BASE CATALYSED HYDROLYSIS OF CERTAIN FUROCOUMARINS

DISSERTATION

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By

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Chapter 1

Coumarins and their reactivity

Coumarins are naturally occurring oxygen heterocycles[1]. They contain a benzo-α-pyrone (2*H*-1-benzopyran-2-one) (I) nucleus as the main structural unit. A considerable number of hydroxyl- and methoxy-coumarins, and their glycosides, have been isolated from plant sources[2] and chemically synthesized[3].
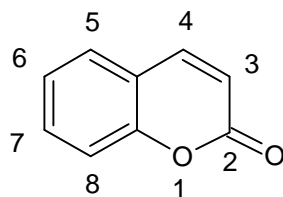

(I)

1.1 CLASSIFICATION OF COUMARINS

Coumarins are classified on the basis of their chemical structure into the following types[4]:

1) Simple coumarins: coumarin (I) and its hydroxylated, alkoxylated, alkylated derivatives and their glycosides.

2) Furanocoumarins: coumarins containing a furan ring fused to the benzopyrone nucleus including dihydrofurocoumarins, for example psoralen (II), furo[3, 2 *c*]coumarins (III).

3) Pyranocoumarins: six membered ring analogues of furocoumarins. eg. Xanthyletin (IV).

4) Coumarins substituted in the pyrone ring: 3 or 4 substituted coumarins like 4-hydroxycoumarins (V), 4-phenylcoumarins (VI) and 3, 4-benzocoumarins (VII).

5) Isocoumarins: lactones of benzenecarboxylic acids with a hydroxylated side chain unsaturated in the β-position, isomeric with coumarins (VIII).
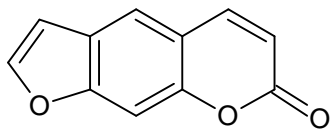
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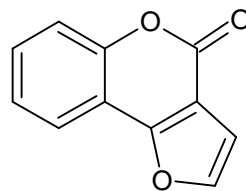
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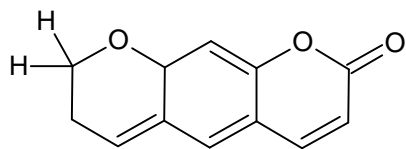
(IV)

(V)

(VI)

(VII)

(VIII)

Coumarins show a wide range of biological activities. They are used as anticoagulants[5], antifungals, antibacterials, insecticides[6], antioxidants[7], anti-HIV[8] and antitumour agents[3]. They
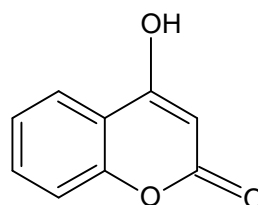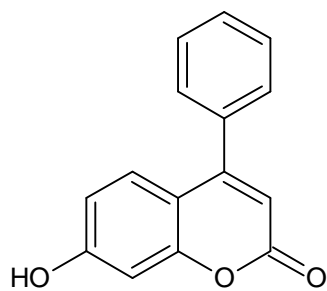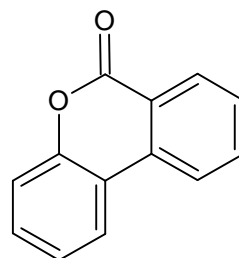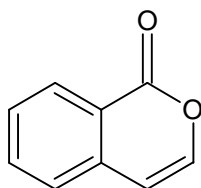
are central nervous system active compound[9] and possess urease inhibitory properties[10]. Due to their bitter-sweet fragrance, they are used as additives in pipe tobacco, alcoholic beverages, perfumes, cosmetic products, soaps and detergents[3]. Coumarin and its derivatives have been tested for the treatment of schizophrenia[11], microcirculation disorders, angiopathic ulcers[12] and high protein edemas in animals[13]. They are also used in dye lasers[14] and in electroplating[15].

1.2 CHEMICAL REACTIVITY OF COUMARINS

Coumarins are easily attacked by electrophilic and nucleophilic reagents. The pyrone ring shows little aromatic character. As such the double bond between C3-C4 undergoes usual addition reactions such as Diels–Alder reaction[1], bromine addition[16].

Coumarin is not protonated by aqueous acids, but with triethyloxonium tetrafluoroborate it gives the 2-ethoxy-benzo[b]pyrylium salt (IX)[17], (Scheme 1).

80%

(IX)
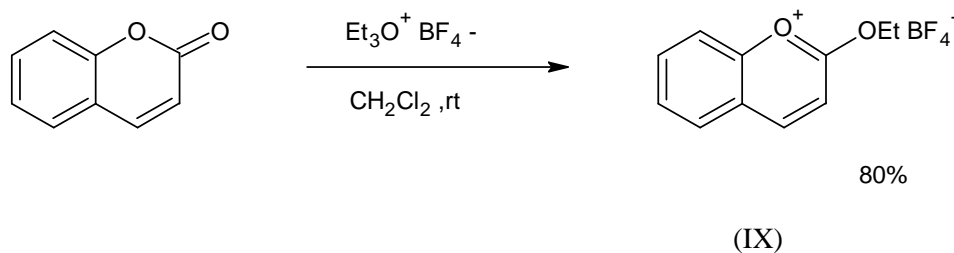
Scheme 1

Chloromethylation[18] occurs at C-3 whereas nitration[19] and sulphonation cause C-6 substitution (Scheme 2). C-3 halogenation is achieved with Copper (II) halides/ alumina in refluxing chlorobenzene[20]. Bromine in the presence of excess of aluminium chloride converts coumarin into 6-bromocoumarin[21].
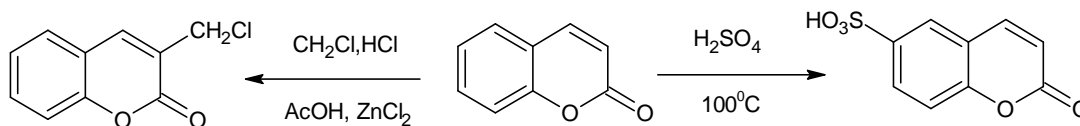
Scheme 2

The photochemical properties of coumarins have been extensively studied. In the absence of a sensitizer a syn head-to-head dimer is obtained and an anti isomer (X) is formed by using benzophenone as the sensitizer[22], (Scheme 3). The syn head-to-tail dimer is obtained by irradiation in acetic acid. Sensitizer promoted cycloaddition of coumarins or 3-acyl-oxycoumarins, with alkenes, ketene diethyl acetal or cyclopentene yields cyclobutane containing products[23].

96%

(X)
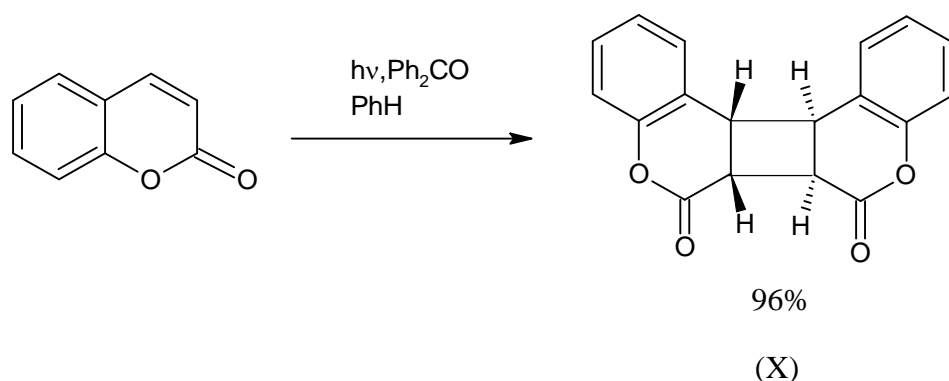
Scheme 3

1.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

a) Carbon nucleophiles:

Grignard reagent initially attacks at the carbonyl carbon and in many cases a mixture of products is obtained resulting from ring opening of the carbonyl adduct. Coumarin (I) reacts with a second molecule of Grignard reagent to give 2, 2-dimethylchromene (XI) and the products(XII) resulting from opening of the lactone ring[24], (Scheme 4).With milder nucleophiles such as cyanide anion the addition occurs at C-4.
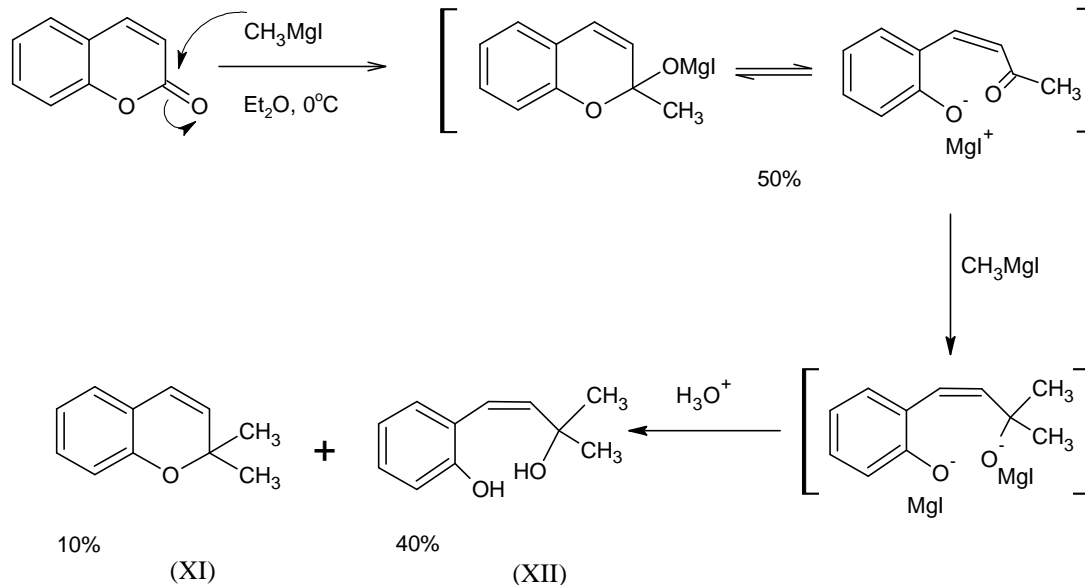
Scheme 4

b) Ammonia and amines:

Coumarins do not react with ammonia and amines to produce α-quinolones, even under forced conditions[17]. The reaction is not favourable since it involves a non-aromatic intermediate.

c) Hydroxides and other bases:

The reaction of coumarins with hydroxides involves initial addition to the carbonyl carbon, followed by opening of the lactone ring to give yellow solutions of the salts of the corresponding *cis*-cinnamic acids (coumarinic acids)[5] (XIII), (Scheme 5).
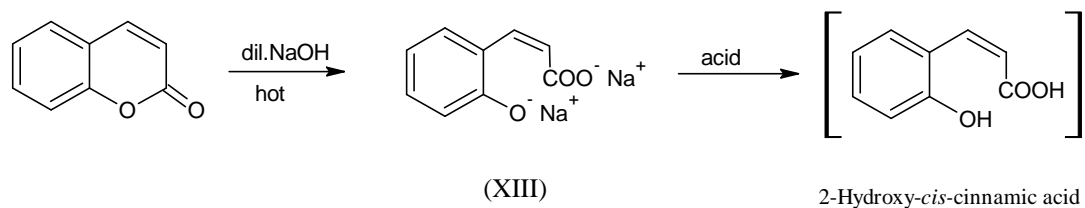
Scheme 5

1.4 REACTION OF SUBSTITUTED COUMARINS WITH BASES

When substituted coumarin derivatives are treated with bases, ring transformations occur in addition to the usual ring-opening mechanism. Some of the transformations reported include the ring shortening of 4-Chloromethylcoumarin in presence of hydroxides[25] and cyclopropanation of C3-C4 double bond in 3-substituted coumarins, in the presence of strong bases[26], (Scheme 6).
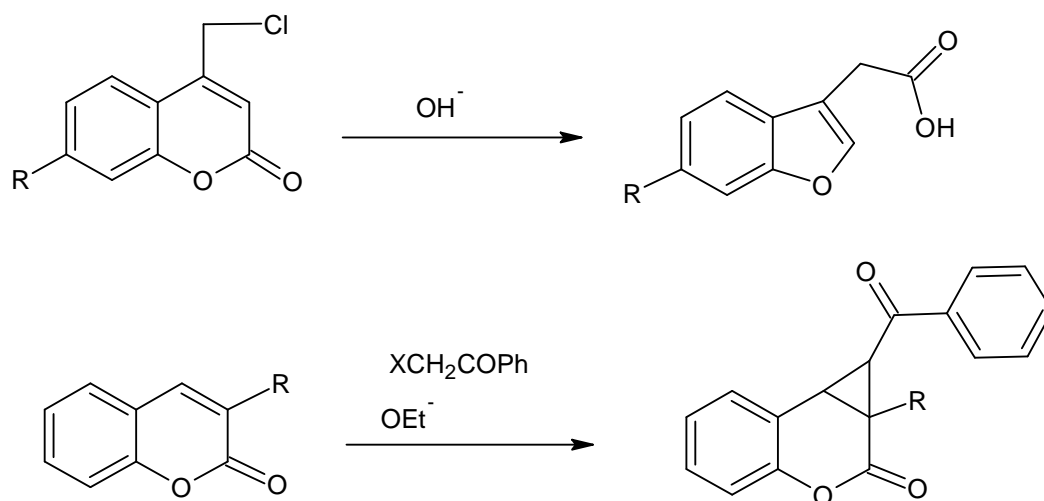
Scheme 6

In case of reactions of coumarins involving weak bases, substitutions have been observed in 3-acetylcoumarin at position-3[27], (Scheme 7).
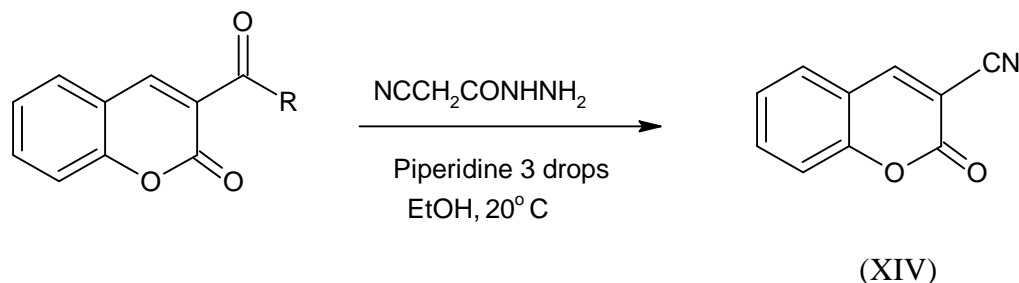
Scheme 7

These transformation and substitutions can be explained by considering the lactone ring openings as reactions of α,β-unsaturated carbonyl compounds with nucleophiles. As such the reactions of coumarins with bases can occur by two mechanisms: 1, 2(or direct) addition and 1, 4 (or conjugate) addition.

1, 2 mechanism involves the initial addition of the nucleophile to carbonyl carbon followed by ring opening. 1, 4-mechanism starts with Michael addition at the electrophilic carbon atom β to the carbonyl carbon leading to a substitution product[28] (XIV), (Scheme 8).
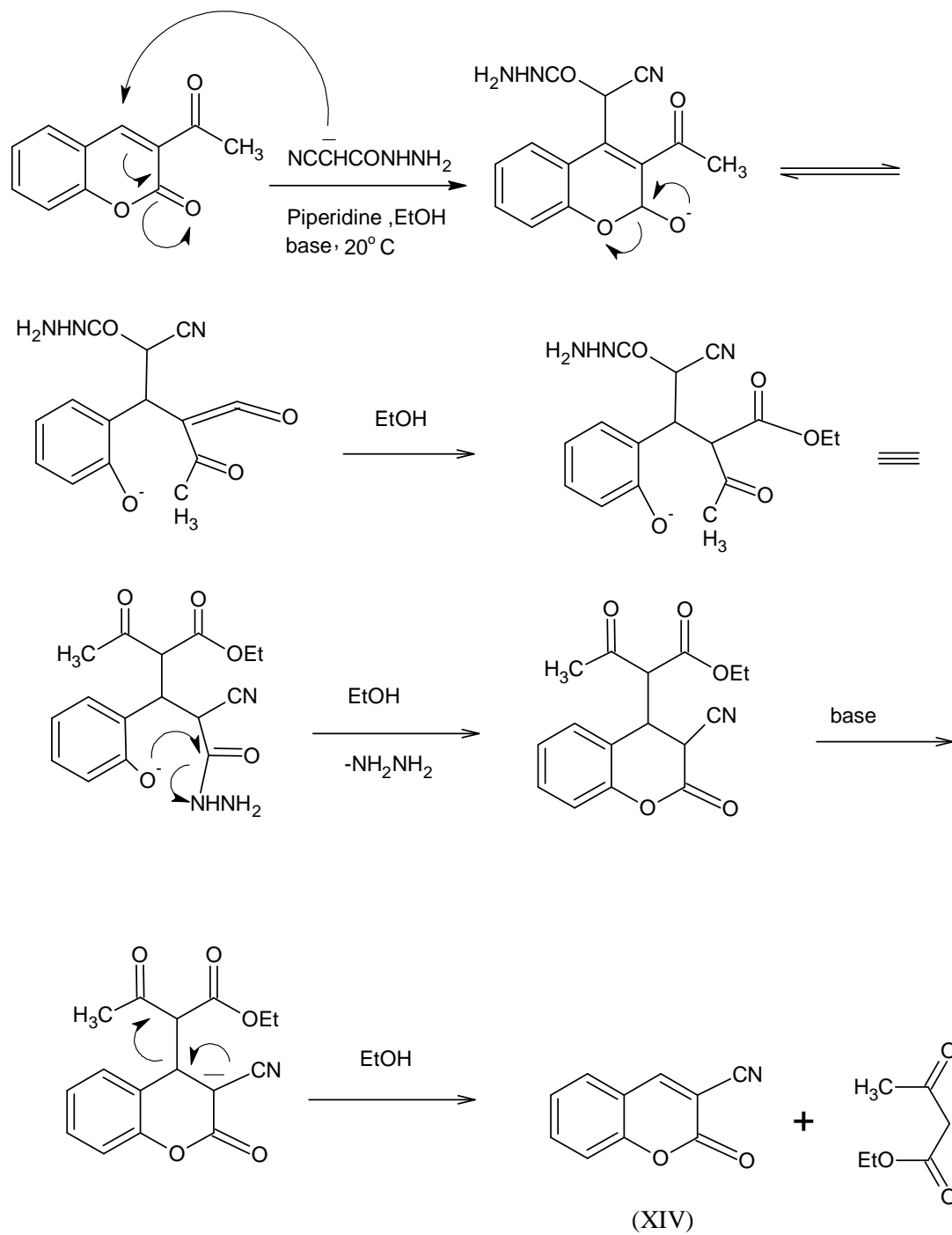
Scheme 8

The current work is focussed on the base hydrolysis of furocoumarins. Furocoumarins form an important class of coumarins. They absorb ultraviolet radiations and intercalate with the

pyrimidine bases present in the DNA molecules of micro-organisms. The reaction involves a [2+2] photocycloaddition resulting in the cross-linking of DNA and prevention of microorganism's reproduction[29].

The chemical structure of furocoumarins consists of a furan ring fused with a coumarin nucleus. The linear annulation of the furan ring to the α-benzopyrone nucleus gives the linear furocoumarins of which the unsubstituted, basic example is psoralen. Psoralen has been extensively used in photochemotherapy[30], PUVA (psoralen + Ultraviolet A) effective against various skin diseases such as vitiligo, psoriasis, atopic dermatitis, mycosis fungoides. 8-Methoxy psoralen (xanthotoxin) has been used to cure T-cell lymphoma, and is effective in preventing rejection of organ transplant[31]. Angular fusion of furan ring gives angular furocoumarins ,angelicin forming the core example. Angelicin derivatives depress RNA synthesis and inhibit the incorporation of amino acids into proteins[5]. Antimicrobial activity for a variety of organisms has been established for several furocoumarins. Tuberculostatic and enzyme inhibitory activity has also been observed[5]. Fusion of the furan ring on the α-pyrone ring results in furo[3,2-c]coumarins. Neo-tanshinlactone is known as a furo[3,2-c]coumarin isolated from Salvia miltiorrhiza Bunge, which is an anti-breast cancer agent[32]. Due to their vast pharmacological potential, furocoumarins and the compounds derived from them are suitable for further biological evaluation.
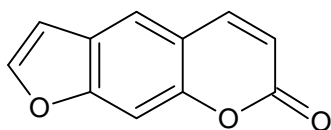
Psoralen
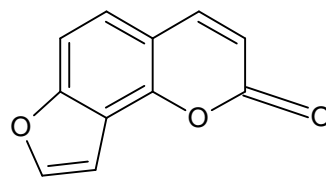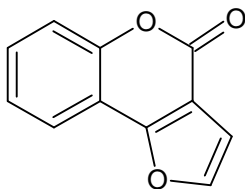
Furo[3,2-*c*]coumarin

Angelicin

1.5 BASE HYDROLYSIS OF COUMARINS

Originally the lactonic nature of coumarins was used to separate them from other plant constituents[33]. The treatment of dilute solutions of alkali metal hydroxides to coumarins generated water-soluble alkali metal coumarinates from which other components could be removed by ether extraction. Acidification in most cases resulted in spontaneous lactonization and generation of the coumarin. Lactone separation is a useful technique, however many coumarins are alkali- and/or acid- sensitive and in many cases the original coumarin is not recovered back.

Hydrolysis, followed by methylation is used for the identification of coumarins. The formation of *o*-methoxycinnamic acid is an indication that the substance is a coumarin[34]. The hydrolysis reaction is also useful in differentiating a chromone from a coumarin. In case of a chromone, the hydrolysis product is an *o*-hydroxy diketone where as in case of coumarins its coumaric acid[35].

All coumarins react with alkali to give alkali metal coumarinates. Fusion with alkali degrades coumarins and furocoumarins to the phenols of the basic aromatic nucleus[5]. The reactivity of coumarins towards bases and the nature of the products formed depend largely on the structure of the coumarin and the reaction conditions.

Lactone-ring opening

Coumarin [*2H*-1-benzopyran-2-one] (I) on treatment with hot dilute aqueous sodium hydroxide, hydrolyses slowly to give a yellow solution of lactone ring-opened product, sodium coumarinate (XIII), in which the *cis* configuration is retained. Generally the intermediate *orth* –hydroxy-*cis*-cinnamic acid (coumarinic acid) is not isolated[36] (Scheme 9).

(XIII)   2-Hydroxy-*cis*-cinnamic acid
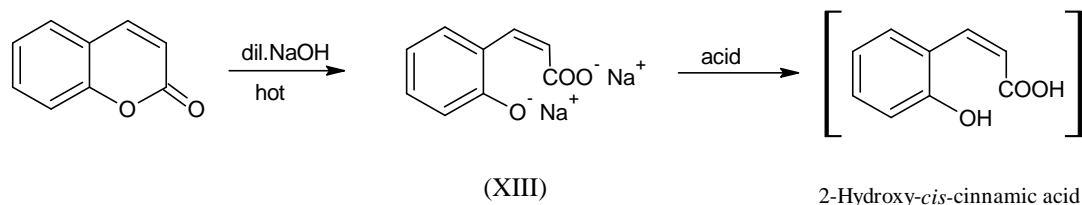
Scheme 9

Prolonged treatment of coumarin (I) with hot dilute sodium hydroxide results in *cis* to *trans* inversion, on acidification *ortho*-hydroxy-*trans*-cinnamic acid (*o*-coumaric acid) (XV) is obtained[17]. On Treatment of coumarin (I) with ethanolic sodium ethoxide, the salt of ethyl o-coumarate is obtained. Subsequent treatment with water and evaporation of the solvent, followed by acidification produces *o*-coumaric acid in 82% yield. The reaction is probably involves an addition-elimination pathway with hydroxide ion adding to C-4 of the coumarinate, thereby permitting rotation about the single bond from C-3 to C-4[37], (Scheme 10).
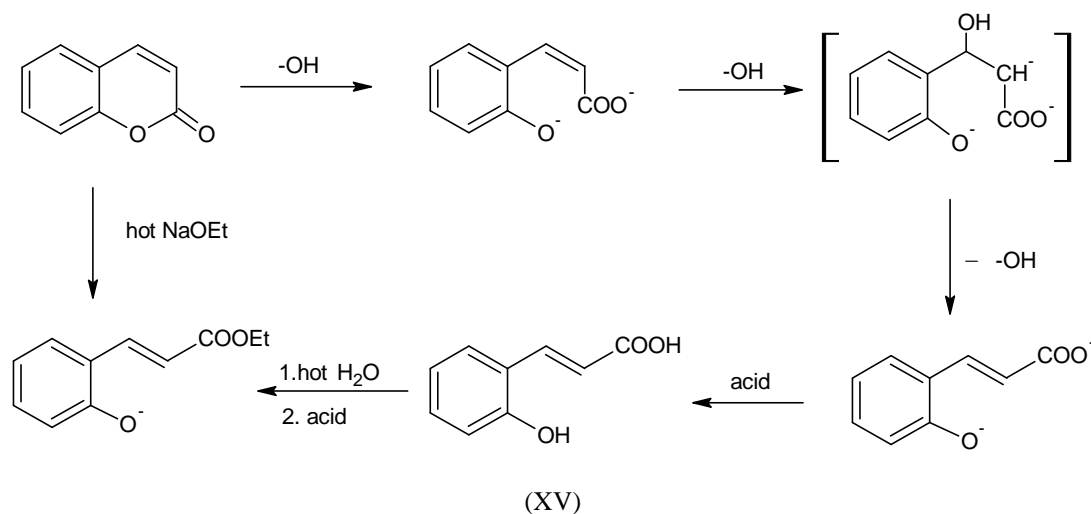
Scheme 10

Certain coumarins are converted to the corresponding *o*-coumaric acids by shaking the powdered coumarin with dilute alkali and a small quantity of freshly prepared mercury(II) oxide[38]. Poncitrin (XVI) on treatment with 20% aqueous sodium hydroxide in methanol at room temperature gave the *cis*-acid whereas hot 50% aqueous potassium hydroxide gave the corresponding *trans*-acid, (Scheme 11)[39].

The *trans*-acid can be isolated and on heating decomposes into carbon dioxide and hydroxystyrenes[40,41]. *o*-Coumaric acids can be inverted to the *cis* form by the action of sunlight[42] or by catalytic amounts of mercury(II) chloride[43]. Other methods producing *trans*-to-*cis* inversion include treatment with sulphuric acid at $100^{\circ}C$ and saturated solution of hydrogen chloride in alcohol[44]. Reversion of configuration, *trans* to *cis*, occurs when methyl or ethyl o-coumarate is heated for 5 min giving coumarin I (45%)[40].
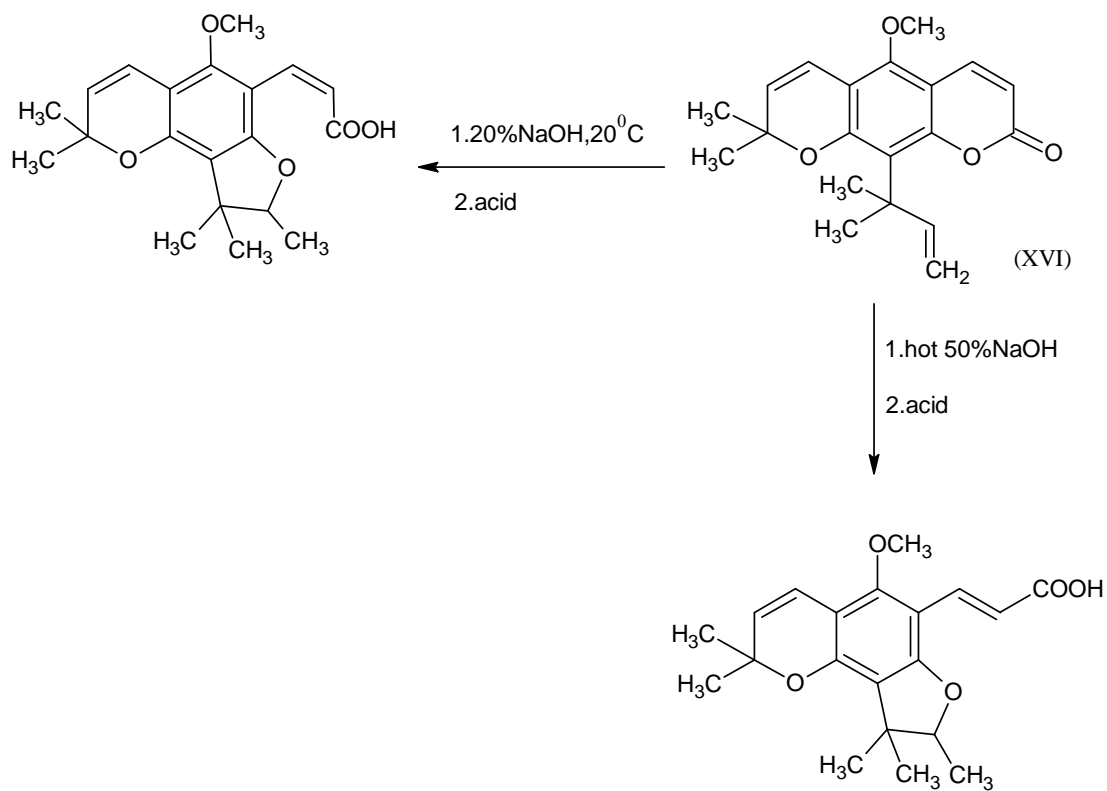
Scheme 11

Effect of substitution:

A C-8 acyl substituent as in calophyllolide (XVII) can stabilize the acidified lactone ring-opened product by chelation with the liberated phenolic group, thus preventing spontaneous relactonization on acidification. The coumarin is regenerated only when the derived coumarinic acid is heated, (Scheme 12)[45].
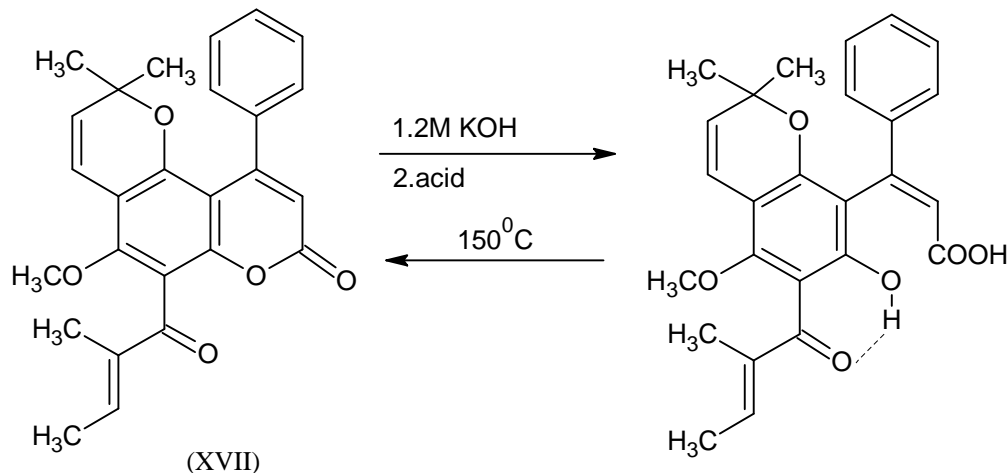
Scheme 12

When an epoxide is present in the side chain attached to C-8, opening of the lactone ring is followed by the attack of the freed phenolate anion to the epoxide . This prevents the relactonization of the acid, as seen in the conversion of sibiricin (XVIII) to sibiricic acid (Scheme 13)[46].
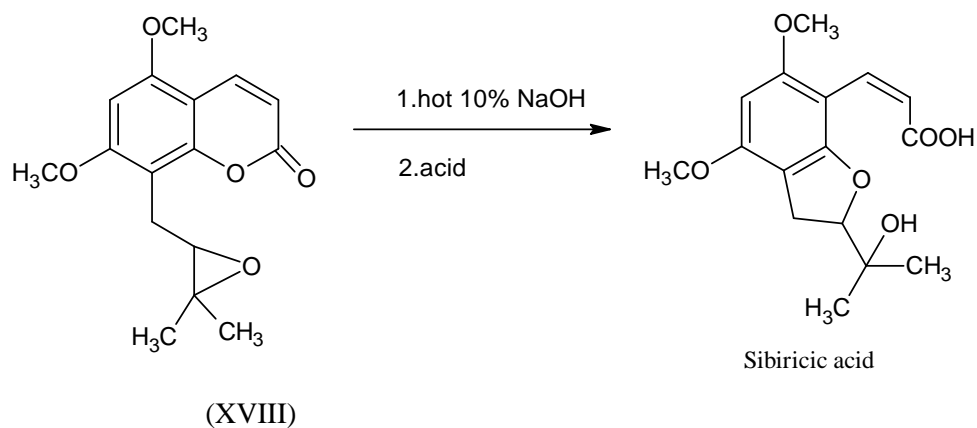
Scheme 13

When a free phenolic group is present at C-5, the coumarinate salt on acidification can lactonize to an alternative position resulting in an isomer of the original coumarin. In case of Mammein (XIX), the substituents at C-6 and C-8 are interchanged, when allowed to stand overnight with

5% potassium hydroxide in methanol followed by acidification a yellow isomer, Isomammein is obtained, (scheme 14)[48].

(XIX)   Isomammein
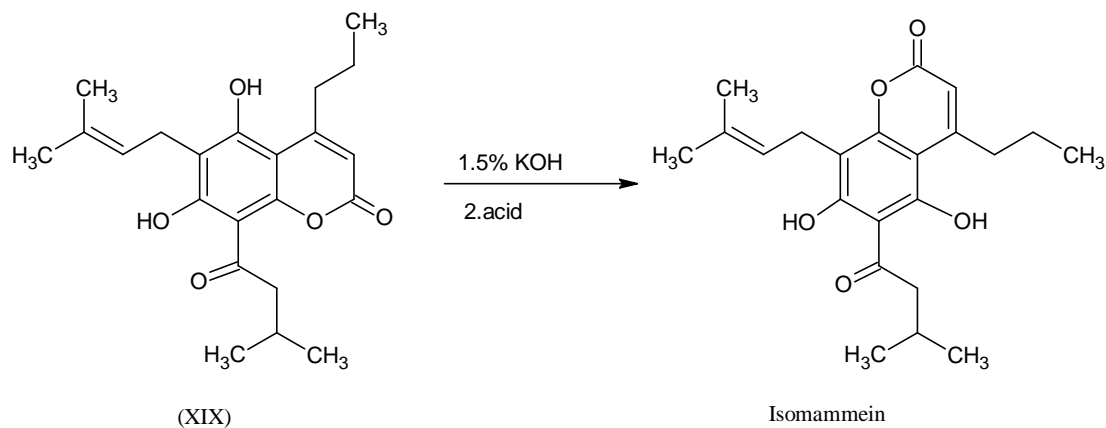
Scheme 14

7-Methoxycoumarin (XX) is much harder to hydrolyse than coumarin (I) as electron delocalization renders the carbonyl group less sensitive to nucleophilic attack[48] (Scheme 15). 7-hydroxycoumarin, which forms a phenolate ion, is even more difficult to hydrolyse[5]. The rates of ring opening of 7-hydroxycoumarins substituted at C-3 and C-4 with methyl and phenyl groups have been determined fluorometrically in 0.7 M potassium hydroxide[49].

(XX)
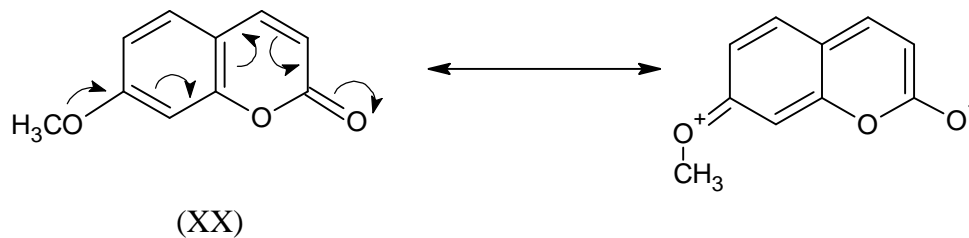
Scheme 15

The hydrolysis of 3-chlorocoumarin, 3-bromocoumarin, and 3- and 4-methylcoumarin were studied in 30% dioxane for acid-lactone equilibrium. The halogen substitution accelerates the hydroxide ion attack on the carbonyl carbon, whereas methyl substitution shows little effect[50].

Effect of solvent:

Studies conducted on the alkaline hydrolysis of 4-methoxycoumarin indicate that the reaction occurs in two stages, opening of the lactone ring and methanolysis. Methanolysis occurs at C-4 and involves un-ionised phenolic group, thus is inversely related to the base concentration. This unusual behaviour has been attributed to solvent effects[51]. The rate constants of base hydrolysis of coumarin and thiocoumarin in different aqueous-methanolic mixtures have been evaluated[52].

Lactone ring fragmentation

A vigorous treatment of coumarins with alkali leads to the fission of the opened lactone ring giving acetic acid together with phenolic acids or ketones. Identification of the degradation products can be utilized in structural studies. The position of free hydroxyl in glaupalol (XXI) was shown to be at C-6 by the isolation of 2, 5-dihydroxytoluene on alkali fusion[53] (Scheme 16).

(XXI)
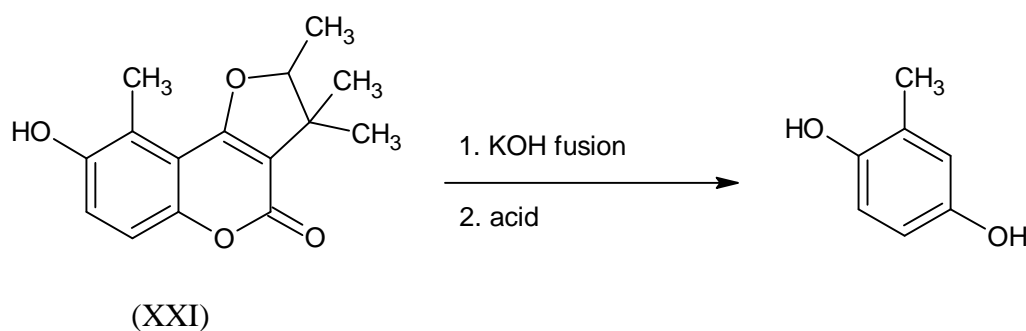
Scheme 16

Fusion with alkali can result in complete removal of the pyrone ring and of side chains on the benzenoid ring, leaving the simple phenolic nucleus of the benzenoid ring[5]. Mammeisin (XXII)

when heated at reflux with 15% aqueous potassium hydroxide for 67h, gives 3-methylbutanoic acid, isopentenylphloroglucinol and acetophenone[54] (Scheme 17).

(XXII)
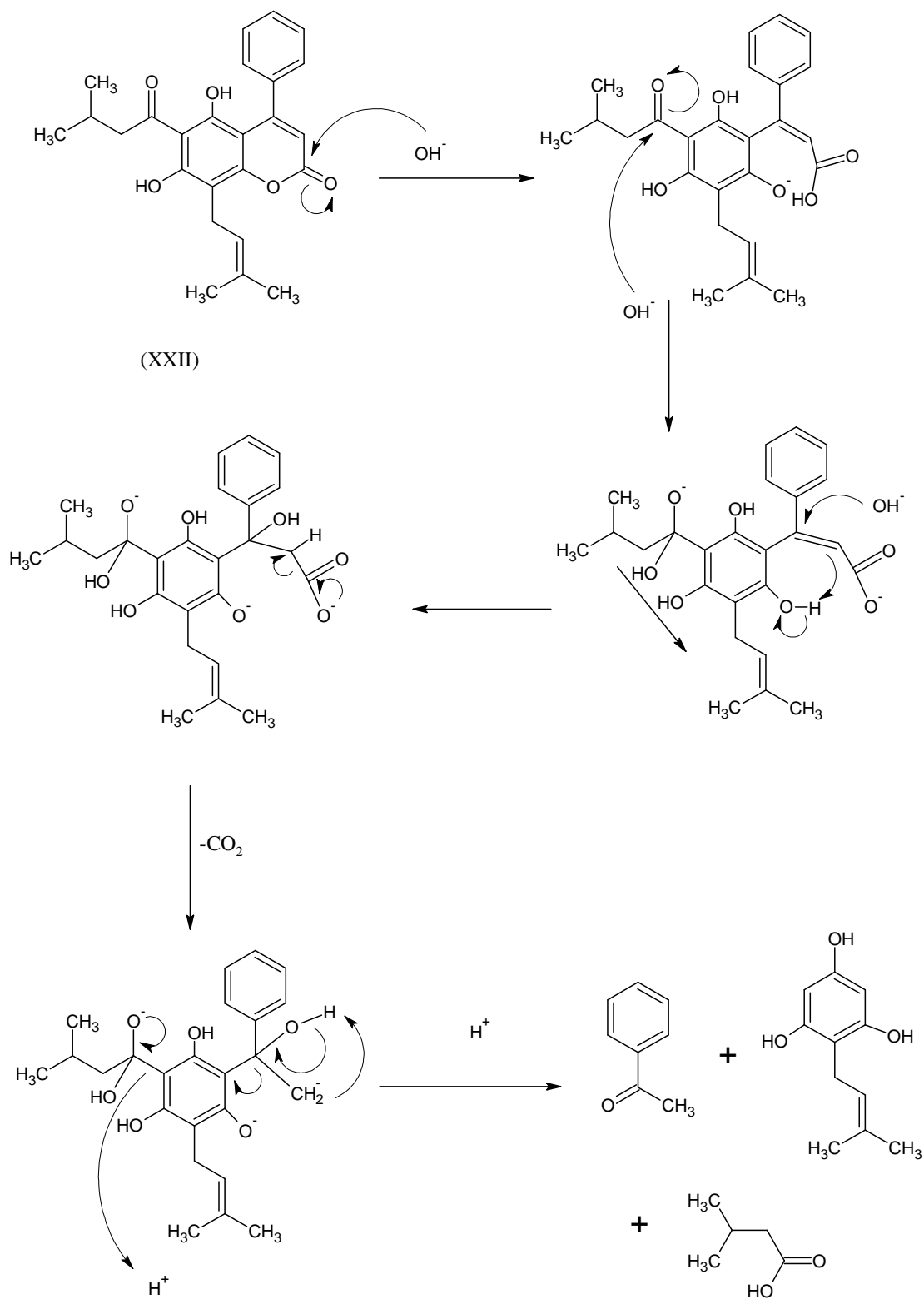
Scheme 17

Alkylative lactone ring opening

When a coumarin is treated with sodium hydroxide and methyl iodide or dimethyl sulphate ,the lactone ring opens and the phenolic hydroxyl group of coumarinic acid is subsequently methylated ,thereby preventing relactonization[5](Scheme 18).
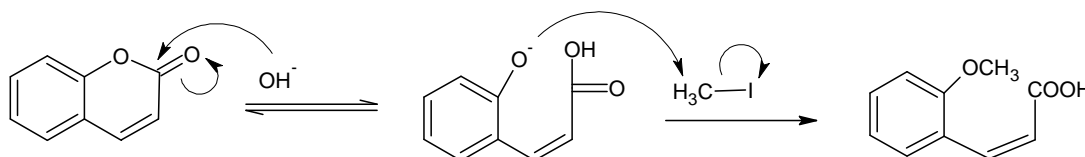
Scheme 18

Thus under basic conditions, the behaviour of coumarins does not follow a single mechanism. Depending upon the strength of the base and the position of substituents on the coumarin nucleus various transformations occur which are worth investigating.

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Chapter 2

Synthesis of dihydrofurocoumarins

The synthesis of substituted furo[3,2-*c*] coumarins has been achieved by the reaction between 4-hydroxycoumarin and α-haloketones involving O-alkylation, cyclization followed by intramolecular aldolization[1], rhodium (II) catalysed (3+2) cycloaddition of 3-diazo-4-hydroxycoumarin and oxygenated alkenes[2] , alkynylation of 3-halo-4-acetoxycoumarin followed by metal catalysed intramolecular hydroalkoxylation[3] , one-pot oxidative pseudo three-component condensation of aldehydes and 4-hydroxycoumarin(2 equiv) in poly(ethylene glycol) as solvent[4], transformation of alkyne substituted chromones via acid-promoted addition-cyclization-oxidation reaction[5].

A 144 member library of differently functionalized furo[3,2-*c*]chromen-4-ones has been prepared from 4-hydroxycoumarin, isocyanides and aldehydes under microwave irradiation[6]. Only a few procedures involving the synthesis of functionalized furo[3,2-*c*]coumarins have been reported and most of them involve vigorous laboratory conditions and average yields. Methods involving rapid and efficient synthesis of furo[3,2-c]coumarins are required.

In the present work the synthesis of 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo [3, 2-*c*][1]benzopyran-4-one was conducted from 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one) by treating it with DMSO-Ac$_2$O reagent. 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one) was synthesized from the reaction between 4-hydroxycoumarin and formaldehyde. In the ongoing work a number of biscoumarins are to be synthesized and attempts made to transform them into the corresponding furocoumarins.

Synthesis of 3,3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)

The reaction of 4-hydroxycoumarin with formaldehyde is a Michael type addition. In this reaction, two molecules of 4-hydroxycoumarin react with one molecule of formaldehyde to give the *bis*(4-hydroxycoumarin), dicoumarol. The first step of the reaction involves aldol(I) formation between 4-hydroxycoumarin and formaldehyde, dehydration of the aldol gives the α,β-unsaturated ketone(II). Condensation of the ketone with another molecule of 4-hydroxycoumarin by Michael reaction gives the 3,3'methylene biscoumarin(III)[7](Scheme 19).
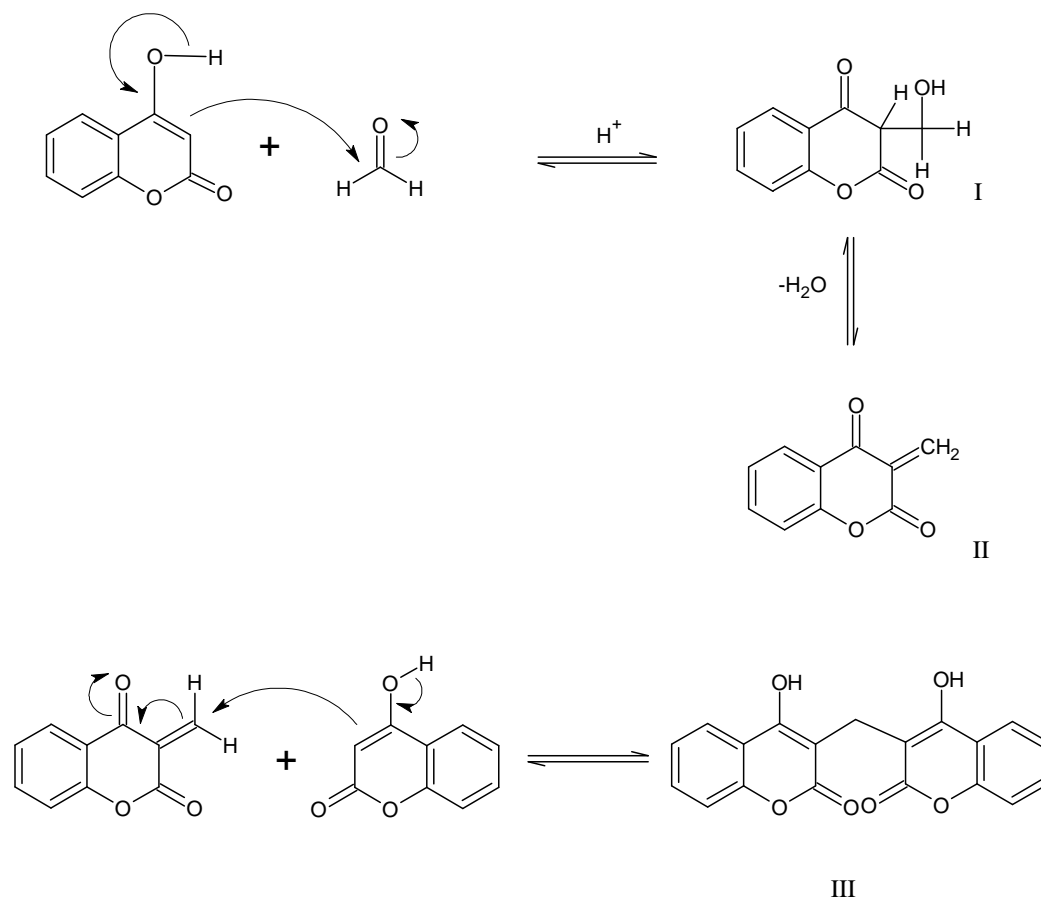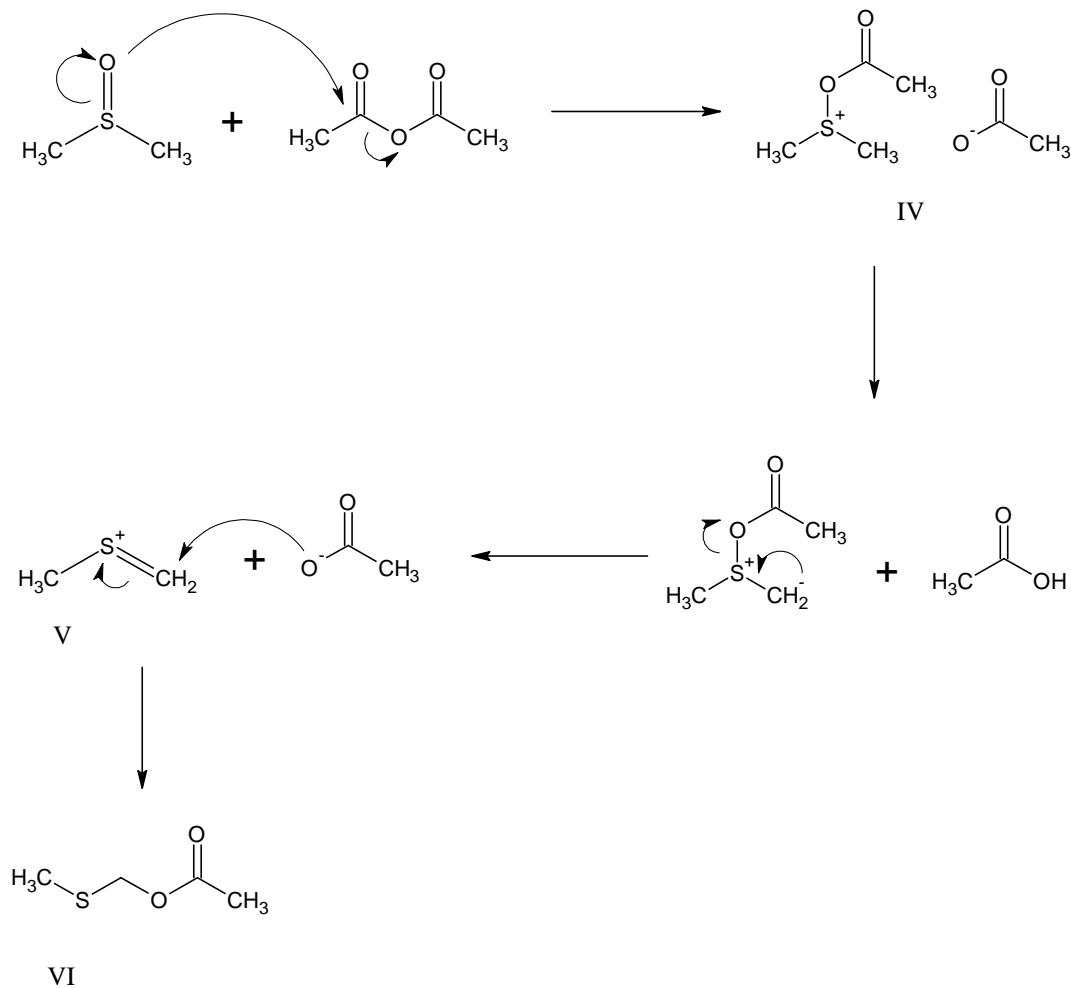
Scheme 19

Synthesis of 2,3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-*c*][1]benzopyran-4-one

The synthesis of 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-*c*][1]benzopyran-4-one was carried out by reacting *bis*(4-hydroxycoumarin) with DMSO-Ac$_2$O reagent[8].

 DMSO is an aprotic solvent used in many reactions as it causes significant enhancement of reaction rates in minor amounts. It is a favoured solvent for displacement reactions[9], reactions involving replacement of reactive groups by nucleophilic ions or molecules. In most of the reactions involving DMSO, a nucleophilic attack occurs on the sulphur atom, aided by prior electrophilic attack on the oxygen atom. The electrophilic reagents which activate DMSO include acetic anhydride[10], sulphur trioxide-pyridine[11], oxalyl chloride[12], trifluoroacetic anhydride[13].

With acetic anhydride the reaction of DMSO, called Pummerer rearrangement, involves the initial formation of acetoxysulfonium salt (IV). The rearrangement involves a ylide(V) formation and the final product is acetoxymethyl methyl sulphide(VI)[14] (Scheme 20).

Scheme 20

The reaction between dicoumarol and DMSO-Ac$_2$O gives 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-c][1]benzopyran-4-one in average yields under microwave irradiation[15]. The

mechanism involves the decarboxylation of a spiran derivative (VII) resulting in the formation of the dihydrofurocoumarin (VIII)[8] (Scheme 21).
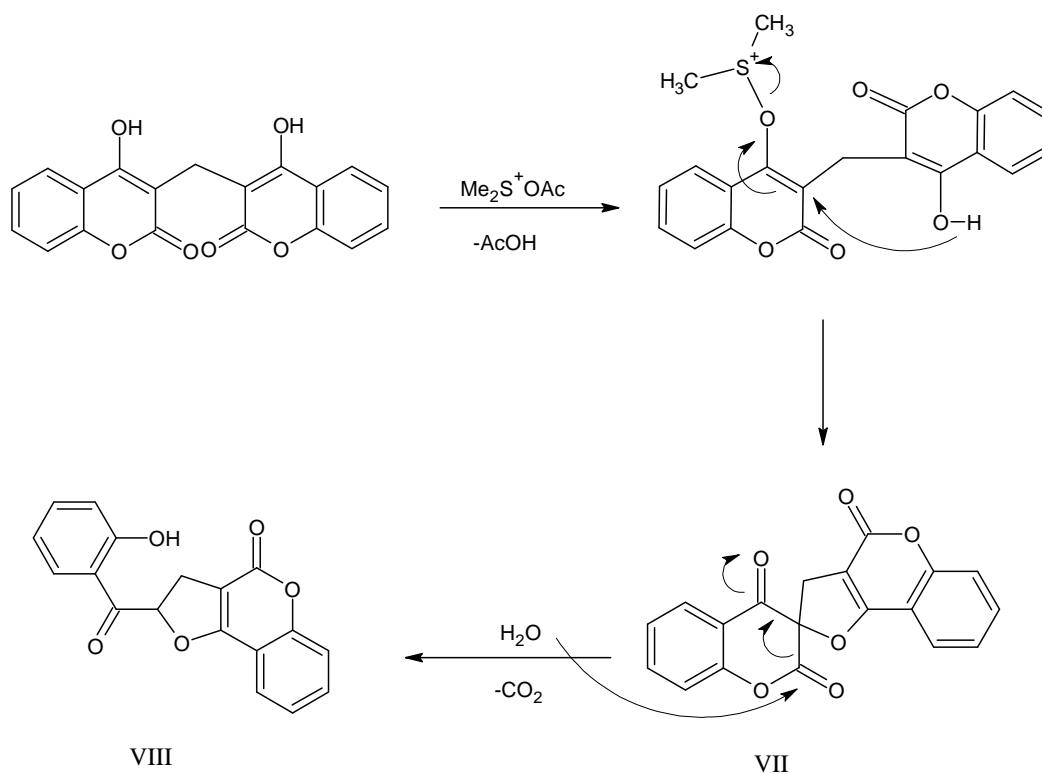
Scheme 21

Experimental

Melting points were taken in open capillaries on Perfit-Melting Point Apparatus and are uncorrected. The microwave assisted reactions were carried out in SHARP 1000W/R-21LC domestic microwave oven. All the chemicals and solvents used were of synthetic grade and DMSO was of analytical grade. The products obtained were identified by comparing their melting points, chemical properties and UV spectra to those reported in the literature.

Reaction of 4-hydroxycoumarin with formaldehyde to yield 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one)

Under convention reflux:

A mixture of 4mmol of 4-Hydroxycoumarin (0.648 g) and 2 mmol of formaldehyde (0.141 ml) was dissolved in ethanol (25 ml) and heated under reflux for 4 hours. The reaction was monitored through TLC. The insoluble product formed was filtered under reduced pressure, washed with ethanol and dried. Yield: 0.574g (85.41%), M.Pt: 278-280^{0}C.

Under microwave irradiation:

4 mmol of 4-Hydroxycoumarin (0.648 g) and 2 mmol of formaldehyde(0.141 ml) were dissolved in ethanol (2 ml).The mixture was taken in a sealed teflon tube and irradiated for 2.5 minutes .The irradiation pattern consisted of 30s cycles followed by a resting time of 5-10 minutes. The reaction mixture was washed with ethanol and filtered under suction to separate the insoluble product, dicoumarol (III). Yield: 0.33g (49.1%), M.Pt: 280^{0}C.

Reaction of 3, 3'-methylene-*bis*(4-hydroxy-*1H*-benzopyran-2-one) with DMSO-Ac$_2$O to yield of 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-*c*][1]benzopyran-4-one

Under microwave irradiation:

A mixture of dicoumarol (0.336 g, 1mmol), DMSO (5 ml) and Ac$_2$O (2.5 ml) was taken in a round-bottomed flask fitted with a guard tube containing silica gel. The assembly was supported by a beaker and irradiated for 2 minutes .After the completion of the reaction, water was added to the yellow coloured oily liquid, extracted with ether and dried. The product so obtained was crystallized from chloroform-petroleum ether to give the dihydrofurocoumarin (IV).Yield: 0.1 g (32.46%), M.Pt: 212-216^{0}C.

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Chapter 3

Base hydrolysis of dihydrofurocoumarins

3.1 Discussion and Results

Furocoumarins of the type, 2, 3-Dihydro-4[*H*]-furo [3, 2-*c*] [1] benzopyran-4-one, being coumarins are susceptible to attack by bases. On exposure to basic hydrolytic conditions the compound undergoes opening of the lactone ring. Upon acidification, lactonization and regeneration of the dihydrofurocoumarin is expected (Scheme 22).


I
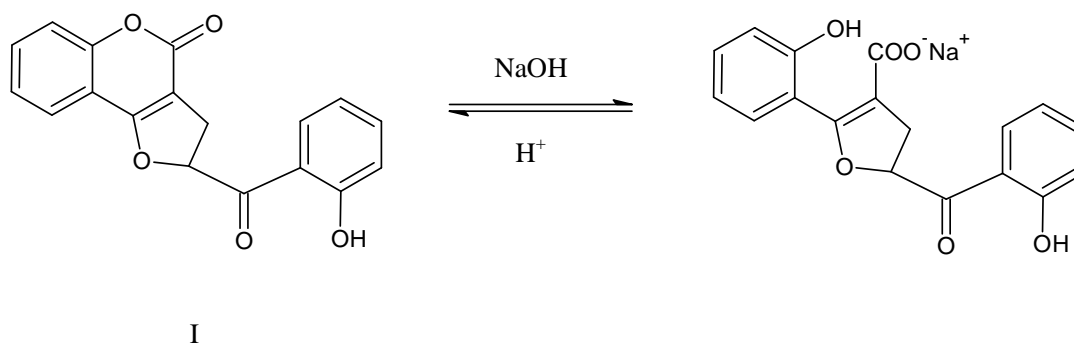
Scheme 22

However the dihydrofurocoumarin (I) undergoes a complex decomposition in alkaline medium involving a rapid opening of the lactone ring to give a pale yellow solution. On acidification the original compound is not regained[1].

The hydrolysis of the corresponding furocoumarin (II) with dilute alkali leads to the formation of a cis-2-hydroxycinnamic acid (III) which is stable and does not relactonise on acidification. The unusual stability of the acid is attributed to the geometry of the furan ring which draws the carboxyl and the hydroxyl groups away from each other[2].

II   III
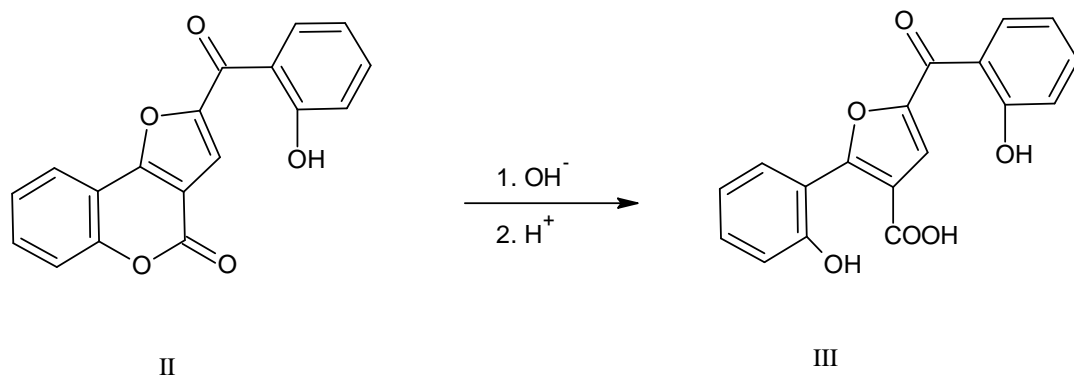
Thus in dihydrofurocoumarin (I) if the acid obtained on hydrolysis does not undergo further degradation, it might be stable enough for isolation. The studies conducted on the alkaline hydrolysis of 4-methoxycoumarin as a model to dihydrofurocoumarin (I) indicate the initial attack of the hydroxyl group on the carbonyl carbon giving hydroxyacetophenone as the main product on treatment with dilute alkali and methoxycoumarinic acid formation (as shown by uv scans) with stronger alkali. The acid obtained is not stable and undergoes rapid lactonization on acidification[3].

It has been observed that the treatment dihydrofurocoumarin (I) with methanolic alkali involves immediate isomerisation to (IV) with no further change induced on increasing the strength of the base and/or the temperature [4] (Scheme 23).
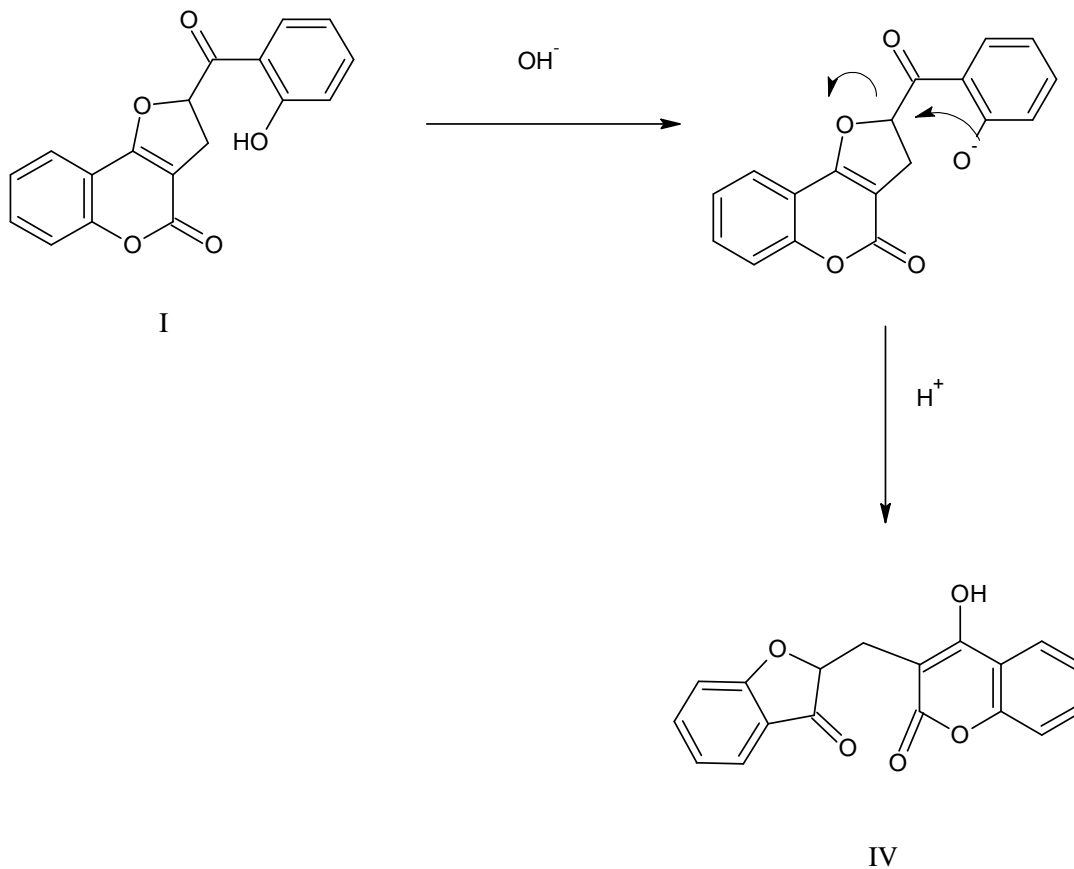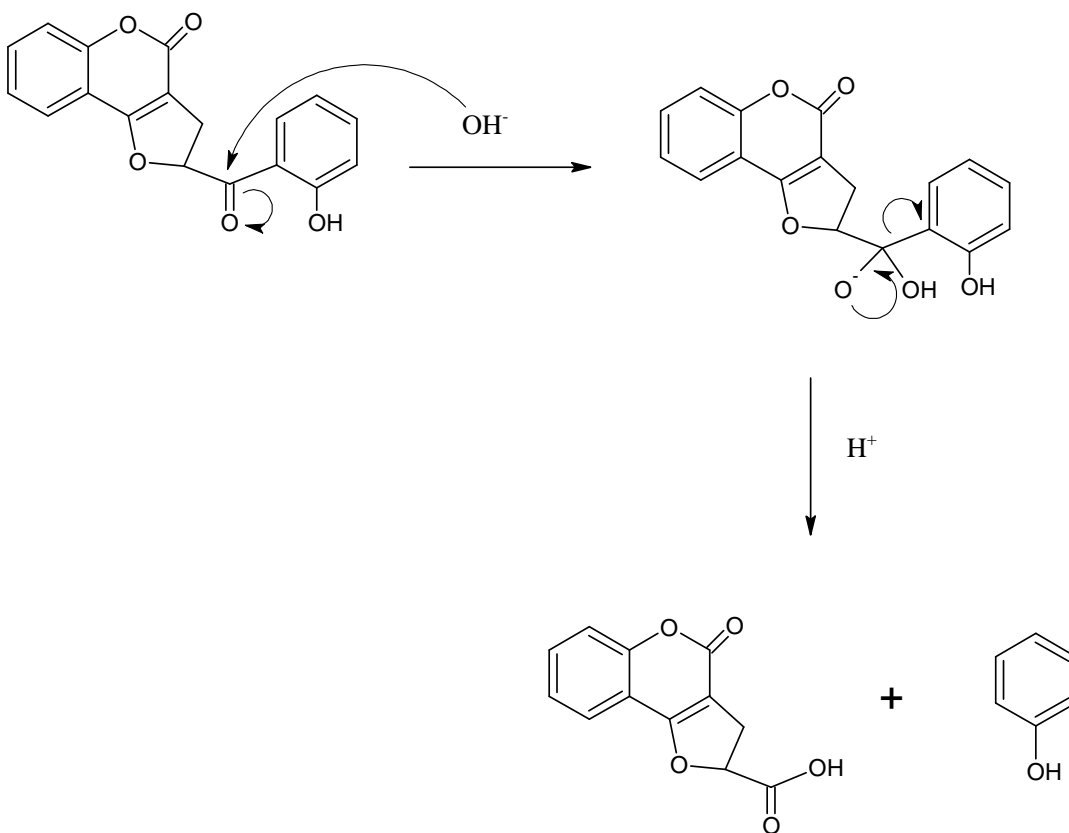

Scheme 23

Although it seems quite possible that the product (IV), once formed should suffer further degradation resulting in the formation of a large number of products (Scheme24).
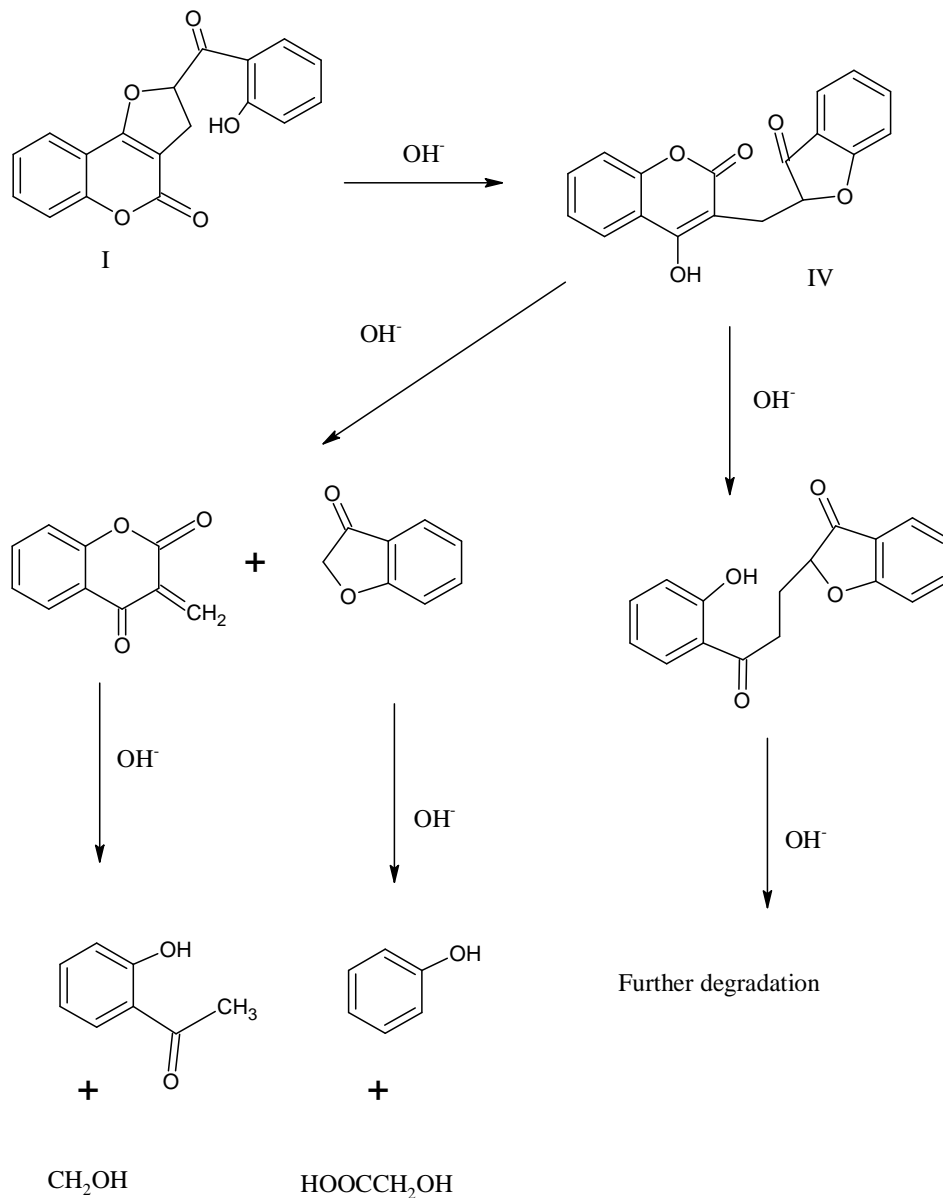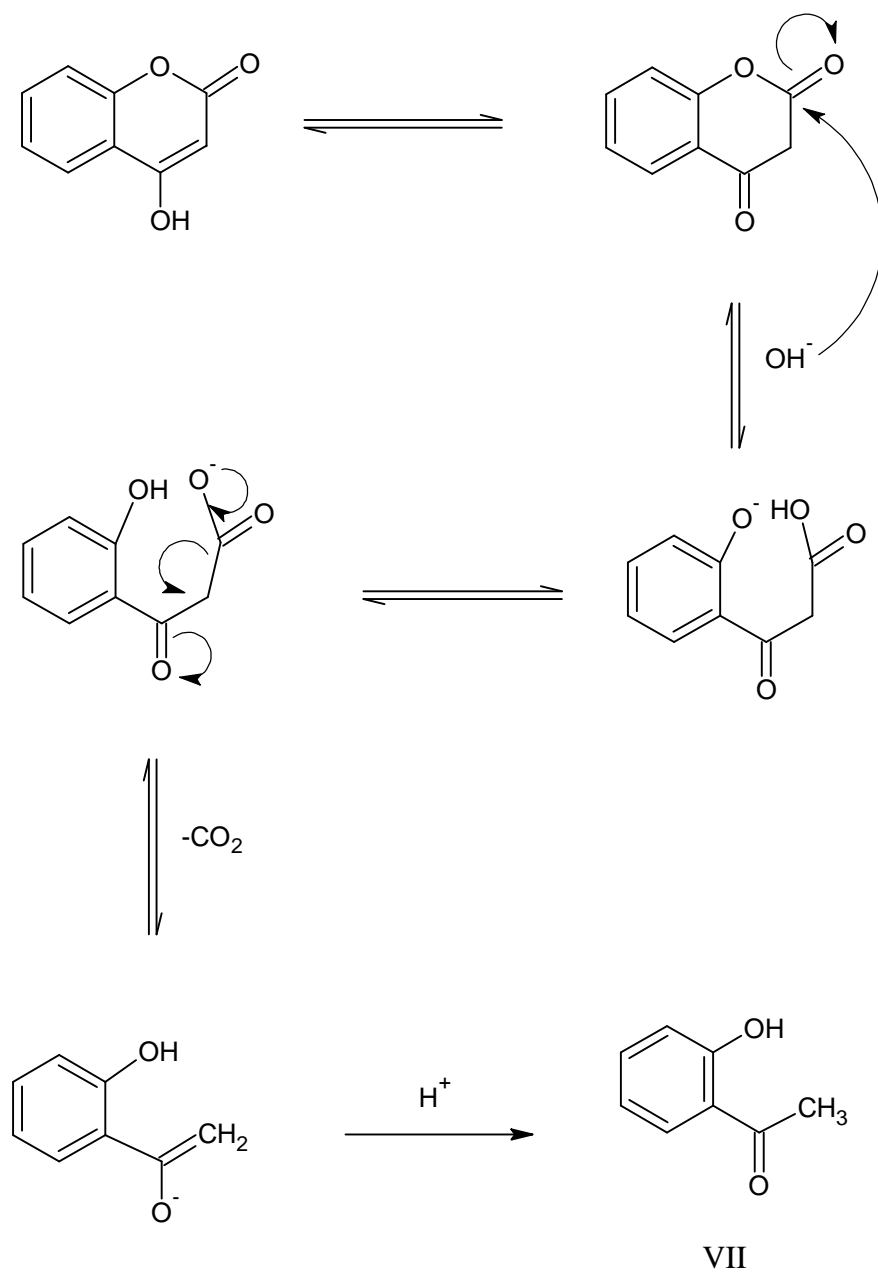

Scheme 24

The attack of the base on the 2-hydroxybenzoyl group can bring about degradation of the molecule leading to formation of phenol and substituted dihydrofurocoumarin (I) (Scheme 25).
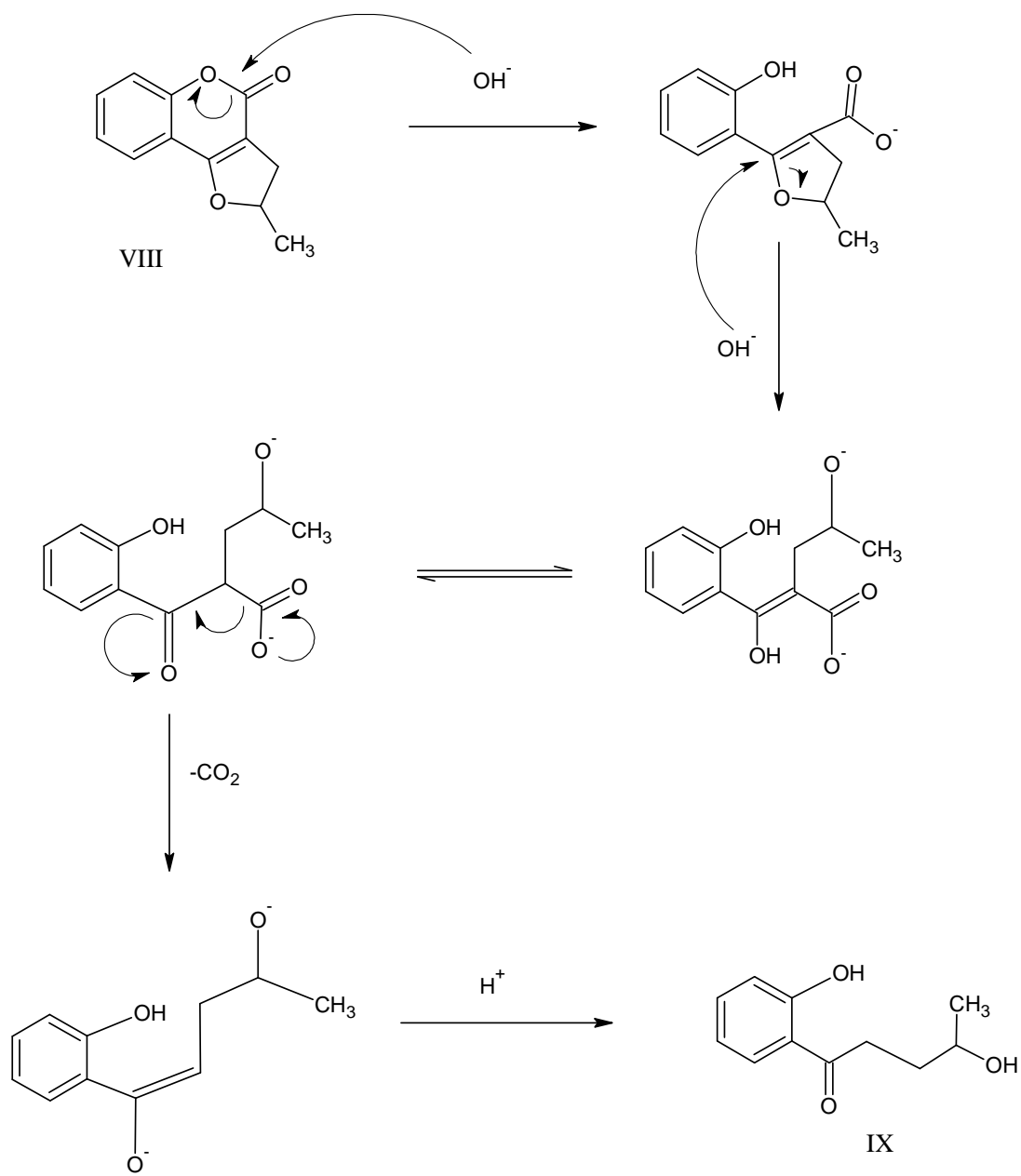
Scheme 25

The base hydrolysis of 4-hydroxycoumarin involves opening of the lactone ring followed by decarboxylation giving *o*-hydroxyacetophenone(VII)[5] (Scheme 26).
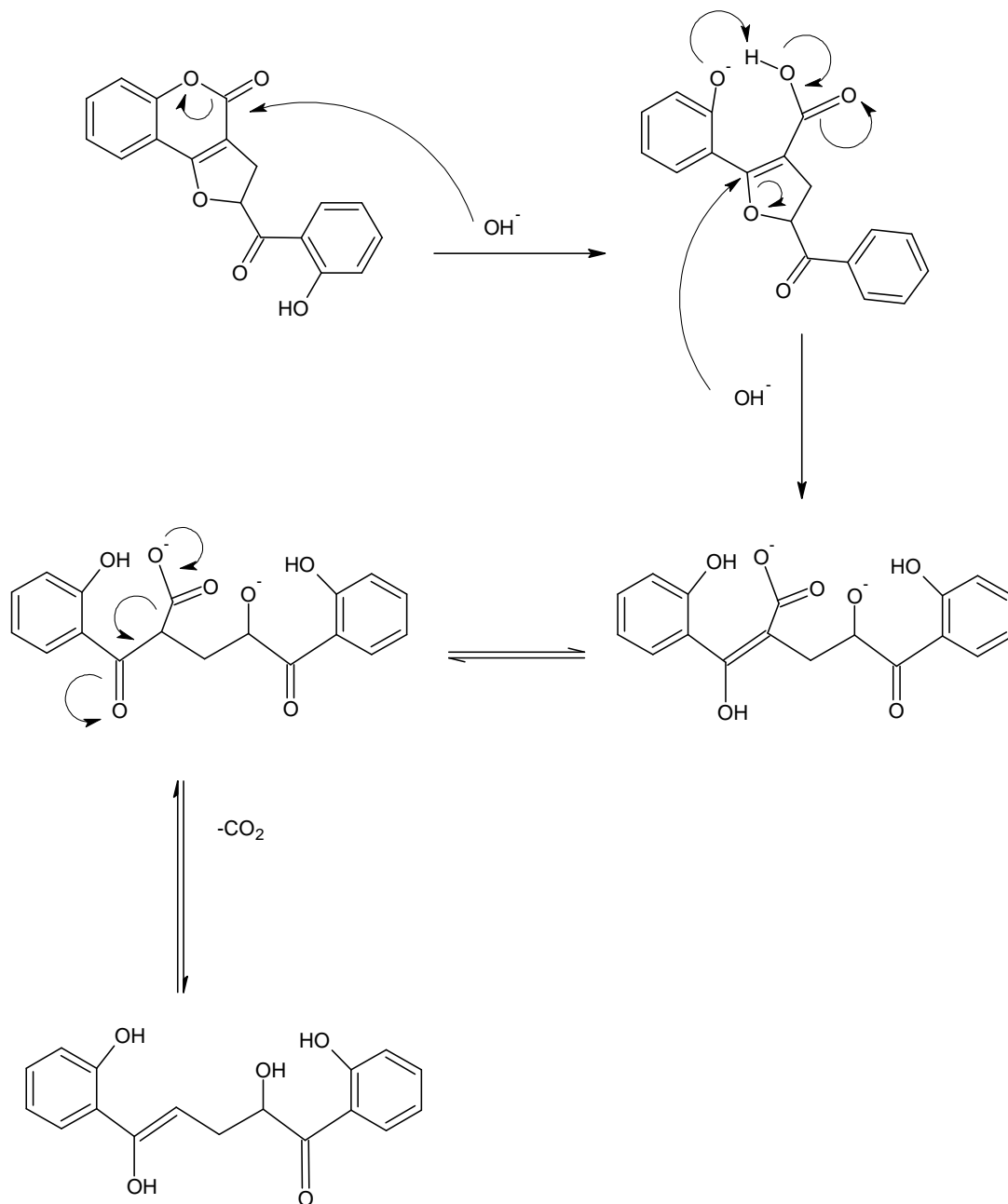
Scheme 26

The alkaline hydrolysis of 2, 3-Dihydro-2-methyl-4*H*-furo [3, 2-c] benzopyran-4-one (VIII) furnishes the ketonic alcohol (IX)[3]. The reaction mechanism most probably involves the loss of the carboxyl group (Scheme 27).

Scheme 27

A similar hydrolysis of Dihydrofurocoumarin (I) can be suggested involving the initial attack by the nucleophile at the carbonyl carbon of the pyrone ring followed by opening of the furan ring by nucleophilic attack at C-4. The reaction may also involve decarboxylation followed by nucleophilic attack at the carbonyl carbon of the 2-hydroxybenzoyl group leading to the generation of a ketonic alcohol (X) (Scheme 28).

Scheme 28

In the present work the hydrolysis of dihydrofurocoumarin (I) was conducted in strong as well as weakly basic medium. The UV-spectra of the products obtained were similar in both cases. In case of strongly alkaline medium, the yield of the product obtained is low. At room temperature and weakly basic conditions, the spectrophotometric monitoring indicated a change in the

spectrum after 24 hours, however no product could be isolated. Under water bath temperatures, only 5 minutes are required for the completion of the reaction and the yield obtained is quantitative.

3.2 <u>EXPERIMENTAL</u>

The reactions were conducted in methanolic alkali. NaOH was used as the base. The completion of the reaction was monitored spectrophotometrically. The ultra-violet spectra were obtained using Schimadzu UV-1650PC UV-Visible Spectrophotometer, with a temperature regulator maintained at 25°C. Methanol was used as the solvent.

Reaction of 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-*c*][1]benzopyran-4-one with 0.1M methanolic sodium hydroxide.

A solution of methanolic NaOH (0.1M, 3 ml) was added to 50 mg of dihydrofurocoumarin (I) and the reaction mixture was heated on a water bath for 10 minutes. After the completion of the reaction, water was added and the reaction mixture was acidified with hydrochloric acid. The precipitate obtained was filtered, washed with water and crystallised from methanol. Yield: 0.020g, M.Pt: 80 ^{0}C.

Reaction of 2, 3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-*c*][1]benzopyran-4-one 0.05M methanolic sodium hydroxide.

A solution of methanolic NaOH (0.05M, 3 ml) was added to 30 mg of dihydrofurocoumarin (I) and the reaction mixture was heated on a water bath for 10 minutes. After the completion of the reaction, water was added and the reaction mixture was acidified with hydrochloric acid. The precipitate obtained was filtered, washed with water and crystallised from methanol. Yield: 0.017g, M.Pt: 138-140 ^{0}C.
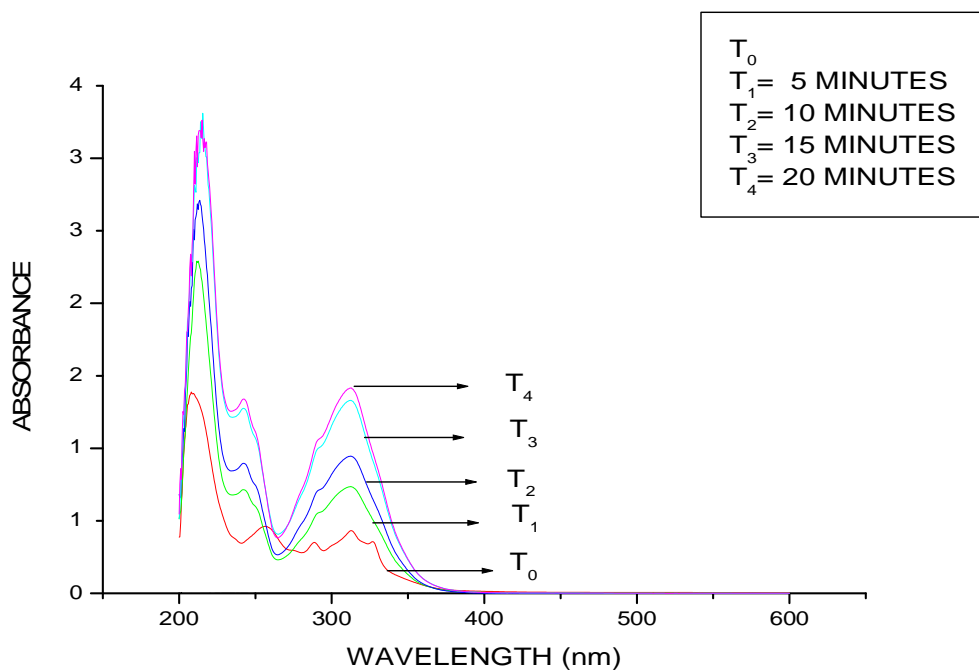
Figure 1: *UV spectrum of the base hydrolysis of dihydrofurocoumarin (I) in 0.05 M methanolic NaOH at water bath temperature.*
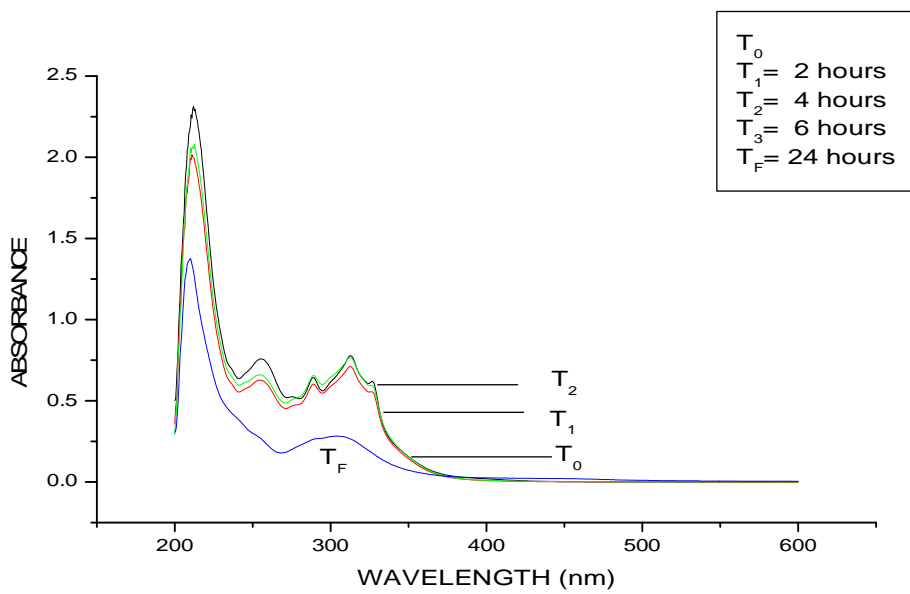
Figure 2: UV spectrum of the base hydrolysis of dihydrofurocoumarin (I)in 0.05 M methanolic NaOH at room temperature.
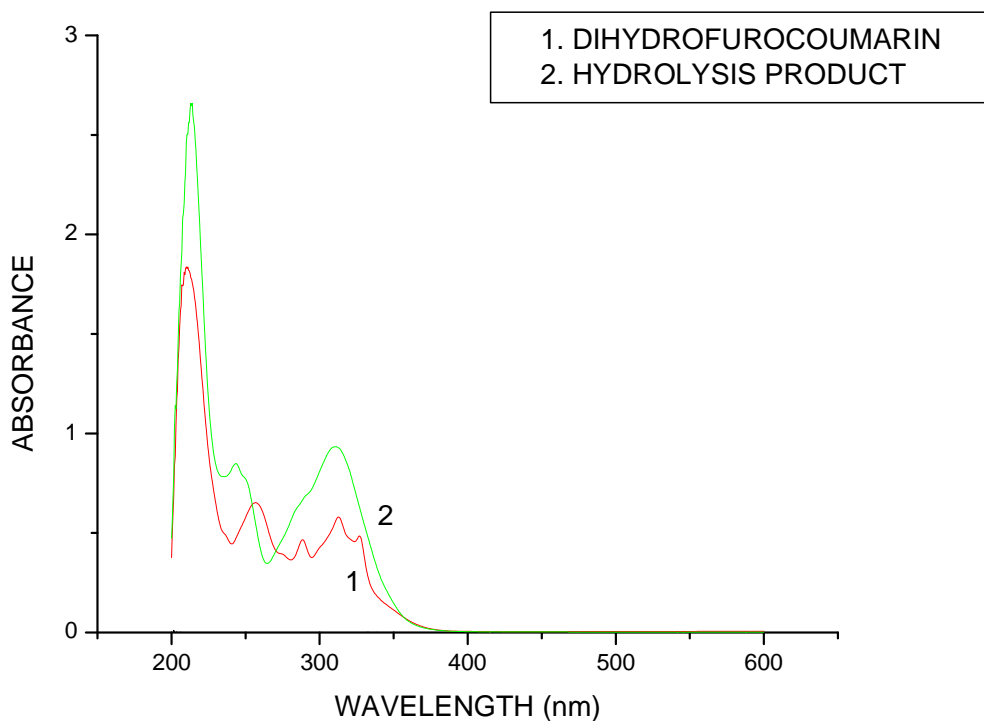

Figure 3:

Comparison of UV spectra of the dihydrofurocoumarin (I) and the hydrolysis product.

3.3 CONCLUSION

Due to the presence of a lactone ring, 2-hydroxybenzoyl group and dihydrofuran ring, the dihydrofurocoumarin (I) is susceptible to attack by a base. The base hydrolysis of dihydrofurocoumarin (I) is strongly influenced by the strength of the base and the temperature. The reaction is well controlled in weakly basic medium resulting in the isolation of a single product as precipitate on subsequent acidification The presence of –OH group in 2-hydroxybenzoyl is crucial in aiding further degradation as the corresponding methylated derivative on treatment with a base undergoes rapid opening of the lactone ring with no further

degradation..The corresponding furocoumarin of dihydrofurocoumarin(I) undergoes opening of the lactone ring on treatment with a base and does not react further suggesting the role of dihydrofuran ring in the degradation of the molecule. The UV-visible spectrum of the product obtained is different from dihydrofurocoumarin (I) as such it can be concluded that base induces actual degradation/isomerisation of the molecule rather than simple lactone ring opening. It can be suggested that strongly basic conditions and prolonged heating lead to a more complex breakdown of the dihydrofurocoumarin (I) as a mixture of products is obtained which are difficult to separate. The ongoing work is aimed at the synthesis of variously substituted dihydrofurocoumarins in order to study the effect of substitution on the hydrolysis reaction. The products obtained are coumarin derivatives which have significant pharmacological importance as such conditions are being optimized to isolate the products in better yields.

3.4 REFERENCES

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