CHAPTER-I

INTRODUCTION

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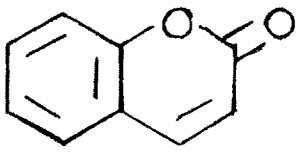
Benzopyran-2-ones, generally known as coumarins are widely occuring natural products.[1,2] They are found in plants with four major families, the Umbelliferae (e.g. parsley, parsnip, celery, ammi majus, Angelica archangelica), Rutaceae (e.g. Bergamot fruit, lime gas plant, cloves, common rue) ; Leguminose (psoralea corylifolia, xanthoxylum flavum) ; and Moraceae (e.g. Ficus cariea).[3] They are found in all parts of plants from roots to leaves, fruits and flowers.

The word coumarin originates from caribbean word coumarou[4] for tonka tree which was botanically known as coumarouna odorata Abul. Coumarin is the accepted trival name for compound (1) and the parent name for the group of naturally occuring lactones. Some of the naturally occurring coumarins are Umbelliferon (2) Aesculetin (3) Ayapin (4) Daphentin (5) and Scopoletin (6).

STRUCTURAL TYPES

Apart from coumarin (1), recently found in Onoseries hyssopifolia[5,6,7] all natural coumarins bear oxygen atoms at one or more of six available nuclear positions as phenolic, etheral or glycosidic groups. Many Reviewers[8-14] have classified coumarins according to whether the structures were one of the following types :

(1) Simple, which has implied coumarin (1) and its hydroxylated, alkoxylated, alkylated derivatives and their glycosides.



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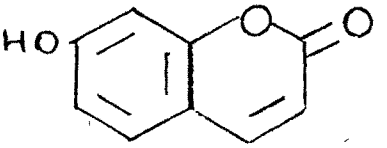

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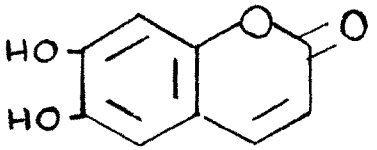

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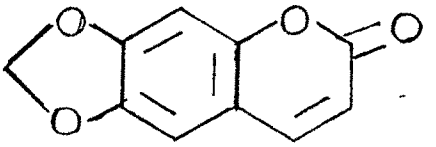

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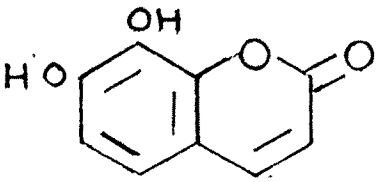

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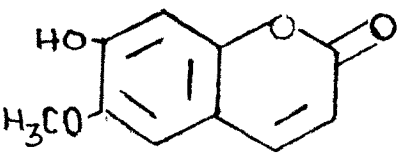


(6)

(2) Furocoumarins, linear psoralen (7) type or angular, angelicin (8) type with substituents at one or both of the remaining benzenoid positions and including dihydrofurano coumarins.

(3) Pyronocoumarins, six membered ring analogues of (2).

(4) Coumarin substituted in the pyrone ring such as 4-hydroxy coumarin (9), 3-phenyl coumarin (10) and 3,4-benzocoumarin.

Some important linear and angular furo-benzopyran-2-ones are as follows :

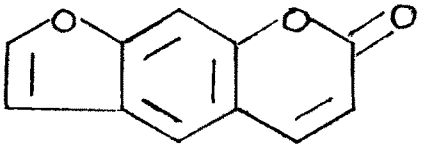
Bergaptan (11), Xanthotoxin (12), Pimpillin (13) and Oreoselene (14).

EXTRACTION AND ISOLATION

The majority of naturally occurring coumarins have been isolated from higher plants and from microorganisms. For isolation of coumarins dried plant material is extracted with different solvents in order as light petroleum ether, benzene, ether, acetone, methanol and ethylacetate. The solvents are evaporated and the products are purified by column chromatography.[15-21]

PHARMACOLOGICAL PROPETIES

Coumarins have anticoagulent, antifungal, insecticidal and photochemotherapeutic properties.



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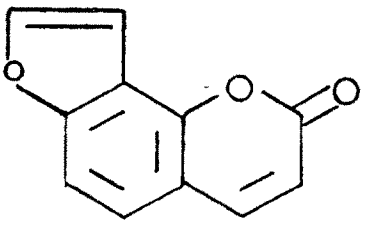

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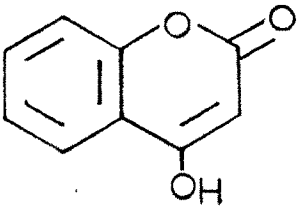

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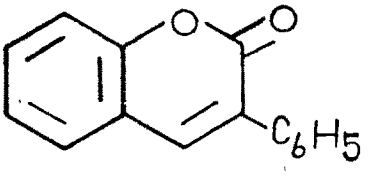

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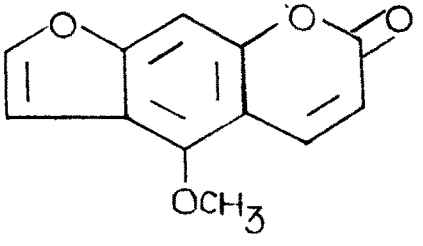

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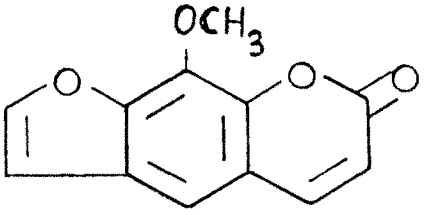

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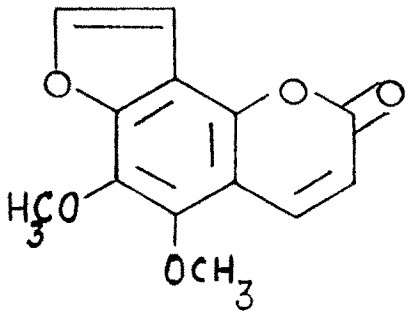

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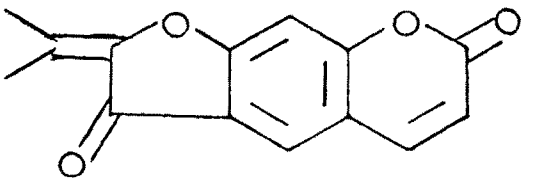

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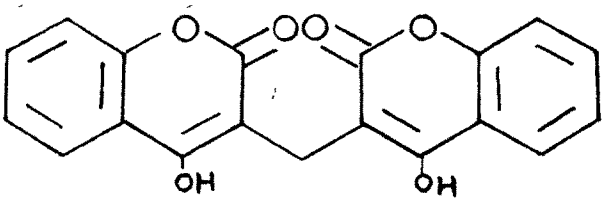

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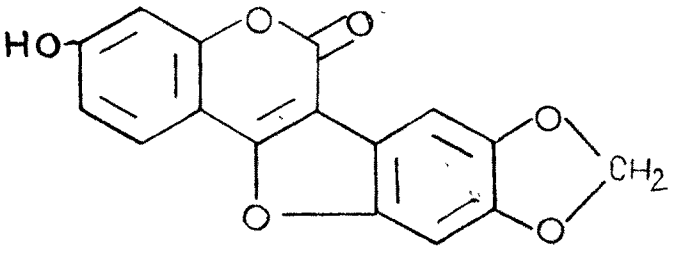


(16)

Coumarin(1) itself inhibits the germination and subsequent root growth of plants. It shows toxicity against p. infestans and inhibits the phytophthora growth. It acts as narcotic for some animals and as a sedative and hypnotic for mice.[22] Coumarin and some of its derivatives having melting point lower than 70-100°C have been found to have strong anthelmintic action[23] while many natural coumarins, particularly those with furan ring systems are toxic to fish. Kelb[24] observed toxic effect of coumarin on alge and Singmund[25] observed the effect of both daphentin and its isomer esculetin on seed germination.

Psoralens are photochemotherapeutic agents in the treatment of psoriasis, leucoderma, vitiligo and certain viral, bacterial and fungal infections.[26,27] The antiproliferative activity of psoralens is useful in skin diseases characterised by hyperproliferative conditions.

L. Fountain[28,29] has tested antiinflammatory and anticoagulent activity of 4-hydroxy coumarin derivatives into rats, guinea pigs and rabbits. Yen Teh Fu[30] and his coworkers have shown 4-hydroxy coumarin and its analogs or heparin and its analogs as anticlotting agents. They inhibit formation of prothrombin and of thrombin and thromboplasting respectively. Both classes have their own antagonists namely protaminesulfate and vitamin K types exhibiting antihemorr-

hagic properties. K.P. Link[31] discovered the haemorrhagic principal of sweet clover as 3,3'-methylenebis-(4-hydroxy) coumarin or dicoumerol (15) which led to the preparation and testing of several 4-hydroxy coumarins as anticoagulent drugs. Number of very effective drugs of this group such as warfarin, coumachlor and marcoumar are in market. Novobiocin,[31a] an antibiotic isolated from streptomyces sp., has found to be a 4-hydroxy coumarin derivative.

It is quite interesting to note that some simple coumarins have the opposite effect. Harmarin and ayapin have been found to possess remarkable haemostatic property and are active both in vivo and vitro.[32] They are well tolerated by and are nontoxic to rabbits. Some 4-hydroxy coumarin derivatives are also active against mycobacterium tuberculosis, fungicidal agents and inhibits aggeregation of thrombocytes. 7-hydroxy-3-methyl coumarin, 3-methyl-4-hydroxy coumarin and aesculetins showed significant chloretic activity into rats.[33] Hydroxylation at position 7 was favourable for activity while 5 or 8-methyl substitution decreases activity.

Coumestans (16) are a new class of compounds which were isolated from alfalfa[34] are closely related to antifungal agent pistin. Coumestrol(17) is a non-stereoidal estrogenic substance and has effect on lipid metabolism in male rat. R.L. Lyman[35] has shown that coumestrol has definite estro-

genatic effect on the uterus of young female rat but is inactive or apparently non-toxic for adult male animals.

7-Dimethyl amino-4-methyl coumarin is used as optical brightening agent for cellulose, polyacrylonitrile polyamides and polyester fibres.

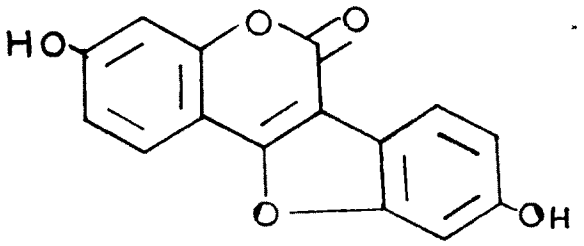
METHODS OF SYNTHESIS

Simple coumarin was prepared by Perkin reaction of o-hydroxybenzaldehyde with sodium acetate and acetic anhydride. Acetate ion adds to aldehyde group and is trapped as the acetate which gives rise to simple coumarin [Scheme-1].

Perkin reaction was employed for the synthesis of umbelliferone,[37] aesculetin[38] and dephentin. Two main difficulties encountered in Perkin reactions are preparation of requisite o-hydroxybenzaldehydes and the poor yields observed in some cases.

Knoevenagel condensation of o-hydroxybenzaldehyde with diethylmalonate in hot pyridine gives corrosponding 3-carbethoxy coumarin which on hydrolysis with 10% sodium hydroxide gave corrosponding coumarin-3-carboxylic acid in good yields[39] [Scheme-2].

Pechmann[40] reported his synthesis, an alternative method to overcome the problem of Perkin reaction. In this method, suitable phenol was heated with malic acid and sulfuric acid



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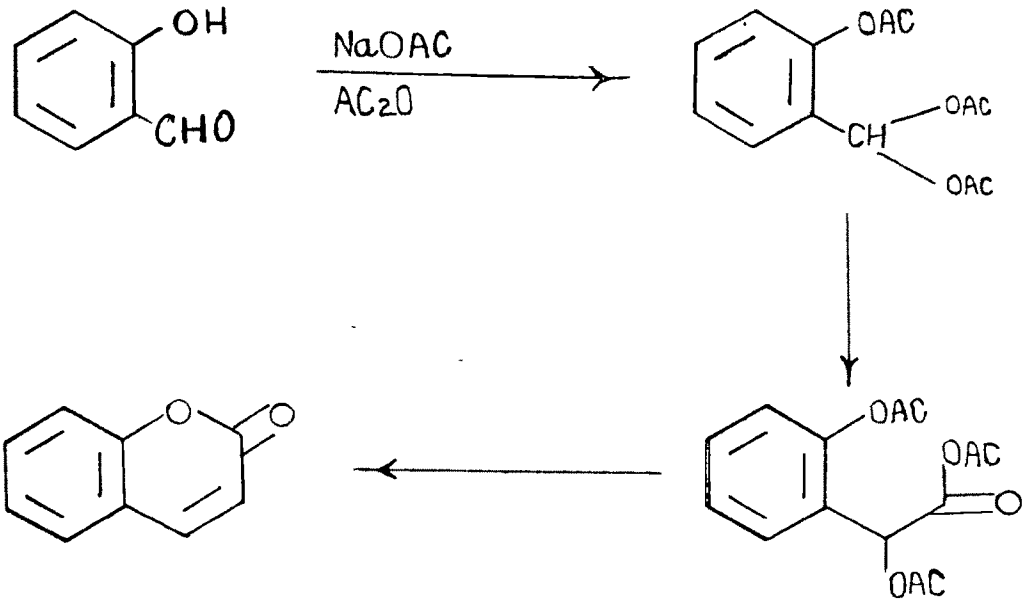
Scheme-1 Perkin Method



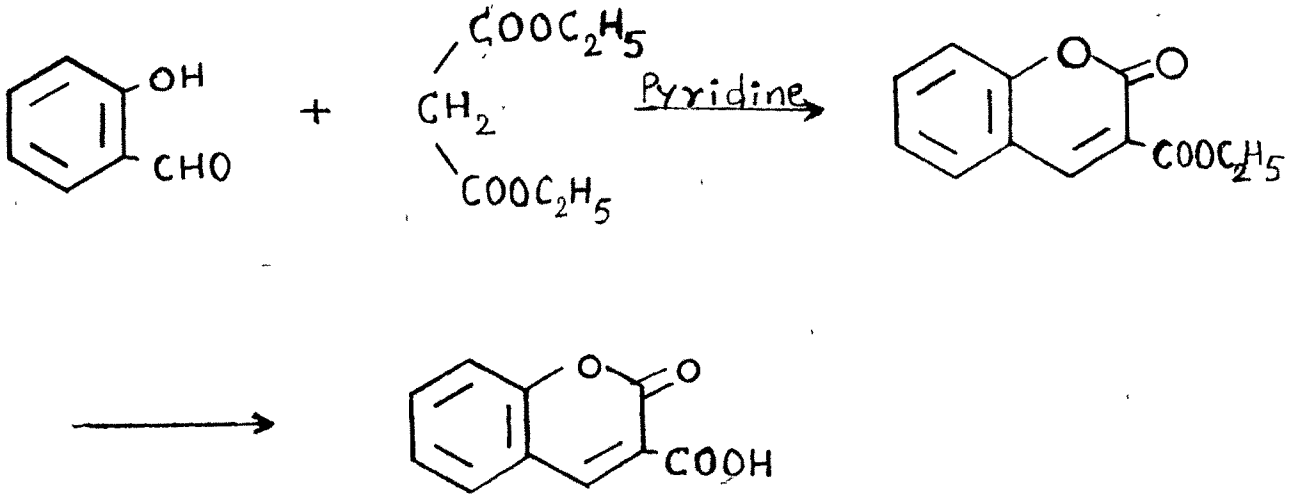
at 120°C until gas evolution is complete. 7-Hydroxy coumarin was obtained by this method from resorcinol and malic acid [Scheme-3].

Pechmann and Duisberg[41] found an easy method to prepare 4-substituted coumarins in good yields by using condensation of β-keto-esters with different phenols in presence of concentrated sulfuric acid. This method has wide scope. 7-Hydroxy-4-methyl coumarin was prepared from resorcinol and ethylaceto-acetate [Scheme-4].

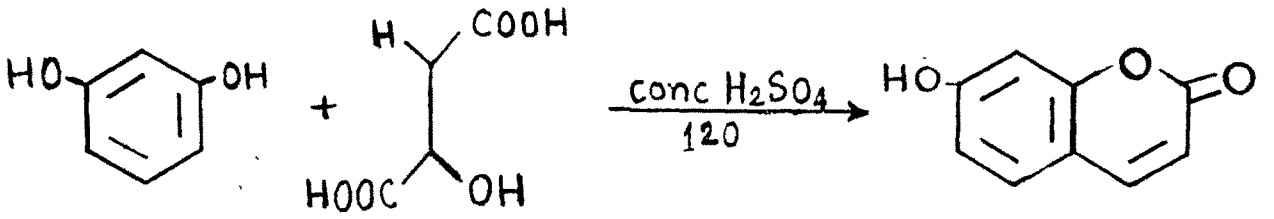
Later Kaufmann and kelly[42] in 1965 found that 5,7-dihydroxy coumarin could be prepared in one step by heating a mixture of phloroglucinol dihydrate, ethyl propynoate and zinc chloride [Scheme-5].

There are number of methods available for the synthesis of 4-hydroxy coumarins. In simplest, a phenol is treated with equimolar amount of malonic acid and two molar amount of zinc chloride and phosphoryl chloride at 60-70°C[42] [Scheme-6]. Many other coumarins have been synthesised by this method.[43,44] Hoesch condensation of phenols with ethylcyno-acetate followed by acid hydrolysis also afford 4-hydroxy coumarin.[45] The intermediate imine was obtained in 90% yield which on acid hydrolysis gave corrosponding 4-hydroxy coumarin [Scheme-7].

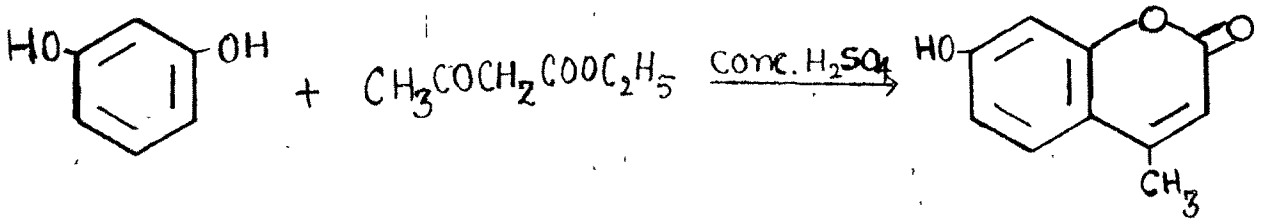
Scheme-2 Knoevenagel Condensation[39]



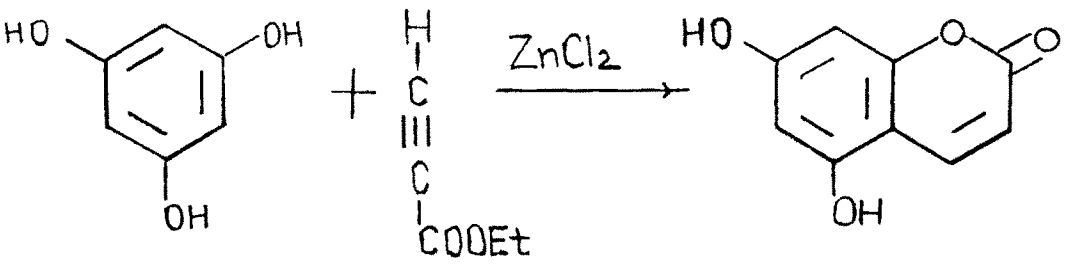
Scheme-3 Pechmann Condensation[40]



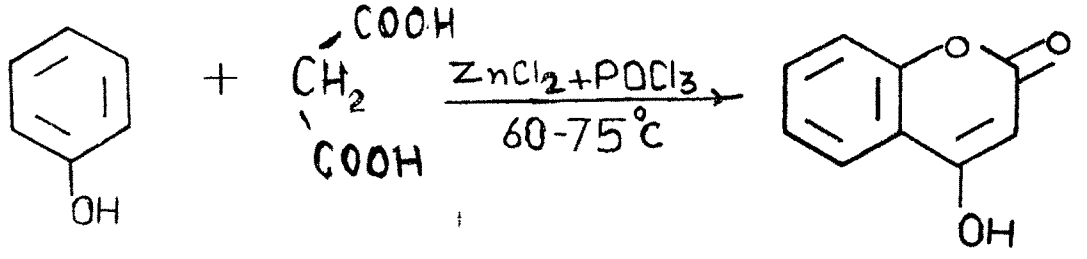
Scheme-4 Pechmann and Duisberg[41]



Scheme-5 Kaufmann and Kelly[42]



Scheme-6



Boyd and Robertson[46] obtained 4-hydroxy coumarin by condensation of o-hydroxyacetophenones with sodium and diethyl-carbonate [Scheme-8].

3-Aryl-4-hydroxy coumarin[47] was obtained from treatment of o-hydroxyphenylbenzylketone with methylchloroformate and potassium carbonate. Emerson and Bickoff[47,48] obtained coumestrol by this procedure followed by demethylative ring closure using hot anilinium chloride [Scheme-9].

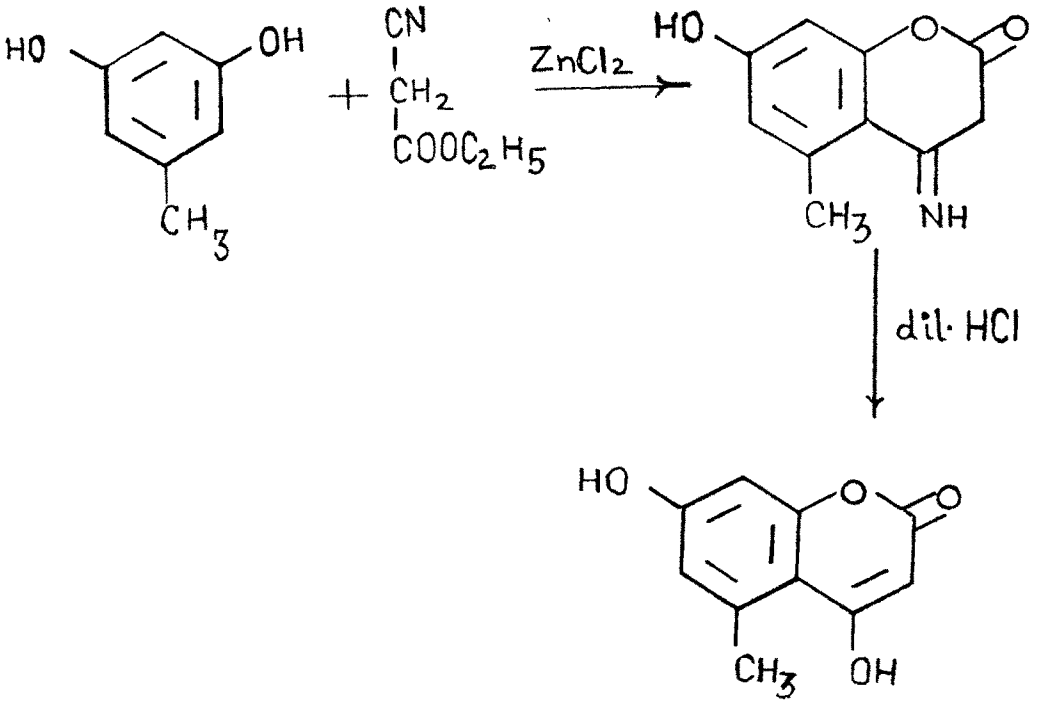
There are number of methods available for the synthesis of different coumarin derivatives. They have been reviewed by Sethna and Shah.[49]

CHARACTERISATION; CHEMICAL AND SPECTRAL METHODS

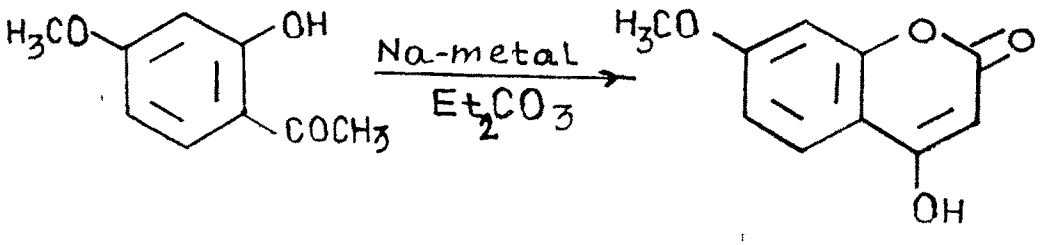
In many of earlier comprehensive reviews[6,9,10,12,13,45,50] there is discussion of chemical investigations employed in structural elucidation of natural coumarins. They have been found to undergo variety of interesting chemical transformations.

All coumarins react withalkali which opens up the lactone ring to o-hydroxy cinnamic acid which generates original coumarin on acidification. When refluxed with strong alkali coumarin breaks up to give the starting phenol [Scheme-10).

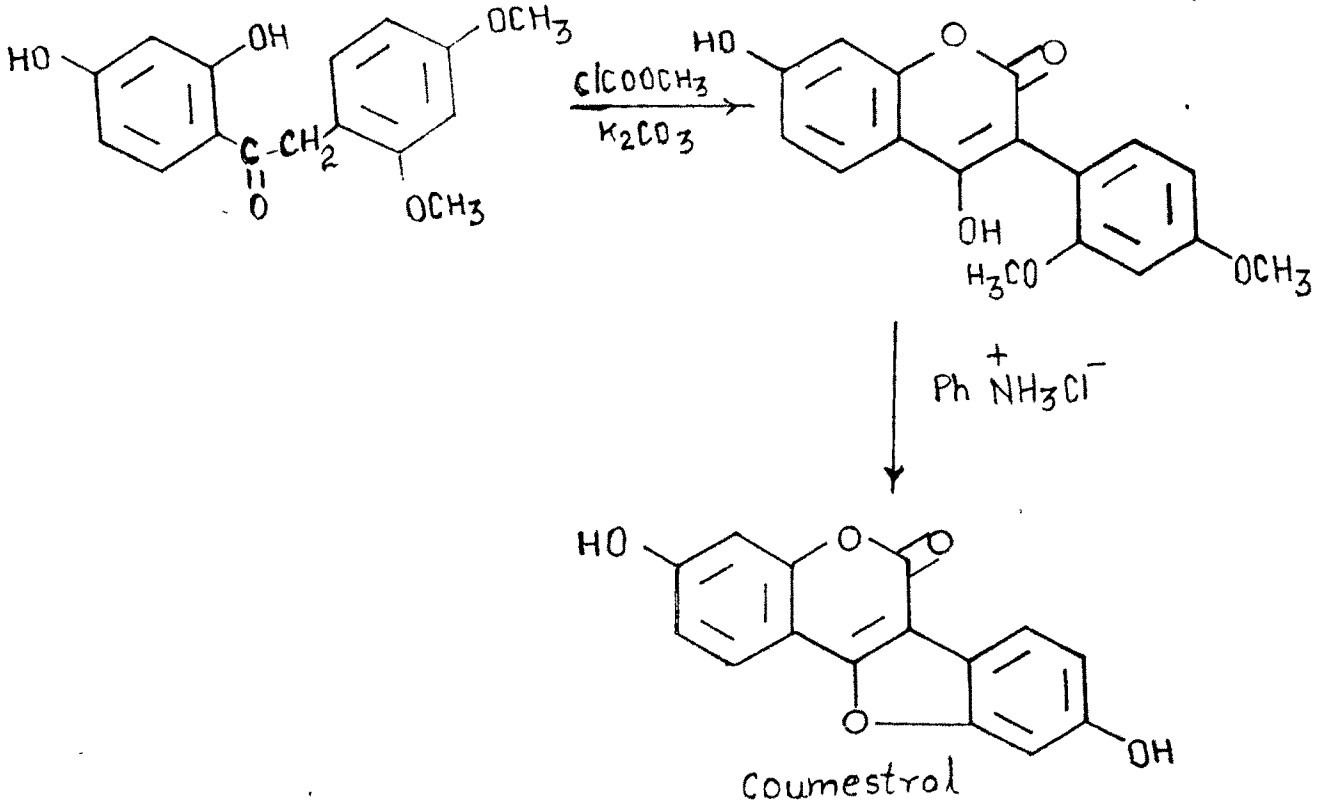
Scheme-7



Scheme-8 Boyd and Robertson[46]

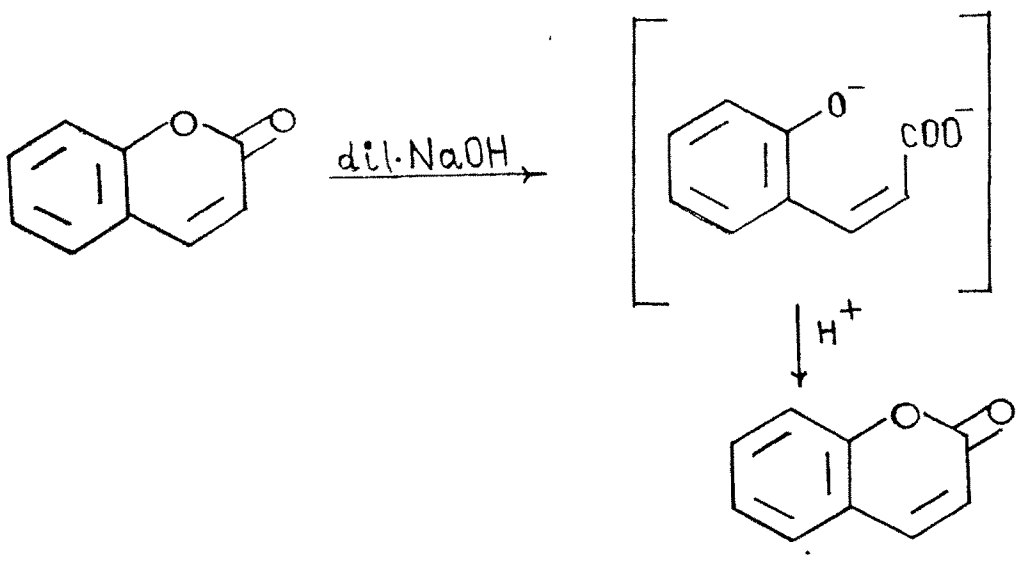


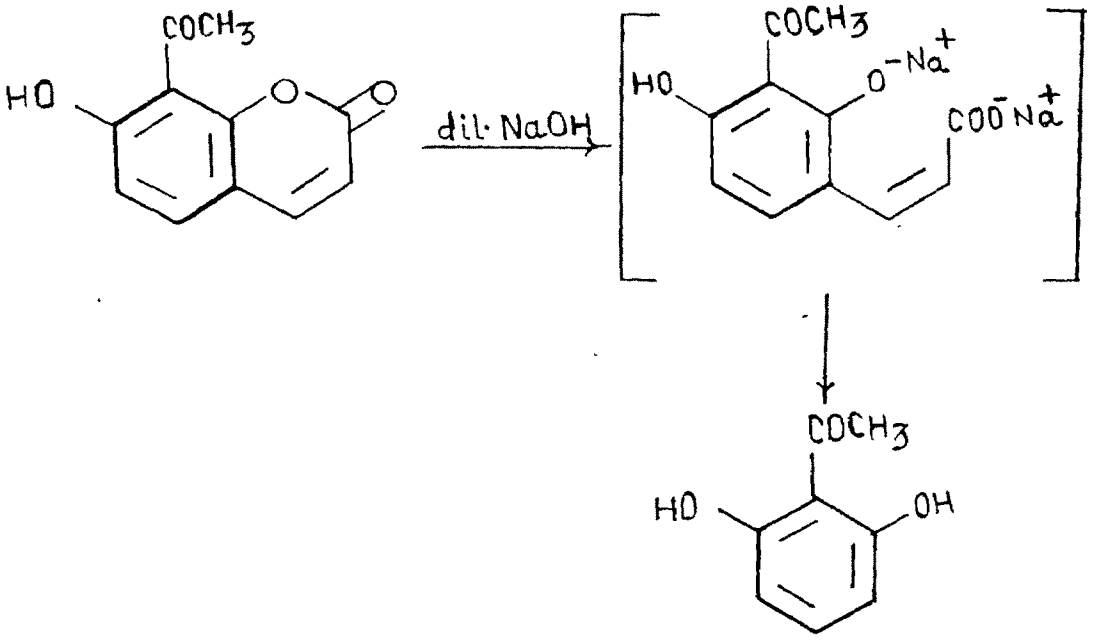
Scheme-9 Emerson and Bickoff[48]



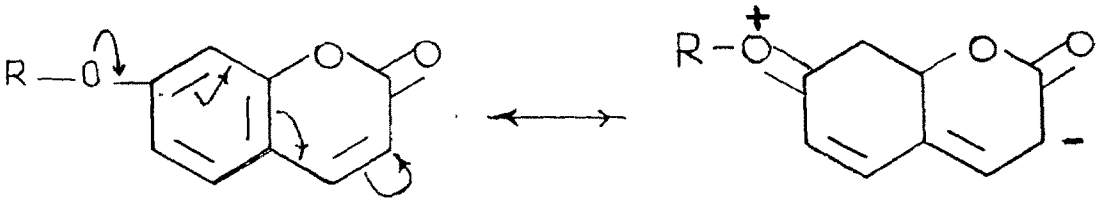
Coumestrol

Scheme - 10





Scheme -11



U/V SPECTROSCOPY

UV absorption spectra are useful for distinguishing coumarins from chromones. Chromones have a strong absorption at 240-250 nm ($\log \epsilon$ 3.8) whereas coumarins have a minimum at this wavelength. Coumarin shows absorption bands at 274 and 311 nm ($\log \epsilon$ 4.03 and 3.72) which are of benzene and pyrone ring respectively.[51] Substitution of methyl group at C-3 leads to small hypsochromic shift in 311 nm while substitution at C-5, C-7 or C-8 leads to a bathochromic shift of the 274 nm leaving 311 nm max. unchanged.

The introduction of hydroxy group into the coumarin nucleus causes bathochromic shift of the principal absorption band. The position of new maximum depends on the ability of the hydroxyl group to conjugate with the chromophoric systems.

UV spectroscopy and spectral change induced by the addition of acid or alkali are particularly useful in deducing the orientation of the acyl groups in mammea type 4,6,8-trisubstituted-5,7-dihydroxy coumarins[17,52-54] The acyl group may be at C-6 or C-8 leads to characteristically different UV base shifts. In 4-alkyl series, the long wavelength band at $\sim$ 325 nm in spectra of 6-acyl coumarin undergoes large bathochromic shift to $\sim$ 400nm, on addition of alkali while in contrast 8-acyl coumarins shows only a small bathochromic

shift and replacement of the absorption near 290 nm with a weaker absorption near 260 nm. Similar is the case with 4-phenyl coumarins.

Linear and angular furo coumarins can be easily distinguished by their maxima. Linear furocoumarins show four zones of absorption at 205-225 (log ϵ 4.0), 240-255 (log ϵ 4.06-4.45), 260-270 (4.18 - 4.26) and 298-316 nm (3.85 - 4.13)[55] while in case angular furocumarins maxima at 240-245 and 260-270 are absent which are characteristic of linear furocoumarins.

IR SPECTROSCOPY

Two or three bands of weak to medium intensity have been observed in the region 3025-3175 cm^{-1} in the spectra of furano coumarins due to C-H stretching vibrations of the pyrone, benzene and furan rings.[56]

The pyrone-carbonyl stretching frequency of coumarin is usually found in the region 1700-1750 cm^{-1}.[55,56] The IR spectra of pyranocoumarins show a strong absorption band at 1717-1730 cm^{-1} which shifts to 1735-1750 cm^{-1} in dihydropyranocoumarins. The C=C skeletal vibratins show three strong absorption bands in region 1600-1660 cm^{-1} in IR spectra of coumarins, which differentiate it from isomeric chromones, the absorption of which is generally much simpler.[10]

Furocoumarins show two bands in region 1088-1109 and 1253-1274 cm^{-1} due to C-O stretching vibrations of the furan group and bands in 740-760 and 870-885 cm^{-1} regions due to in plane and out plane deformations respectively of furan C-H bands.[57]

^{1}H NMR SPECTROSCOPY

Coumarins with substituents at different positions give signals at different field, in NMR spectra.[58] The characteristic signals arise from H-3 and H-4 protons as a pair of doublets J=9.5Hz, centred at δ 6.1-6.4 and 7.5-8.3 in ^{1}H NMR spectra. The majority of natural coumarins have an oxygen function at C-7 which by electron release [Scheme-11] leads to an increase in electron density at C-3, compared to simple coumarin thereby causing the resonance of H-3 to move to higher field by $\sim$ 0.17 ppm.[59]

Electron release by an oxygen at C-5 has similar, though smaller effect, since this involves less favourable orthoquinonoid electron distribution.[59]

Measurements of nuclear Overhauser effects have proved to be considerable assistance in assigning the geometry of certain unsaturated side chains and have been especially useful in structure elucidation of number of coumarins in which all four positions on the benzenoid ring are substituted.[60,61]

^{13}C SPECTROSCOPY

^{13}C spectroscopy has become a sensitive and powerful tool in structural elucidation of natural products. There are many publication in which complete assignment of ^{13}C chemial shifts have been given for hydroxy and methoxy coumarins[62,63] prenylated and related coumarins[63,64] furanocoumarins and dihydrofurano coumarins.[64,65]

The chemical shift of carbonyl carbon atom has been found to be approximately the same δ 160 for most coumarins. The chemical shifts 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 methoxyl groups on the benzenoid ring is quite characteristic. In that the signal from the newly formed quarternary carbon atom is found approximately30 ppm downfield from the value observed in coumarin, while the carbons ortho and para to the substituent move upfield by $\sim$ 13 and $\sim$ 8 ppm respectively.[66]

MASS SPECTROSCOPY

The mass spectra of coumarins are characterised by intense molecular ion peak indicating stable heterocyclic ring system. The latter ion is formed directly from the molecular ion by loss of carbon monoxide (CO), highly stable neutral particle from the pyrone ring.[67,68] Thus benzofuran

ion formed, further fragmented by typical loss of CO and hydrogen atom consecutively [Scheme-12].

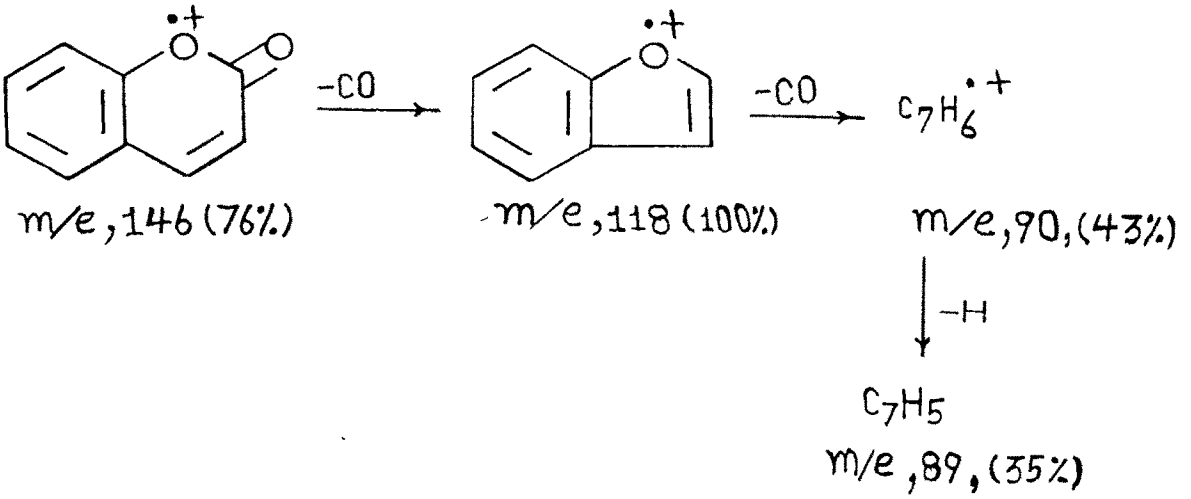
When ring A is substituted [Scheme-13], charge lies on ring A, then goes to ring B with the loss of $-C_2H_2O$ in case of 4-hydroxy coumarins. If ring B is substituted, still charge lies on ring A with the typical loss of CO and $-CH_3$ depending on substituents [Scheme-14].

The presence of furan or pyran ring in furano or pyrano-coumarins does not alter the fundamental fragmentatin process observed in simple coumarins, namely the easy elimination of CO from the pyrone ring. But in case of methoxy substituted furano or pyrano coumarins, the fragmentation pattern is dominated by loss of methyl group and generation of stable benzofurylium or benzopyrylium ion[67] followed by loss of CO ion [Scheme-15].

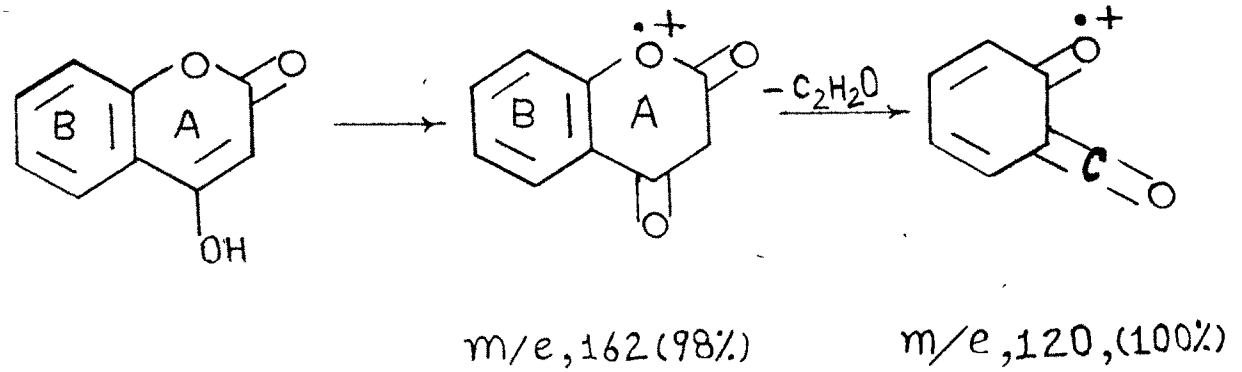
REACTIONS OF COUMARINS

Bergelline and Monti[69] discovered that coumarins can be hydroxylated at C-6 by alkaline potassium persulfate. The lactone ring opens in the alkaline medium, liberating a phenol from which phenolate anion is immediately generated. In ensuing Elbs persulfate oxidation, hydroxy group at the activated para position is inserted. Acidification then regenerates lactone ring giving rise to 6-hydroxy coumarin [Scheme-16].

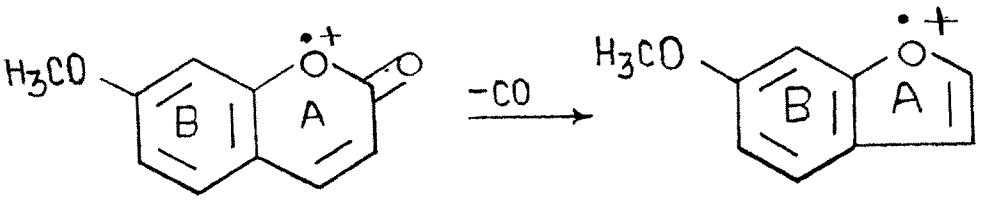
Scheme -12



Scheme -13

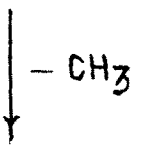


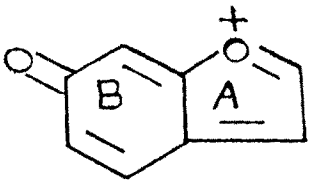
Scheme-14



m/e, 176, (100%)

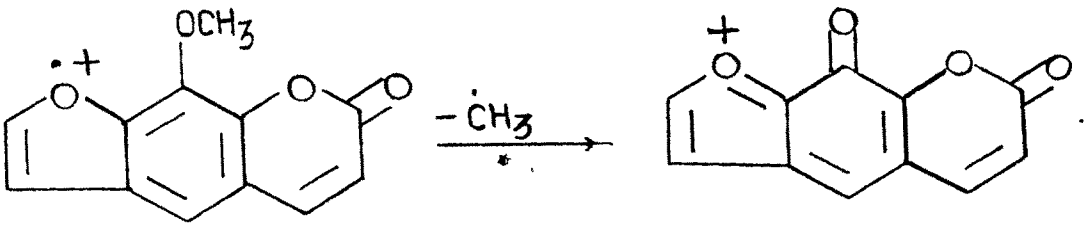
m/e, 148, (82%)





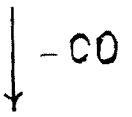
m/e, 133, (83%)

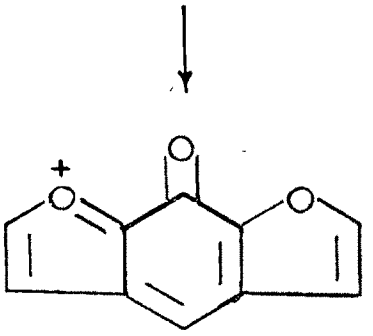
Scheme-15



m/e, 216, (100%)

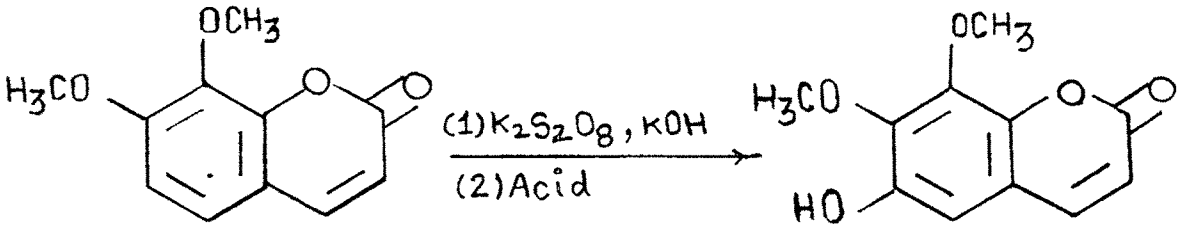
m/e, 201, (22%)





m/e, 173, (56%)

Scheme-16



Phenolic hydroxyl group of coumarin behave normally and can be alkylated or acylated[70] easily. C-alkylation of coumarins[71,72] is also easily possible. Coumarins can undergo different reactions such as halogenation[73-76] (chlorination, bromination, iodination), chloromethylation,[77] nitration[79] and formylation.[78]

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