CHAPTER-1

INTRODUCTION

CHAPTER - I

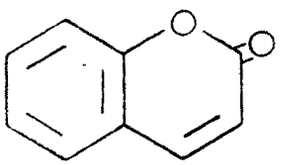
INTRODUCTION

Benzo- α-pyrones, commonly known as coumarins, occur widely in nature. Most of them are isolated from plants especially, the Umbelliferae (e.g. parsley, parnsip, celery, ammi majus, angelica archangelic), Rutaceae (e.g. bergamot fruit, lime gas plant, cloves) ; Leguminose (psoralea corylifolia, xanthoxylum flavum) and a few from animals or microorganism. Some of these naturally occuring coumarins are pharmacologically active as anticoagulants, rodenticides and insecticides. The following are examples of some simple coumarinsoccuring in nature : e.g. Coumarin (1), Umbelliferone (2), Scopoletin (3), Aesculetin (4), Daphnetin (5), Fraxetin (6) and Ayapin (7).

These naturally occuring coumarins are classified into seven major groups.

(i) Coumarins substituted with one or more hydroxyl or methoxyl groups in the benzene ring e.g. umbelliferone (2), Aesculetin (4).

(ii) Coumarins substituted with isoprenoid residues e.g. Auraptene (8), Suberosin (9), Xanthyletin (10), Samidin (11).



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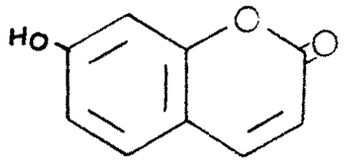

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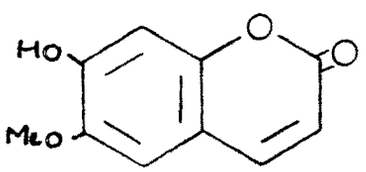

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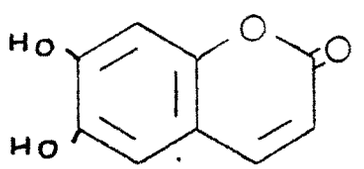

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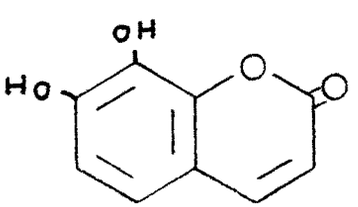

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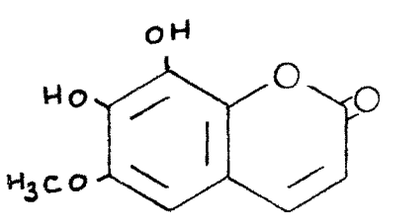

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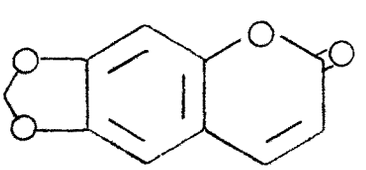

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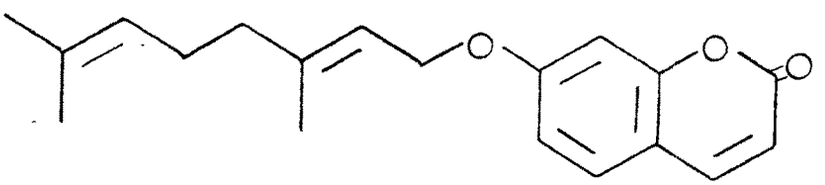

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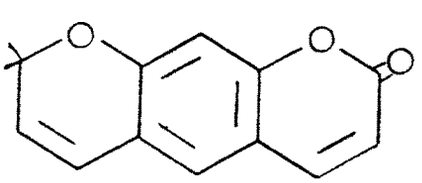

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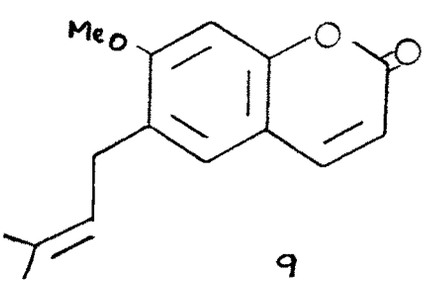

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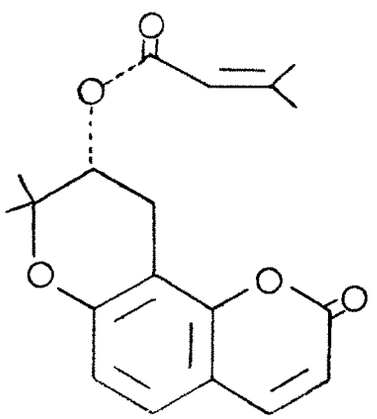

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(iii) Furocoumarins with substituents at one or both of the remaining benzenoid positions, e.g. Psoralen (12), Angelicin (13), Xanthotoxin (14)

(iv) 3-Phenylcoumarins e.g. Pachyrrhizin (15)

(v) 4-substituted coumarins they are 4-alkylcoumarins, 4-OH coumarins, 4-phenyl coumarins e.g. Mammein (16), Dicoumarol (17), Dalbergin (18).

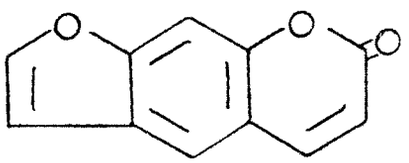
(vi) 3-Phenyl-4-OH-coumarins, e.g. Scandinin (19).

(vii) 3,4-Benzocoumarins, e.g. Ellagic acid (20)

Coumarins generallyabsorb a wide range of UV light and generate intense fluorescence usually blue. The occurence of coumarin types I, II, III is very frequent while that of others is rather rare. Although all are basically coumarins but some classify 3-phenyl derivatives as isoflavanoids, 4-phenylcoumarins as neo isoflavanoids while others classify 3-phenyl coumarins as coumestans.

Properties

Simple coumarin is the sweet smelling constituent of white clover. It is the internal lactone of 2-hydroxy cis cinnamic acid, and the ring is opened with alkalis giving salts of coumarinic acid. Bromine[2] adds up easily to the



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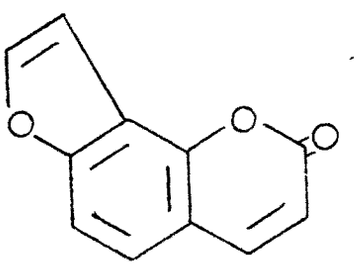

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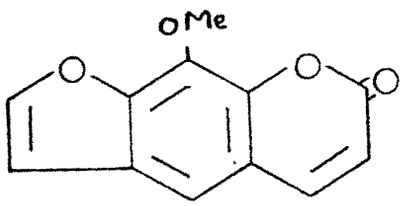

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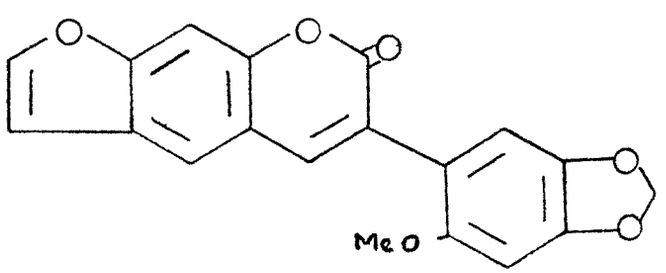

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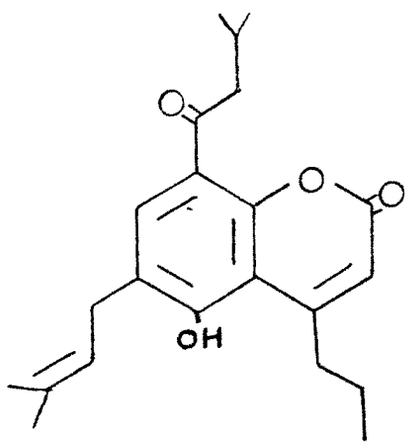

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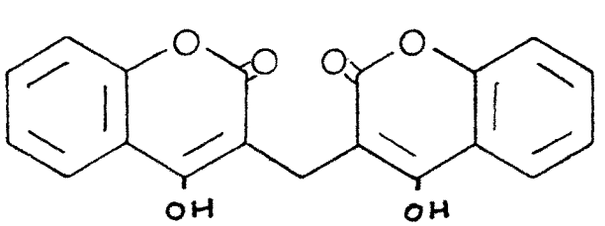

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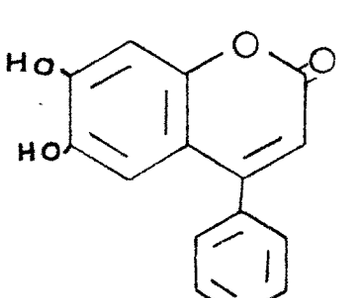

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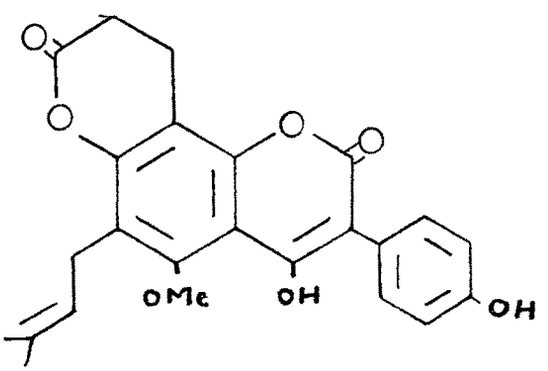

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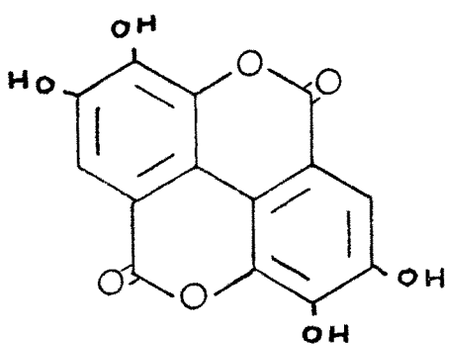

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3,4 double bond giving a dibromide which readily looses HBr, to give 3-bromocoumarin. Electrophilic attack on coumarin as exemplified by nitration or diazo coupling takes place at position 6.[3]

Identification

Many natural coumarins and synthetic derivatives are highly fluorescent. The fluorescence is directly related on environmental factors such as pH and solvent polarity. Fluorescence is useful in locating and recovering natural coumarin spots on a chromatogram without the use of chemical spray.

Goodwin and Kavangh[4,5] studied the fluorescence of a large number of coumarins as a function of pH. However they could not establish a clear relation between the structure and fluorescence.

UV Spectroscopy

UV absorption spectra are useful for distinguishing coumarins from chromones. Chromones normally have a strong absorption at 240-250 nm where as coumarins have a minimum at this wavelength. The substitution of a methyl group or larger chain alkyl groups normally does not effect the

absorption characteristics of the coumarins while the introduction of a hydroxyl group into coumarin nucleus causes a bathochromic shift and the positions of the new maxima depends on the ability of hydroxyl group to conjugate with chromophoric system.

5,7-Dioxygenated coumarins and 7,8-dioxygenated coumarins have very similar spectra and resemble to those of 7-oxygenated coumarins except that the maxima between 250 and 270 nm are slightly intense. A 6,7-dioxygenated coumarin can be readily differentiated from a 5,7 or a 7,8 dioxygenated since the two strongest bands are found at ≈230 and 340-350 nm while the two bands of almost the same intensity appear at ≈260 nm and 300 nm.[6]

Similarly linear furocoumarins which has a pattern at 240-255, 260-270 and 290-316 nm[7] can readily be distinguished from angular which do not show maxima at 240-255 nm and 260-270 nm as they are the characteristics of the linearity.

IR Spectroscopy

IR spectroscopy is principally used in detecting the functional groups. Apart from identifying the functional groups, IR spectra is useful in revealing the conjugated lactone function. Coumarins are isomeric with chromones

but these two differ considerably in their IR pattens. The carbonyl stretching frequency in coumarins (α-pyrones) is observed in the region 1700-1750 cm^{-1} where as in chromones (γ-pyrones) it is at 1650 cm^{-1}. It is observed[8] that psoralens show C=O band at a frequency higher than 1720 cm^{-1} when an alkyl group is attached to C-5 with C-8 unsubstituted, but when the alkoxyl group is at C-8, a frequency lower than 1720 cm^{-1} is found.

The IR spectra of pyranocoumarins show a strong absorption at 1717-1730 cm^{-1} which shifts to 1735-1750 cm^{-1} in dihydropyranocoumarin. 3-Aryl coumarins with a free hydroxyl group at C-2' show the carbonyl absorption at 1660-1680 cm^{-1}. This is presumably due to the intramolecular hydrogen bonding between the 2'-hydroxyl and the pyrone carbonyl group.[9-10]

NMR Spectroscopy

A wide range of NMR techniques have been applied to the structural elucidation of naturally occuring coumarins. The most important publication is of Steck and mazurek,[11] who in 1972 drew up spectra-structure correlation rules. These are very helpful in arriving possible structure for any novel or unfamiliar coumarin which the researcher encounters.

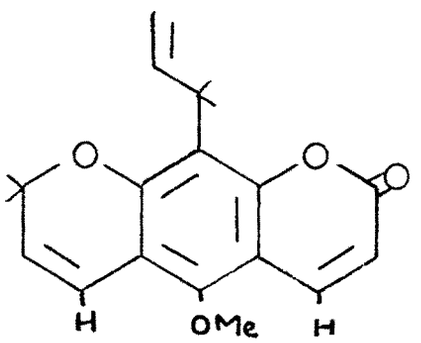
Observation of a pair of doublets J=9.5Hz centered

at δ 6.1-6.4 and 7.5-8.3 in the H^1 NMR spectrum in $CDCl_3$ normally reveals that the coumarin is unsubstituted in the pyrone ring. These characteristic signals are of C_3 and C_4 protons respectively.

Many 7-oxyginated coumarins are known with alkyl or alkoxylgroups at C_8. The signals for H-5 is found at δ7.3 downfield from H-6 which resonates at δ 6.8. The presence of these two ortho related protons can be recognised instantly since they give rise to another pair of doublets having coupling constants of 9Hz. An exception is angelicin which exhibits a sharp two-proton singlet at δ 7.37, this chemical shift is so close to that of protons of benzene δ7.36. This is due to the anisotropic effects of furan and pyrone rings on these protons which are approximately equal but opposite in sign.[12]

Some times measurement of nuclear Overhauser effects provide considerable assistance in assigning the geometry of the coumarins especially when all the four positions on the benzonoid ring are substituted. In the absence of benzene ring protons, as many as 12 possible structures have theoretically been possible for each natural product.

In Poncitrin (21) the methoxy substituent is at C-5.



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On saturation of the methoxy signal at δ 3.82, the integrated intensities of the doublets arising from H-4 and H-4' were increased by 9% and 13% respectively. From this it was concluded that the methoxyl group must be close to H-4 and hence must be located at C-5 and also proximate to the pyran ring which therefore had to be linearly fused.[13,14]

^{13}C Spectroscopy

With the introduction of ^{13}C NMR spectroscopy attention has been directed towards naturally occuring coumarins and a number of useful publications have appeared in which complete assignment of ^{13}C Chemical shifts and extensive assignments of carbon-proton coupling have been presented.[15-17]

The chemical shift of carbonyl carbon atom has been found to be approximately the same δ160 for most of the coumarins. The chemical shift for simple coumarin are as follows :

C_2 160.4, C_3 116.4, C_4 143.6, C_{4a} 118.8,
C_5 128.1, C_6 124.4, C_7 131.8, C_8 116.4 and
C_{8a} 153.9

The effect of hydroxyl and methoxy groups on the benzenoid is quite characteristic. In that, the signal from the newly formed quarternary carbon atom is found approximately 30 ppm

downfield from the value observed in coumarin, while the carbons ortho and para to the substituent move upfield by ≈ 13 and ≈ 8 ppm respectively.[18]

^{13}C NMR spectroscopy have proved valuable for identifying the coumarin glycosides, not only the characterisation of glycoside, but also the exact position of sugar substitution in coumarin glycosides.

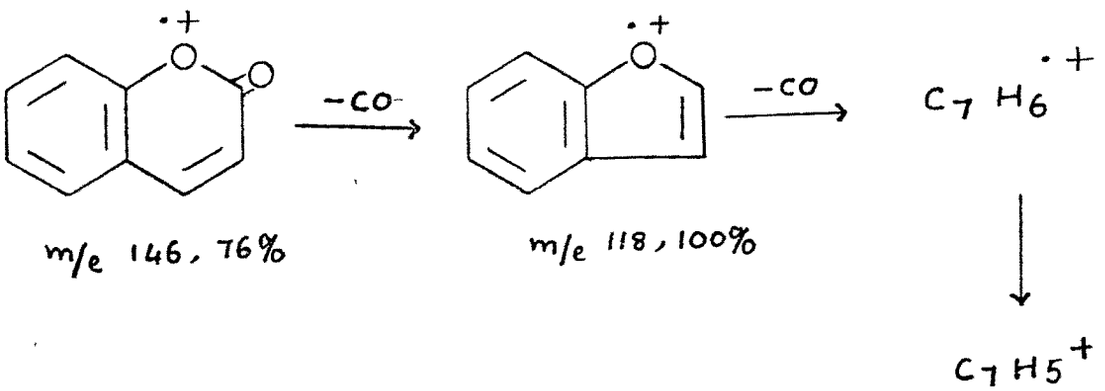
Mass Spectroscopy

The mass spectra of coumarins are characterised by intense molecular ion peak indicating stable heterocyclic ring system. Coumarin givesa strong molecular ion (M^+, m/e 146, 76%) on electron impact and a base peak (m/e 118, 100%) 28 mass units lower. The latter ion formed directly from the molecular ion by the loss of carbon monoxide from the pyrone ring[19,20] resulting a molecular ion benzofuran, which further looses consecutively CO and hydrogen atom. [Scheme-1]

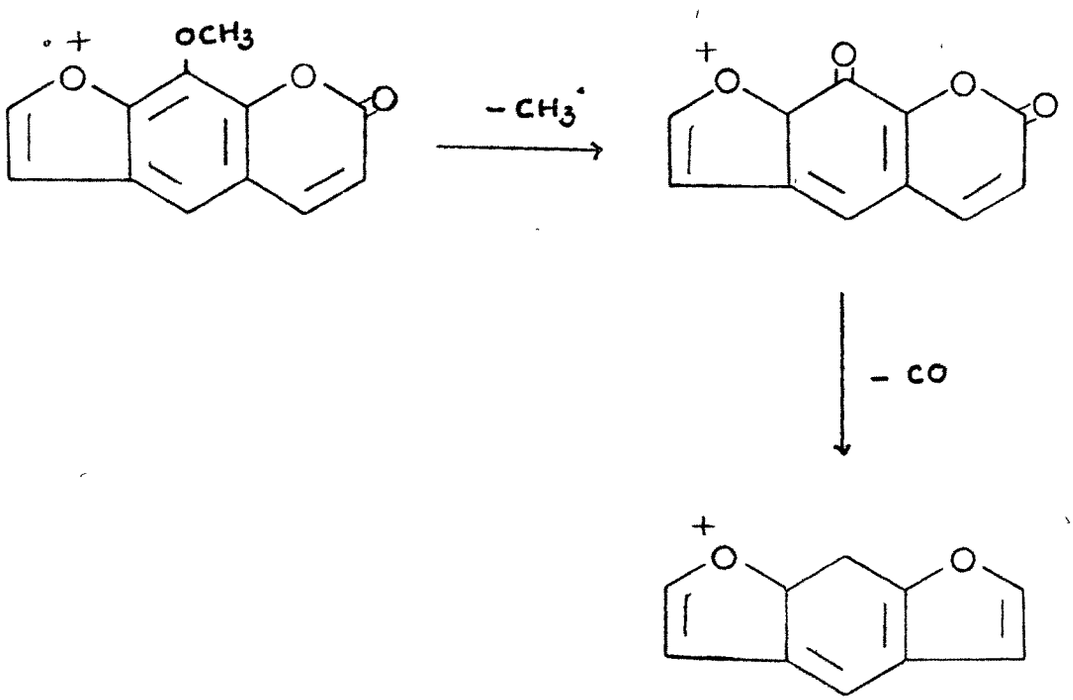
This kind of fragmentation is normally observed in coumarins with the exception 4-OH coumarin where the characteristic loss of CO is absent, instead a loss of C_2H_2O probably ketene is observed.[21]

The presence of a furan ring in furanocoumarins normally

SCHEME-1



SCHEME-2



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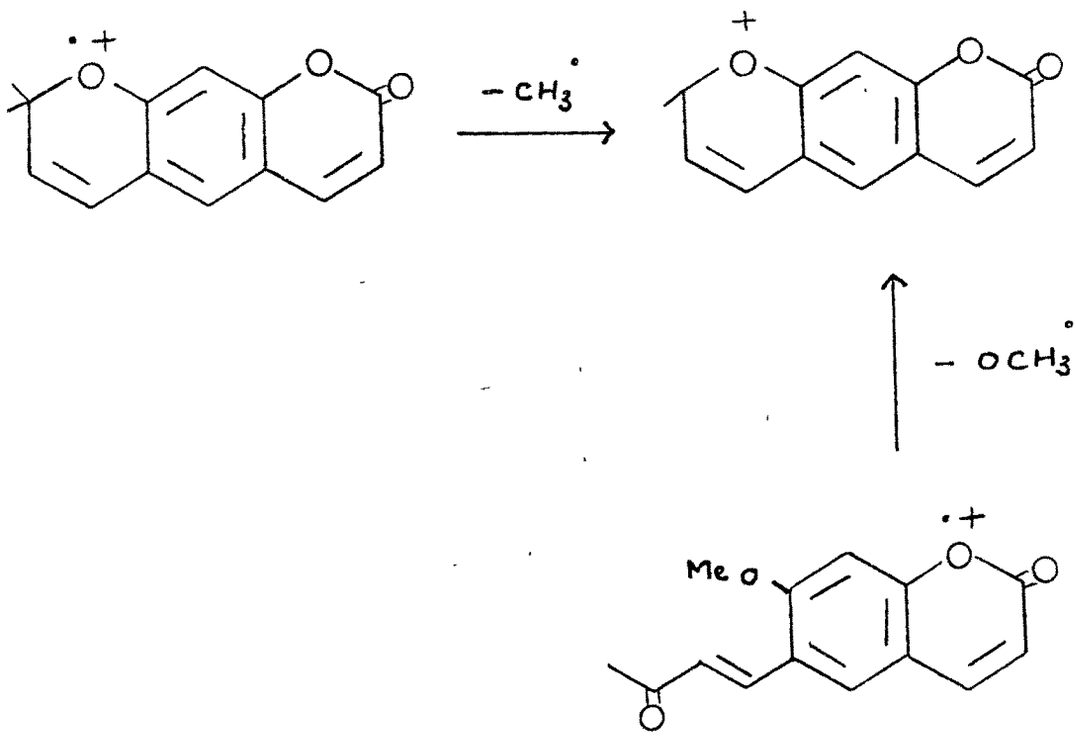


does not alter the fragmentation. However in methoxy furanocoumarins such as in xanthotoxin, loss of methyl radical give rise to conjugated oxonium ion.[19] [Scheme-2] while in the mass spectrum of 2,2'-dimethylpyrano coumarin, the loss of methyl radical is dominated giving the benzopyrylium ion which is the base peak. The stability of such ions is revealed by the observation of loss of 31 mass units in Suberenon also.[22,23] [Scheme-3]

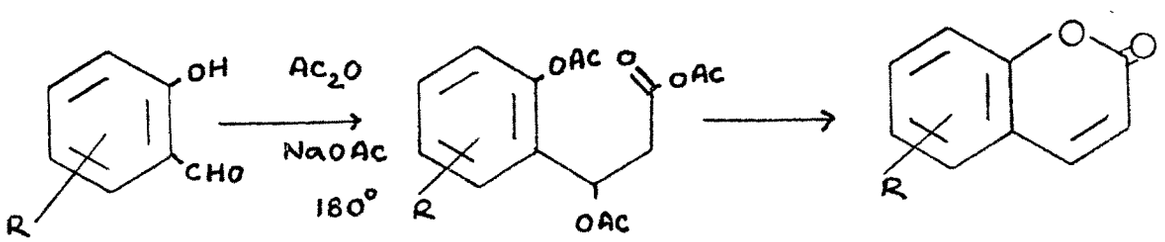
Methods of Synthesis

Total synthesis of many natural coumarins have been achieved by many workers. The key step in many cases has been the formation of pyrone ring. In some cases a phenol containing the requisite substituents of the natural coumarin has been prepared first and this then modified by steps such as nuclear oxigination, O or C-alkylation and building up of additional rings.

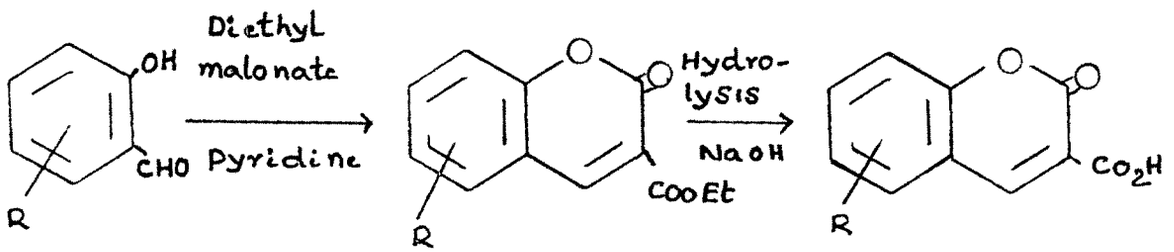
Many novel approaches have been developed for the formation of pyrone ring by many workers. The following are some popular methods to synthesise coumarins, Perkin synthesis, Knoevenagel condensation, Pechmann sydnthesis and Pechmann and Duisberg method. [Scheme-4]

SCHEME-4

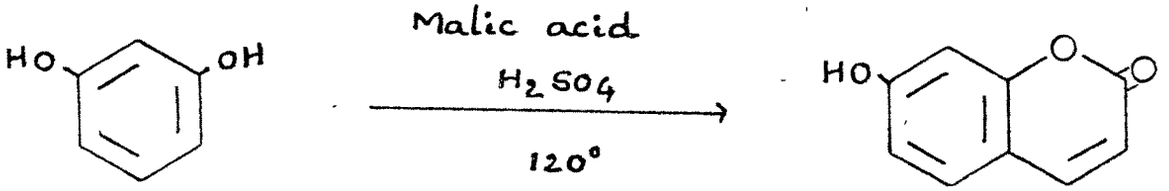
PERKIN SYNTHESIS



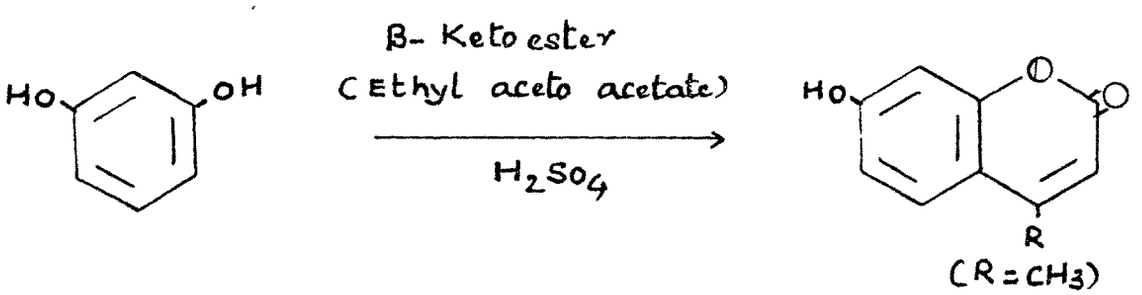
KNOEVENAGEL CONDENSATION



PECHMANN SYNTHESIS



PECHMANN and DUISBERG METHOD



Two main difficulties encountered with Perkin reaction are, the preparation of the requisite ortho hydroxy benzaldehyde to make coumarin and poor yields. Pechmann[24] reported an alternative method to overcome the problems associated in preparing suitable o-hydroxybenzaldehyde. In this phenol is heated with malic acid and sulphuric acid at 120° untill the gas evolution is complete. But many phenols do not undergo the reaction and so furocoumarins can not be prepared by this method due to the sensitivity of furan ring towards acids.

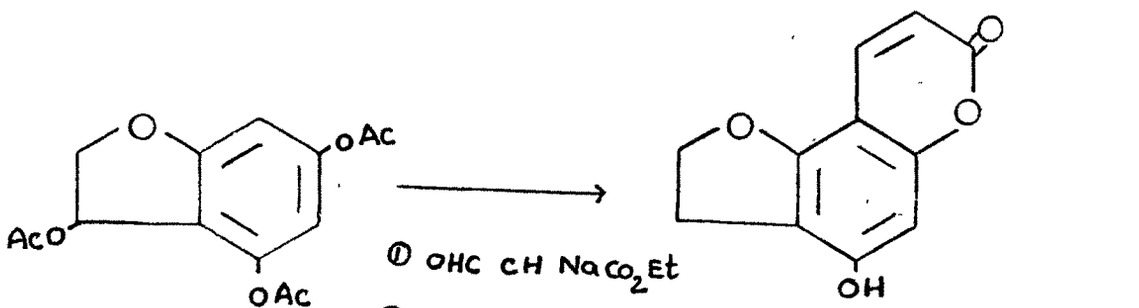
As a modification of Pechmann synthesis, Spath et al.[25] used sodium salt of ethyl 3-oxopropanoate in a sealed tube for condensation to make Furanocoumarins [Scheme-5].

A related two step process of limited applicability has also been developed.[26,27] In this phenol is condensed with methyl acrylate or acrylonitrile under acidic conditions to give 3,4-dihydrocoumarin which on dehydrogenation with Pd/c in refluxing diphenylether furnish coumarin. [Scheme-6]

Many times appropriately substituted phenols may prove difficult to get, to synthesise some naturally occuring coumarins. In order to overcome the difficulty for the introduction of oxygen functionally in to the benzonoid

SCHEME-5

Spath et al [25]



Allo bergaptol (major)

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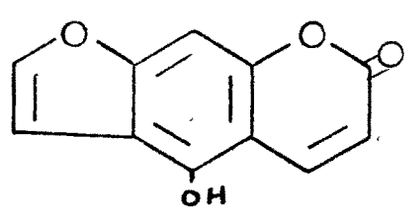
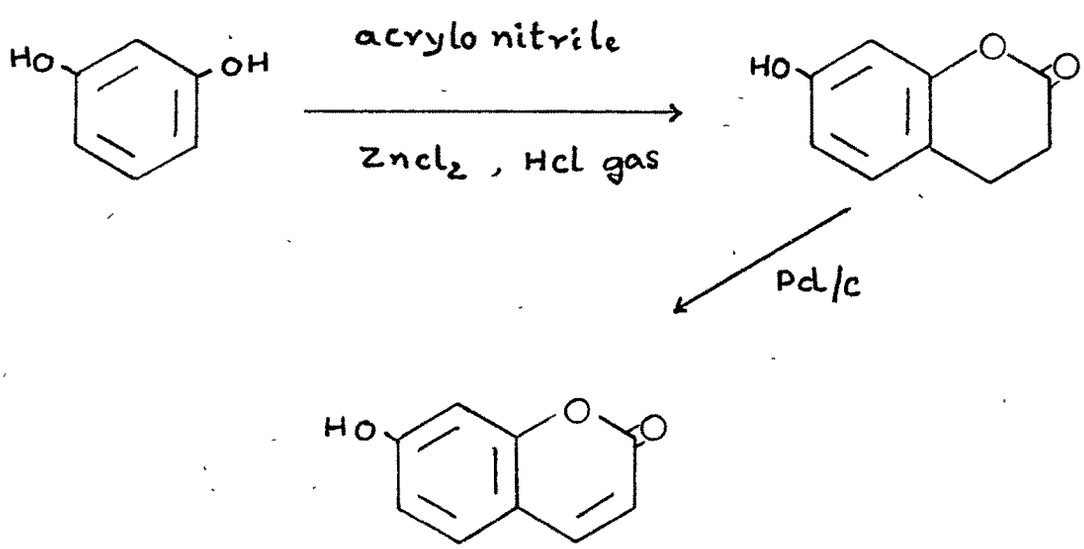


bergaptol (minor)

SCHEME-6

Sen et al [26], Usgaonkar et al [27]



SCHEME-7

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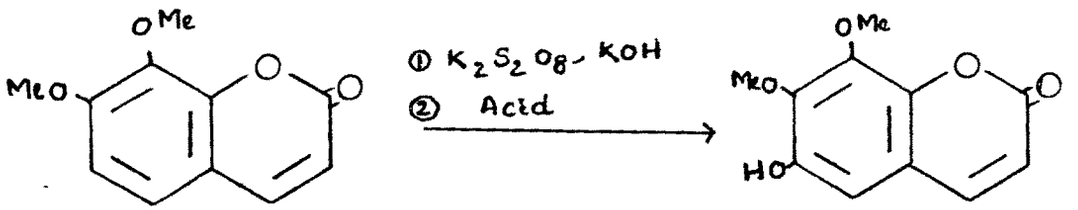
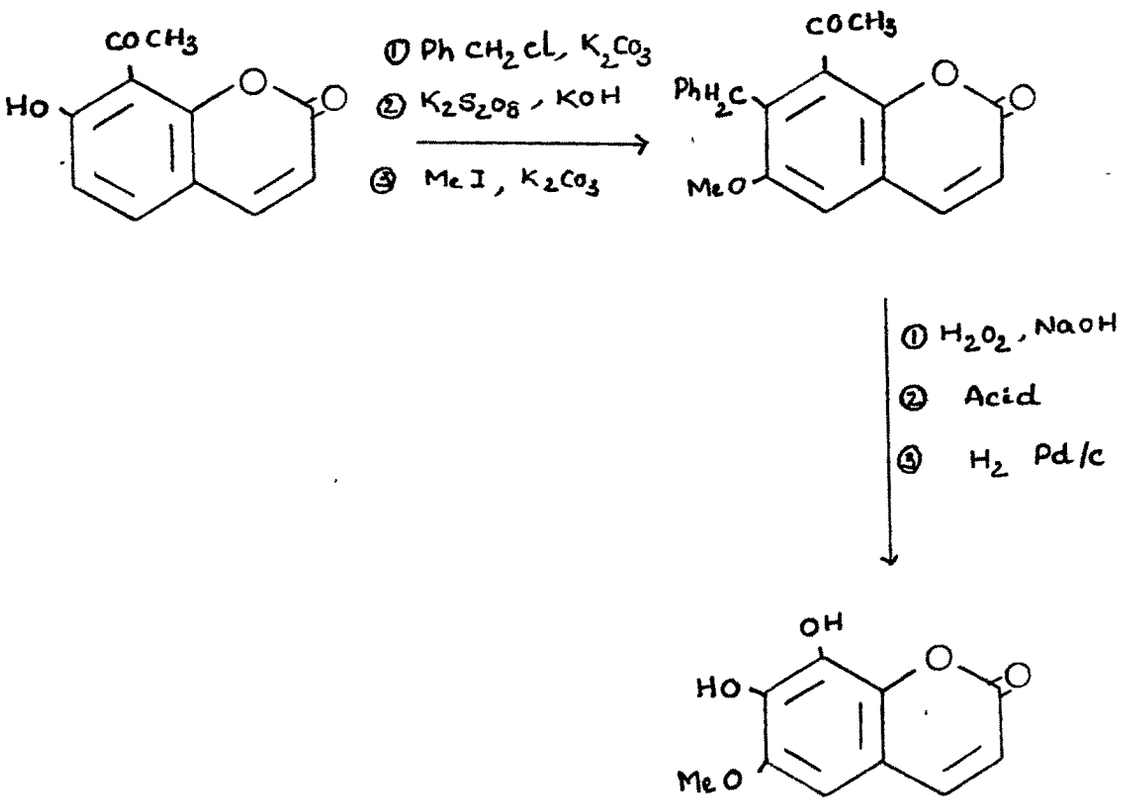
BERGELLINI and MONTI METHOD



(Ayscotin)

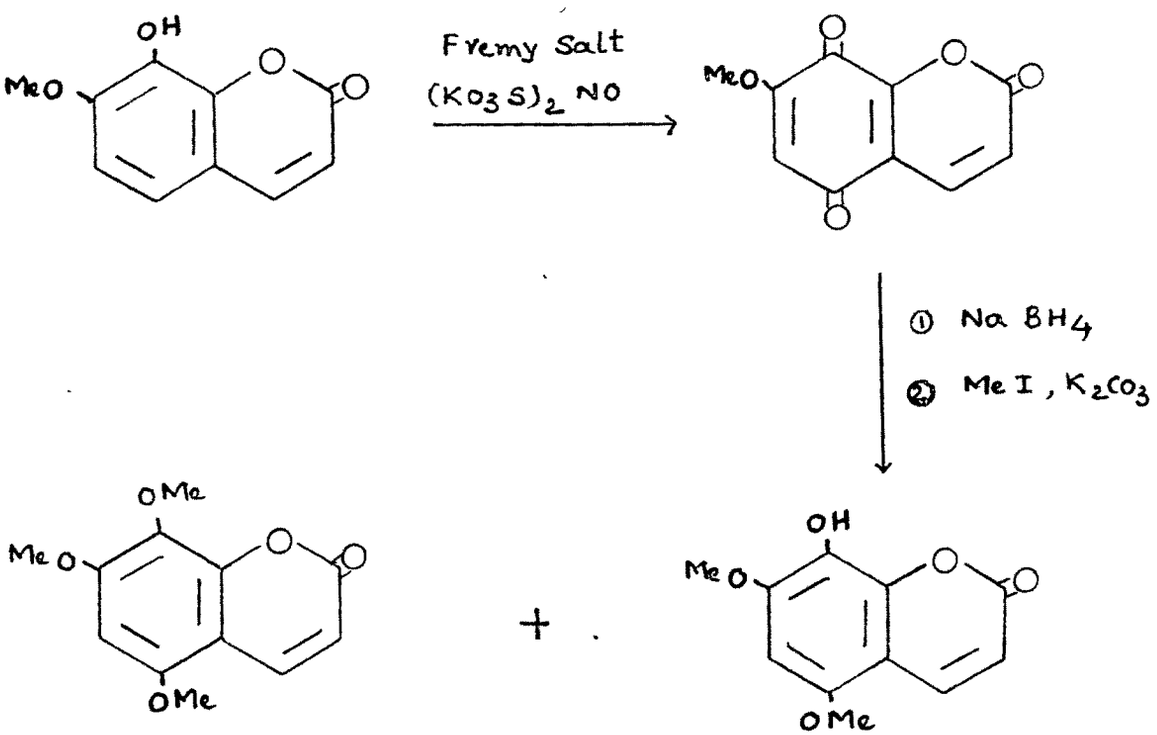
29

CHAUHAN and MATHUR METHOD

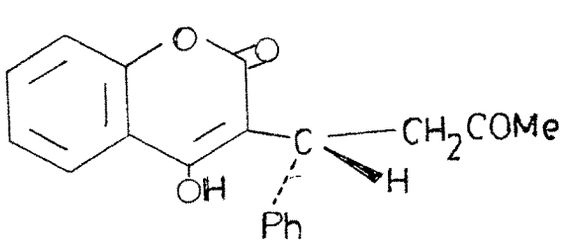


(Fraxetin)

DEAN et al[30]



laptodactylone



ring after the construction of basic coumarin, methods have been developed by Bergellini and Monti,[28] Chauhan and Mathur[29] and Dean et al.[30] [Scheme-7]

All most all natural coumarins contain one or more alkyl or functionalized alkyl groups attached to oxygen. Consequently to synthesise many natural coumarins methods have been devised for affecting both O- and C-alkylations regiospecifically. O-Alkylation may be affected by heating acetone solution of phenol with allyl bromide and anhydrous K_2CO_3. A large number of allyl ethers, prenyl ethers and cinnamylethers have been prepared by using this method. Some of them are natural coumarins while others served as precursors for C-alkylated coumarins in Claisen rearrangement. Many consider this as very convenient route to synthesise furocoumarins.

Pharmacological properties

Coumarins and its derivatives created considerable interest due to their varied physiological and bio-chemical properties.

Coumarin itself inhibits the germination and root growth of the plants. Coumarin in high concentration 100-1000 ppm inhibits or markedly retards the germination of the

spores which shows that coumarins act mainly as fungistatic agent rather than fungitoxic.[31] It also suggest, that coumarins cntrol the pathways of metabolism involved in the utilization of energy.

From the ancient times Chinese, Tibetians used coumarins containing plants in the medicines. Yang, Ling-Ling et al.[32] nearly isolated three dozen coumarins from Taiwanese plants and Chinese crude drugs.

Coumarins are well known for anticoagulant and rodenticidal properties. A naturally occuring toxin present in Clover is a 4-OH coumarin derivative. This property has been well exploited in pharmaceuticals and are used in the treatment of cardiovascular diseases e.g. Warfarin (22) developed as redenticide is a useful anticoagulant drug.

Jean La Barve et al.[33] synthesised 3- (acetonyl benzoyl)-4-hydroxy coumarin (22) and reported that it is less toxic (LD_{100} in guinea high 647 mg/1 Kg) and has stronger and more rapid anticoagulant effect in the rabit. In the clinical trials stabilisation of the prothrombin rate is obtained from 7th day of treatment and easy to maintain, overdosage is rapidly reversed by Vitamin K.

Mentzer reported[34] that in 3,3'-methylene bis (4-hydroxy-coumarin) or dicoumarol which isanother important anticoagulating agent, the presence of hydroxyl groups are responsible for the activity and methylation or acetylation destroys the activity.

3-Allyl-4-hydroxy, 3-cinnamyl-4-hydroxy and 3-p-nitro-cinnamyl coumarin are also as active as Dicoumarol but 3-methyl-4-OH coumarin shows an opposite behaviour and behaves like Vitamin K.[35]

3,4-Diamino coumarins and 4-amino-thio coumarins reported to have neutropic activity. Simple diamine was a weak depressant on the CNS system. Substituents on the 4-amino group increase CNS activity.[36]

Coumarins with furan ring system are toxic to fish. Psoralens are photochemotherapeutic agents in the treatment of psoriasis, vitiligo and certain viral, bacterial and fungal infections.[37,38]

Besides, the derivatives of coumarins found to have blood cholesterol lowering activity[39] and anti-spermatogenic activity.[40]

3-Aryl coumarins and 3,4-diarylcoumarin derivative[41] have potential carcinostatic and virusstatic properties. Some 3-phenylcoumarin derivatives possess optical brightening properties for fabrics also.

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