CHAPTER I

GENERAL INTRODUCTION

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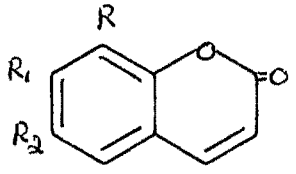
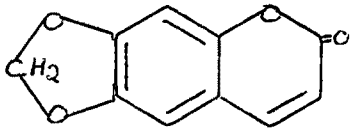
The chemistry of coumarins dates back to the year 1820 when simple coumarin was first isolated from the tonka beans. They are found to occur widely in nature and the few examples given below indicate the wide variety of structural features found in the naturally occurring coumarins. Coumarin, scopoletin, aesculetin, ayapin, fraxetin and daphnetin are a few of the simple coumarins found in nature.



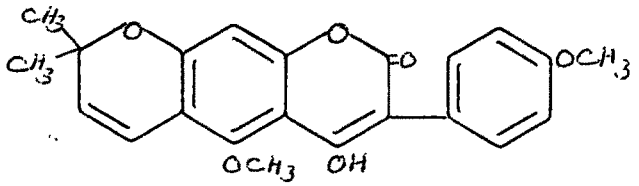


Ayapin

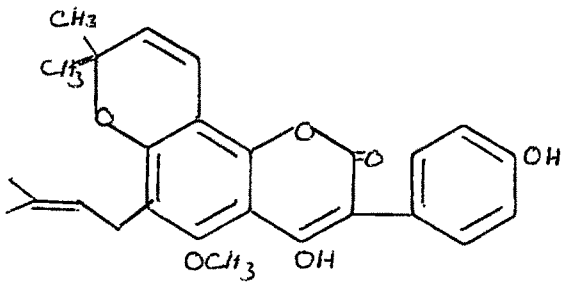
	R	R_1	R_2
Coumarin	H	H	H
Scopoletin	H	OH	OCH_3
Aesculetin	H	OH	OH
Fraxetin	OH	OH	OCH_3
Daphnetin	OH	OH	H

Some of them such as robustic acid (i), scandenin (ii) and lonchocarpic acid (iii) contain the 4-hydroxy-3-phenylcoumarin unit.[1,2] Among those derived

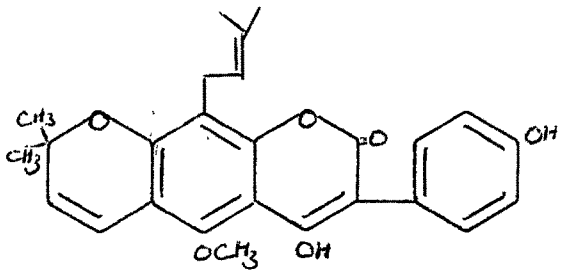
from 4-hydroxy-3-phenylcoumarins are coumestrol[3] (iva) coumestan[4] (ivb) and wedelolactone[5] (v),



I



II



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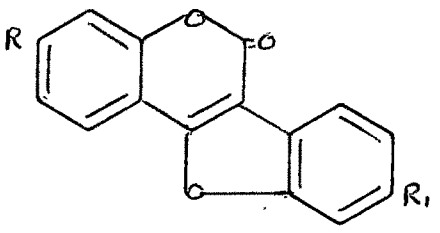
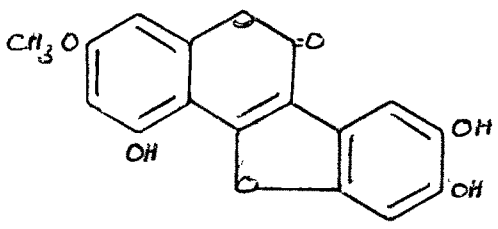


IV

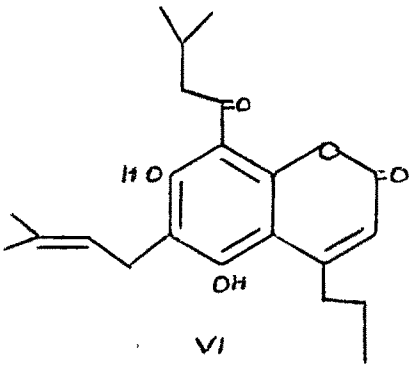
(a) $R = R_1 = OH$

(b) $R = R_1 = H$

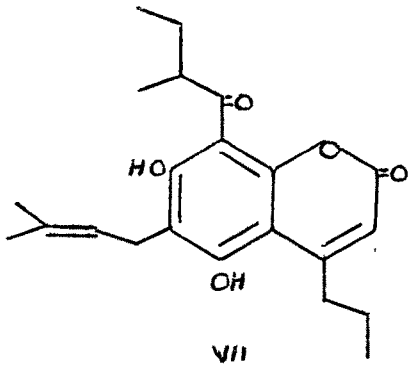


V

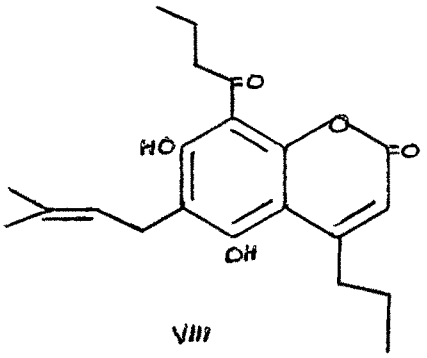
One group of naturally occurring coumarin derivatives contain the 4-alkylcoumarin units. Mammea B/BA (vi), Mammea B/BB (vii), Mammea B/BC (viii) and Mammea C/BB are a few of such type isolated by Crombie et al.[6]



VI



VII

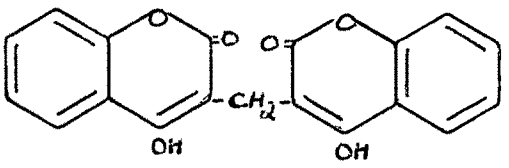


VIII

A group of interesting naturally occurring coumarin derivatives are the furocoumarins. These are described in some detail in chapter III.

The interest in coumarin derivatives has increased considerably in recent years because of the discovery of their varied biochemical properties[7], industrial uses and analytical applications. A few of these may be mentioned here.

Link and his coworkers[8] discovered that 3,3'-methylene bis-4-hydroxycoumarin named dicoumarol(IX) was the haemorrhagic principle of the spoiled sweet clover. Further synthetic work in this field led to the preparation of anticoagulant drugs such as warfarin, tromexan, coumachlor and marcoumar. It is interesting to note that some simple coumarins have the opposite effect. For example, herniarin and ayapin have been found to possess haemostatic property and are active both in vitro and in vivo[9].



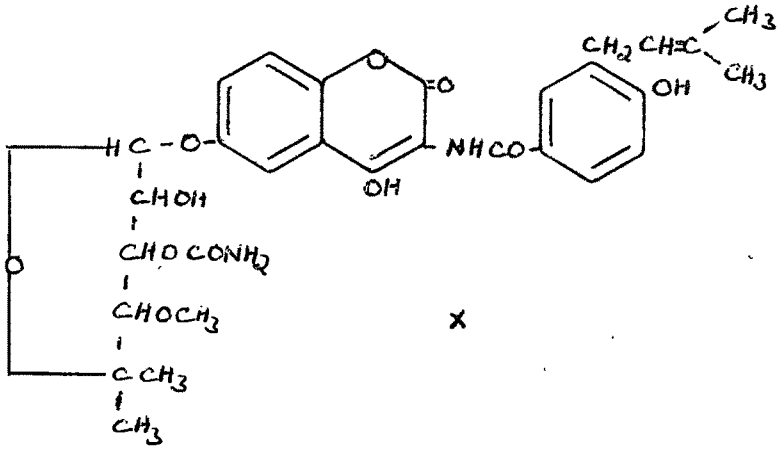
IX

Some of the coumarin derivatives are found to possess blastocholine effect i.e. the property of suppressing the germination of seeds[10] at low concentrations. Coumarin itself inhibits the germination and subsequent root growth of plants. Kelbs[11] observed its toxic action on algae. Sigmund[12] noted the effects of both daphnetin and its isomer aesculetin on seed germination. Some coumarin derivatives are found to be growth regulators in a number of plants[13].

Quercioli[14] studied the cytohistological and macroscopical effects of coumarin and its derivatives. Buu-Hoi and coworkers[15] prepared a series of hydroxylated 3-arylcoumarins as potential carcinostatic and virustatic agents and Elderfield and Roy[16] have synthesised nitrogen

mustards from 6-substituted coumarins as potential anticancer agents. Various 3- and 4-pyridyl coumarins are reported to be potential central nervous system depressants[17]. Coumarin acts as a narcotic for some animals and as a sedative and hypnotic for mice[18]. Fraxin has been found to be superior to atophan in the treatment of gout[19].

Novobiocin,[20] an antibiotic, isolated from streptomyces sp. has been found to be a coumarin derivative having the structure (X).



X

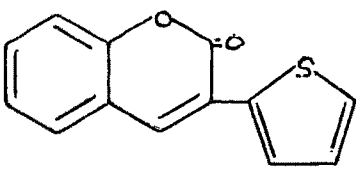
The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin.

Kawaguchi and coworkers[21] have isolated a new antibiotic coumermycin, a coumarin derivative from the filtrate (pH_5) residue of the fermentation beers of streptomyces rishiriensis.

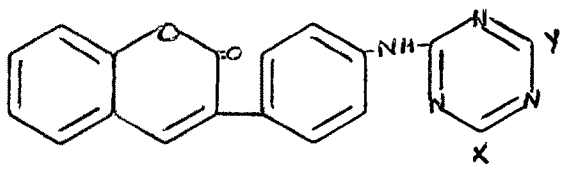
Strong anthelmintic action is exhibited by coumarin and some of its derivatives[22]. Some coumarins particularly those with furan ring systems such as bergapten, pimpinellin and isopimpinellin are found to be very good fish poisons[23].

Several Mannich bases derived from coumarins are found to have central nervous system stimulating action[24]. The use of coumarin derivatives as indicators[25] or as complexing agents[26] in analytical chemistry have been investigated.

Some of the coumarin derivatives are found to have optical brightening properties for cellulose, polyacrylic nitrile, polyamides and polyester fibres. 3-(2-Thienyl)coumarin of the type (XI)[27], 6-alkyl-7-alkylaminocoumarin[28], 3-(triazol-1-yl)coumarin and more complex coumarin derivatives such as (XII) obtained by reacting cyanuric chloride with 3-(p-aminophenyl)coumarin and treating the compound formed with N-ethylcyclohexylamine, 7-(1,2,3-triazol-2-yl)-3-phenyl-2-coumarin[29] and substituted 7-(3-triazinylamino)-3-arylcoumarin[30,31] are a few of the coumarin derivative which have good optical brightening properties.



XI

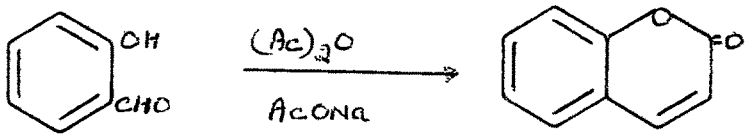


XII

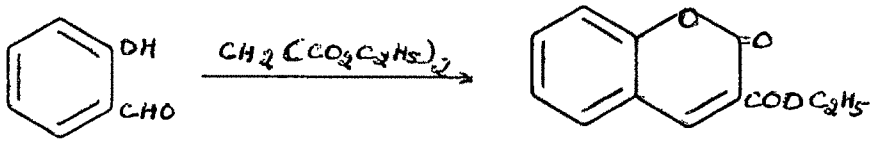
X = Cl , Y = N-ethyl cyclohexylamine

General methods for the synthesis of coumarins: A number of methods are available for the synthesis of coumarins. The three methods for the coumarin synthesis viz. Perkin reaction[32], Knoevenagel reaction[33] and Pechmann reaction which have been used in the present work may be briefly mentioned here.

Perkin reaction consists in heating an o-hydroxy aldehyde with an acid anhydride and its sodium salt at 175-80° for 5-6 hours when a coumarin is formed.

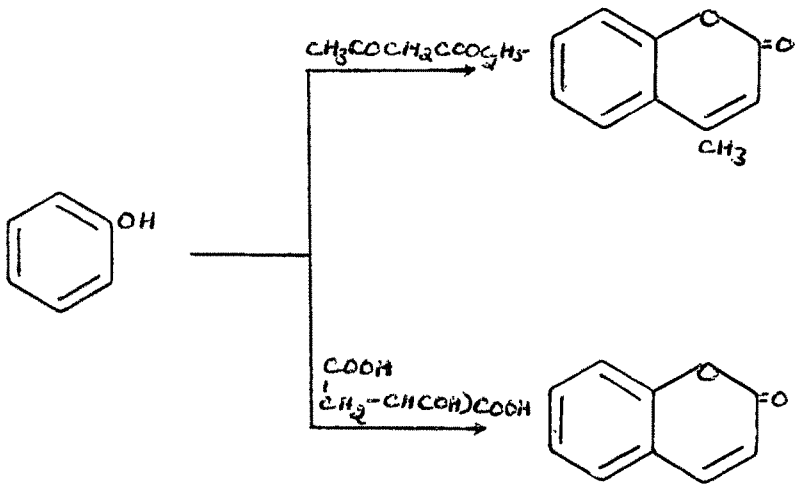


A method developed by Knoevenagel is the condensation of an o-hydroxy aldehyde with esters containing a reactive methylene group such as diethyl malonate, ethyl acetoacetate and ethyl cyanoacetate in the presence of piperidine, pyridine and other organic bases.

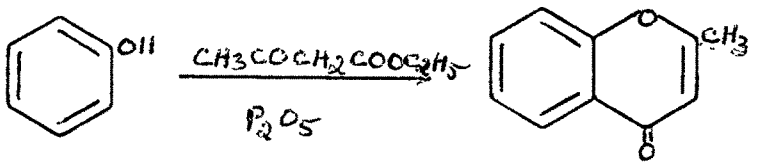


A detailed account of this reaction has been published by Jones[34].

Pechmann reaction : Pechmann reaction consists in the condensation of phenols with malic acid[35] or β-ketonic esters[36] in the presence of concentrated sulphuric acid when coumarins are obtained.



Simonis and his coworkers[37,38,39] used phosphorus pentoxide as the condensing agent in the place of sulphuric acid and reported the formation of chromones.



Later, it was found that chromones are formed only in some cases, especially where the phenol either reacts with difficulty or does not react at all in the presence of sulphuric acid with a β-ketonic ester. Other condensing agents which are used in the Pechmann reaction, are phosphorus oxychloride, phosphoric acid, zinc chloride, anhydrous aluminium chloride, ferric chloride, stannic chloride, sodium ethoxide, boric anhydride, hydrogen fluoride,[40] boron trifluoride etherate[41] and polyphosphoric acid[42]. The course of this reaction depends on all the three factors viz. the nature of the β-ketonic ester, nature of the phenol and the nature of the condensing agent. The various aspects of this reaction and the work done till 1949 in this field was reviewed by Sethna and Phadke[43] and these are therefore not discussed here.

An interesting observation was made by Mentzer and his coworkers[44,45,46] that the β-ketonic esters condense with phenols to give chromones on prolonged heating between 200-250° without using any condensing agent. Later, Desai et al.[47] found that the same condensations took place in 20 minutes to 2 1/2 hours if the phenol and the β-ketonic

ester were heated in a high boiling solvent such as diphenyl ether, phenetole, nitrobenzene or acetylene tetrachloride and chromones were obtained.

Besides these, there are other methods developed for the synthesis of coumarin derivatives. These have been enumerated in a number of reviews[48a, 48b].

Substitution in the coumarin ring system : The coumarin derivatives have been subjected to various substitution reactions. Some of the important substitution reactions applied to coumarins are given here to indicate the pattern of substitution in different coumarin derivatives.

Halogenation :

(a) Chlorination: Coumarin on chlorination gives 3-chlorocoumarin[49]. Dey et al.[50] obtained two products from 7-methylcoumarin-4-acetic acid viz. 7-methylcoumarin-4-chloroacetic acid and the decarboxylated product 7-methyl-4-chloromethylcoumarin. Seshadri and coworkers[51] chlorinated 7-hydroxy-4-methylcoumarin, its methyl ether and its acetoxy derivative and obtained the corresponding 3-chloro derivatives. Lindemann[52] had earlier given the 8-chloro structure to the chlorination product of 7-hydroxy-4-methylcoumarin. 4-Hydroxycoumarin gives the 3-chloro derivative[53].

(b) Bromination : The bromination of coumarin has been very extensively studied. The first bromine atom usually enters the 3-position. The second one enters the 6- or the

8-position. Where there is a reactive methylene group as in the case of coumarin-4-acetic acid one of the active hydrogen may be replaced by bromine and coumarin-4-bromo-acetic acid may be obtained.[50]

Peters and Simonis[54] obtained 3-bromo,3,6-dibromo-, and 3,6,8-tribromo derivatives from 4-methylcoumarin. 4,7-Dimethylcoumarin gave the 3-bromo derivative[55]. Seshadri and coworkers[56] obtained the 3,6-dibromo derivative from 4,7-dimethylcoumarin. 4,5,7-Trimethylcoumarin brominated in the 3-position[57]. Dey and Radhabai[50] obtained 7-methyl-coumarin-4-bromoacetic acid along with 7-methyl-4-bromo-methylcoumarin in the bromination of 7-methylcoumarin-4-acetic acid.

Several hydroxycoumarins have been brominated. Dalvi and Sethna[58] brominated 7-hydroxy-4-methylcoumarin, its 6-carboxy- and 6-carbomethoxy derivatives and their methylethers and found that in all cases the first bromine atom enters the 3-position. 7-Hydroxy-4-methylcoumarin on further bromination gave a mixture of the 3,6- and 6,8-dibromo derivative but the acid and the ester gave the 3,8-dibromo derivative.

Borsche[59] assigned the 5,7-dibromo structure to the bromination product from 6-hydroxy-4-methylcoumarin. 3-Hydroxycoumarin has been found to give the 4-bromo derivative[60] and 8-hydroxycoumarin and its methyl ether gave the 5-bromo derivative[61].

The bromination of 5-hydroxy-4-methyl- and 5-hydroxy-4,7-dimethylcoumarin and their methyl ethers

has been studied under different conditions[62]. The first bromine atom was found to enter the 8-position. On further bromination both the coumarin derivatives gave the 6,8-dibromo and the 3,6,8-tribromo derivatives.

Lele and Sethna[63] in their study of bromination of dihydroxycoumarin derivatives found that in the bromination of 4,7-dihydroxycoumarin the 3-bromo derivative was obtained and thus the 8-bromo structure earlier assigned by Bauer and Schoder[64] was incorrect. They brominated 7,8-dihydroxy-4-methylcoumarin and its methyl ether and obtained the 3-bromo derivatives. On further bromination they obtained a dibromo derivative which they found was the 3,6- and not the 3,4-dibromo derivative as reported by Sakai and Kato[65].

Some work has been carried out using N-bromo-succinimide as the brominating agent and interesting results have been obtained. Molho and Mentzer[66] obtained 3-bromo-methylcoumarin and 7-methoxy-3-bromo-4-methylcoumarin by the action of N-bromo succinimide on 3-methylcoumarin and 7-methoxy-4-methylcoumarin. 7-Methoxy-3-ethyl-4-methyl-coumarin gave a mixture of 7-methoxy-3-(1-bromoethyl)-4-methylcoumarin in good yield and 7-methoxy-6-bromo-3-ethyl-4-methylcoumarin in poor yield. Lecocq and Buu-Hoi[67] studied the action of N-bromosuccinimide on methylcoumarins and found that it reacts only with methyl groups in the benzene ring and not with methyl groups in the heterocyclic ring. Thus 6-methyl-,4,6-dimethyl- and 4,7-dimethylcoumarin gave 6-bromomethyl-,4-methyl-6-bromomethyl- and

4-methyl-7-bromomethylcoumarin respectively. Lecocq[68] obtained 3-bromo-4-methylcoumarin from 4-methylcoumarin on reaction with N-bromosuccinimide. Molho and Mentzer[66] observed halogen migration in certain brominations. Thus bromination of 3-ethyl- and 3-propyl-4-methyl-7-methoxy-coumarin with N-bromosuccinimide gave 3-ethyl-6-bromo- and 3-propyl-6-bromo-4-methyl-7-methyoxycoumarin, the 3-(α-bromoalkyl)compound being the intermediate. Bromination of 7-hydroxy-4-methyl-8-acetyl and 5-hydroxy-4-methyl-6-acetylcoumarin with cupric bromide in dioxane has been found to provide the ω-bromoacyl derivatives[69].

(c) Iodination : The iodination of various coumarins with different iodinating agents such as iodine monochloride, iodine and iodic acid, iodine and ammonia has been studied by Sethna and his coworkers[70,71]. 7-Hydroxy-4-methylcoumarin gave first the 8-iodo derivative and then with more of the iodinating agent the 3,8-diiodo and the 3,6,8-triiodo derivatives. Its methyl ether, however, gave first the 3-iodo and then the 3,6-diiodo derivative with more of the iodinating agent. 5-Hydroxy-4-methylcoumarin and its methyl ether gave first the 8-iodo derivative. Further iodination led to the 6,8-diiodo derivative in the case of 5-hydroxy-4-methylcoumarin. The authors have converted some of these iodo coumarins into the cyanocoumarins by Rosenmund reaction i.e. by heating with cuprous cyanide.

Nitration : Several studies on the nitration of coumarins have been made. Morgan[72] reported the formation of 6-nitro-

coumarin in the nitration of coumarin. Dey and Krishnamurthi[73] found that in the nitration of coumarin, both the 6- and 8-isomers were formed. Clayton[74] observed that further nitration of 6-nitrocoumarin and 8-nitrocoumarin yielded first the 3,6-dinitro and the 3,8-dinitrocoumarin respectively and then the 3,6,8-trinitrocoumarin. Clayton[74] also studied the nitration of 7-methyl-, 6,7-dimethyl- and 4,6,8-trimethylcoumarin and obtained various nitro derivatives. The ease of nitration was found to increase with the introduction of alkyl groups.

Several hydroxycoumarins have also been nitrated. 5-Hydroxy-4-methylcoumarin gave the 8-nitro and the 6,8-dinitro derivatives while 5-hydroxy-6-carboxy-4-methyl-coumarin and its esters gave the 8-nitro derivative[75]. 7-Hydroxy-4-methylcoumarin and its methyl ether gave the 6-nitro and the 3,6,8-trinitro derivatives[76].

The nitration of 8-hydroxycoumarin and its methyl ether gave the 7-nitro- and the 5-nitro derivative respectively[61], and the 5,7-dinitro derivative[77]. 4-Hydroxy-coumarin gave the 3-nitro and 3,6-dinitro derivatives[78]. The nitration of 6-hydroxy-4-methylcoumarin gave the 5-nitro and the 5,7-dinitro derivatives[79].

Sulphonation : Krüger[80] studied the sulphonation of some methyl coumarins and assumed that the sulphonic acid group entered the 6-position in each case. Coumarin on sulphonation with chloro sulphonic acid gave the 6-sulphonyl chloride derivative[81]. 4-Hydroxycoumarin on sulphonation with fuming sulphuric acid gave the 3-sulphonic acid[67].

Merchant and Shah[82] in an extensive study of the sulphonation with chlorosulphonic acid of various 7-hydroxy-4-methyl-coumarin with alkyl, bromo and carboxy groups in different positions found that the 6-sulphonic acid derivative was obtained where the 6-position was free. When it was occupied by another substituent the sulphonation took place in the 8-position. In the case of 6-nitrocoumarin however, the sulphonic acid group entered the 3-position. With larger amounts of chlorosulphonic acid they obtained the 3,6-disulphonic acid derivatives from coumarin and 7-methoxy-4-methylcoumarin. 7-Hydroxy-4-methylcoumarin and 7-hydroxy-3,4-dimethylcoumarin gave the 6,8-disulphonic acids. The former also gave the 3,6,8-trisulphonic acid. 5-Hydroxy-4-methylcoumarin gave the 8-sulphonic acid, the 3,6-disulphonic acid and the 3,6,8-trisulphonic acid derivatives.

Fries migration and Friedel-Crafts reaction: Limaye[83] carried out the Fries migration of various esters of 7-hydroxycoumarin derivatives and in all cases obtained the 8-acylcoumarin derivatives accompanied in some cases with traces of the 6-acyl isomer. The same 8-acyl derivatives were also obtained in the Friedel-Crafts acylation of 7-hydroxycoumarin derivatives. These 8-acyl coumarins on hydrolysis with hot alkali gave 2-acyl resorcinols. Shah and Shah[84] studied the Fries migration of 5-acetoxy, 5-benzoyloxy, 5-propionoxy and 5-butyroxy-4-methylcoumarin and obtained the corresponding 6-acyl derivatives which were also obtained from the Friedel-Crafts acylation of

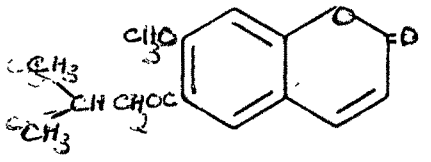
5-hydroxy-4-methylcoumarin. Thakor[85] studied the Fries migration of 6-acetoxy and 6-benzoyloxycoumarin and obtained the corresponding 5-acyl derivatives which were also obtained in the Friedel-Crafts acetylation and benzoylation of 6-hydroxycoumarin.

Bhavsar and Desai[86] studied the Fries migration of 4-methylcoumarinyl-7-p-toluene sulphonate and obtained the 8- and the 6-p-toluene sulphonyl derivatives. The Fries migration of 4,7-dimethyl-5-coumarinyl-p-toluene sulphonate yielded the 6-p-toluene sulphonyl derivative. The Fries migration of 4-methyl-7-coumarinylbenzene sulphonate yielded the 8-phenyl sulphonyl derivative but when the isomerisation was carried out in nitrobenzene the 6-isomer was also obtained along with the 8-isomer[87].

3-Acyl derivatives were obtained from 4-acyloxy-coumarins on Fries migration, which were also obtained by condensing 4-hydroxycoumarin with various organic acids in the presence of phosphoryl chloride[88]. The Fries rearrangement of 5,7-diacetoxy-3-chloro-4-methylcoumarin in the presence of boron trifluoride gave the 8-acetyl derivative and that of 5,7-diacetoxy-3-chloro-4,8-dimethylcoumarin in the presence of aluminium chloride gave the 6-acetyl derivative.[89] The Fries rearrangement of 3-acetoxycoumarin gave the 4-acetyl derivative which was also obtained on the Friedel-Crafts acetylation of 3-hydroxycoumarin.[90]

The natural coumarin known as Geijerin which is 7-methoxy-6-isovalerylcoumarin (xiii) was synthesised by Shah and co-workers[91] by the Fries migration of

7-isovaleroxycoumarin and subsequent methylation of the 6-isomer. This was obtained in very low yield of 0.1 g. from 22.5 g. of the ester whereas the yield of the 8-isomer was 2 g. from 11 g. of the ester.



XIII

Formylation : Sen and Chakravarti[92] prepared 6-formylcoumarin by heating coumarin with aqueous potassium hydroxide solution and chloroform. Späth and Pailer[93] obtained the 8-formyl derivative from 7-hydroxycoumarin by the Duff and Bills method. 6-Hydroxy- and 6-hydroxy-4-methylcoumarin gave the 5-formylcoumarin[94] and 5-hydroxy-4-methyl and 5-hydroxy-4,7-dimethylcoumarin with hexamethylene tetramine gave the 6,8-diformyl derivative and 7,8-dihydroxy-4-methylcoumarin gave the 6-formyl derivative[95a]. Formylation of 5-hydroxy-4-methylcoumarin with N-methylformanilide furnished the 6-formyl derivative whereas the 5-hydroxy-4,7-dimethylcoumarin furnished both the 6-formyl- and the 8-formyl derivative[95b]. Ziegler and Maier[96] formylated 4-hydroxycoumarin in chlorobenzene with N-methylformanilide in the presence of phosphorus oxychloride and obtained the 3-formyl derivative.

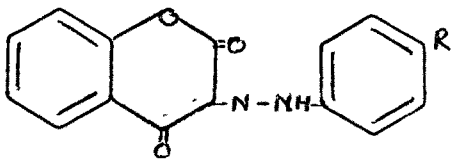
Claisen Rearrangement : 7-Allyloxy- and 7-allyloxy-4-methylcoumarin gave the 8-allyl derivative on Claisen rearrangement[97,98]

and 5-allyloxy-4,7-dimethylcoumarin gave the 6- or the 8-allyl derivative depending on the temperature of the reaction[99]. The Claisen migration of y-dimethyl allyl ether of 5-hydroxy-, 6-hydroxy-, 7-hydroxy- and 8-hydroxy-coumarin did not give the C-allyl derivatives. Only degradation to the corresponding hydroxy coumarins and isoprene took place, possibly due to the bulky methyl groups on the y-carbon atom[100].

Elbs persulphate oxidation: A number of coumarin derivatives have been subjected to this reaction. 6-Hydroxycoumarins are invariably obtained in this reaction if that position is free. If it is occupied, then the reaction usually does not take place. Bargellini and Monti[101] oxidised simple coumarin and its 7-methoxy derivative. 7,8-Dimethoxy-[102] and 8-methoxycoumarin[103] were also oxidised. Sethna and co-workers[104,105] applied this reaction to 4-methyl-, 7-methoxy-4-methyl-, 5-methoxy-4-methyl-, 5-methoxy-4,7-dimethyl-, 5,7-dimethyoxy-4-methyl-, and 7,8-dimethoxy-4-methylcoumarin. In all these cases, the corresponding 6-hydroxycoumarin derivatives were obtained. Bhavsar and Desai[106] applied this reaction to several coumarins after protecting the hydroxy group by preparing its p-toluene sulphonyl derivative. They could prepare isomeric methoxy hydroxy coumarins by this method. Oliverio et al.[107] oxidised 5-hydroxy-6-acetyl-4-methylcoumarin and obtained 5,8-dihydroxy-6-acetyl-4-methylcoumarin. This reaction has been very useful in the synthesis of natural and new coumarins.

Coupling reaction : Borsche[108] observed that when coumarin is coupled with diazonium salts the coupling takes place at 6-position. 7-Hydroxy and 7-hydroxy-4-methylcoumarin were condensed with diazotised p-nitroaniline by Rangaswamy and Seshadri[109]. They observed that when caustic soda was employed, the formation of diazodyes took place, but when sodium carbonate was employed monoazodyes alone were produced. Rangaswamy and Rao[110] condensed 5-hydroxy-7-methyl-, 5-hydroxy-4,7-dimethyl- and 7-hydroxy-5-methylcoumarin with diazotised p-nitroaniline at 0^{0} and obtained monoazo as well as diazodyes.

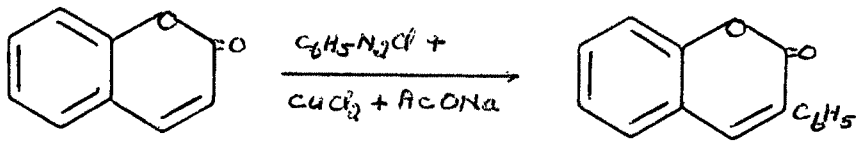
Huebner and Link[111] observed that in the coupling of 4-hydroxycoumarin with diazotised amines in sodium carbonate solution, a product separated immediately after coupling without acidification to which the hydrazone structure (XIV) was assigned.



XIV

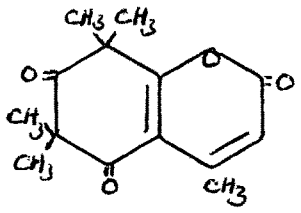
Meerwein reaction : Meerwein et al.[112] observed that α,β-unsaturated compounds and their derivatives react under suitable conditions with an aromatic diazo compound during which nitrogen is split off and in most cases the aryl group of the diazo compound replaces the hydrogen attached to α C atom. He obtained 3-phenylcoumarin in 26 % yield and 3-p-nitrophenylcoumarin in 50 % yield from the

Condensation of coumarin with the corresponding diazonium salt in acetone solvent.

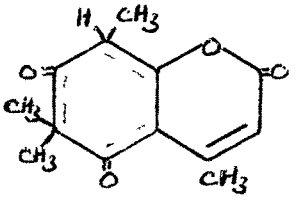


Freund[113] used this method for the synthesis of 3-(p-arsonophenyl)coumarin. Siddiqui et al.[114] condensed p- and m-nitrobenzene diazonium chloride with coumarin and obtained 4'-nitro and 3'-nitro-3-phenylcoumarin. Sawhney and Seshadri[115] obtained a number of 3-phenyl coumarins by this method.

Nuclear methylation : The nuclear methylation of typical hydroxy coumarins with methyl iodide was studied by Gupta and Seshadri[116]. 7-Hydroxy and 7-hydroxy-4-methylcoumarin did not undergo any change at 0° but in boiling methanolic solution they underwent substitution in the 8-position. 5,7-Dihydroxy-4-methylcoumarin underwent substitution in the position 6 at 0° and on prolonged reaction in boiling methanolic solution it gave a mixture of 4,6,6,8,8-pentamethyl-5,7-diketo-5,6,7,8-tetrahydrocoumarin (XV) and 4,6,6,8-tetramethyl-5,7-diketo-5,6,7,8-tetrahydrocoumarin(XVI).



XV



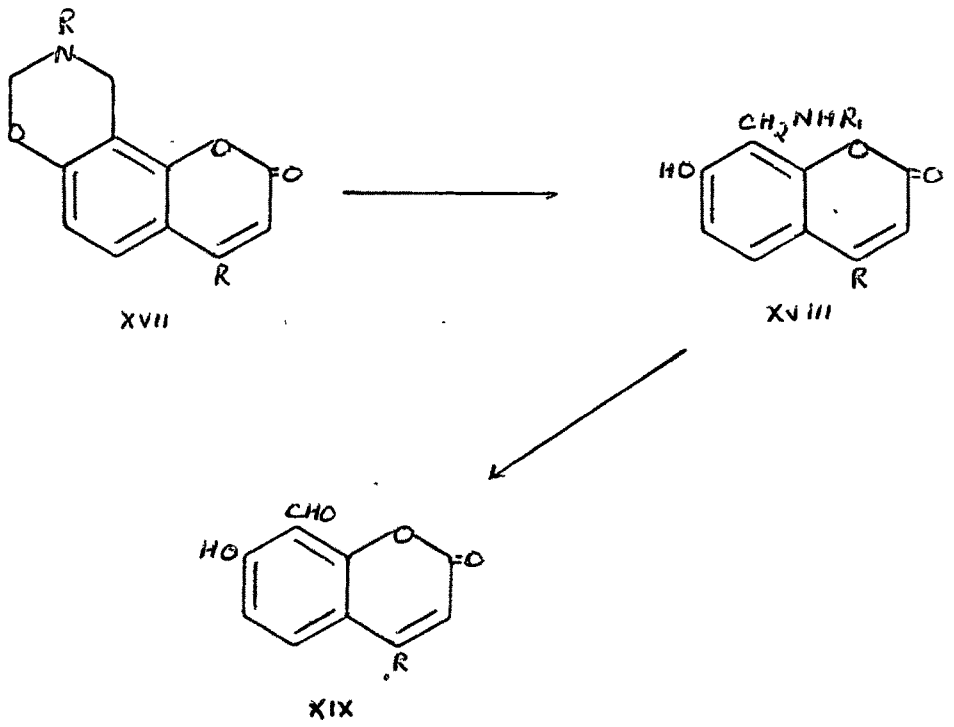
XVI

Chloromethylation : Sethna and co-workers[117,118] studied the chloromethylation of a number of coumarin derivatives. Coumarin, 4-methylcoumarin and 7,8-dimethoxy-4-methylcoumarin gave the 3-chloromethyl derivatives. 7-Methoxy-4-methylcoumarin gave under different conditions 6-chloromethyl-, 3,6-dichloromethyl-, 3,8-dichloromethyl- and 3,6,8-trichloromethyl derivatives. 5-Methoxy-4-methylcoumarin gave the 3,8-dichloromethyl derivative and 6-hydroxy-4-methylcoumarin gave the 5-chloromethyl derivative. The chloromethylation of some other substituted coumarins such as methyl-7-hydroxy-4-methyl and methyl-5-hydroxy-4-methylcoumarin-6-carboxylate and 4-methyl-1,2-naphtha-α-pyrone have also been studied.

Mannich reaction : Robertson and Link[119] prepared a series of 3-substituted aminomethyl-4-hydroxycommarins from 4-hydroxycoumarin by reacting it with paraformaldehyde and aminohydrochlorides. Gupta et al.[120] synthesised Mannich bases from 7-hydroxy- and 7-hydroxy-4-methylcoumarin and

found them to be powerful nervous system and respiratory stimulants. Da Re et al.[24] found that of the 50 coumarin derivatives examined, 6-methoxy-5-dimethylaminomethyl-coumarin was the most active in stimulating the central nervous system. They further found that the Mannich bases from coumarins were less active than those from the corresponding chromones and flavones.

5-Hydroxy-, 6-hydroxy- and 7-hydroxy-4-methyl-coumarins were found to give the oxazino derivatives when the primary amines were used[121]. 6-Hydroxy-, 7-hydroxy- and 8-hydroxycoumarins gave Mannich bases with secondary amines and oxazinocoumarins (XVII) with primary amines[122,123]. The oxazino derivatives were decomposed with dilute hydrochloric acid and the Mannich base (XVIII) obtained. Mannich bases were converted into the corresponding formyl derivatives (XIX) by Sommelet reaction.



Coumarins have been subjected to a number of other reactions such as Diels-Alder reaction[124,125] and Michael reaction.[126,127,128,129]

A great deal of work has been done on the synthesis of coumarino-α-pyrones, coumarino-γ-pyrones and furocoumarins in which the α-or γ-pyrone or the furan ring has been built up on the benzenoid or the heterocyclic part of the coumarin ring system. This work has been discussed in Chapter III.

PRESENT WORK

The present work deals with some studies on coumarin derivatives.

Chapter II deals with some studies made on 4,6-dimethyl-, 4,7-dimethyl-, 7-methyl- and 6-methyl-coumarin. These have been subjected to chloromethylation and the structures of the chloromethyl derivatives obtained have been established by reduction to the corresponding methylcoumarins of known orientation. Mannich bases have been prepared from the above chloromethylcoumarins. The above methylcoumarins have been converted into the 6- and 7-bromomethyl derivatives through the action of N-bromosuccinimide. On Sommelet reaction, the bromomethyl group is replaced by the formyl group and the formylcoumarins so obtained have been subjected to Perkin acetylation to get the β-coumarinyl acrylic acids. With hippuric acid the formyl coumarins gave the azlactones which have been

converted into β-coumarinyl alanines by heating with hydriodic acid and red phosphorus. The formyl coumarins have also been converted into 2'-chromonylcoumarins through condensation with o-hydroxy acetophenone and cyclisation of the coumarinyl vinyl phenyl ketones formed with selenium dioxide in iso-amyl alcohol.

Chapter III deals with the synthesis of 3'-carboxy-4-methylcoumarino (6,7 ; 6',5')α-pyrone and the synthesis of 4-methyl furo(5',4' :6,7)coumarin from 4-methyl-7-formylcoumarin. The attempted sunthesis of coumarino (6,7 ; 6',5')α-pyrone and its 4-methyl derivative and furo (5',4' ;6,7)coumarin have also been described.

Chapter IV deals with studies on 3-(4'-hydroxy-phenyl)coumarin. This has been converted into 3-(4'-hydroxy-3'-formyl phenyl)coumarin and 3-(4'-hydroxy-3'-acetyl phenyl) coumarin and d these intermediates have been used to build up the various oxygen heterocyclic rings such as α-pyrone, γ-pyrone and furan rings to synthesise coumarins with coumarinyl,chromonyl,flavonyl and benzofuranyl groups in the 3-position.

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