INTRODUCTION

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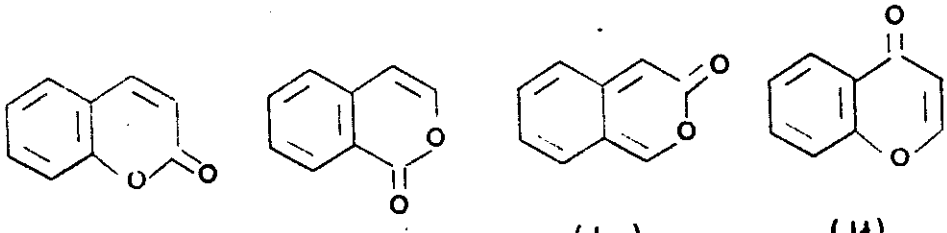
BENZOPYRANONES

The most important derivatives of pyranones are the benzopyranone derivatives.

There are four possible isomers of benzopyranones; coumarin or 5,6 benzopyran-2-one (I_a), isocoumarin or 3,4-benzopyran-2-one (I_b) or 4,5-benzopyran-2-one (I_c) and chromone or 5,6-benzopyran-4-one (I_d).



(I_a) (I_b) (I_c) (I_d)

The introduction comprises into two main parts:

A. Part I:

In this part the synthesis and chemical properties of coumarins is outlined.

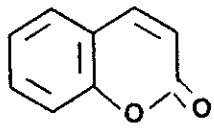
B. Part II:

This part includes a general review about the chemistry of chromones.

PART I

COUMARINS

Coumarins are substituted heterocyclic α,ß-unsaturated δ-lactones; they can be regarded as derivatives of 5,6-benzopyran-2-one (I_a).



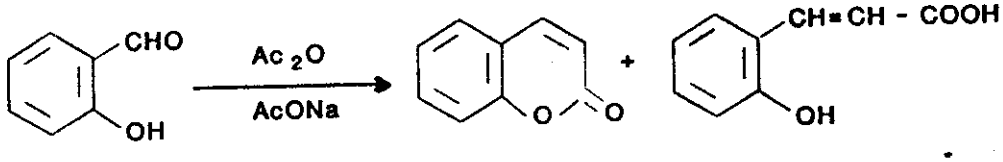
(I_a)

SYNTHESIS OF COUMARINS:

Coumarins could be synthesized by one of the following methods:

(1) Perkin synthesis :

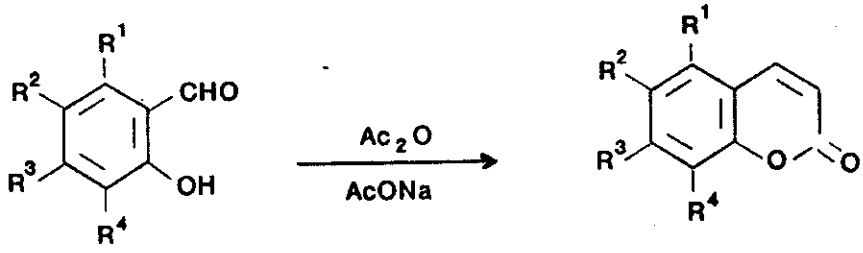
The classic synthesis was discovered by Perkin[1] who prepared coumarin (I_a) and coumarinic acid (II) by heating salicylaldehyde with a cetic anhydride and anhydrous sodium acetate.



(I_a) (II)

This was the first example of the reaction which bears his name; in its more general form it involves the reaction of an aromatic aldehyde (III) with the

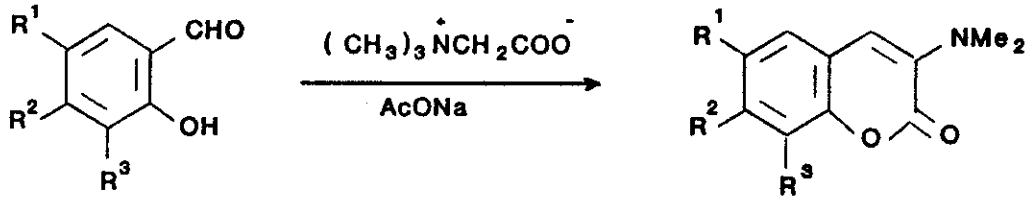
anhydride of an aliphatic acid in the presence of the sodium salt of its acid to give the coumarin (IV)[2-5].



(III) (I V)

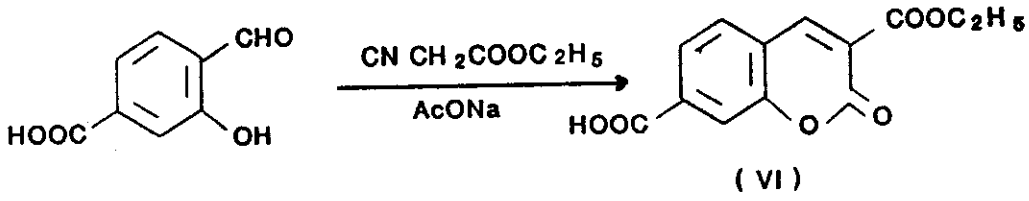
Recently, coumarin (I_a) was prepared in good yield by treating salicylaldehyde and acetic anhydride with anhydrous sodium flouride as catalyst in molar ratio 1:3.1:1.6. The reaction time was reduced and the operation was simple in comparison with the classical synthesis of coumarin catalyzed sodium acetate[6].

The reaction of salicylaldehyde, betaineand acetic anhydride afforded -3-dimethylaminocoumarin (V)[7].

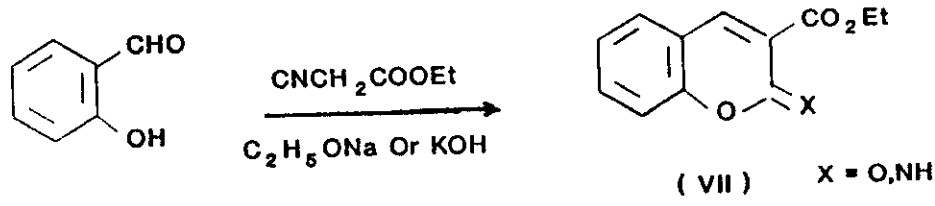


(V)

3-Hydroxy-4-formylbenzoic acid, ethyl cyanoacetate and sodium acetate gave-3- carbethoxy coumarin (VI)[8]. The reaction of salicylaldehyde with ethyl cyanoacetate in the presence of sodium ethoxide or potassium hydroxide gave the derivatives (VII)[9].

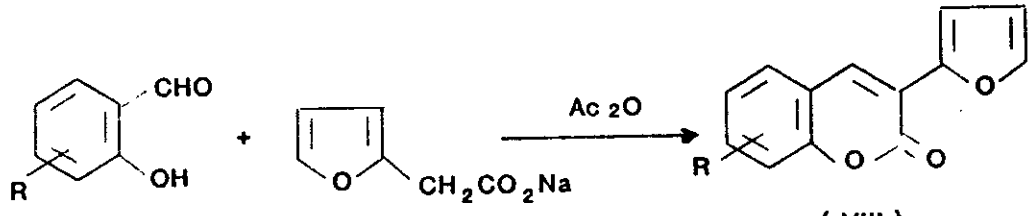


(VI)



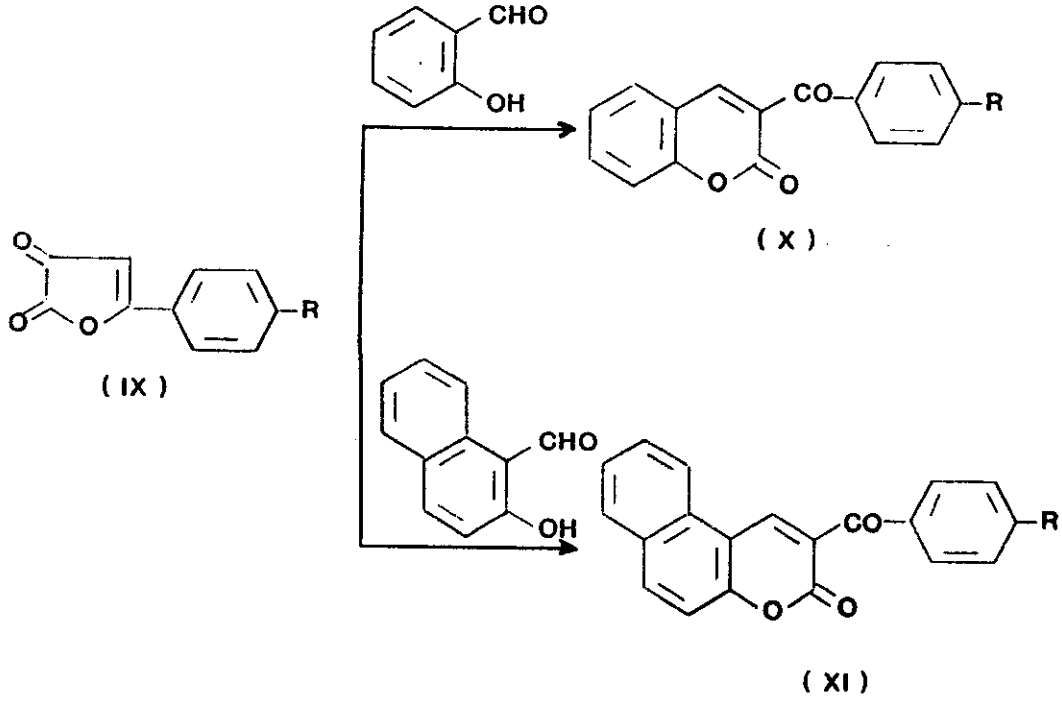
(VII) X = O,NH

Sodium furylacetate with substituted o-hydroxybenzaldehyde in the presence of acetic anhydride gave 3-(2-furyl)-coumarin derivatives (VIII)[10].

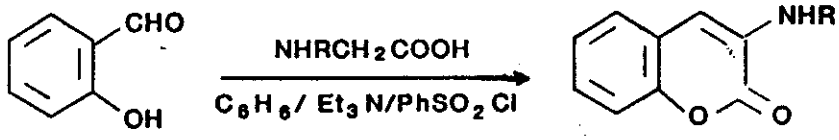


(VIII)

The benzopyranones (X) and naphthopyranones (XI) were prepared by treating the corresponding 2-aldehyde with furandione (IX)[11].

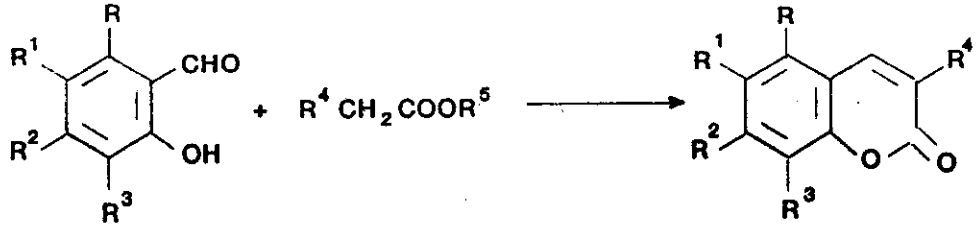


3-(N-Substituted) aminocoumarin derivatives (XII)[12] were prepared according to the following equation.



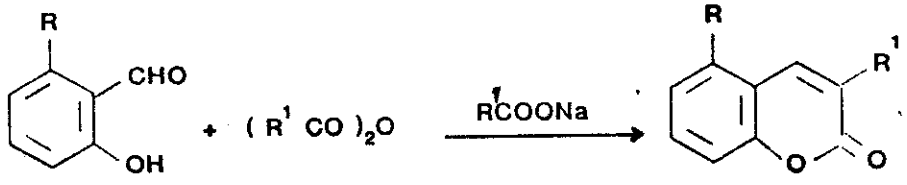
(XII)

3-Substituted coumarins (XIII)[13-18] were prepared by reacting substituted 2-hydroxybenzaldehyde or its derivatives with α- substituted acetic acid, its sodium salt and/or its ethyl or methyl ester in the presence of acetic anhydride and base like sodium acetate, triethylamine, diethyl ammonium chloride or piperidine.



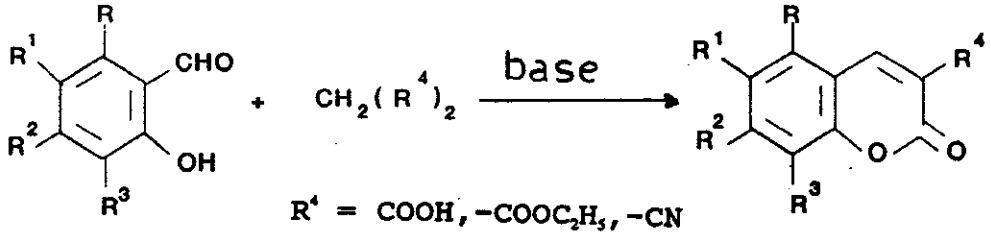
(XIII)

Fatty aliphatic acid anhydrides and their salts may replace acetic derivatives to give 3-alkylcoumarins (XIV)[19,20].



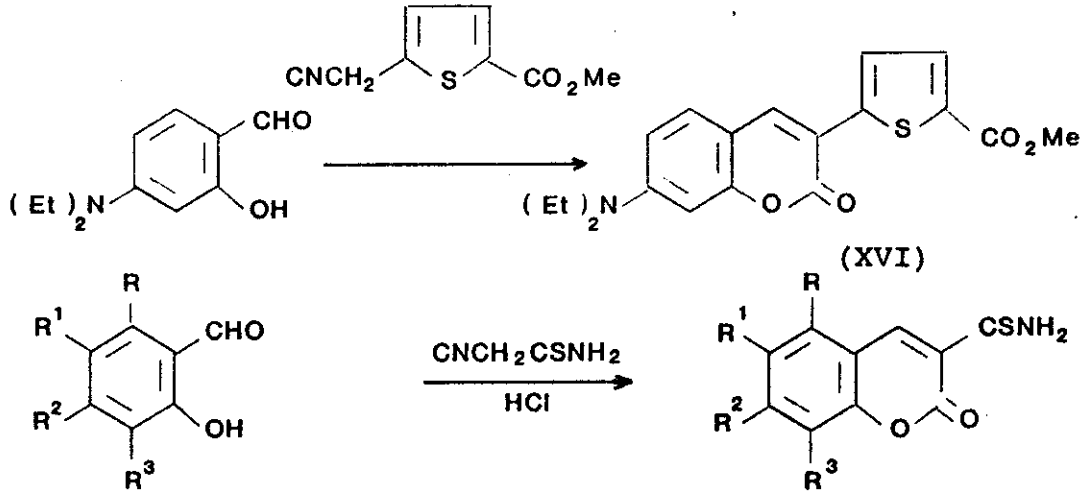
(XIV)

By somewhat similar reaction of Knoevenagel[21-24] o-hydroxybenzaldehyde derivatives condensed with compounds containing active methylene groups such as malonic acid, diethylmalonate and malononitrile in presence of organic base to yield 3-substituted coumarins (XV).



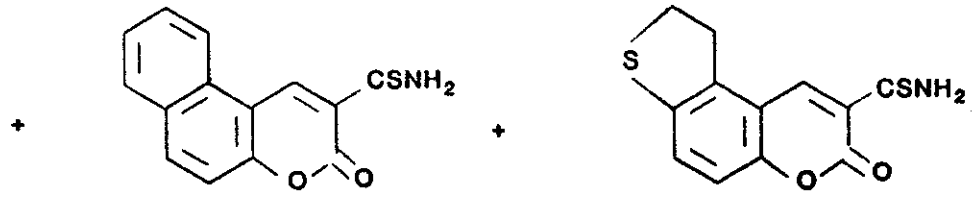
(XV)

Also, O-hydroxybenzaldehyde derivatives condensed with methyl-2-(cyanomethyl)-thiophene-5-carboxylate in presence of pyrrolidine and gave the coumarin derivative (XVI)[25]. But the condensation of cyanothioacetamide with o-hydroxybenzaldehyde derivatives in presence of hydrochloric acid gave the corresponding 3- thioamido coumarin derivatives (XVII-XIX)[26].



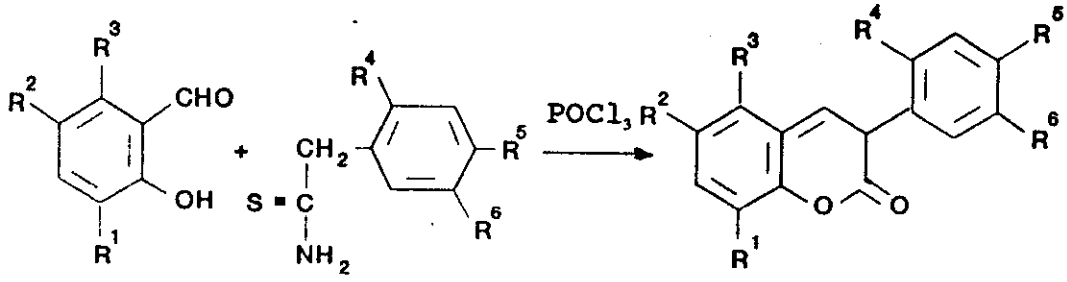
(XVI)

(XVII)



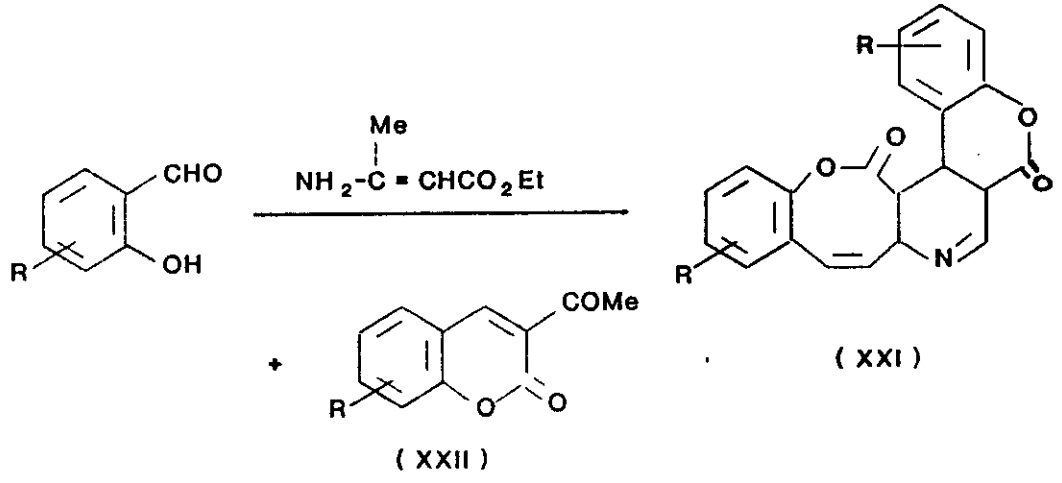
(XVIII) (XIX)

Salicylaldehyde derivatives were treated with phenylthioacetamides and phosphorus oxychloride and gave coumarins (XX)[27].



(XX)

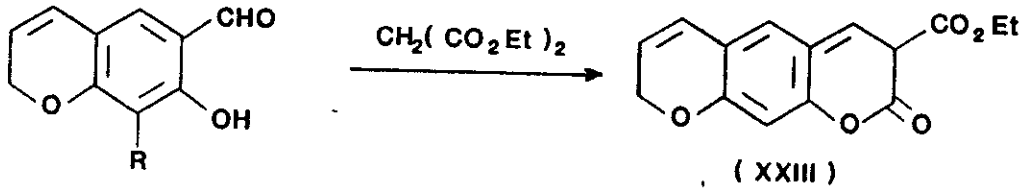
Refluxing equimolar amount of O-hydroxybenzaldehyde derivatves with ß-amino ethylcrotonate in the presence of traces of acetic acid gave the oxacins (XXI) and the coumarins (XXII)[28].



(XXI)

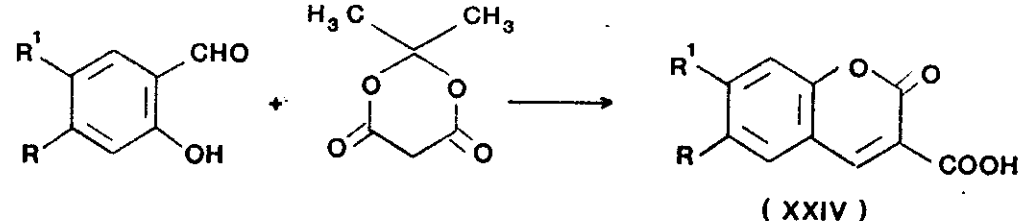
(XXII)

3-Substituted coumarins (XXIII)[29] were prepared by cyclization of the corresponding o-hydroxy aldehyde with diethylmalonate.

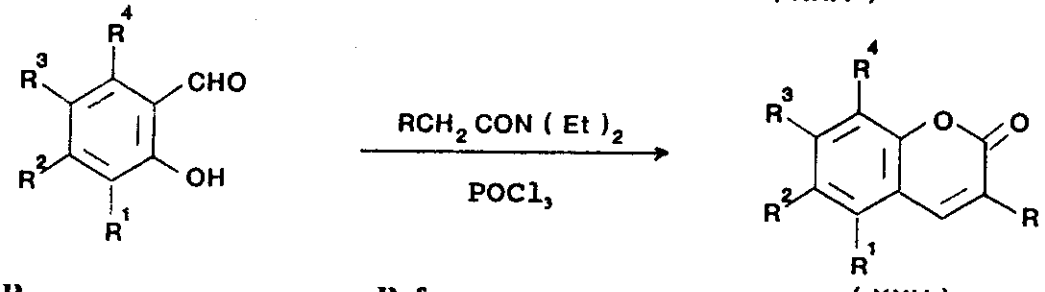


(XXIII)

Recently, 3-substituted coumarins (XXIV) and (XXV) were prepared by treating salicylaldehyde derivatives with 1,3-dioxan in the presence of water as a solvent and an alkaline reagent[30] or N,N-diethylacidamides in the presence of phosphorus oxychloride[31-33].



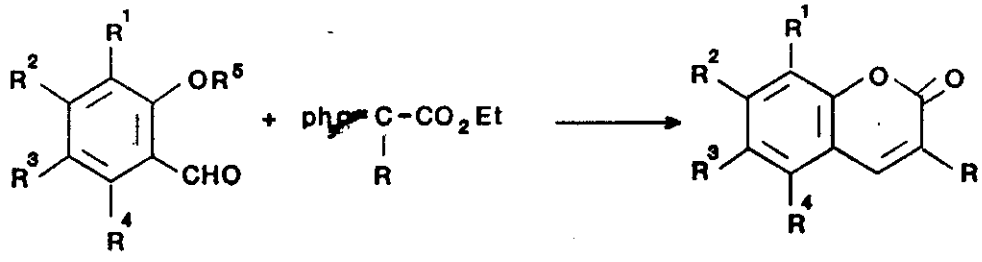
(XXIV)



(XXV)

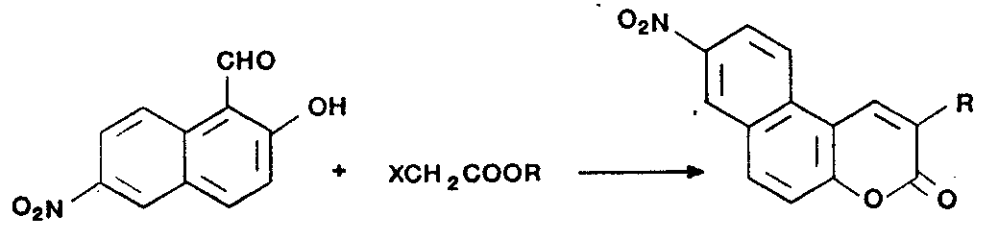
R	Ref
I	31,32
α-naphthol	33

The coumarin derivatives (XXVI) were prepared by the condensation of o-hydroxy or o-methoxybenzaldehyde derivatives with α-substituted carbethoxy-methylene triphenylphosphorane[34-39].



(XXVI)

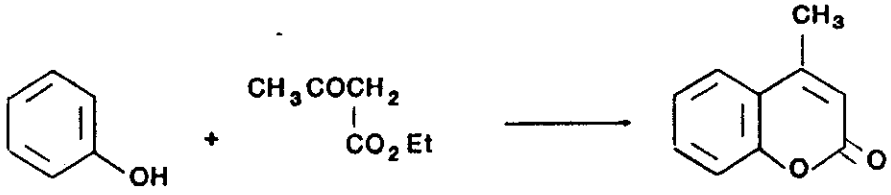
Cyclocondensation of 2-hydroxy-6-nitro-1-naphthaldehyde with malonic acid, its ester and/or ethyl acetoacetate yielded naphthopyranones (XXVII)[40].



(X = COOH,$COCH_3$) (XXVII)

II) Bechmann reaction:

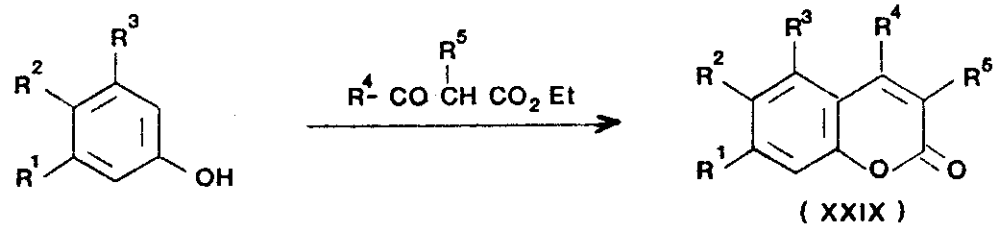
Bechmann and Duisberg[41] suggested that the reactive hydrogen of the phenol in the o-position to the hydroxyl group of phenols added to the carbonyl group of the ß-ketoester to give an intermediate hydroxyester. Ring closure may then takes place with the elimination of one molecule of water and one molecule of ethanol to give 4-methylcoumarin (XXVIII).



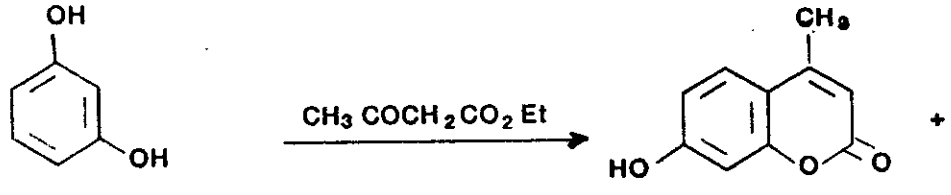
(XXVIII)

Among the substituted phenols it was found that the reactivity depends on both the nature and the position of the substituent in the phenol,alkyl groups in general have very little inhibitting effect in the Bechmann reaction, halogens exert somewhat more,when the substituents like the nitro or carboxylic acid groups are present, the reactions may not takes place at all[42-44].

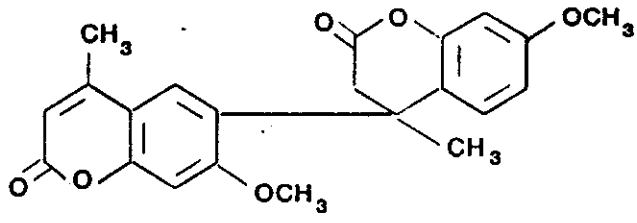
Thus phenol derivatives undergo Bechmann condensation with ethyl aceto-acetate or its corresponding compounds in presence of conc. sulphuric acid, hydrogen fluoride, trifluoroacetic acid, hydrogen chloride, aluminium chloride or borontrifluoride-ethyl ether complex to gave 4-substituted coumarin derivatives (XXIX)[45-63], (XXX)[64] and (XXXI)[64].



(XXIX)

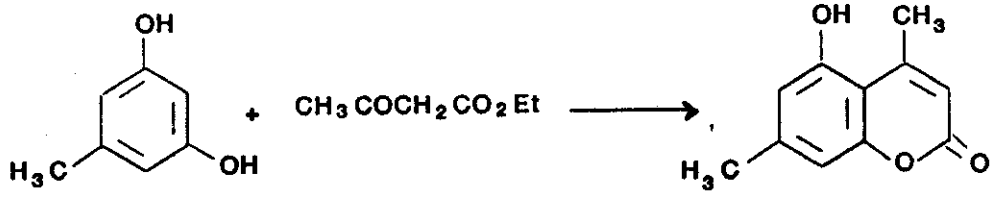


(XXX)



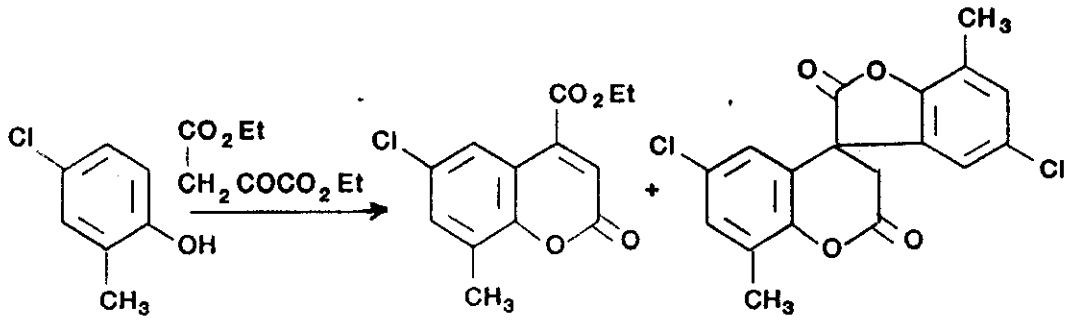
(XXXI)

Alkyl groups in the 5-position in resorcinol altered the course of the reaction and instead of the 7-hydroxycoumain derivatives, the 5-hydroxy isomers were obtained. Thus, orcinol condensed with ethyl acetoacetate and gave 5-hydroxy 4,7-dimethylcoumarin (XXXII)[64-50]



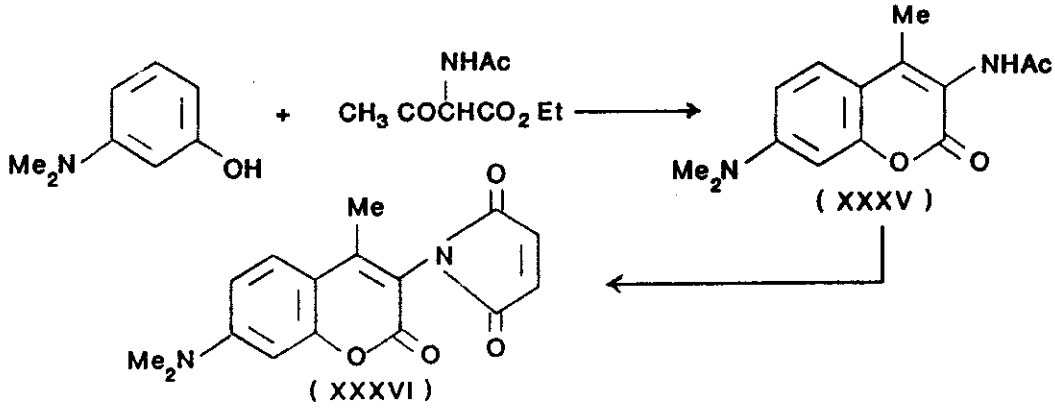
(XXXII)

Also, the condensation of ethyl ester of ß-carbethoxy pyruvic acid with 4-chloro-2-methylphenol in presence of sulphuric acid gave 6-chloro-8-methyl-4-carbethoxy coumarin (XXXIII) as main product and spirodilactone (XXXIV)[65].



(XXXIII) (XXXIV)

Bechmann condensation of 3-dimethyl aminophenol and α-acetamide ethyl acetoacetate yielded directly the substituted 3-acetamido coumarin (XXXV) which was readily converted into N-[7-(dimethyl amino)-4-methylcoumarin-7-yl]-maleimide (XXXVI)[66].

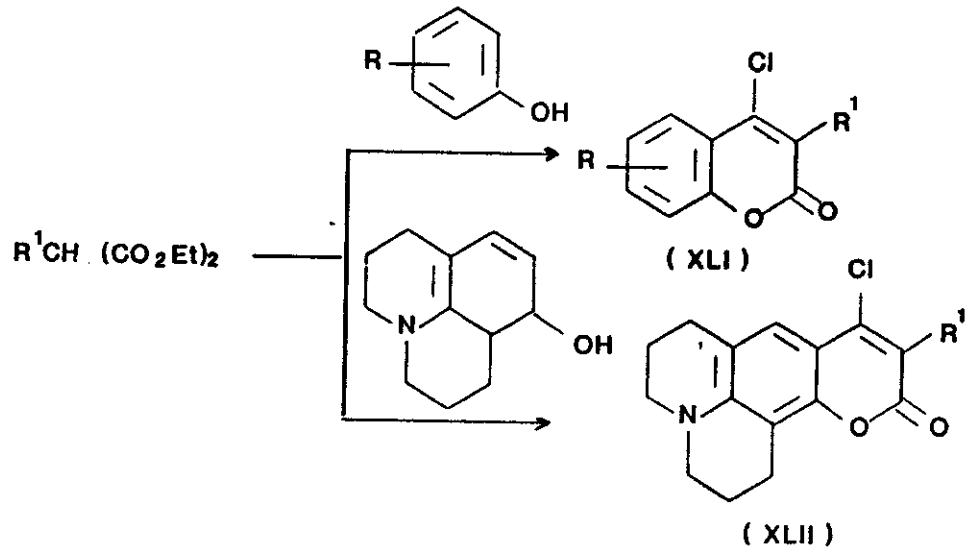


(XXXV)

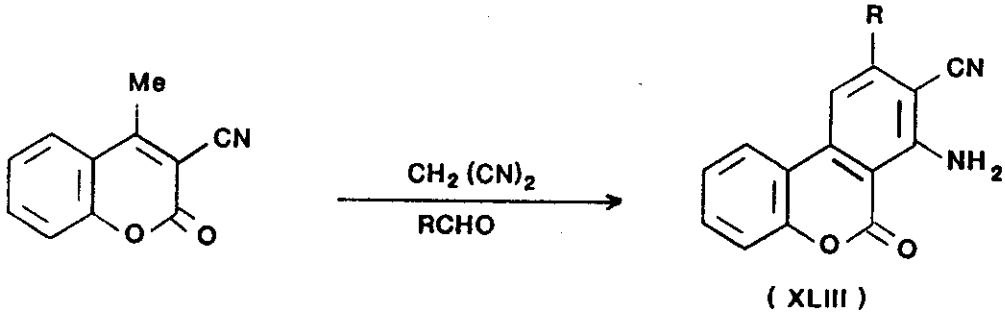
(XXXVI)

Bechmann condensation had been carried out with ethyl benzoyl-acetate[67,68].Thus ethyl benzoyl acetate condensed with phloroacetophenone and gave 8-acetyl-5,7-dihydroxy-4-phenyl coumarin (XXXVII) and 6-acetyl 5,7-dihydroxy-4-phenyl coumarin (XXXVIII).

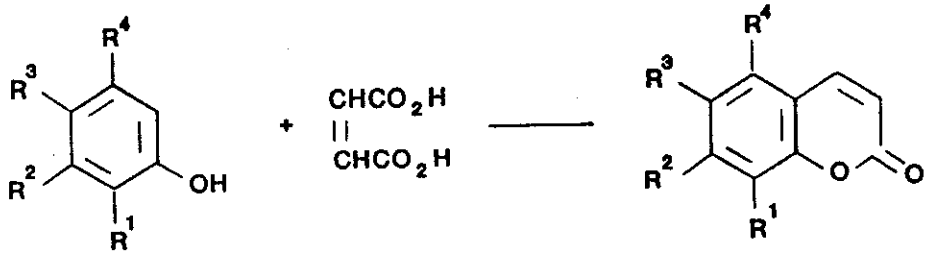
Ethyl benzoylacetate condensed also with 2-hydroxy – 4,6-dimethoxy



Benzocoumarins (XLIII) were conveniently prepared in one step synthesis by the ternary condensation of aldehydes, malononitrile and 3-cyano-4-methyl-coumarin[78].

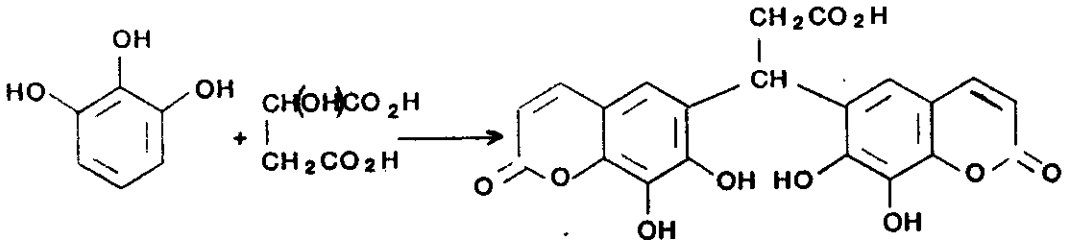


Maleic acid condensed with substituted phenol and gave the coumarin derivatives (XLIV)[79-81].

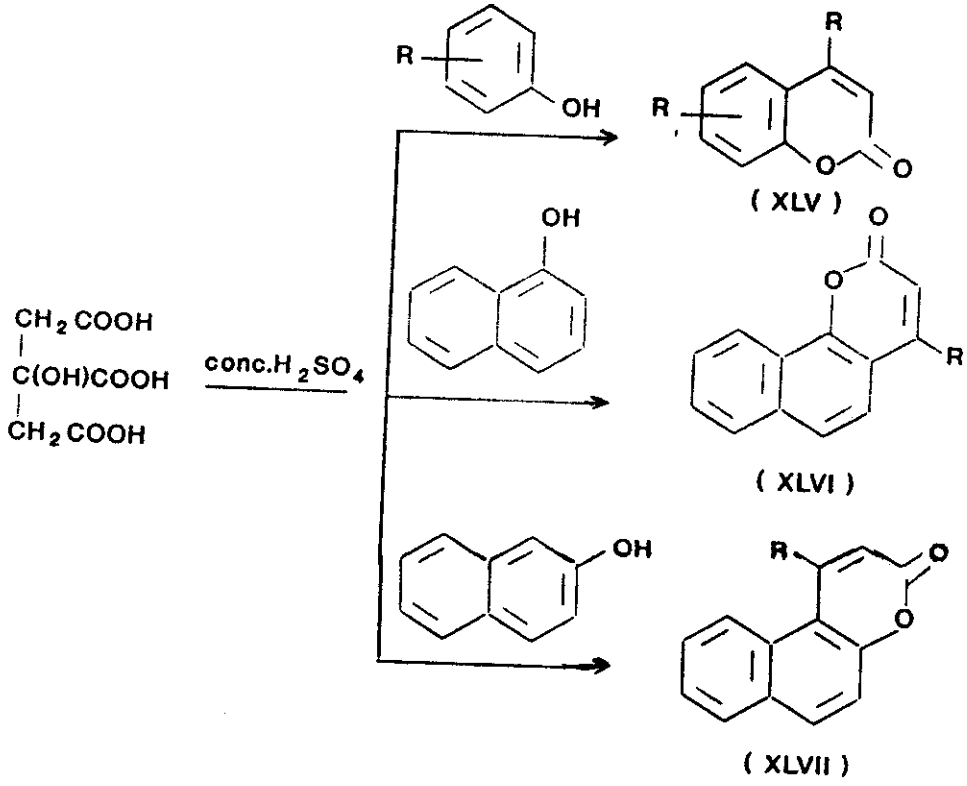


(XLIV)

Dicoumarin[80] **was obtained by Bechmann condensation of pyrogallol with malic acid in the presence of concentrated sulphuric acid at 100-2°C.**



Substituted benzopyranones (XLV), naphthopyranones (XLVI) and (XLVII) were prepared by cyclocondensation of phenols with citric acid in the presence of concentrated sulphuric acid[81,82].

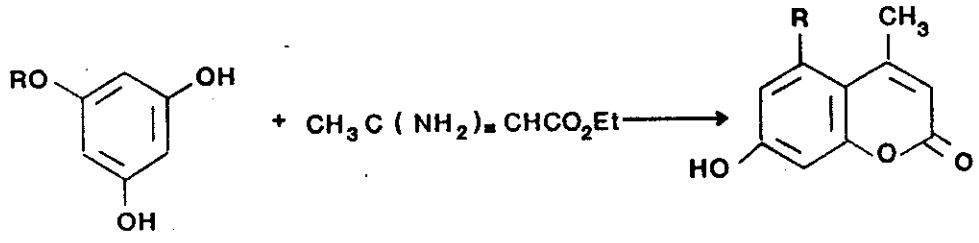


(XLV)

(XLVI)

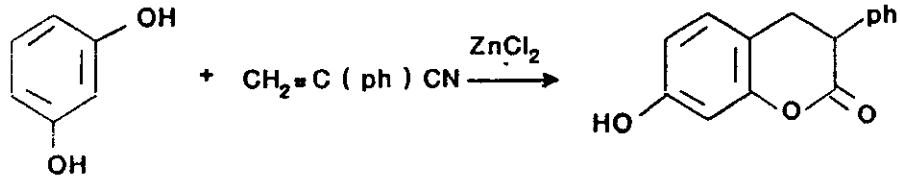
(XLVII)

Also, the reaction of orcinol, resorcinol and/or phloroglucinol with ethyl-ß-amino-crotonate in the presence of a catalyst as sulphuric acid, phosphoric acid or titanium tetrachloride gave the coumarin derivative (XLVIII)[83-85].



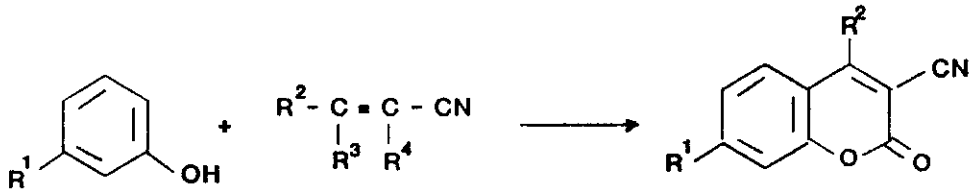
(XLVIII)

By means of the Hoesch reaction 3-phenyl-7-hydroxydihydrocoumarin (XLIX)[86,87] had been prepared from resorcinol.



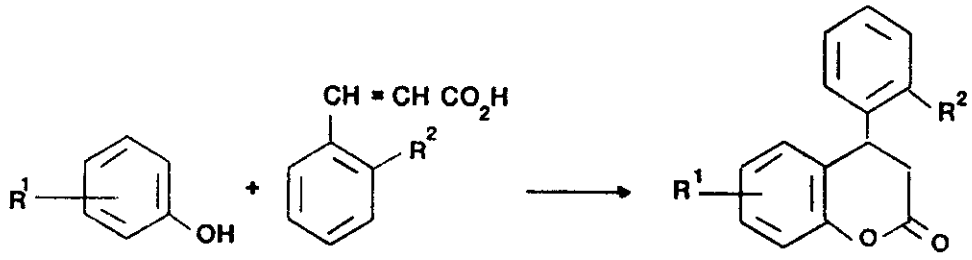
(XLIX)

Cycloaddition of substituted phenols with the nitrile derivatives (L) gave the 3-cyanocoumarin derivatives (LI)[88,89].



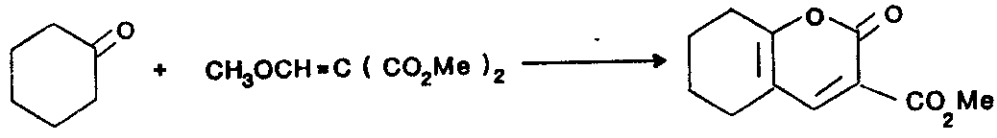
(L) (LI)

4-Substituted phenyl-3,4-dihydorcoumarins (LII) were obtained by the reaction of substituted phenol with cinnamic acid or its derivatives[90-93].



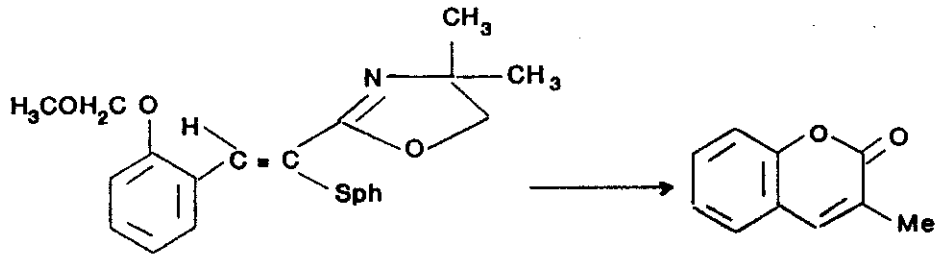
(LII)

Methyl-2-oxo-5,6,7,8-tetrahydor-2H-1-benzopyran-3-carboxylate (LIII) was prepared from the reaction of cyclohexanone with methoxy methylene dimethyl malonate[94].



(LIII)

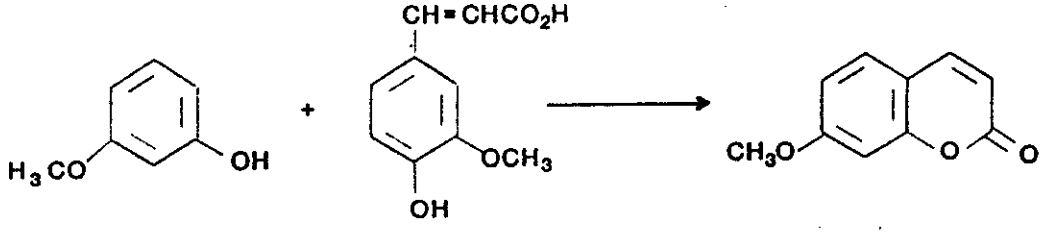
The reaction of (Z)-oxazolinyl (phenylthio) styrene (LIV) with $NaBH_3CN$ followed by butyl lithium and then quenching with methyl iodide, deprotection-lactonization and oxidation elimination gave coumarin derivative (LV)[95].



(LIV)

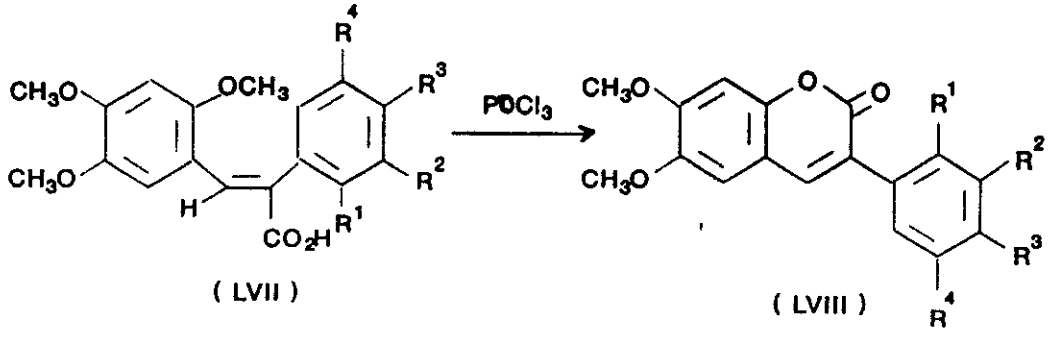
(LV)

Cyclization of the cinnamic acid derivative (LVI) with resorcinol monomethylether in the presence of polyphosphoric acid gave 7-methoxycoumain in a single step which involves transfer of the C_3-unit of cinnamic acid to the phenol used[96].



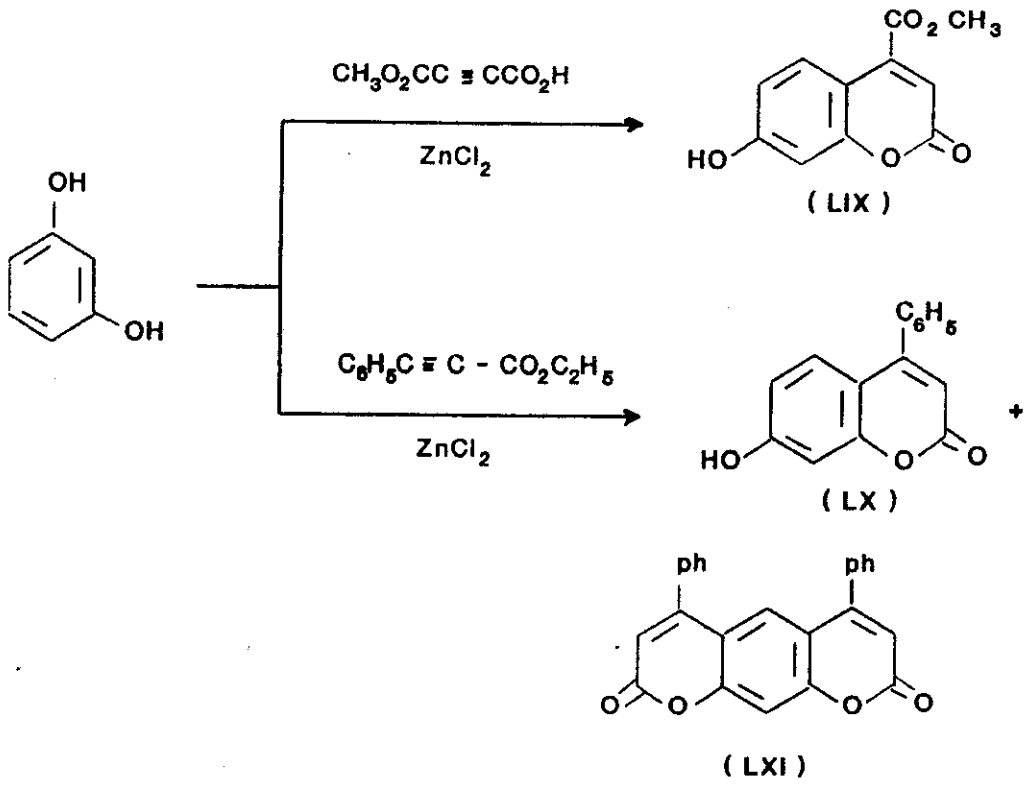
(LVI)

Recently,3-phenylcoumarins (LVIII) were obtained on heating (E)-α-phenylcinnamic acids (LVII) with pyridine /phosphorus oxychloride[97].



(LVII) (LVIII)

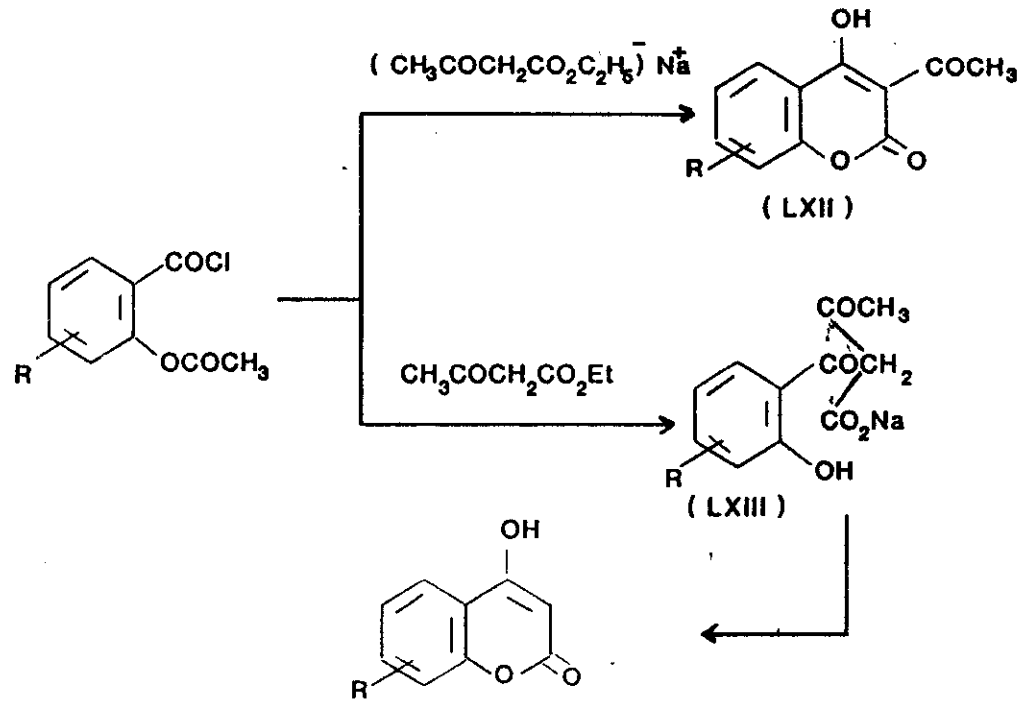
The Bechmann condensation has also been carried with unsaturated dicarboxylic acids or their related compounds. The reaction of resorcinol with methyl acetylene dicarboxylate and $ZnCl_2$ gave 7-hydroxy-4-carbomethoxy coumarin (LIX)[92]. The reaction of ethyl phenyl propiolate with resorcinol yielded 4-phenyl - 7-hydroxycoumarin (LX), (LXI)[84,85,86-88,92,98].



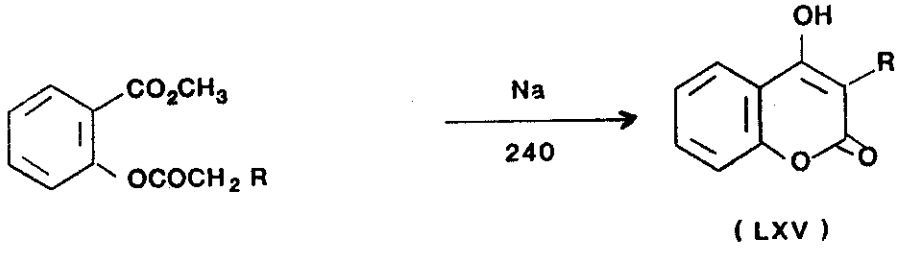
III) From salicylic acid derivatives:

Acylation of the sodium derivatives of ethyl acetoacetate by substituted o-acetoxybenzoyl chloride derivatives gave 3-acetyl-4-hydroxycoumarin (LXII)[99,100].

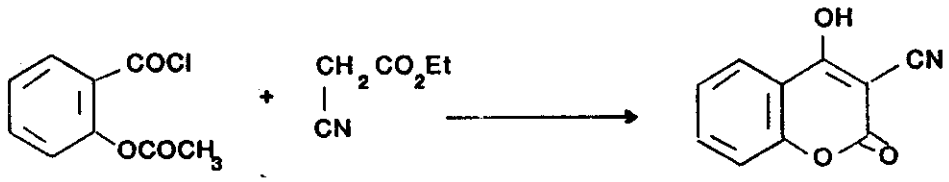
Also, the reaction of the o-acetoxybenzoylchloride with ethyl acetoacetate 40% NaOH and deacylation followed by cyclization and hydrolysis of intermediate (LXIII) gave 4-coumarinol (LXIV)[101].



Claisen condensation of methyl acetyl salicylate yielded the substituted coumarins (LXV)[102].



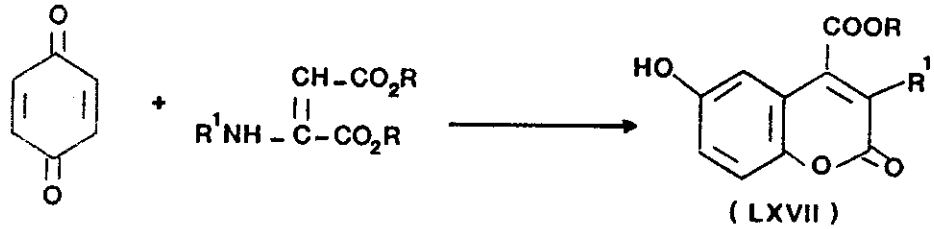
The condensation of ethyl cyanoacetate with acetylsalicylic acid chloride gave 3-cyano-4-hydroxycoumarin (LXVI)[103].



(LXVI)

IV) From quinones:

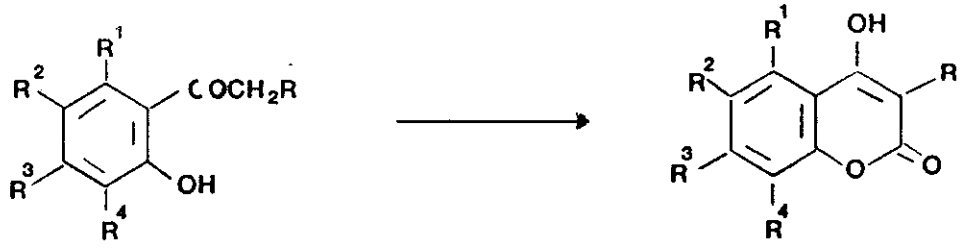
Aminofumarate derivatives on treatment with p-benzoquinone in the presence of zinc chloride or borontrifluoride in ether gave an adduct which decomposed in water and gave 3N-substituted amino-4- carboxylate-6-hydroxy-coumarin (LXVIIa)and(LXVIIb)[104,105].When the reaction was carried out at-75°C it gave 3,6-dihydroxy-4- carbethoxycoumarin (LXVIIc)[105].



(LXVII)

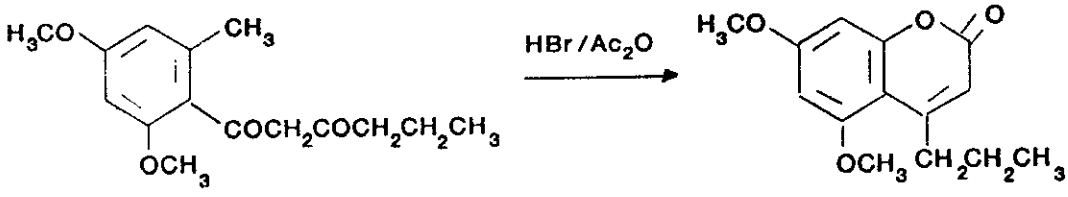
V) From-o-hydroxyphenyl ketones:

4-Hydroxycoumarins (LXVIII) were obtained by treatment of substituted 2-hydroxy acetophenone derivatives with diethyl carbonate[106-108]or an equivalent of selenium and carbon monoxide[109].



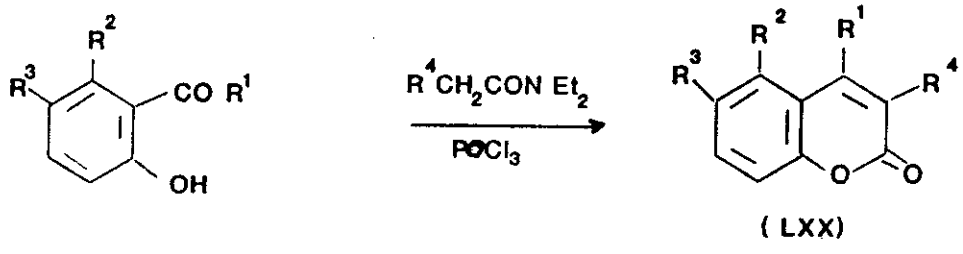
(LXVIII)

Ahluwalia and his co-workers[110] suggested that 5,7-dimethoxy-4-propylcoumarin (LXIX) was obtained by ring closure of ω-butyroyl (2,4-dimethoxy-6-methyl) acetophenone.



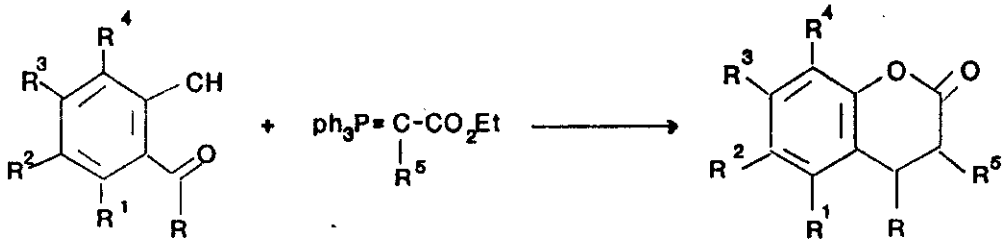
(LXIX)

The reaction of o-hydroxy phenyl ketones with N,N-diethylacetamide derivative and phosphorus oxychloride gave the coumarins (LXX)[111-113].



(LXX)

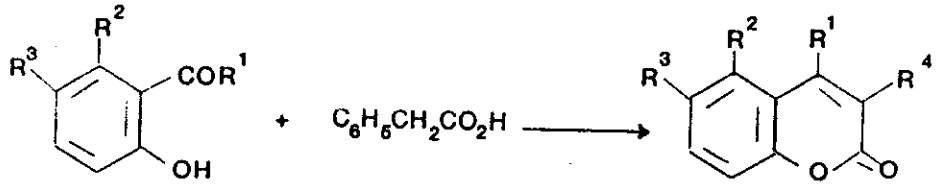
The substituted coumarins (LXXII) were obtained from phenol derivatives (LXXI) and α-substituted carbethoxy methylene triphenyl phosphorane[114,115].



(LXXI)

(LXXII)

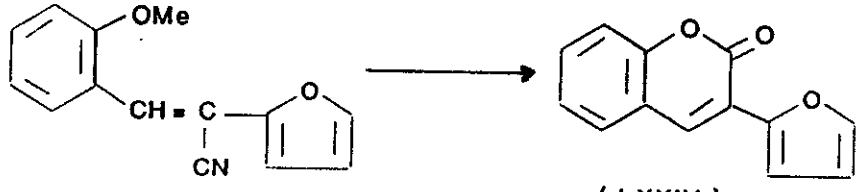
Similarly, the reaction of O-hydroxy phenyl ketones with phenylacetic acid yielded the coumarin derivatives (LXXIII)[116].



(LXXIII)

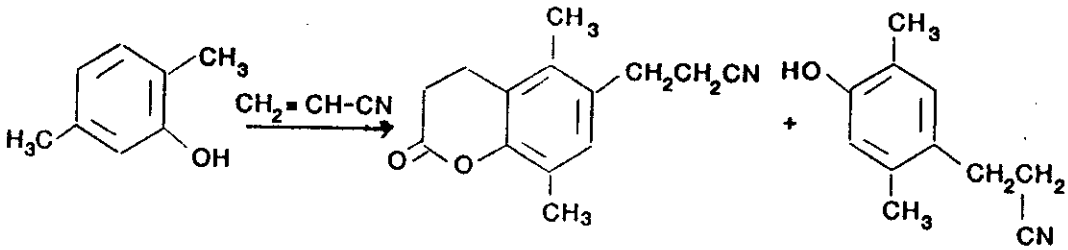
VI) From acrylo compounds:

3-(2-Furyl) coumarin (LXXIV)[117] was synthesised by cyclizing 2-(o-methoxyphenyl-1-furyl acrylonitrile) with pyridine HCl.



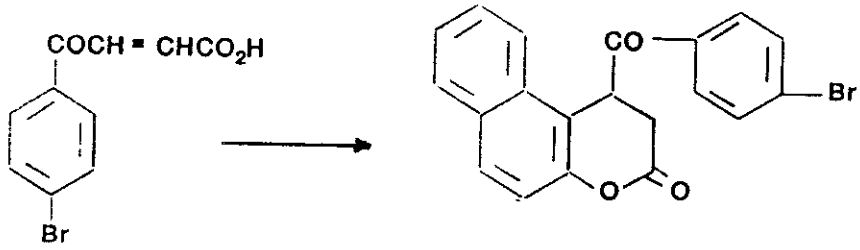
(LXXIV)

3,4-Dihydrocoumarin (LXXV) and (LXXVI)[118] were obtained by the reaction of 2,5-dimethylphenol with acrylonitrile.



(LXXV) (LXXVI)

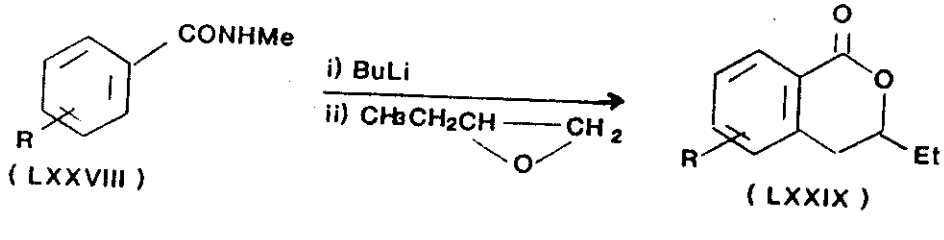
5,6-Benzo-4-(p-bromobenzoyl)-3,4-dihydrocoumarin (LXXVII)[119] was obtained by the reaction of ß-naphthol with p-bromo benzoylacrylic acid.



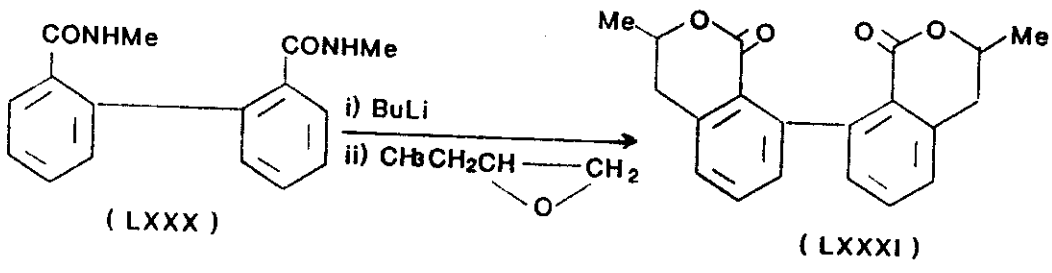
(LXXVII)

VII) Ortho- lithiation reaction:

Substituted 3-ethyl-3,4-dihydroisocoumarins (LXXIX) and 3,3-4,4-tetrahydro-8,8-bisisocoumarin (LXXXI) were prepared by ortho-lithiation of the corresponding N-methyl benzamide (LXXVIII) or the diamide (LXXX) with butyl lithium followed by alkylation with an alkene oxide[120,121].



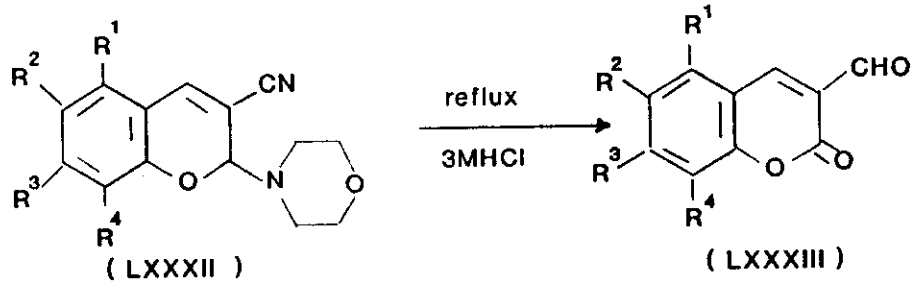
(LXXVIII) (LXXIX)



(LXXX) (LXXXI)

VIII) From chromene:

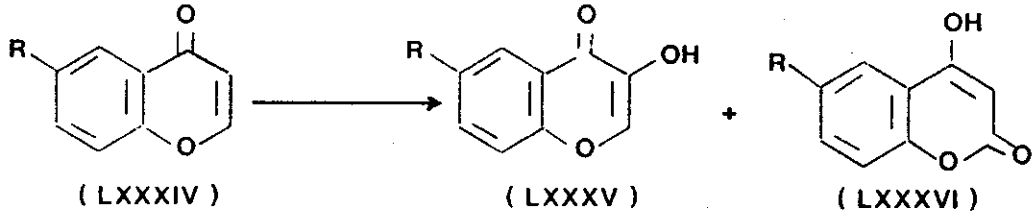
Refluxing chromenes (LXXXII) in concentrated hydrochloric acid (3M) gave 41-85% coumarins (LXXXIII)[122].



(LXXXII) (LXXXIII)

IX) From chromone:

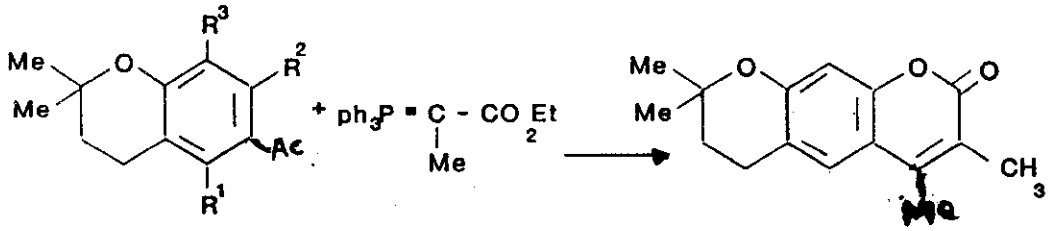
When the chromones (LXXXIV) were oxidized by m-chloroperbenzoic acid hydroxy chromones (LXXXV) were obtained with small amounts of 4-hydroxy coumarins (LXXXVI)[123].



(LXXXIV) (LXXXV) (LXXXVI)

X) From Chromans:

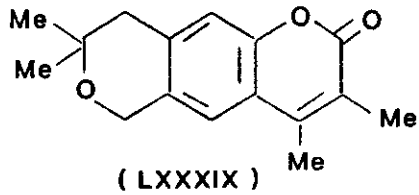
Benzodipyran-2-ones (LXXXVIII) and benzodipyran-2-one (LXXXIX) were obtained by Witting reaction of hydroxy acetyl chromans (LXXXVII) with α-methyl carbethoxy methylene triphenyl phosphorane[124] .



(LXXXVII)

(LXXXVIII)

+



(LXXXIX)

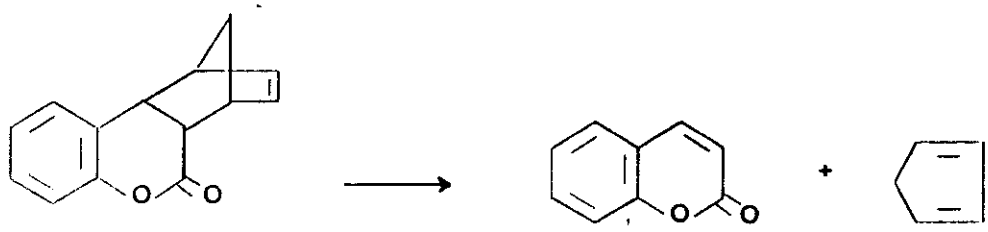
XI) Miscellaneous:

A)-Baeyer-Villiger oxidation of the danones (XC) and dehydrogenation of the resulting dihydrocoumarins afforded the 4-substituted coumarin (XCI)[125] .

(XC)

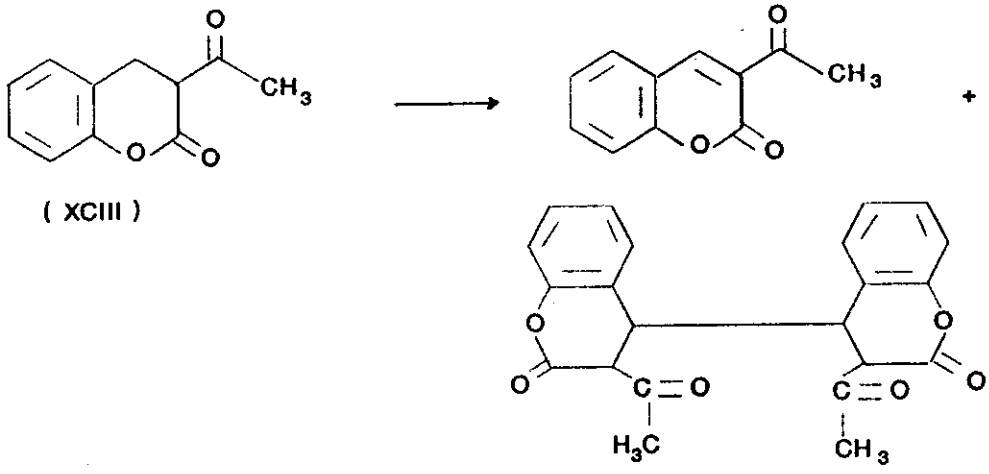
(XCI)

B)-Palladium-catalysed reaction of 2-iodophenol, carbon monoxide and norborandiene gave fused benzopyranone derivatives (XCII) which underwent retro-Diels-Alder reaction and gave coumarin (Ia) and cyclopentadiene[126].



(XCII)

C) The U.V. irradiation of air-saturated alcoholic solutions of 3-acetyl - 3,4 dihydrocoumarin (XCIII) yielded 3-acetylcoumarin and 3,3-diacetyl-3,3,4,4-tetrahydro 4,4-biscoumarin (XCIV)[127].

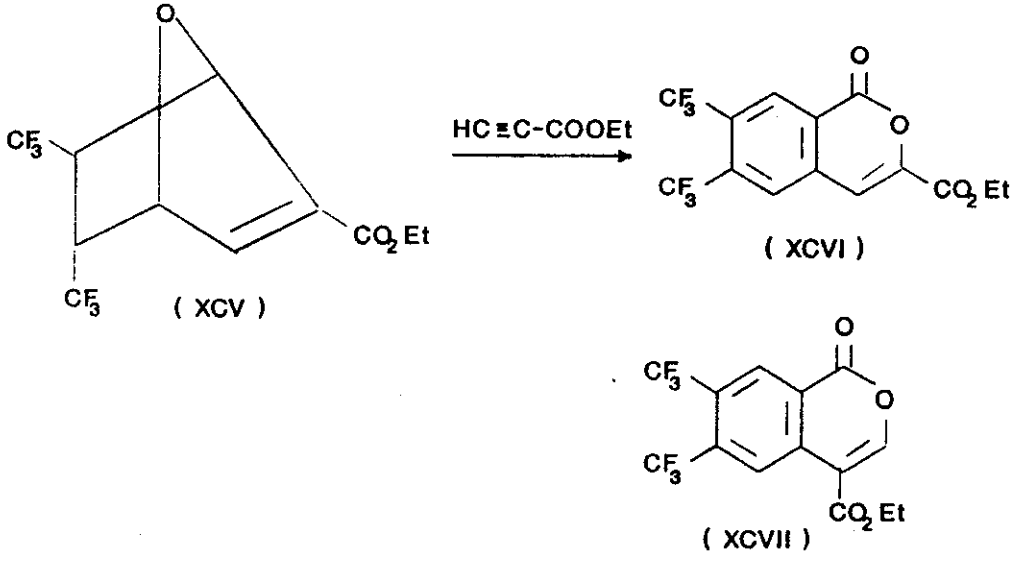


(XCIII)

(XCIV)

D) Reaction of ethyl propynoate with 3,4- bis (trifluoromethyl) furan afforded

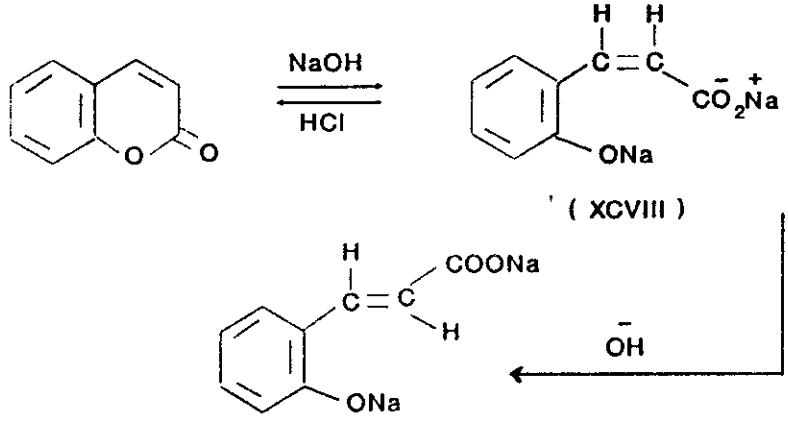
a mixture of isocoumarins (XCVI) and (XCVII) in the ratio 52:9 produced by Diels-Alder cycloaddition of the alkyne to the α, ß-unsaturated ester function of the initially formed 1:1 adduct (XCV) followed by opening of the oxygen bridge and elimination of ethanol[128].



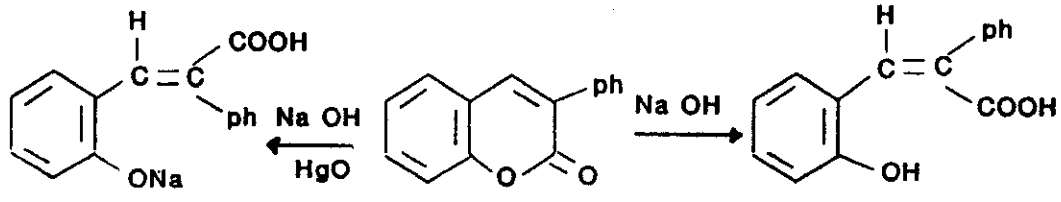
REACTIONS OF COUMARINS

I) Hydrolysis:

The action of alkali[129] upon coumarin is varied and dependent upon structure. Coumarin, as lactones was readily hydrolysed by alkali to salt of the corresponding coumarinic acid (XCVIII) which usually cannot be isolated as the acid revert immediately to the coumarins. The coumarinic acids were found to have the cis-configuration and were converted by prolongated treatment with alkali into salt of the more stable trans-coumarinic acid (XCIX)[130,131] .

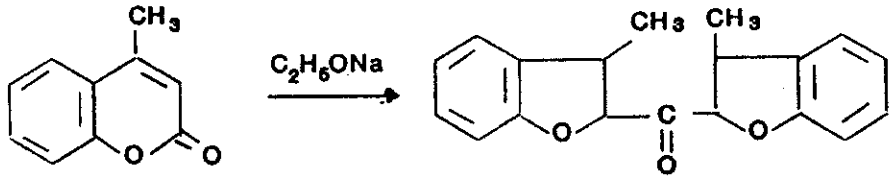


3-Phenyl coumarin (C)[132] reacted with sodium hydroxide and mercuric oxide and yielded trans-o-hydroxy-α-phenylcinnamic (CI)[133] while with sodium hydroxide only the cis-isomer (CII) was obtained.



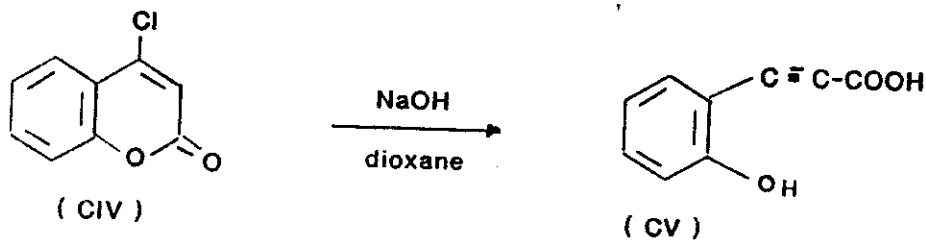
(CI) (C) (CII)

Treatment of 4-methylcoumarin (XXVIII) with sodium ethoxide yielded bis-dihydrobenzofuran ketone (CIII).



(XXVIII) (CIII)

On heating 4-chlorocoumarin (CIV) with sodium hydroxide in dioxane, o-hydroxyphenyl propiolic (CV)[134] was obtained.

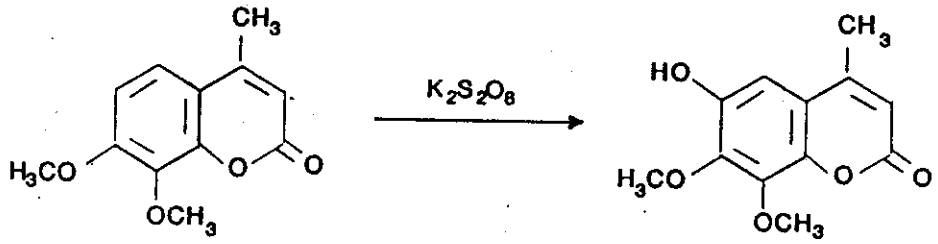


(CIV) (CV)

II) Oxidation:

The oxidation of coumarins by alkaline $K_2S_2O_8$[135] introduced a hydroxyl group in the 6-position, but if the 6-position was occupied, no oxidation took place.

Thus, oxidation of 4-methyl 7,8-dimethoxy coumarin (CVI) gave 4-methyl-6-hydroxy -7,8-dimethoxycoumarin (CVII).

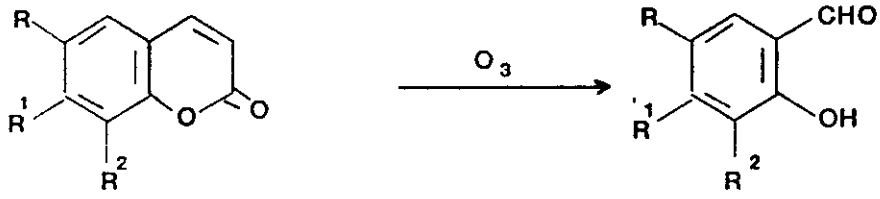


(CVI)

(CVII)

Oxidation of coumarins with permanganate usually causes extensive degradation to salicylic acid derivatives, while chromic acid is relatively ineffective reagent, it is not included to attack the pyrone ring[136,137]

Rios et al[138,139] reported that ozonolysis of 6,7,8-trisubstituted coumarin (CVIII) gave the corresponding substituted,salicylaldehyde(CIX).



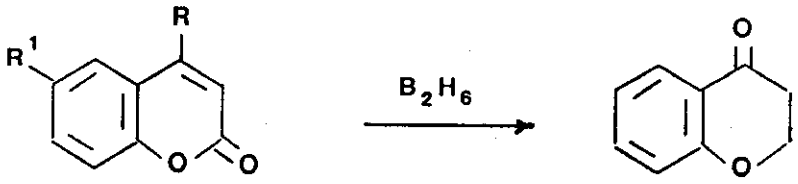
(CVIII)

(CIX)

Oxidation of coumarins (CX) with selenium dioxide gave the acylcoumarins (CXI)[140-142].

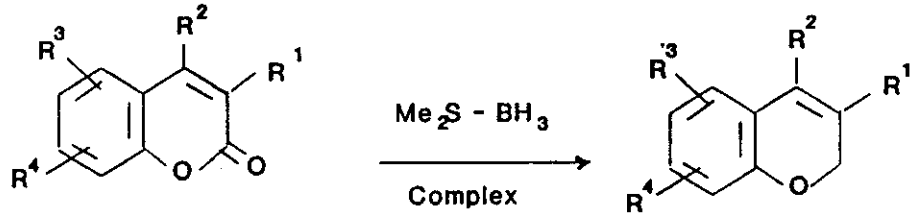
Sodium and alcohol convert coumarin (I) into δ-(o-hydroxyphenyl) propyl alcohol (CXVI).

Hydroboration of substiuted coumarins (CXVIII) followed by oxidation by using chromic acid gave 4-chromanones (CXVIII)[146].



(CXVII) (CXVIII)

Coumarins (CXIX) were treated with Me_2S-BII, complex to give 2H-chromanes (CXX)[147].



(CXIX) (CXX)

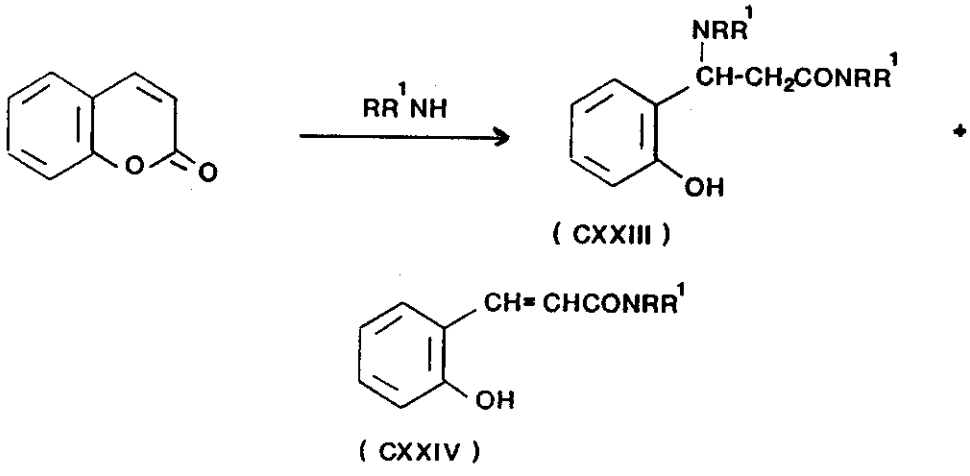
The reduction of 4-substituted-3-nitrocoumarins (CXXI) with $Na_2S_2O_4$ gave (CXXII), a direct substitution of the nitro group for an amino group[148, 149], a hydrogen atom[148,149] and amercapto group[149].

(CXXI)

(CXXII)
R = NH_2,H,SH

IV) Action of amines:

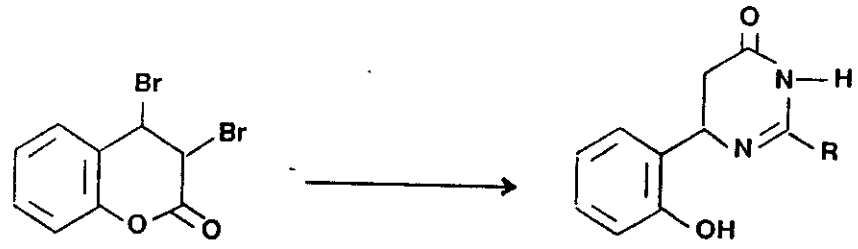
Heating coumarin with secondary amines in absolute alcohol yielded ß-substituted amino- o-hydroxyhydrocinnamic acid amides (CXXIII) and o-hydroxy cinnamamid (CXXIV)[150,151].



(CXXIII)

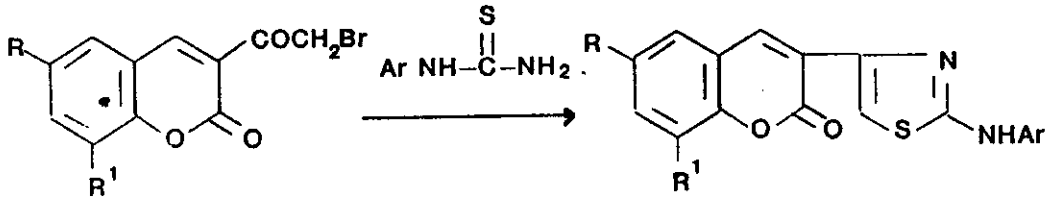
(CXXIV)

Reaction of dibromodihydrocoumarin (CXXV) with acetamidine or benzamidine gave dihydropyrimidines (CXXVI)[152].



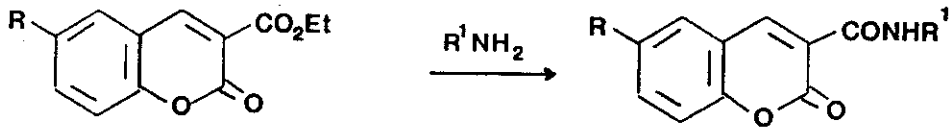
(CXXV) (CXXVI)

Thiazolyl coumarins (CXXVII)[153,154] were prepared by condensation of 3-(ω-bromo acetyl) coumarin with arylthiourea derivatives.



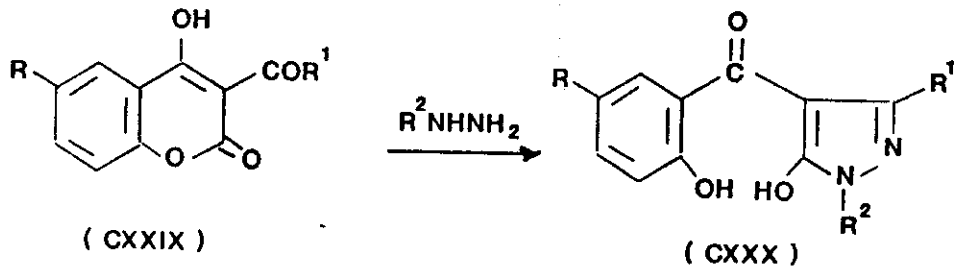
(CXXVII)

Sammour et al[155-158], reported that treatment of 3-carboxycoumarin derivatives with primary aliphatic and aromatic amines afforded the corresponding carbamide derivatives (CXXVIII).



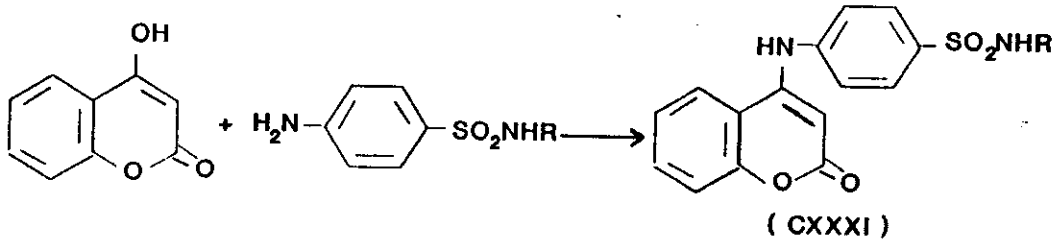
(CXXVIII)

Hydroxycoumarins (CXXIX) reacted with hydrazines in boiling acetic acid to form pyrazolones (CXXX)[159].



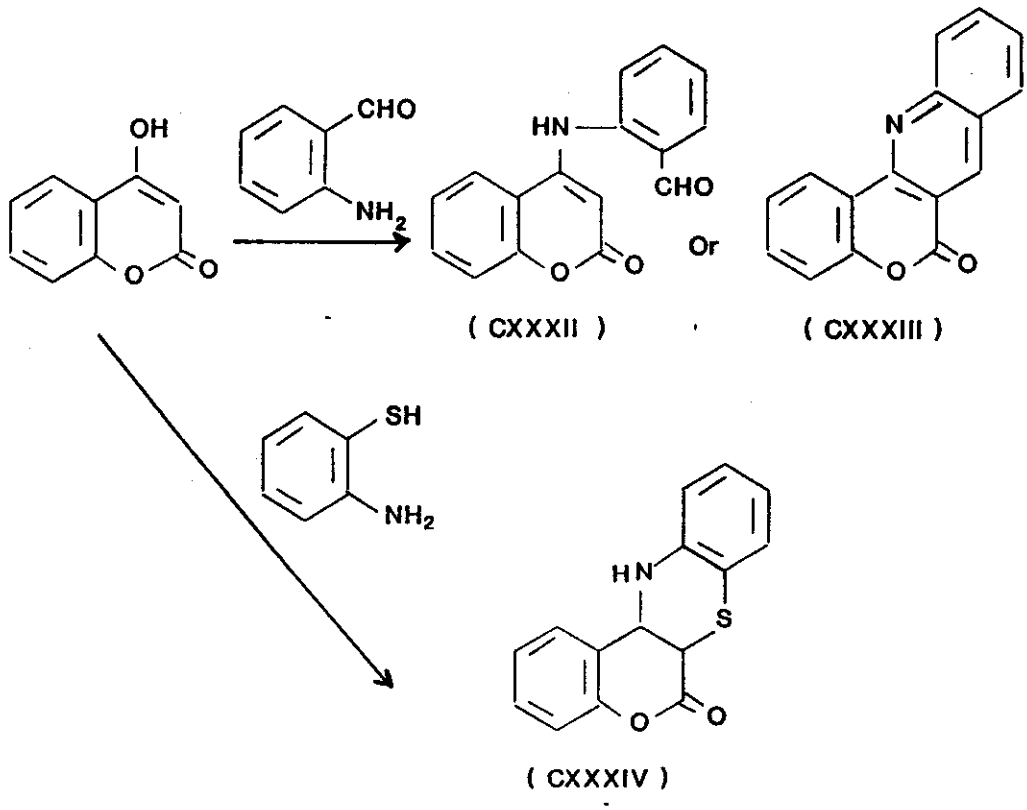
(CXXIX) (CXXX)

The reaction of 4-hydroxycoumarin with different sulfadrugs afforded the coumarins (CXXXI)[160] .



(CXXXI)

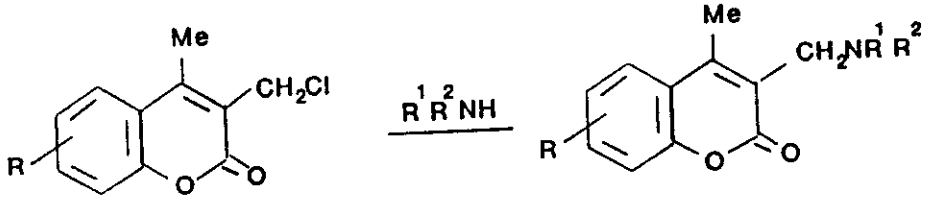
When 4-hydroxycoumarins and o-aminobenzaldehyde were refluxed in ethanol containing piperidine, benzopyranone (CXXXII) or benzopyranoquinoline (CXXXIII) were obtained depending upon the time of reflux. While on heating it with 2-aminothiophenol in dimethylsulphoxide gave benzopyranobenzothiazinone (CXXXIV)[161].



(CXXXII) (CXXXIII)

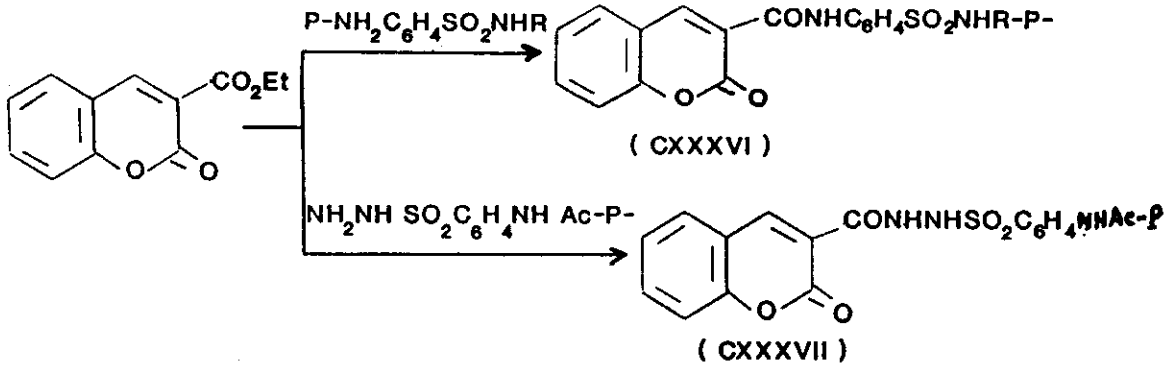
(CXXXIV)

3-(Chloromethyl) coumarin derivatives was treated with amines and gave aminomethylcoumarin derivatives (CXXXV)[162-165].



(CXXXV)

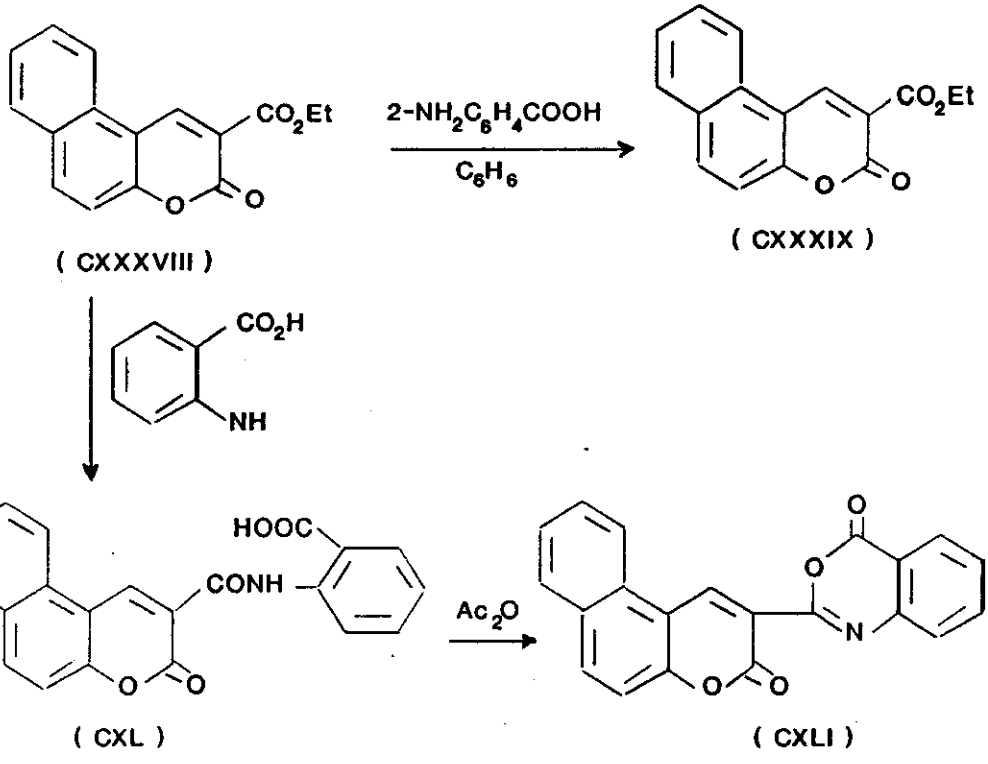
Amidation of 3-carbethoxycoumarin and p-$NH_2C_6H_4SO_2NHR$, p-$AcHNC_6H_4SO_2NHNH_2$ gave (CXXXVI) and (CXXXVII)[166].



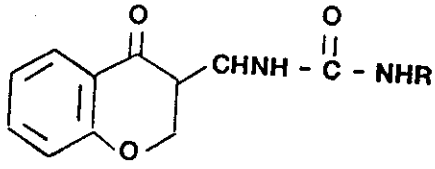
(CXXXVI)

(CXXXVII)

Treatment of 3-carbethoxy-5,6-benzocoumarin (CXXXVIII) with anthranilic acid in refluxing benzene gave 3,4-dihydro 5,6-benzocomarin (CXXXIX). The action of o anthranilic acid on (CXXXVIII) without solvent at 170 °C gave (CXL), cyclization of (CXL) with Ac_2O gave 3-(3,1-benzoxazin-4-one) 5,6-benzocoumarin (CXLI)[167] .



3-Ureido methylene coumarin (CXLII) was prepared by condensation of substituted urea with 4-hydroxycoumarins in the presence of ethyl ortho formate[168].

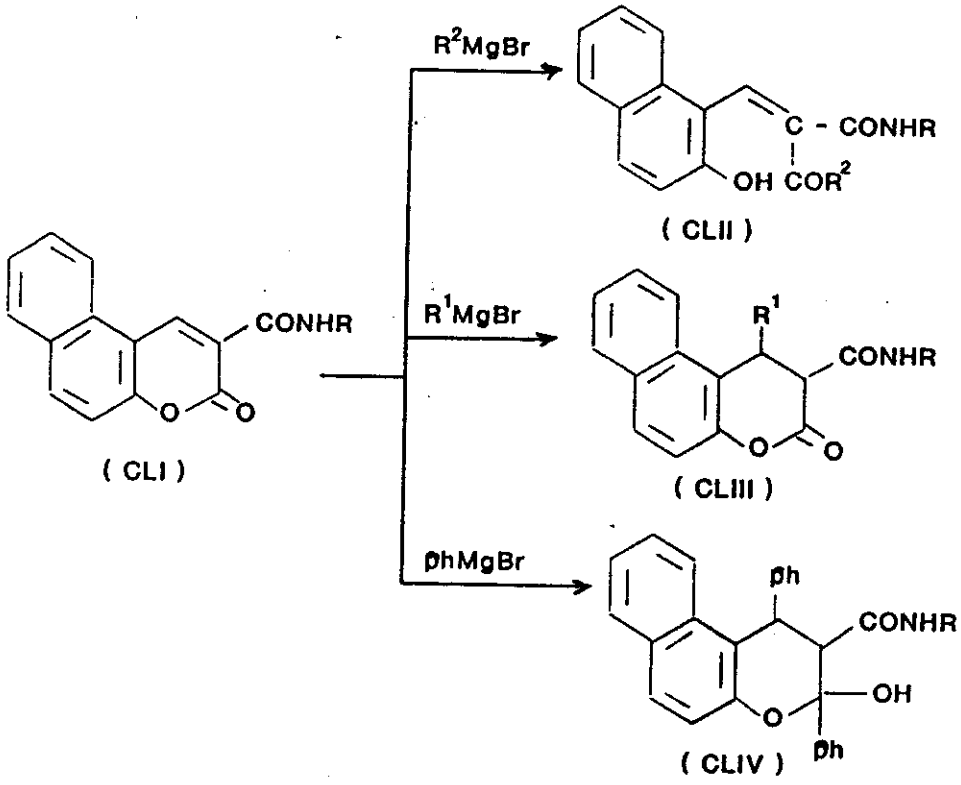


(CXLII)

V) Action of Grignard reagents:

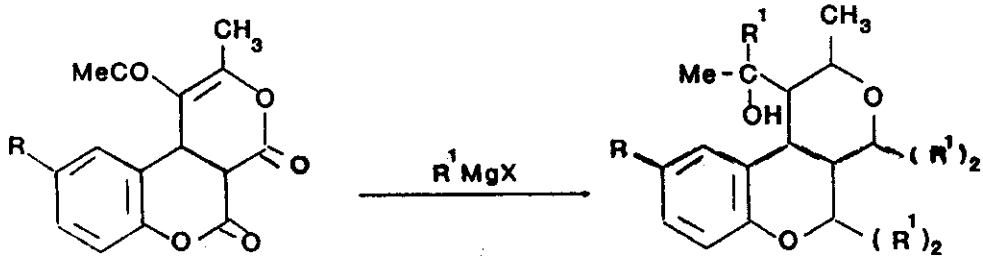
It was found that[169,170] coumarin (Ia) reacted with Grignard reagents to give products may be 2,2-dialkyl-3-chromene (CXLIII), 2-alkyl-2-hydroxy-3-chromene

Reactions of arylcarboxamidonaphthopyranone (CLI) with R^2MgBr gave arylcarboxamidobenzoyl naphthyl ethylene (CLII), whereas with R^1MgBr ($R^1=C_{1-4}$ alkyl) gave (CLIII)[176-180] and with PhMgBr gave the alcohol (CLIV)[179].



(CLI) (CLII) (CLIII) (CLIV)

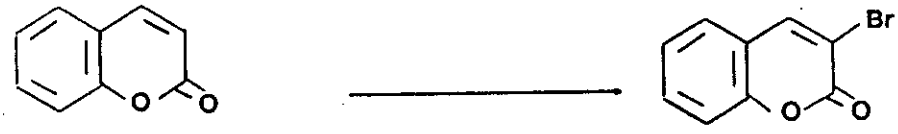
El-Kady et al[181], found that acetyldihydropyranobenzopyrandiones (CLV) reacted with Grignard reagents and gave 1-methylalkyl (or aryl) carbinol-4a-1b-dihydro-2-methyl-9-bromo-4H-5H, 4-bisalkyl (or bisaryl) pyrano [3,4-C]-(1) 5,5-dialkyl (or diaryl) chroman (CLVI).



(CLV) (CLVI)

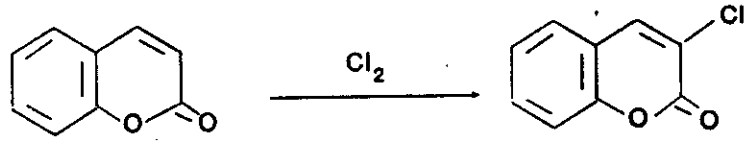
VI) Halogenation:

Bromination of coumarin (Ia) led to the formation of 3-bromocoumarin (CLVII)[182,183] which can be also obtainded by means of N-bromosuccinimide.



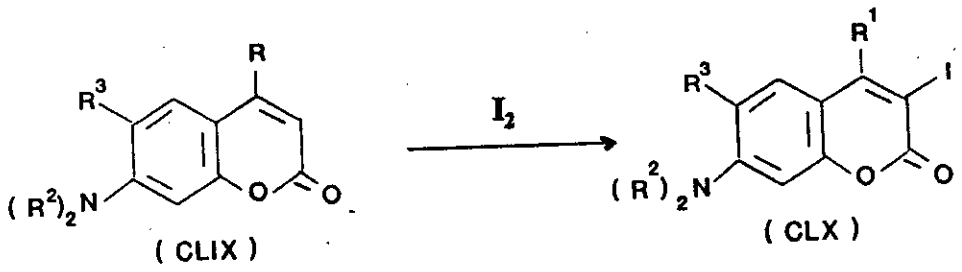
(I_a) (CLVII)

Also, 3-chlorocoumarin (CLVIII)[184] can be obtained by chlorination of coumarin (I_a) in acetylene tetrachloride.

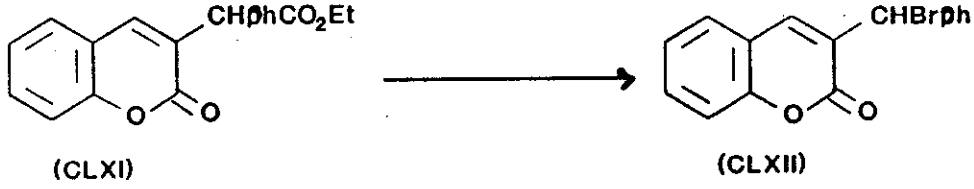


(I_a) (CLVIII)

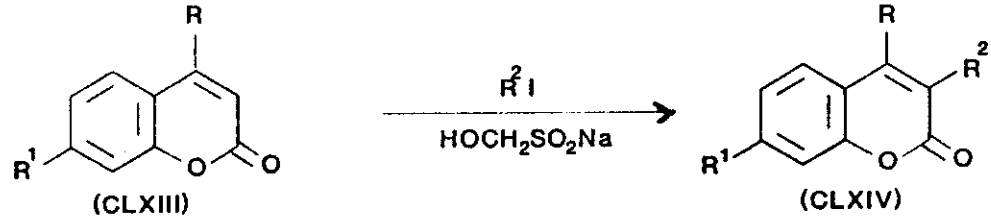
Substituted 3-iodo-7-dialkylaminocoumarins (CLX) were prepared by the reaction of the-7-dialkylamino coumarins (CLIX) with iodine in dioxane or T.H.F. as the organic solvent in the presence of pyridine as catalyst in the molar ratio of coumarin/iodine/catalyst = 1:(4.6):5 at 20-40 °C[185].



The bromobenzyl benzopyran (CLXII)[186] was prepared by treatment of coumarin (CLXI) with HBr.



3-Perfluoroalkylated coumarins (CLXIV) were prepared by reaction of coumarins (CLXIII) with perfluoro alkyl iodides in presence of sodium hydroxymethane sulfinate[187]



$[R^2 = C_6H_{13}, C_7H_{15}, ClC_4H_8, ClC_6F_{12}, ClC_8F_{16}]$.

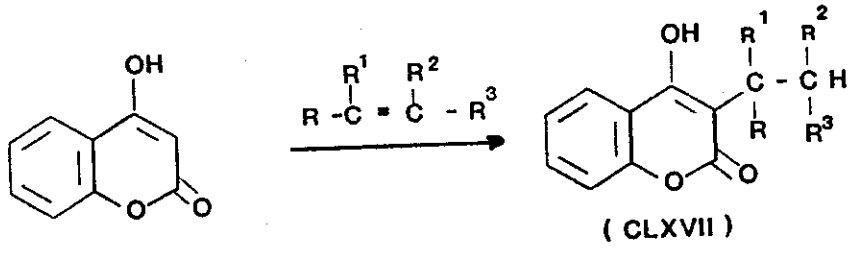
On the other hand, the regioselective reaction of coumarin (CLXV) with $R(CO_2)_2$ in a solution of methylene chloride and $CF_2Cl\text{-}CCl_2F$ gave 3-perfluoro-alkylated coumarins (CLXVI)[188].

(CLXV) (CLXVI)

[$R^2 = CF_3(CF_2)_2$, $CF_3CF_3(CF_2)_6$]

VII) Michael reaction:

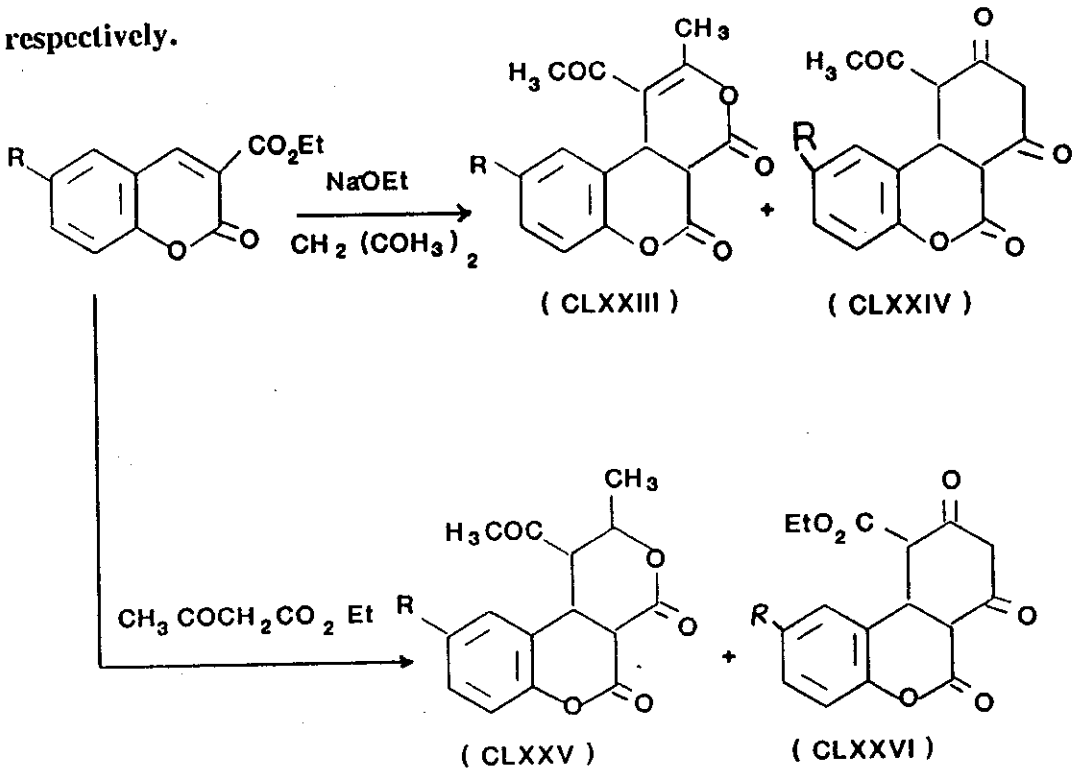
Active olefinic double bond was added to 4-hydroxycoumarin in position-3-with the formation of the 3-substituted 4-hydroxycoumarin (CLXVII)[189-191].



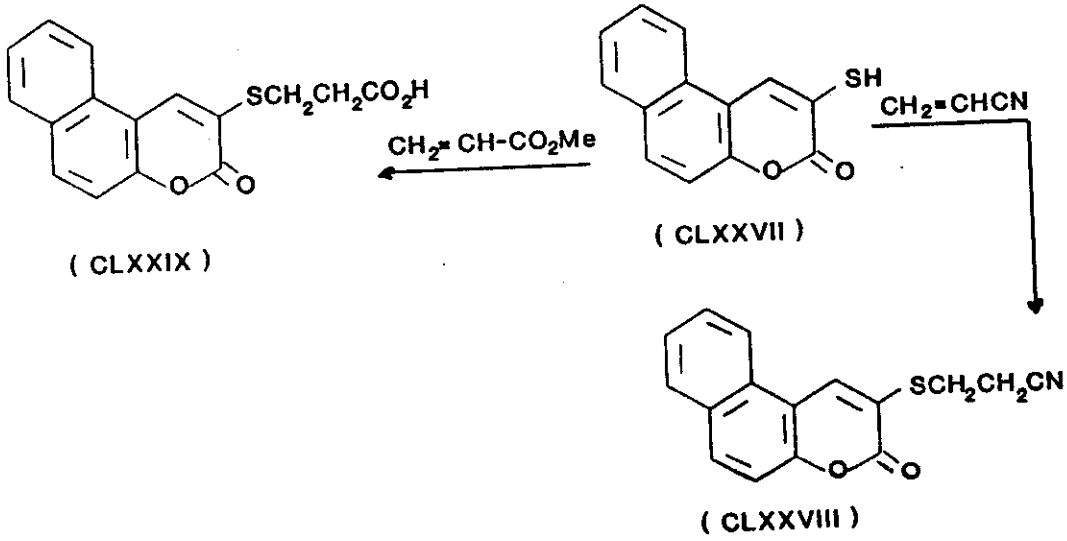
(CLXVII)

On the other hand, arylisocyanate, arylisothiocyanate, benzophenone, Schiff bases were added to 4-hydroxycoumarin to g ve the corresponding 3- substituted -

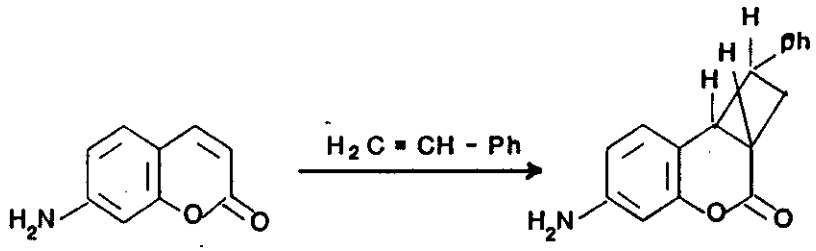
ethoxide and gave (CLXXIII) and (CLXXIV) or (CLXXV) and (CLXXVI) respectively.



Michael addition of benzocoumarin (CLXXVII) with acrylonitrile and methylacrylate gave (CLXXVIII) and (CLXXIX)[199] respectively.

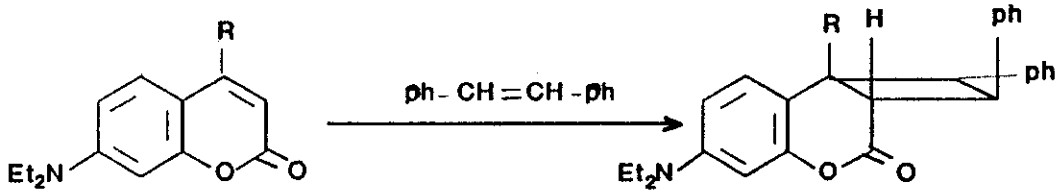


Also, photocycloaddition reactions of aminocoumarins with styrene afforded adducts (CLXXXI)[202].



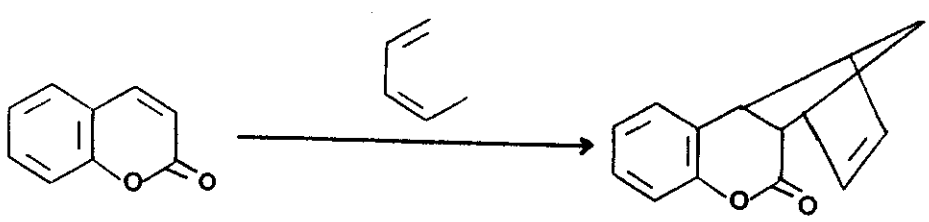
(CLXXXII)

Recently, photocycloaddition of trans-stilbene to coumarin (CLXXXIII) gave 55-63% adducts (CLXXXIV)[203] via a stereoselective [2+2] cycloaddition at the 3-4 bond.



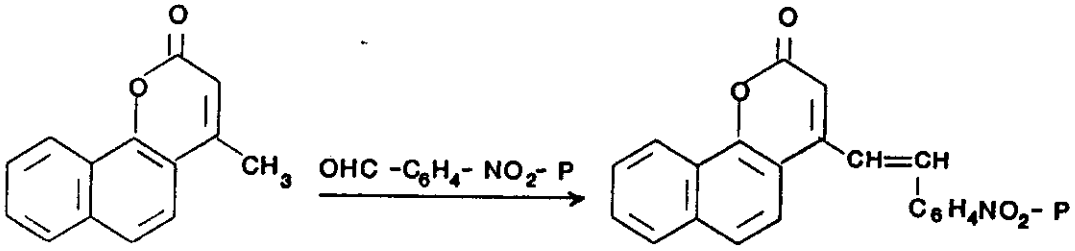
(CLXXXIII) (CLXXXIV)

The pd-catalyzed reaction of 2-IC_6H_4OH,CO, and norbornadiene gave fused benzopyranone (Ia) which underwent retro Diels-Alder reaction gave coumarin and cyclopentadiene (CLXXXV)[204].



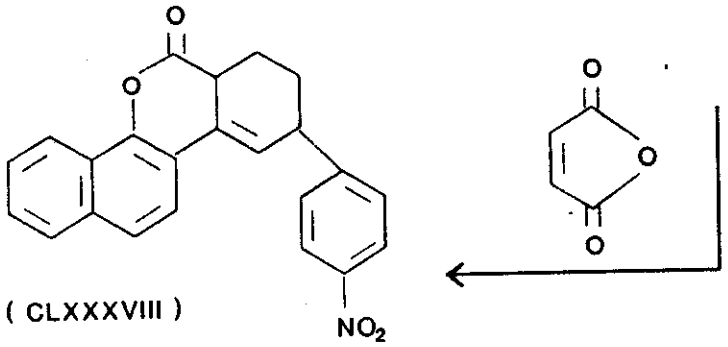
(Ia) (CLXXXV)

Also, naphthopyranone (CLXXXVI) reacted with p-$O_2NC_6H_4CHO$ gave (CLXXXVII) which underwent cycloaddition with maleic anhydride to gave benzonaphthopyranone (CLXXXVIII)[205].



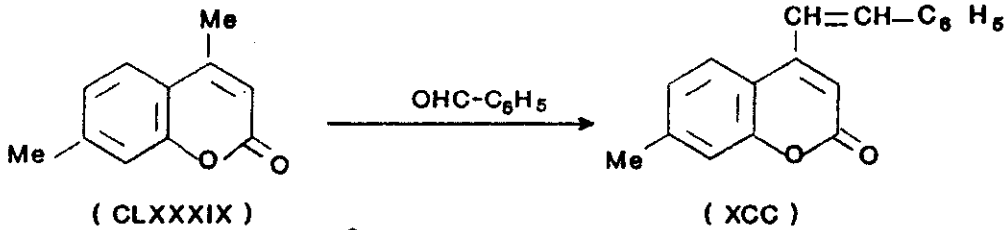
(CLXXXVI)

(CLXXXVII)



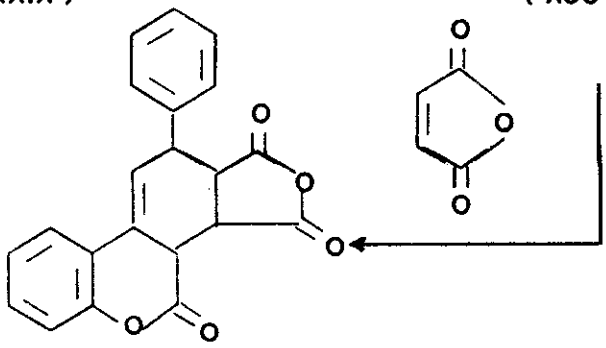
(CLXXXVIII)

More recently, 4,7-dimethylcoumarin (CLXXXIX) reacted with C_6H_5CHO in the presence of pyridine afforded the ethylene benzopyrans (XCC) which upon treatment with maleic anhydride gave the isobenzofurobenzopyrans (XCCI)[206].



(CLXXXIX)

(XCC)

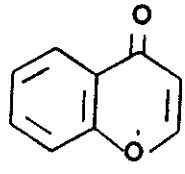


(XCCI)

PART II

CHROMONES

Chromones (II) are substituted heterocyclic α,ß-unsaturated ketones, they can be considered as benzoderivatives of ϒ-Pyrone.



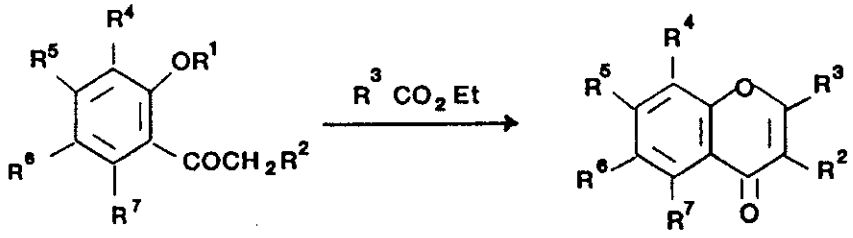
(Id)

SYNTHESIS OF CHROMONES :

Chromones could be synthesized by one of the following methods:

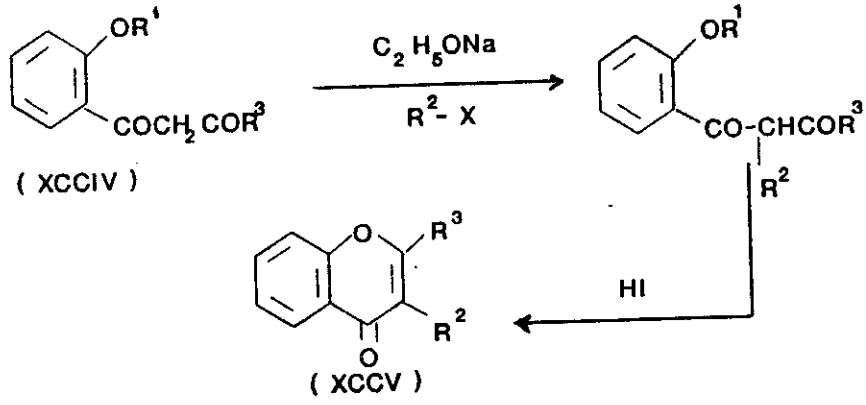
I) From o-alkanoyl phenols:

Cyclocondensation of o-alkoxyphenyl ketones (XCCII) with an ester gave the chromone derivative (XCCIII)[207-213].



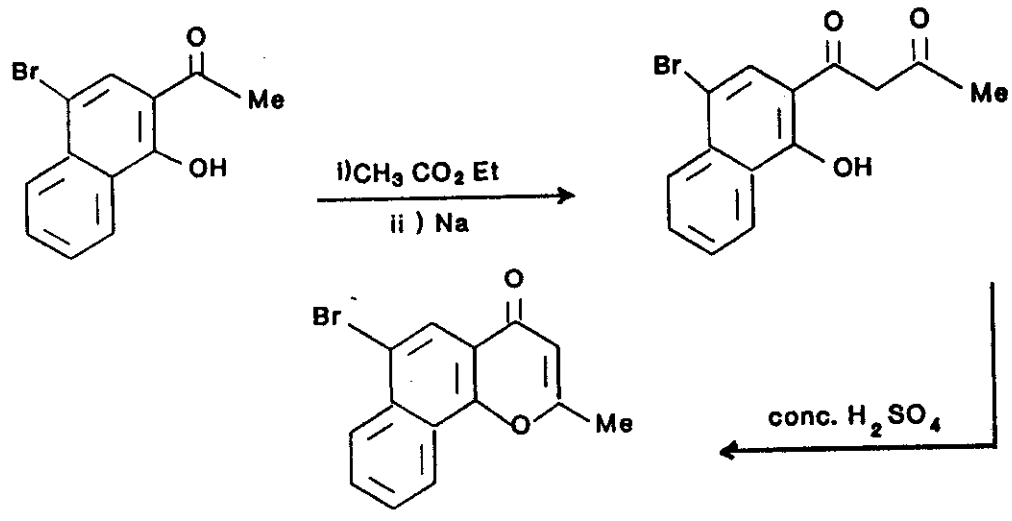
(XCCII) (XCCIII)

2,3-Disubstituted chromones (XCCV) were also obtained by alkylation of the β-diketone (XCCIV) on the active methylene group followed by cyclization[209-224].



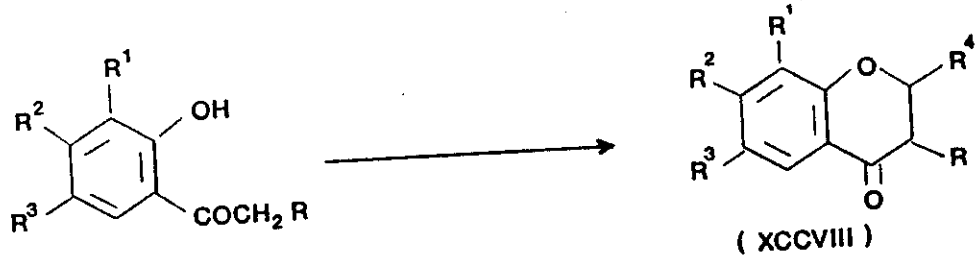
(XCCIV) (XCCV)

The cyclization of o-alkoxy-ß-diketones was carried out by hydroiodic acid, or in the presence of acetic anhydride or by hydrobromic acid in acetic acid[228] or thermally[226]. If a free o-hydroxyl group was present sulpuric acid[227], hydrochloric acid[225], sodium acetate in acetic acid, boron trifluoride were sufficient distillation under vacuum had also been reported to affect cyclization[229]. Alos 6-bromo-7,8-benzo-2-methylchromone (XCCVI) was obtained via the condensation of 2-acetyl-4-bromo-1-naphthol with ethyl acetate in presence of sodium pellets which followed by cyclization[230].



(XCCVI)

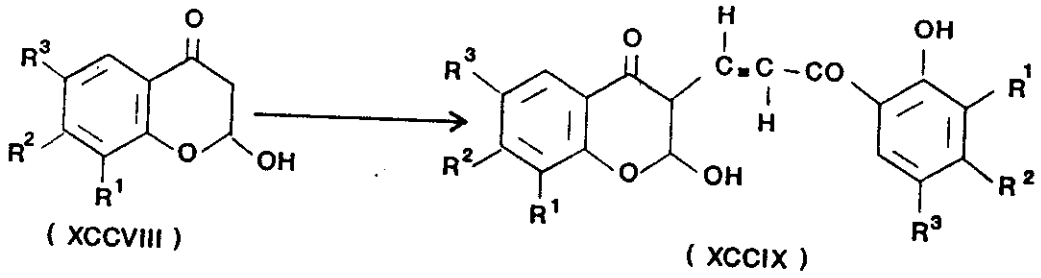
Similarly, the chromanones (XCCVIII$_a$)[231] and flavanones (XCCVIII$_b$)[232] were obtained from the o-hydroxy acetophenones (XCCVII).



(XCCVII) (XCCVIII)

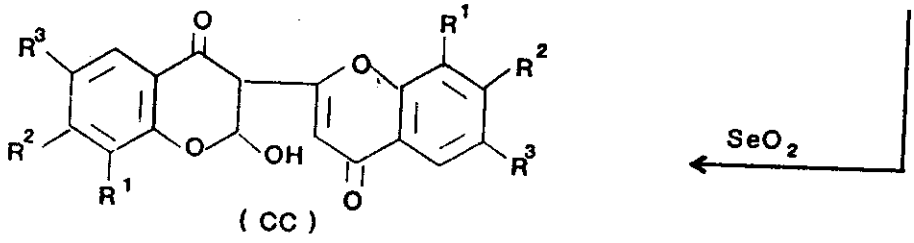
	R	R'	ref.
a,	H	OH	231
b,	P-C$_6$H$_4$F	H	232

Heating the 2-hydroxy chromones (XCCVIII$_b$) above their m.p. afforded the ethylene derivatives (XCCIX) which were cyclized to dioxobisbenzopyran derivatives (CC) by selenium dioxide[231].



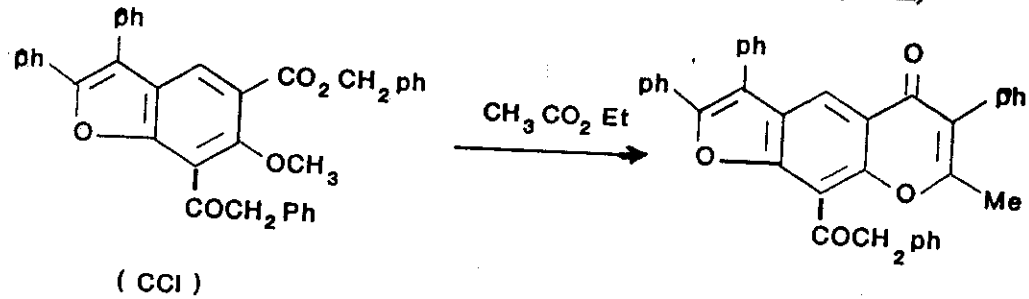
(XCCVIII)

(XCCIX)



(CC)

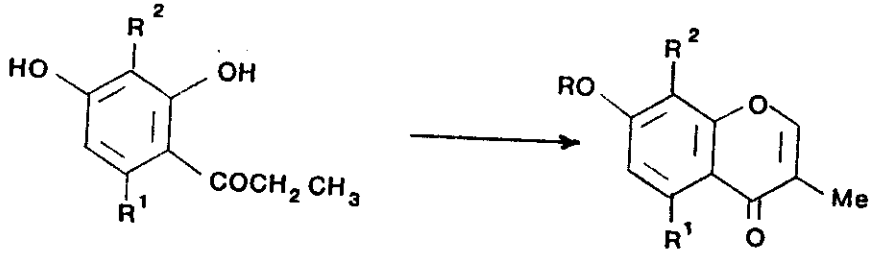
Claisen condensation of 2,3-diphenyl-6-methoxy-5,7-diphenyl acetyl benzo-furan (CCI) with ethyl acetate gave chromone derivatives (CCII)[233].



(CCI)

(CCII)

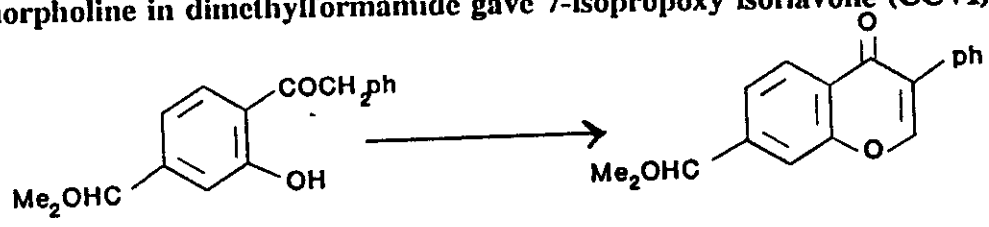
Chromones (CCIV) were prepared by treating 2-hydroxypropiophenones (CCIII) with dimethyl formamide, boron trifluoride-ether and dimethylsulphonyl chloride[234].



(CCIII)

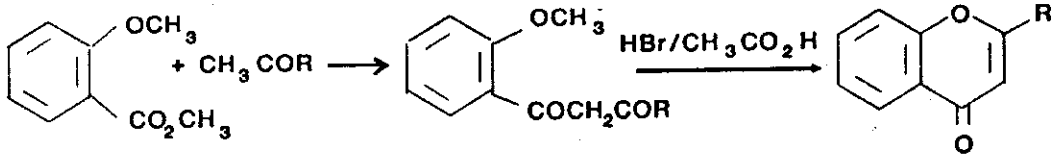
(CCIV)

Recently, treatment of the ether (CCV) with ethyl orthoformate and morpholine in dimethylformamide gave 7-isopropoxy isoflavone (CCVI)[235].

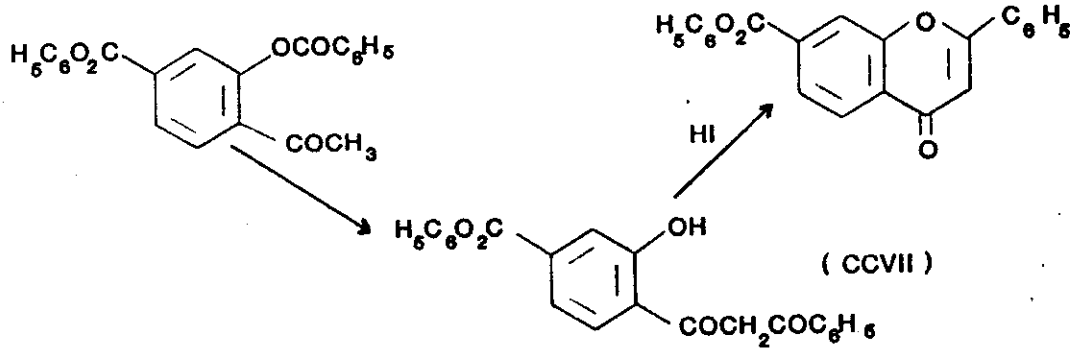


(CCV) (CCVI)

A modification of Claisen condensation was carried out using methyl-o-methoxybenzoate[228,236], methyl 2-methoxy-3-naphthoate and methyl 1-methoxy-2-naphthoate[237] and acetone or acetophenone[237,238] and gave the corresponding chromone.



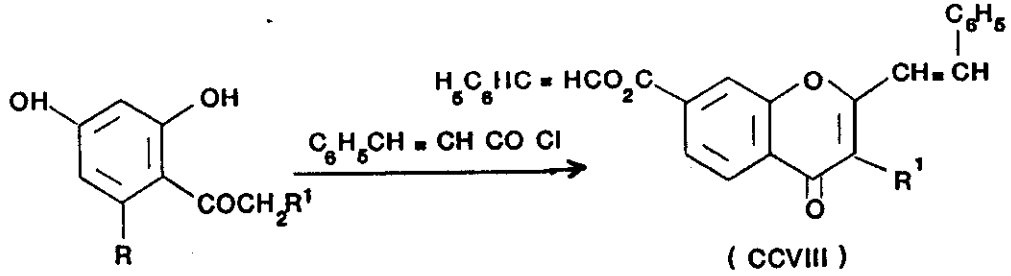
ß-Diketone prepared from acyl and aroyl derivatives of o-hydroxy-acetophenones by an interamolecular Claisen condensation could be easily cyclized to the corresponding chromones (CCVII)[227,228,239-241].



(CCVII)

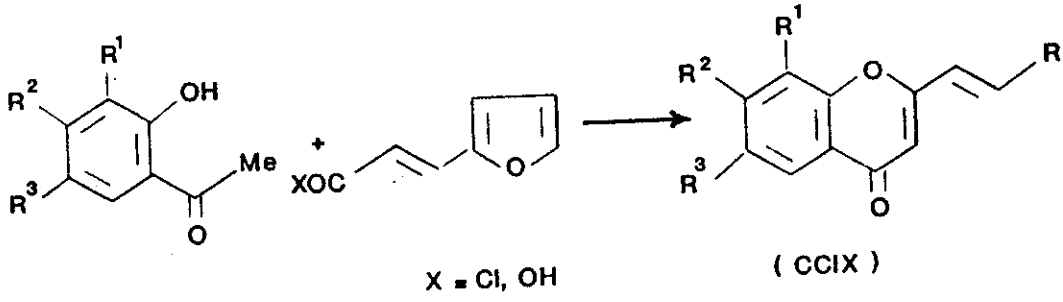
Ester other than the benzoate have been used[242-245].

Cyclocondensation of an alkanoylphenol with cinnamoylchloride, gave the 2-styrylchromones[239,246] (CCVIII).



(CCVIII)

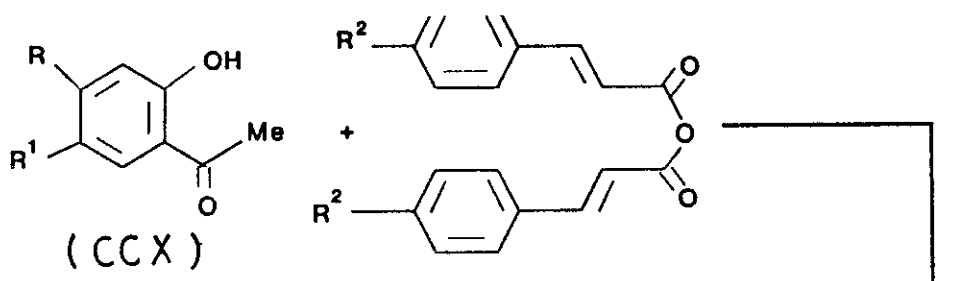
2-(2-Furylvinyl) chromones (CCIX) were prepared by successive esterification of o-Hydroxyacetophenones with β-2-furyl acrylic acid or its chloride, Baker-Venkataraman rearrangment, and cyclization[247,248].



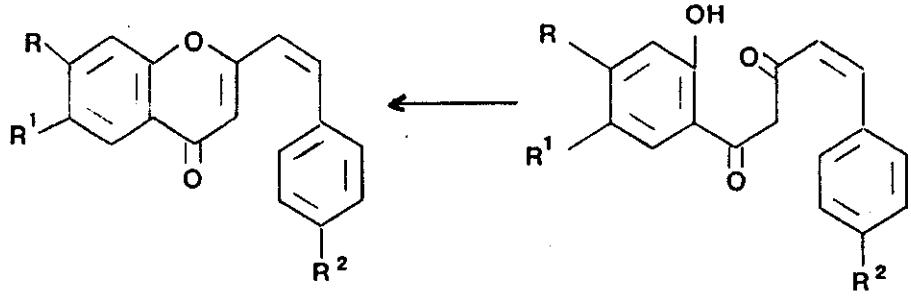
X = Cl, OH

(CCIX)

Condensation of 2-hydroxyacetophenones (CCX) with cinnamic anhydrides in the presence of tetrabutyl ammonium hydrogen sulphate gave 1-(2-hydroxy-phenyl) 5-phenyl-4-pentene 1,3-diones which on cyclodehydration using p-toluene sulphonic acid in dimethyl sulphoxide gave 2-styrylchromones (CCXI)[249].

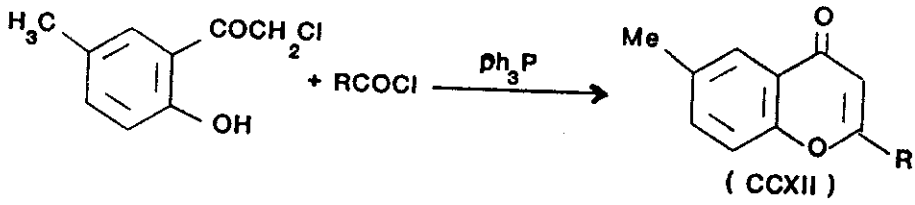


(CCX)



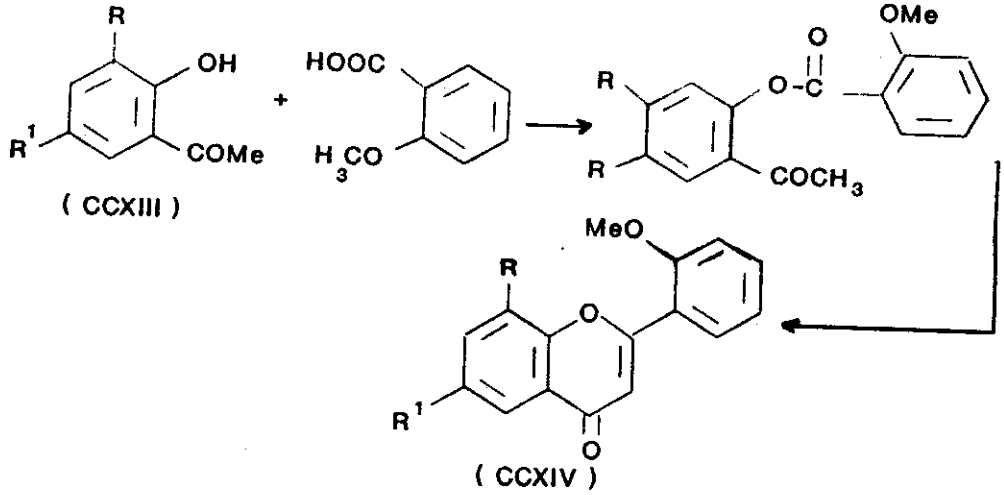
(CCXI)

Chromones (CCXII) were prepared by cyclocondenstation of substituted ω-chloroacetophenone and RCOCl in the presence of Ph_3P[250].



(CCXII)

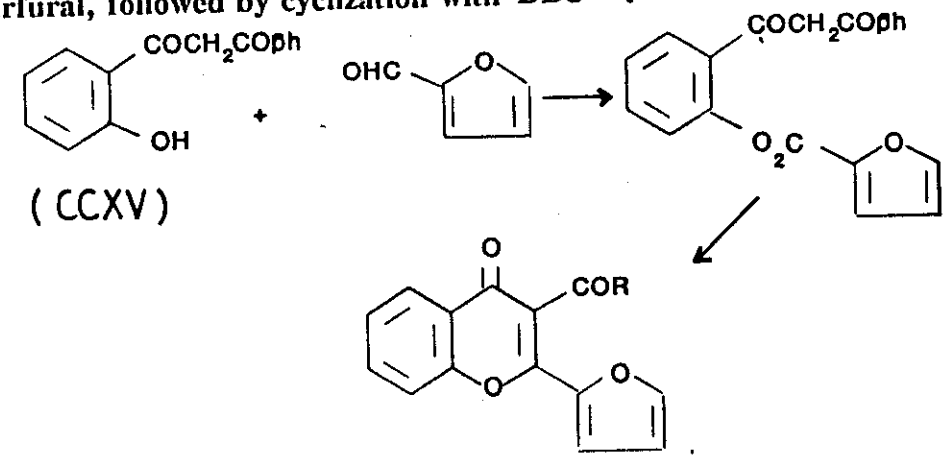
Condensation of o-hydroxyacetophenone (CCXIII) with 2-methoxybenzoic acid gave 2-(2'-methoxybenzoyloxy) acetophenones which underwent rearrangment cyclocondensation and gave 2-(2'-methoxyphenyl) chromones (CCXIV)[251].



(CCXIII)

(CCXIV)

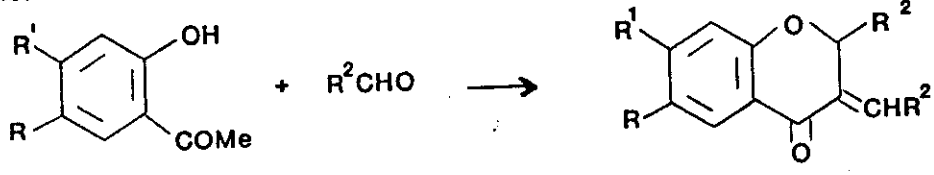
Furylchromones (CCXVI) were prepared by condensation of (CCXV) with furfural, followed by cyclization with DBU[252].



(CCXV)

(CCXVI)

Recently,3-arylidene flavanones (CCXVIII) could be formed only from 2-hydroxyacetophenones (CCXVII) bearing 5-OH group (R=OH,H) during condensation with aromatic aldehydes in alkaline medium[253]. The observed inability of (CCXVII) (R=H,OMe) in this respect condtradicts the findings of several recent reports.



(CCXVII)

(CCXVIII)

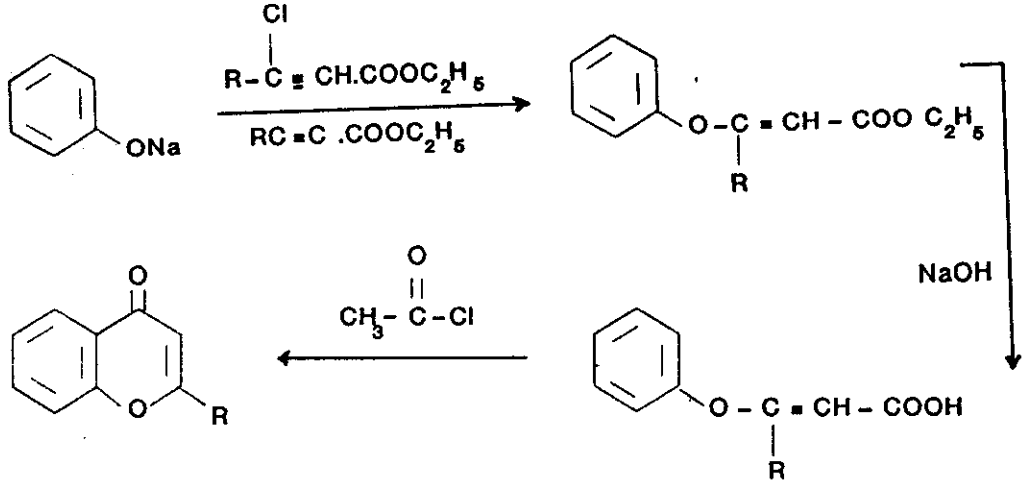
II) From phenols:

(A): Phenols can be converted into ß-phenoxyacrylic acids by adding the sodium derivatives to either ethyl acetylene dicarboxylate, ethyl phenyl proipolate[254] or ethyl propiolatein toluene or ether[255].

Similar products are also formed when ethyl chlorofumarate, ethyl ß-

chlorocinnamate is treated with sodium phenoxide.

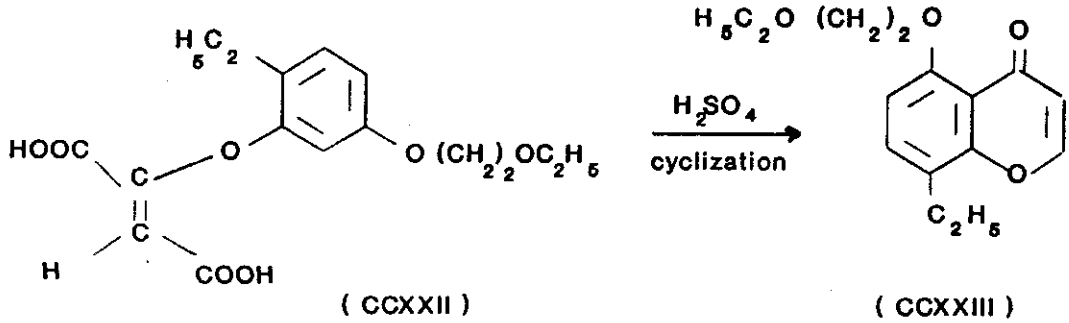
The ß-phenoxy acrylic acid (CCXIX) obtained by saponification can be cyclized to chromones (CCXX) or flavones (CCXXI) either by acetylchloide or sulphuric acid[256]. This method has been used with various substituted phenols, naphthols, thiophenols[257], 2-hydroxybiphenyl and 3-phenanthgrol[258].



(CCXX) , R = alkyl
(CCXXI),R = aryl

(CCXIX)

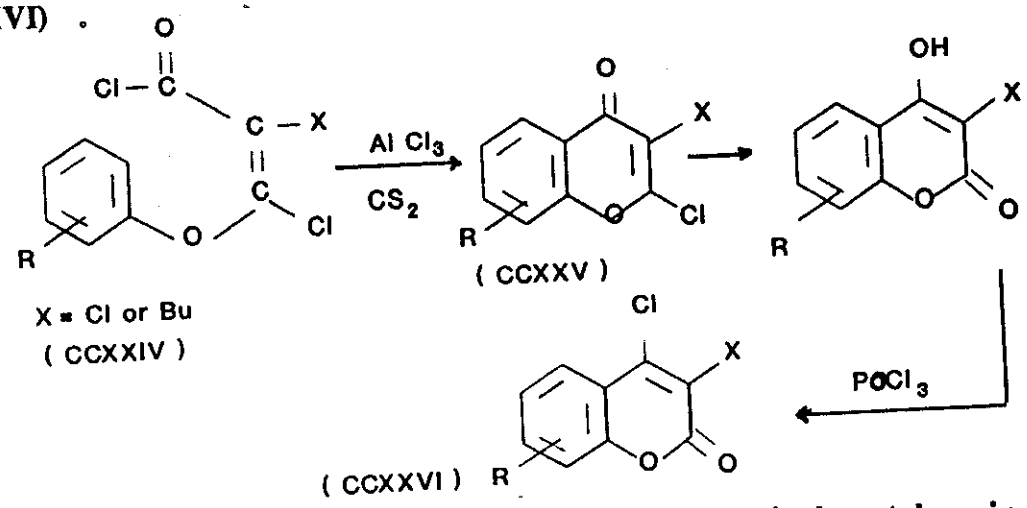
Fitzmaurice[259] has been found that the reaction of 5-(2-ethoxyethoxy)-2-ethylphenol with dimethyl acetylene dicarboxylate in the presence of $C_6H_5CH_2MeN^+$-OH leads to the formation of 5-(2-ethoxyethoxy)-2-ethyl-ß-phenoxyfumaric acid (CCXXII) which was cyclized with sulphuric acid to chromone (CCXXIII).



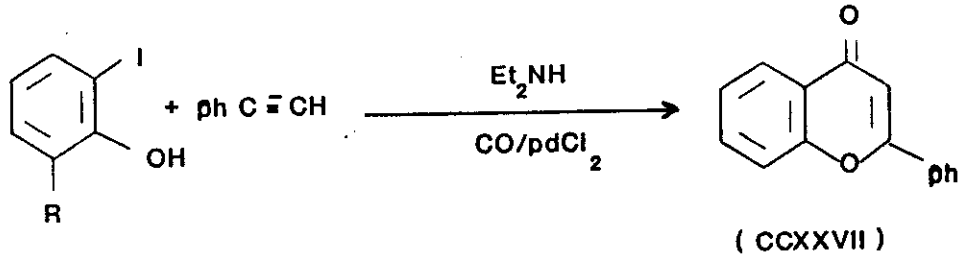
(CCXXII)

(CCXXIII)

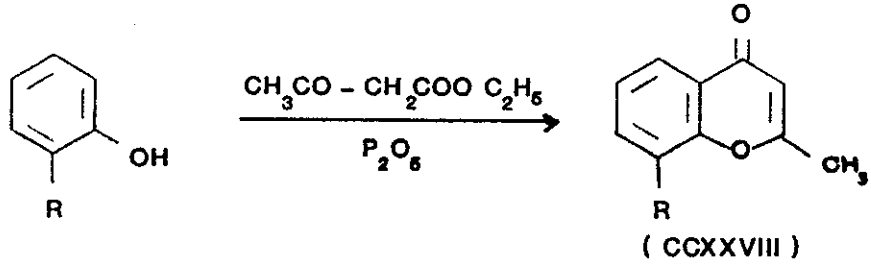
ß-Chloro-α-halo-ß-aryloxyacryl chloride (CCXXIV) were cyclized with aluminium chloride in carbon disulphide to the corresponding 2,3-dihalochromene (CCXXV)[260] which on hydrolysis followed by treatment with $POCl_3$ gave the isomeric (CCXXVI)[261].



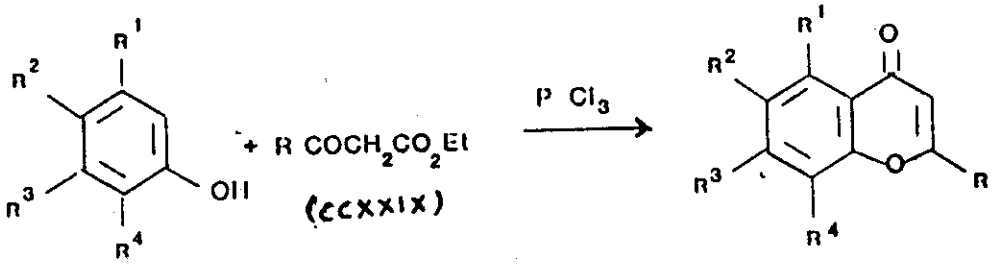
Carbonylative coupling of o-iodophenols with terminal acetylene in the presence of palladium catalysts gave the flavone (CCXXVII)[262].



(B): The Semois reaction in which phenol and ß-ketoester were heated with phosphorus pentoxide and gave chromone derivatives (CCXXVIII)[263-272].

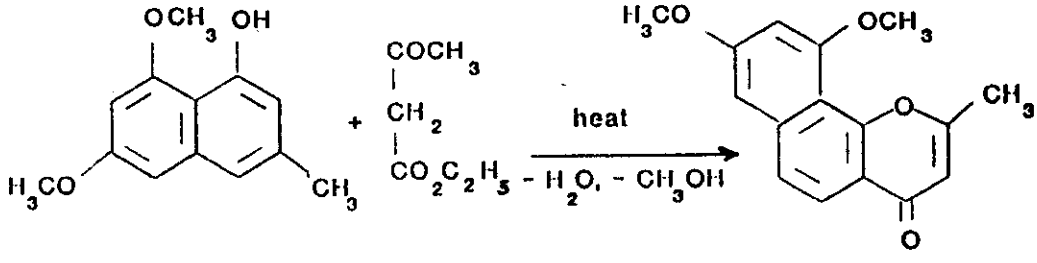


Substituted 2-(alkylamino chromenes (CCXXX) were obtained by cyclocondensation of suitable phenols with (CCXXIX)[273,274].



(CCXXX)

The dimethyl ether of eleutherinol (CCXXXII) has been made by heating the corresponding α-naphthol (CCXXXI) with E.A.A. in the absence of acids[272,275,276].



(CCXXXI) (CCXXXII)

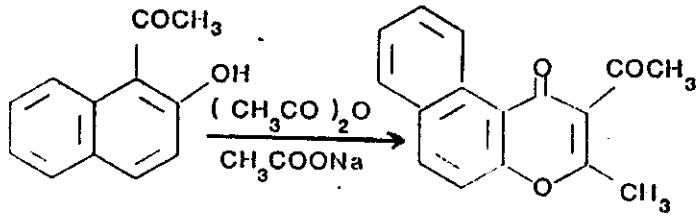
Naphthoflavones (CCXXXIII) and (CCXXXIV)[277] were prepared by ,,locondensation of α-and ß-naphthols with $RCOCH_2CO_2Et$.

(CCXXXIII) (CCXXXIV)

III) Kostanecki-Robinson reaction:

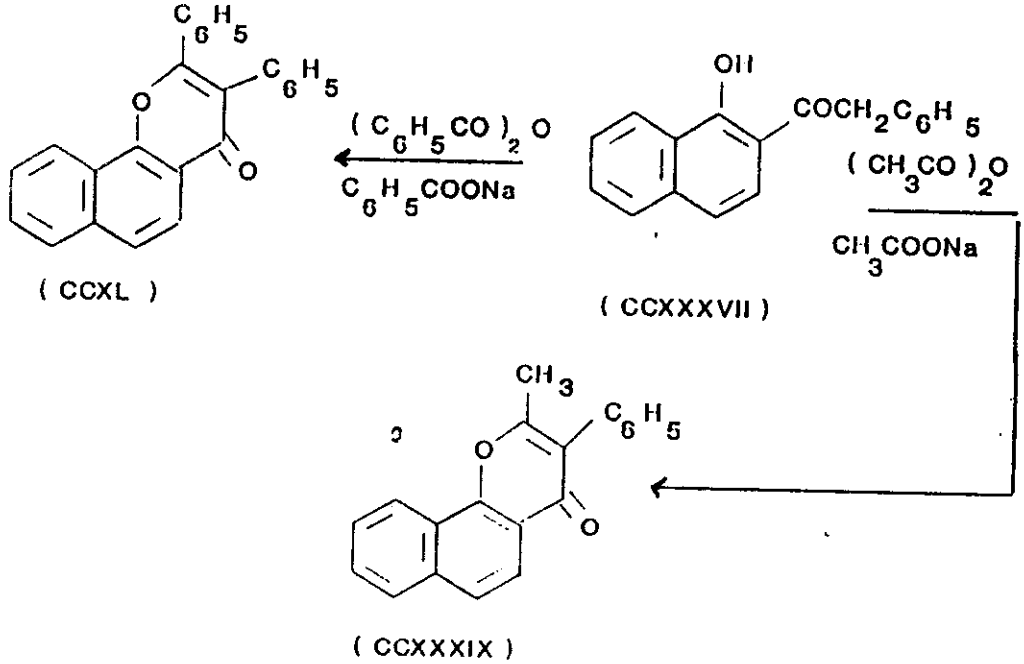
Acid anhydrides in combination with their sodium salts reacted with o-hydroxyaryl-alkyl ketones and gave a product which depended upon the condit

ions[279-280] used in the reaction and in working up the product. Heating 1-acetyl 2-Naphthol (CCXXXV) with acetic anhydride and sodium acetate afforded 2- methyl 1,4-α,ß-naphthopyrone (CCXXXVI)[281].



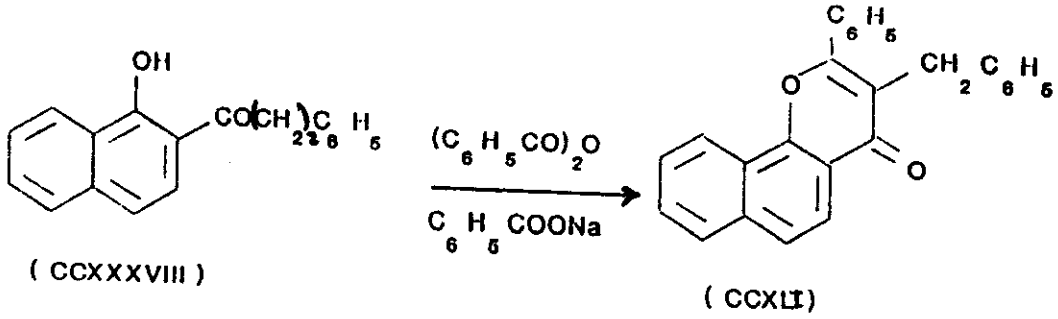
(CCXXXV) (CCXXVI)

The 1,4-α,ß-naphthopyranones (CCXXXIX) and (CCXL) and the α-naphthoflavone (CCXLI) were obtained by treatment of 2-phenylacetyl-1-naphthol (CCXXXVII) and 2-ß-phenylpropionyl-1-naphthol (CCXXXVIII) with acetic anhydride and benzoic anhydride under the usual conditions for chromone synthesis[282].



(CCXL) (CCXXXVII)

(CCXXXIX)



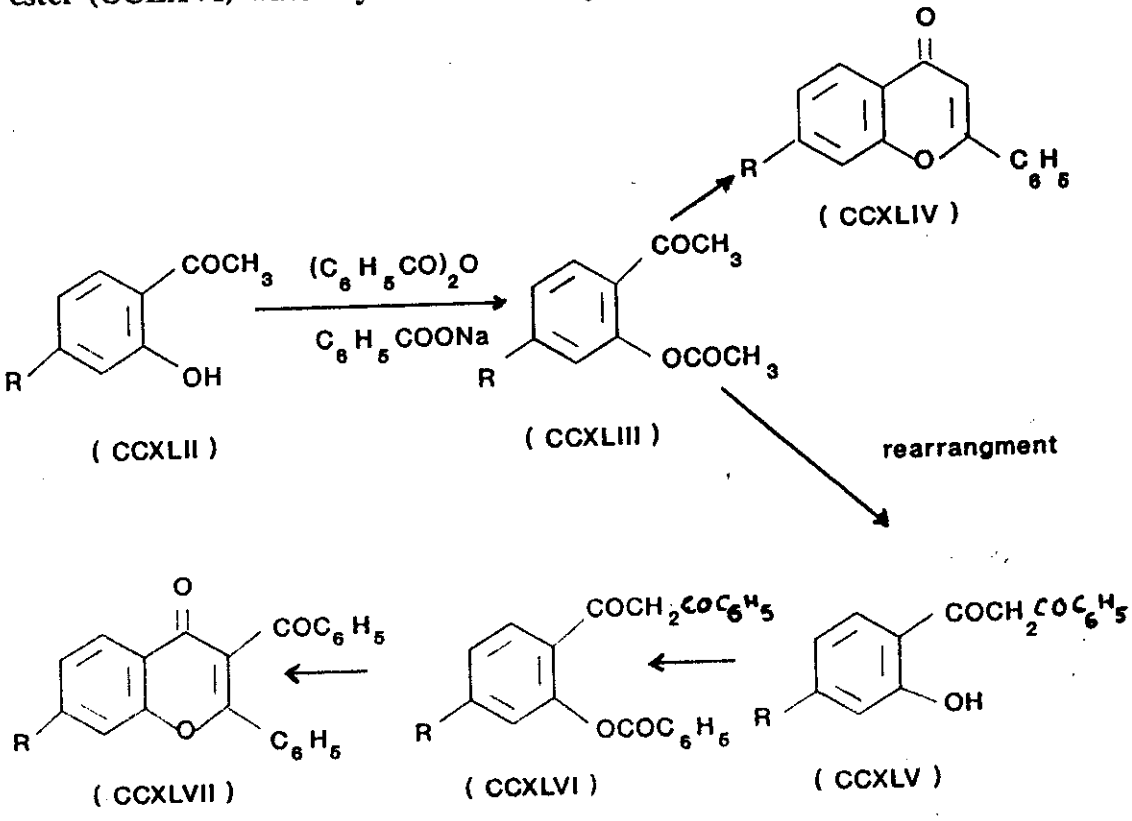
(CCXXXVIII) (CCXLI)

Baker[239] suggested the following mechanism for the preparation of chromones and 3-acylated chromones when an o-hydroxyacetophenones is heated with the anhydride and the sodium salt of carboxylic acid.

a- Acylation of the phenolic group in (CCXLII) gave an ester (CCXLIII) .

b- The ester may be cyclized to flavone (CCXLIV) directly or rearranged to the ß-diketone (CCXLV).

C- The ß-diketone (CCLXV) reacts a gain with the acyl anhydride to give an ester (CCLXVI) which cyclized to the acylchromone (CCXLVII).



The formation of the flavone (CCXLIV) from the acetophenone ester (CCXLIII) has been a ccomplished by phosphorous pentoxide, hydrogen chloride in acetic acetic[283], potassium acetate in boiling alcohol, or boiling acetic anhydride[284].

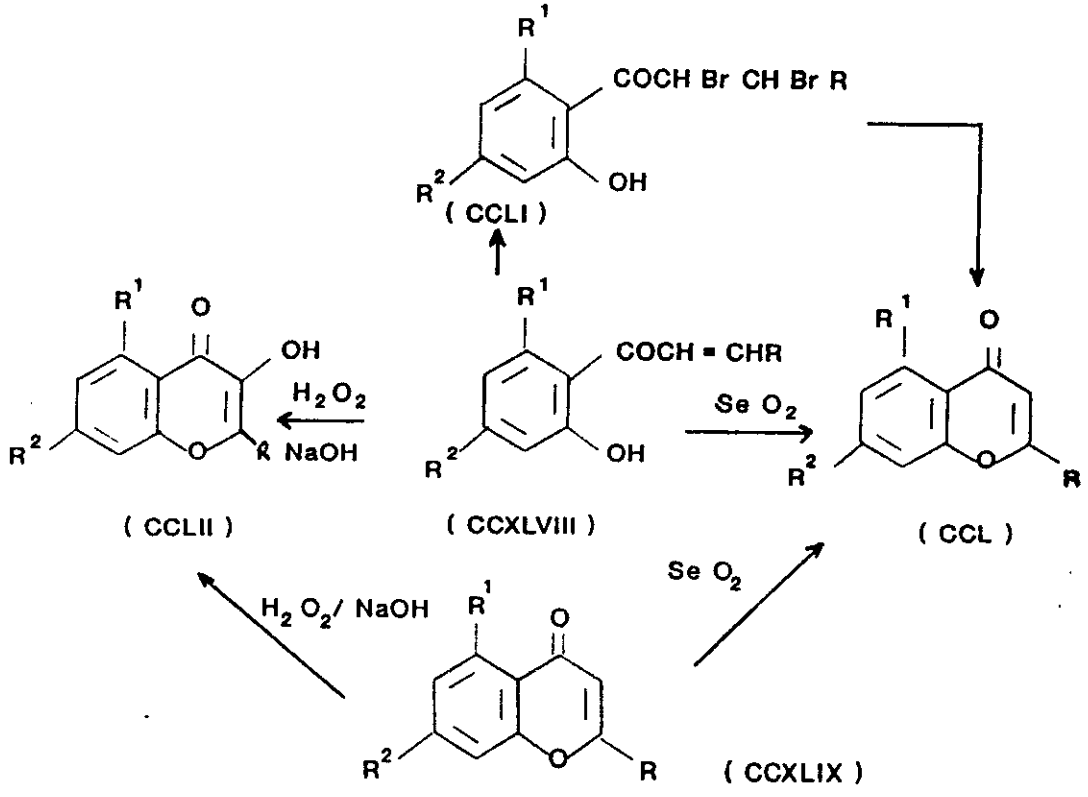
Using trimethylamine instead of the sodium salt of the acid increase, the yield of the flavone from 10% to approximately 30%[285]. Since the 3-acylflavone (CCXLVII) is α,ß-diketone the acyl group may be removed by refluxing with aqueous sodium carbonate[286] or dilute sulphuric acid[287].

IV) From chalcones & flavanones:

o-Hydroxychalcones (CCXLVIII) and flavanones (CCXLIX) may be converted into flavones (CCL) by means of selenium dioxide[288-290] or by phosphorus pentachloride in benzene[291,292] or by chloranil[293] or by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[294].

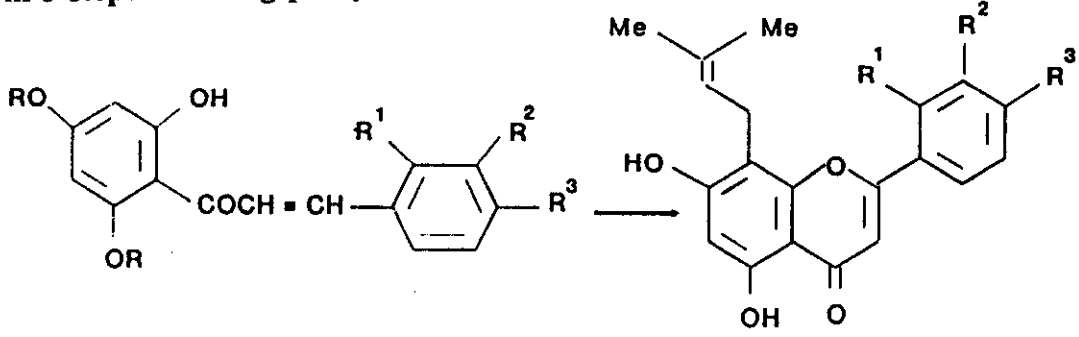
Treatment of the chalcones dibromide (CCLI) with alcoholic potassium cyanide or heated above the melting point under reduced pressure gave flavones (CCL)[295].

Treatment of chalcones (CCXLVIII)[296] or flavanones (CCXLIX)[297] with hydrogen peroxide afforded the flavanols (CCLII)[290,298-300].



2,3-Dihydro-5,7-dihydroxy-8-(3-methyl-2-butenyl)-2-substituted aryl-4H-1-

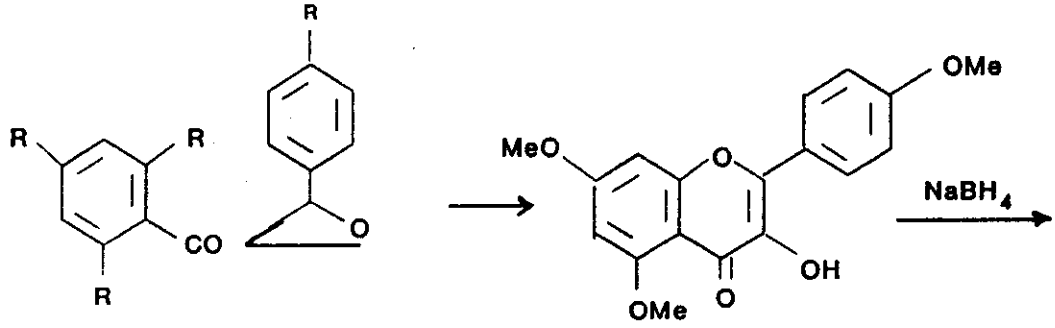
benzopyran-4-one derivatives (CCLIV) were prepared from chalcones (CCLIII)[310,302] in 3 steps involving prenylation, cyclization, and dimethoxymethylation.



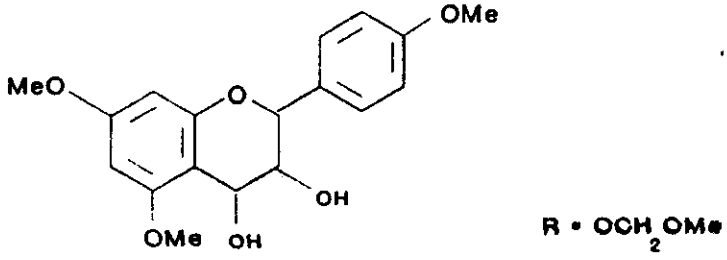
(CCLIII) (CCLIV)

Stereoselective cyclization of the two enantiomeric chalcone epoxide (CCLV) by hydrochloric acid, followed by methylation and preparative HPLC gave pure aromadendrin trimethyl ether (CCLVI) and its enantiomer[303].

Reduction of pure (CCLVI) and its enantiomer with sodium boronhydride gave four flavan-3,4-diol trimethyl ethers (CCLVII).



(CCLV) (CCLVI)

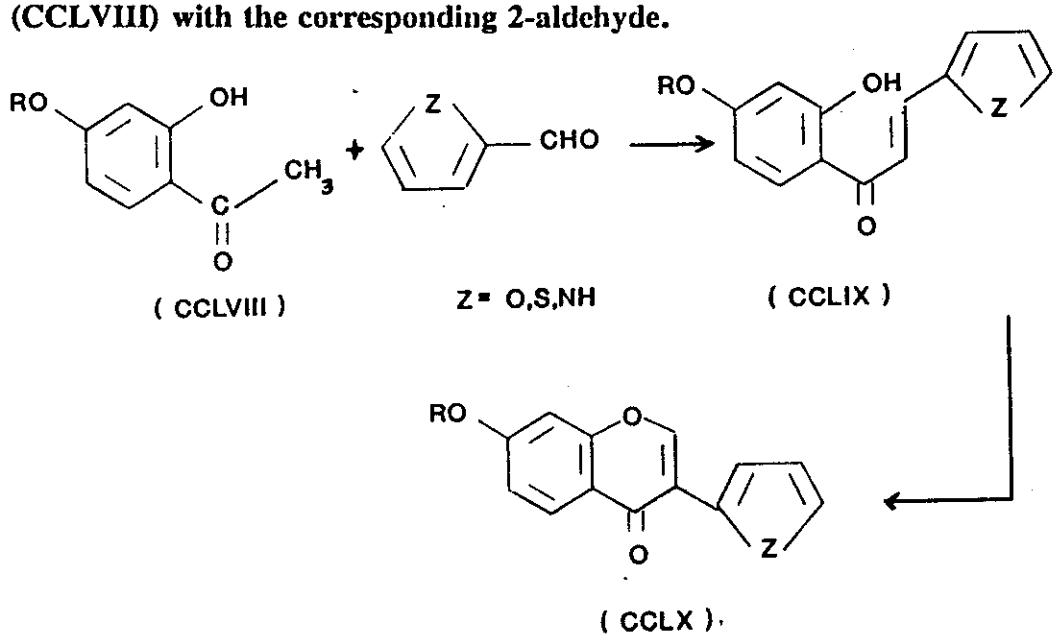


(CCLVII)

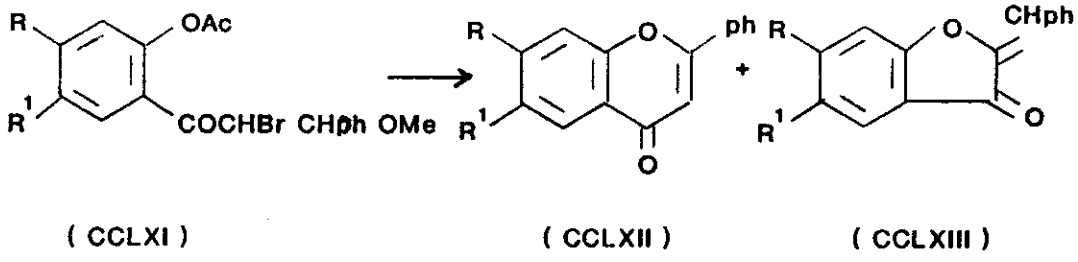
2-Heterochromones (CCLX)[304] were prepared by cyclization of propenyl

phenols (CCLIX).

(CCLIX) were prepared by condensation of 2-hydroxyacetophenones (CCLVIII) with the corresponding 2-aldehyde.

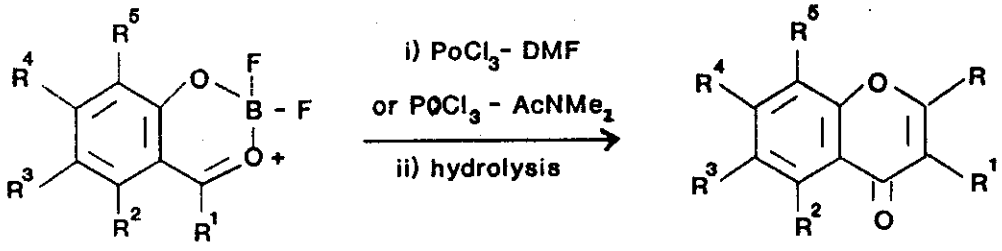


Dihydrochalcones (CCLXI)formed by bromomethoxylation of the side chain of 4,5 2RR (AcO) $C_6H_3COCH{=}CHph$, were found to produce mixtures of flavones (CCLXII) and ourones (CCLXIII) when cyclized by aqueous ethanolic sodium hydroxide[305,306].



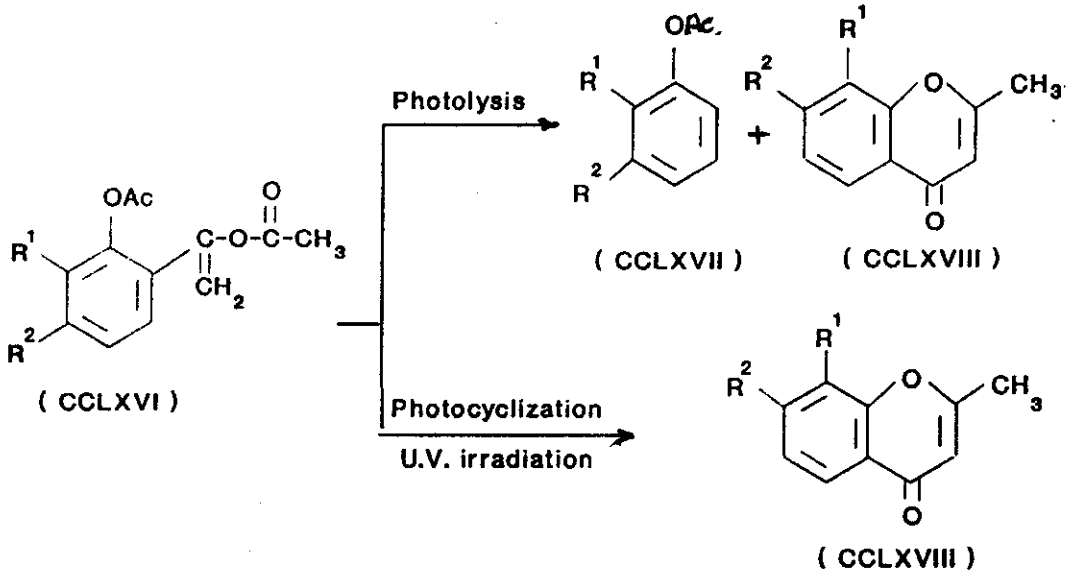
V) Miscellaneous:

(A) Several chromones (CCLXV) were also prepared by treating the appropriate 1,2,3-benzodioxaborin (CCLXIV) (result from the interaction of 2-hydroxyphenyl ketones with FB_3. EtO_2) with $POCl_3$-DMF or $POCl_3$AcNMe$_2$ followed by hydrolysis[307].



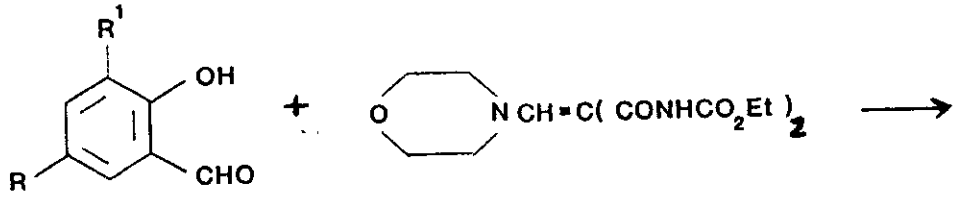
(CCLXIV) (CCLXV)

(B) Hermenegildo[308,309] had shown that enol acetates of o-acetoxy acetophenone (CCLXVI) led to the formation of either (CCLXVII) and (CCLXVIII) by photolysis or by U.V. irradiation.

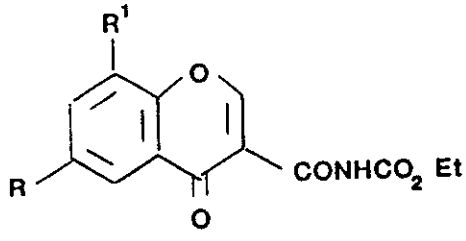


(CCLXVI) (CCLXVII) (CCLXVIII) (CCLXVIII)

C) Chromones (CCLXXI) were prepared by cyclocondensation of salicylaldehyde (CCLXIX) with enamine (CCLXX)[310].



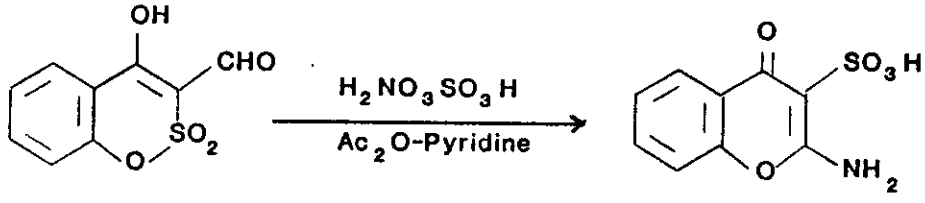
(CCLXIX) (CCLXX)



(CCLXXI)

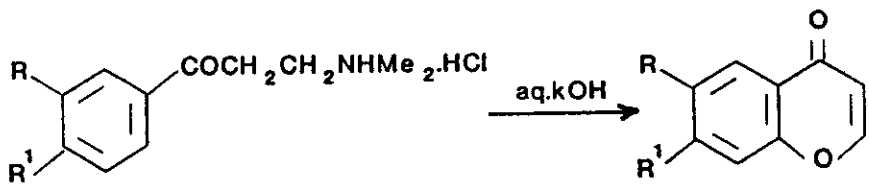
(D) Benzoxathiin-chromone ring transformation:

The chromone sulfonic acid (CCLXXIII)[311] was prepared by reaction of benzothii (CCLXXII) with hydroxylamine sulfate in the presence of pyridine-acetic anhydride.



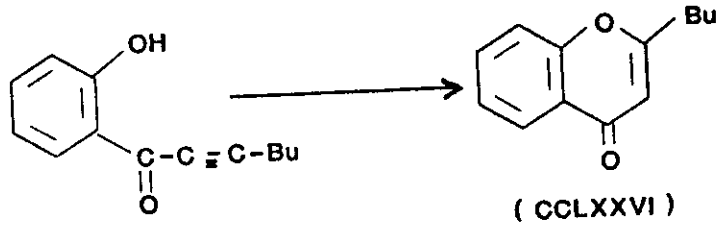
(CCLXXII) (CCLXXIII)

(E) Mannich base salts (CCLXXIV) prepared from the corresponding acetophenone, formaldehyde and dimethylamine hydrochloride were cyclized and gave the 4-chromone (CCLXXV)[312].



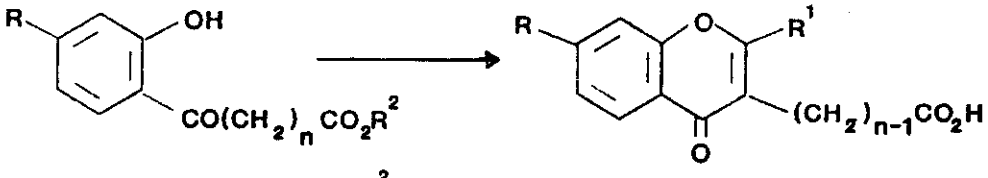
(CCLXXIV) (CCLXXV)

(F) 2-Butylchromone (CCLXXVI) was synthesized by cyclization of 1-(2-hydroxyphenyl) 2-ynones[313].



(CCLXXVI)

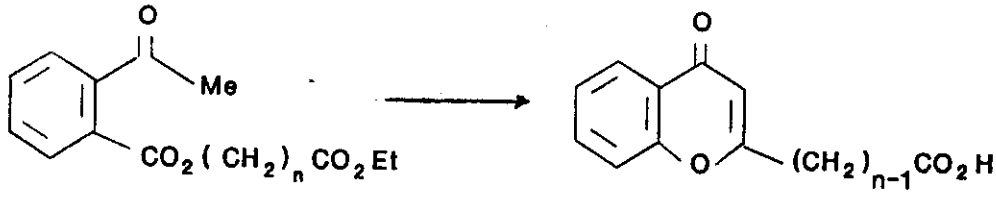
(G) W-(3-Chromonyl) alkanoic acids (CCLXXVIII) were synthesized by cyclization of the corresponding methyl W-(2-hydroxybenzoyl) alkanoate (CCLXXVII) with N,N-dimethylformamide-dimethylacetate or acetic anhydride DBU followd by hydrolysis[314].



(CCLXXVII) R^2 = Me, Et (CCLXXVIII)

(H) Similarly, W (2-chromonyl) alkanoic acids (CCLXXX) were obtained from

cyclization of o-acetylphenyl ethyl alkanedioate (CCLXXIX) with DBU followed by hydrolysis[315].

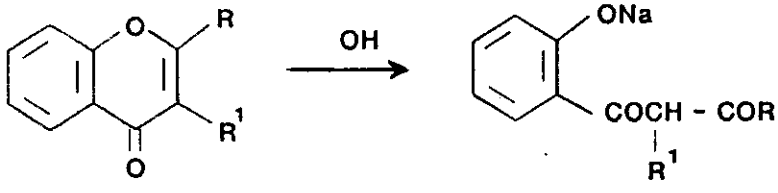


(CCLXXIX) (CCLXXX)

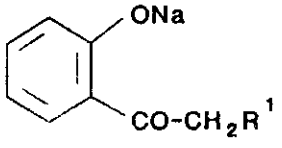
REACTIONS OF CHROMONES

I) Action of alkali:

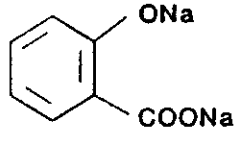
The reaction of chromones with alkali is very valuable for structure determination and for separation of chromones from non hydroxylated coumarins[316], cold alkali or sodium ethoxide formed at first the o-hydroxy ß-diketone (CCLXXXI) which cleaved under prolonged heating and gave either a mixture of (CCLXXXII) and (CCLXXXIII) or one of them.



(CCLXXXI)



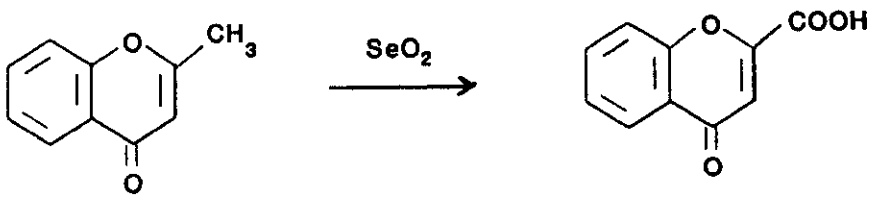
(CCLXXXII)



(CCLXXXIII)

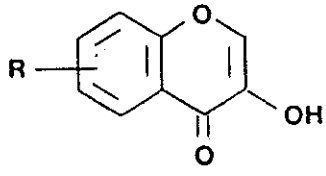
II) Oxidation:

Oxidation of 2-methylchromone with selenium dioxide in aqueous dioxane gave chromone 2-carboxylic acid (CCLXXXIV)[242].



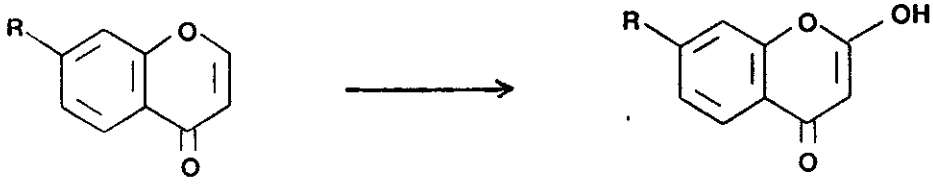
(CCLXXXIV)

Baeyer-Villiger oxidation of chromone 3-carboxaldehydes gave 3-hydroxychromone (CCLXXXV)[317].



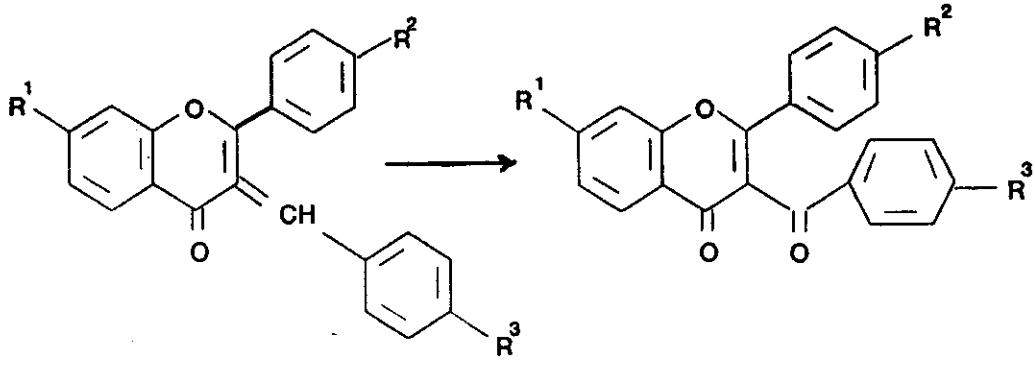
(CCLXXXV)

3-Hydroxychromones (CCLXXXVII) were obtained by oxidation of chromones (CCLXXXVI) by 3-chloroperbenzoic acid[318].



(CCLXXXVI) (CCLXXXVII)

Methylene blue sensitized photooxygenation of 3-arylidene 2-aryl-2,3 dihydro -4H-1-benzopyran 4-ones (CCLXXXVIII) gave 3-aroyl-2-aryl-4H-1-benzopyran 4-ones (CCLXXXIX)[319].

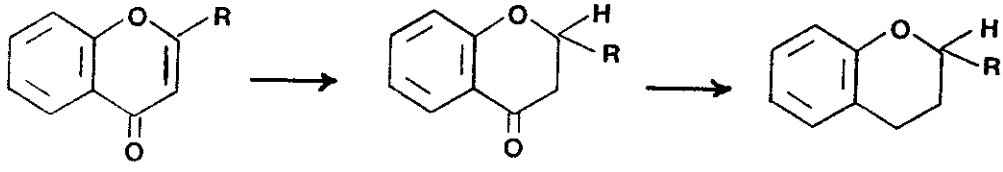


(CCLXXXVIII) (CCLXXXIX)

III) Reduction:

Reduction of chromones gave various products depending on the type of reducing agent.

i-Catalytic reduction over platinium[320] or palladium[321,322] gave chromones[323-325] (XCCC) and finally chromans (XCCCI).



(XCCC) (XCCCI)

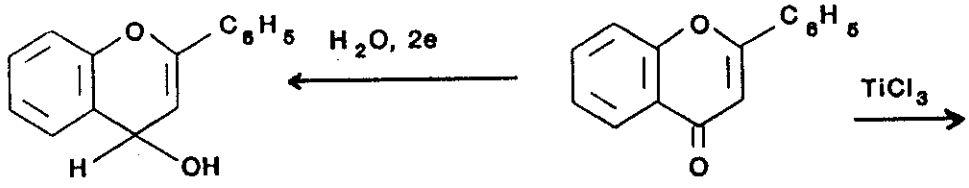
ii- Raney nickel reduced 2-ethylchromone at 120-130°C giving a mixture of (XCCCII) and (XCCCIII)[326].

(XCCCII) (XCCCIII)

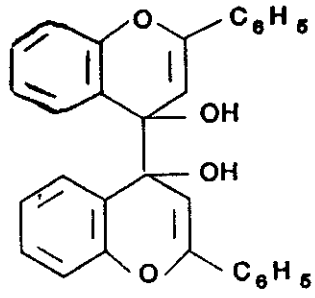
iii- Titanium trichloride formed a small amount of pinacol (XCCCIV)

together with a large amount of an unidentifiable oil[327].

Polarographic studies indicated that the chromenol (XCCCV) was a product of electrolytic reduction of flavones[328].

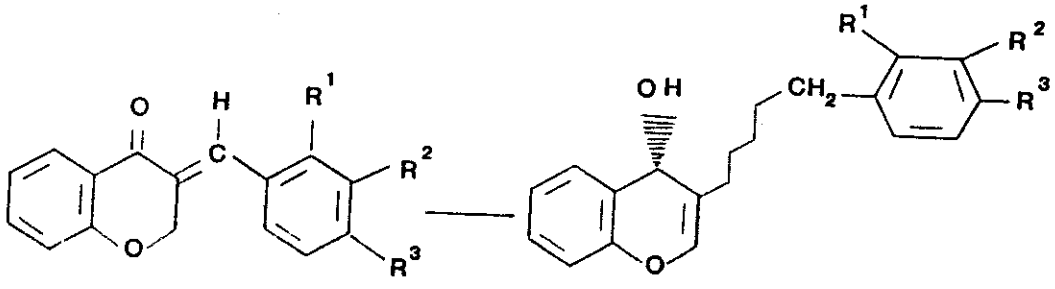


(XCCCIV)



(XCCCV)

Reduction of 3-arylidene 4-chromanones (XCCCVI) led to a mixture of cis and trans 3-(arylmethyl) 4-chromanols (XCCCVII)[329].

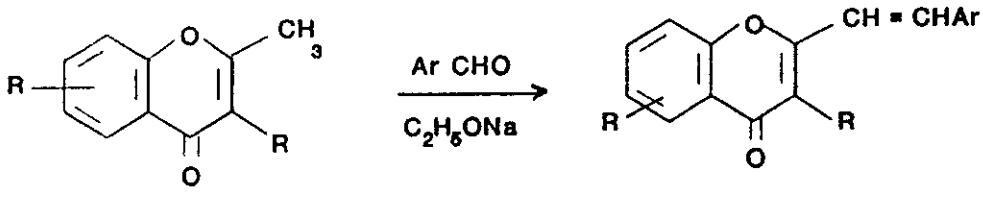


(XCCCVI)

(XCCCVII)

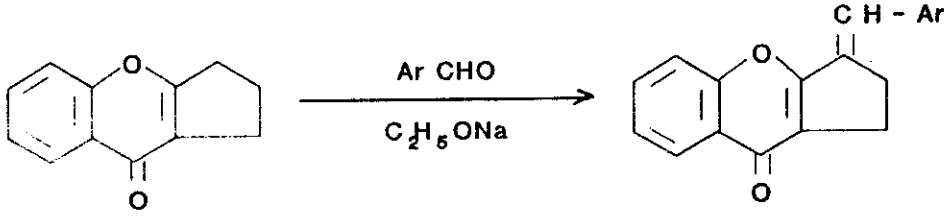
IV) Condensation reactions:

A methyl group in the 2-position is activated by the carbonyl group and condenses with aromatic aldehydes in the presence of sodium ethoxide to give styrylchromones (XCCCVIII)[330-335].



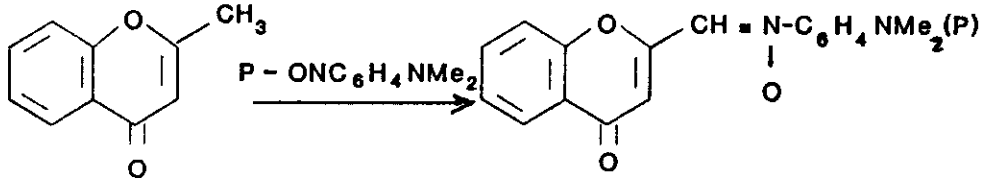
(XCCCVIII)

2-Ethyl, 2-propyl and 2-methyl 3-acylchromones did not react but 2,3-cyclopentene chromone (XCCCIX) condensed[336].



(XCCCIX)

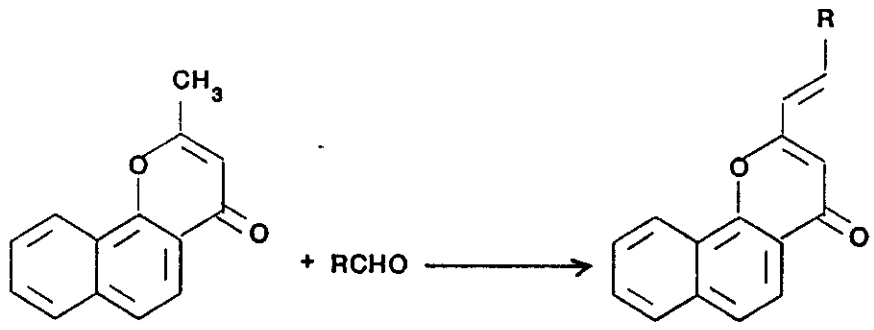
2-Methylchromone (CCC) condensed with p-nitrosodimethylaniline and gave the nitrone derivative (CCCI)[337,338].



(CCC) (CCCI)

2-Methylnaphtho (1,2-b) pyran 4-one (CCCII) was condensed with various

aromatic aldehydes to give styryl derivatives (CCCIII)[339].

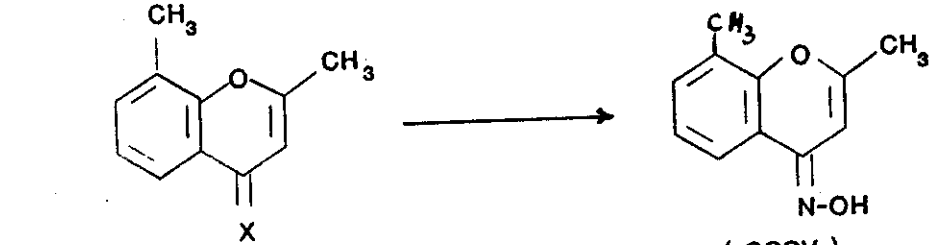


(CCCII) (CCCIII)

V) Action of amines:

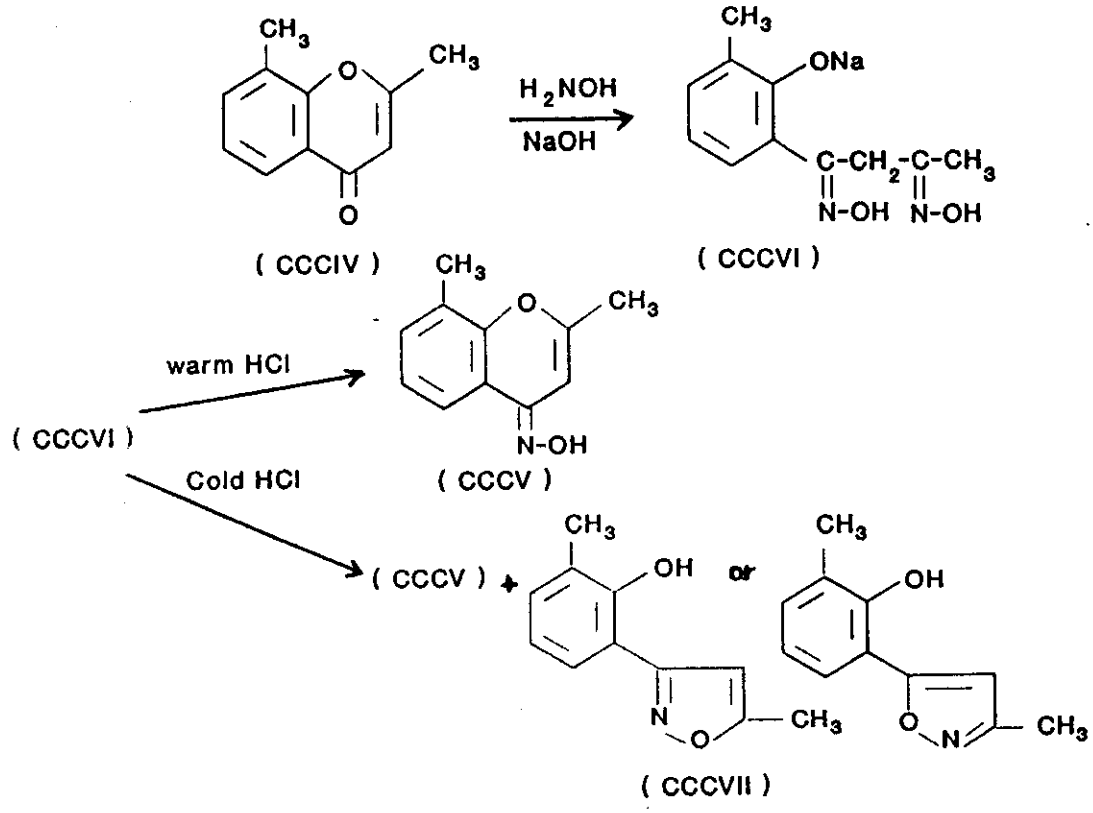
a-Reaction with hydroxylamine:

In neutral or anhydrous solution chromone and 4-thiochromone (CCCIV) give the corresponding oxime (CCCV)[340,441]

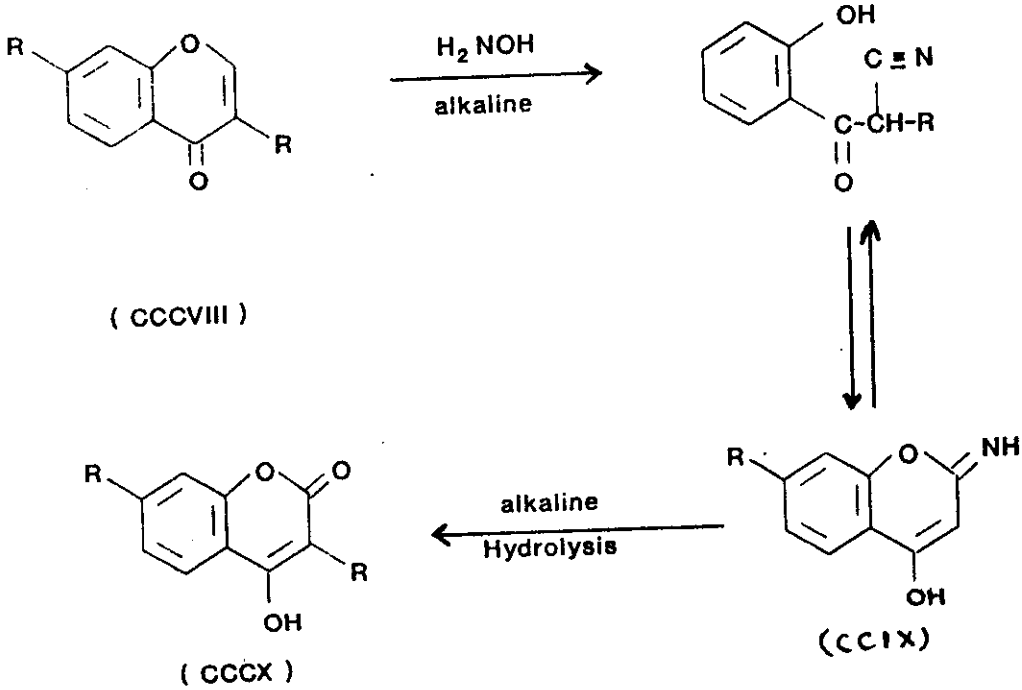


(CCCIV) (CCCV)

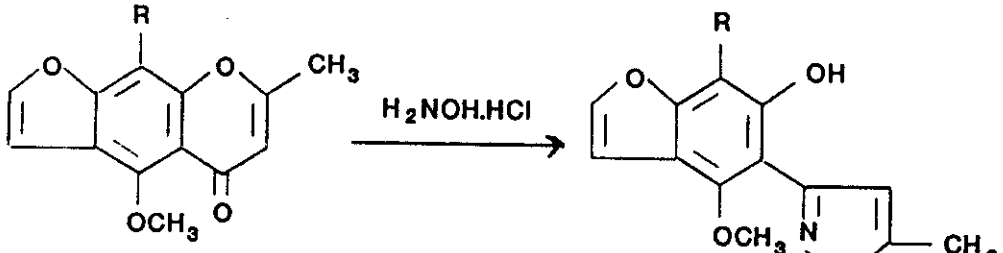
In alkaline media, a dioxime (CCCVI) was obtained. This dioxime when warmed with hydrochloric acid gave the chromone oxime (CCCV). However with cold acids it gave beside (CCCV) an alkali soluble isoxazole derivative (CCCVII)[340].



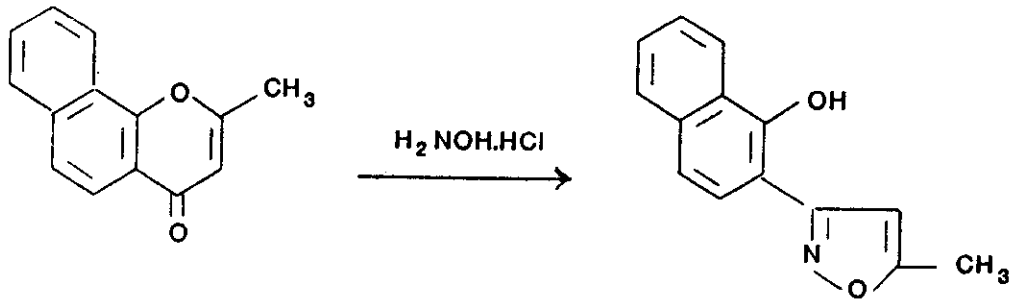
Treatment of chromones (CCCVIII) with H_2NOH under alkaline conditions gave the corresponding coumarinimins (CCCIX) which was converted into 4-hydroxycoumarins (CCCX) under the influence of alkaline hydrolysis[342].



Schönberg et al showed that visnagine (CCCXI)[343] and 2-methyl-1,4-α-naphthopyrone(CCCXII)[344] reacted with hydroxylamine hydrochloride in pyridine at the boiling point of the a mixture and gave the isoxazole derivatives (CCCXIII) and (CCCXIV).

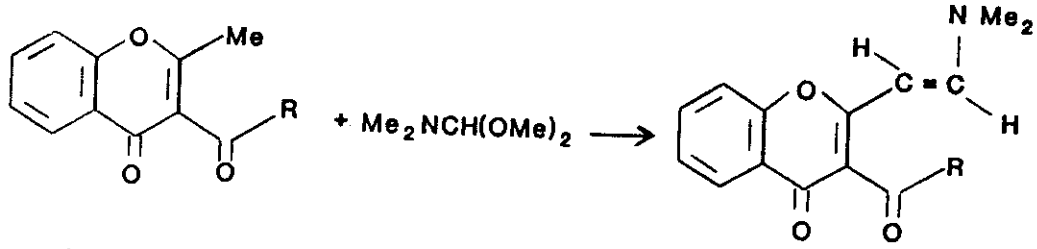


(CCCXI) (CCCXIII)

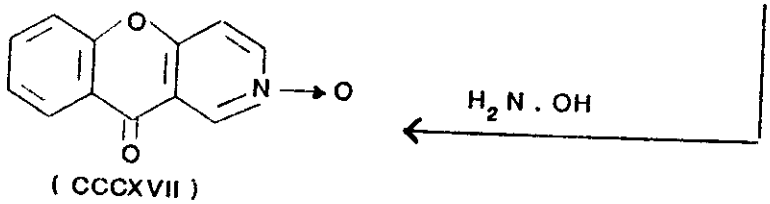


(CCCXII) (CCCXIV)

The enamines (CCCXVI) prepared from benzopyranone (CCCXV) and Me_2-NCH- $(OMe)_2$ on treatment with hydroxylamine gave the pyridine-N-oxide (CCCXVII)[345]



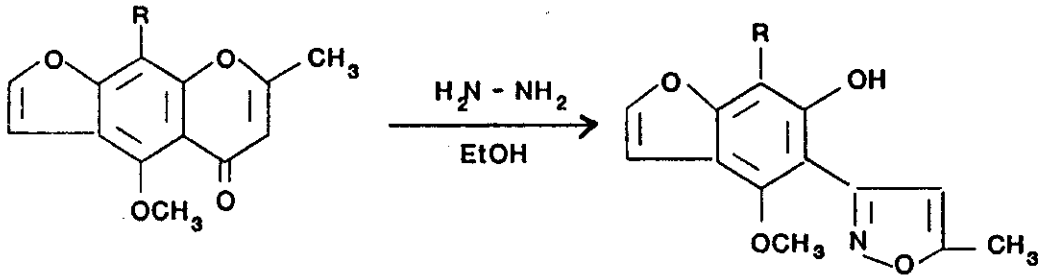
(CCCXV) (CCCXVI)



(CCCXVII)

b- Reaction with hydrazines:

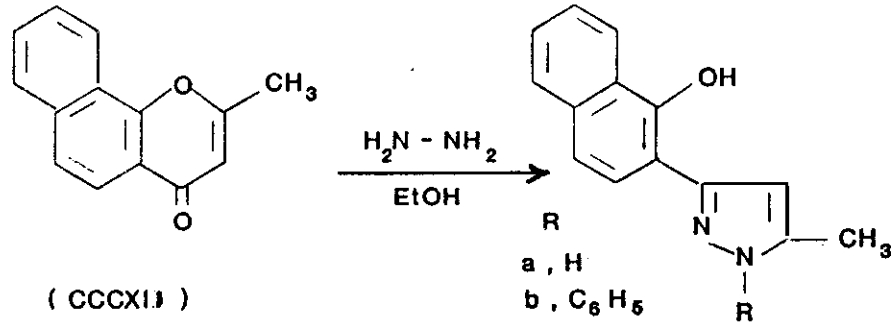
Schönberg et al[343,344] investigated the action of hydrazines on visnagin (CCCXI) and 2-methyl-1,4-α-naphthopyrone (CCCXII) and suggested the formation of the oxazole and pyrazole derivatives (CCCXVIII), (CCCXIX) and (CCCXX).



(CCCX I.)

(CCCXVIII), R = H

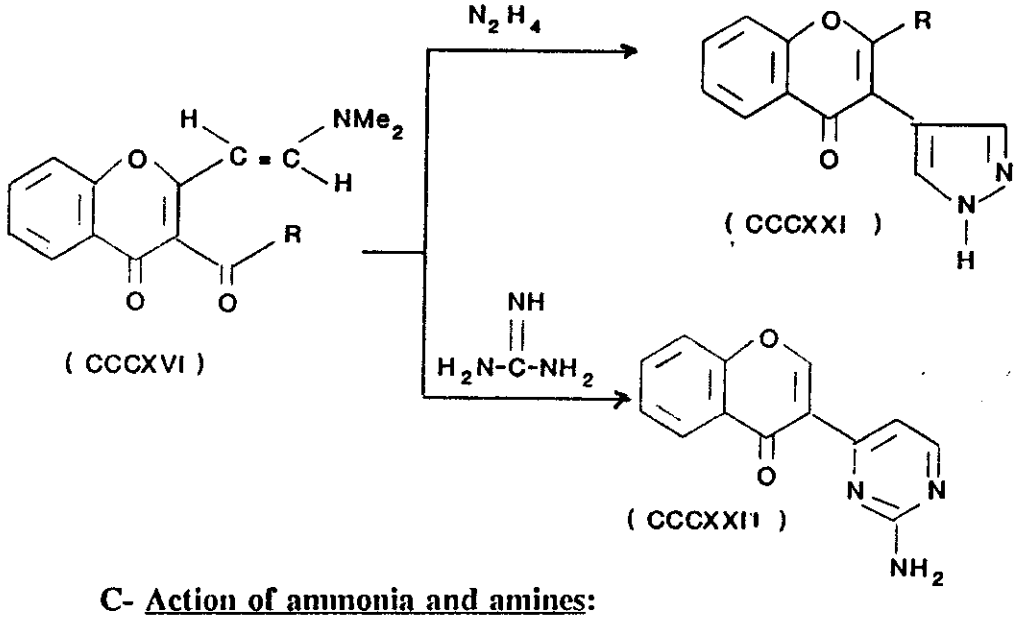
(CCCXIX), R = OCH_3



(CCCXII)

(CCCXX)

Hydrazine and guanidine underwent initial 1,6-addition to (CCCXVI) ultimately giving pyrazoles (CCCXXI) and pyrimidines (CCCXXII), respectively[345].



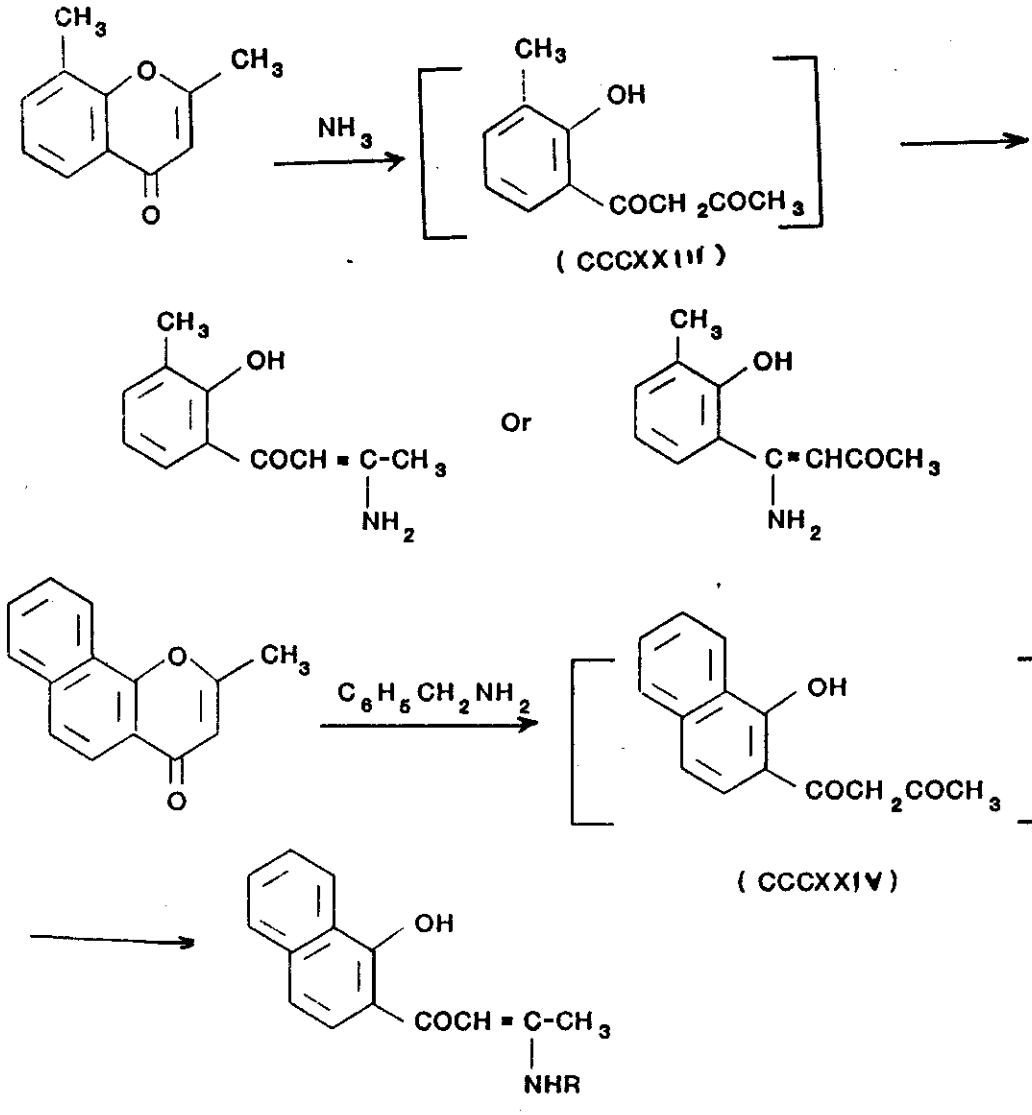
(CCCXVI)

(CCCXXI)

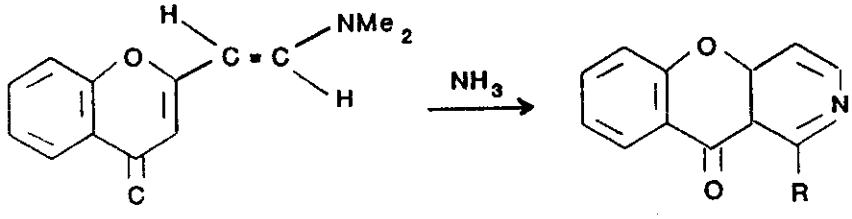
(CCCXXII)

C- Action of ammonia and amines:

Chromones on treatment with ammonia or primary aliphatic amines gave products which were derived from the β-diketones (CCCXXIII) and (CCCXXIV)[346-349].

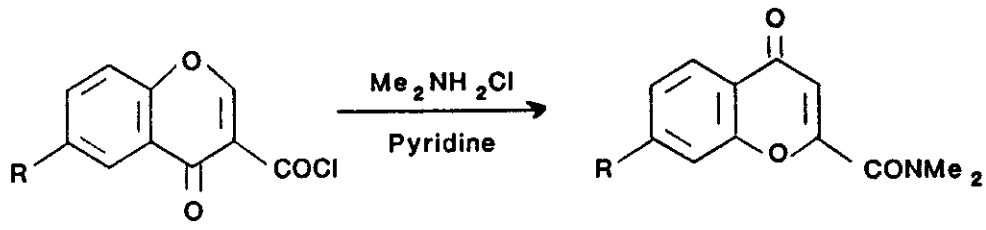


On treatment of enamine (CCCXVI) with ammonia gave the fused pyridine (CCCXXV)[345].



(CCCXVI) (CCCXXV)

Chromone 2-carboxylic acids are efficiently transformed into the N,N-dimethyl chromone 2-carboxamides (CCCXXVII) by reacting the corresponding acid chlorides (CCCXXVI) with dimethylamine hydrochloride in pyridine[350].

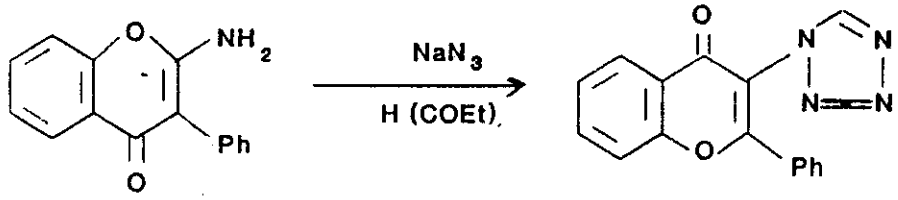


(CCCXXVI)

(CCCXXVII)

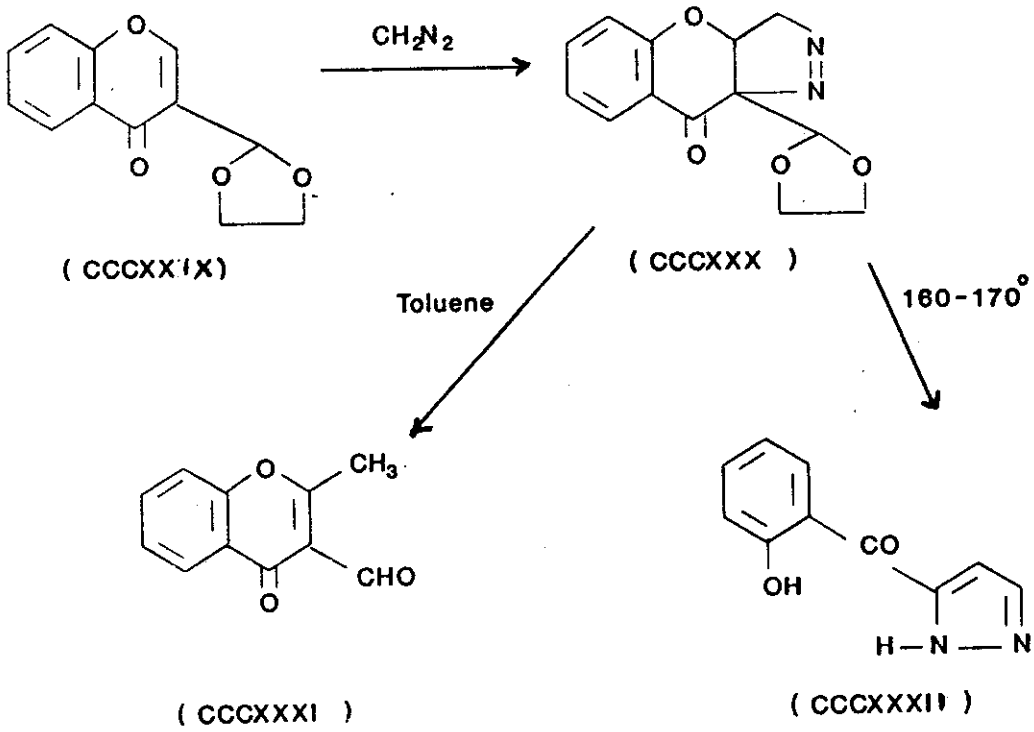
(VI) Action of azides and diazomethane:

3-(1-Tetrazoyl)-benzopyranoids (CCCXXVIII) were prepared by reaction of aminobenzopyranones, e.g. 3-aminoflavone, with sodium azide and ethylortho-formate in acetic acid[351].



(CCCXXVIII)

Treatment of the 3-(cyclic ethylene acetal) of 4-oxo-4H-1-benzopyran-3-carboxaldehyde (CCCXXIX) with diazomethane in methylene chloride-ether gave fused pyrazolidine (CCCXXX)[352] which after thermolysis and acid hydrolysis gave 2-methylchromone (CCCXXXI). 3 (5) Salicyloyl pyrazole (CCCXXXII) was obtained when (CCCXXX) was heated at 160-170°C.

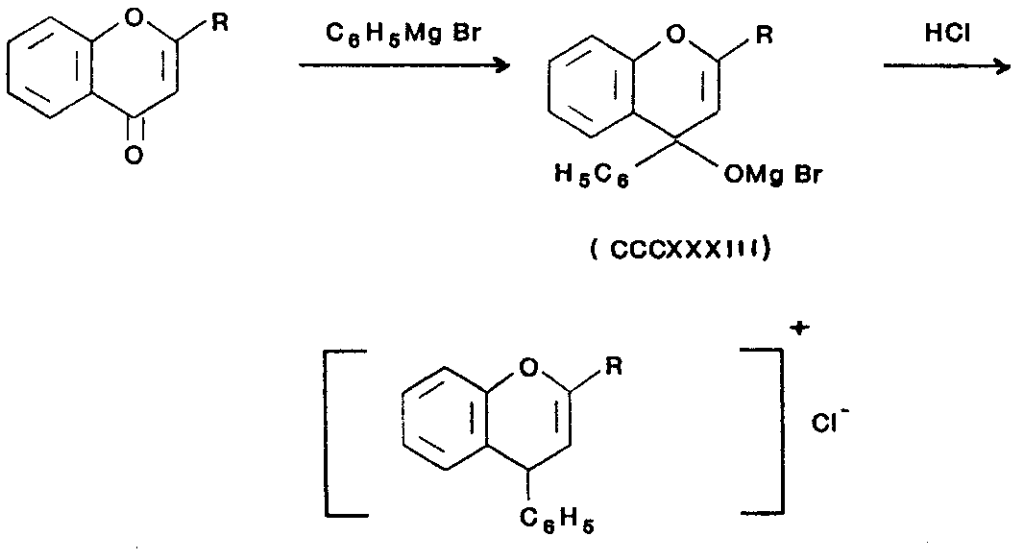


(CCCXXIX) (CCCXXX) (CCCXXXI) (CCCXXXII)

VII) Action of Grignard reagents:

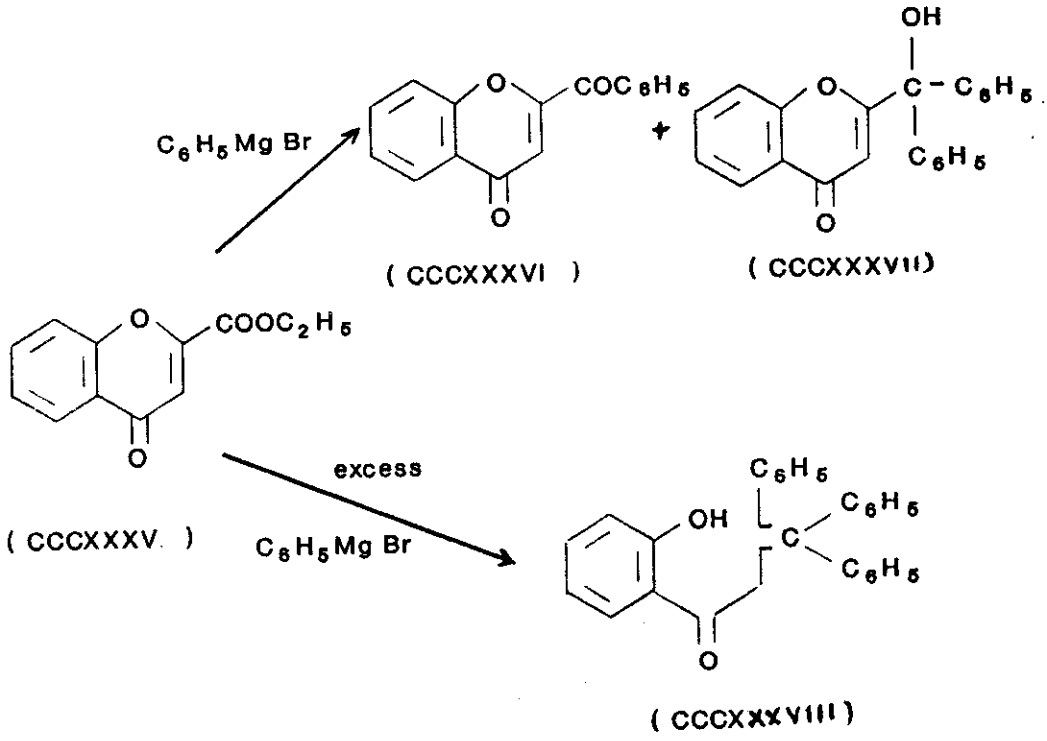
Both aliphatic and aromatic Grignard reagents added to chromones[353-356] and gave α-chromenols (CCCXXXIII) which were easily converted by acids to the benzopyrylium salts (CCCXXXIV)[357].

3-Methyl-5,6-benzochromones was reported not to react satisfactorily with Grignard reagents due to the steric hinderance[357].



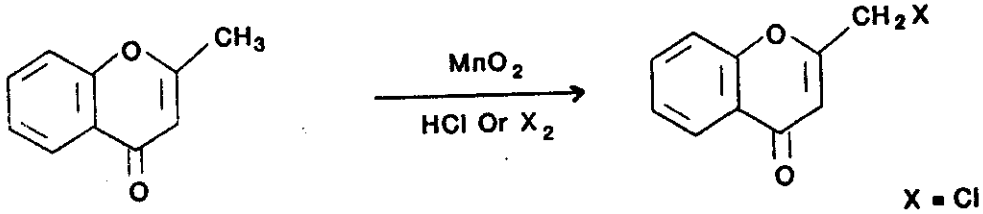
(CCCXXXIII) (CCCXXXIV)

Phenylmagnesium bromide reacted with ethyl chromene 2-carboxylate (CCCXXXV) gave (CCCXXXVI) and (CCCXXXVII). A large excess of the 1-(o-hydroxyphenyl)-3,4,4-triphenyl 3-buten-1-one (CCCXXXVIII)[358].



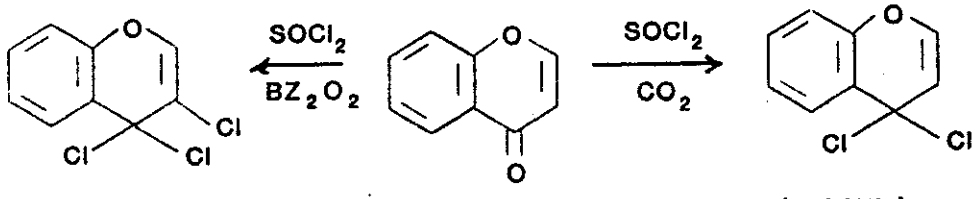
(VIII) Halogenation:

Halogenation of 2-methylchromones(CCC) with N-bromosuccimide or with halogen in presence of manganese dioxide gave 2-chloromethylchromone (CCCXXXIX)[359,360]. The corresponding bromomethyl and iodomethyl derivatives can be obtained by using bromine and iodine and manganese dioxide.



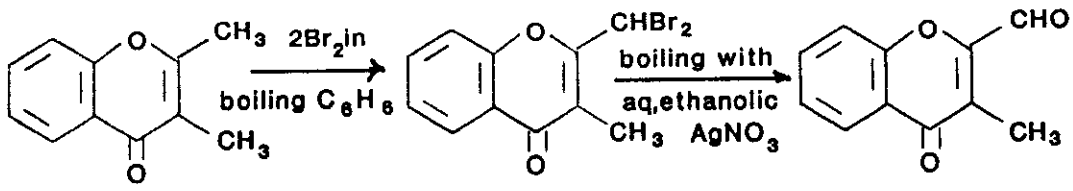
(CCC) (CCCXXXIX)

With excess thionyl chloride and under CO_2, chromone (II_a) gave 4,4-dichlorochromene (CCCXL), while in the presence of benzoylperoxide it gave 3,4,4-trichlorochromene (CCCXLI)[361].

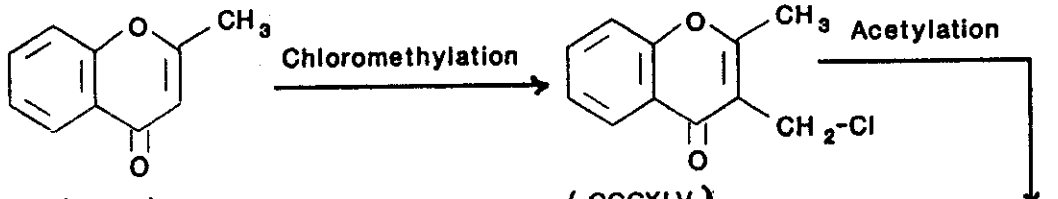


(CCCXLI) (II_a) (CCCXL)

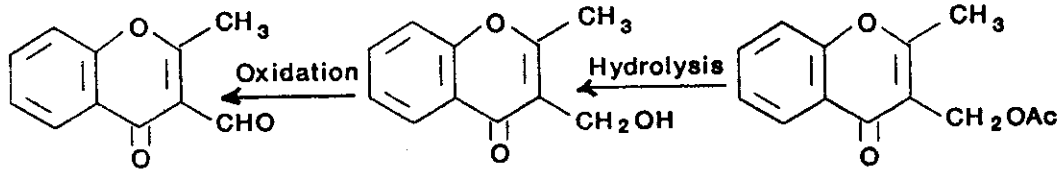
Bromination of 2,3-dimethylchromone (CCCXLII) in boiling benzene proceeded in one side chain, giving rise to 2-dibromomethyl 3-methyl chromen-4- one (CCCXLIII) which hydrolysed by an aqueous ethanolic $AgNO_3$ to give 3-methyl-4H-chromene-4-one-2-carboxaldehyde (CCCXLIV), while sequential treatment of-2-methylchromen-4-one (CCC) with chloromethylation, acetylation and hydrolysis gave 2-methyl-4-oxo-chromen-3-carboxaldehyde (CCCXLVIII)[362].



(CCCXLII) (CCCXLIII) (CCCXLIV)



(CCC) (CCCXLV)

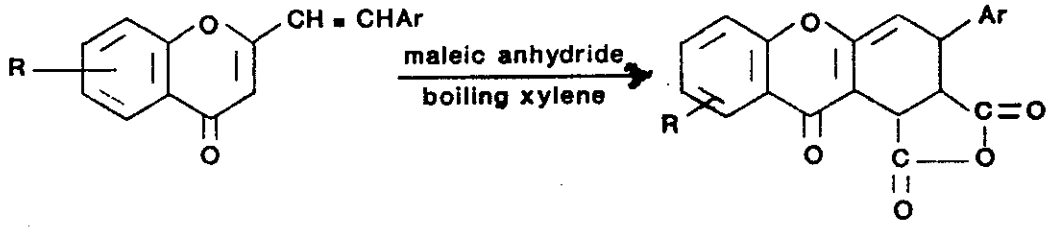


(CCCLVIII) (CCCLVII) (CCCXLVI)

(IX) Addition to unsaturated compounds:

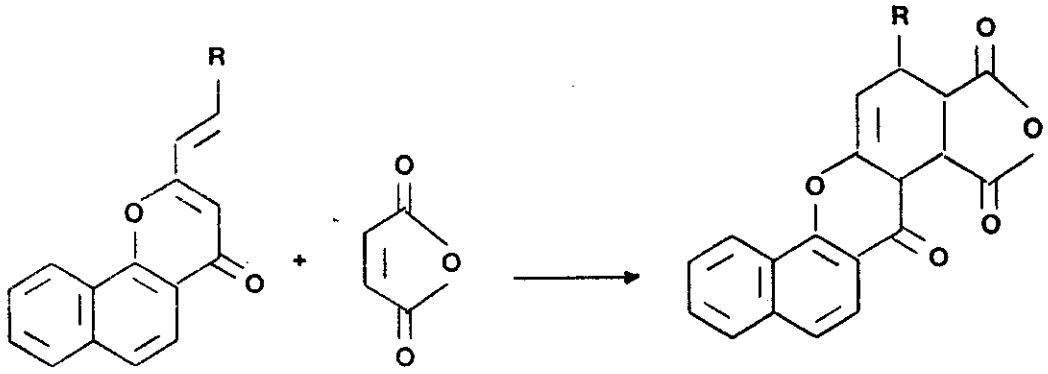
a) Diels-Alder reaction:

2- Styrylchromones behave as a diene and underwent Diels-Alder reaction with dienophiles such as maleic anhydride, maleic acid. N-arylmalimides and trans diaroylethylenes and gave xanthone derivatives. Thus 2-styrylchromones (CCCXLIX) reacted with maleic anhydride and gave the tetrahydroxanthone derivative (CCCL)[227,334,335,363,364].



(CCCXLIX) (CCCL)

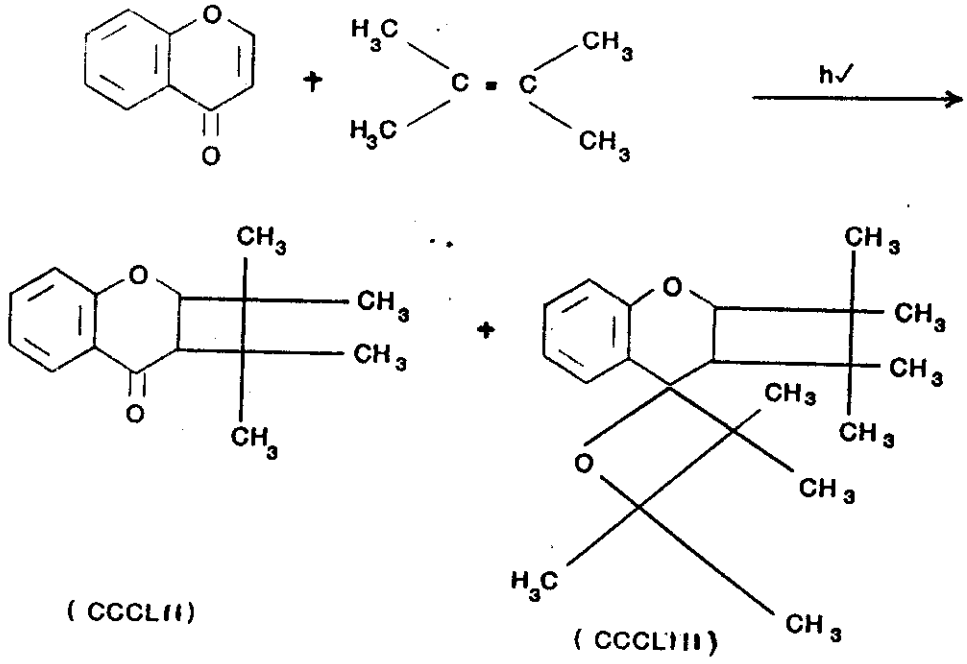
Similarly, the sytyryl derivatives (CCCIII) reacted with maleic anhydride and gave the tetrahydroxanthone derivative (CCCLI)[339].



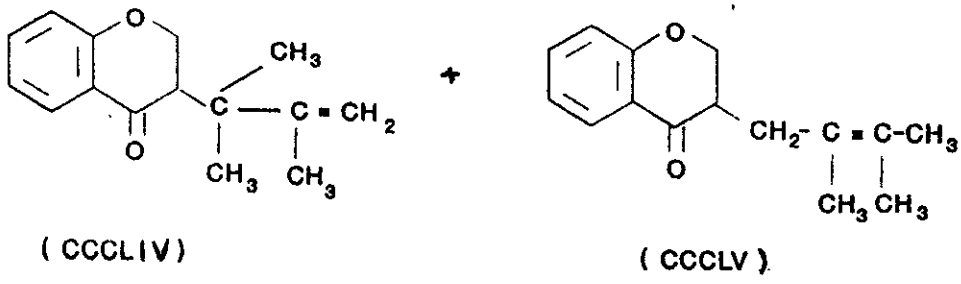
(CCCIII) (CCCLI)

b) Photoaddition:

Chromone underwent photoaddition reactions to olefins and acetylenes and gave 1:1 primary photoproducts[365,366]. Irradiation of a solution of chromone, tetramethylethylene and dioxane produced four photoadducts which were isolated and identified as (CCCLII - CCCLV).

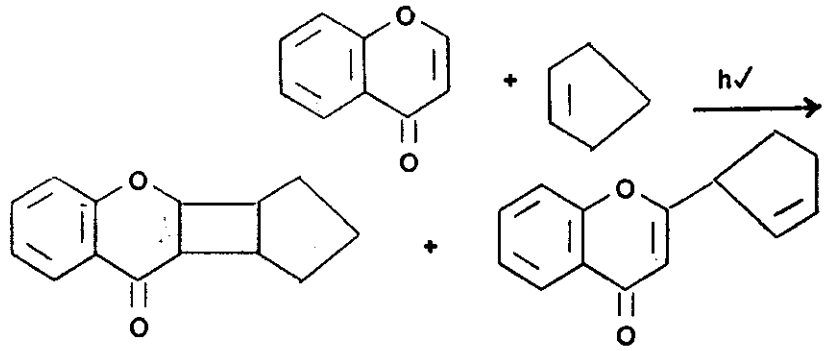


(CCCLII) (CCCLIII)



(CCCLIV) (CCCLV)

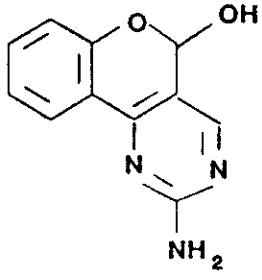
Irradiation of as solution of chromone and cyclopentene yielded (CCCLVI) and (CCCLVII).



(CCCLVI) (major) (CCCLVII) (minor)

X) Michael addition:

Chromone 3-carboxaldehyde underwent Michael (1,4) addition with guanidine to give the 5H-(1) benzopyrano (4,3-d) pyrimidine (CCCLVIII)[367]

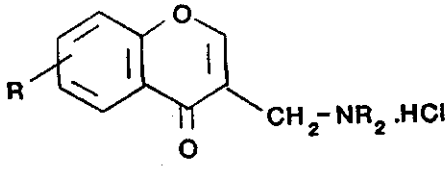


(CCCLVIII)

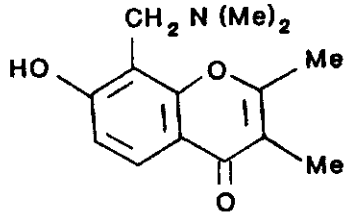
XI) Reaction with formaldehyde:

(a) Mannich reaction:

Chromones unsubstituted in the 2-and 3-position yielded with formaldehyde and secondary amines hydrochloride the 3-dialkylaminomethyl derivative (CCCLIX)[217].



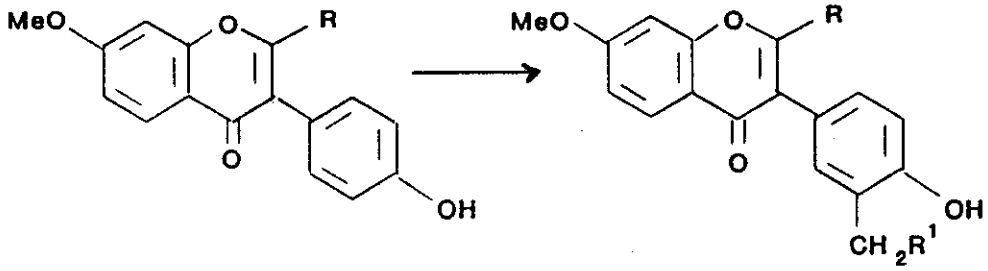
(CCCLIX)



(CCCLX)

7-Hydroxy-2,3-dimethylchromone reacted with formaldehyde and dimethylamine and gave 7-hydroxy 8-dimethylaminomethyl 2,3-dimethylchromone (CCCLX)[368].

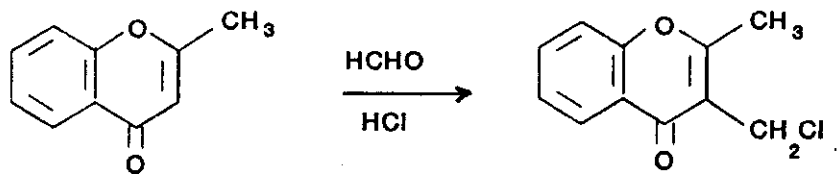
Chromones (CCCLXII) were prepared by Mannich reaction of isoflavones (CCCLXI)[369].



(CCCLXI) (CCCLXII)

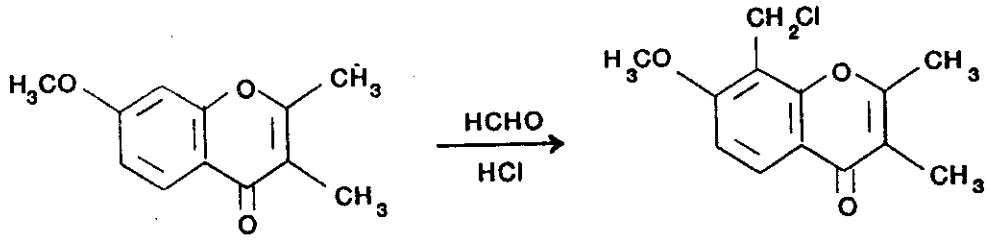
b) Chloromethylation:

Chloromethylation of 2-methylchromones using formaldehyde and hydrogen chloride gas gave 3-chloromethyl 2-methylchromone (CCCLXIII)[370].



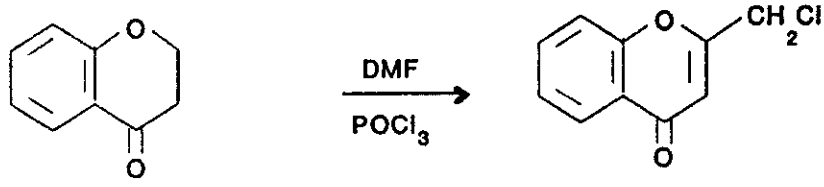
(CCCLXIII)

7-Methoxy 2,3-dimethylchromone (CCCLXIV) on chloromethylation gave the 8-chloromethyl derivative (CCCLXV)[371].



(CCCLXIV) (CCCLXV)

Oxidative formylation of chromanone by excess DMF-$POCl_3$, at 100°C afforded chloromethylchromone (CCCXXXIX)[372].



(CCCXXXIX)