[
\text{(CIV)} \quad \text{[0.05 eq. Cu(I) salt]} \quad \text{(CV)}
\]

Oxidation of naphthols using copper amine complexes has been studied and the dimerized products were obtained \(^9\).

\[
\begin{align*}
\text{(CVI)} & \quad \text{[a. } R = H \text{]} \\
\text{[b. } R = OH \text{]} \\
\text{(CVIII)} & \quad \text{(CVII)} \\
\text{(CVIX)} &
\end{align*}
\]
Oxidation of simple phenols and some aniline with vanadium oxytrichloride and vanadium tetrachloride afforded dimeric products\textsuperscript{97,98} which are coupled predominantly at the para position. Equimolar quantity of phenol with vanadium tetrachloride in an inert solvent followed by hydrolysis (ed. to the isolation of 4,4'-diphenyl, 2,4'-diphenyl and 2,2'-diphenyl in an approximate ratio of 8:4:1. The remaining part is unreacted phenol and <5\% chlorinated product. Phenol itself was not oxidized with vanadium oxytrichloride under conditions of vanadium tetrachloride oxidation. However these phenol derivatives with lower oxidation potential were coupled by vanadium oxytrichloride. Thus 1,2-nephthol reacted smoothly with vanadium oxytrichloride to produce 4,4'-dihydro binaphthyl and 2,2'-dihydro binaphthyl in 55\% and 60\% yield.

The oxidative coupling of free radical species, derived from phenolic substrates is now widely accepted as the pathway by which many complex natural products are biosynthesized\textsuperscript{15,99}. Such a route has been suggested as being involved in the formation of the group of compounds known as the biflavonyls, which possess the apigenin moiety as a common structural feature\textsuperscript{100}. Thus the parent biflavonyls, amento flavone\textsuperscript{101}, cuppressoflavone\textsuperscript{102}, Hinoki flavone\textsuperscript{103} and Ochna flavone\textsuperscript{104} together with various O-methyl ethers exhibit either C-C or C-O linked dimer which
might be expected through oxidative coupling of an apigenin derived radical by three of the many modes of dimerization theoretically possible.
Molyneux et al. have investigated the oxidative coupling of apigenin using alkaline potassium ferricyanide and isolated two biflavones CX and CXI with interflavone linkages [I-3, II-3] and [I-3, II-3'] respectively. Later on, Taiwania flavone (CXI) has been encountered in nature.

These synthetic compounds CX and CXI appear to arise presumably by appropriate spin pairing of the mesomeric radicals, although none of the symmetrical linked dimer, which might also be expected to be formed, could be isolated. These observations are consistent with the findings of the Kuhnle et al., who studied the electron spin resonance spectra of flavanoid anion radicals (derived from polyhydroxy flavone and having a 5-hydroxy function) and concluded that
the delocalization of an unpaired electron initially generated at the 4'-hydroxyl group in apigenin occurs only in ring B and C. Thus in order to achieve and interflavone linkage to ring A, Molyneux et al.\textsuperscript{105} believe that a radical initially generated at 4'-hydroxyl group in apigenin and delocalized, attacks electrophilically the electron rich C-6 or C-8 positions of the phloroglucinol ring of an intact apigenin molecule i.e. radical substitution occurs in preference to radical pairing.

\begin{center}
\begin{tikzpicture}
\draw (0,0) circle (1cm);
\draw (0,0) circle (1cm);
\end{tikzpicture}
\end{center}

\textbf{(CXII)}

Sheshadri et al.\textsuperscript{108} have carried out oxidative coupling of 4',7-dimethoxy-5-hydroxy flavone with ferric chloride in boiling dioxane and reported that the properties of the product were similar but not identical with those of the corresponding cupressuflavone derivatives. In a reinvestigation of this reaction by Chandramouli et al.\textsuperscript{109}, the crude product after the removal of the unchanged starting
Material was completely methylated and methylated product was identified as homocupressuflavone hexamethyl ether (CXIV).

![Diagram of CXIV]

Parthasarthy et al.\textsuperscript{110} have recently reported that oxidative coupling of phloroacetophenone-2,4-dimethylether (CXV) using $[\text{Fe(DMF)}_3\text{Cl}_2]^+\text{[FeCl}_4^-\text{ produces } 5,5'\text{-bis(2-hydroxy-4,6-di-O-methyl phloroacetophenone)} (CXVI) which is converted into hexa-O-methyl-I-6,II-6-biapigenin (CXVII) via bis chalcone which undergoes cyclization in the presence of ethanolic $\text{H}_2\text{SO}_4$ giving hexa-O-methyl-I-6,II-6-binaringenin (CXVIII) which on dehydrogenation using $\text{I}_2/\text{AcOH}$ in $\text{AcOK}$ affords CXVII.
1.7. **Nuclear oxidation**

Nuclear oxidation\(^{111}\) can be either a one stage process employing alkaline potassium persulphate or a two stage process involving formylation and than Dakins reaction. But this method is having some difficulty in case of flavanone because of alkaline medium. Alkaline persulphate oxidation of 5-hydroxy-7-methoxy and 5-hydroxy 7,4'-dimethoxy flavanone yield the corresponding 5,8-dihydroxy-7-methoxy flavanone and 5,8-dihydroxy, 7,4'-dimethoxy flavanone. These are originally considered as 5,6-dihydroxy flavanone\(^{112}\). Later their structure has been established as 5,8-dihydroxy flavanone\(^{113}\). In two stage oxidation the first step of formylation may be accomplished either by Duff's or by Gattermann's reaction.

Naturally occurring flavanone has been examined and yield an aldehyde which on Dakin's oxidation yields isocarthamidin\(^{114}\).

![Chemical structures](CXI) (CXII) (CXIII)
This tetrahydroxy flavanone was originally obtained along with carthamidin by hydrolysis of carthamin which is the main glucosidic pigment of the carthamus tinctorius. Later Narasimhachari et al.\textsuperscript{115} prepared, this compound by demethylation of synthetic 5,6,7,4'-tetramethoxy flavanone and 5,7-dimethoxy-6,4'-dihydroxy flavanone\textsuperscript{116}.

Para oxidation can be performed at the acetophenone, chalcone or flavone stage. Oxidation with alkaline persulphate\textsuperscript{117} and oxidation with potassium nitroso disulphonate (Fremy : Salt)\textsuperscript{118} both are suitable methods for nuclear oxidation at para position of the hydroxyl group already present in a compound. m-chloro perbenzoic acid\textsuperscript{119} can also be used for nuclear oxidation. Para-oxidation of C-5/C-8, C-2'/C-5 and C-3'/C-6' in flavone and C-2'/C-5' p-oxidation in chalcone have been developed by Sheshadri et al.\textsuperscript{111,113,114}. When more than one hydroxyl group with free p-position are present, the oxidation by persulphate shows no selectivity. The 5,8,p-oxidation, however results in high yield if the 7-hydroxyl group is free. Flavanols give good yield in nuclear oxidation at para position of 3-hydroxyl group is methylated. Potassium nitroso disulphonate is more suitable method for the preparation of 2',6' or 3',5'-dihydroxy substituents in B-ring as compared to alkaline persulphate method. In the presence of several oxygen functions with the para position free,
only the free hydroxyl chelated with a neighbouring carbonyl group does not react. A series of flavanones and flavanols with 3',6'-dihydroxy substitution have been synthesized by potassium nitroso disulphonate. This method can be used for the synthesis of flavanone p-quinones remerin (CXXIIa) breverin (CXXIIb) and scaberin (CXXIIc) recently isolated from Cyperus spp.
Halogenation of flavanoids have been investigated from different reagents. Reaction of thionyl chloride\(^\text{121}\) with flavone at elevated temperature gave 3-chloro flavone (CXXIII), the action of thionyl chloride as a chlorinating agent in this case to yield the hitherto unknown (CXXIV). The reaction of sulphuryl chloride\(^\text{122}\) with flavone also give 3-chloro flavone (CXXIII) and 2,3,3-trichloroflavanone (CXXIV). Treatment of flavone or 3-chloro flavone in anhydrous benzene under reflux with an excess of sulphuryl chloride for 15 hrs. gave 2,3,3-trichloroflavanone (CXXIV).

\[
\text{2-hydroxy-5-methyl dibenzoyl methane (CXXV) react with sulphuryl chloride in refluxing dioxane to give the 3-chloro-}
\]

\[
\begin{align*}
\text{flavone} & \xrightarrow{\text{SOCl}_2} \text{3-chloro flavone (CXXIII)} \\
\text{flavone} & \xrightarrow{\text{SOCl}_2} \text{2,3,3-trichloroflavanone (CXXIV)} 
\end{align*}
\]
6-methyl flavone (CXXVI). This is a one step direct synthesis \(^{123}\) of 3-chloroflavone.

\[
\begin{align*}
\text{(CXXV)} & \quad \text{(CXXVI)} \\
\end{align*}
\]

Ghiya et al. \(^{124}\) observed that heating of 2'-hydroxy-4-methoxy-5'-methyl chalcone dibromide (CXXVII) with pyridine gave the nuclear helogenated chalcone (CXXVIII). Jadhav et al. \(^{125}\) studied the reactions of a larger number of chalcone dibromide and found that these are converted to either \(\alpha\)-bromo chalcone, flavone or aurones, depending upon the nature and position of the substituents in the aromatic nuclei.

\[
\begin{align*}
\text{(CXXVII)} & \quad \text{(CXXVIII)} \\
\end{align*}
\]
Pyridine reaction has also been studied by different types of substituted chalcone dibromide and their halogenated flavones have been isolated. The reaction of 2'-hydroxy chalcone dibromide (CXXIXa) gave the mono-nuclear halogenated flavone, 6-bromo flavone (CXXXa). 4-chloro-2'-hydroxy chalcone dibromide (CXXIXb) also unsubstituted in the 3',5'-positions gave the mono-nuclear brominated compound 6-bromo-4'-chloroflavone (CXXXb) together with the unbrominated 4'-chloroflavone. 2'-hydroxy-4-methoxy chalcone dibromide (CXXIXc) on the other hand gave the dihalogenated product 6,8-dibromo-4'-methoxy flavone (CXXXc). The mono halogenated flavone 8-bromo-4'-methoxy-6-methyl flavone (CXXXd) was obtained from 2'-hydroxy-4-methoxy-5'-methyl chalcone dibromide (CXXIXd). Chalcone dibromide substituted at both 3',5'-positions gave the corresponding flavones.
(CXXXIa)  

(a) $R_1=R_2=R_3=H$
(b) $R_1=R_2=H, R_3=Cl$
(c) $R_1=R_2=H, R_3=OMe$
(d) $R_1=H, R_2=CH_3, R_3=OMe$
(e) $R_1=R_2=Br, R_3=H$
(f) $R_1=R_2=Br, R_3=Cl$

(CXXX)  

(a) $R_1=Br, R_2=R_3=H$
(b) $R_1=Br, R_2=H, R_3=Cl$
(c) $R_1=R_2=Br, R_3=OMe$
(d) $R_1=CH_3, R_2=Br, R_3=OMe$
(e) $R_1=R_2=Br, R_3=H$
(f) $R_1=R_2=Br, R_3=Cl$

Heating of 2'-hydroxy chalcone with $\text{I}_2\text{-DMSO.H}_2\text{SO}_4$ gave 3-iodo flavone. This method is a one step synthesis of 3-iodo flavone from chalcone. 2'-hydroxy 4',6',4'-trimethoxy chalcone (CXXXIa) was first heated at 100°C for 10 mts with dimethyl sulphoxide and a small amount of sulphuric acid, then the catalytic amount of iodine was added and the mixture was further heated for 40 mts at 100°C, the 3-iodo flavone (CXXXIIa) was obtained as major product.
The synthesis of 3-iodo flavone is interesting from both synthetic and mechanistic view points, 3-iodo flavone have not been previously described in the literature, they are of potential use for synthesizing C-3 linked biflavones by the Ullmann reaction.

A number of biflavanoids with different interflavanoid linkage have been synthesized by the application of Ullmann coupling reactions. Nakazawa accomplished the synthesis of amento flavone hexamethyl ether by mixed Ullmann coupling reaction between 3-iodo 5,7,4'-trimethoxy flavone and 8'-iodo 5,7,4'-trimethoxy flavone, cupressuflavone hexa methyl ether was obtained as a by product and was found identical the one obtained from natural source.