GENERAL INTRODUCTION

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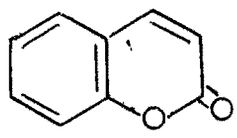
Benzo-α-pyrones, generally known as coumarins, are found to be widely distributed in the plant kingdom, either in the free or in the combined state. Coumarin (1), scopoletin (2), aesculetin (3), ayapin (4), fraxetin (5) and daphnetin (6) are a few of the simple coumarins occurring in nature.



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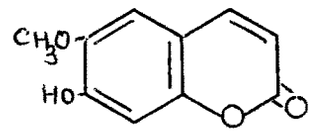

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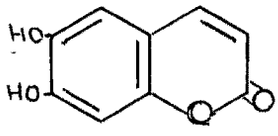

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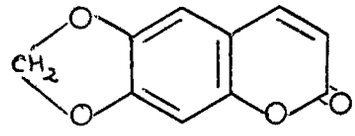

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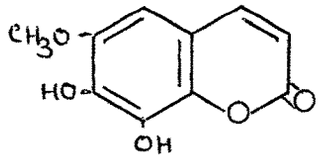

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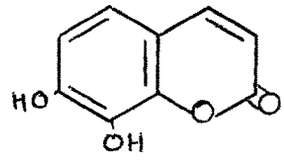
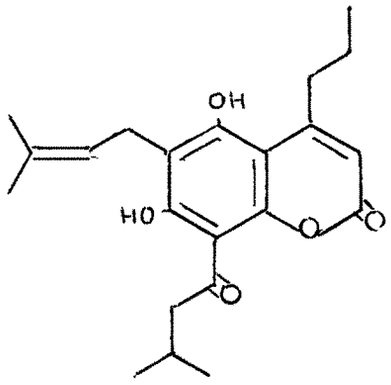


(6)

Recently L.Crombie and coworkers[1] have isolated four different 4-alkylated coumarin derivatives, mammea B/BA (7), mammea B/BB (8), mammea B/BC (9) and mammea C/BB (10) from the seeds of the insecticide bearing plant Mammea Americana L.(Gutliferae).



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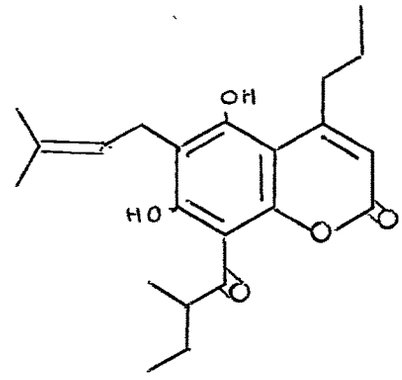

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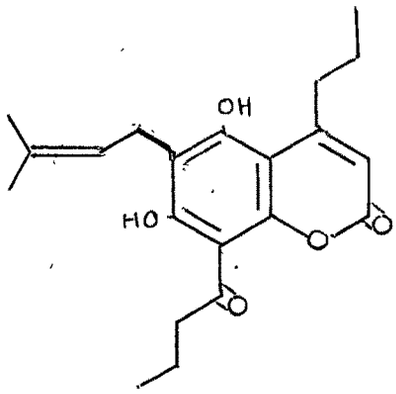

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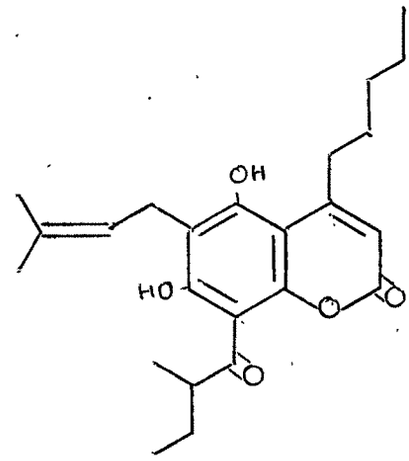
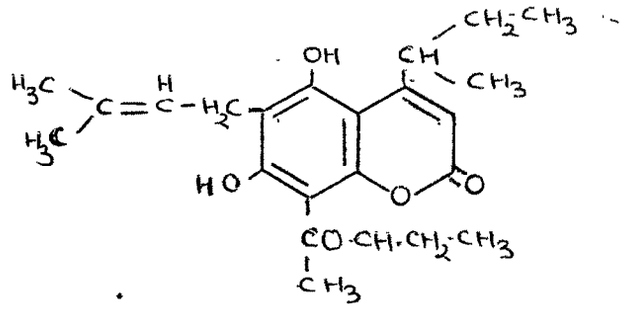


(10)

Structures of these coumarin derivatives have been established on the basis of analysis, I.R., U.V. and N.M.R.Spectra.

Govindachari, Pai and coworkers[2] have recently isolated 4-alkylcoumarin derivative, ferruol-A, from the trunk bark of Mesua ferrea L.



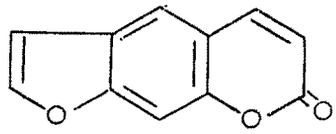
(11)

The authors have established the structure of (11) on the basis of analytical data, I.R., U.V., N.M.R. spectral data and also by degradation methods.

Another group of the interesting naturally occurring coumarin derivatives are the furocoumarins. Psoralene (12), angelicin (13), bergaptan (14), xanthotoxin (15), pimpinellin (16), isopimpinellin (17) and oreoselone (18) are a few members of this group.

The interest in coumarin derivatives has considerably increased in recent years because of the discovery of their varied biochemical properties, industrial uses and analytical applications ; a few of these may be briefely reviewed here.

Many natural coumarins affect the living cells of plants and animals in various ways. Bose[3] has reviewed the biochemical properties of natural coumarins. Coumarin



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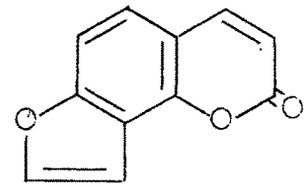

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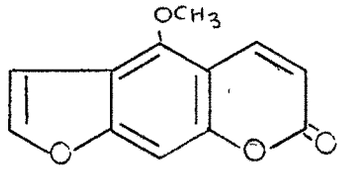

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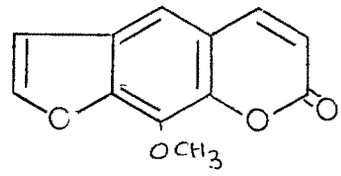

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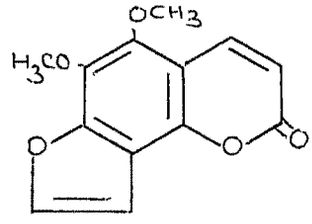

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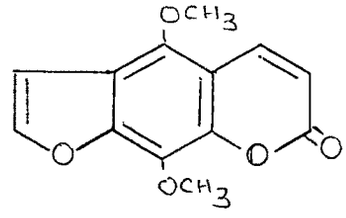

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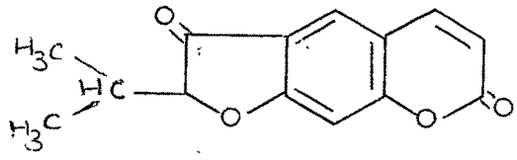


(18)

itself, inhibits the germination and subsequent root growth of plants. Kelbs[4] observed its toxic action on algae. Sigmund[5] noted the effects of both daphnetin and its isomer aesculetin on seed germination. It has since been shown that a number of unsaturated lactones, including coumarin, possess what is called the "blastocholine" effect i.e. the property to suppress the germination at low concentrations, on seeds[6] as well as on animals[7].

There is also a good probability that coumarins act as growth regulators in a number of plants[8].

Coumarins have interesting cytogenetic properties.[9] Cytohistological and macroscopical effects of coumarin and its derivatives have been studied by Quercioli[10].

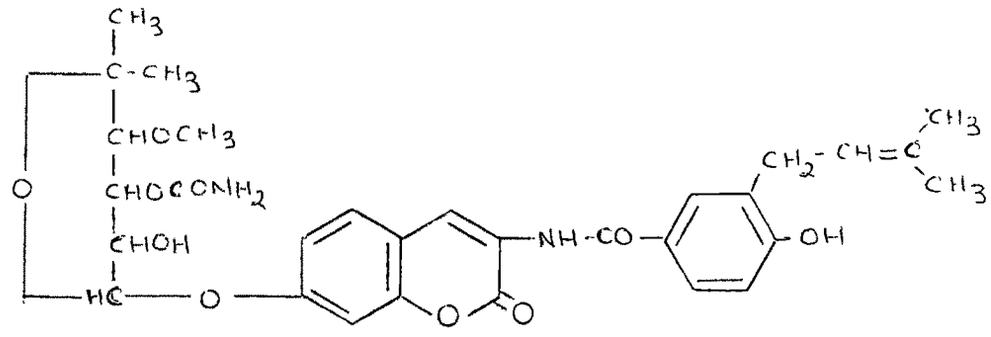
Coumarin acts as a narcotic for some animals and as a sedative and hypnotic for mice[11].

Fraxin causes paralysis of the central nervous system of frogs and mice on intravenous injections[12]. Fraxin has been found to be superior to atophan in the treatment of gout[13].

Link et al.[14] discovered that the haemorrhagic principle of the spoiled sweet clover was 3,3'-methylene bis-(4-hydroxycoumarin) also known as dicoumarol. This has led to the preparation and testing of several 4-hydroxycoumarin derivatives as anticoagulant drugs and a number of very effective drugs of this group such as warfarin, tromexan, coumachlor and marcoumar are on the market. It is interesting to note that some simple

coumarins have the opposite effect. Herniarin and ayapin have been found to possess a remarkable haemostatic property and are active both in vitro and in vivo[15].

Novobiocin[16], an antibiotic, isolated from streptomyces sp., has been found to be a coumarin derivative having the structure (19). The antibacterial spectrum of this antibiotic corresponds generally with that of penicillin and erythromycin but in vitro it is less potent than penicillin and erythromycin.

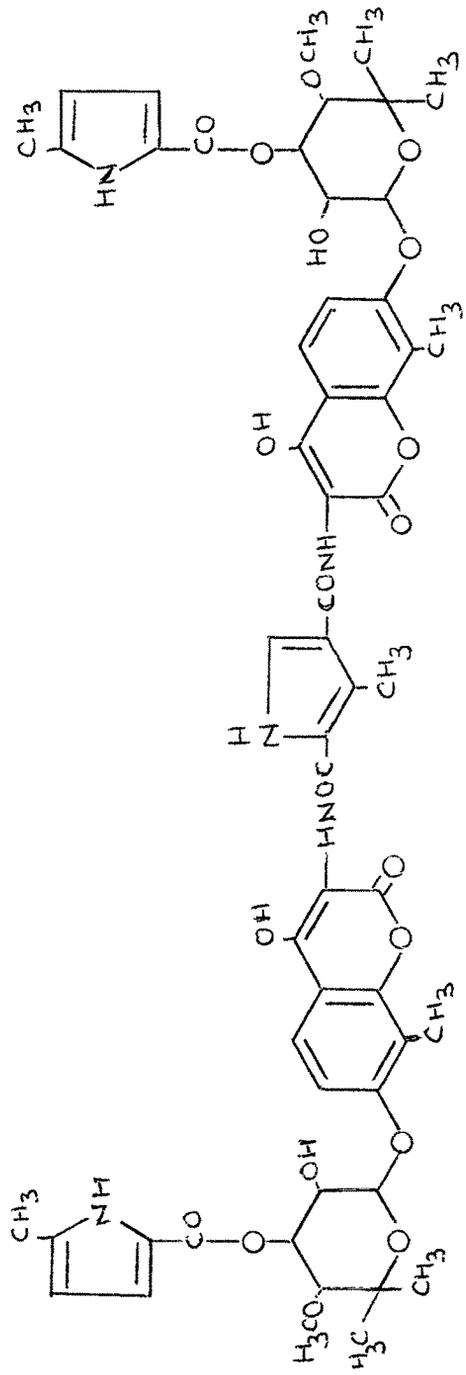


(19)

Recently Kawaguchi and coworkers[17] have obtained new antibiotic coumermycin, a coumarin derivative, from the filtrate (pH5) residue of the fermentation beers of streptomyces rishiriensis having the structure (20).

Coumermycin A_1 inhibits the growth of gram positive, gram negative and acid fast bacteria and against staphylococai it is about 30 times more potent than novobiocin.

Tuberculostatic activity[18] is exhibited by pimpinellin and isopimpinellin.



(20)

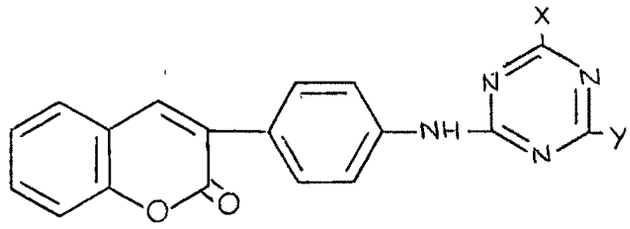
Coumarin and some of its derivatives having m.ps. lower than 70-100° have been generally found to possess strong anthelmintic action[19]. An examination of a number of simple coumarin derivatives employing fish and the turning time as a measure of toxicity has now established that they have weak toxic properties[20,21]. While coumarins particularly those with furan ring system are toxic to fish[22].

In recent years the discovery of photodynamic action of some of the furocoumarins has led to considerable work in this field[23].

The photodimerization of coumarins is being increasingly studied. The photodimerization product of 7-methoxycoumarin was formulated as a head to head dimer.[24] Simple coumarin however, was found to give both, the head to head and the head to tail dimers.[25] Hammond et al.[26] investigated the mechanism of photodimerization of coumarin. The solvent effects on the photodimerization of coumarin have also been studied.[27]

A number of substituted coumarin derivatives are found to have optical brightening properties for cellulose, polyacrylic nitrile, polyamides and polyester fibres and the literature has been growing in this field[28,29,30]. More complex coumarin derivatives such as (21) obtained by reacting cyanuric chloride with 3(p-aminophenyl) coumarin and treating the compound formed with N-ethyl cyclohexylamine ; 7-(1,2,3-triazol-2-yl)-3-phenyl-2-coumarin[31] and substituted 7-(3-triazinylamino)-3-

arylcoumarin[32,33] are a few of the coumarin derivatives which have good optical brightening properties.



X = Cl

Y = N-ethylcyclohexylamine

Buu-Hoi and coworkers[34] prepared a series of hydroxylated-3-arylcoumarins as a potential carcinostatic and virustatic agents and Elderfield and Roy[35] have very recently synthesised nitrogen mustards from 6-substituted coumarins as potential anticancer agents.

There are number of methods available for the synthesis of coumarin derivatives. These have been reviewed by Sethna and Shah[36] and Wawzonek[37] and need not be enumerated here.

The coumarin derivatives have also been subjected to various substitution reactions such as chlorination,[38,39,40,41] bromination,[42,43,44,45,46,47,48,49,50] iodination,[51,52] chloromethylation,[53] nitration,[54,55,56,57,58,59] Fries and Friedel-Crafts reaction,[47,60,61,62,63,64] formylation,[65,66,67,68,69] sulphonation[70,71,72] and other reactions.

The present work deals with some aspects of the chemistry of coumarins.

Chapter I deals with the studies on the synthesis of different 2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran derivatives and furocoumarins, starting with different 4-hydroxycoumarins. It also deals with the synthesis of furocoumarins in which furan ring is built up on benzenoid part of 4-hydroxycoumarin ring systems.

In chapter II, the syntheses of benzofuro(3,2-c) coumarins by condensing different 4-hydroxycoumarins with catechol have been described.

In chapter III, the syntheses of different 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran derivatives have been described.

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CHAPTER I

Studies in the Synthesis of Coumarino-α-pyrones and Furocoumarins

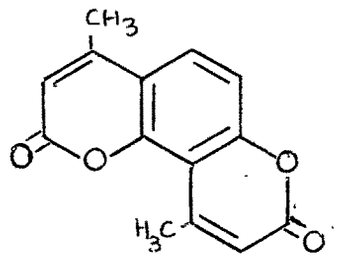
CHAPTER I

T H E O R E T I C A L

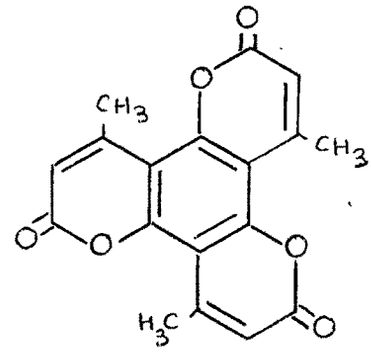
Studies in the synthesis of coumarino-α-pyrones and furocoumarins :

The benzo-α-pyrones or coumarins and the 2-phenylbenzo-γ-pyrones or flavones are found in nature in abundance. The α- and γ-pyrone derivatives have also gained importance in recent years because of their important physiological properties. Recently they have been found to have coronary dilating activity[1].

Hantzsch and Zurcher[2] condensed resorcinol and phloroglucinol with 2 and 3 moles of ethyl acetoacetate in the presence of sulphuric acid and obtained pyrano-benzopyran derivatives (1) and (2) respectively in poor yields.



(1)



(2)

Sen and Chakravarti[3] condensed umbelliferone and 4-methylumbelliferone with malic acid in the presence of sulphuric acid and obtained 2,6-dioxo-2H,6H-pyrano(2,3-h) benzopyran (coumarino-7,8-α-pyrone)* (3a) and 8-methyl-2,6-dioxo-2H,6H-pyrano(2,3-h)benzopyran (4-methylcoumarino-

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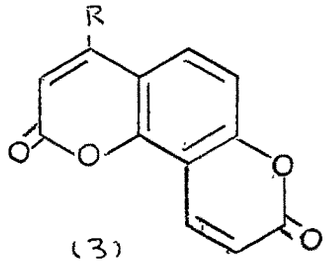
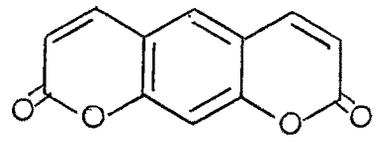
* Nomenclature of the compounds given in the brackets is according to the authors as published in the papers.

7,8-α-pyrone) (3b). Daphnetin,4-methyldaphnetin,homo-umbelliferone and 4-methylhomoumbelliferone on similar condensation with malic acid gave corresponding pyranobenzopyran derivatives.



(3)

a) R = H
b) R = CH_3

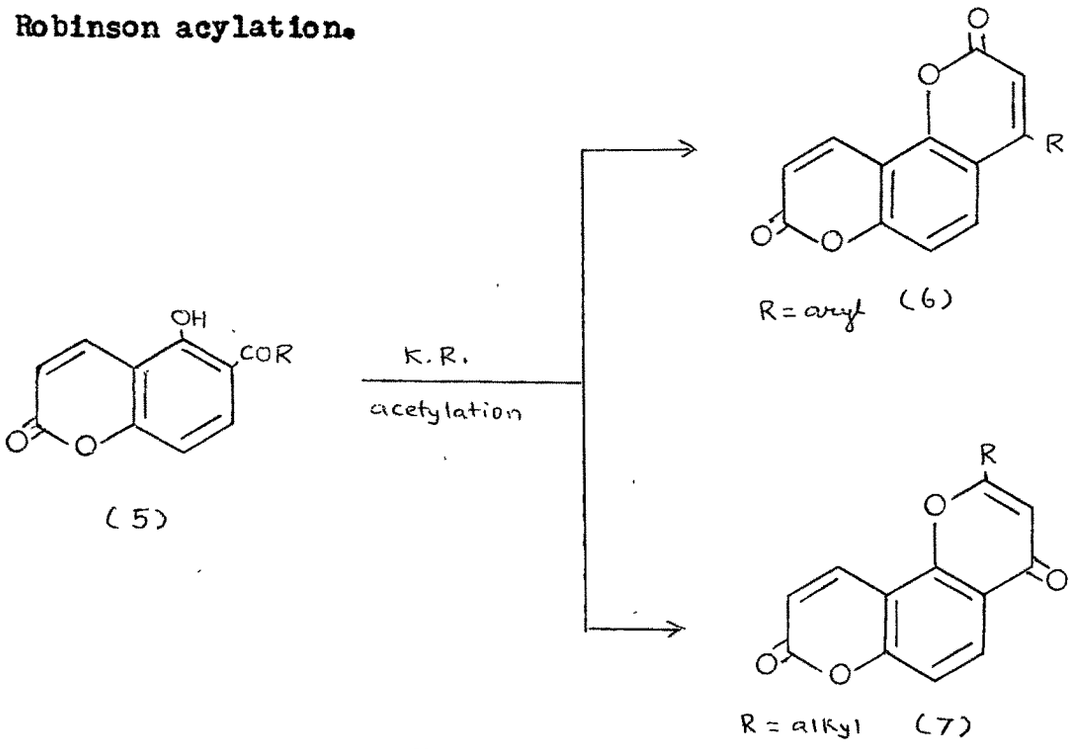


(4)

They, however, did not prove the structures of the coumarino-α-pyrones formed. Rangaswami and Seshadri[4] showed that when umbelliferone is condensed with malic acid both the angular (3a) and the linear (4) pyranobenzopyran derivatives are formed but the latter is obtained in poor yield. Under the same experimental conditions 4-methylumbelliferone gives only the angular coumarino-α-pyrone (3b). They proved the structure of 2,6-dioxo-2H,6H-pyrano (2,3-h)benzopyran (3a) by its synthesis from 7-hydroxy-8-formylcoumarin (5) by Perkin reaction. In a similar way the constitution of 8-methyl-2,6-dioxo-2H,6H-pyrano(2,3-h) benzopyran was also proved.

Biswas[5] condensed 7-hydroxy-3-chloro-4-methyl-, 5-hydroxy-3-chloro-4,7-dimethyl-, and 7,8-dihydroxy-3-chloro-4-methylcoumarin derivatives with malic acid and obtained the corresponding pyranobenzopyran derivatives.

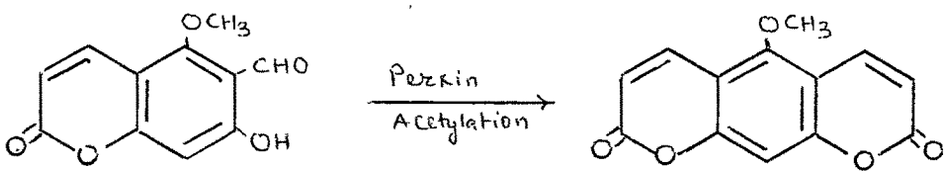
Shah and coworkers[6] synthesised several coumarino-α-pyrones (6) and coumarino-γ-pyrones (7) by subjecting 5-hydroxy-6-acylcoumarin derivatives (5) to Kostanecki-Robinson acylation.



(5)

Limaye and Ghate[7] obtained 4,6-dimethyl-10-ethyl-2,8-dioxo-2H,8H-pyrano(3,2-g)benzopyran (4,4'-dimethyl-8-ethylcoumarino-7,6-α-pyrene) and 7-acetyl-4,8-dimethyl-2,6-dioxo-2H,6H-pyrano(3,2-g)benzopyran (2',4-dimethyl-8-ethyl-3'-acetylcoumarino-γ-pyrone) from 7-hydroxy-8-ethyl-6-acetyl-4-methylcoumarin by Kostanecki-Robinson acetylation.

Mustafa, Starkovsky and Zaki[8] prepared 5-methoxy-2,8-dioxo-2H,8H-pyrano(3,2-g)benzopyran (5-methoxy-coumarino-7,6-α-pyrone) (9) by Perkin acetylation of apoxanthoxyletin (8).

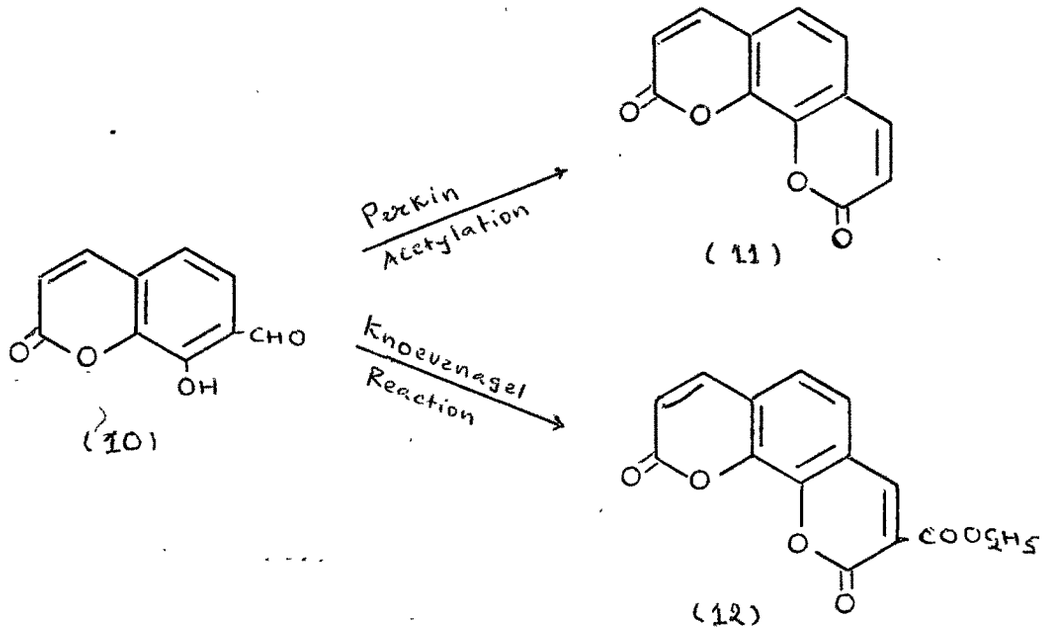


(8) (9)

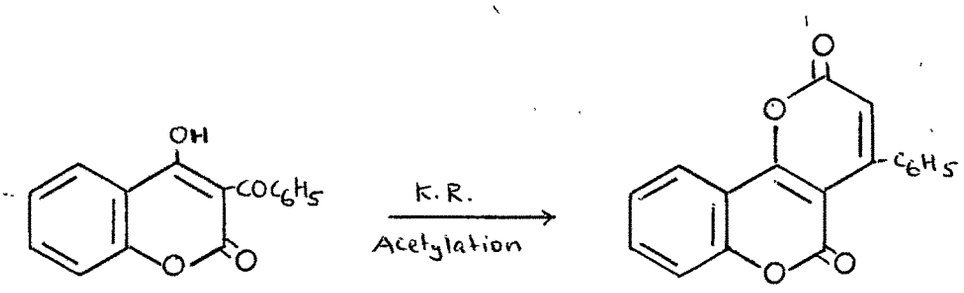
Trivedi and Sethna[9] prepared 3,4-dimethyl-2,8-dioxo-2H,8H-pyrano(2,3-h)benzopyran (3,4-dimethylcoumarino-7,8-α-pyrone) and 3,4,9-trimethyl-2,6-dioxo-2H,6H-pyrano (2,3-f)benzopyran (3,4,7-trimethylcoumarino-5,6-α-pyrone) by the condensation of 7-hydroxy-3,4-dimethylcoumarin and 5-hydroxy-3,4,7-trimethylcoumarin with malic acid. They also synthesised 3,4-dimethyl-10-hydroxy-2,8-dioxo-2H,8H-pyrano(3,2-g)benzopyran (8-hydroxy-3,4-dimethylcoumarino-7,6-α-pyrone), 3-bromo-4-methyl-2,8-dioxo-2H,8H-pyrano(2,3-h)benzopyran (3-bromo-4-methylcoumarino-7,8-α-pyrone) and 3-bromo-4-methyl-10-hydroxy-2,8-dioxo-2H,8H-pyrano(3,2-g)benzopyran (3-bromo-4-methyl-8-hydroxycoumarino-7,6-α-pyrone) from 7,8-dihydroxy-3,4-dimethylcoumarin, 7-hydroxy-3-bromo-4-methylcoumarin and 7,8-dihydroxy-3-bromo-4-methylcoumarin respectively. They proved the structures by Perkin acetylation of the corresponding formylated coumarin derivatives.

Mehta[10] prepared coumarino-α-pyrones by carrying out Perkin acetylation and Knoevenagel reaction on 8-hydroxy-7-formylcoumarin (10) and obtained 2,9-dioxo-

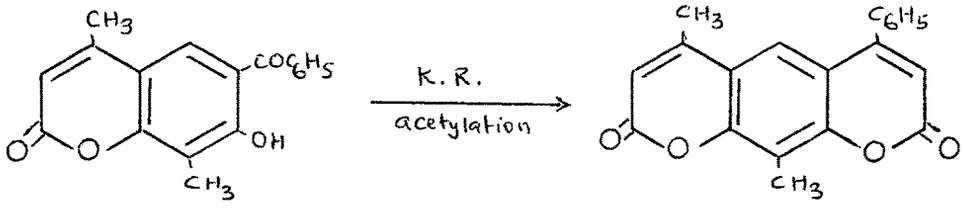
2H,9H-pyrano(3,2-h)benzopyran (α-pyrano-5',6',7,6-coumarin) (11) and 3-carboethoxy-2,9-dioxo-2H,9H-pyrano(3,2-h) benzopyran (3'-carboethoxy-α-pyrano-5',6',7,6-coumarin)(12) respectively.



Mustafa and coworkers[11] carried out Kostanecki-Robinson acetylation on 4-hydroxy-3-benzoylcoumarin (13) and obtained 4-phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (14).



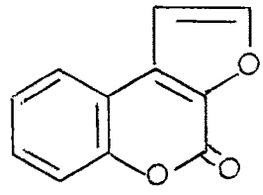
Trivedi and coworkers[12] recently synthesised 4,10-dimethyl-6-phenyl-2,8-dioxo-2H,8H-pyrano(3,2-g) benzopyran (16) by carrying out Kostanecki-Robinson acetylation on 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin (15). The structure of pyranobenzopyran (16) was established on the basis of I.R.Spectra.



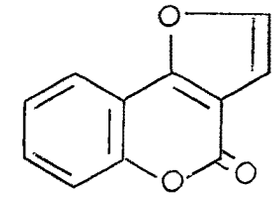
(15) (16)

Furocoumarins :

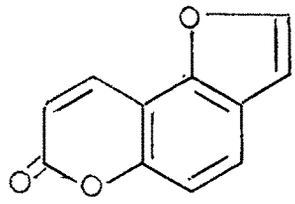
If the furan ring is built on a suitably substituted coumarin derivative, it leads to the synthesis of furocoumarin. Alternately one can start with an appropriate coumarone derivative and build up the α-pyrone ring on it. Eight isomeric forms of furocoumarins are found in the literature.



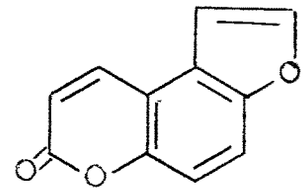
(A)



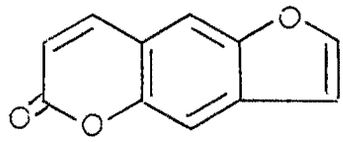
(B)



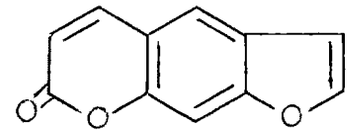
(C)



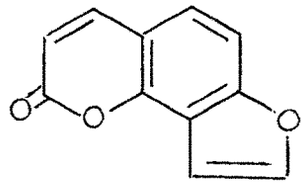
(D)



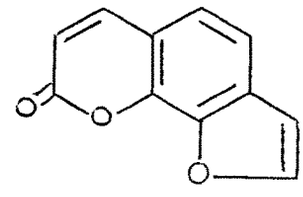
(E)



(F)



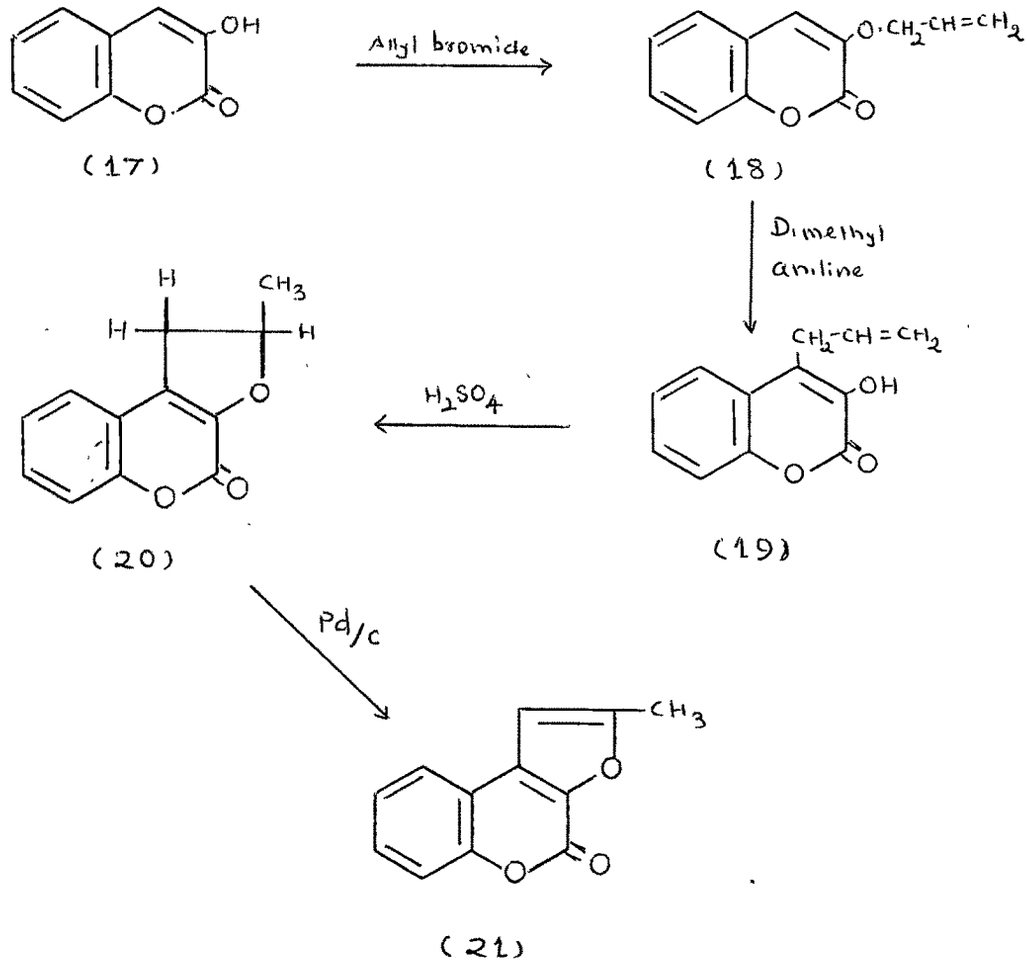
(G)



(H)

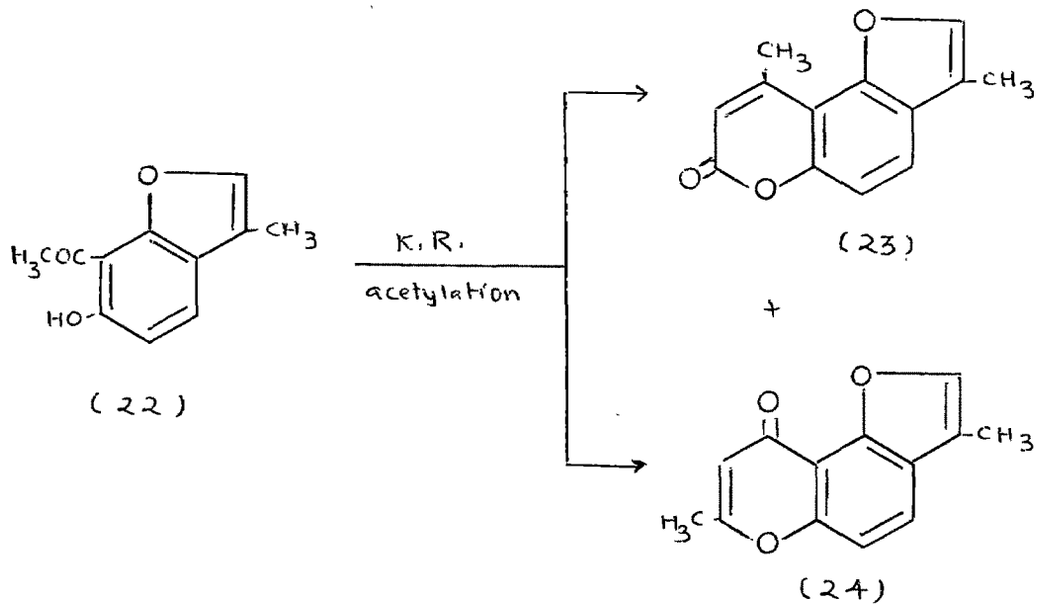
The methods of synthesis of furocoumarins are briefly reviewed here.

Furocoumarins of type (A) has been recently synthesised by Shaikh and Trivedi[13]. 3-Hydroxycoumarin (17) was allylated with allyl bromide and the allyl ether(18) on Claisen rearrangement in dimethyl aniline afforded 3-hydroxy-4-allylcoumarin (19) which was cyclised by trituration with con.sulphuric acid. This dihydrofuro-coumarin (20) was then dehydrogenated with palladised charcoal to 2-methyl-9-oxo-9H-furo(2,3-c)benzopyran (21).



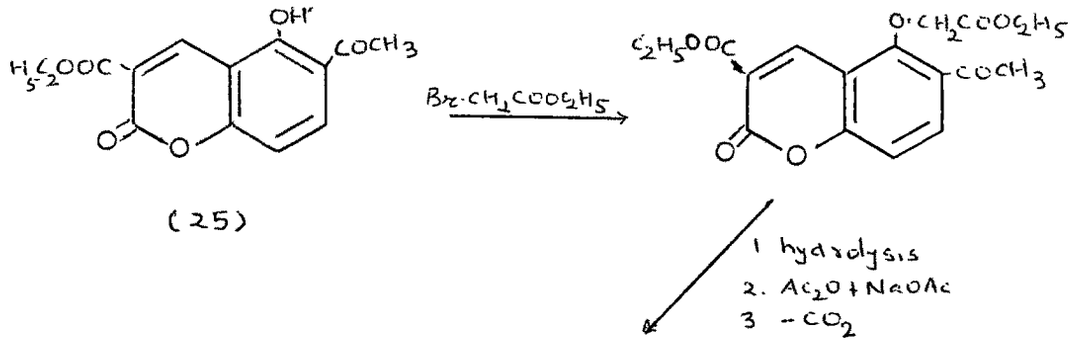
Furocoumarin of type (B) forms the subject matter of this chapter and hence will be discussed later.

. Furocoumarins of type (C) have been synthesised by several workers. Limaye and Sathe[14] subjected 6-hydroxy-7-acetyl-3-methylcoumarone (22) to Kostanecki-Robinson acetylation and obtained 3,9-dimethyl-7-oxo-7H-furo(2,3-f) benzopyran (furo-3',4-dimethyl-4',5',6,5-coumarin) (23) in poor yield along with 3,7-dimethyl-9-oxo-9H-furo(2,3-f) benzopyran (furo-2,3'-dimethyl-4',5',6,5-chromone) (24).



(22) (23) + (24)

Shah and Shah[15] synthesised 3-alkyl-7-oxo-7H-furo(2,3-f)benzopyran (3'-alkyl-furo-4',5',6,5-coumarin) (26) by condensing 5-hydroxy-6-acetyl-3-carboethoxy-coumarin (25) with ethyl bromoacetate followed by hydrolysis,cyclisation and subsequent decarboxylation.

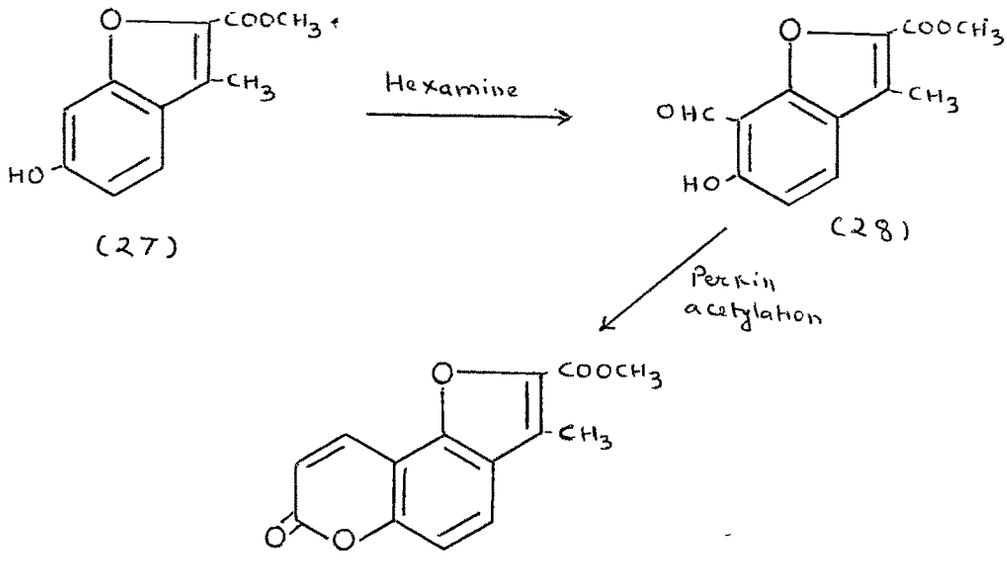


(25)

(26)

Chudger and Shah[16] synthesised several 3-alkyl-9-methyl-7-oxo-7H-furo(2,3-f)benzopyran derivatives (3'-alkyl-4-methyl-furo-4',5',6,5-coumarin derivatives) by condensing 5-hydroxy-6-acyl-4-methylcoumarin with ethyl bromoacetate followed by hydrolysis and subsequent cyclisation.

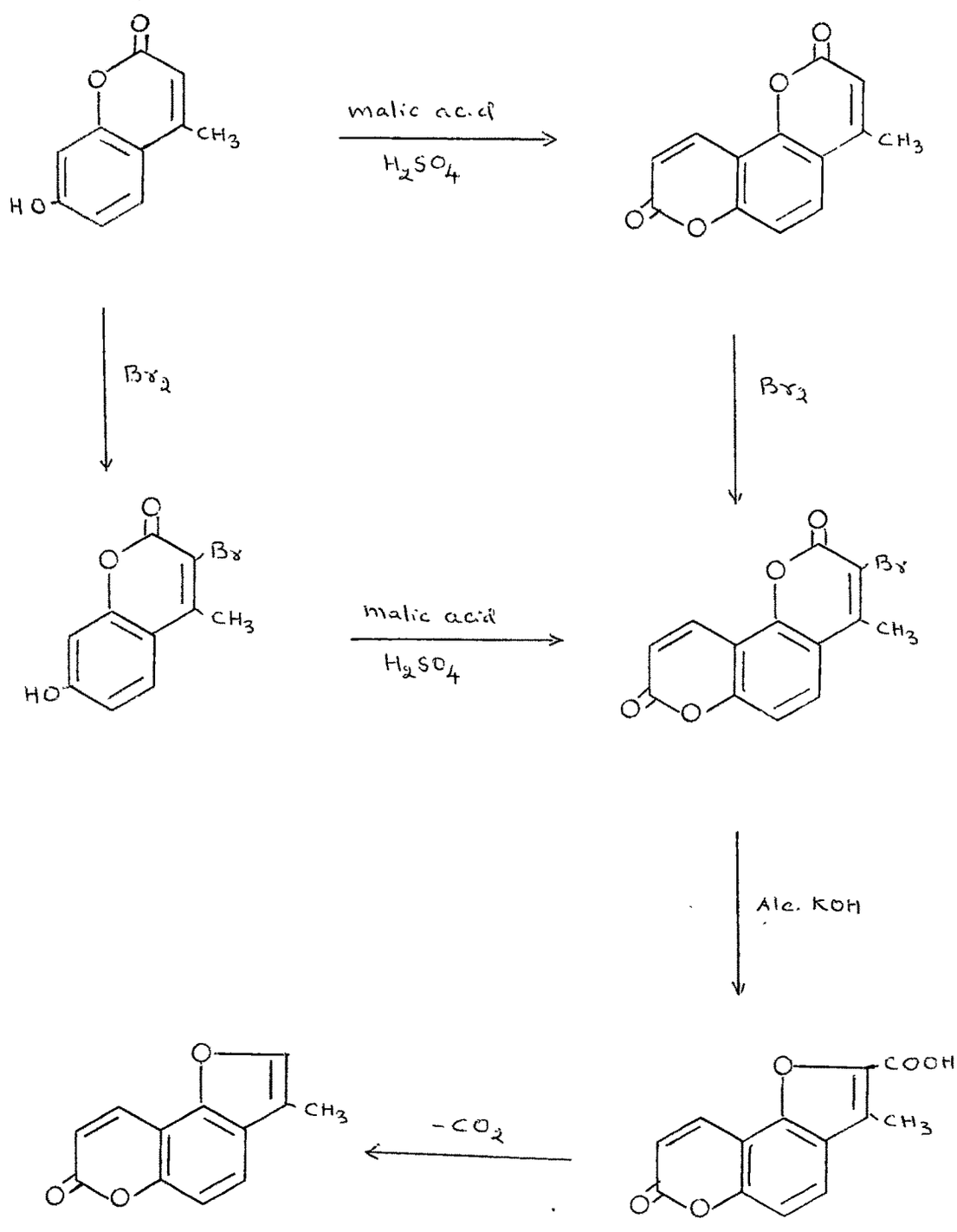
Salvi and Sethna[17] also synthesised furo-coumarins of this type by starting with a benzofuran derivative. Methyl 6-hydroxy-3-methylcoumarilate (27) on reaction with hexamine gave the 7-formyl derivative (28) which on Perkin acetylation gave 2-carbomethoxy-3-methyl-7-oxo-7H-furo(2,3-f)benzopyran (furo-2'-carbomethoxy-3'-methyl-5',4',5,6-coumarin)(29).



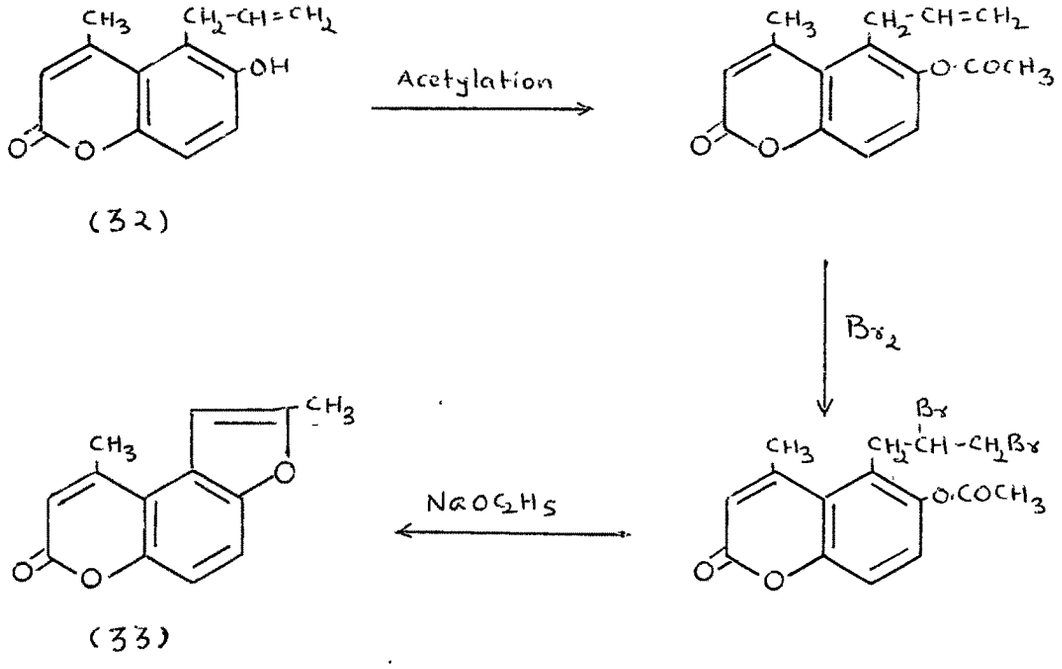
(27) (28) (29)

Trivedi and Sethna[18] made new approach to synthesise furocoumarins. They studied the hydrolysis of 3-halogen substituted coumarino-α-pyrones and obtained corresponding furocoumarins. Thus 3-methyl-7-oxo-7H-furo (2,3-f)benzopyran (furo-3'-methyl-5',4',5,6-coumarin) (31) was prepared from coumarino-α-pyrone derivative (30) through the following sequence of reactions.

[P.T.O.


malic acid
H_2SO_4
Br_2
Br_2
malic acid
H_2SO_4
Alc. KOH
$-CO_2$
HO
CH_3
Br
COOH

Kaufmann et al.[19] developed a new method for the synthesis of furocoumarin of type (D) from o-hydroxy allylcoumarin. Thus 6-hydroxy-5-allyl-4-methylcoumarin (32) was first acetylated and then brominated. The dibromo derivative was cyclised to 2,9-dimethyl-7H-furo(3,2-f) benzopyran-7-one (33) when refluxed with sodium ethoxide in absolute ethanol.



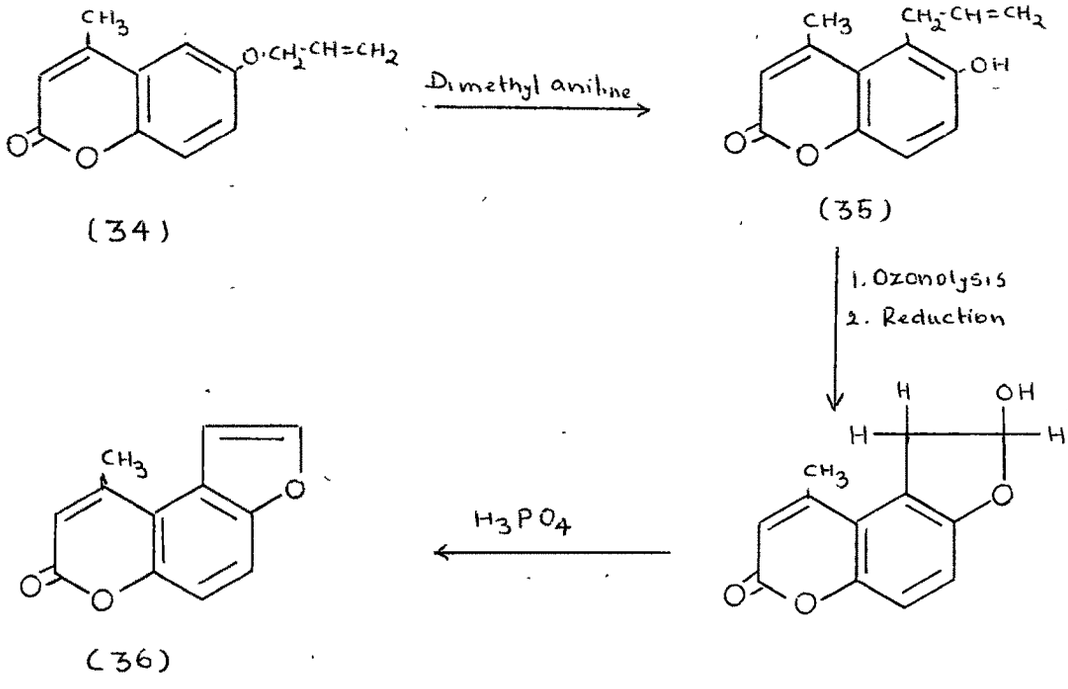
(32)

(33)

They have also synthesised a furocoumarin, 9-methyl-7H-furo(3,2-f)(1) benzopyran-7-one. (36), by condensing 5-formyl-6-hydroxy-4-methylcoumarin with methyl bromoacetate, followed by hydrolysis and subsequent cyclisation with partial decarboxylation.

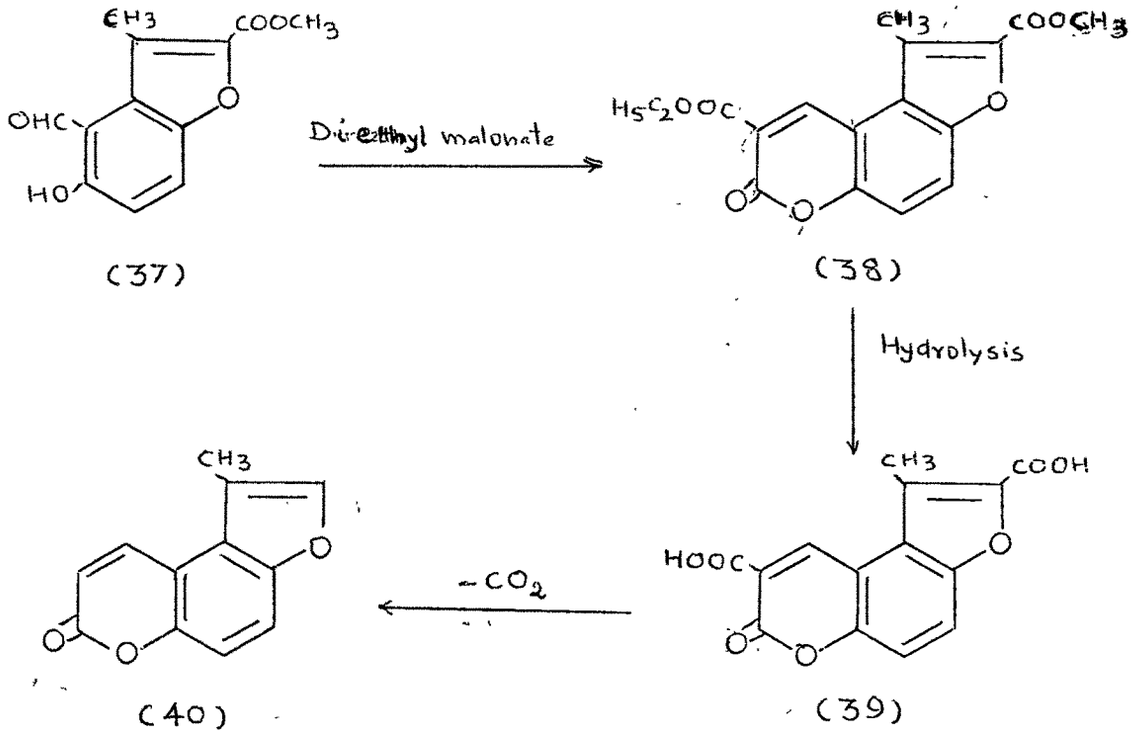
The above authors prepared the same furocoumarin, 9-methyl-7H-furo(3,2-f) (1) benzopyran-7-one, through an alternate route. 6-Hydroxy-4-methylcoumarin was converted

to an allyl ether (34) by reaction with allyl bromide and the Claisen rearrangement was carried out by refluxing it with dimethyl aniline. The 5-allyl derivative (35) was subjected to ozonolysis, catalytic reduction and then heated with o-phosphoric acid to get the furo-coumarin (36).



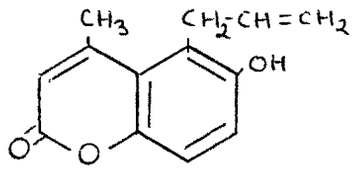
Salvi and Sethna[29] first formylated the hydroxybenzofurans and then carried out the syntheses of furocoumarins by Perkin or Knoevenagel reaction. Methyl 4-formyl-5-hydroxy-3-methylcoumarilate (37) on reaction with diethyl malonate gave ethyl-2-carbo-methoxy-3-methyl-6-oxo-6H-furo(3,2-f)benzopyran-5-carboxylate (ethyl furo-2',carbomethoxy-3'-methyl-4',5',5,6-coumarin-3-carboxylate) (38) which on hydrolysis and subsequent decarboxylation gave 3-methyl-6-oxo-6H-furo

(3,2-f)benzopyran (furo-3'-methyl-4',5',5,6-coumarin) (40).



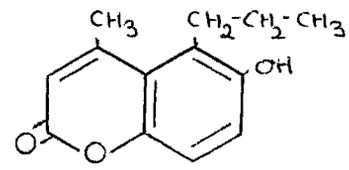
Furocoumarin of the type (E) was synthesised by Kaufmann et al.[19] as follows :

5-Allyl-6-hydroxy-4-methylcoumarin (41) was catalytically hydrogenated to 6-hydroxy-4-methyl-5-n-propylcoumarin (42), which was converted to an allyl ether by reaction with allyl bromide. Refluxing it in diethylaniline caused the Claisenn rearrangement and with the 5-position occupied the allyl group was forced to the 7-position giving 7-allyl-6-hydroxy-5-n-propyl-4-methyl-coumarin (43). Ozonolysis, catalytic reduction and heating with o-phosphoric acid gave 8-methyl-9-n-propyl-6-oxo-6H-furo(2,3-g)benzopyran (44).



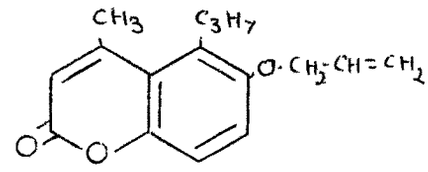
(41)

H_2

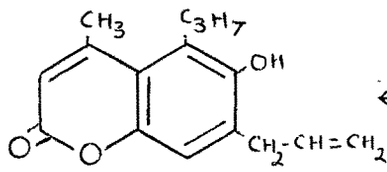


(42)

Allyl bromide

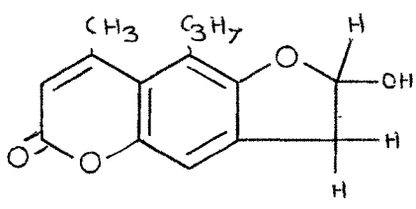


Dimethyl aniline

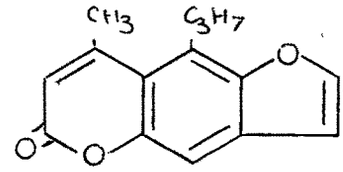


(43)

1. Ozonolysis
2. Reduction

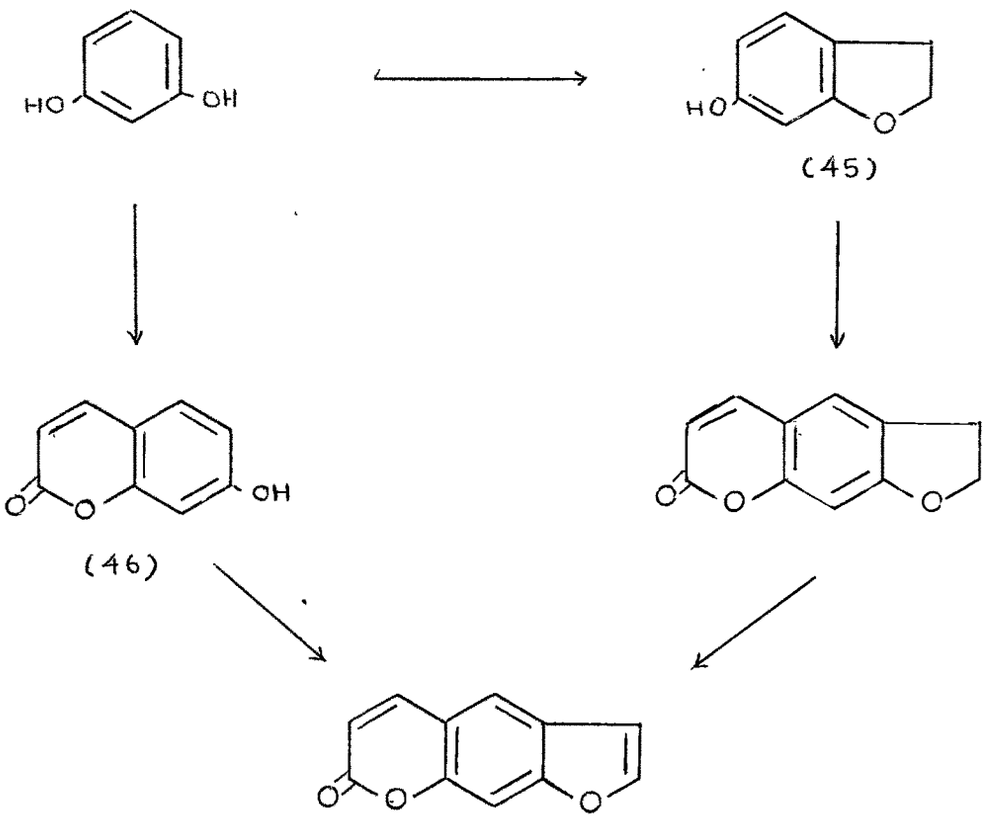


H_3PO_4

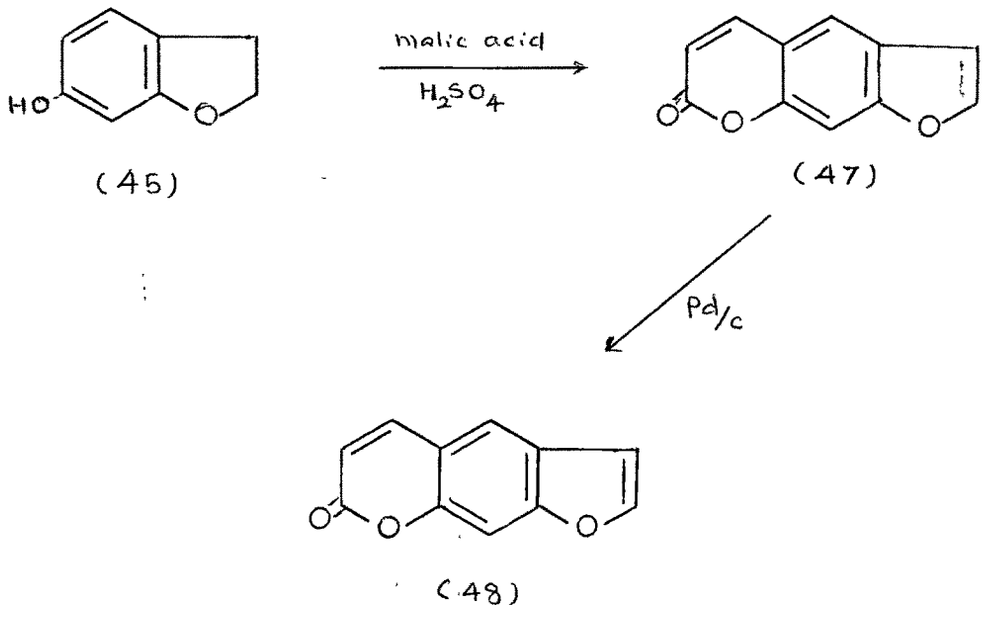


(44)

The synthesis of linear furocoumarins of type (F) such as psoralene, is difficult. Two routes are available for its synthesis, either (a) via conversion of 6-hydroxycoumaran (45) or (b) through umbelliferone (46). Both of these can be obtained from resorcinol as follows :



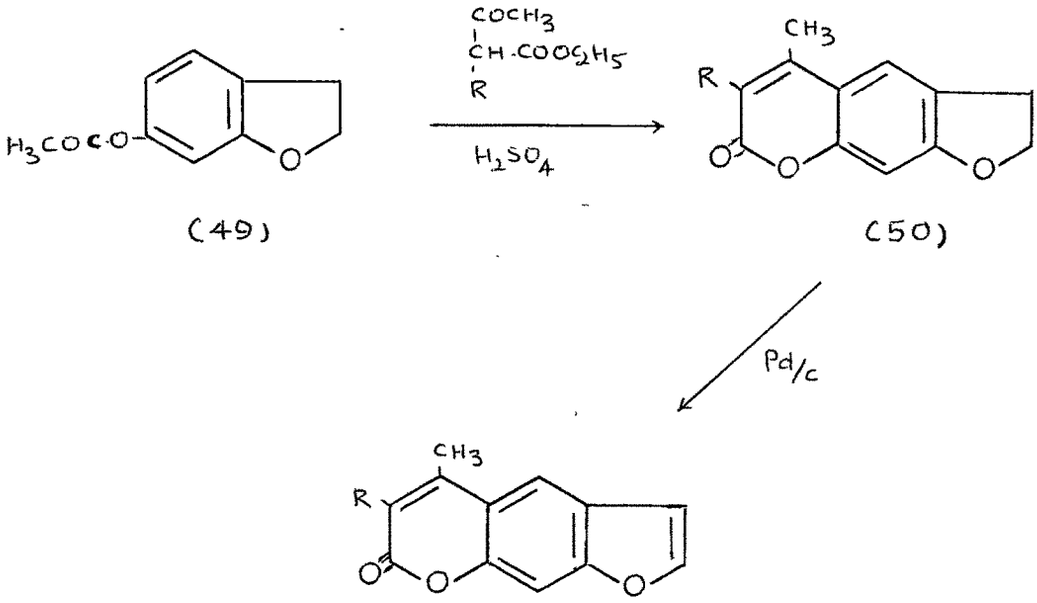
Spath and Pailer[21] carried out the condensation of 6-hydroxycoumaran (45) with malic acid in the presence of con.sulphuric acid and obtained 2,3-dihydropsoralene (47) which on dehydrogenation gave psoralene (48).



(45) (47) (48)

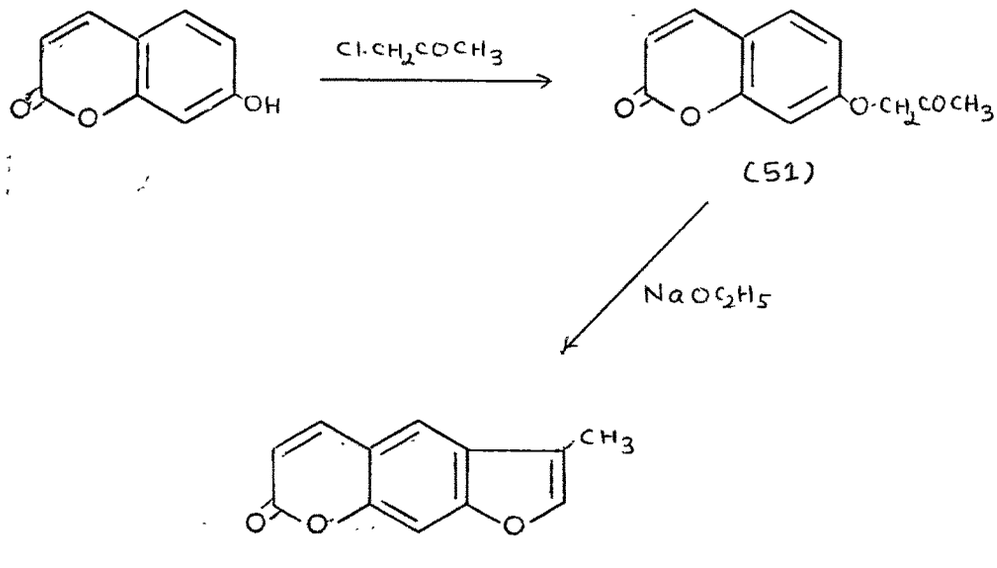
Later Horning and Reisner[22] prepared different 5-substituted-2,3-dihydropsoralenes by condensing 6-acetoxycoumaran with a variety of β-ketonic esters in the presence of sulphuric acid. Esse and Christensen[23] have extended this reaction to obtain 6-alkyl-2,3-dihydro-5-methylpsoralenes (50) by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxycoumaran (49). The main drawback in this method is that the dehydrogenation of dihydropsoralene derivatives with palladised charcoal gives poor yields of psoralene.

Ray, Silooja and Vaid[24] had approached the problem of psoralene synthesis by starting with umbelliferone. In this procedure, they carried out the cyclisation of 7-acetoxyloxycoumarin (51), obtained by



(49) (50)

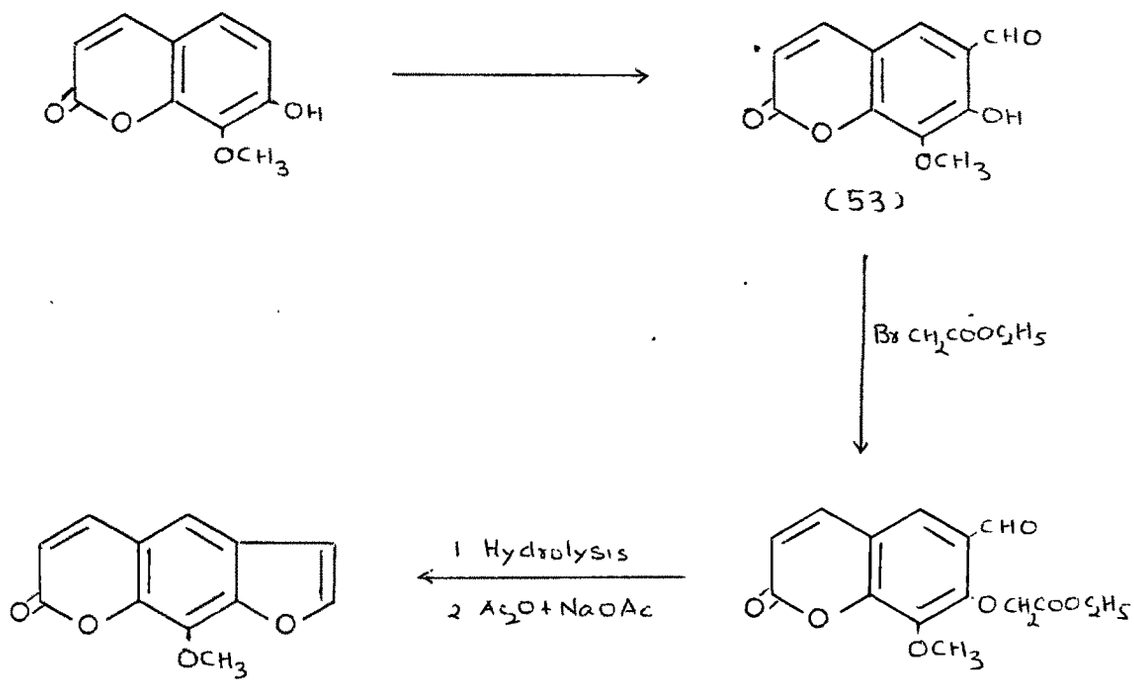
treating umbelliferone with chloracetone, in the presence of sodium ethoxide to 3-methylpsoralene (52).



(51)

(52)

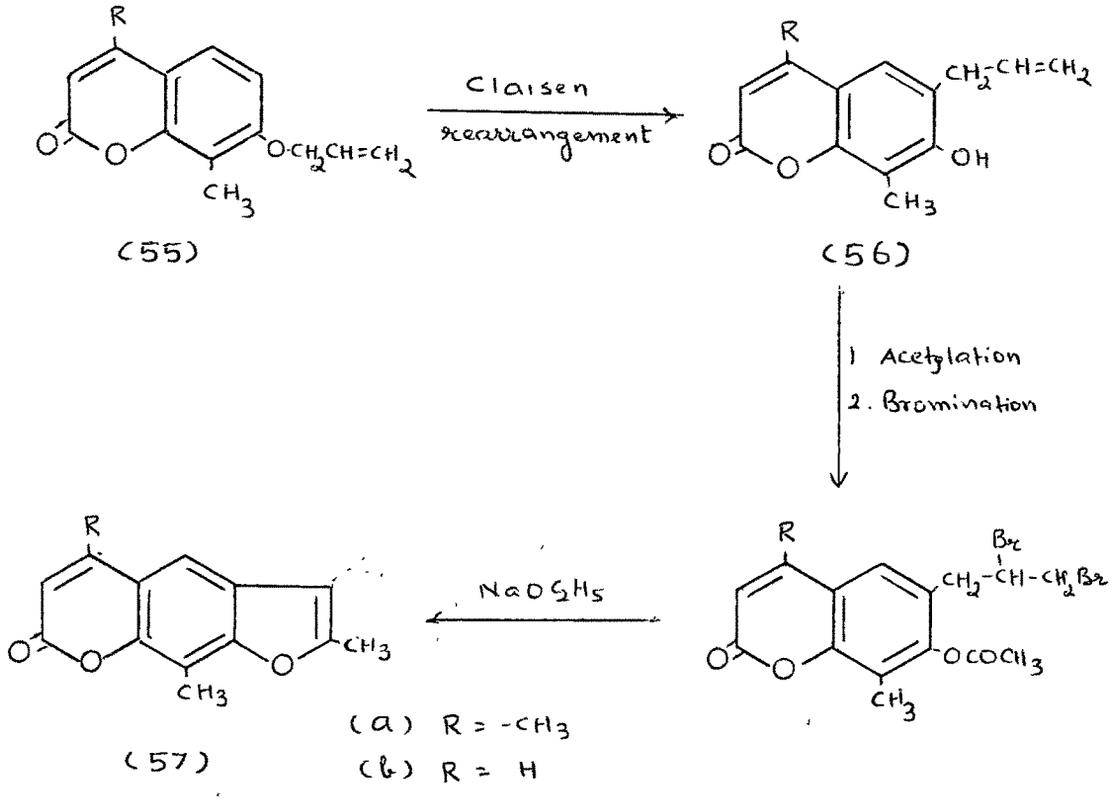
Rodighiero and Antonello[25] synthesised xanthotoxin (54) by first preparing 7-hydroxy-8-methoxy-6-formylcoumarin (53) and then treating it with ethyl bromoacetate followed by hydrolysis, cyclisation and decarboxylation.



Limaye and Gangal[26] synthesised 3,4-dimethyl-psoralene from 7-hydroxy-6-acetyl-4-methylcoumarin using the same procedure.

Foster et al.[27] synthesised psoralene by first subjecting 6-hydroxycoumaran to Gattermann aldehyde synthesis and then condensing the 6-hydroxy-5-formyl-coumaran with cyanoacetic acid followed by decarboxylation and dehydrogenation.

Kaufmann[28] prepared 4,5',8-trimethylpsoralene (57 a) and 5',8-dimethylpsoralene (57 b) by first carrying out Claisen rearrangement of 7-allyloxy-4,8-dimethyl-(55 a) and 7-allyloxy-8-methylcoumarin (55 b) to 7-hydroxy-6-allyl-4,8-dimethyl-,(56 a) and 7-hydroxy-6-allyl-8-methyl-coumarin (56 b) respectively. These were then acetylated, brominated and cyclised to obtain psoralene derivatives.



(55) (56)

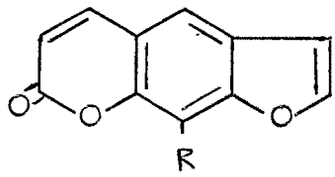
(57)

(a) R = -CH3

(b) R = H

Using the similar procedure Kaufmann synthesised 4,5'-dimethylpsoralene.

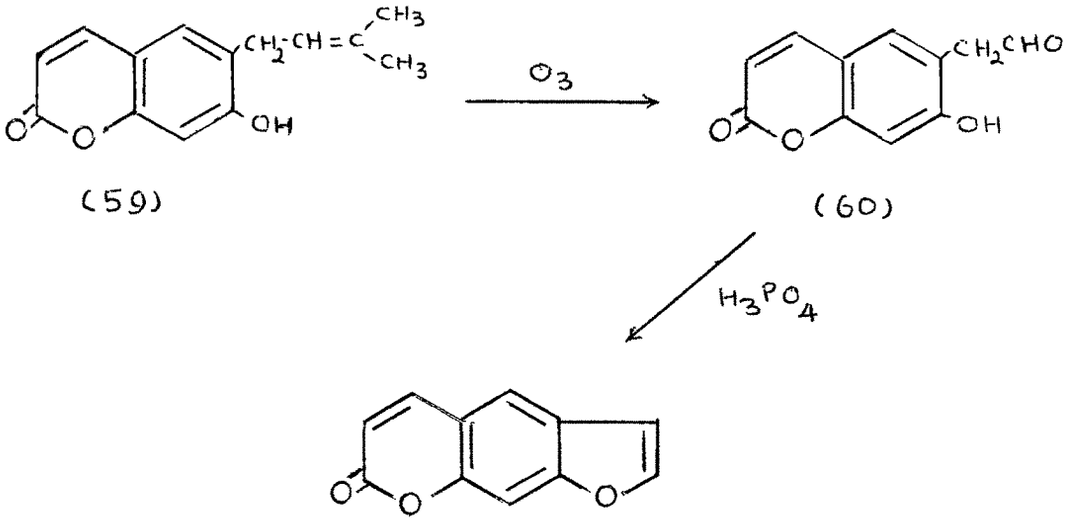
Kaufmann and coworkers[29] synthesised psoralene derivatives (58) having different groups such as Cl,Br, CN,$N(CH_3)_2$ etc. in 8-position using 8-aminopsoralene as an intermediate product.



(58)

R = Cl, Br, CN, $N(CH_3)_2$, NH_2 etc.

Seshadri and coworkers[30] have successfully obtained psoralene by ozonolysis of 6-dimethylallyl-7-hydroxycoumarin (59) , followed by cyclisation of the aldehyde (60) with o-phosphoric acid.

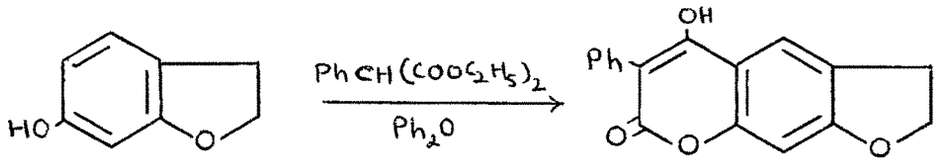


(59) (60)

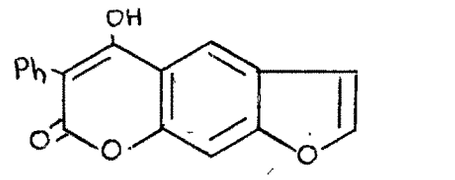
Following the same procedure they have also synthesised xanthotoxin (54).

Goudou and Blanchecotte[31] have condensed 6-hydroxycoumaran and phenyl diethyl malonic ester in

diphenyl ether and obtained 4',5'-dihydro-4-hydroxy-3-phenylfuro-2',3',6,7-coumarin (61) which was then dehydrogenated over palladium to give 4-hydroxy-3-phenylpsoralene (4-hydroxy-3-phenylfuro-2',3',6,7-coumarin)(62).



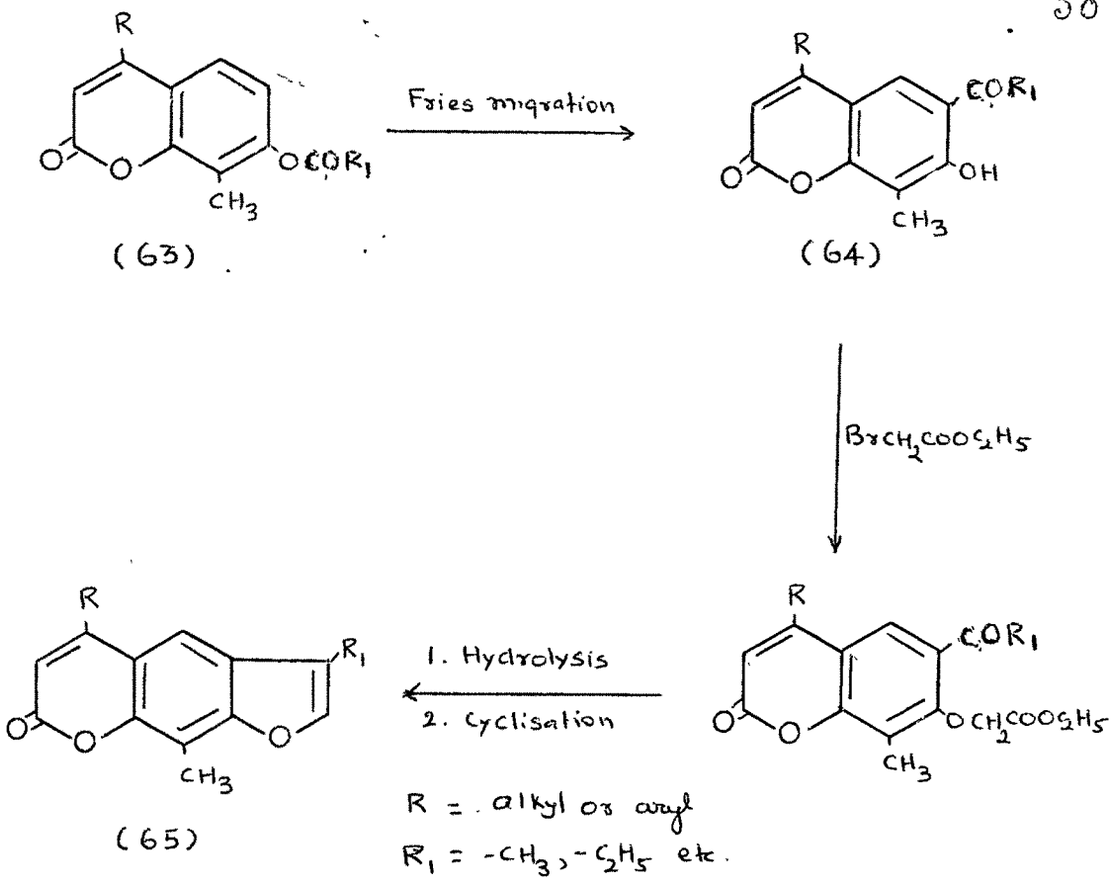
(61)



(62)

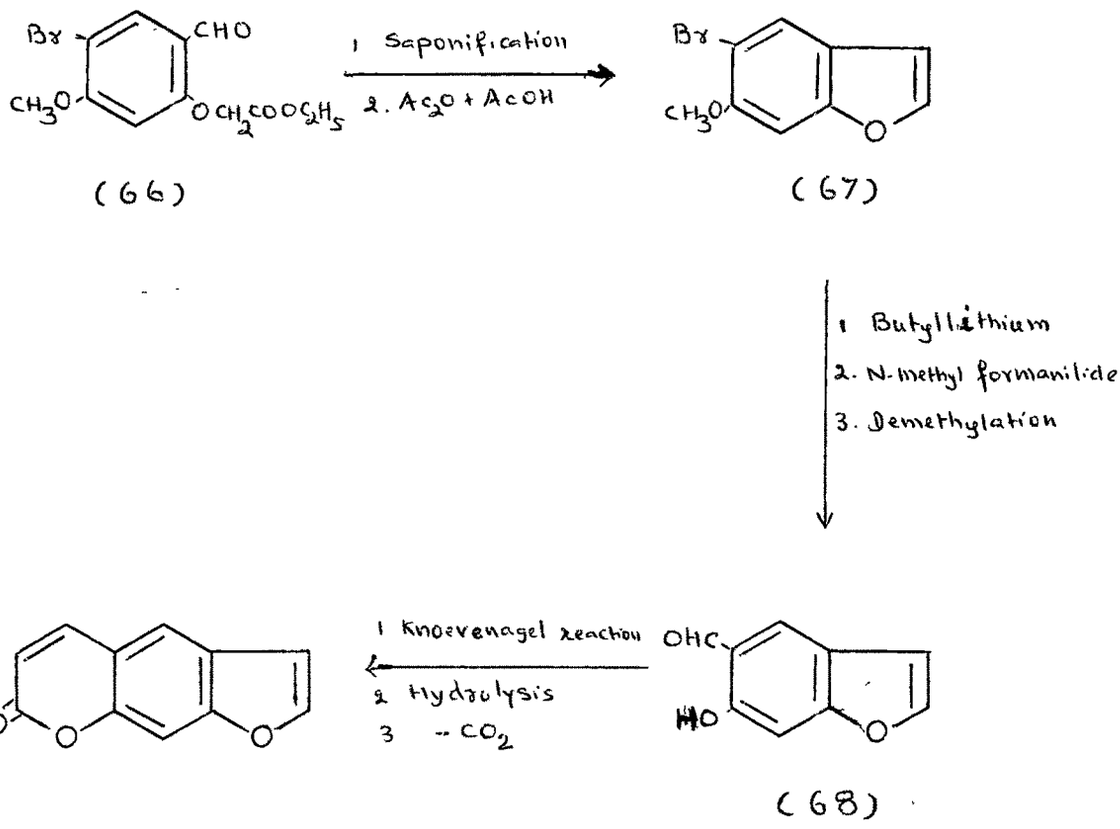
Trivedi and coworkers[32] have recently synthesised different alkylpsoralenes having alkyl or aryl substituents in 4-position. 7-Acyloxy-4-alkyl or aryl-8-methylcoumarin (63) on Fries migration afforded 7-hydroxy-6-acyl-4-alkyl or aryl-8-methylcoumarin (64) which on condensation with ethyl bromoacetate, followed by hydrolysis and subsequent cyclisation yielded 4-alkyl or aryl-4',8-alkylpsoralene (65).

Recently Kaufmann and coworkers[33] have developed a new synthetic route to synthesise psoralene. Bromination of ethyl(2-formyl-5-methoxyphenoxy)acetate gave the 4-bromo derivative (66), which was saponified



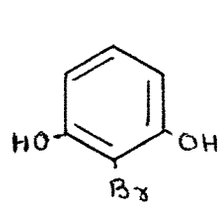
and simultaneously cyclised and decarboxylated to 5-bromo-6-methoxybenzofuran (67). Lithium-bromine interchange and then formylation and demethylation gave 5-formyl-6-hydroxybenzofuran (68) which was condensed with diethyl malonate to furnish psoralene after hydrolysis and decarboxylation of the Knoevenagel product.

Pardanani and Trivedi[34] have synthesised 4-methylpsoralene by condensing 2-bromo resorcinol with ethyl acetoacetate in the presence of con.sulphuric acid and obtained 7-hydroxy-8-bromo-4-methylcoumarin (69)



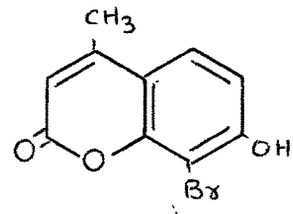
which was allylated to (70). This allyl ether (70) on Claisen rearrangement in dimethyl aniline gave 7-hydroxy-6-allyl-4-methylcoumarin (71), bromine in the 8-position being knocked off during the reaction. This coumarin (71) was then subjected to ozonolysis, hydrogenation and subsequent cyclisation with o-phosphoric acid to give 4-methylpsoralene (72).

Angelicin is a naturally occurring furocoumarin of type (G) and was synthesised by Spath and Pailer[35] by condensing sodium salt of umbelliferon-8-aldehyde with iodoacetic ester under pressure and the product thus



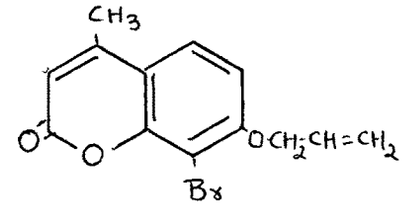
Ethyl acetoacetate

H_2SO_4



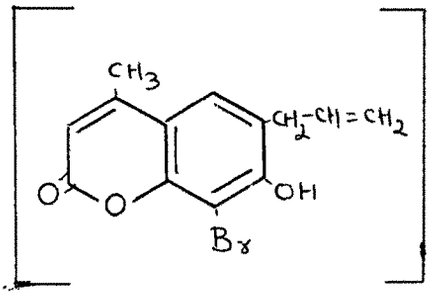
(69)

Allyl bromide

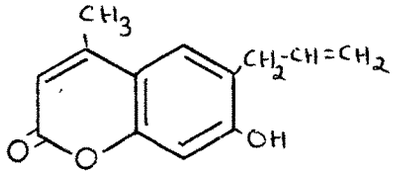


(70)

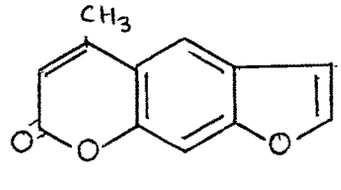
Dimethyl aniline



1. O_3
2. Reduction
3. H_3PO_4



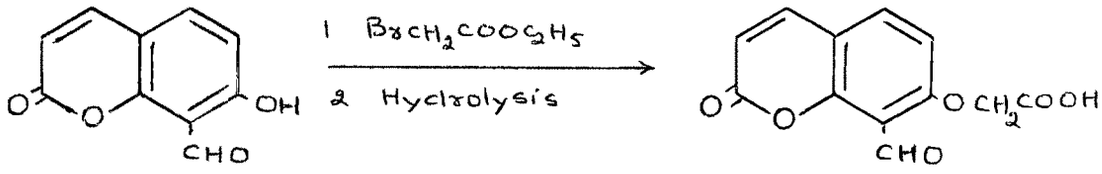
(71)



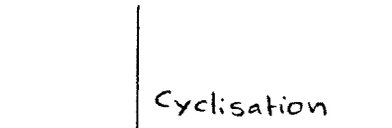
(72)

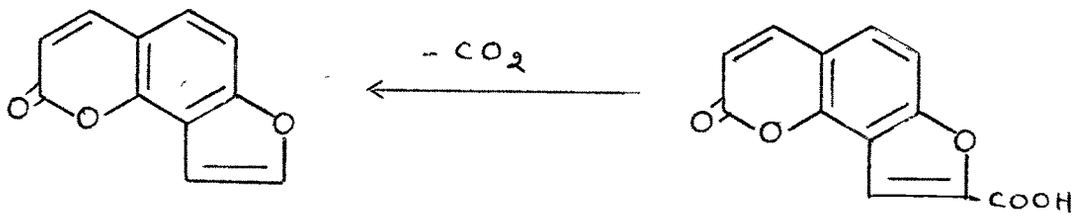
obtained was subjected to hydrolysis followed by cyclisation.

Naik and Thakor[36] repeated this work using ethyl bromoacetate and acetone. They observed that the melting point of 7-(8-formylcoumarinoxy)-acetic acid (73) was 248-49° instead of 178-81° as reported by Spath and Pailer[35]. They also observed that on cyclisation of this product angelicin-2-carboxylic acid (74) which was not isolated by Spath and Pailer was obtained and it underwent decarboxylation when heated with copper and quinoline to angelicin.



(73)



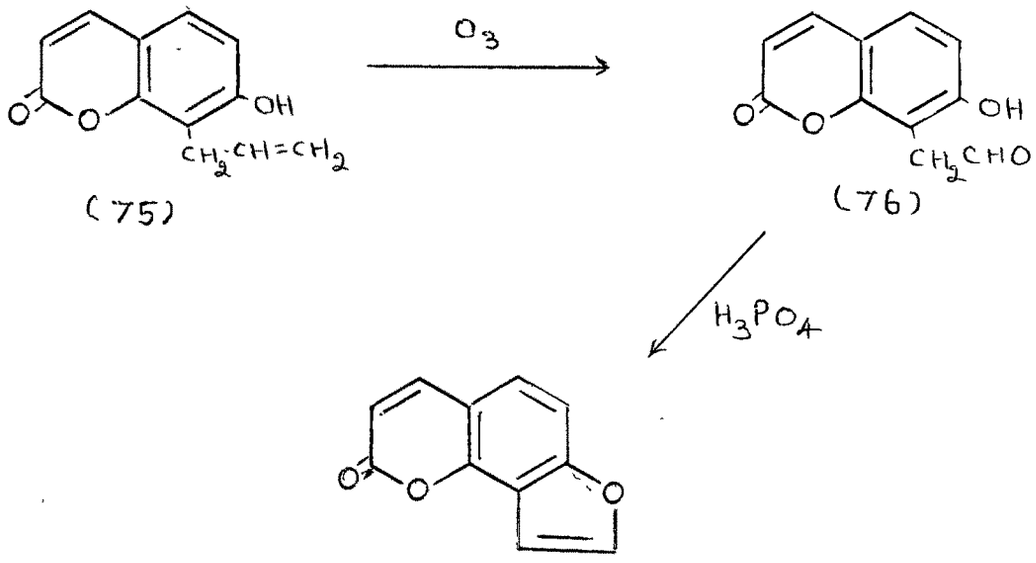


(74)

Using the same method Shah and Shah[37] synthesised 3-methyl-5-oxo-5H-furo(2,3-h)benzopyran (furano-3',4',5',8,7-coumarin) from 7-hydroxy-8-acetylcoumarin.

Limaye[38] synthesised angelicin by preparing 4-hydroxy-5-formylcoumarone from 4-hydroxycoumarone and then subjecting it to Perkin reaction.

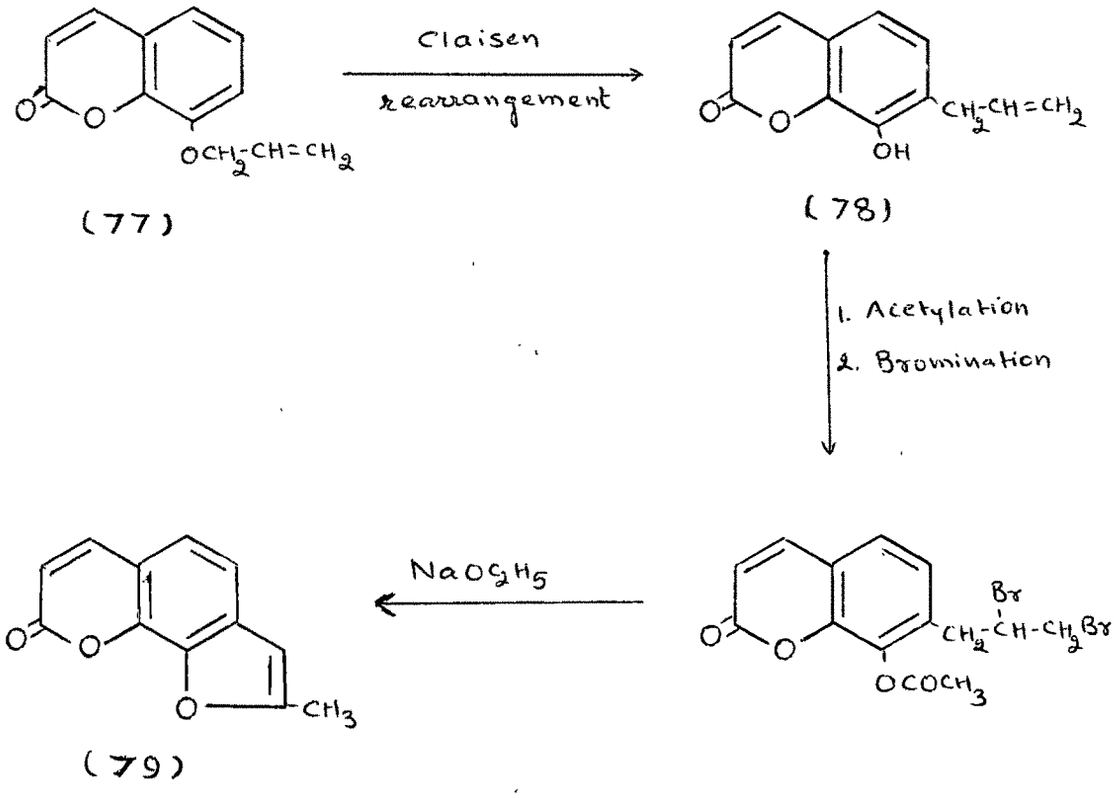
Aneja, Mukherjee and Seshadri[39] synthesised angelicin by subjecting first 7-hydroxy-8-allylcoumarin (75) to ozonolysis and subsequent cyclisation of 7-hydroxy-coumarin-8-acetaldehyde (76) with o-phosphoric acid.



(75) (76)

Furocoumarin of the type (H) was synthesised by Kaufmann and Russey[40]. They carried out the Claisen rearrangement of 8-allyloxycoumarin (77) and obtained 7-allyl-8-hydroxycoumarin (78), the acetyl derivative

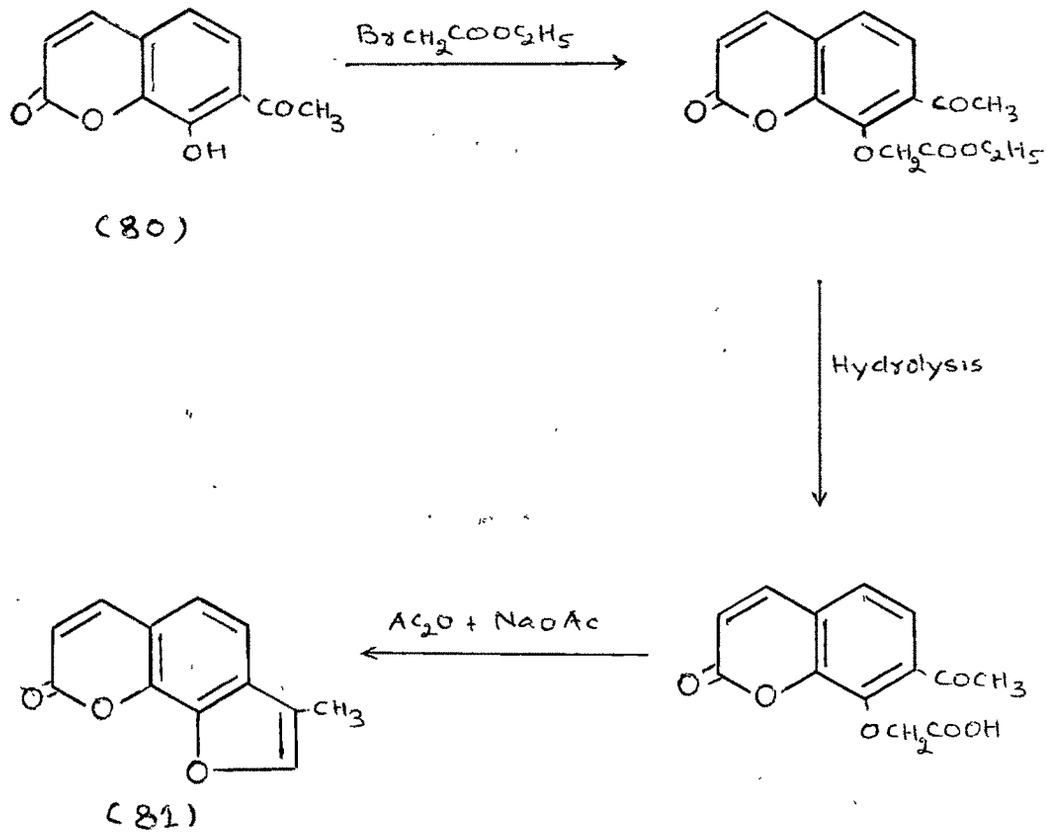
of which was brominated. This bromo derivative underwent cyclisation to 2-methyl-8-oxo-8H-furo(3,2-h)benzopyran (2'-methylfuro-4',5',7,8-coumarin) (79) when refluxed with sodium ethoxide in absolute ethanol.



(77) (78) (79)

Mehta and Sethna[41] synthesised 3-methyl-8-oxo-8H-furo(3,2-h) benzopyran (furo-3'-methyl-4',5',7,8-coumarin) (81) by condensing 8-hydroxy-7-acetylcoumarin (80) with ethyl bromoacetate, followed by hydrolysis and cyclisation.

As the present work deals with the syntheses of pyranobenzopyrans and furobenzopyrans in which a pyrone ring or a furan ring is built up either on a-pyrone ring or on benzene ring of 4-hydroxycoumarin

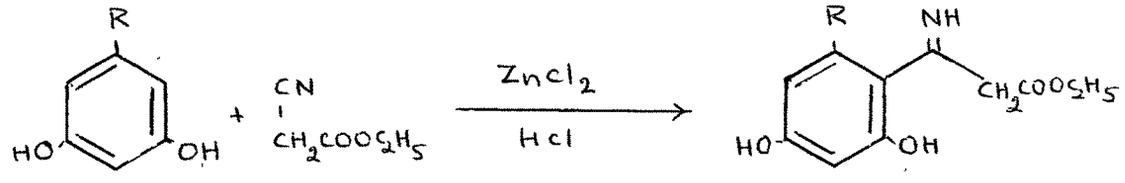


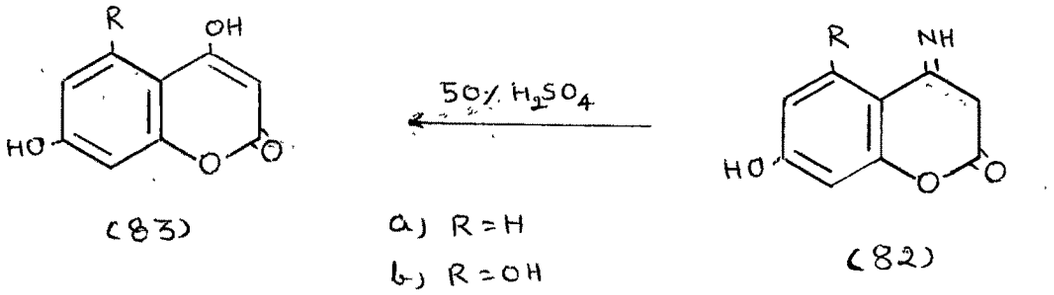
(80)

(81)

moieties, it will be important to review a few of the important methods of synthesis of 4-hydroxycoumarin derivatives.

Sonn[42] and Bauer and Schoder[43] synthesised 4-hydroxycoumarin derivatives by using Hoesch synthesis. They condensed cyanoacetic ester with resorcinol and phloroglucinol in the presence of hydrochloric acid and zinc chloride followed by the hydrolysis of the intermediate ketimine (82) and obtained 4,7-dihydroxy- (83 a) and 4,5,7-trihydroxycoumarin (83 b) respectively.





(83)

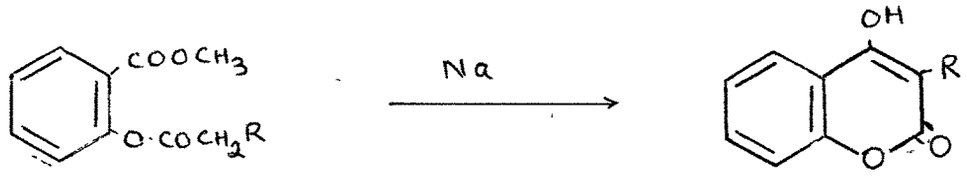
a) R=H

b) R=OH

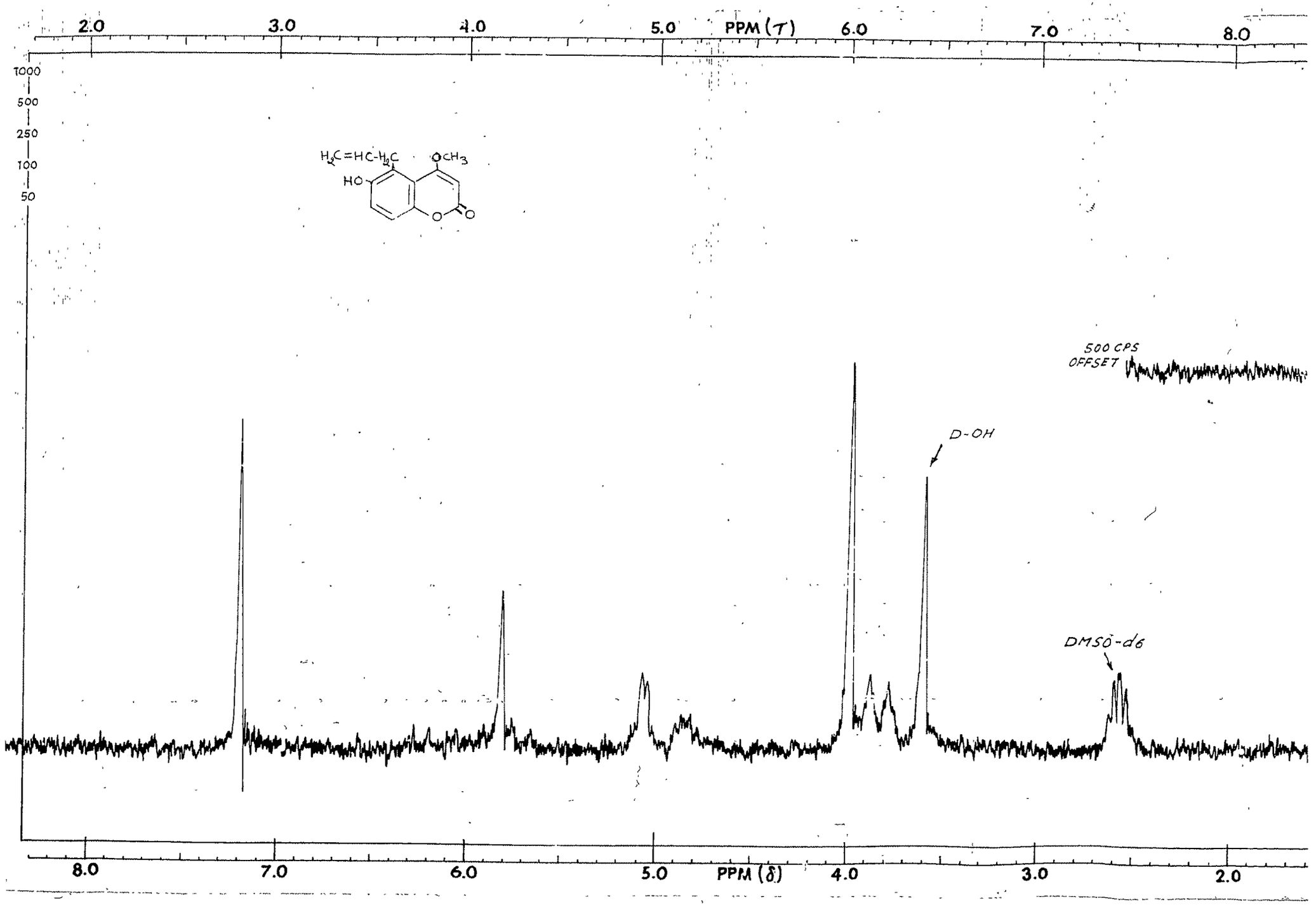
(82)

This method is applicable mainly to m-dihydric phenols and their derivatives.

Pauly and Lockemann[44] synthesised 4-hydroxy-coumarin derivatives (84) from methyl acetyl salicylate by adding metalic sodium to the molten ester.

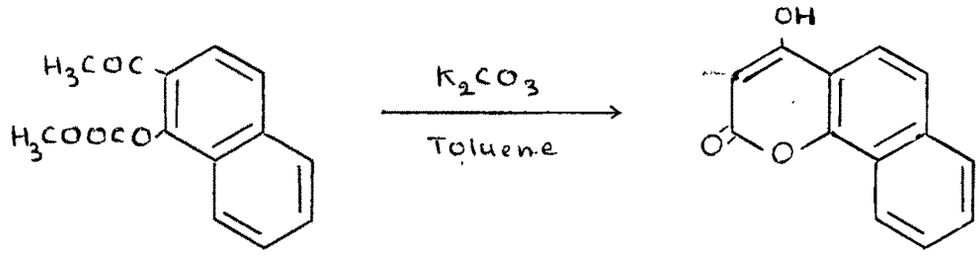


(84)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
1000
500
250
100
50
H2C=HC-H2C
OCH3
HO
O
O
500 CPS
OFFSET
D-OH
DMSO-d6
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0

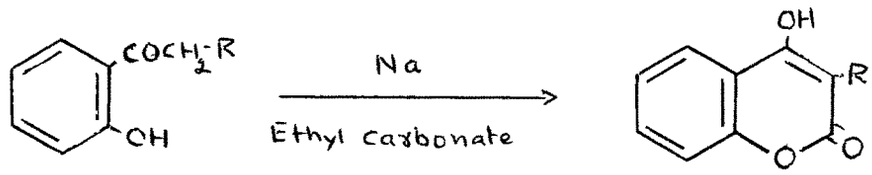
This method involves condensation with sodium at high temperature. This procedure was reinvestigated by Jensen and Jensen[45] but they did not obtain the yields given by Pauly and Lockemann : Stahmann, Wolff and Link[46] reported that the optimum temperature for the condensation is 240-50°.

Anand and Venkataraman[47] synthesised 4-hydroxy-7,8-benzocoumarin (86) by the internal condensation of o-carbomethoxy-2-acetyl-1-naphthol (85) in the presence of sodamide, anhydrous potassium carbonate, metallic sodium or sodium ethoxide in appropriate solvents.



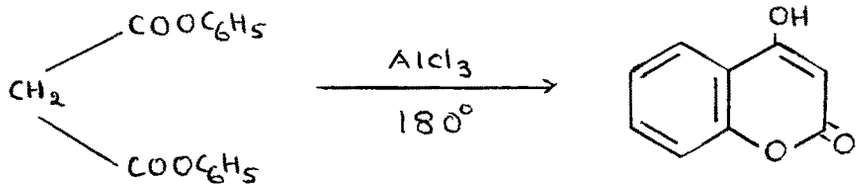
(85) (86)

Boyd and Robertson[48] found that o-hydroxy-acetophenone and its ω-substituted derivatives readily condensed with ethyl carbonate in the presence of sodium to give 4-hydroxycoumarin derivatives in good yields.

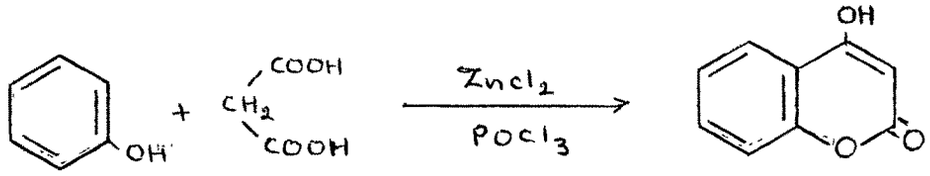


This is a very convenient method for the synthesis of 4-hydroxycoumarin derivatives and its scope has been demonstrated by its application to a variety of o-hydroxyacetophenones.

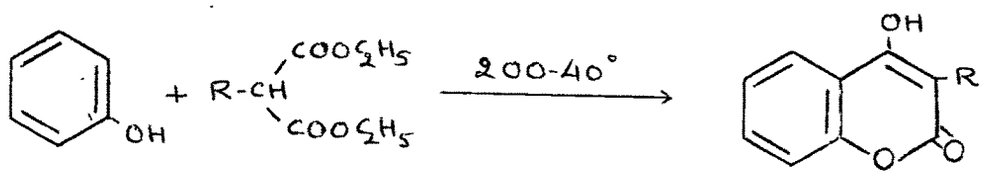
Ziegler and Junek[49] obtained 4-hydroxycoumarin derivatives by the cyclisation of diaryl malonates in the presence of anhydrous aluminium chloride at 180°.



Shah, Bose and Shah[50] have prepared 4-hydroxy-coumarin derivatives in good yields by the condensation of phenols with malonic acids in the presence of freshly fused zinc chloride and phosphorus oxychloride.

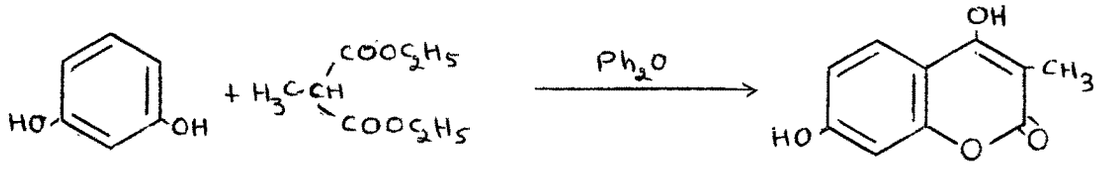


3-Alkyl-4-hydroxycoumarins have been prepared by heating phenol with ethyl monoalkyl malonates at 200-40° for 48 hours.[50]

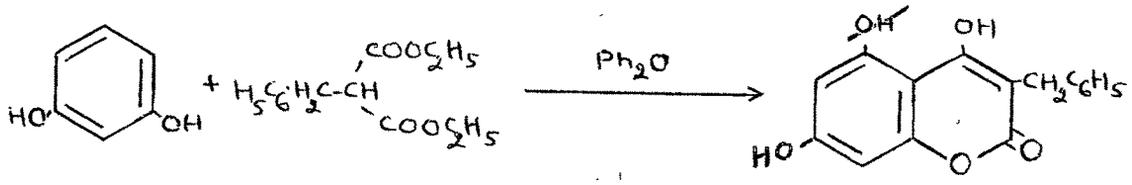


R = $-CH_3$, $-C_6H_5$, $-CH_2C_6H_5$

Trivedi[51] prepared 3-methyl-(87) and 3-benzyl-4-hydroxycoumarin (88) derivatives by the condensation of different phenols with ethyl methyl malonate or ethyl benzyl malonate in refluxing diphenyl ether. He observed that in the case of reactive phenols such as resorcinols, phloroglucinols and α-naphthols the yields are over 60 % but they are poor in the case of less reactive phenols such as phenol and β-naphthol.

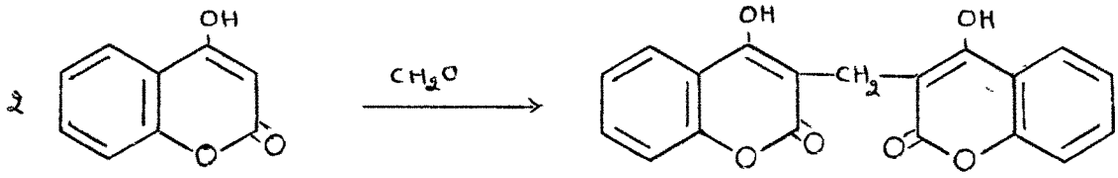


(87)



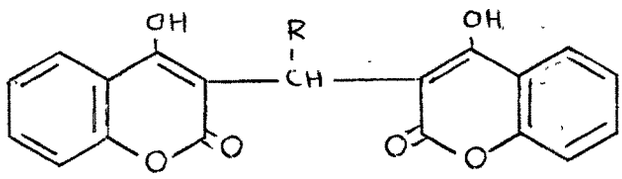
(88)

In recent years 4-hydroxycoumarin derivatives have assumed importance because of their anticoagulant properties. Link and coworkers[52] found that cattle, feeding on spoiled sweet clover hay, suffer from a condition characterised by a sharp increase of the blood clotting time. The pathogenic haemorrhagic principle of sweet clover hay was found by them to be 3,3'-methylene bis-(4-hydroxycoumarin), popularly called Dicoumarol (89). Dicoumarol is synthesised by reacting formaldehyde with 4-hydroxycoumarin and it is a good anticoagulant of blood.



(89)

Since this discovery the chemistry of 4-hydroxy-coumarins has assumed great importance. Tromexan (90 a), the analogous compound with a $-COOC_2H_5$ group in methane carbon bridge has been developed to give more rapid onset of the recovery from anticoagulant symptoms[53].



(90)

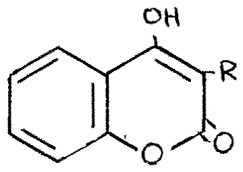
(a) R = $-COOC_2H_5$, (b) R = $-CH_2OCH_3$, (c) R = $-CH_3$.

Many attempts have been made to vary the structure of dicoumarol and thereby prepare more active anticoagulant drugs. (90 b) is obtained by reacting 4-hydroxycoumarin with β-methoxy propionaldehyde is another such compound with anticoagulant properties similar to that of dicoumarol.

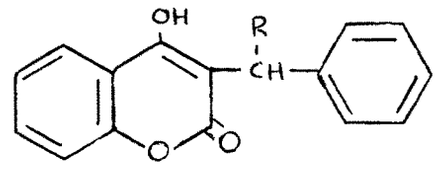
Mentzer, Meunier, Buu-Hoi and Cagniant[54] tested the compounds in which heterooxygens of dicoumarol were replaced either by sulphur or nitrogen and found them to be feebly active compounds.

Lehmann[55] showed that the replacement of bridge $-CH_2-$ by ethylidene bridge $-CH\cdot CH_3-$ gave compound (90 c) which possessed higher anticoagulant properties than dicoumarol.

Meunier et al.[56] observed that while the corresponding 3-bromo (91 b) and 3-chloro-4-hydroxy-coumarins (91 c) have slight anticoagulant properties, 3-methyl-4-hydroxycoumarin (91 a) possesses coagulant properties like vitamin K.



(91)



(92)

(a) R = CH_3 (b) R = Br (a) R = $-CH_2COCH_3$

(c) R = Cl (d) R = naphthyl (b) R = $-C_2H_5$

(e) R = $-CH_2C_6H_5$

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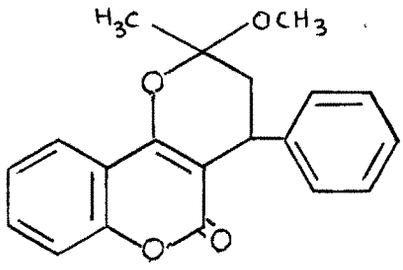
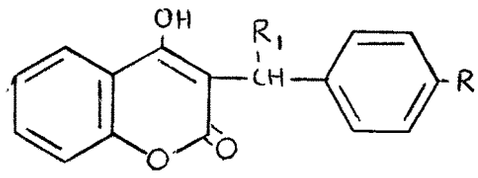
Moraux et al.[57] have prepared 3-naphthyl-4-hydroxycoumarin (91 d) which is equal to dicoumarol in activity and less toxic.

3-Benzyl-4-hydroxycoumarin (91 e) has slight activity but the acetonyl derivative, warfarin (92 a), is a powerful anticoagulant and rodenticide and shows a remarkable specificity for rats in which the action of minute doses has fatal results[58].

Link et al.[59] prepared cyclocoumarol or 3,4(2'-methyl-2'-methoxy-4'-phenyl)dihydropyranocoumarin (93) by treating warfarin with 4 % hydrogen chloride in methanol and found that it possessed greater activity than dicoumarol.



(93)



(94)

(a) R = Cl ; R_1 = $-CH_2-CO-CH_3$

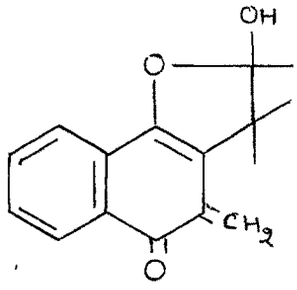
(b) R = NO_2 ; R_1 = $-CH_2-CO-CH_3$

Other compounds which are related to warfarin and possess anticoagulant property are coumarchlor(94 a), sintron (94 b) and marcoumar (92 b).

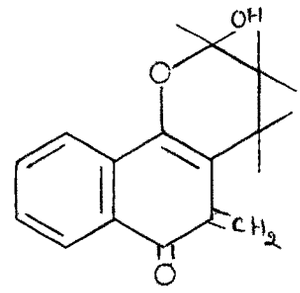
Link and coworkers[60] prepared different esters of dicoumarol and found that the activity of these compounds is less than that of dicoumarol.

From their studies of various 4-hydroxycoumarin derivatives, Link and coworkers[58] have put forward the minimum structural requirements for a substance to possess anticoagulant properties. The first essential condition is that there should be an intact 4-hydroxycoumarin residue and that the 3 position must be substituted by a C residue. Every compound fulfilling this requirement is active. For high activity a bis-4-hydroxycoumarin structure is specially required. Such an arrangement was considered important also by Mentzer et al.[61] An alternation in this structure results in decrease in activity. Compounds containing one 4-hydroxy-coumarin residue with an alkyl or aryl group in 3 position show diminished activity.

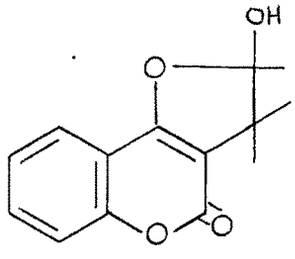
Chmielewska and Cieslak[62] analysed the structural requirements for coumarin anticoagulants from the point of view of their vitamin K antagonism. They postulated that the active forms of vitamin K can be represented by the formulae (95) and (96). On the other hand an anticoagulant which is an antivitamin K should have the structure (97) and (98) which are cyclic hemiacetals obtained from the appropriate 3-substituted-4-hydroxycoumarins. For such acetal formation the carbon chain in position 3 should carry a carbonyl group or a potential carbonyl group in position 2' or 3'. Keeping this in view they suggested a revision of the structure of dicoumarol (99).



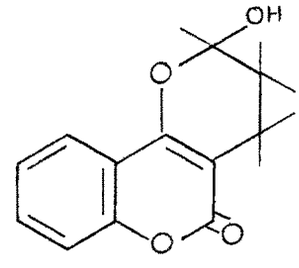
(95)



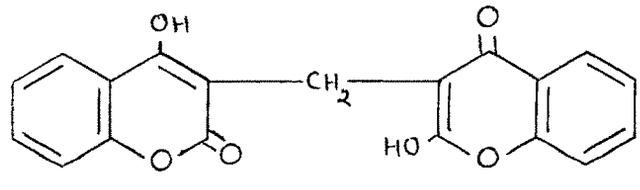
(96)



(97)



(98)

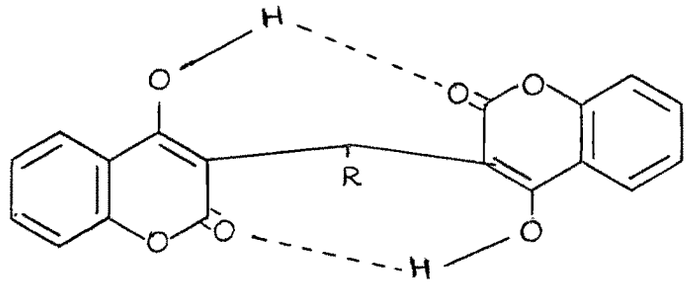


(99)

Seshadri and coworkers[63] have synthesised many bridge-substituted dicoumarols and studied their anticoagulant properties. They found in agreement with Link and coworkers[58] that 3,3'-benzylidenebis-4-hydroxycoumarin is much less active than dicoumarol. The introduction of substituents in the phenyl ring on the bridge has varying effects depending on their nature and on their positions.

The authors also supported the Chmielewska and Cieslak hypothesis of cyclic ketal form of the type (97) and (98) for anticoagulant activity.

Recently Hutchinson and Tomlinson[64] have revised the structure of dicoumarol and suggested the structure (100) on the basis of NMR and I.R.Spectra.



(100)

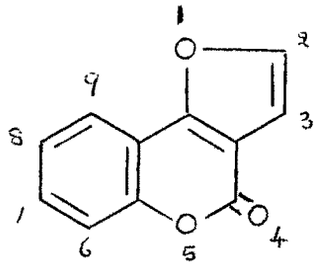
They studied the NMR spectra of dicoumarol and showed that there is a complex multiplet between 1.5 and 2.0 τ due to two protons as well as multiplet due to six protons in the region 2.2 to 3.0 τ . The low field multiplet is presumably due to the deshielded protons C_5 and C_5' and is evidence for the partial C = O character of the C_4- oxygen bond caused by the formation of a hydrogen bond between the hydroxyl group and the carbonyl group of

the adjacent ring.

In the I.R.spectrum, the carbonyl stretching frequency occurs at 1660 cm^{-1}. This is due to the carbonyl group in the side chain which is hydrogen bonded to the 4-hydroxy group of the coumarin moiety.

They have also suggested that in biological systems, the formation of these intramolecular hydrogen bonds may hold dicoumarol(100) in a suitable configuration for binding to an enzyme and hence may be an important factor in the biological activities of this compound.

It was,therefore, thought of interest to prepare 4-oxo-4H-furo(3,2-c)benzopyran (101) and compounds having substituents in the benzonoid part as well as in the furan part of the furocoumarin ring systems to test for anticoagulant property. The compound (101) is a dehydrated product of the hypothetical compound (97) as suggested by Chmielewska and Cieslak[62] in their theory.



(101)

The following furocoumarins are synthesised :

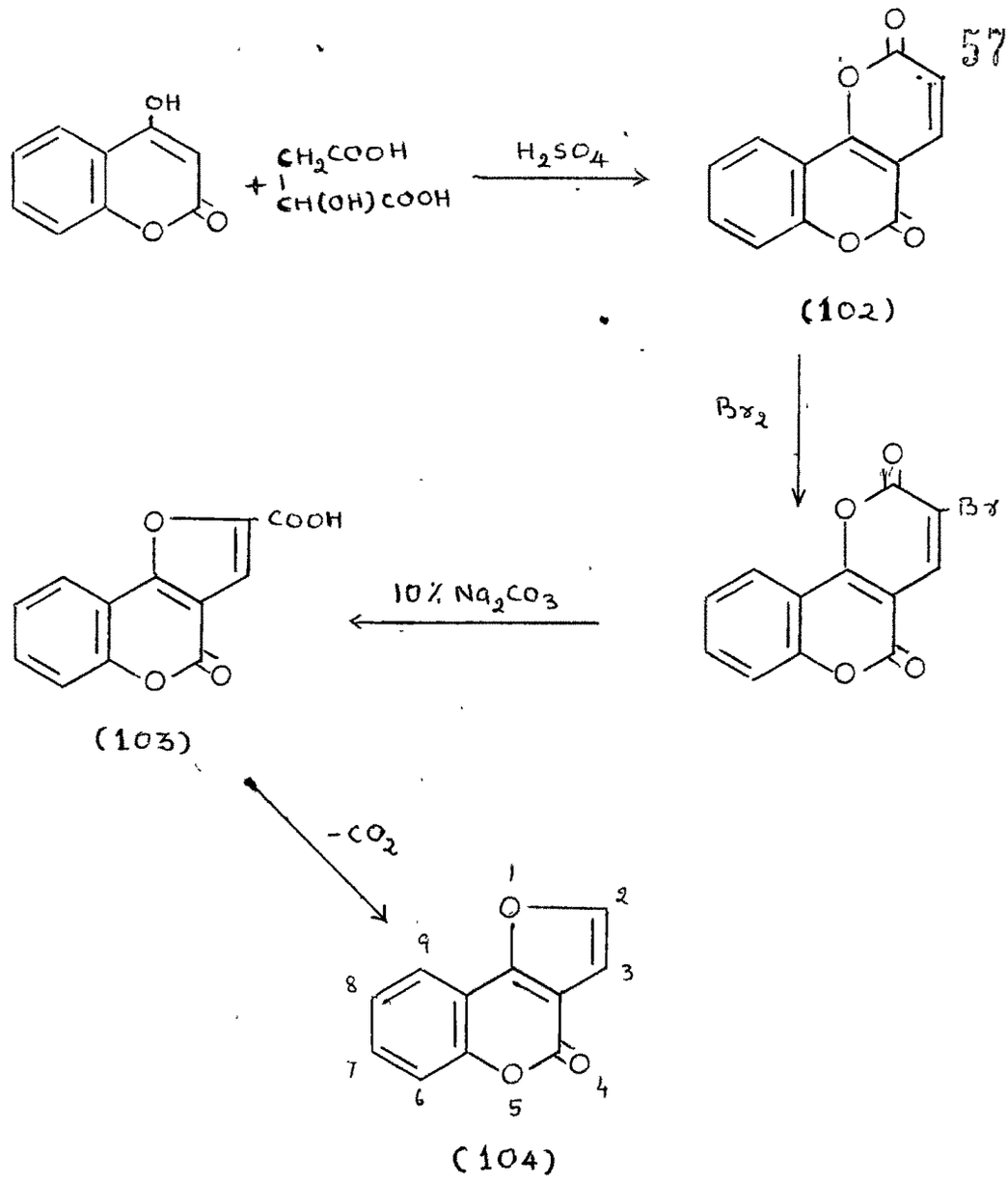
1. 4-Oxo-4H-furo(3,2-c)benzopyran.
2. 3-Methyl-4-oxo-4H-furo(3,2-c)benzopyran.
3. 3,8-Dimethyl-4-oxo-4H-furo(3,2-c)benzopyran.
4. 3-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran.
5. 3,6-Dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran.

Synthesis of 4-Oxo-4H-furo(3,2-c)benzopyran (104) : Pechmann condensation of 4-hydroxycoumarin with malic acid : 2,5-Dioxo-2H,5H-pyrano(3,2-c)benzopyran (102) :

4-Hydroxycoumarin on Pechmann condensation with malic acid in the presence of sulphuric acid gave a product which was insoluble in sodium bicarbonate solution ; 2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (102) structure was assigned to it.

4-Oxo-4H-furo(3,2-c)benzopyran (104) :

2,5-Dioxo-2H,5H-pyrano(3,2-c)benzopyran (102) was brominated with bromine in acetic acid to yield 3-bromo derivative which was hydrolysed by 10 % sodium carbonate solution to 4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid (103). This acid on decarboxylation with copper and quinoline gave 4-oxo-4H-furo(3,2-c)benzopyran (104).

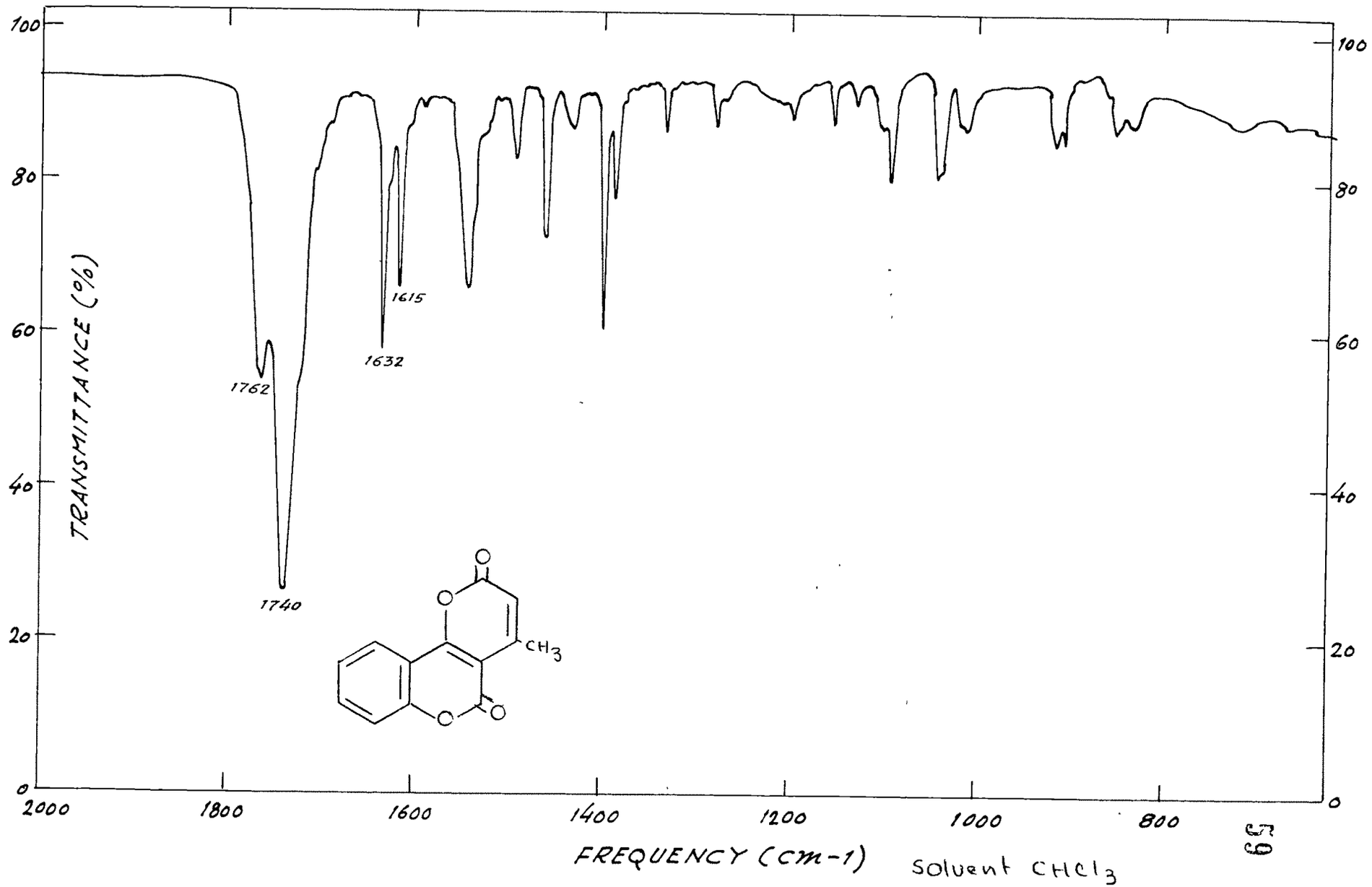


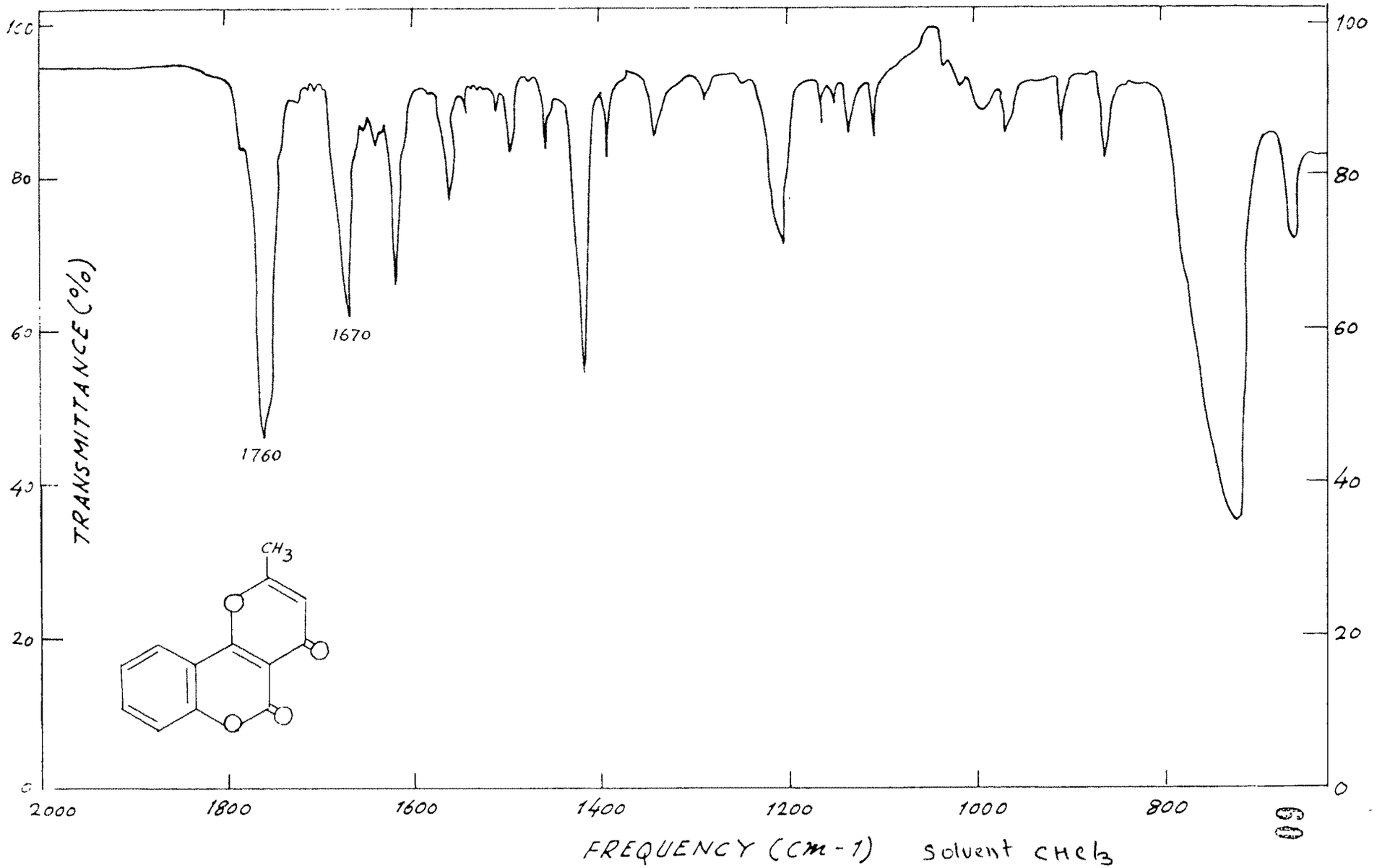
Synthesis of 3-Methyl-4-oxo-4H-furo(3,2-c)benzopyran (108): Pechmann condensation of 4-hydroxycoumarin with ethyl acetoacetate : 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (106) :

Mustafa and coworkers[65] condensed 4-hydroxycoumarin with ethyl acetoacetate in the presence of sulphuric acid

and the product was assigned 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (106) structure. The same product was also synthesised by Patell and Usgaonker[66] when they condensed 4-hydroxycoumarin with ethyl acetoacetate in the presence of anhydrous aluminium chloride.

Woods[67] condensed 4-hydroxycoumarin with ethyl acetoacetate in the presence of trifluoroacetic acid and claimed to have obtained 2-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran (105), m.p. 252°, principal absorption bands in I.R.region, 3344, 1727,1631,1613 cm^{-1}. Mustafa et al.[65] synthesised (105), m.p. 246°, carbonyl stretching frequencies 1754 and 1667 cm^{-1} in I.R.region, by different routes and claimed that it was identical in all respects with the compound prepared according to Woods[67]. It has now been found that 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (106), m.p. 243°, carbonyl stretching frequency in I.R.region 1740 cm^{-1}, is the only isolable product when the condensation was carried out in the presence of trifluoroacetic acid. The mixed m.p. with an authentic sample prepared according to Mustafa et al.[65] or Patell and Usgaonker[66] was not depressed, but the mixed m.p. with the sample prepared according to Mustafa et al.[65] by heating 4-hydroxy-3-acetylcoumarin with sodium and ethyl acetate and subsequent cyclisation with 25 % sulphuric acid, m.p. 246°, carbonyl stretching frequencies in I.R.region 1760 and 1670 cm^{-1}, was depressed by 20°.


100
80
60
40
20
0
TRANSMITTANCE (%)
1762
1740
1632
1615
CH3
2000
1800
1600
1400
1200
1000
800
FREQUENCY (cm-1)
Solvent CHCl3

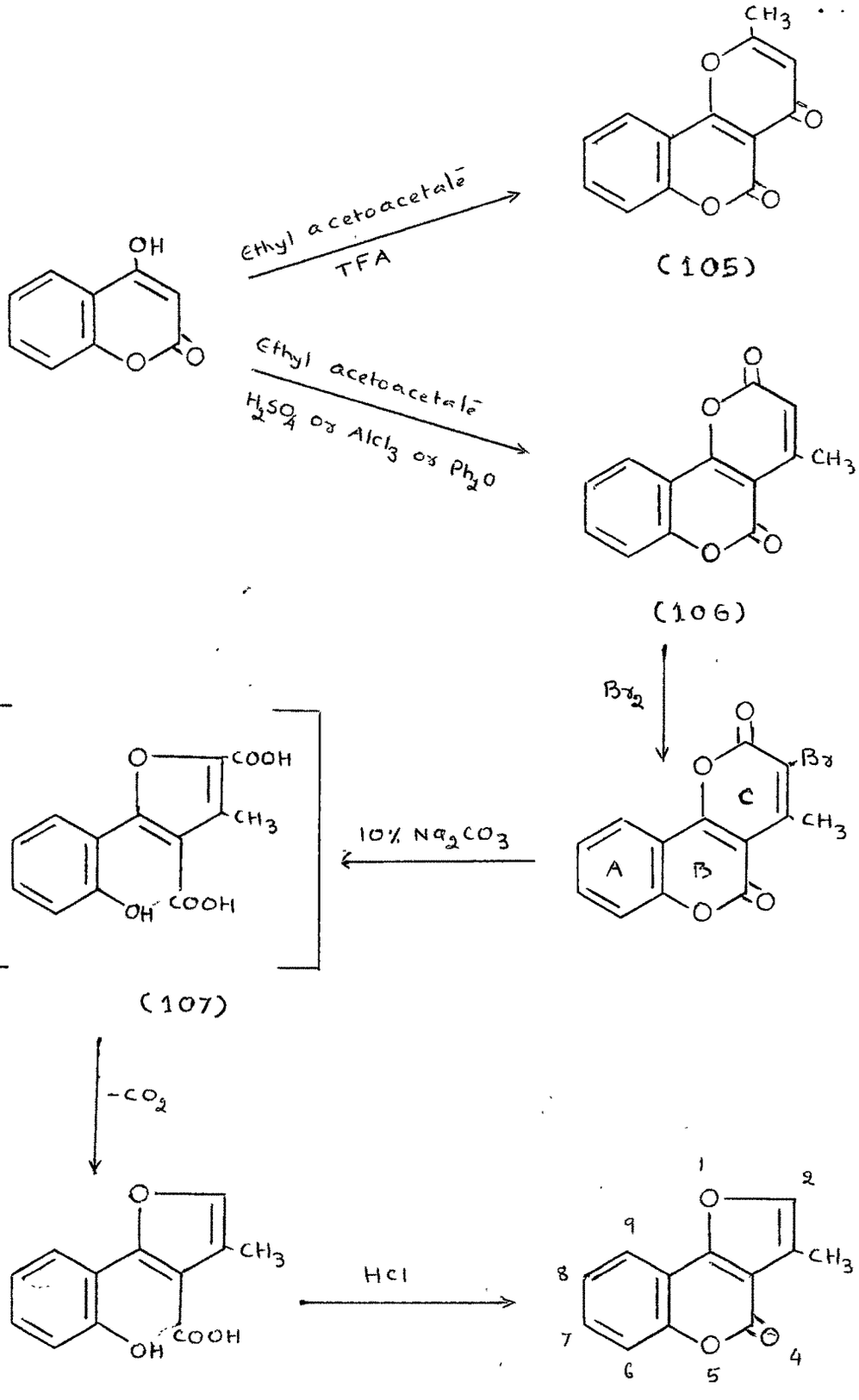

100
80
60
40
20
0
TRANSMITTANCE (%)
1760
1670
CH3
2000
1800
1600
1400
1200
1000
800
FREQUENCY (Cm-1)
Solvent CHCl3

Desai,Trivedi and Sethna[68] condensed different phenols with β-ketonic esters in the presence of refluxing diphenyl ether and obtained benzo-γ-pyrones. When 4-hydroxycoumarin was condensed with ethyl acetoacetate in the presence of refluxing diphenyl ether only 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (106) was obtained and not the expected 2-methyl-4,5-dioxo-4H,5H-pyrano-(3,2-c)benzopyran (105). This was also confirmed by mixed m.p. and I.R.spectra.

3-Methyl-4-oxo-4H-furo(3,2-c)benzopyran (109) :

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (106) on bromination with bromine in acetic acid gave 3-bromo derivative, which was hydrolysed by refluxing it with 10 % sodium carbonate solution to give 2-(o-hydroxy-phenyl)-4-methylfuran-3-carboxylic acid (108) and not the corresponding 3-methyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid as obtained in the previous case of 4-unsubstituted pyranobenzopyran. This is a typical behaviour observed in the case of 4-methylpyranobenzopyran derivatives. The formation of (108) can be explained as follows :

When 4-methyl-3-bromo-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran is hydrolysed, the ring contraction of ring (C) takes place to form a furan ring having a carboxylic group in 2-position, but at the same time α-pyrone ring (B) of the coumarin ring system also opens up to give an intermediate (107) which could not be isolated. This intermediate (107) undergoes decarboxylation

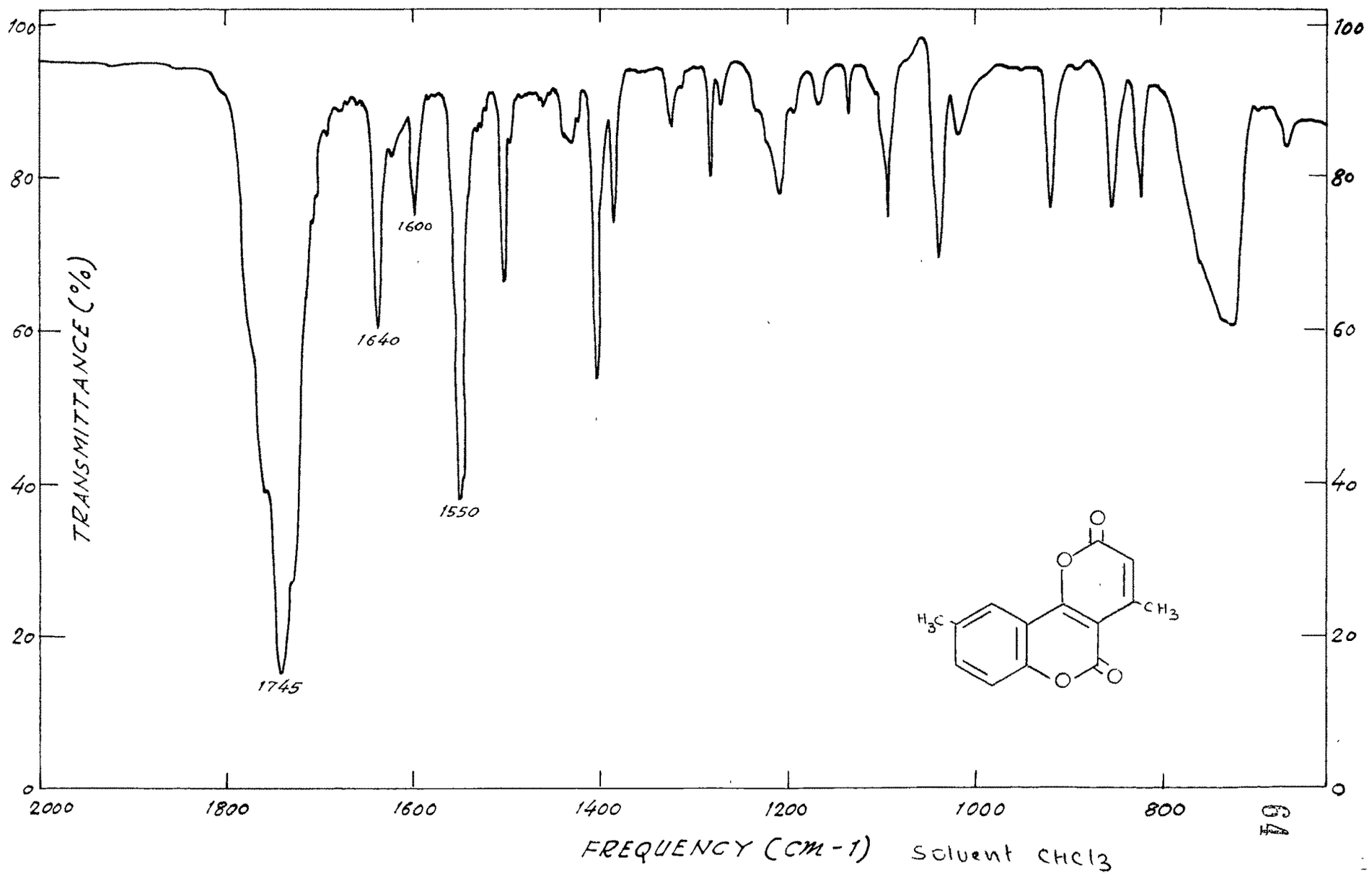

OH
Ethyl acetoacetate
TFA
CH3
(105)
Ethyl acetoacetate
H2SO4 or AlCl3 or Ph2O
CH3
(106)
Br2
Br
C
CH3
A
B
10% Na2CO3
COOH
CH3
OH
COOH
(107)
-CO2
CH3
OH
COOH
HCl
1
2
9
CH3
3
8
7
6
5
4

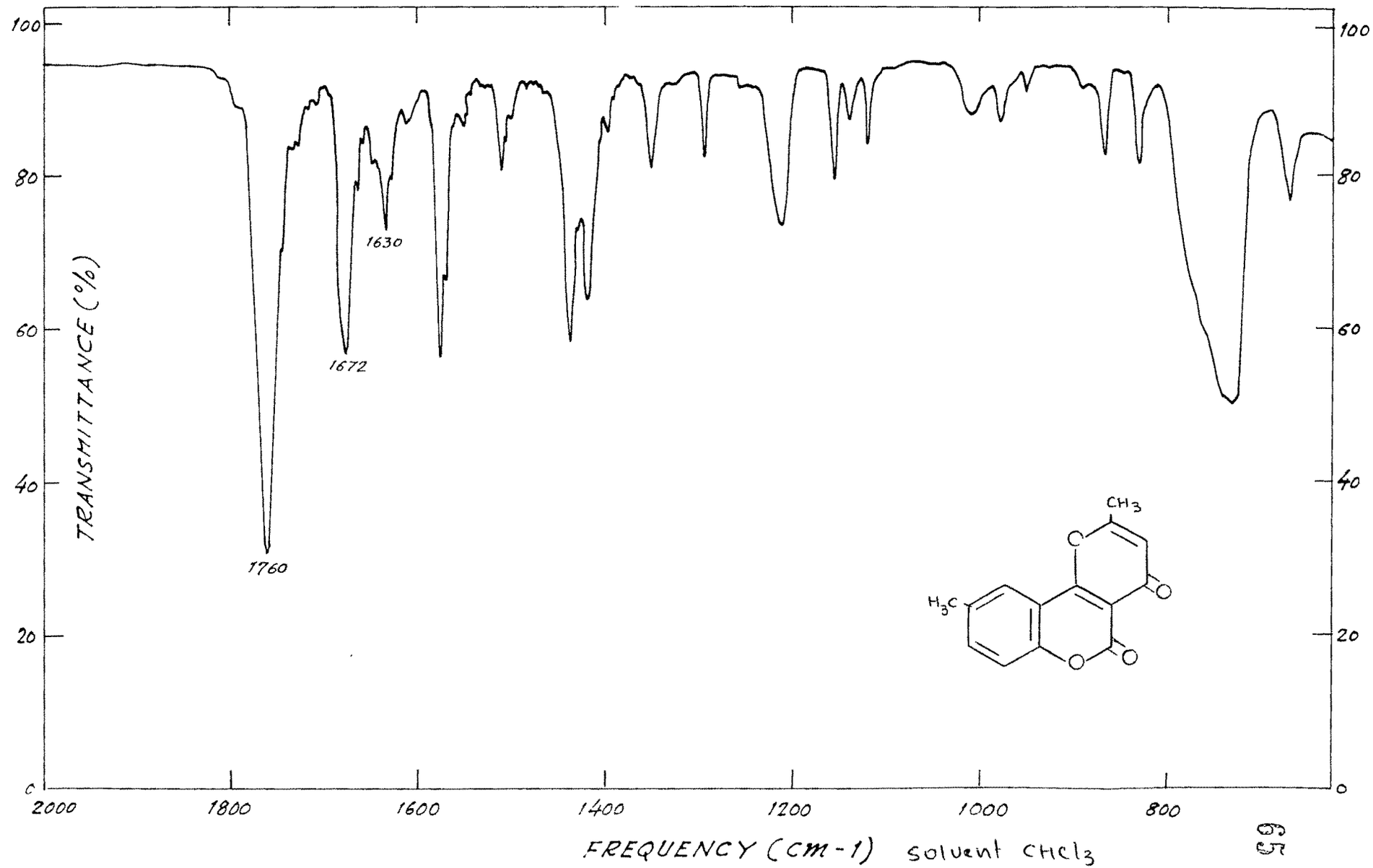
to give 2-(o-hydroxyphenyl)-4-methylfuran-3-carboxylic acid (108). This hydroxy acid was then cyclised by refluxing it with hydrochloric acid to 3-methyl-4-oxo-4H-furo(3,2-c)benzopyran (109).

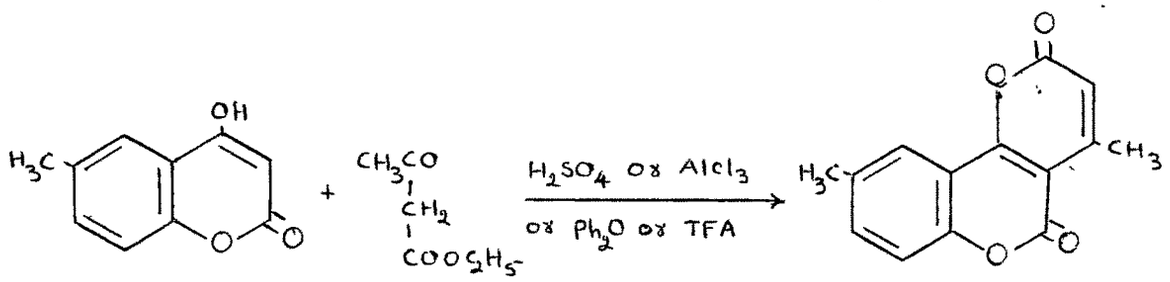
Synthesis of 3,8-Dimethyl-4-oxo-4H-furo(3,2-c) benzopyran (113) :

Pechmann condensation of 4-hydroxy-6-methylcoumarin with ethyl acetoacetate : 4,9-Dimethyl-2,5-dioxo-2H,5H-pyrano (3,2-c) benzopyran (110) :

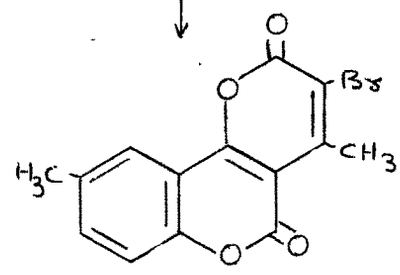
4-Hydroxy-6-methylcoumarin was condensed with ethyl acetoacetate in the presence of trifluoroacetic acid and 4,9-dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (110), m.p. 198°, carbonyl stretching frequency in I.R. region 1745 cm^{-1} was obtained. Mixed m.p. with an authentic sample prepared according to Patell and Usgaonker[66] did not depress. But the mixed m.p. with 2,9-dimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (Chapter III) prepared by heating 4-hydroxy-3-acetyl-6-methylcoumarin with sodium and ethyl acetate and subsequent cyclisation with 25 % sulphuric acid, m.p. 248°, carbonyl stretching frequencies 1760 and 1672 cm^{-1}, was depressed. When condensation was carried out in the presence of refluxing diphenyl ether, the same 4,9-dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (110) was obtained. M.P. and I.R. spectra were identical with the compound prepared by using trifluoro-acetic acid or aluminium chloride.

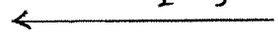

100
80
60
40
20
0
TRANSMITTANCE (%)
1745
1640
1600
1550
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
Solvent CHCl3
H3C
CH3
O
O
O
O

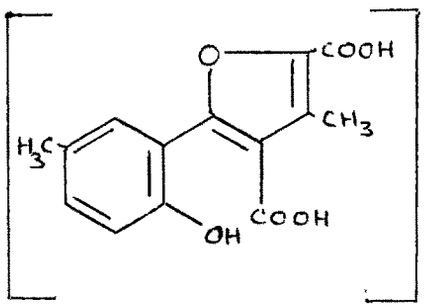

100
80
60
40
20
0
TRANSMITTANCE (%)
1760
1672
1630
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1) solvent CHCl3
CH3
H3C
O
O
O
O



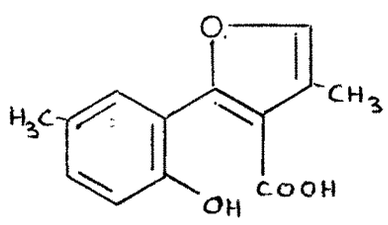
(110)



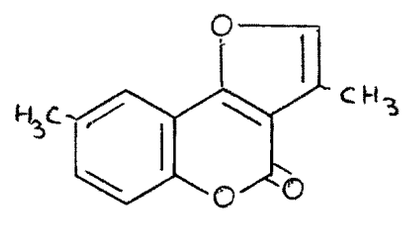




(111)



(112)



(113)

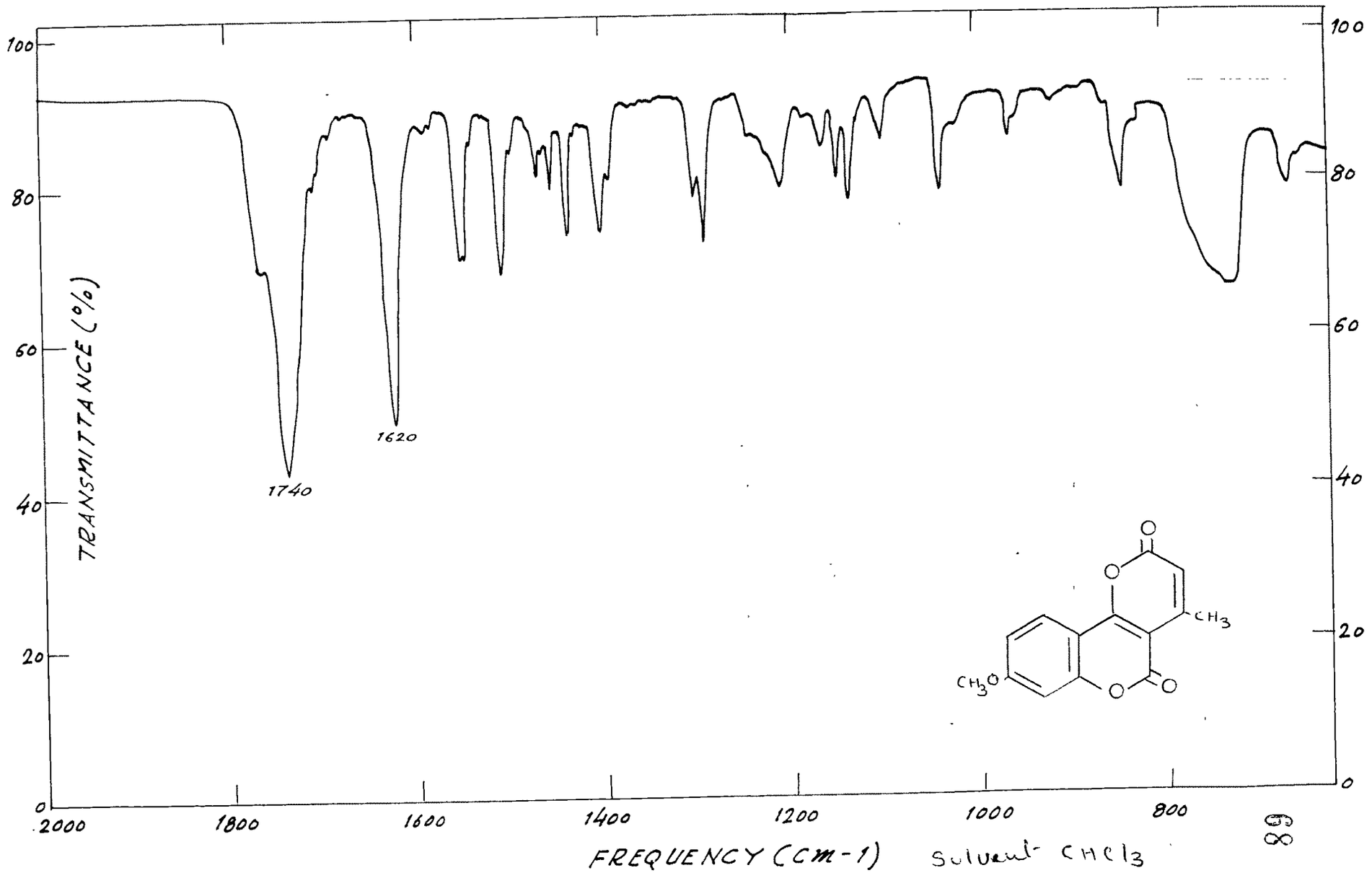
3,8-Dimethyl-4-oxo-4H-furo(3,2-c)benzopyran (113) :

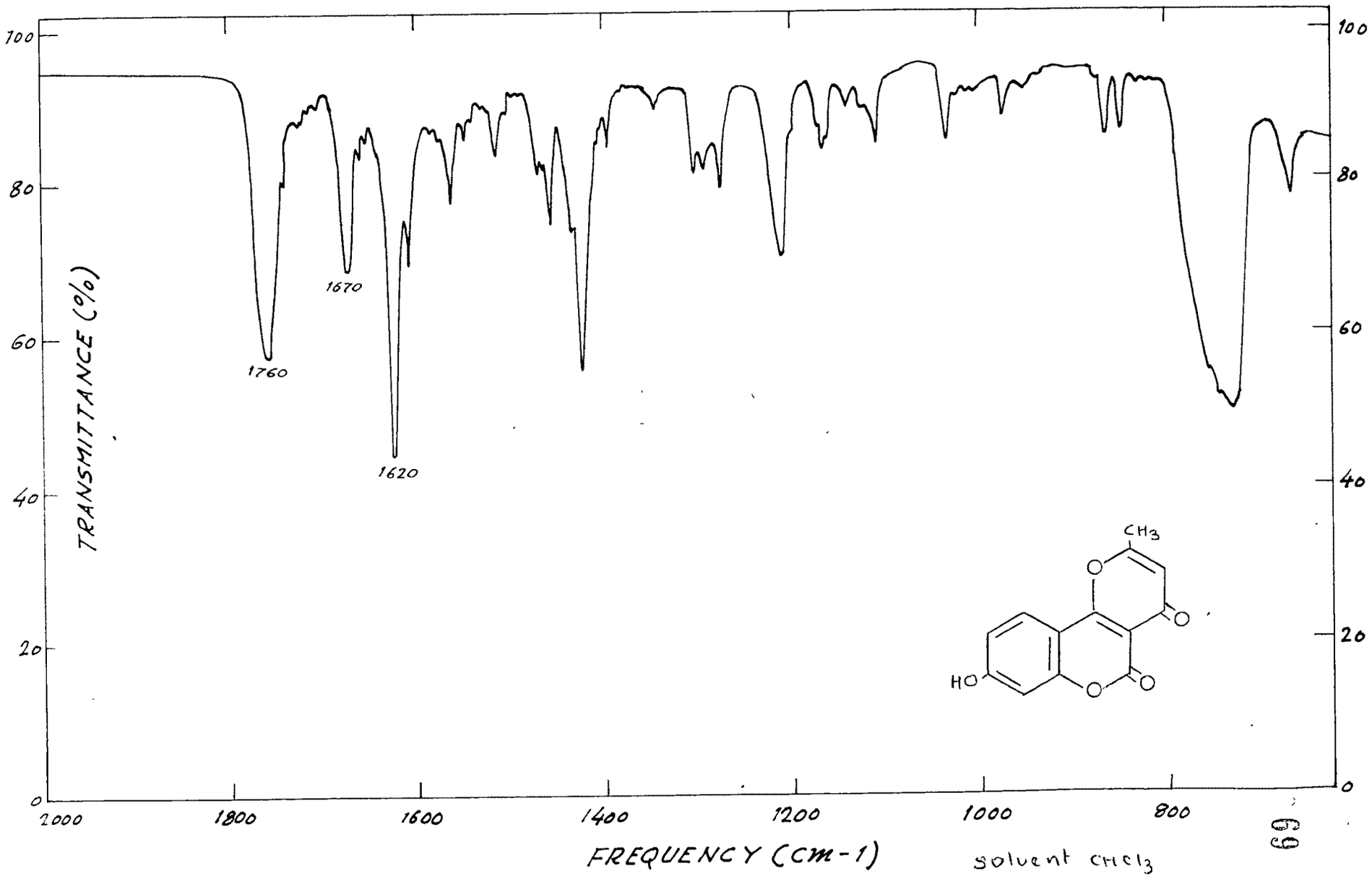
4,9-Dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (110) was brominated with bromine in acetic acid and the 3-bromo derivative was hydrolysed by 10 % sodium carbonate solution to give 2-(2'-hydroxy-5'-methylphenyl)-4-methylfuran-3-carboxylic acid (112) through the intermediate (111). This hydroxy acid (112) was then cyclised by refluxing it with hydrochloric acid to 3,8-dimethyl-4-oxo-4H-furo(3,2-c)benzopyran (113).

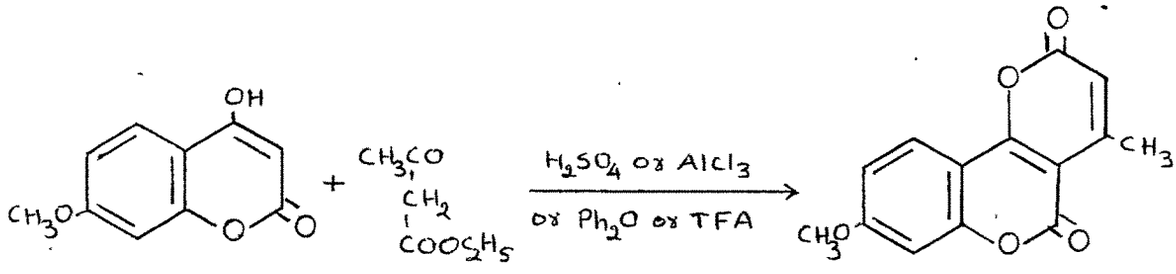
Synthesis of 3-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran (116) :

Pechmann condensation of 4-hydroxy-7-methoxycoumarin with ethyl acetoacetate : 4-Methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (114) :

4-Hydroxy-7-methoxycoumarin on Pechmann condensation with ethyl acetoacetate in the presence of sulphuric acid afforded 4-methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (114). When anhydrous aluminium chloride was used as condensing agent, the same product was obtained. 4-Hydroxy-7-methoxycoumarin was also condensed with ethyl acetoacetate in the presence of trifluoroacetic acid and refluxing diphenyl ether to give the same 4-methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (114), carbonyl stretching frequency 1740 cm^{-1} and not 2-methyl-8-methoxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran.

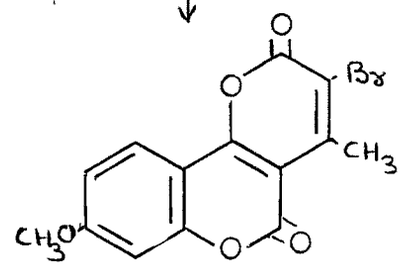

100
80
60
40
20
0
TRANSMITTANCE (%)
1740
1620
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
Solvent- CHCl3
CH3
CH3O
O
O
O
O
O


100
80
60
40
20
0
TRANSMITTANCE (%)
1760
1670
1620
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
CH3
O
O
O
O
HO
solvent CHCl3

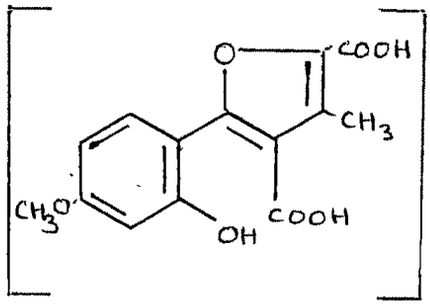

OH
CH3O
O
O
CH3CO
CH2
COOC2H5
H2SO4 or AlCl3
or Ph2O or TFA
CH3
CH3O
O
O
O

(114)

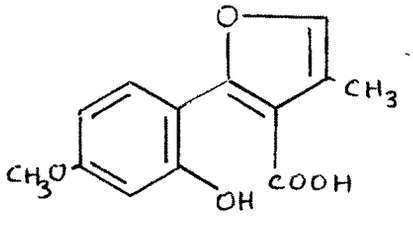
Br2


Br
CH3
CH3O
O
O
O

10% Na2CO3

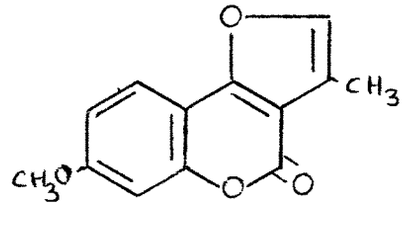

COOH
CH3
CH3O
OH
COOH

-CO2


CH3
CH3O
OH
COOH

(115)

HCl


CH3
CH3O
O
O

(116)

While preparing 2-methyl-8-methoxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran by heating 4-hydroxy-3-acetyl-7-methoxycoumarin with sodium and ethyl acetate and subsequent cyclisation, demethylation took place and 2-methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (Chapter III), carbonyl stretching frequencies 1760 and 1672 cm^{-1}, was obtained.

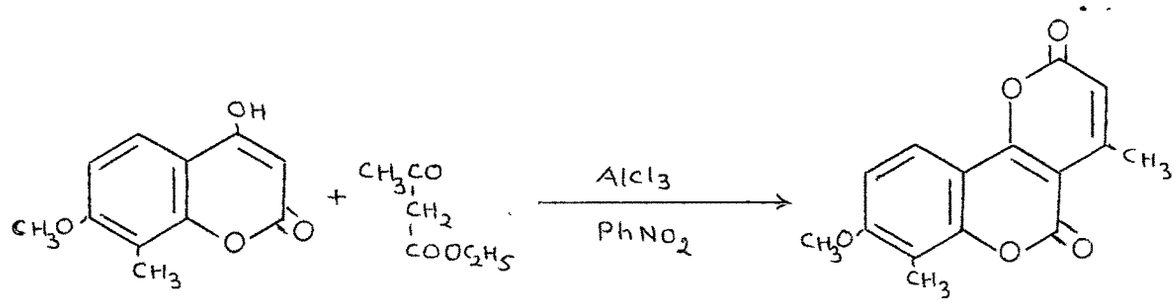
3-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (116):

4-Methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran (114) on bromination gave 3-bromo derivative, which on hydrolysis with 10 % sodium carbonate solution afforded 2-(2'-hydroxy-4'-methoxyphenyl)-4-methyl-furan-3-carboxylic acid (115). This hydroxy acid (115) on cyclisation with hydrochloric acid gave 3-methyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (116).

Synthesis of 3,6-Dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran (119) :

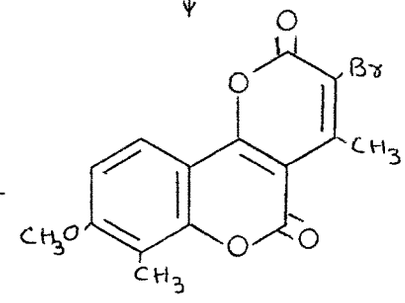
Pechmann condensation of 4-hydroxy-7-methoxy-8-methyl-coumarin with ethyl acetoacetate : 4,7-Dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (117):

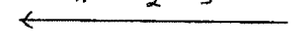
4-Hydroxy-7-methoxy-8-methylcoumarin on Pechmann condensation with ethyl acetoacetate in the presence of anhydrous aluminium chloride afforded a product which was insoluble in sodium bicarbonate solution ; the structure 4,7-dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (117) was assigned to it.

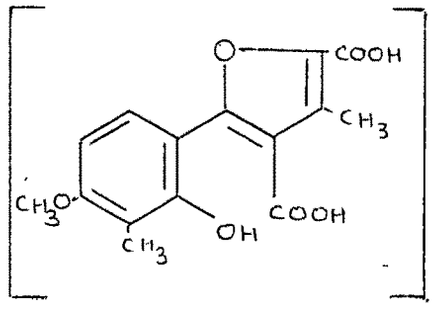

OH
CH3O
O
O
CH3
+
CH3CO
CH2
COOC2H5
AlCl3
PhNO2
CH3
CH3O
O
O
CH3

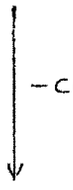
(117)

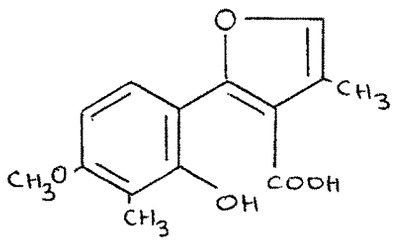
Br2


O
O
Br
CH3
CH3O
O
O
CH3

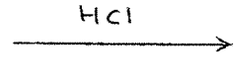

10% Na2CO3

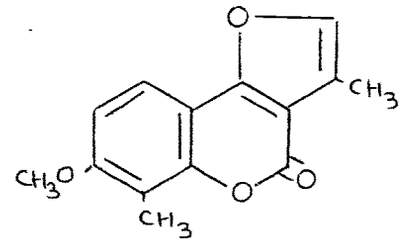

O
COOH
CH3
CH3O
OH
COOH
CH3


-CO2


O
CH3
CH3O
OH
COOH
CH3

(118)


HCl


O
CH3
CH3O
O
O
CH3

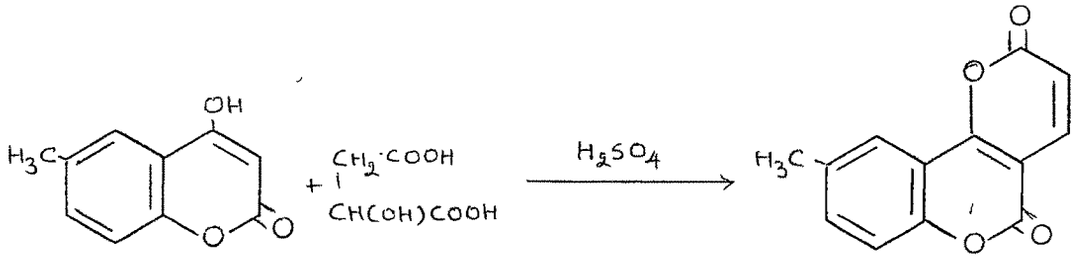
(119)

3,6-Dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (119) :

4,7-Dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran (117) on bromination yielded 3-bromo derivative which on hydrolysis with 10 % sodium carbonate solution gave 2-(2'-hydroxy-3'-methyl-4'-methoxyphenyl)-4-methylfuran-3-carboxylic acid (118). This hydroxy acid was then cyclised by refluxing it with hydrochloric acid to 3,6-dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (119).

Pechmann condensation of 4-hydroxy-6-methylcoumarin with malic acid : 9-Methyl-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran (120) :

4-Hydroxy-6-methylcoumarin on Pechmann condensation with malic acid gave a product which was insoluble in sodium bicarbonate solution ; the structure 9-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (120) was assigned to it. It was not possible to prepare a furocoumarin from this pyrano benzopyran (120) as it was obtained in very poor yield.

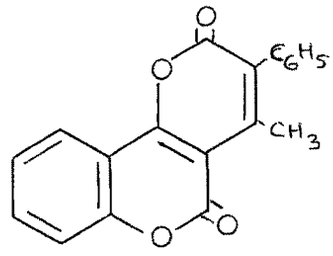


(120)

It is interesting to know the structural features of the compounds like warfarin (92 a), marcoumer (92 b), coumachlor (94 a) and sintron (94 b) which possess anticoagulant activity. The general feature of these compounds is that they have a phenyl ring separated from 4-hydroxycoumarin ring by one carbon atom at 3-position of coumarin ring system.

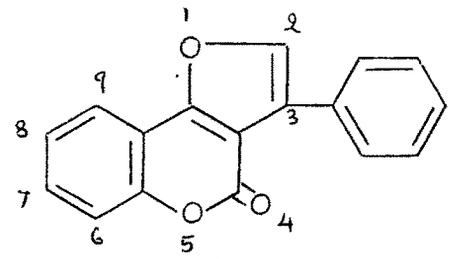
Cyclocoumarol or 3,4-(2'-methyl-2'-methoxy-4'-phenyl) dihydropyranocoumarin (93) which also possesses the above feature prepared by Link et al.[60] has greater anticoagulant activity than dicoumarol.

It is interesting to know here that 4-methyl-3-phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (121) possesses anticoagulant activity comparable to that of dicoumarol according to Arora and Mathur[69].



(121)

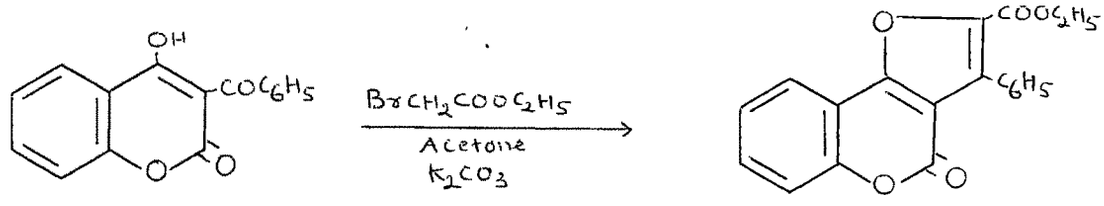
It was, therefore, thought of interest to synthesise compounds having similar structural features present in (122). To attain this a furan ring or a α-pyrone ring is built up on 3,4-position of 4-hydroxycoumarin ring systems which has a phenyl ring separated from the coumarin ring systems by one carbon atom.



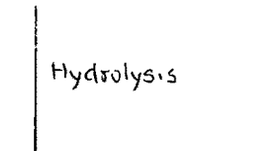
(122)

Synthesis of 3-Phenyl-4-oxo-4H-furo(3,2-c)benzopyran(126):

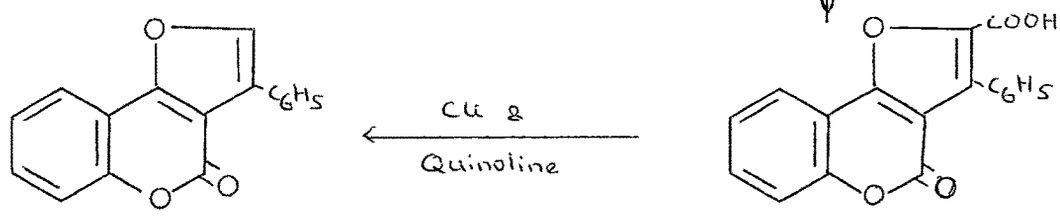
4-Hydroxy-3-benzoylcoumarin[70] (123) was condensed with ethyl bromoacetate in acetone to give the ester ethyl-3-phenyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate (124) and not the ethyl 3-benzoyl-4-coumarinyloxyacetate.



(123) (124)



Hydrolysis

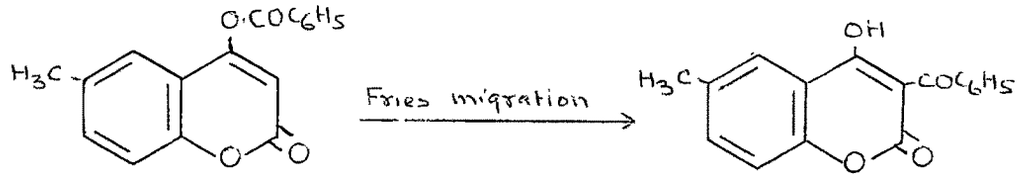


(126) (125)

The ester (124) was then hydrolysed by refluxing it with 10 % sodium hydroxide solution to 3-phenyl-4-oxo-4H-furo-(3,2-c)benzopyran-2-carboxylic acid (125). This acid on decarboxylation with copper and quinoline gave 3-phenyl-4-oxo-4H-furo(3,2-c)benzopyran (126).

Synthesis of 4-Hydroxy-3-benzoyl-6-methylcoumarin (127): Fries migration of 4-benzoyloxy-6-methylcoumarin :

4-Hydroxy-6-methylcoumarin was benzoylated with benzoyl chloride in pyridine and a few drops of piperidine at 0-5°. 4-Benzoyloxy-6-methylcoumarin on Fries migration with anhydrous aluminium chloride afforded 4-hydroxy-3-benzoyl-6-methylcoumarin (127).

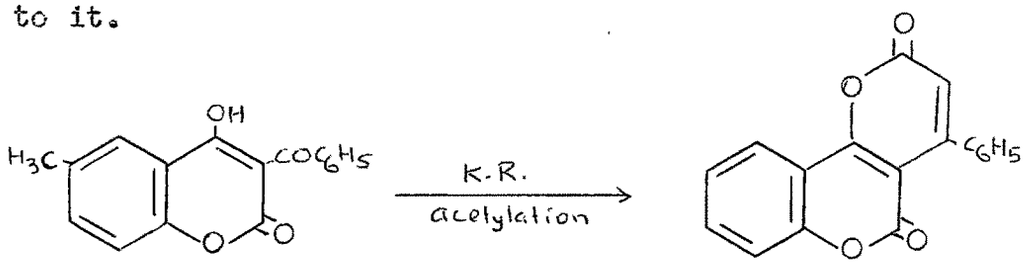


(127)

K.R.Acetylation of 4-hydroxy-3-benzoyl-6-methylcoumarin : 4-Phenyl-9-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (128) :

4-Hydroxy-3-benzoyl-6-methylcoumarin (127) on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate gave a product insoluble in sodium

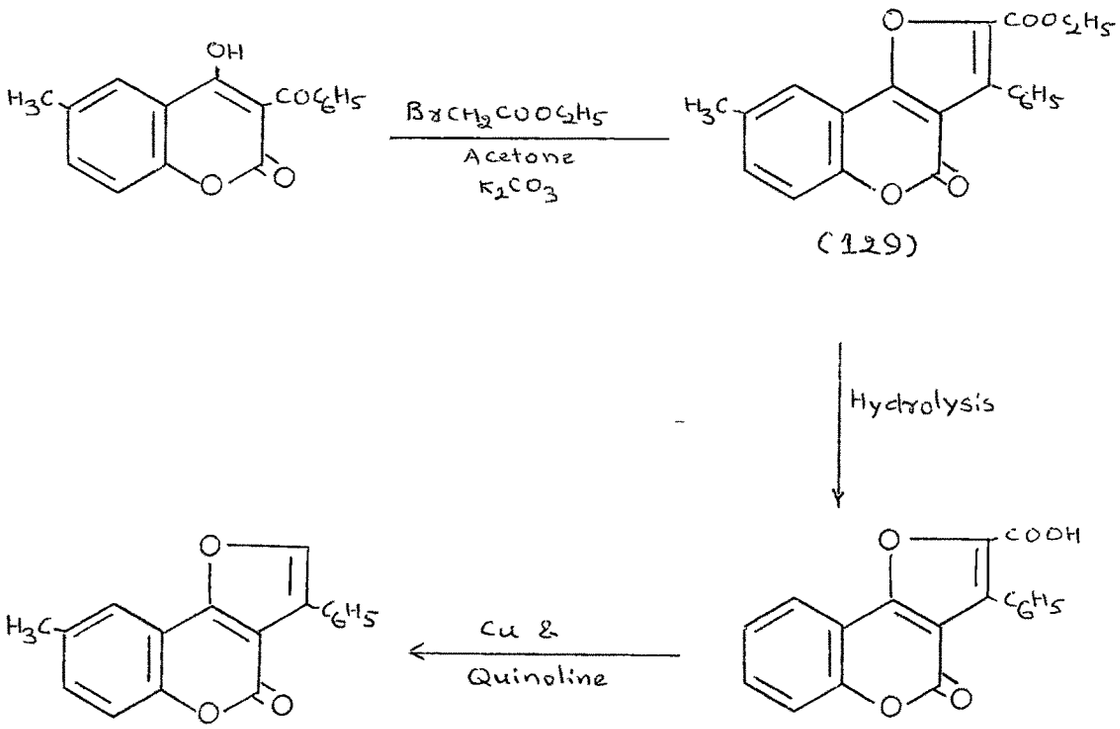
bicarbonate solution. The structure 4-phenyl-9-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (128) was assigned to it.



(128)

Synthesis of 3-Phenyl-8-methyl-4-oxo-4H-furo(3,2-c) benzopyran (131) :

4-Hydroxy-3-benzoyl-6-methylcoumarin (127) on condensation with ethyl bromoacetate in acetone gave the



(129)

ester ethyl 3-phenyl-8-methyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate (129). This ester was then hydrolysed by refluxing it with 10 % sodium hydroxide solution to 3-phenyl-8-methyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid (130) which on decarboxylation afforded 3-phenyl-8-methyl-4-oxo-4H-furo(3,2-c)benzopyran (131).

Syntheses of 2-Methyl-4-oxo-4H-furo(3,2-c)benzopyran derivatives :

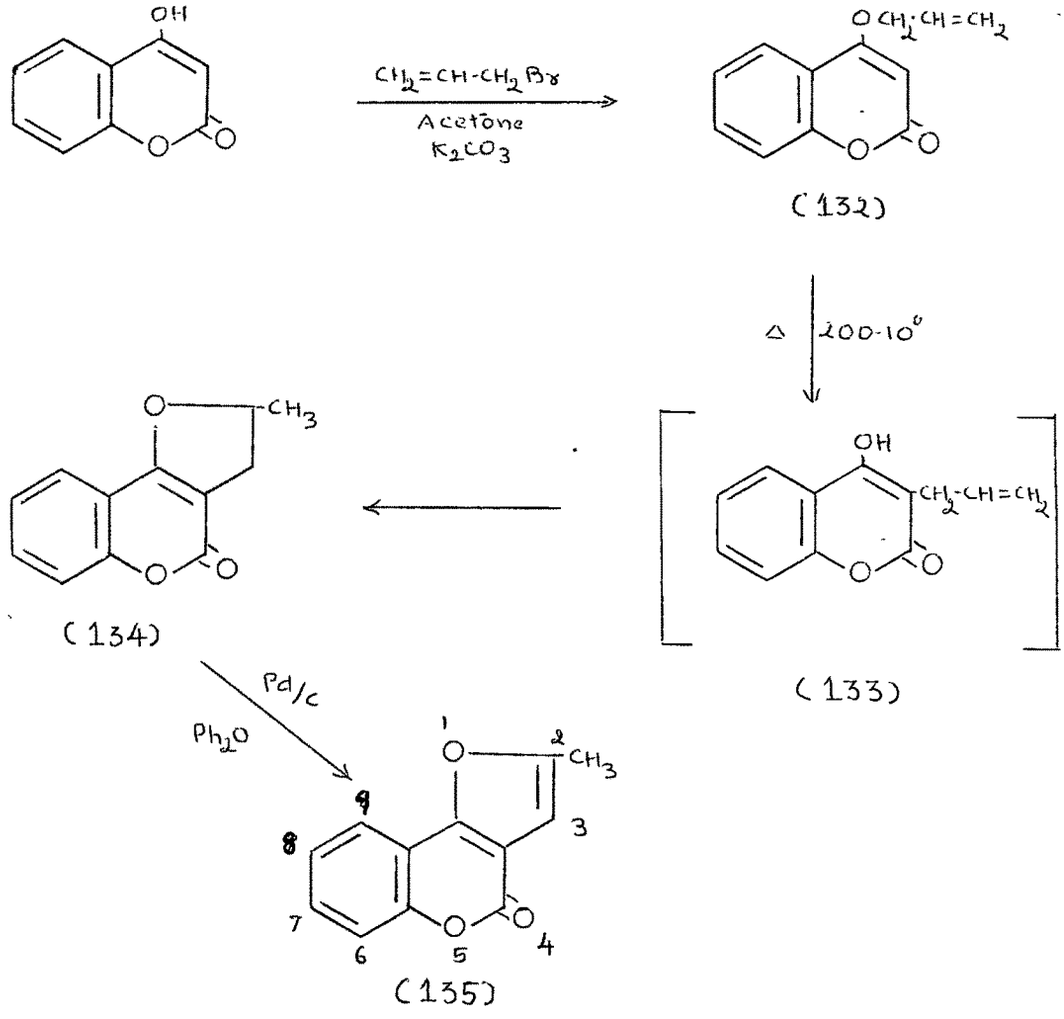
In recent years, the importance of o-hydroxy allylcoumarins has been increased because of the fact that these can be used as starting materials for the synthesis of 2-substituted furocoumarins as well as unsubstituted furocoumarins which occur in nature. It was, therefore, thought of interest to study the Claisen rearrangement of different 4-allyloxycoumarin derivatives and thereby to prepare 2-methylfurobenzopyran derivatives.

The following 2-methyl-4-oxo-4H-furo(3,2-c) benzopyran derivatives are synthesised :

1. 2-Methyl-4-oxo-4H-furo(3,2-c)benzopyran.
2. 2,8-Dimethyl-4-oxo-4H-furo(3,2-c)benzopyran.
3. 2-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran.
4. 2,6-Dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran.
5. 2-Methyl-6,7-dimethoxy-4-oxo-4H-furo(3,2-c) benzopyran.

Synthesis of 2-Methyl-4-oxo-4H-furo(3,2-c)benzopyran (135) :

4-Hydroxycoumarin was allylated with allyl bromide and anhydrous potassium carbonate in acetone to 4-allyloxycoumarin (132).

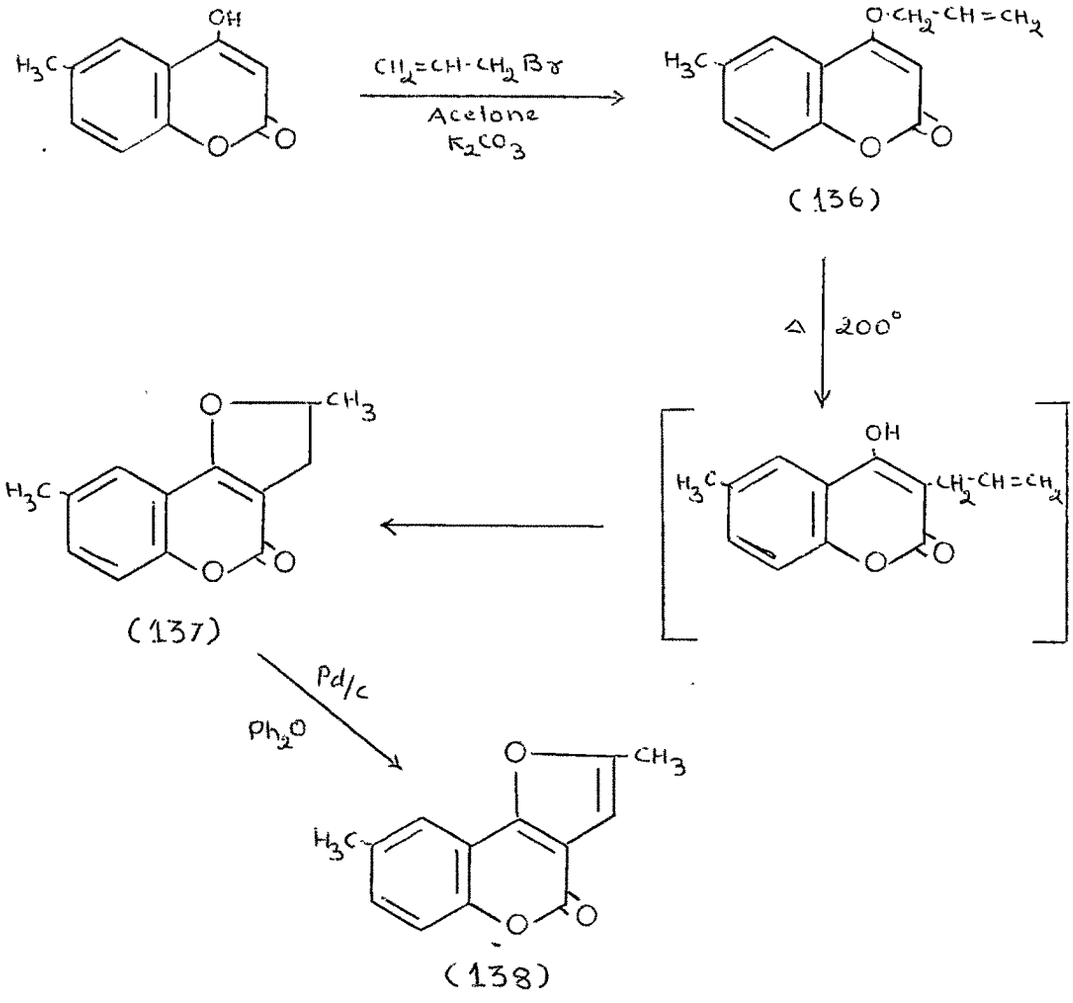


4-Allyloxycoumarin (132) on Claisen rearrangement when heated in an oil bath at 200-10° for 2 hr. gave a alkali insoluble product, to which 2-methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran (134) structure was assigned

and not 4-hydroxy-3-allylcoumarin (133). On Claisen rearrangement, the allyl group migrated to 3-position but at the same time was cyclised to give dihydrofurocoumarin (134). This dihydrofurocoumarin on dehydrogenation with palladised charcoal in dipheryl ether afforded 2-methyl-4-oxo-4H-furo(3,2-c)benzopyran (135).

Synthesis of 2,8-Dimethyl-4-oxo-4H-furo(3,2-c) benzopyran (138) :

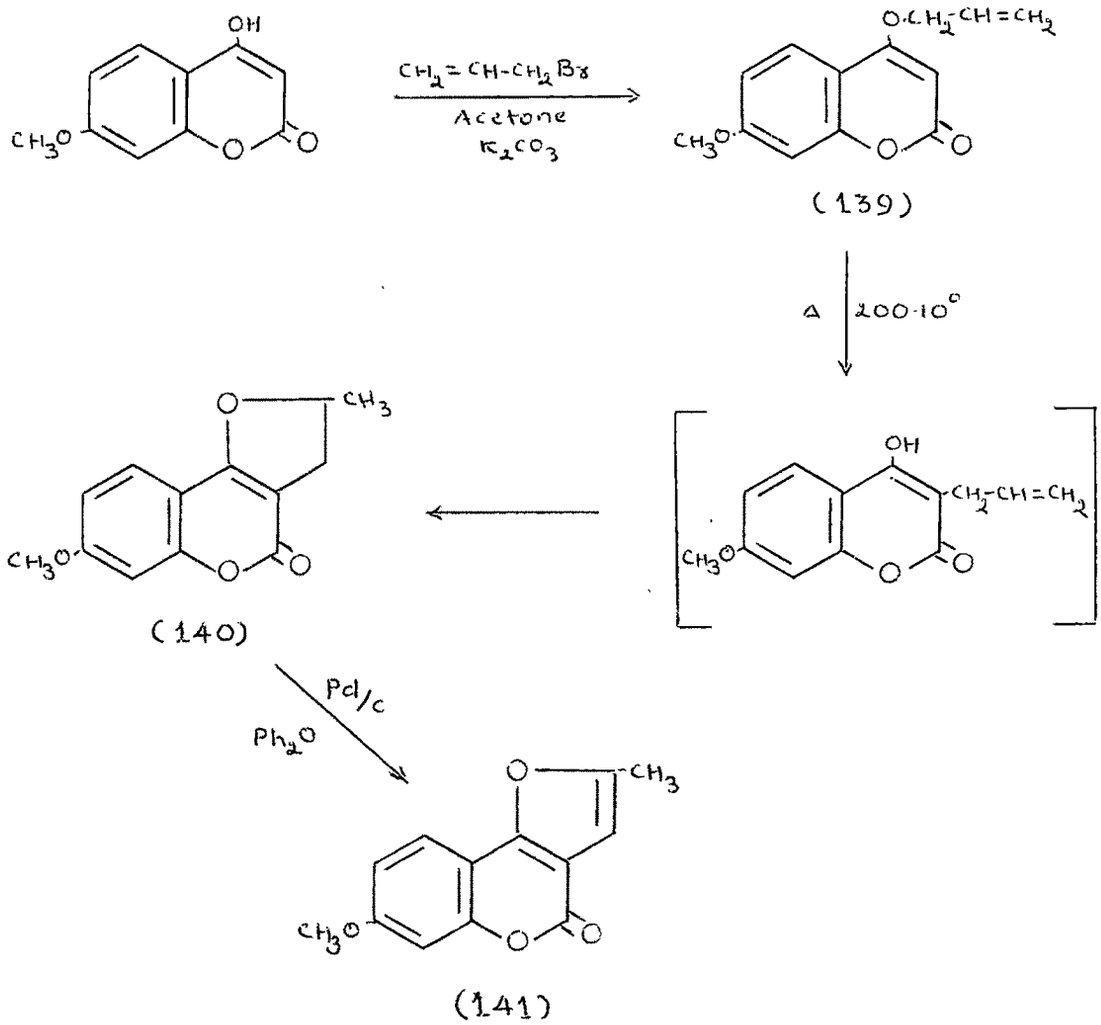
4-Hydroxy-6-methylcoumarin was allylated with allylbromide in acetone to give 4-allyloxy-6-methylcoumarin (136).



The above allyloxycoumarin (136) on Claisen rearrangement gave 2,8-dimethyl-2,3-dihydro-4-oxo-4H-furo (3,2-c)benzopyran (137) and not 4-hydroxy-3-allyl-6-methyl-coumarin. This dihydrofurocoumarin on dehydrogenation afforded 2,8-dimethyl-4-oxo-4H-furo(3,2-c)benzopyran (138).

Synthesis of 2-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran (141):

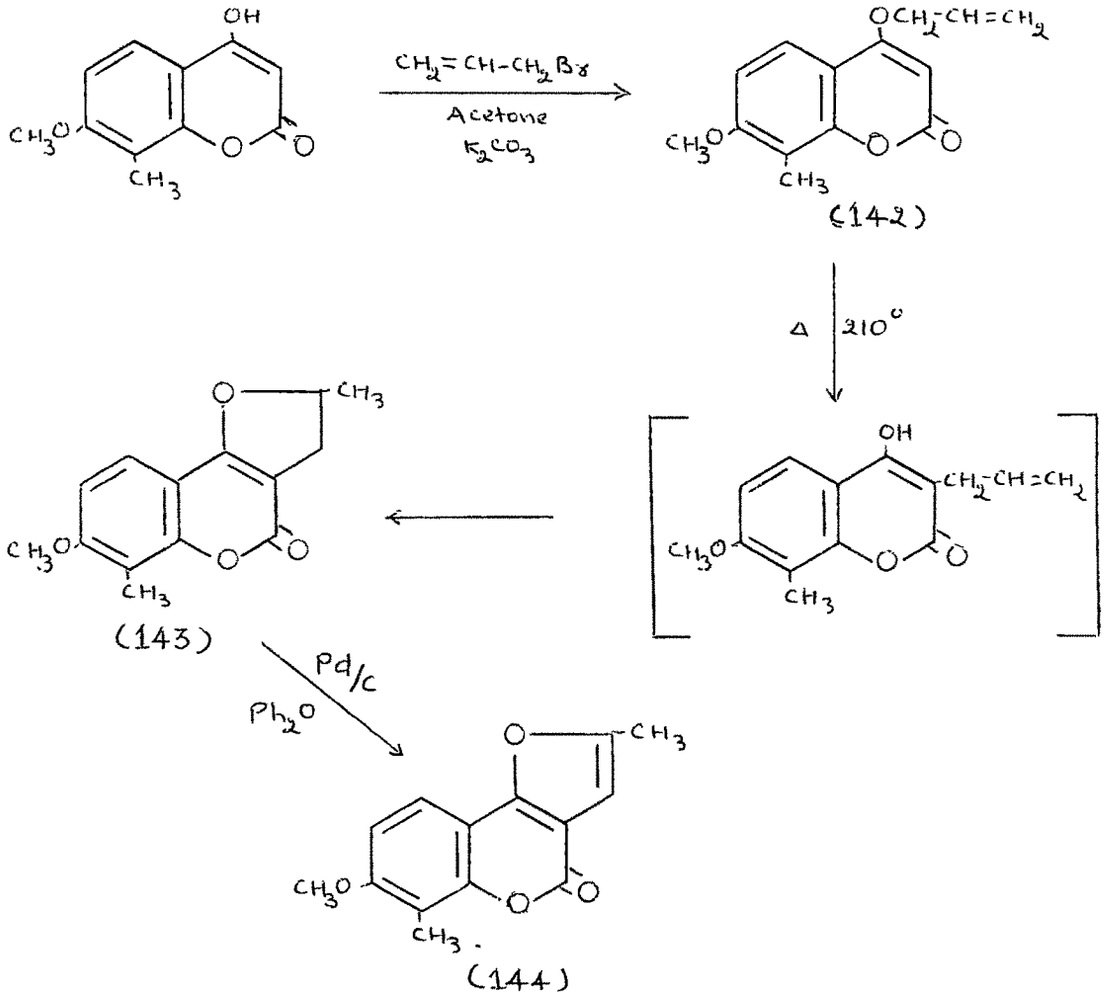
4-Hydroxy-7-methoxycoumarin on allylation with allyl bromide afforded 4-allyloxy-7-methoxycoumarin (139).



4-Allyloxy-7-methoxycoumarin (139) on Claisen rearrangement gave 2-methyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran (140) as before. This dihydrofurocoumarin on dehydrogenation afforded 2-methyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (141).

Synthesis of 2,6-Dimethyl-7-methoxy-4-oxo-4H-furo (3,2-c)benzopyran (144) :

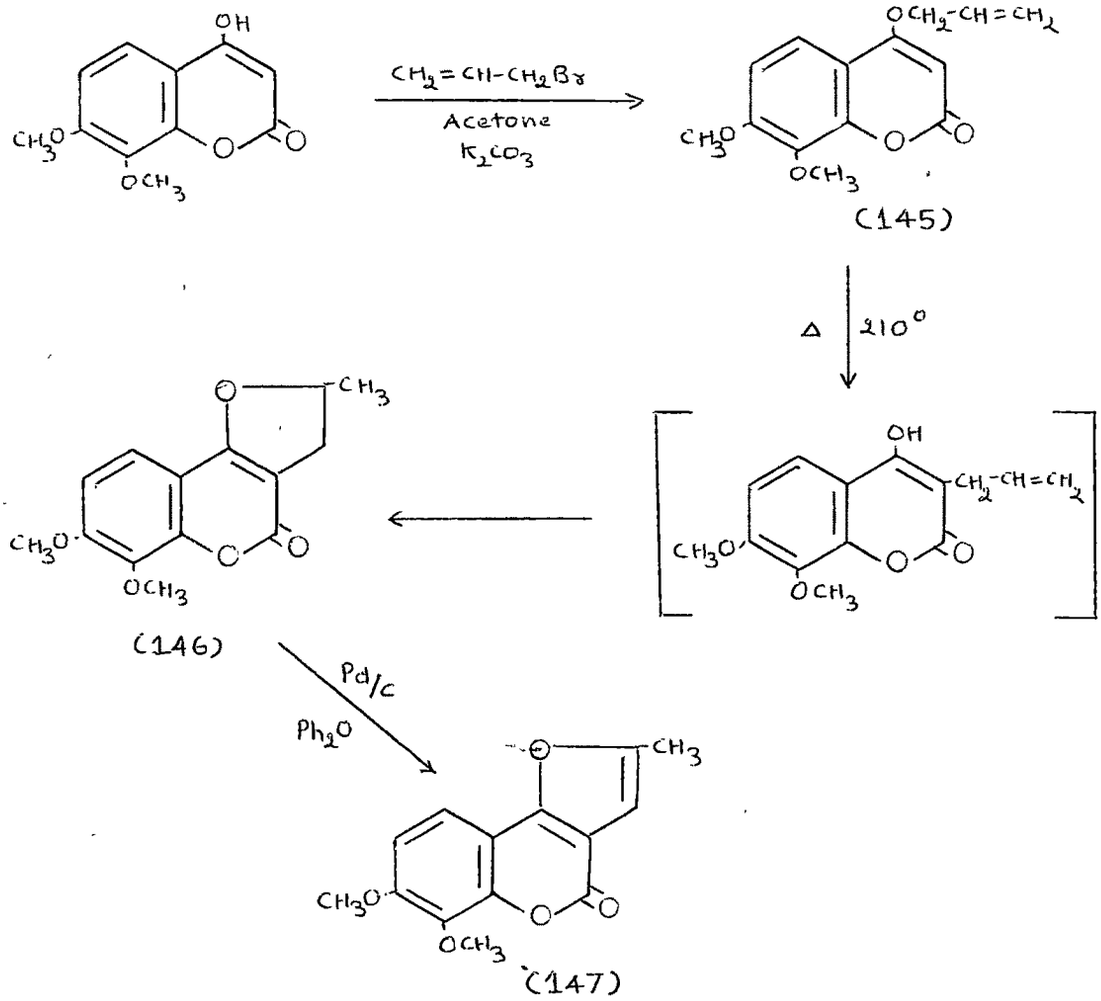
4-Hydroxy-7-methoxy-8-methylcoumarin on allylation with allyl bromide gave 4-allyloxy-7-methoxy-8-methylcoumarin (142).



4-Allyloxy-7-methoxy-8-methylcoumarin on Claisen rearrangement yielded 2,6-dimethyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran (143). This dihydrofurocoumarin on dehydrogenation gave 2,6-dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran (144).

Synthesis of 2-Methyl-6,7-dimethoxy-4-oxo-4H-furo (3,2-c)benzopyran (147) :

4-Hydroxy-7,8-dimethoxycoumarin on allylation with allyl bromide afforded 4-allyloxy-7,8-dimethoxy-coumarin (145).



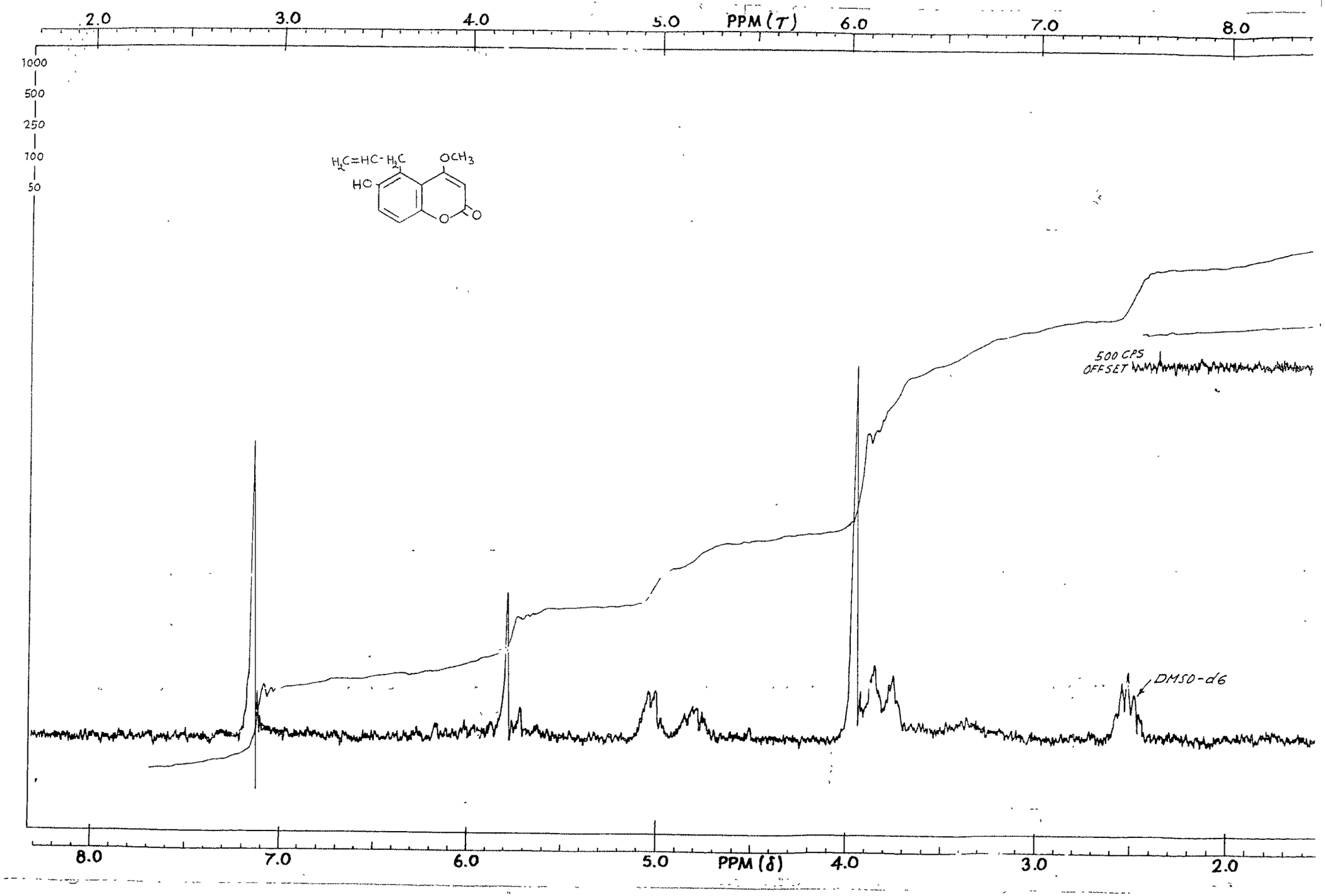
This 4-allyloxy-7,8-dimethoxycoumarin on Claisen rearrangement gave 2-methyl-6,7-dimethoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran (146) which on dehydrogenation gave 2-methyl-6,7-dimethoxy-4-oxo-4H-furo(3,2-c)benzopyran (147).

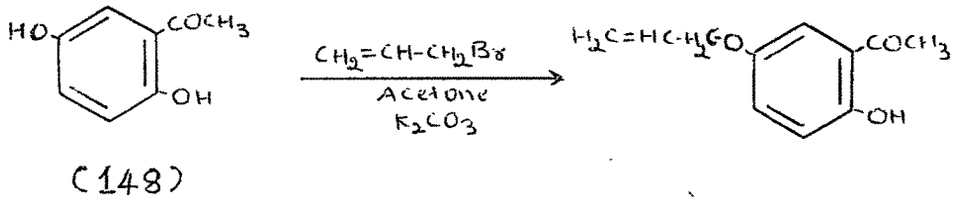
In view of therapeutic properties of furocoumarin and 4-hydroxycoumarin derivatives, it was thought of interest to synthesise furocoumarin derivatives having furan ring fused to the benzenoid part of the 4-hydroxycoumarin ring moiety.

Synthesis of 4-Hydroxy-2-methyl-6-oxo-6H-furo(3,2-f) benzopyran (154) : (Type D)

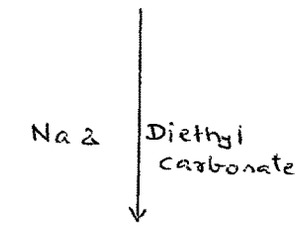
2,5-Dihydroxyacetophenone (148) was allylated by heating it with allyl bromide and anhydrous potassium carbonate in acetone to 2-hydroxy-5-allyloxyacetophenone.[71] It was then treated with pulverised sodium and diethyl carbonate on a water bath to give 4-hydroxy-6-allyloxy-coumarin (149) which was subsequently methylated to 4-methoxy-6-allyloxycoumarin (150). This methyl ether on Claisen rearrangement in dimethyl aniline afforded 4-methoxy-6-hydroxy-5-allylcoumarin (151). The structure of this allylcoumarin (151) was proved by NMR spectra.

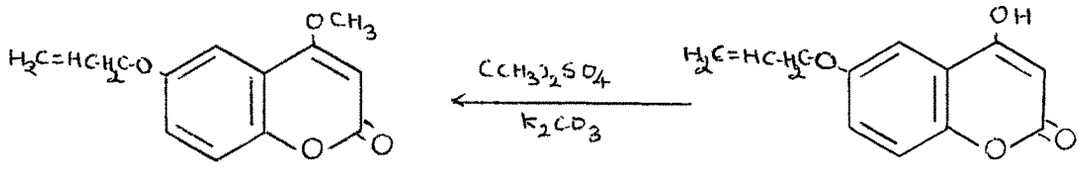
This allylcoumarin was cyclised to 4-methoxy-2-methyl-2,3-dihydro-6-oxo-6H-furo(3,2-f)benzopyran (152) by triturating it with con.sulphuric acid. It was then dehydrogenated with palladised charcoal in diphenyl ether to 4-methoxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran (153)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
1000
500
250
100
50
H2C=HC-H2C
OCH3
HO
O
O
500 CPS
OFFSET
DMSO-d6
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0

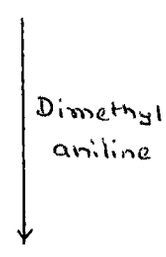


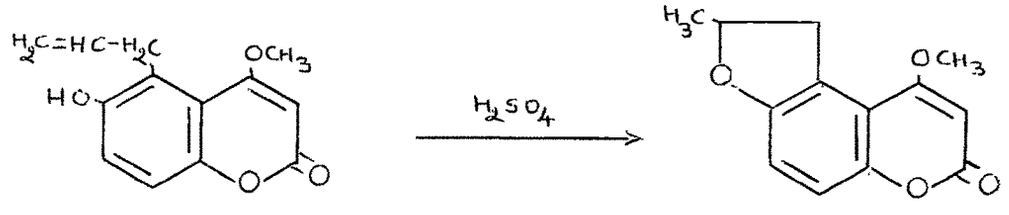
(148)



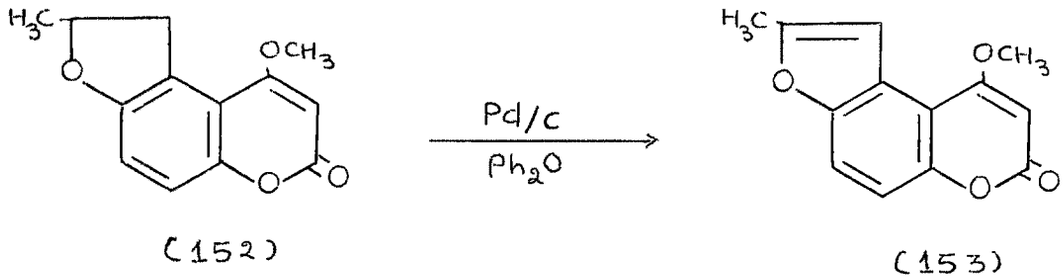


(150) (149)

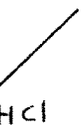


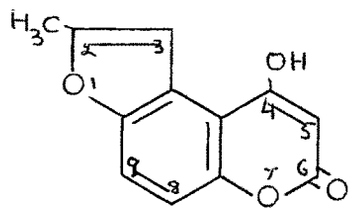


(151) (152)



(152) (153)





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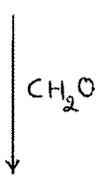
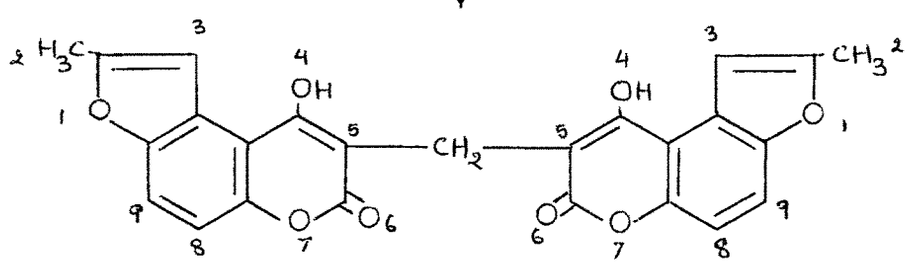




(155)

and subsequently demethylated to 4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran (154) by refluxing it with con. hydrochloric acid .When this furocoumarin was refluxed with formaldehyde solution in alcohol it gave 5,5'-methylene bis [4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran](155).

Synthesis of furocoumarin of the type (F) :

In recent years furocoumarins of the type (F) i.e. psoralene type have received considerable attention on account of their therapeutic properties. Xanthotoxin or 9-methoxypsoralene is a fish poison[72] but it is relatively non-toxic to mammals. Schoenberg and Latif[73] observed that it possesses molluscacidal activity. It was demonstrated by Elwi[74] that it produces fatty degenaration of liver and adrenal haemorrhage if it is administered in large doses to mammals. In the case of human beings the compound has found medical acceptance for the treatment of leucoderma.[75] The most recent applications have made use of the fact that it alters the erythermal response to ultra violet light, a property which has been used clinically to prevent sun-burns[76]. There is some evidence that xanthotoxin under certain conditions may be carcinogenic[77].

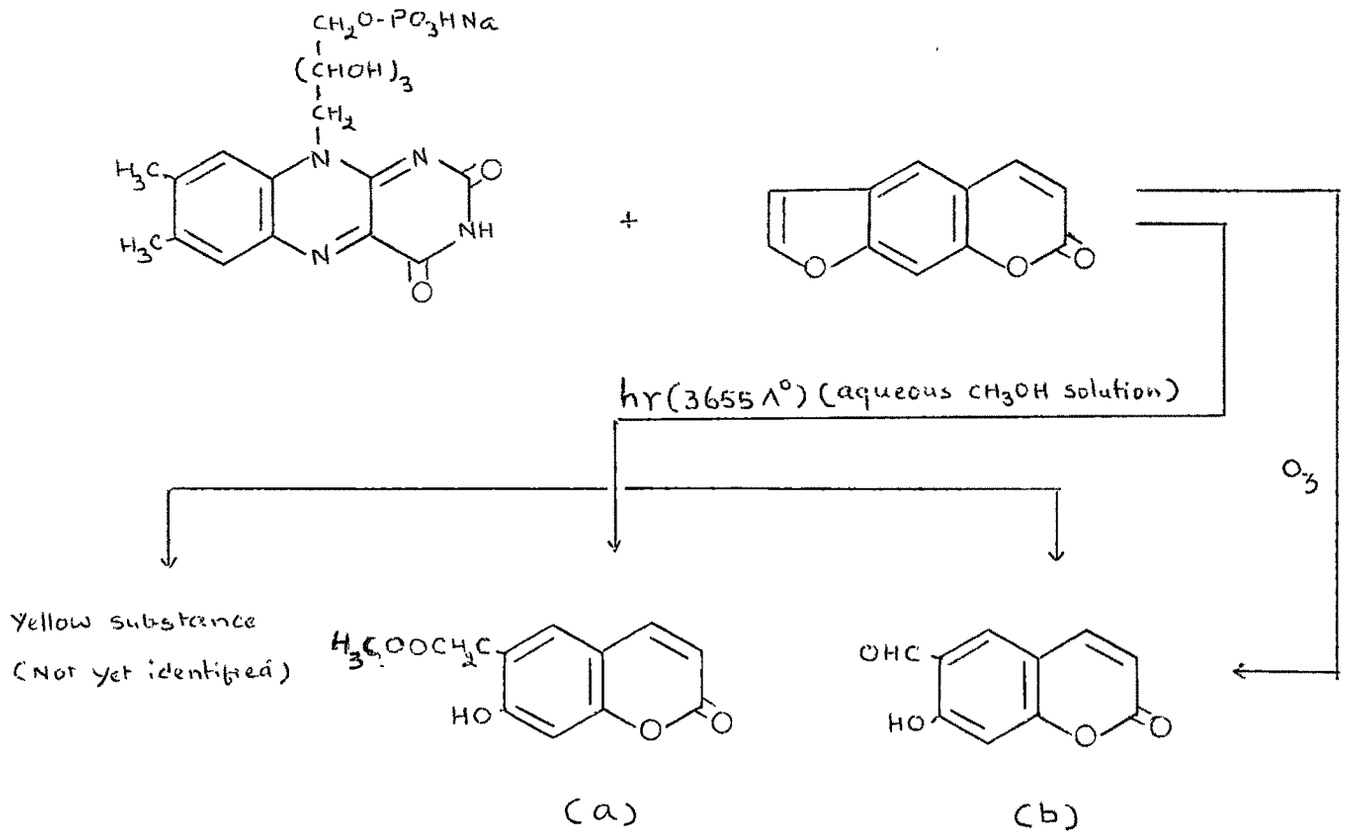
Pathak and Fellman[78] have studied the activating and fluorescent wave lengths of 37 furocoumarins and their biological photosensitising action was also investigated. Furocoumarins which induced difinite photosensitised erythermal response on mammalian skin showed activation peaks in the region of 340-380 mμ and concommitantly the fluorescent peaks in the region of 420-460 mμ. The inactive

furocoumarins did not show these specific activating and fluorescent peaks. Psoralene, xanthotoxin, bergapten etc. have been found to be active but 8-hydroxypsoralene, 5,8-dimethoxypsoralene etc. were found to be inactive.

Recently Musajo and coworkers[79] have observed that flavinmononucleotide (FMN) will react only with the furocoumarins that are photodynamically active and that the reaction products appear to have been modified mainly in the furan ring. Furthermore, they have demonstrated that FMN in large amounts acts against erythema expected from the psoralene type molecule. Three new coumarin derivatives have been isolated in the bergapten photoreaction, namely 7-hydroxy-5-methoxycoumarin-6-acetic acid, its methyl or ethyl ether according to the presence of methyl or ethyl alcohol in the irradiated solution and probably 4',5'-dihydro-4'-oxo-5-methoxyfurocoumarin.

Two substances have been obtained by the photoreaction of FMN and psoralene in a water-methyl alcohol solution, namely the methyl ester of 7-hydroxycoumarin-6-acetic acid (a) and 6-formyl-7-hydroxycoumarin (b). No new compounds are formed in the photoreaction of FMN and xanthotoxin.

Rodighiero and coworkers[80] found that psoralene and xanthotoxin significantly inhibited the growth of the tubercle bacillus. The antifungal activity of furocoumarins has been studied by Chakraborty and coworkers[81] who reported that psoralene and imperatorin were the most effective antifungal agents tested..


CH_2O-PO_3HNa
$(CHOH)_3$
CH_2
H_3C
H_3C
N
N
N
NH
O
O
+
O
O
O
$h\nu$ (3655 A°) (aqueous CH_3OH solution)
O_3
Yellow substance
(Not yet identified)
H_3COOCH_2C
HO
O
O
(a)
OHC
HO
O
O
(b)

Synthesis of 4-Hydroxy-5',8-dimethylpsoralene* (163) :

2,4-Dihydroxy-3-methylacetophenone (156) was allylated by refluxing it with allyl bromide and anhydrous potassium carbonate in acetone to 4-allyloxy-2-hydroxy-3-methylacetophenone (157). This was then treated with pulverised sodium and diethyl carbonate on a water bath to give 4-hydroxy-7-allyloxy-8-methylcoumarin (158). This coumarin was methylated and the methyl ether (159) was refluxed in diethyl aniline to yield 4-methoy-6-allyl-7-hydroxy-8-methylcoumarin (160).

The above allylcoumarin (160) was then cyclised to 4-methoxy-5',8-dimethyl-4',5'-dihydropsoralene (161) by triturating it with con.sulphuric acid. This method of cyclisation was found superior to earlier methods which used hydrobromic acid or pyridine hydrochloride. This dihydrofurocoumarin (161) on dehydrogenation with palladised charcoal afforded 4-methoxy-5',8-dimethylpsoralene (162), the U.V.Spectra of which showed the characteristic band at 326 mu (log e 3.93). It underwent demethylation to 4-hydroxy-5',8-dimethylpsoralene (163) when refluxed with con.hydrochloric acid. 4-Hydroxy-5',8-dimethylpsoralene was refluxed with formaldehyde solution in alcohol to give 3,3'-methylene bis (4-hydroxy-5',8-dimethylpsoralene) (164).

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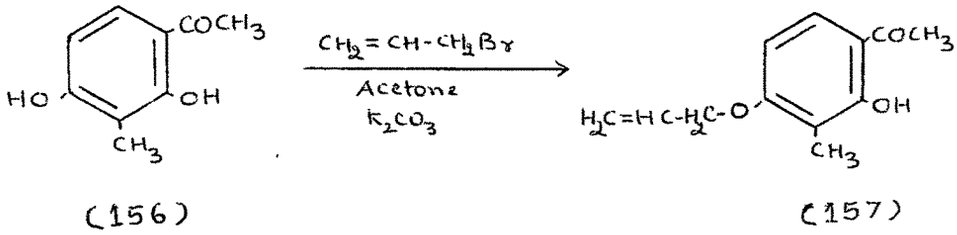
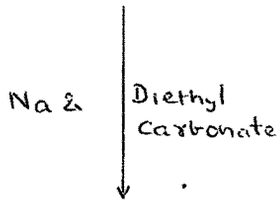
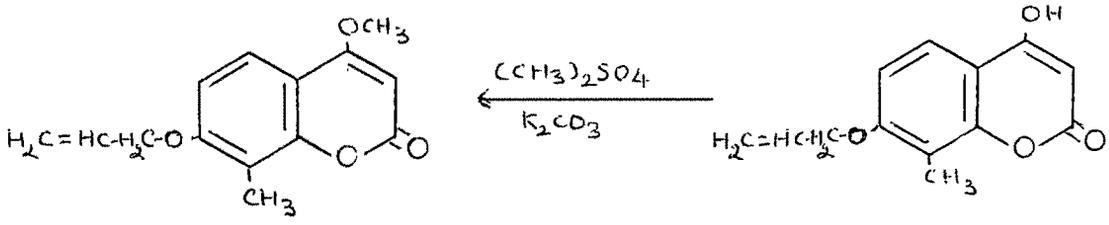
* The nomenclature is according to A.C.Curtius, J. Invest.Dermatol., 32, 133 (1959).



(156) (157)





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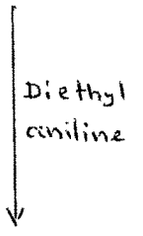

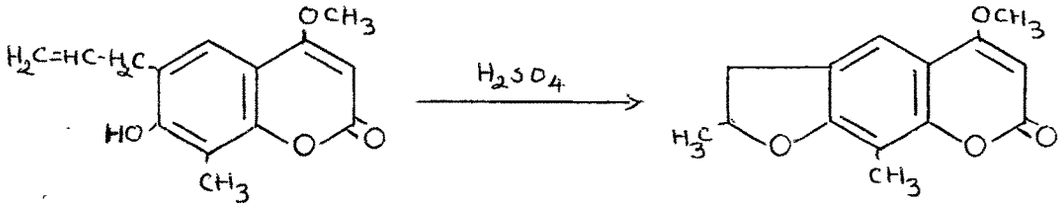

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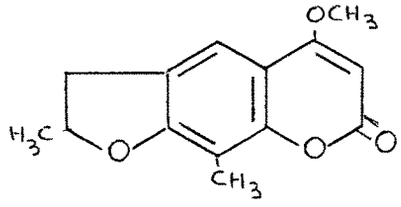
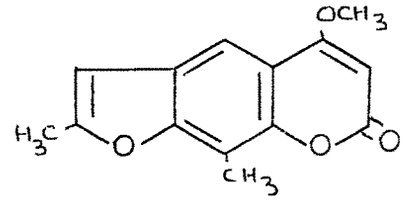


(161)

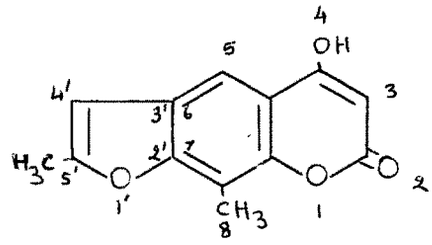
Pd/c

Ph_2O



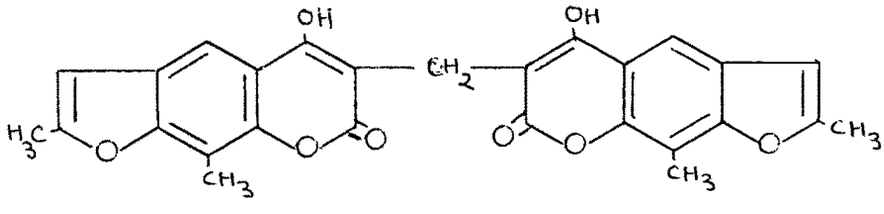
(162)

HCl



(163)

CH_2O



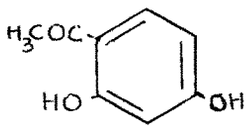
(164)

Synthesis of 7-hydroxy-2-methyl-5-oxo-5H-furo (2,3-h)benzopyran (174) : Type (G)

Resacetophenone (165) was allylated with allyl bromide in acetone to 4-allyloxyresacetophenone[71] (166). This was then converted to 4-hydroxy-7-allyloxycoumarin (167) by heating it with sodium and ethyl carbonate. This was then methylated and the methyl ether (168) on Claisen rearrangement in dimethyl aniline afforded 4-methoxy-7-hydroxy-8-allylcoumarin (169). This allylcoumarin was cyclised with con.sulphuric acid to 7-methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran (170).

The above dihydrofurocoumarin was also synthesised by another route. 3-Allylresacetophenone[71] was cyclised to 2-methyl-4-hydroxy-5-acetylcoumaran (171) by treating it with con.sulphuric acid. This was converted to 7-hydroxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran (172) by heating it with sodium and diethyl carbonate. This was then methylated to (170).

It was then dehydrogenated to 7-methoxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran (173) by refluxing it with palladised charcoal in diphenyl ether which underwent demethylation to 7-hydroxy-2-methyl-5-oxo-5H-furo(2,3-h) benzopyran (174) when refluxed with con.hydrochloric acid. This furocoumarin when refluxed with formaldehyde solution in alcohol gave 6,6'-methylene bis[7-hydroxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran](175).

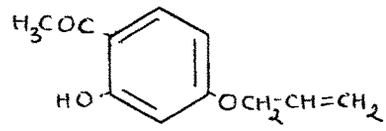


(165)

$CH_2=CH-CH_2Br$

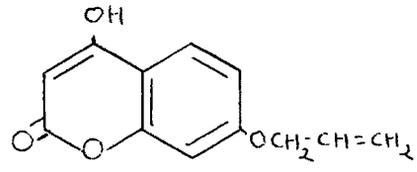
Acetone

K_2CO_3



(166)

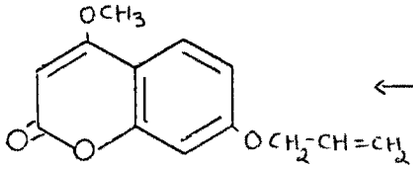
Na & Diethyl carbonate



(167)

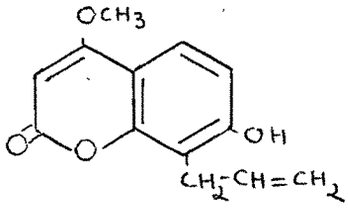
$(CH_3)_2SO_4$

K_2CO_3



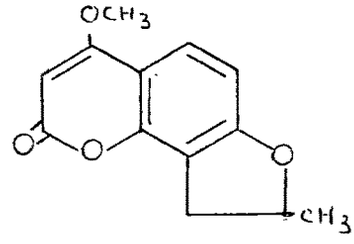
(168)

Dimethyl aniline

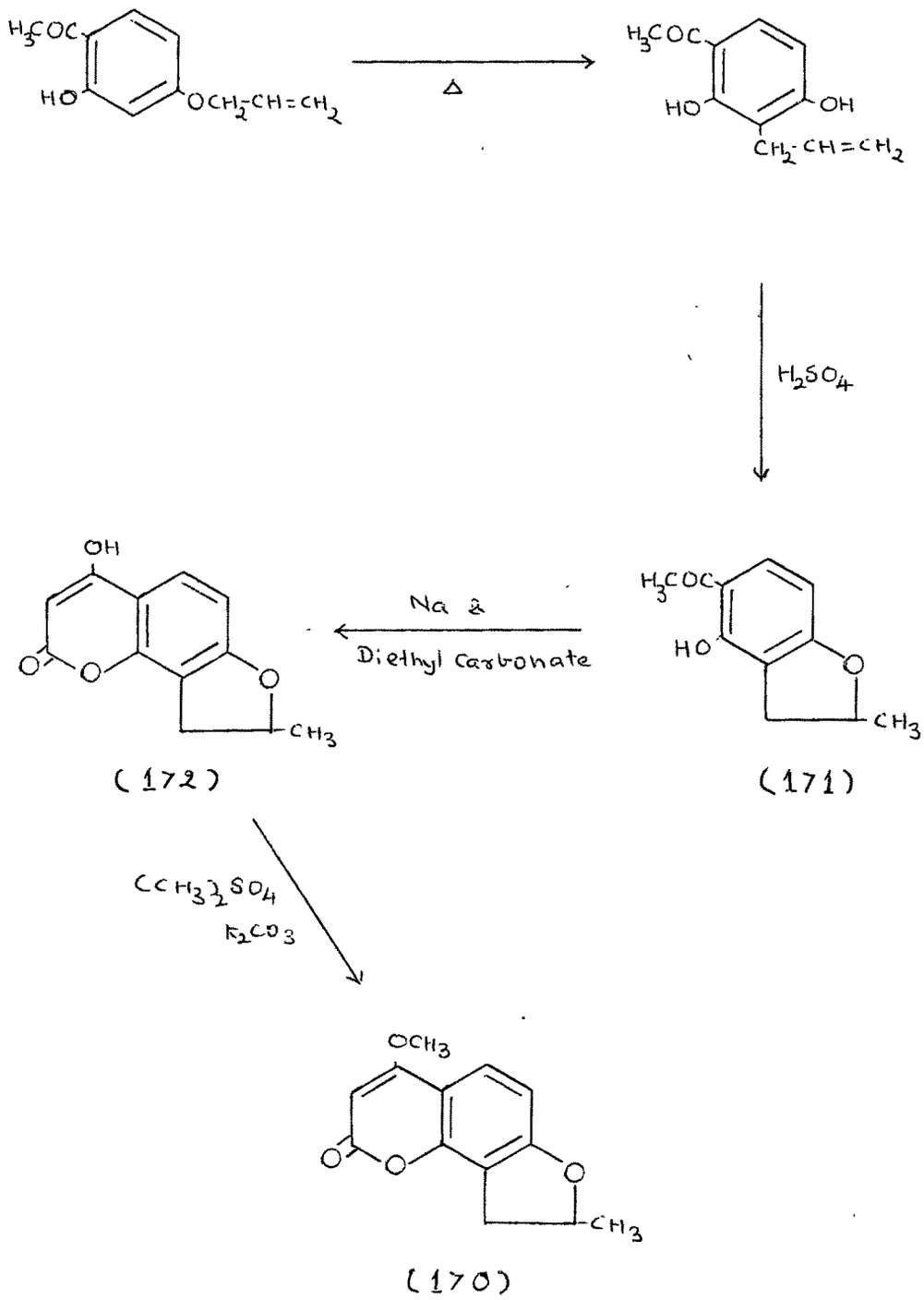


(169)

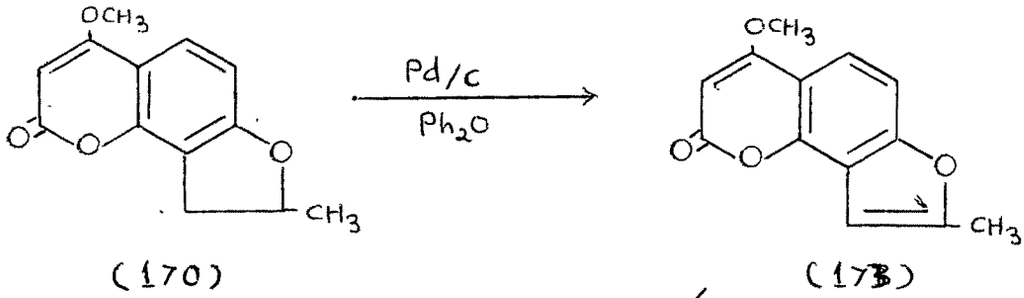
H_2SO_4



(170)


H3COC
HO
OCH2-CH=CH2
Δ
H3COC
HO
OH
CH2-CH=CH2
H2SO4
OH
Na &
Diethyl Carbonate
H3COC
HO
CH3
CH3
(172)
(171)
(CH3)2SO4
K2CO3
OCH3
CH3

(170)



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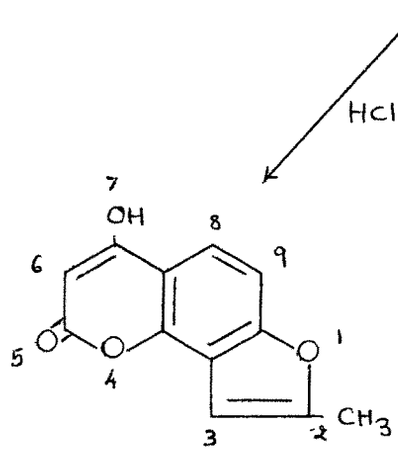
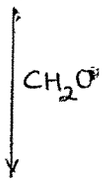
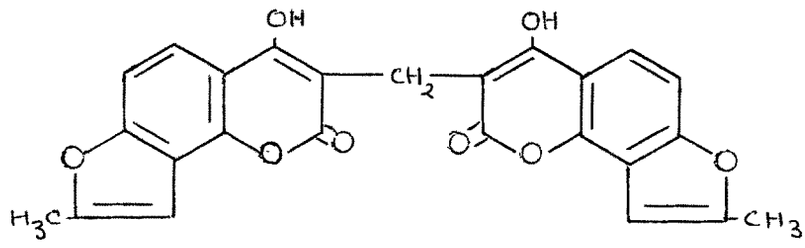


(174)





(175)

EXPERIMENTAL

I.R.Spectra ($CHCl_3$)were determined with a Perkin-Elmer 237 grating spectrophotometer.

NMR Spectra were recorded on Varian A 60 spectrophotometer and DMSO-d_6 was used as solvent, using TMS as internal indicator.

The ultraviolet absorption spectra was measured with Beckmann model DU spectrophotometer.

Synthesis of 4-Oxo-4H-furo(3,2-c)benzopyran:

Pechmann condensation of 4-hydroxycoumarin with malic acid : 2,5-Dioxo-2H,5H-pyrano(3,2-c)benzopyran :

A mixture of 4-hydroxycoumarin (5 g.) and malic acid (5 g.) was heated on a steam bath with gradual addition of sulphuric acid (50 ml. ; 80 %) in 45 minutes period. Heating was continued for further 4 hr. The reaction mixture was added to ice and the product filtered,washed with sodium bicarbonate solution,dried and crystallised from acetic acid,m.p. 142°. Yield 2 g.

Analysis : Found : C,67.21 ; H,2.65 %.

$C_{12}H_6O_4$ requires : C,67.29 ; H,2.82 %.

3-Bromo-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran :

2,5-Dioxo-2H,5H-pyrano(3,2-c)benzopyran (2 g.) was dissolved in minimum amount of acetic acid and bromine dissolved in acetic acid (30 ml. ; 20 % ; 4 mole) was added and the mixture heated on a water bath for 2 hr. The reaction mixture was then added to ice and the bromo derivative was filtered,dried and crystallised from acetic acid,m.p.211°. Yield 1 g.

Analysis : Found : Br, 27.22 %.

$C_{12}H_5O_4Br$ requires : Br, 27.30 %.

4-Oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid :

3-Bromo-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (1 g.) was refluxed with sodium carbonate solution (10 ml.; 10 %) for 45 minutes. The reaction mixture was allowed to cool and acidified. The product was treated with sodium bicarbonate solution and crystallised from dil.ethyl alcohol, m.p. 290°. Yield 0.4 g.

Analysis : Found : C,62.44 ; H,3.07 %.

$C_{12}H_6O_5$ requires : C,62.62 ; H,2.63 %.

Decarboxylation of 4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid : 4-Oxo-4H-furo(3,2-c)benzopyran :

4-Oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid (0.4 g.) was heated on a sand bath with quinoline (5 cc.) and copper bronze (0.2 g.) for 1 hr. The reaction mixture was filtered hot and the filtrate acidified with hydrochloric acid and filtered again. The filtrate was diluted with water and extracted with ether. The product obtained after evaporation of ether was washed with sodium bicarbonate solution, dried and crystallised from petroleum ether, m.p. 93°. Yield 0.1 g.

Analysis : Found : C,70.71 ; H,3.10 %.

$C_{11}H_6O_3$ requires : C,70.97 ; H,3.25 %.

Synthesis of 3-Methyl-4-oxo-4H-furo(3,2-c)benzopyran : Pechmann condensation of 4-hydroxycoumarin with ethyl-acetoacetate : 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran :

A mixture of 4-hydroxycoumarin (5 g.) and ethyl

acetoacetate (8 ml.) in diphenyl ether (25 ml.) was heated on a wire gauze for 4 hr. The reaction mixture was kept overnight. The separated product was filtered and washed with sodium bicarbonate solution, dried and crystallised from acetic acid, m.p. 242°. Yield 2 g.

A mixture of 4-hydroxycoumarin (1 g.) and ethyl acetoacetate (2 ml.) in trifluoroacetic acid (5 ml.) was heated on a sand bath for 15 hr. After the completion of the reaction, a few ml. of ethyl alcohol were added and kept overnight. The separated product was filtered and washed with sodium bicarbonate solution. The residue crystallised from acetic acid, m.p. 242°. Yield 0.3 g. Mixed m.p. with an authentic sample prepared by Mustafa et al. and Patell and Usgaonker did not depress. carbonyl stretching frequency in I.R.region, 1740 cm^{-1}.

3-Bromo-4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran :

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (5 g.) was dissolved in hot acetic acid and a solution of bromine in acetic acid (35 ml. ; 20 % ; 2 mole) was added with stirring and the mixture was left overnight. The separated bromo derivative was filtered, dried and crystallised from acetic acid, m.p. 258°. Yield 2.5 g.

Analysis : Found : Br, 26.15 %.

$C_{13}H_7O_4Br$ requires : Br, 26.06 %.

2-(o-Hydroxyphenyl)-4-methylfuran-3-carboxylic acid :

3-Bromo-4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (2 g.) was refluxed with sodium carbonate solution (20 ml. ; 10 %) for 3 hr. The reaction mixture was allowed to cool and acidified. The separated product was treated with sodium bicarbonate solution,dried and crystallised from hot water, m.p. 155°. Yield 0.8 g.

Analysis : Found : C,66.27 % ; H,4.38 %.

$C_{12}H_{10}O_4$ requires : C,66.05 % ; H,4.62 %.

Cyclisation : 3-Methyl-4-oxo-4H-furo(3,2-c)benzopyran :

2-(o-Hydroxyphenyl)-4-methylfuran-3-carboxylic acid (0.8 g.) was dissolved in ethanol (5 ml.) and refluxed with hydrochloric acid (5 ml.) for 4 hr. The separated product was filtered (charcoal),washed with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p. 166°. Yield 0.2 g.

Analysis : Found : C,71.89 ; H,4.00 %.

$C_{12}H_8O_3$ requires : C,71.99 ; H,4.03 %.

Synthesis of 3,8-Dimethyl-4-oxo-4H-furo(3,2-c)benzopyran : Pechmann condensation of 4-hydroxy-6-methylcoumarin with ethyl acetoacetate : 4,9-Dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran :

A mixture of 4-hydroxy-6-methylcoumarin (3.5 g. ; 1 mole) and ethyl acetoacetate (5.2 g. ; 2 mole) in diphenyl ether (25 ml.) was heated on a wire gauze for

4 hr. The reaction mixture was kept overnight. The separated product was filtered and washed with sodium bicarbonate solution, dried and crystallised from acetic acid, m.p. 198°. Yield 1.5 g.

A mixture of 4-hydroxy-6-methylcoumarin (1 g.) and ethyl acetoacetate (2 ml.) in trifluoroacetic acid (5 ml.) was refluxed on a sand bath for 15 hr. A few ml. of ethanol were added after the completion of reaction and kept overnight. The separated product was filtered, washed with sodium bicarbonate solution and crystallised from acetic acid, m.p. 198°. Yield 0.3 g. Mixed m.p. with an authentic sample prepared by Patell and Usgaonker did not depress. Carbonyl stretching frequency in I.R. region 1745 cm^{-1}.

3-Bromo-4,9-dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran :

4,9-Dimethyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran (5 g.) was dissolved in hot acetic acid and solution of bromine in acetic acid (35 ml. ; 20 % ; 2 mole) was added with stirring and the mixture was kept overnight. The separated product was filtered, dried and crystallised from acetic acid, m.p. 250°. Yield 2 g.

Analysis : Found : Br, 24.77 %.

$C_{13}H_7O_4Br$ requires : Br, 24.92 %.

2-(2'-Hydroxy-5'-methylphenyl)-4-methylfuran-3-carboxylic acid :

3-Bromo-4,9-dimethyl-2,5-dioxo-2H,5H-pyrano

(3,2-c)benzopyran (2.0 g.) was refluxed with sodium carbonate solution (20 ml. ; 10 %) for 6 hr. The reaction mixture was allowed to cool and acidified. The separated product was filtered,treated with sodium bicarbonate solution,dried and crystallised from water, m.p. 178°. Yield 0.7 g.

Analysis : Found : C,67.39 ; H,4.75 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

Cyclisation : 3,8-Dimethyl-4-oxo-4H-furo(3,2-c) benzopyran :

2-(2'-Hydroxy-5'-methylphenyl)-4-methylfuran-3-carboxylic acid (0.7 g.) was dissolved in ethanol (5 ml.) and refluxed with hydrochloric acid (6 ml.) for 3 hr. The separated product was filtered (charcoal) and washed with sodium bicarbonate solution, dried and crystallised from dil.acetic acid, m.p. 157°. Yield 0.3 g.

Analysis : Found : C,72.59 ; H,4.43 %.

$C_{13}H_{10}O_3$ requires : C,72.89 ; H,4.71 %.

Synthesis of 3-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran :

Pechmann condensation of 4-hydroxy-7-methoxycoumarin with ethyl acetoacetate : 4-Methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran :

A mixture of 4-hydroxy-7-methoxycoumarin (5 g.) and ethyl acetoacetate (7 ml.) was heated on a steam bath with gradual addition of sulphuric acid (50 ml. ; 80 %.) for 45 minutes period. Heating was continued for further 4 hr.

The reaction mixture was then added to ice and the separated product was filtered,washed with sodium bicarbonate solution and crystallised from acetic acid, m.p. 237°. Yield 2.0 g. Carbonyl stretching frequency in I.R.region 1740 cm^{-1}.

Analysis : Found : C,65.16 ; H,3.85 %.

$C_{14}H_{10}O_5$ requires : C,65.12 ; H,3.90 %.

A mixture of 4-hydroxy-7-methoxycoumarin (5 g.) and ethyl acetoacetate (10 ml.) was added to a solution of anhydrous aluminium chloride (6.5 g.) in dry nitrobenzene (30 ml.) and was heated at 130° in an oil bath for 4 hr. The reaction mixture was decomposed with ice and hydrochloric acid and nitrobenzene was steam distilled. The separated product was washed with sodium bicarbonate solution,dried and crystallised from acetic acid, yield 4.5 g. Mixed m.p. with the above sample was not depressed.

A mixture of 4-hydroxy-7-methoxycoumarin (1 g.) and ethyl acetoacetate (1.5 ml.) was refluxed in boiling diphenyl ether (10 ml.) on a wire gauze for 4 hr. The reaction mixture was kept overnight. The separated product was filtered,washed with sodium bicarbonate solution and crystallised from acetic acid, yield 0.4 g. Mixed m.p. with the above sample was not depressed.

A mixture of 4-hydroxy-7-methoxycoumarin (1 g.) and ethyl acetoacetate (1 ml.) and trifluoroacetic acid (5 ml.) was refluxed on a sand bath for 15 hr. After the completion of reaction a few ml. of ethanol were added and kept overnight. The separated product was filtered,washed

with sodium bicarbonate solution and crystallised from acetic acid. Yield 0.4 g. Mixed m.p. with the above products was not depressed.

3-Bromo-4-methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran :

4-Methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran (4.5 g.) was dissolved in hot acetic acid and bromine in acetic acid (14 ml. ; 20 % ; 1 mole) was added with stirring. The bromo derivative,which separated immediately, was filtered,dried and crystallised from acetic acid, m.p. 278°. Yield 3 g.

Analysis : Found : Br, 23.60 %.

$C_{14}H_9O_5Br$ requires : Br, 23.74 %.

2-(2'-Hydroxy-4'-methoxyphenyl)-4-methylfuran-3-carboxylic acid :

3-Bromo-4-methyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (2 g.) was refluxed with sodium carbonate solution (20 ml. ; 10 %) for 5 hr. The reaction mixture was cooled and acidified. The product was filtered and purified by the treatment with sodium bicarbonate solution and crystallised from water, m.p. 201°. Yield 0.8 g.

Analysis : Found : C,62.77 ; H,4.76 %.

$C_{13}H_{12}O_5$ requires : C,62.90 ; H,4.87 %.

Cyclisation : 3-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran :

2-(2'-Hydroxy-4'-methoxyphenyl)-4-methylfuran-3-carboxylic acid (0.8 g.) was dissolved in ethanol (5 ml.)

and refluxed with hydrochloric acid (10 ml.) for 3 hr. The separated product was filtered (charcoal), washed with sodium bicarbonate solution and crystallised from dilute acetic acid, m.p. 173°. Yield 0.3 g.

Analysis : Found : C,67.64 ; H,4.22 %.
$C_{13}H_{10}O_4$ requires : C,67.82 ; H,4.38 %.

Synthesis of 3,6-Dimethyl-7-methoxy-4-oxo-4H-furo (3,2-c)benzopyran :

Pechmann condensation of 4-hydroxy-7-methoxy-8-methyl-coumarin with ethyl acetoacetate : 4,7-Dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran :

A mixture of 4-hydroxy-7-methoxy-8-methyl-coumarin (5 g.) and ethyl acetoacetate (10 ml.) was added slowly to a solution of anhydrous aluminium chloride (6.5 g.) in dry nitrobenzene (30 ml.) and was heated in an oil bath at 130-40° for 4 hr. The reaction mixture was decomposed with ice and hydrochloric acid and nitrobenzene was steam distilled. The product was filtered, washed with sodium bicarbonate solution and crystallised from acetic acid, m.p. 238°. Yield 4.3 g.

Analysis : Found : C,66.67 ; H,4.37 %.
$C_{15}H_{12}O_5$ requires : C,66.17 ; H,4.44 %.

3-Bromo-4,7-dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran :

4,7-Dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran (2.5 g.) was dissolved in hot acetic acid

and to the hot solution bromine in acetic acid (8 ml. ; 20 % ; 1 mole) was added with stirring. The product, which separated immediately was filtered, dried and crystallised from acetic acid, m.p. 250°. Yield 1.5 g.

Analysis : Found : Br, 22.76 %.

$C_{15}H_{11}O_5Br$ requires : Br, 22.79 %.

2-(2'-Hydroxy-3'-methyl-4'-methoxyphenyl)-4-methylfuran-3-carboxylic acid :

3-Bromo-4,7-dimethyl-8-methoxy-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (1.0 g.) was refluxed with sodium carbonate solution (10 ml. ; 10 %) for 5 hr. The reaction mixture was cooled and acidified. The product was filtered, treated with sodium bicarbonate solution,dried and crystallised from water, m.p. 216°. Yield 0.5 g.

Analysis : Found : C,63.63 ; H,5.15 %.

$C_{14}H_{14}O_5$ requires : C,64.11 ; H,5.38 %.

Cyclisation : 3,6-Dimethyl-7-methoxy-4-oxo-4H-furo (3,2-c)benzopyran :

2-(2'-Hydroxy-3'-methyl-4'-methoxyphenyl)-4-methyl-furan-3-carboxylic acid (0.5 g.) was dissolved in ethanol (5 ml.) and refluxed with hydrochloric acid (10 ml.) for 3 hr. The separated product was filtered (charcoal),washed with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p. 160°. Yield 0.2 g.

Analysis : Found : C,68.42 ; H,5.21 %.

$C_{14}H_{12}O_4$ requires : C,68.84 ; H,4.95 %.

Pechmann condensation of 4-hydroxy-6-methylcoumarin with malic acid : 9-Methyl-2,5-dioxo-2H,5H-pyrano (3,2-c)benzopyran :

A mixture of 4-hydroxy-6-methylcoumarin (5 g.) and malic acid (5 g.) was heated on a steam bath with gradual addition of sulphuric acid (50 ml. ; 80 %.) in 45 minutes period. Heating was continued for further 4 hr. The reaction mixture was added to ice and the separated product was filtered,washed with sodium bicarbonate solution,dried and crystallised from dil.acetic acid, m.p. 224°. Yield 0.3 g.

Analysis : Found : C,68.75 ; H,3.96 %.

$C_{13}H_8O_4$ requires : C,68.42 ; H,3.53 %.

Synthesis of 3-Phenyl-4-oxo-4H-furo(3,2-c)benzopyran : Ethyl 3-phenyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate :

4-Hydroxy-3-benzoylcoumarin was prepared according to Eisenhauer and Link[70].

A mixture of 4-hydroxy-3-benzoylcoumarin (2 g.), ethyl bromoacetate (2 ml.), anhydrous potassium carbonate (4 g.) in dry acetone (50 ml.) was refluxed on a water bath for 25 hr. After the evaporation of acetone, water was added to the mixture. The separated product was filtered and washed with sodium bicarbonate solution. The residue crystallised from dil.alcohol, m.p. 162°. Yield 1 g.

Analysis : Found : C,71.93 ; H,3.77 %.

$C_{20}H_{14}O_5$ requires : C,71.85 ; H,4.22 %.

3-Phenyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylic acid :

Ethyl 3-phenyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate (1 g.) was dissolved in ethanol (5 ml.) and refluxed with sodium hydroxide solution (10 ml. ; 10 %) on a water bath for 45 minutes. The reaction mixture was allowed to cool and acidified. The separated product was filtered, treated with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p. 262°. Yield 0.6 g.

Analysis : Found : C,70.82 ; H,3.28 %.

$C_{18}H_{10}O_5$ requires : C,70.59 ; H,3.29 %.

Decarboxylation : 3-Phenyl-4-oxo-4H-furo(3,2-c) benzopyran :

A mixture of 3-phenyl-4-oxo-4H-furo(3,2-c) benzopyran-2-carboxylic acid (0.5 g.), copper bronze (0.4 g.) and quinoline (5 ml.) was heated on a sand bath for 1 hr. The product obtained on pouring the reaction mixture in dilute hydrochloric acid was filtered, washed with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p.161°. Yield 0.1 g.

Analysis : Found : C,77.76 ; H,3.78 %.

$C_{17}H_{10}O_3$ requires : C,77.85 ; H,3.84 %.

Benzoylation of 4-hydroxy-6-methylcoumarin :

4-Benzoyloxy-6-methylcoumarin :

To a solution of 4-hydroxy-6-methylcoumarin (5 g.) in dry pyridine (40 ml.) and piperidine (1 ml.) was slowly

benzoyl chloride (7.5 ml.)was slowly added at 0° with stirring. After the addition, the reaction mixture was kept for 5-10 minutes and then was decomposed with ice and hydrochloric acid. The separated product was filtered, washed with sodium bicarbonate solution, dried and crystallised from dil.alcohol, m.p. 131°. Yield 4.8 g.

Analysis : Found : C,72.61 ; H,4.11 %.

$C_{17}H_{12}O_4$ requires : C,72.85 ; H,4.32 %.

Fries migration: 4-Hydroxy-3-benzoyl-6-methylcoumarin :

A mixture of 4-benzoyloxy-6-methylcoumarin (4 g.) and anhydrous aluminium chloride (12 g.) was heated in an oil bath at 140-50° for 2 hr. The reaction mixture was decomposed with ice and hydrochloric acid. The separated product was filtered and purified by the treatment with sodium bicarbonate solution. The product was dried and crystallised from dil.acetic acid, m.p.155°. Yield 2 g.

Analysis : Found : C,72.66 ; H,4.21 %.

$C_{17}H_{12}O_4$ requires : C,72.85 ; H,4.32 %.

K.R.Acetylation of 4-hydroxy-3-benzoyl-6-methylcoumarin : 4-Phenyl-9-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzopyran :

A mixture of 4-hydroxy-3-benzoyl-6-methylcoumarin (1 g.), freshly fused sodium acetate (1.5 g.) and acetic anhydride (20 ml.) was heated at 150-60° in an oil bath for 6 hr. After the completion of reaction, the reaction mixture was poured into ice and water. The separated product was filtered, washed with sodium bicarbonate

solution, dried and crystallised from acetic acid, m.p.233°. Yield 0.5 g.

Analysis : Found : C,74.81 ; H,4.22 %.

$C_{19}H_{12}O_4$ requires : C,74.99 ; H,3.97 %.

Synthesis of 3-Phenyl-8-methyl-4-oxo-4H-furo(3,2-c) benzopyran :

Ethyl-3-phenyl-8-methyl-4-oxo-4H-furo(3,2-c)benzopyran-2-carboxylate :

A mixture of 4-hydroxy-3-benzoyl-6-methylcoumarin (2 g.),ethyl bromoacetate (1.8 ml.),anhydrous potassium carbonate (4 g.) in dry acetone (50 ml.) was refluxed on a steam bath for 25 hr. After the evaporation of acetone the separated product was filtered,washed with sodium bicarbonate solution and crystallised from dil.alcohol, m.p.193°. Yield 0.7 g.

Analysis : Found : C,72.08 ; H,5.10 %.

$C_{21}H_{16}O_5$ requires : C,72.40 ; H,4.63 %.

Hydrolysis : 3-Phenyl-8-methyl-4-oxo-4H-furo(3,2-c) benzopyran-2-carboxylic acid :

Ethyl-3-phenyl-8-methyl-4-oxo-4H-furo(3,2-c) benzopyran-2-carboxylate (0.5 g.) was dissolved in ethanol (5 ml.) and was refluxed with sodium hydroxide solution (10 ml. ; 10 %.) on a water bath for 45 minutes. The reaction mixture was allowed to cool and acidified. The separated product was filtered and purified by the treatment with sodium bicarbonate solution and crystallised

from dil.acetic acid, m.p. 261°. Yield 0.3 g.

Analysis : Found : C,71.61 ; H,4.13 %.

$C_{19}H_{12}O_5$ requires : C,71.25 ; H,3.78 %.

Decarboxylation : 3-Phenyl-8-methyl-4-oxo-4H-furo (3,2-c)benzopyran :

A mixture of 3-phenyl-8-methyl-4-oxo-4H-furo (3,2-c)benzopyran-2-carboxylic acid (0.3 g.), copper bronze (0.2 g.) and quinoline (5 ml.) was heated on a sand bath for 1 hr. The reaction mixture was filtered hot and allowed to cool. It was decomposed with ice and hydrochloric acid and the separated product was filtered,washed with sodium bicarbonate solution and crystallised from dil.acetic acid , m.p. 198°. Yield 0.1 g.

Analysis : Found : C,78.14 ; H,4.50 %.

$C_{18}H_{12}O_3$ requires : C,78.25 ; H,4.38 %.

Synthesis of 2-Methyl-4-oxo-4H-furo(3,2-c)benzopyran :

Allylation of 4-hydroxycoumarin : 4-Allyloxycoumarin :

A mixture of 4-hydroxycoumarin (5 g.),anhydrous potassium carbonate (6 g.),allyl bromide (4 g.) in dry acetone (50 ml.) was refluxed on a steam bath for 20 hr. The product which was obtained on evaporation of acetone, was filtered,washed with sodium bicarbonate solution and crystallised from benzene-petroleum ether,m.p.115°.
Yield 3 g.

Analysis : Found : C,71.03 ; H,4.94 %.

$C_{12}H_{10}O_3$ requires : C,71.28 ; H,4.99 %.

Claisen rearrangement of 4-allyloxycoumarin : 2-Methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran :

4-Allyloxycoumarin (1.5 g.) was heated at 210-20° in an oil bath for 2 hr. After cooling the product was washed with petroleum ether and dissolved in benzene. This solution was then run over alumina column. The product, which obtained on evaporation of benzene, was washed with sodium bicarbonate solution and crystallised from petroleum ether (60-80°), m.p. 100°. Yield 0.7 g.

Analysis : Found : C,71.03 ; H,4.64 %.

$C_{12}H_{10}O_3$ requires : C,71.28 ; H,4.99 %.

Dehydrogenation of 2-methyl-2,3-dihydro-4-oxo-4H-furo (3,2-c)benzopyran : 2-Methyl-4-oxo-4H-furo(3,2-c) benzopyran :

2-Methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c) benzopyran (0.5 g.) was refluxed with palladised charcoal (0.3 g. ; 10 %) in boiling diphenyl ether (4 ml.) for 8 hr. The reaction mixture was filtered hot and allowed to cool. The separated product was filtered, washed with petroleum ether and crystallised from dil.acetic acid, m.p.174°. Yield 0.2 g.

Analysis : Found : C,71.81 ; H,4.09 %.

$C_{12}H_8O_3$ requires : C,71.99 ; H,4.03 %.

Synthesis of 2,8-Dimethyl-4-oxo-4H-furo(3,2-c) benzopyran :

Allylation of 4-hydroxy-6-methylcoumarin : 4-Allyloxy-6-methylcoumarin :

A mixture of 4-hydroxy-6-methylcoumarin (5 g.), allyl bromide (3 ml.) and anhydrous potassium carbonate (6 g.) was refluxed in dry acetone (50 ml.) on a water bath for 25 hr. The product, which obtained on evaporation of acetone was washed with petroleum ether and then with sodium bicarbonate solution. The residue crystallised from petroleum ether (60-80°), m.p. 108°. Yield 1.5 g.

Analysis : Found : C,72.02 ; H,5.38 %.

$C_{13}H_{12}O_3$ requires : C,72.21 ; H,5.59 %.

2,8-Dimethyl-2,3-dihydro-4-oxo-4H-furo(3,2-c) benzopyran :

4-Allyloxy-6-methylcoumarin (1 g.) was heated at 200° in an oil bath for 2 hr. After cooling, the product was washed with petroleum ether and dissolved in benzene. The solution was then run over alumina column. The product, which obtained on evaporation of benzene was washed with sodium bicarbonate solution and crystallised from petroleum ether (60-80°), m.p.111°. Yield 0.5 g.

Analysis : Found : C,72.33 ; H,5.92 %.

$C_{13}H_{12}O_3$ requires : C,72.21 ; H,5.59 %.

Dehydrogenation of 2,8-dimethyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran : 2,8-Dimethyl-4-oxo-4H-furo(3,2-c)benzopyran :

2,8-Dimethyl-2,3-dihydro-4-oxo-4H-furo(3,2-c) benzopyran (0.4 g.) was refluxed with palladised charcoal (o.3 g. ; 10 %) in boiling diphenyl ether (2 ml.) for 6 hr. The reaction mixture was filtered hot and allowed to cool. The separated product was filtered, washed with petroleum ether and crystallised from dil.acetic acid, m.p.155°. Yield 0.2 g.

Analysis : Found : C,72.86 ; H,4.67 %.

$C_{13}H_{10}O_3$ requires : C,72.89 ; H,4.71 %.

Synthesis of 2-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c) benzopyran :

Allylation of 4-hydroxy-7-methoxycoumarin : 4-Allyloxy-7-methoxycoumarin :

A mixture of 4-hydroxy-7-methoxycoumarin (5 g.), allyl bromide (3 ml.) and freshly ignited potassium carbonate (6 g.) was refluxed in dry acetone (60 ml.) on a water bath for 20 hr. The reaction mixture was worked up as before and the product crystallised from petroleum ether, m.p. 114°. Yield 1.2 g.

Analysis : Found : C,67.07 ; H,5.37 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

2-Methyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c) benzopyran :

4-Allyloxy-7-methoxycoumarin (1.2 g.) was heated at 200-210° in an oil bath for 2 hr. The reaction mixture was allowed to cool and worked up as described before. The product crystallised from petroleum ether (60-80°), m.p.106°. Yield 0.6 g.

Analysis : Found : C,67.70 ; H,5.20 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

Dehydrogenation of 2-methyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran : 2-Methyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran :

2-Methyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo (3,2-c)benzopyran (0.5 g.) was refluxed with palladised charcoal (0.4 g. ; 10 %) in boiling diphenyl ether (3 ml.) for 8 hr. The reaction mixture was filtered hot and worked up as described before. The product crystallised from dil.acetic acid,m.p.176°. Yield 0.2 g.

Analysis : Found : C,67.63 ; H,4.57 %.

$C_{13}H_{10}O_4$ requires : C,67.82 ; H,4.38 %.

Synthesis of 2,6-Dimethyl-7-methoxy-4-oxo-4H-furo (3,2-c)benzopyran :

Allylation of 4-hydroxy-7-methoxy-8-methylcoumarin : 4-Allyloxy-7-methoxy-8-methylcoumarin :

A mixture of 4-hydroxy-7-methoxy-8-methylcoumarin

(5 g.),allyl bromide (3 ml.) and anhydrous potassium carbonate (6 g.) was refluxed in dry acetone (50 ml.) on a water bath for 20 hr. The reaction mixture was worked up as usual and the product crystallised from benzene,m.p. 163°. Yield 2 g.

Analysis : Found : C,68.25 ; H,5.36 %.

$C_{14}H_{14}O_4$ requires : C,68.28 ; H,5.73 %.

2,6-Dimethyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo (3,2-c)benzopyran :

4-Allyloxy-7-methoxy-8-methylcoumarin (2 g.) was heated in an oil bath at 210° for 2 hr. The reaction mixture was allowed to cool and worked up as usual. The product crystallised from petroleum ether (60-80°) , m.p. 135°. Yield 0.6 g.

Analysis : Found : C,67.87 ; H,5.77 %.

$C_{14}H_{14}O_4$ requires : C,68.28 ; H,5.73 %.

Dehydrogenation of 2,6-dimethyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran : 2,6-Dimethyl-7-methoxy-4-oxo-4H-furo(3,2-c)benzopyran :

2,6-Dimethyl-7-methoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran (0.5 g.) was refluxed with palladised charcoal (0.4 g. ; 10 %) in diphenyl ether. The reaction mixture was worked up as usual and the product crystallised from dil.acetic acid, m.p. 155°. Yield 0.2 g.

Analysis : Found : C,68.52 ; H,4.84 %.

$C_{14}H_{12}O_4$ requires : C,68.84 ; H,4.95 %.

Synthesis of 2-methyl-6,7-dimethoxy-4-oxo-4H-furo (3,2-c)benzopyran :

Allylation of 4-hydroxy-7,8-dimethoxycoumarin :

4-Allyloxy-7,8-dimethoxycoumarin :

A mixture of 4-hydroxy-7,8-dimethoxycoumarin (4 g.), allyl bromide (2.5 ml.) and anhydrous potassium carbonate (6 g.) in dry acetone (50 ml.) was refluxed on a water bath for 20 hr. The reaction mixture was worked up as usual and the product crystallised from petroleum ether (60-80°), m.p. 134°. Yield 2 g.

Analysis Found : C,64.57 ; H,5.52 %.

$C_{14}H_{14}O_5$ requires : C,64.11 ; H,5.38 %.

2-Methyl-6,7-dimethoxy-2,3-dihydro-4-oxo-4H-furo (3,2-c)benzopyran :

4-Allyloxy-7,8-dimethoxycoumarin (1.5 g.) was heated in an oil bath at 210° for 2 hr. The reaction mixture was allowed to cool and worked up as described earlier. The product crystallised from petroleum ether (60-80°), m.p. 110°. Yield 0.8 g.

Analysis : Found : C,64.31 ; H,5.64 %.

$C_{14}H_{14}O_5$ requires : C,64.11 ; H,5.38 %.

Dehydrogenation of 2-methyl-6,7-dimethoxy-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzopyran : 2-Methyl-6,7-dimethoxy-4-oxo-4H-furo(3,2-c)benzopyran :

2-Methyl-6,7-dimethoxy-2,3-dihydro-4-oxo-4H-

furo(3,2-c)benzopyran (0.5 g.) was refluxed with palladised charcoal (0.3 g. ; 10 %) in diphenyl ether (3 ml.) for 8 hr. and the reaction mixture was worked up as described earlier. The product crystallised from dil.acetic acid, m.p.179°. Yield 0.2 g.

Analysis : Found : C,64.18 ; H,4.33 %.

$C_{14}H_{12}O_5$ requires : C,64.61 ; H,4.65 %.

Synthesis of 4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f) benzopyran (Type D) :

2-Hydroxy-5-allyloxyacetophenone was prepared according to Baker and Lothian[71] as follows :

A mixture of quinacetophenone (5 g.),freshly ignited potassium carbonate (6 g.) and allyl bromide (4.5 g.) in dry acetone (50 ml.) was refluxed on a steam bath for 9 hr. After the evaporation of acetone the remaining liquid was acidified and ether extracted. The ethereal layer was shaken with 10 % sodium hydroxide solution and the separated sodium salt was filtered and acidified. The solution was extracted with ether and ether was evaporated. The product crystallised from petroleum ether.

4-Hydroxy-6-allyloxycoumarin :

A mixture of 2-hydroxy-5-allyloxyacetophenone (4 g.),diethyl carbonate (20 ml.) and pulverised sodium (3 g.) was heated on a water bath for 2 hr. The unreacted sodium was decomposed with little alcohol and the reaction mixture was poured into water. It was extracted with ether

and aqueous layer was acidified. The separated product was filtered, treated with sodium bicarbonate solution and crystallised from acetic acid, m.p.221°. Yield 3.5 g.

Analysis : Found : C,65.63 ; H,4.26 %.

$C_{12}H_{10}O_4$ requires : C,66.05 ; H,4.62 %.

4-Methoxy-6-allyloxycoumarin :

A mixture of 4-hydroxy-6-allyloxycoumarin (3.5 g.), anhydrous potassium carbonate (6 g.) and dimethyl sulphate (3 ml.) in dry acetone (50 ml.) was refluxed on a steam bath for 6 hr. The product, obtained on evaporation of acetone crystallised from benzene-petroleum ether, m.p.106°. Yield 2.5 g.

Analysis : Found : C,67.01 ; H,4.84 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

Claisen rearrangement of 4-methoxy-6-allyloxycoumarin :

4-Methoxy-6-hydroxy-5-allylcoumarin :

4-Methoxy-6-allyloxycoumarin (2 g.) was refluxed on a wire gauze in dimethyl aniline (6 ml.) for 3 hr. The reaction mixture was kept overnight and the separated product was filtered, treated with dilute sodium hydroxide solution, dried and crystallised from dilute acetic acid, m.p.208°. Yield 1 g.

Analysis : Found : C,67.20 ; H,5.10 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

Cyclisation of 4-methoxy-6-hydroxy-5-allylcoumarin : 4-Methoxy-2-methyl-2,3-dihydro-6-oxo-6H-furo(3,2-f) benzopyran :

4-Methoxy-6-hydroxy-5-allylcoumarin (0.8 g.) was triturated with con.sulphuric acid (3 ml.) for 10 mimutes. The reaction mixture was then decomposed with ice and water. The separated product was filtered,washed with dilute sodium hydroxide solution and crystallised from dil.acetic acid, m.p. 187°. Yield 0.6 g.

Analysis	: Found	: C,66.94 ; H,5.29 %.
$C_{13}H_{12}O_4$	requires	: C,67.23 ; H,5.21 %.

Dehydrogenation of 4-methoxy-2-methyl-2,3-dihydro-6-oxo-6H-furo(3,2-f)benzopyran : 4-Methoxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran :

4-Methoxy-2-methyl-2,3-dihydro-6-oxo-6H-furo (3,2-f)benzopyran (0.5 g.) was refluxed with palladised charcoal (0.4 g. ; 10 %) in boiling diphenyl ether (3 ml.) for 8 hr. The reaction mixture was filtered hot and allowed it to cool. The separated product was filtered,washed with petroleum ether and crystallised from dil.acetic acid,m.p. 201°. Yield 0.3 g.

Analysis	: Found	: C,67.64 ; H,4.32 %.
$C_{13}H_{10}O_4$	requires	: C,67.82 ; H,4.38 %.

Demethylation : 4-Hydroxy-2-methyl-6-oxo-6H-furo (3,2-f)benzopyran :

4-Methoxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran (0.3 g.) was dissolved in ethanol (5 ml.) and refluxed with con.hydrochloric acid (5 ml.) for 1 hr. The reaction mixture was diluted with water and the separated product was filtered,treated with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p.295°. Yield 0.1 g.

Analysis : Found : C,66.58 ; H,3.87 %.

$C_{12}H_8O_4$ requires : C,66.67 ; H,3.73 %.

Synthesis of 5,5'-methylene bis[4-hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran]:

4-Hydroxy-2-methyl-6-oxo-6H-furo(3,2-f)benzopyran (0.1 g.) was dissolved in ethanol (5 ml.) and refluxed with formaldehyde solution (0.2 ml.) for 30 minutes. The separated product was filtered and dried, m.p. 335°.

Analysis : Found : C,67.44 ; H,3.44 %.

$C_{25}H_{16}O_8$ requires : C,67.57 ; H,3.63 %.

Synthesis of 4-Hydroxy-5,8-dimethylpsoralene : (Type F)

Allylation of 2,4-dihydroxy-3-methylacetophenone :

2-Hydroxy-3-methyl-4-allyloxyacetophenone :

A mixture of 2,4-dihydroxy-3-methylacetophenone (5 g.), anhydrous potassium carbonate (10 g.) and allyl bromide (4.5 g.) in dry acetone (50 ml.) was refluxed on a steam bath for 8 hr. After the evaporation of acetone the remaining solution was acidified and extracted with ether. The ethereal layer was shaken with 10 % sodium hydroxide solution and the separated sodium salt was filtered off. It was then acidified and extracted with ether. On evaporation of ether yellow colour liquid was obtained which was used for further reaction.

4-Hydroxy-7-allyloxy-8-methylcoumarin :

A mixture of 2-hydroxy-3-methyl-8-allyloxy-acetophenone (5 g.),diethyl carbonate (25 ml.) and pulverised sodium (4 g.) was heated on a water bath for 1 hr. Little ethanol was added to decompose unreacted sodium and then mixture was poured into water. It was then extracted with ether and aqueous layer was acidified. The separated product was filtered,treated with sodium bicarbonate solution,dried and crystallised from dil. acetic acid,m.p. 215°. Yield 4 g.

Analysis : Found : C,66.74 ; H,5.14 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

4-Methoxy-7-allyloxy-8-methylcoumarin :

A mixture of 4-hydroxy-7-allyloxy-8-methylcoumarin (5 g.), anhydrous potassium carbonate (10 g.) and dimethyl sulphate (4 ml.) in dry acetone (60 ml.) was refluxed on a steam bath for 8 hr. Acetone was evaporated and the separated product was filtered, washed with sodium bicarbonate solution and crystallised from dil. acetic acid, m.p. 173°. Yield 3.5 g.

Analysis : Found : C, 68.54 ; H, 5.79 %.

$C_{14}H_{14}O_4$ requires : C, 68.28 ; H, 5.73 %.

Claisen rearrangement of 4-methoxy-7-allyloxy-8-methylcoumarin : 4-Methoxy-7-hydroxy-6-allyl-8-methylcoumarin :

4-Methoxy-7-allyloxy-8-methylcoumarin (3 g.) was refluxed in diethyl aniline (5 ml.) on a wire gauze for 3 hr. The reaction mixture was allowed to cool. The separated product was filtered and treated with dilute sodium hydroxide solution, dried and crystallised from acetic acid, m.p. 218°. Yield 1.5 g.

Analysis : Found : C, 68.10 ; H, 5.62 %.

$C_{14}H_{14}O_4$ requires : C, 68.28 ; H, 5.73 %.

Cyclisation of 4-methoxy-7-hydroxy-6-allyl-8-methylcoumarin : 4-Methoxy-5',8-dimethyl-4',5'-dihydropsoralene :

4-Methoxy-7-hydroxy-6-allyl-8-methylcoumarin (1.2 g.) was triturated with con. sulphuric acid (3 ml.) for

10 minutes. The reaction mixture was decomposed with ice and water. The product was filtered off, washed with dilute sodium hydroxide solution and crystallised from dil.acetic acid, m.p. 198°. Yield 0.8 g.

Analysis : Found : C,68.27 ; H,5.30 %.

$C_{14}H_{14}O_4$ requires : C,68.28 ; H,5.73 %.

Dehydrogenation of 4-methoxy-5',8-dimethyl-4',5'-dihydropsoralene : 4-Methoxy-5',8-dimethylpsoralene :

4-Methoxy-5',8-dimethyl-4',5'-dihydropsoralene (0.7 g.) was refluxed with palladised charcoal (0.5 g. ; 10 %) in diphenyl ether (5 ml.) for 8 hr. The reaction mixture was filtered hot and allowed to cool. The separated product was filtered,dried and crystallised from dil.acetic acid, m.p. 232°. Yield 0.4 g.

$\lambda_{max.}^{methanol}$ (log e) 288 (3.12), 326 (3.93).

Analysis : Found : C,68.41 ; H,5.39 %.

$C_{14}H_{12}O_4$ requires : C,68.84 ; H,4.95 %.

Demethylation : 4-Hydroxy-5',8-dimethylpsoralene :

4-Methoxy-5',8-dimethylpsoralene (0.3 g.) was dissolved in ethanol (5 ml.) and refluxed with con. hydrochloric acid (5 ml.) on a wire gauze for 1 hr. The reaction mixture was then diluted with water and the separated product was filtered off, treated with sodium bicarbonate solution and crystallised from dil.acetic

acid, m.p. 305°. Yield 0.1 g.

$\lambda^{chloroform}_{max.}$ (log e) 286 (4.06), 296 (4.09), 326 (3.89).

Analysis : Found : C,67.51 ; H,4.19 %.

$C_{13}H_{10}O_4$ requires : C,67.82 ; H,4.38 %.

Synthesis of 3,3'-methylene bis (4-hydroxy-5',8-dimethyl-psoralene) :

4-Hydroxy-5',8-dimethylpsoralene (0.1 g.) was dissolved in ethanol (5 ml.) and refluxed with formaldehyde solution (0.2 ml.) on a water bath for 30 minutes. The separated product was filtered hot and dried, m.p. above 320°. Yield 0.1 g.

Analysis : Found : C,68.68 ; H,4.26 %.

$C_{27}H_{20}O_8$ requires : C,68.64 ; H,4.27 %.

Synthesis of 7-Hydroxy-2-methyl-5-oxo-5H-furo(2,3-h) benzopyran (Type G) :

4-Allyloxyresacetophenone was prepared by Baker and Lothian[71] as follows :

A mixture of resacetophenone (5 g.),allyl bromide (4 g.),anhydrous potassium carbonate (6 g.) in dry acetone (50 ml.) was refluxed on a steam bath for 6 hr. After the evaporation of acetone the remaining solution was acidified and extracted with ether. The ethereal layer was shaken with 10 % sodium hydroxide solution. The separated sodium salt was filtered off and acidified. It was once again extracted with ether and on evaporation of ether a

faint yellow colour liquid was obtained which was used for further reactions.

4-Hydroxy-7-allyloxycoumarin :

A mixture of 4-allyloxyresacetophenone (5 g.), diethyl carbonate (25 ml.) and pulverised sodium (4 g.) was heated on a water bath for 1 hr. After the completion of reaction a few ml. of ethanol were added to decompose unreacted sodium and then poured into ice and water. It was extracted with ether and aqueous layer was acidified. The separated product was filtered, treated with sodium bicarbonate solution, dried and crystallised from acetic acid, m.p. 231°. Yield 4.5 g.

Analysis : Found : C,65.99 ; H,4.68 %.

$C_{12}H_{10}O_4$ requires : C,66.05 ; H,4.62 %.

4-Methoxy-7-allyloxycoumarin :

A mixture of 4-hydroxy-7-allyloxycoumarin (4 g.), dimethyl sulphate (3 ml.) and anhydrous potassium carborate (7 g.) in dry acetone (50 ml.) was refluxed on a water bath for 6 hr. After the completion of reaction it was worked up as usual and the product crystallised from benzene-petroleum ether, m.p. 93°. Yield 2.5 g.

Analysis : Found : C,67.66 ; H,5.16 %.

$C_{13}H_{12}O_4$ requires : C,67.23 ; H,5.21 %.

Claisen rearrangement of 4-methoxy-7-allyloxycoumarin : 4-Methoxy-7-hydroxy-8-allylcoumarin :

4-Methoxy-7-allyloxycoumarin (2 g.) was refluxed in dimethyl aniline (5 ml.) for 3 hr. The reaction mixture was allowed to cool. The separated product was filtered, purified by the treatment with sodium hydroxide solution and crystallised from acetic acid, m.p. 248°. Yield 1 g.

Analysis : Found : C, 66.96 ; H, 5.28 %.

$C_{13}H_{12}O_4$ requires : C, 67.23 ; H, 5.21 %.

Cyclisation of 4-methoxy-7-hydroxy-8-allylcoumarin : 7-Methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h) benzopyran :

4-Methoxy-7-hydroxy-8-allylcoumarin (1 g.) was triturated with con. sulphuric acid (3 ml.) for 10 minutes. The reaction mixture was then decomposed with ice and water. The separated product was filtered, washed with dilute sodium hydroxide solution and crystallised from dil. acetic acid, m.p. 178°. Yield 0.8 g.

Analysis : Found : C, 67.17 ; H, 5.30 %.

$C_{13}H_{12}O_4$ requires : C, 67.23 ; H, 5.21 %.

Dehydrogenation of 7-methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran : 7-Methoxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran :

7-Methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo (2,3-h)benzopyran (0.6 g.) was refluxed with palladised

charcoal (0.3 g. ; 10 %) in diphenyl ether (5 ml.) for 6 hr. The reaction mixture was filtered hot and allowed to cool. The separated product was filtered, washed with petroleum ether and crystallised from acetic acid, m.p.217°.
Yield 0.3 g.

Analysis : Found : C,67.63 ; H,4.45 %.
$C_{13}H_{10}O_4$ requires : C,67.82 ; H,4.38 %.

Demethylation : 7-Hydroxy-2-methyl-5-oxo-5H-furo (2,3-h)benzopyran :

7-Methoxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran (0.2 g.) was dissolved in ethanol (5 ml.) and refluxed with con.hydrochloric acid (5 ml.) on a wire gauze for 1 hr. The reaction mixture was diluted with water and the separated product was filtered off, treated with sodium bicarbonate solution and crystallised from acetic acid, m.p.310°.
Yield 0.1 g.

Analysis : Found : C,66.28 ; H,3.53 %.
$C_{12}H_8O_4$ requires: C,66.67 ; H,3.73 %.

Synthesis of 6,6'-methylene bis[7-hydroxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran]:

7-Hydroxy-2-methyl-5-oxo-5H-furo(2,3-h)benzopyran (0.1 g.) dissolved in ethanol (5 ml.) and refluxed with formaldehyde solution (0.2 ml.) on a water bath for 30 minutes. The separated product was filtered hot and dried, m.p.328°. Yield 0.1 g.

Analysis : Found : C,67.45 ; H,3.50 %.
$C_{25}H_{16}O_8$ requires : C,67.57 ; H,3.63 %.

Cyclisation of 3-allylresacetophenone : 2-Methyl-4-hydroxy-5-acetylcoumaran :

3-Allylresacetophenone[71] (2 g.) was triturated with con.sulphuric acid (5 ml.) for 10 minutes. The reaction mixture was then decomposed with ice and water and the separated pasty product was extracted with ether. On evaporation of ether only pasty product was obtained which was used for further reaction.

7-Hydroxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h) benzopyran :

A mixture of 2-methyl-4-hydroxy-5-acetylcoumaran (1.5 g.), diethyl carbonate (10 ml.) and pulverised sodium (1 g.) was heated on a water bath for 2 hr. The unreacted sodium was decomposed with alcohol and the reaction mixture was poured into water. It was extracted with ether and aqueous layer was acidified. The separated product was filtered, treated with sodium bicarbonate solution and crystallised from dil.acetic acid, m.p.258°. Yield 0.8 g.

Analysis : Found : C,65.87 ; H,4.92 %.

$C_{12}H_{10}O_4$ requires : C,66.05 ; H,4.62 %.

7-Methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h) benzopyran :

A mixture of 7-hydroxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran (0.5 g.), dimethyl sulphate (0.3 ml.) and anhydrous potassium carbonate (1 g.) in

acetone (30 ml.) was refluxed on a water bath for 5 hr. The reaction mixture was worked up as usual and the product crystallised from dil.acetic acid, m.p.178°. Mixed m.p. with 7-methoxy-2-methyl-2,3-dihydro-5-oxo-5H-furo(2,3-h)benzopyran as prepared earlier (p. 127) was not depressed.

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