CHAPTER III

SYNTHESIS OF SOME FUROCOUMARINS AND SOME COUMARINO-α- AND -γ-PYRONES

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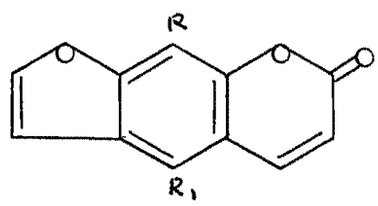
THEORETICAL

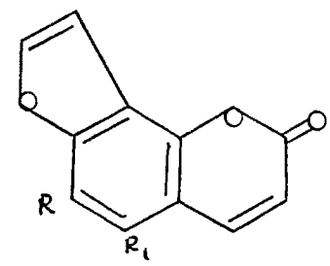
(A) Furocoumarins

As the present work deals with the synthesis of (A) Furocoumarins and (B) Coumarino-α- and γ-pyrones some of the previous work in these fields is briefly reviewed here.

A number of furocoumarins have been isolated from plants. Psoralene, angelicin, bergapten, xanthotoxin, pimpinellin, isopimpinellin and oreoselone are a few members of this group.

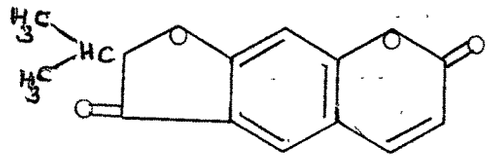


I



II

	R	R_1		R	R_1
Psoralene	H	H	Angelicin	H	H
Xanthotoxin	OMe	H	Pimpinellin	OMe	OMe
Bergapten	H	OMe			
Isopimpinellin	OMe	OMe			
Imperatorin	$OCH_2CH=C(Me)_2$	H			



III

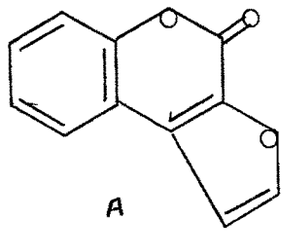
OREOSELONE

Some furocoumarins such as bergapten,pimpinellin and isopimpinellin are very good fish poisons and others such as psoralene, xanthotoxin, imperatorin and bergapten are found to be photosensitizing agents which can bring about pigmentation of the depigmented skin by hastening the formation of melanin. The discovery of this unique activity of the furocoumarins stimulated further work in this field and the structure-activity relationship has been studied by various workers[1,2]. It has been found that the maximum photosensitizing activity lies in the parent linear compound psoralene and the various structurally related compounds have more or less reduced activity. Free phenolic groups inactivate the molecule but the methylethers are active. Thus xanthotoxol and bergaptol are inactive whereas xanthotoxin and bergapten are active. However, the dimethylether, isopimpinellin is inactive. A nuclear methyl group at 4,4',5' or 8-position may or may not inhibit the activity, but a methyl group at the 3-position invariably does so. Introduction

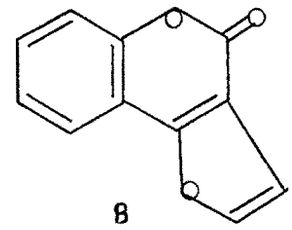
of a nitro, amino or acetyl-amino group does not give active compounds. It was found that the region of activating wave lengths for photosensitizing action of furocoumarins lies between 265 and 280 mμ in the short ultraviolet range and between 340 and 380 mμ in the long ultraviolet range. The fluorescence peaks for these activating wave lengths were in the region of 420-460 mμ.[3] Furocoumarins are dimerized under the influence of irradiation but the dimers are biologically inactive[4]. A number of other studies[5,6] such as isolation of photoreaction products from bergapten, and from the photoreaction of FMN (flavinmononucleotide) and psoralene have been made but the precise mechanism by which furocoumarins function in the treatment of leucoderma is still obscure.

Furocoumarins such as psoralene and imperatorin have also been found to have antifungal activity[7]. The antibiotic action[8], toxicity to fish[9] and molluscacidal activity[10] of the furocoumarins have been studied.

A furocoumarin can be synthesised (A) by building a furan ring on a suitably substituted coumarin derivative or (B) by building an α-pyrone ring on an appropriate benzofuran derivative. Eight isomeric forms of furocoumarins (A to H) are theoretically possible.



A



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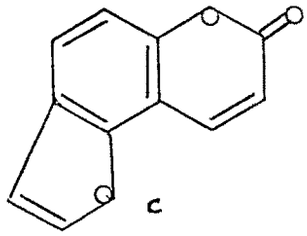
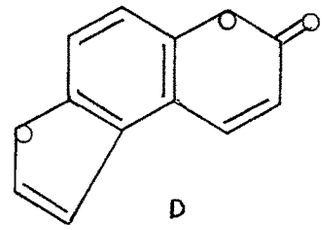


C



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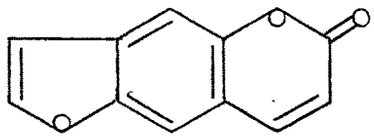

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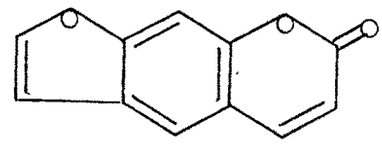

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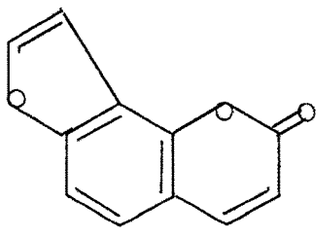
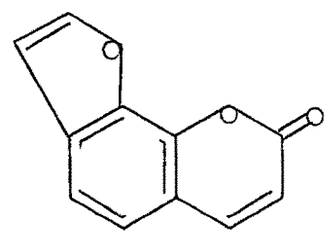


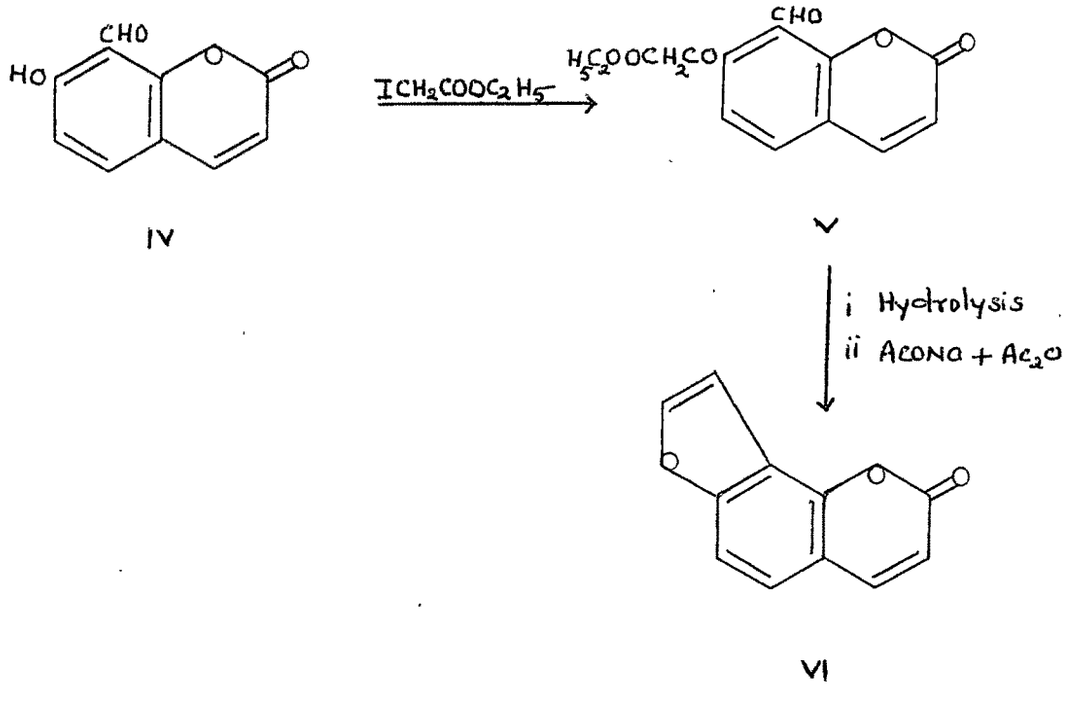
G



H

The parent members and derivatives of many of these types have been synthesised by using one or the other of the above two approaches. Some illustrative examples are given below :

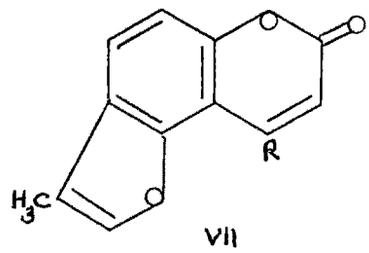
(A) 1. A very convenient method for the synthesis of a furocoumarin from a coumarin derivative is illustrated by the synthesis of angelicin by Spath and Pailer[11]. 7-Hydroxy--8-formylcoumarin (IV) was condensed with iodoacetic ester and the product obtained (V) was hydrolysed to the acid and cyclised in the presence of acetic anhydride to angelicin (VI).



IV V VI

Ethyl bromoacetate is generally used instead of ethyl iodoacetate. This method has been extensively used by later worker for the synthesis of a number of furocoumarins. A few examples are given below :-

Shah and Shah[12] synthesised 3'-methyl-furo-(5',4' : 5,6)coumarin (VIIa) from 5-hydroxy-6-acetyl-3-carbethoxycoumarin. Chudgar and Shah[13] prepared 3',4-dimethylfuro(5',4' : 5,6)coumarin (VIIb) from 5-hydroxy-6-acetyl-4-methylcoumarin.

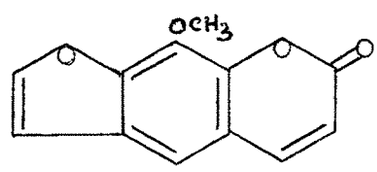


VII

(a) R = H

(b) R = CH_3

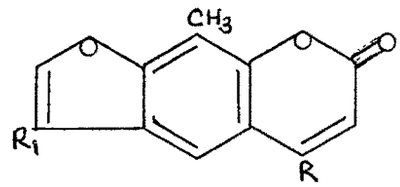
Rodighiero and Antonello[14] applied this method to the synthesis of xanthotoxin (VIII) from 7-hydroxy-8-methoxy--6-formylcoumarin.



VIII

Limaye and Gangal[15] synthesised 4,3'-dimethylfuro-(5',4': 7,6)coumarin from 7-hydroxy-6-acetyl-4-methylcoumarin using the same procedure.

Trivedi and co-workers[16] have recently synthesised different alkyl psoralenes having alkyl or aryl substituents in 4-position. 7-Hydroxy-6-acyl-4-alkyl or aryl-8-methyl-coumarin on condensation with ethyl bromoacetate followed by hydrolysis and subsequent cyclisation f yielded different substituted psoralenes (IX).

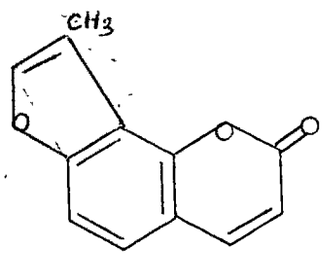


IX

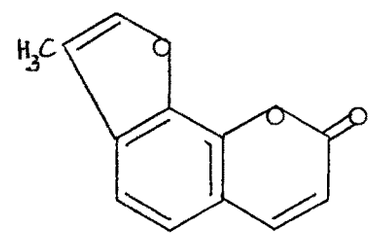
R = alkyl or aryl

R_1= CH_3, $-C_2H_5$, etc.

Using the above method, Shah and Shah[17] synthesised 3'-methyl-furo(5',4' : 7,8)coumarin (X) from 7-hydroxy-8-acetylcoumarin.



X

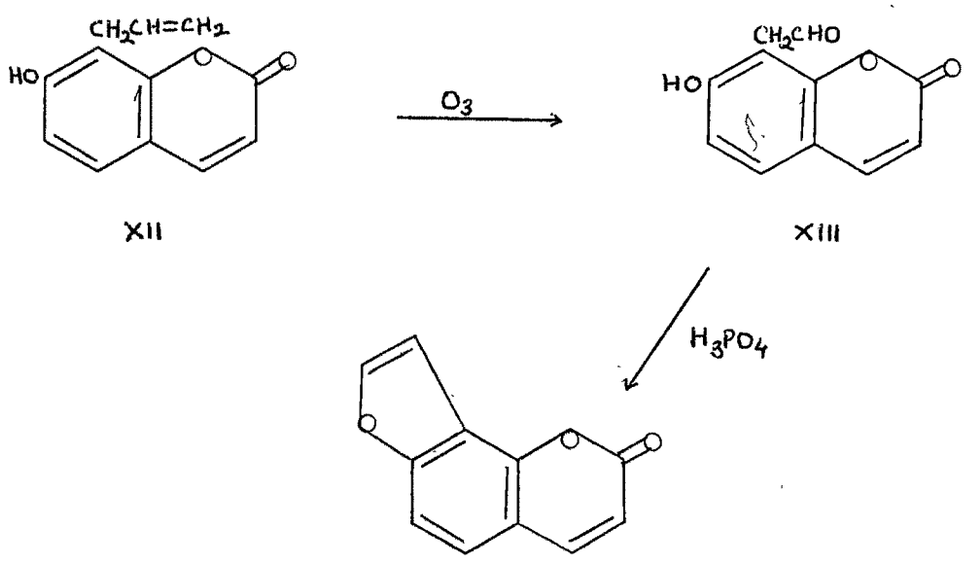


XI

Mehta and Sethna[18] synthesised 3'-methyl-furo-(5',4' : 8,7)coumarin (XI) by condensing 8-hydroxy-7-acetyl-coumarin with ethyl bromoacetate followed by hydrolysis and cyclisation.

Mehta[19] has also prepared 3',8-dimethyl-furo-(5',4' : 7,6)coumarin from 7-hydroxy-6-acetyl-8-methylcoumarin and 3',5-dimethyl-furo(5',4' : 7,8)coumarin from 7-hydroxy-8-acetyl-5-methylcoumarin.

(2) Seshadri and co-workers[20] have developed an interesting method for the synthesis of furocoumarins. They



XII XIII

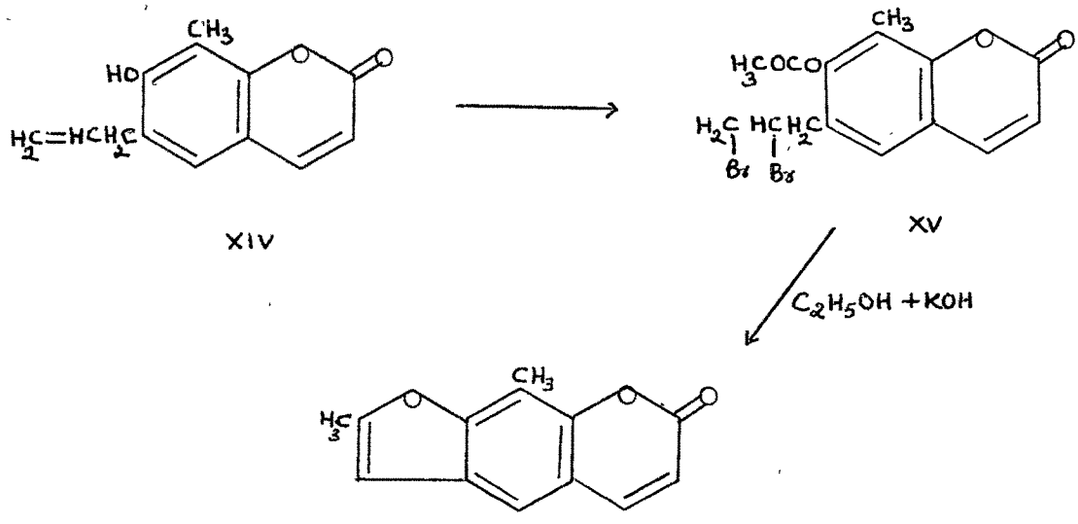
systhesised angelicin by subjecting 7-hydroxy-8-allyl-coumarin (XII) to ozonolysis and cyclised the 7-hydroxy-coumarin-8-acetaldehyde (XIII) formed with orthophosphoric acid.

Pardanani and Trivedi[21] used this method for the synthesis of 8-methyl-4-phenyl-furo(5',4' : 7,6)coumarin from 7-hydroxy-4-phenyl-8-methylcoumarin-6-acetaldehyde.

Following the same procedure, Seshadri and coworkers[20] also synthesised psoralene and xanthotoxin.

(3) Kaufman[22] has developed a versatile method which has proved useful in the synthesis of several furocoumarins. The synthesis of a dimethylpsoralene by this method is given below :-

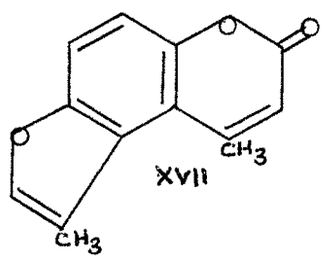
7-Allyloxy-8-methylcoumarin on Claisen rearrangement



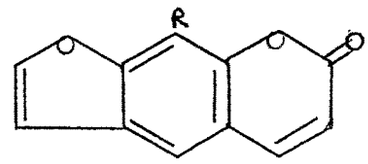
XIV XV XVI

gave 7-hydroxy-6-allyl-8-methylcoumarin (XIV). This was then acetylated and brominated. The dibromo derivative (XV) was cyclised to get the psoralene derivative (XVI).

This method was then extended to the synthesis of furo-2',4-dimethyl(5',4' : 6,5)coumarin (XVII) from 6-hydroxy--5-allyl-4-methylcoumarin[23].



XVII

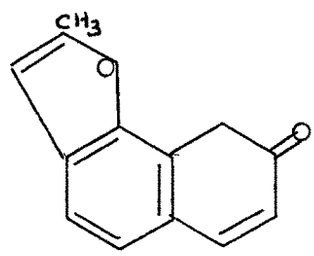


XVIII

R = Cl, Br, $N(CH_3)_2$

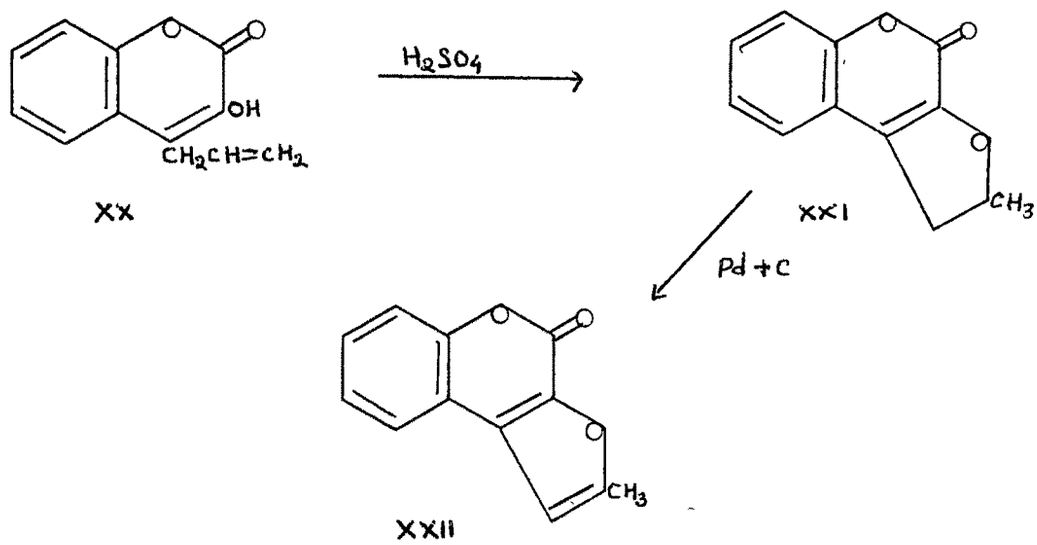
Kaufman and co-workers[24] synthesised psoralene derivative (XVIII) having different groups such as Cl, Br, CN and $N(CH_3)_2$ in the 8-position using 8-aminopsoralene as an intermediate product.

Kaufman and Russey[25] also synthesised 2'-methyl-furo(5',4' : 8,7)coumarin (XIX) from 7-allyl-8-hydroxycoumarin by this method.



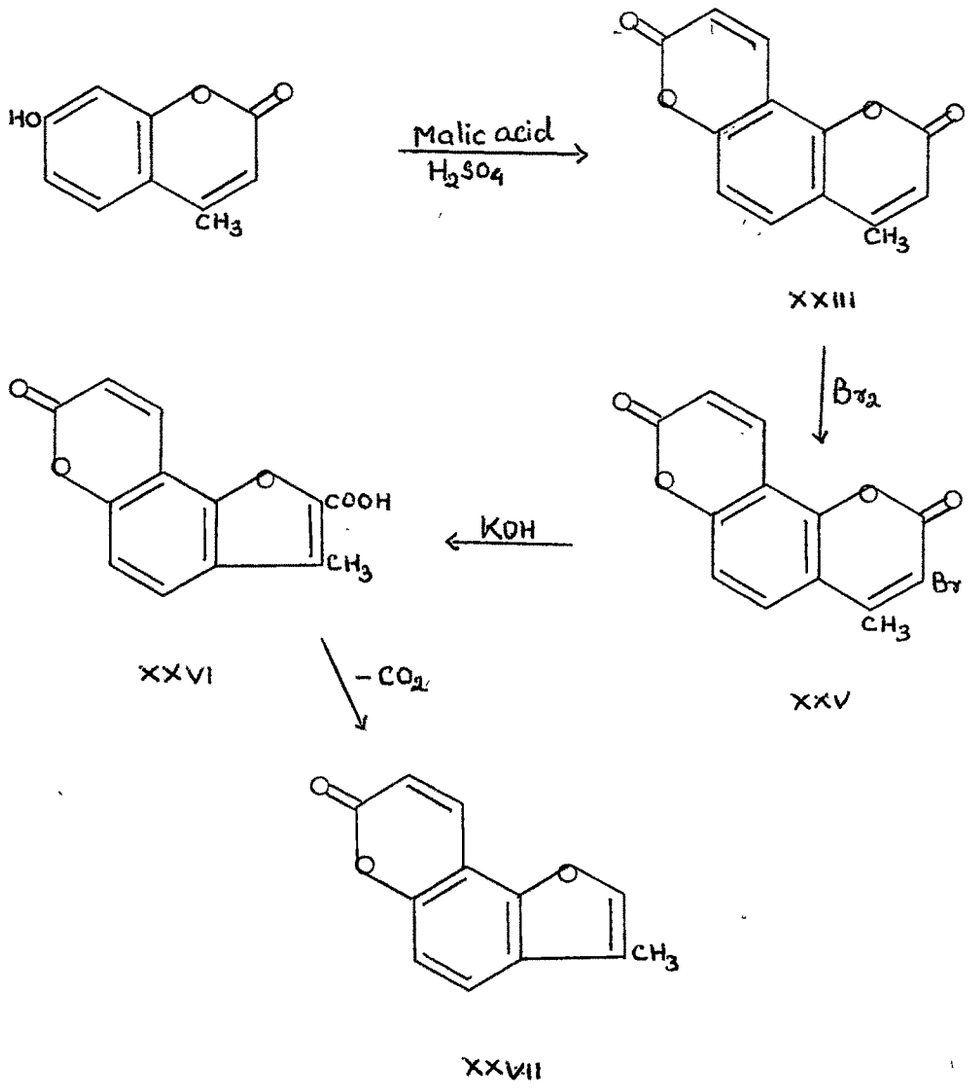
XIX

Shaikh and Trivedi[26] recently synthesised 2'-methyl-furo(5',4' : 3,4)coumarin (XXII) from 3-hydroxycoumarin. 3-Hydroxycoumarin was allylated and the allyloxycoumarin on Claisen rearrangement afforded 3-hydroxy-4-allylcoumarin (XX) which was cyclised by treatment with concentrated sulphuric acid. The dihydrofurocoumarin (XXI) dehydrogenated with a palladised charcoal to 2'-methyl-furo(5',4' : 3,4)-coumarin (XXII).

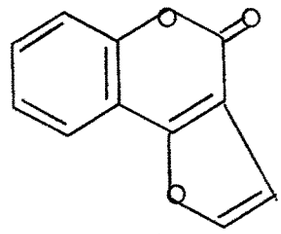


XX XXI XXII

(4) Trivedi and Sethna[27] synthesised 3'-methyl-furo--(5',4' : 5,6)coumarin (XXVII) using a different approach. The coumarino-α-pyrone (XXIV) obtained from 7-hydroxy-4-methylcoumarin (XXIII) was brominated and the 3-bromo derivative (XXV) obtained was treated with alcoholic potassium hydroxide and the acid (XXVI) decarboxylated.

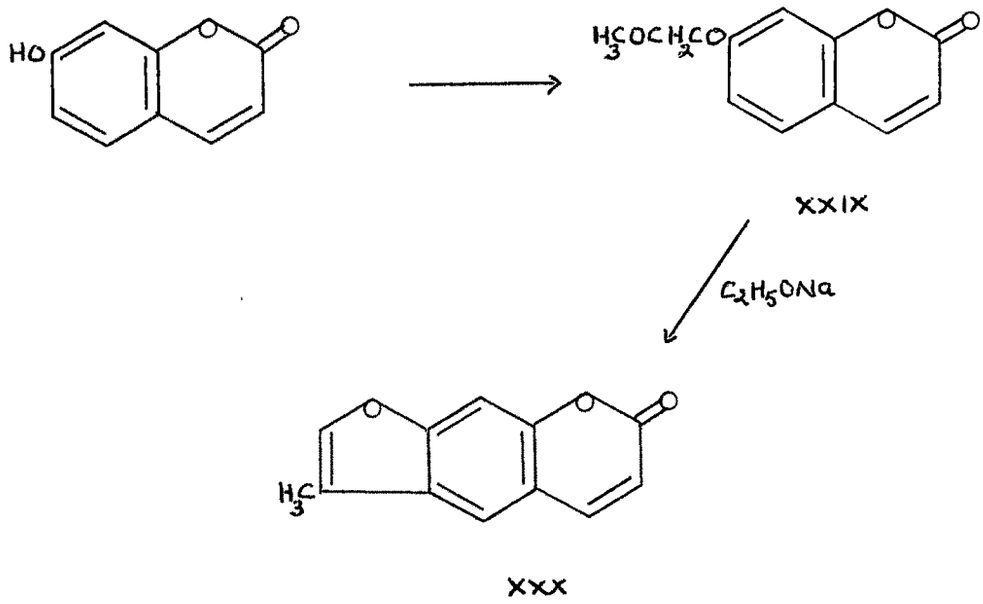


Dholakia and Trivedi[28] applied this method to the synthesis of furo-(5',4' : 4,3)coumarin (XXVIII) starting from 4-hydroxycoumarin.



XXVIII

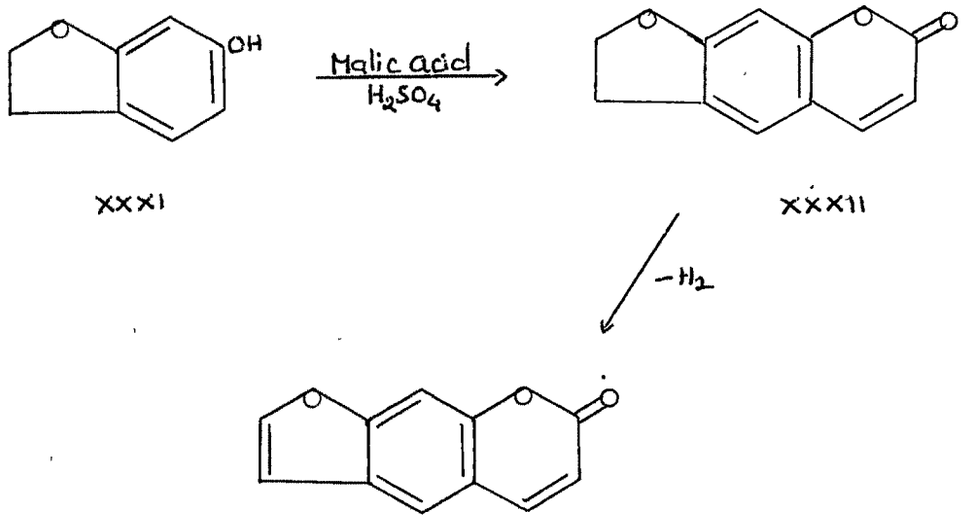
Ray, Silooja and Vaid[29] prepared 3-methylpsoralene (XXX) by the cyclisation of 7-acetonyloxycoumarin (XXIX) with sodium ethoxide.



XXX

(B) A few examples of the other approach viz. building up α-pyrone ring on a substituted benzofuran derivative may now be cited.

Spath et al.[30] carried out the condensation of 6-hydroxy-2,3-dihydro-benzofuran (XXXI) with malic acid in the presence of sulphuric acid and obtained 2,3-dihydro-psoralene (XXXII) which was dehydrogenated to psoralene (XXXIII).

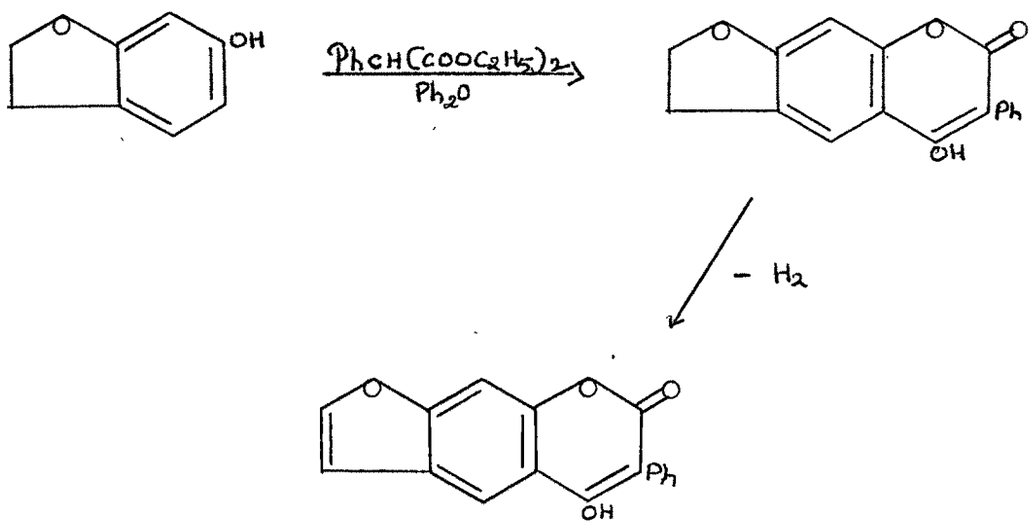


XXXI XXXII XXXIII

Later, Horning and Reisner[31] prepared different 2,3-dihydropsoralenes by condensing 6-acetoxy-2,3-dihydro-benzofuran with a variety of β-ketonic esters in the presence of sulphuric acid. Ease and Christensen[32] have extended this reaction to obtain 6-alkyl-2,3-dihydro-5-

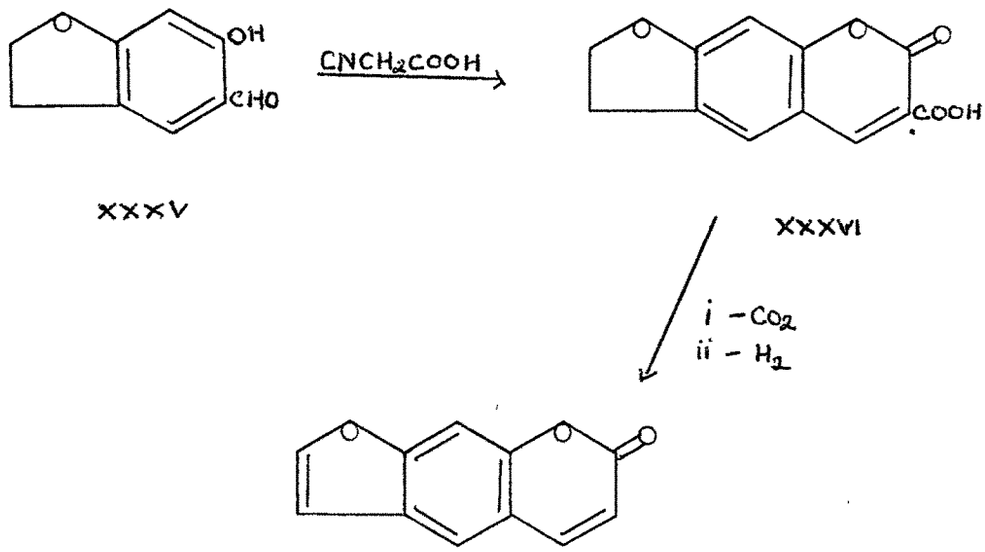
methylpsoralene by condensing appropriate α-alkyl-β-ketonic ester with 6-acetoxy-2,3-dihydrobenzofuran.

Goudau and Blanchecotte[33] synthesised 4-hydroxy--3-phenylpsoralene (XXXIV) from 6-hydroxy-2,3-dihydrobenzofuran.



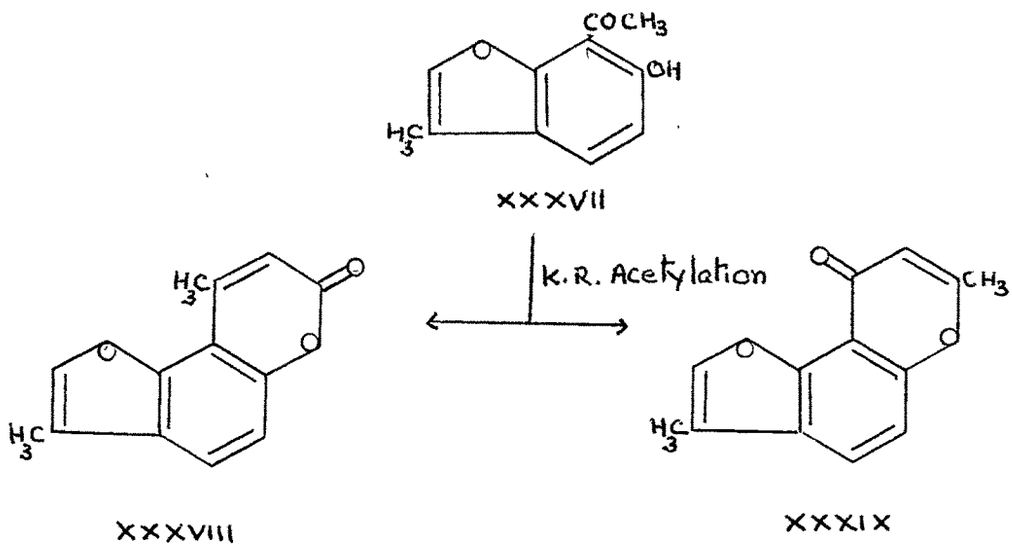
XXXIV

Foster et al.[34] synthesised psoralene by first subjecting 6-hydroxy-2,3-dihydrobenzofuran to Gattermann formylation and then condensing the 5-formyl derivative (XXXV) with cyanoacetic acid under the conditions of Knoevenagel reaction. The acid obtained (XXXVI) was decarboxylated and dehydrogenated to psoralene.



XXXV XXXVI

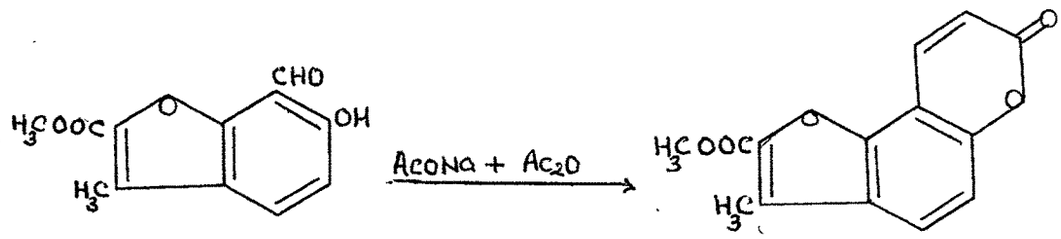
Limaye and Sathe[35] subjected 6-hydroxy-7-acetyl--3-methylbenzofuran (XXXVII) to Kostanecki-Robinson acetylation and obtained furo-3',4-dimethyl(5',4' : 5,6)-coumarin (XXXVIII) in poor yield along with furo-2,3'-dimethyl-(5',4' : 5,6)chromone (XXXIX).



XXXVII

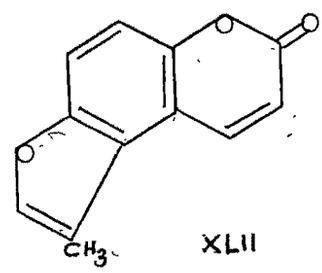
XXXVIII XXXIX

Salvi and Sethna[36] synthesised 2'-carbmethoxy-3'-methylfuro-(5',4' : 5,6)coumarin (XLI) from methyl-6-hydroxy-7-formyl-3-methylcoumarilate (XL) by Perkin acetylation.



XL XLI

They also prepared 3'-methylfuro(5',4' : 6,5)-coumarin (XLII) from methyl-4-formyl-5-hydroxy-3-methyl-coumarilate by Knoevenagel reaction with diethyl malonate.



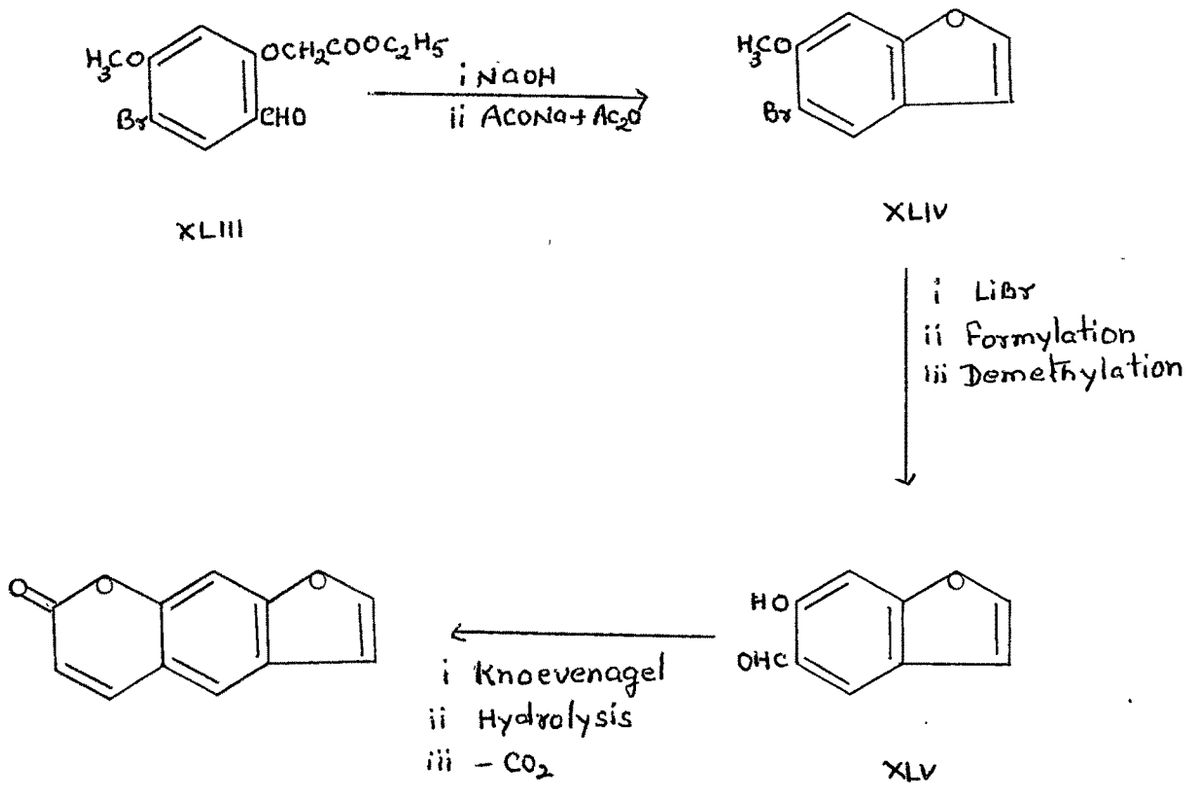
XLII

Limaye[37] synthesised angelicin by preparing 4-hydroxy-5-formylbenzofuran from 4-hydroxybenzofuran and then subjecting it to Perkin reaction.

Recently Kaufman and co-workers[38] have developed a new synthetic route to synthesise psoralene as follows :

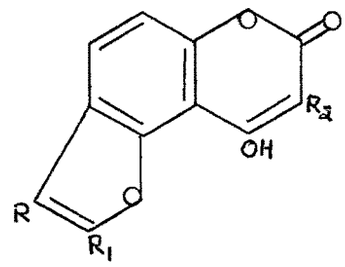
Bromination of ethyl(2-formyl-5-methoxyphenoxy)-acetate gave the 4-bromo derivative (XLIII) which was saponified and simultaneously cyclised and decarboxylated

to 5-bromo-6-methoxybenzofuran (XLIV). Lithium bromide interchange and then formylation and demethylation gave 5-formyl-6-hydroxybenzofuran (XLV) which was condensed with diethylmalonate to furnish psoralene after hydrolysis and decarboxylation of the condensation product.



Shaikh and Trivedi[39] have synthesised 4-hydroxy--furo(5',4' : 5,6)coumarin (XLVI) by the action of sodium and ethyl carbonate on 6-hydroxy-7-acetylbenzofuran. Through

a similar procedure the furocoumarins (XLVIb and c) were synthesised from 6-hydroxy-7-acetyl-3-methylbenzofuran and 6-hydroxy-7-propionyl-3-methylbenzofuran.



XLVI (a) R = R_1 = R_2 = H

(b) R = CH_3; R_1 = R_2 = H

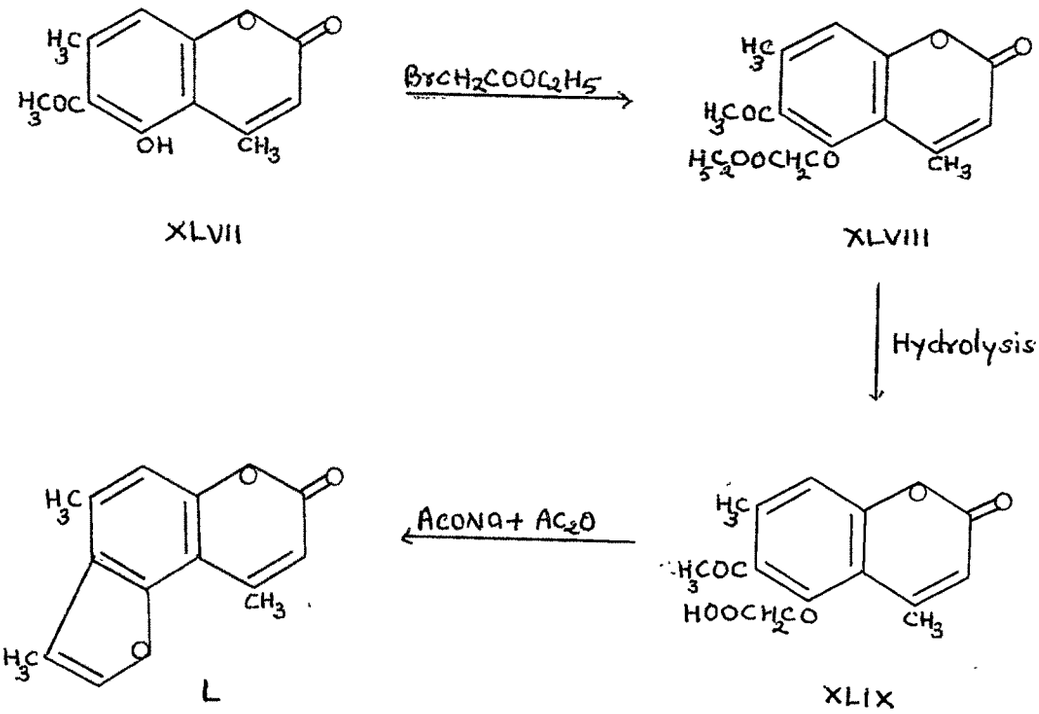
(c) R = R_2 = CH_3; R_1 = H

As the furocoumarins of some of the types (C), (D) and (E) discussed above with methyl groups in the benzeneoid part are not known it was thought of interest to synthesise them.

Synthesis of 4,7,3'-trimethylfuro(5',4' : 5,6)coumarin

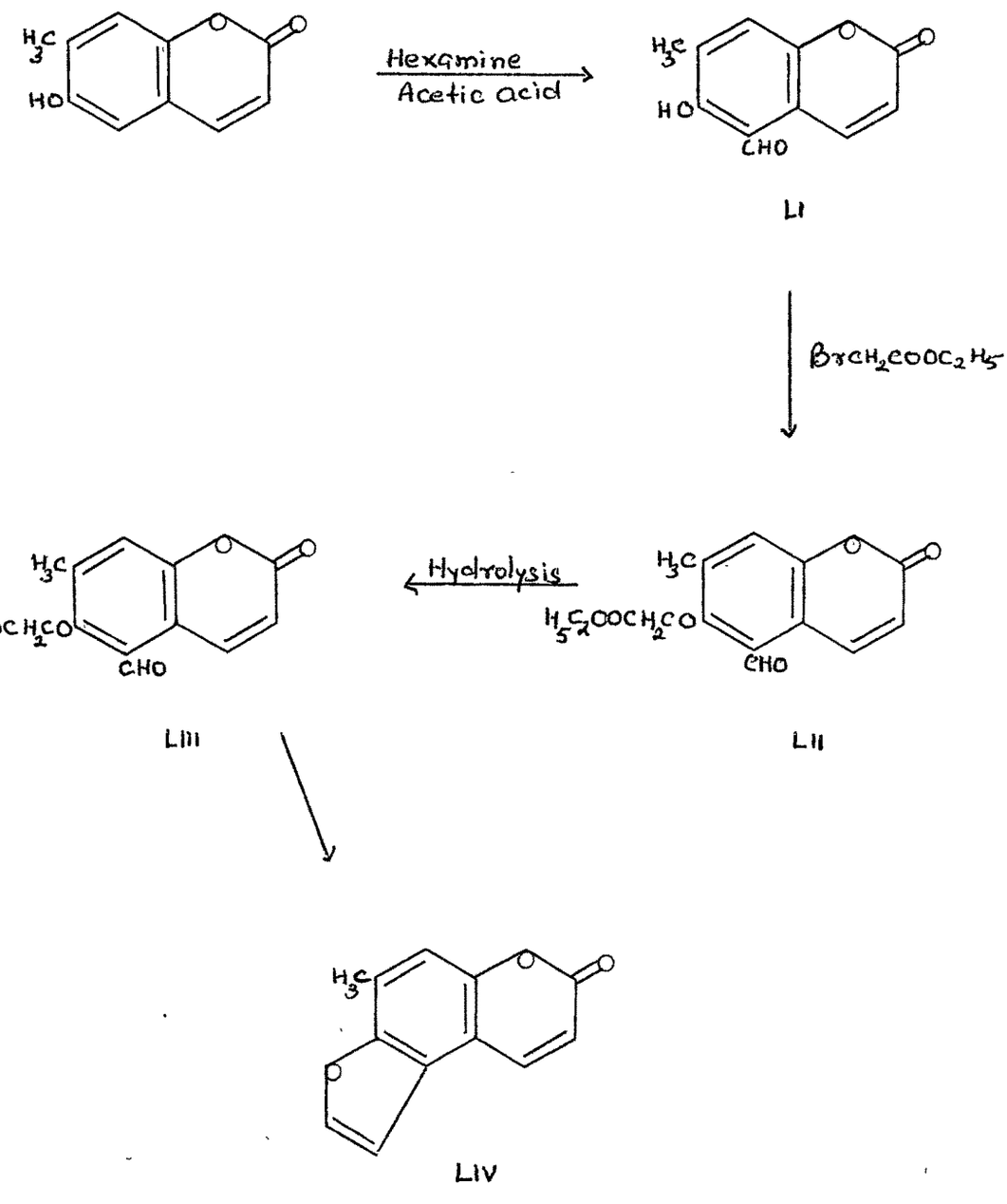
6-Acetyl-5-hydroxy-4,7-dimethylcoumarin (XLVII) was prepared by the Friedel-Crafts acetylation of the known 5-hydroxy-4,7-dimethylcoumarin with aluminium chloride and acetyl chloride according to Thakor and Parikh[40]. This on condensation with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate gave 5-hydroxy-6-acetyl-5-carbethoxymethoxy-4,7-dimethylcoumarin (XLVIII), which was insoluble in alkali. This ester was hydrolysed with 10 % sodium hydroxide solution to 6-acetyl-5-carboxy-

-methoxy-4,7-dimethylcoumarin (XLIX), The acid on heating with sodium acetate and acetic anhydride gave on simultaneous cyclisation and decarboxylation, 4,7,3'-trimethylfuro-(5',4' : 5,6)coumarin (L).



Synthesis of 7-methylfuro(5',4' : 5,6)coumarin

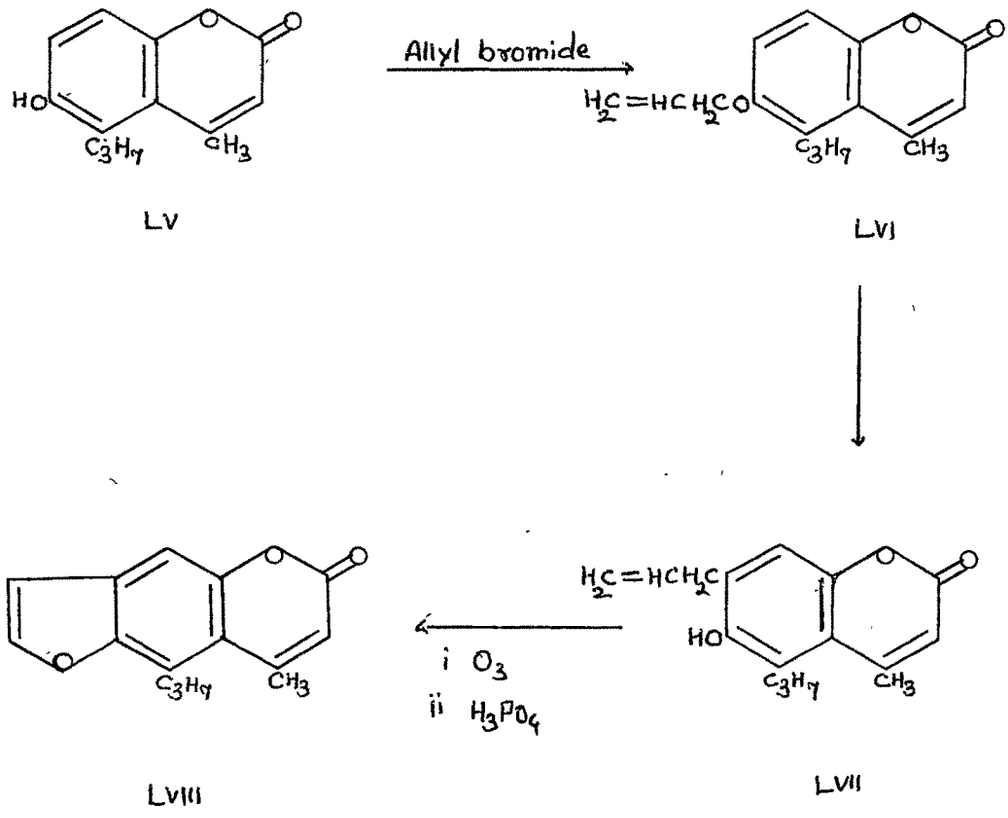
6-Hydroxy-7-methylcoumarin obtained from 2-methylhydroquinone by condensation with ethyl acetoacetate according to Desai and Mavani [41], on formylation with hexamine and acetic acid gave 7-methyl-6-hydroxy-5-formylcoumarin (LI). This was condensed with ethyl bromoacetate in acetone in the presence of anhydrous potassium carbonate. 7-Methyl-6-carbethoxymethoxy-5-formylcoumarin (LII), thus obtained, was hydrolysed by acetic acid and hydrochloric acid to


Hexamine
Acetic acid
LI
BrCH2COOC2H5
Hydrolysis
LII
LIII
LIV

7-methyl-6-carboxymethoxy-5-formylcoumarin (LIII). This acid on cyclisation with sodium acetate gave 7-methylfuro-(5',4' : 6,5)coumarin (LIV).

Furocoumarin of the type (E) has been synthesised by Kaufman et al.[42] through the following sequence of reactions :-

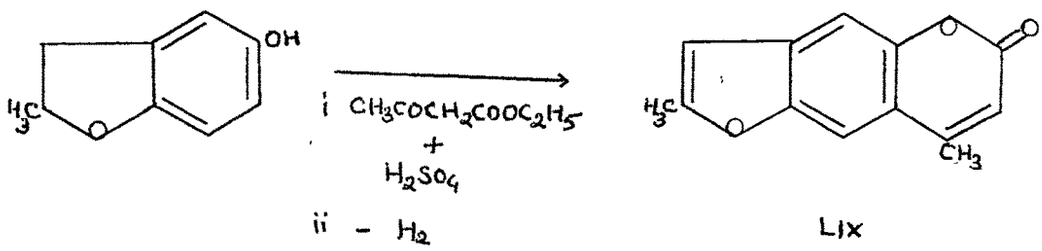
6-Hydroxy-5-n-propyl-4-methylcoumarin (LV) was allylated and the allyl ether (LVI) on Claisen rearrangement gave 7-allyl-6-hydroxy-5-n-propyl-4-methylcoumarin (LVII). This on ozonolysis and heating with o-phosphoric acid gave 4-methyl-5-n-propyl-furo(5',4' : 6,7)coumarin (LVIII).



LV LVI

LVII LVIII

2',4-Dimethyl-furo(5',4' : 6,7)coumarin LIX) was synthesised by the above authors from 5-hydroxy-2-methyl-2,3-dihydrobenzofuran by Pechmann reaction with ethyl aceto-acetate and subsequent dehydrogenation.

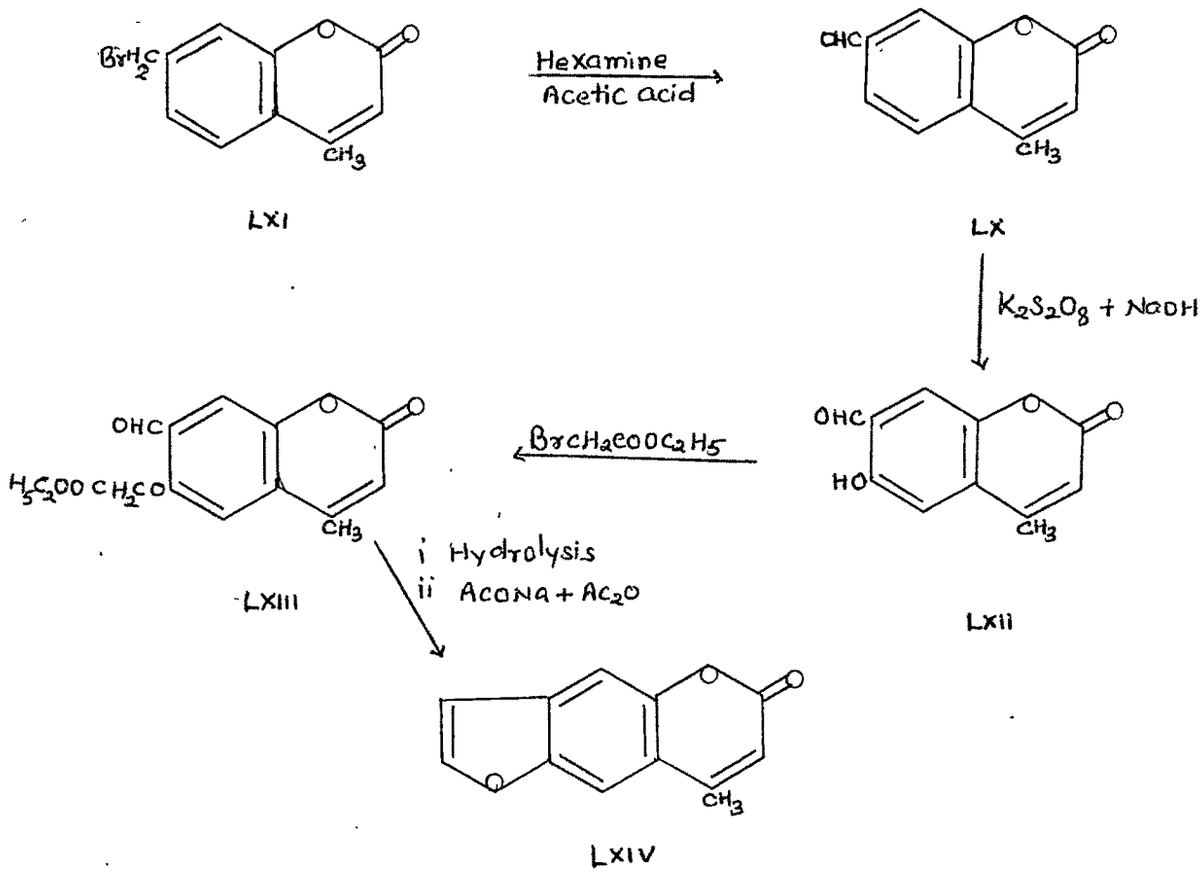


LIX

Jainamma and Sethna[43] synthesided 4-methylfuro-(5',4' : 6,7)coumarin (LXIV) as follows :-

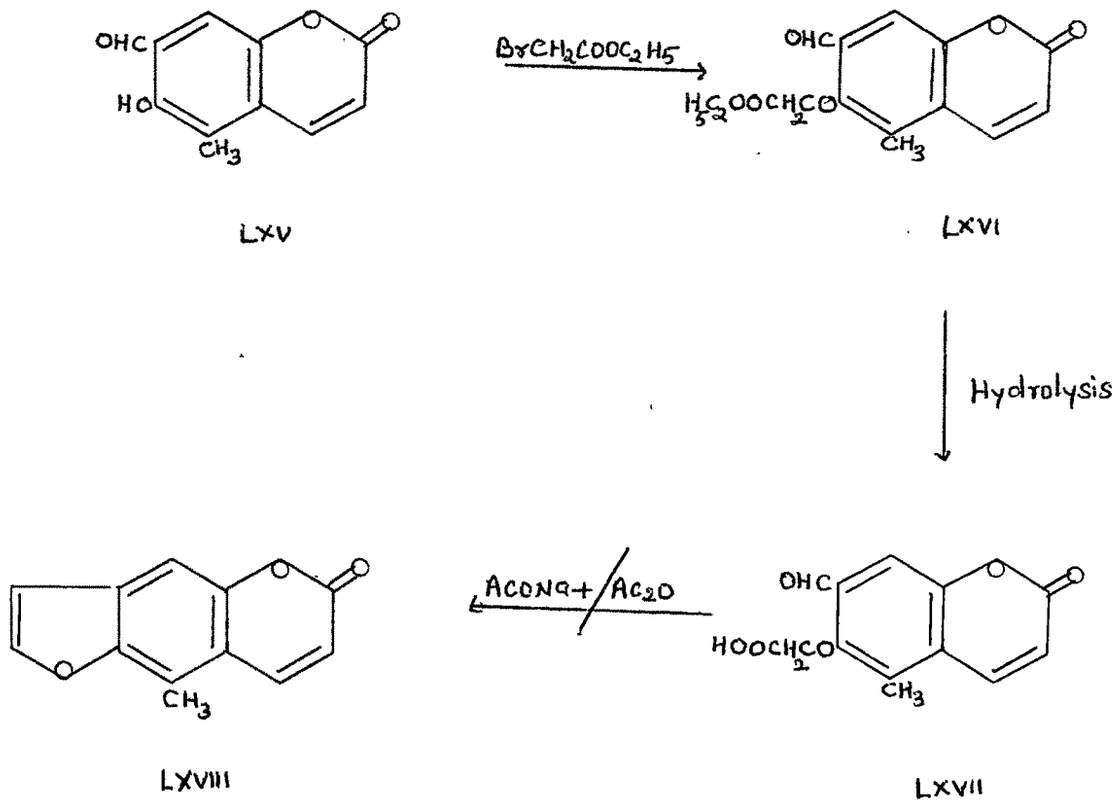
7-Formyl-4-methylcoumarin (LX) prepared from 7-bromomethyl-4-methylcoumarin (LXI), on Elbs persulphate oxidation gave 6-hydroxy-7-formyl-4-methylcoumarin (LXII). On condensation with ethyl bromoacetate it gave the 6-carb-ethoxy derivative (LXIII). The acid obtained on hydrolysis of this was cyclised and decarboxylated to get 4-methylfuro-(5',4' : 6,7)coumarin (LXIV).

Their attempt to synthesise the parent compound furo-(5',4' : 6,7)coumarin from 6-hydroxy-7-formylcoumarin by a similar process, however, did not succeed as the intermediate 6-carbethoxy derivative on hydrolysis gave a polymeric product.



Attempted synthesis of 5-methylfuro(5',4':6,7)coumarin (LXVIII)

With a view to synthesise the linear furocoumarin (LXVIII), 5-methyl-6-hydroxy-7-formylcoumarin (LXV) prepared as described in Chapter I (p. 53) was condensed with ethyl bromoacetate in acetone in the presence of anhydrous potassium carbonate. 5-Methyl-6-carbethoxymethoxy-7-formyl-coumarin (LXVI) thus obtained was hydrolysed by keeping it with 5 % sodium hydroxide solution for 20 hours to the corresponding acid (LXVII). This acid on heating with sodium acetate and acetic anhydride underwent cyclisation to give a product which was insoluble in sodium bicarbonate solution but could not be purified because of its very poor yield.



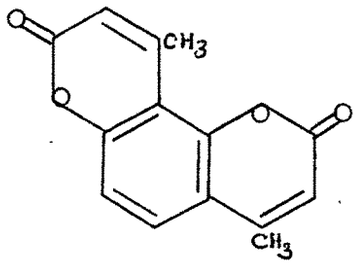
LXV LXVI

LXVIII LXVII

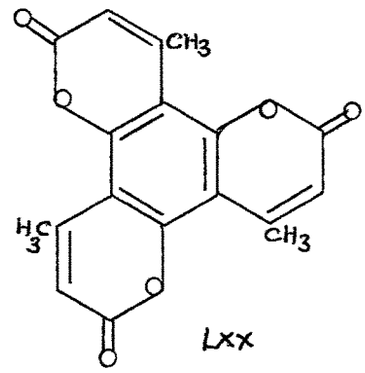
Coumarino-α-pyrones

Several workers have synthesised a number of coumarino-α-pyrones starting with hydroxycoumarins. A few examples are given below :-

Hantzsch and Zurcher[44] synthesised coumarino-α-pyrones (LXIX) and (LXX) by the Pechmann condensation of resorcinol and phloroglucinol with ethyl acetoacetate.

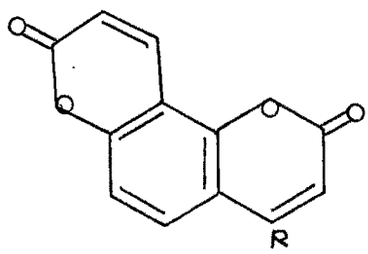


LXIX

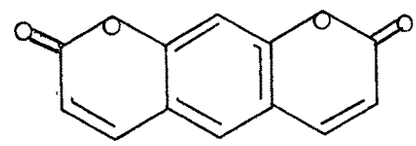


LXX

Sen and Chakravarti[45] condensed 7-hydroxy- and 7-hydroxy-4-methylcoumarin with malic acid in the presence of sulphuric acid and obtained coumarino-(7,8 : 6',5')-α-pyrone (LXXIa) and 4-methylcoumarino(7,8 : 6; 5')-α-pyrone (LXXb) respectively.



LXXI



LXXII

(a) R = H

(b) R = CH_3

Similar condensations were carried out by the above authors with 7,8-dihydroxy-4-methyl-, 7,8-dihydroxy-, 5-hydroxy--7-methyl- and 5-hydroxy-4,7-dimethylcoumarin and they

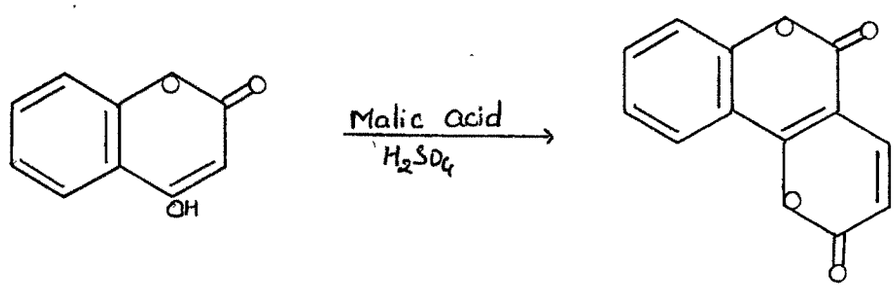
obtained coumarino-α-pyrone derivatives, the structures of which were not established. Rangaswami and Seshadri[46] reported the formation of both the angular (LXXa) and the linear (LXXII) coumarino-α-pyrone derivatives in the condensation of 7-hydroxycoumarin with malic acid, the latter being obtained in poor yield. Under the same experimental conditions 7-hydroxy-4-methylcoumarin gives only the angular coumarino-α-pyrone (LXXIb). The structure of (LXXIa) was established by its synthesis from 7-hydroxy-8-formylcoumarin by Perkin reaction. In a similar way, the constitution of (LXXIb) was also established.

Biswas[47] synthesised 3-chloro-4-methylcoumarino-(7,8 : 6',5')-α-pyrone, 7-methyl-3-chloro-4-methylcoumarino-(5,6 : 6',5')-α-pyrone and 8-hydroxy-3-chloro-4-methylcoumarino-(7,6 : 6',5')-α-pyrone by the condensation of 3-chloro-4-methyl-7-hydroxy-, 3-chloro-5-hydroxy-4,7-dimethyl- and 3-chloro-4-methyl-7,8-dihydroxycoumarin respectively, with malic acid in the presence of sulphuric acid.

Trivedi and Sethna[48] prepared 3,4-dimethylcoumarino-(7,8 : 6',5')-α-pyrone and 3,4,7-trimethylcoumarino-(5,6 : 6',5')-α-pyrone by the condensation of 7-hydroxy-3,4-dimethylcoumarin and 5-hydroxy-3,4,7-trimethylcoumarin with malic acid. Similarly 8-hydroxy-3,4-dimethylcoumarino-(7,6 : 6',5')-α-pyrone and 3-bromo-4-methyl-8-hydroxycoumarino(7,6 : 6',5')-α-pyrone were also synthesised from 7,8-dihydroxy-3,4-dimethylcoumarin, 7-hydroxy-3-bromo-4-methylcoumarin and

7,8-dihydroxy-3-bromo-4-methylcoumarin respectively. They established the structures by Perkin acetylation of the corresponding formylated coumarin derivatives.

Dholakia and Trivedi[49] recently synthesised coumarino-α-pyrone (LXXIV) from 4-hydroxycoumarin (LXXIII) by the Pechmann condensation with malic acid.

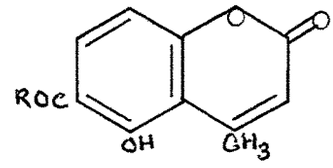


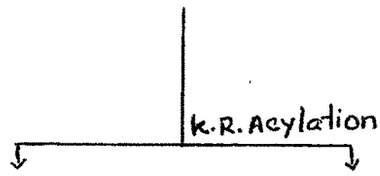
LXXIII LXXIV

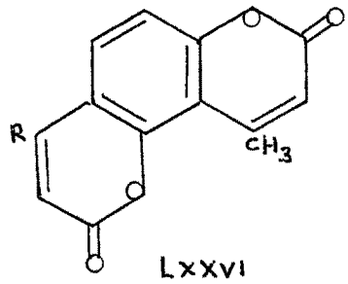
Similarly, 7-methoxy-8-methyl-4'-methylcoumarino-(4,3 : 6',5')-α-pyrone and 6-methylcoumarino-(4,3 : 6',5')-α-pyrone were also synthesised from 7-methoxy-8-methyl-4-hydroxy- and 6-methyl-4-hydroxycoumarin respectively.

Shah and co-workers[50] carried out Kostanecki-Robinson acylation of 5-hydroxy-6-acylcoumarin (LXXV) and obtained coumarino-α-pyrone (LXXVI) and coumarino-γ-pyrone (LXXVII).

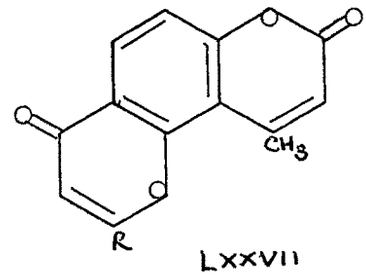
Mustafa and co-workers[51] carried out Kostanecki-Robinson acetylation on 4-hydroxy-3-benzoylcoumarin (LXXVIII) and obtained 4'-phenylcoumarino-(4,3 : 6',5')-α-pyrone (LXXIX).







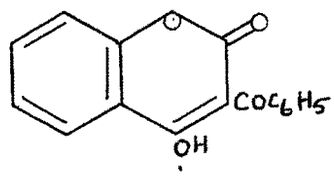
LXXVI



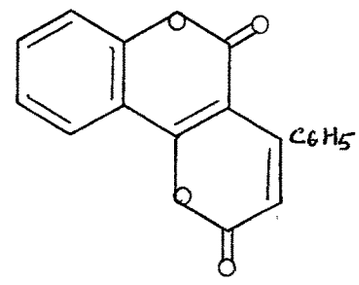
LXXVII

R = alkyl or aryl

4-Hydroxycoumarin on Pechmann condensation with ethyl aceto-acetate yielded 4'-methylcoumarino-(4,3 : 6',5')-α-pyrone.

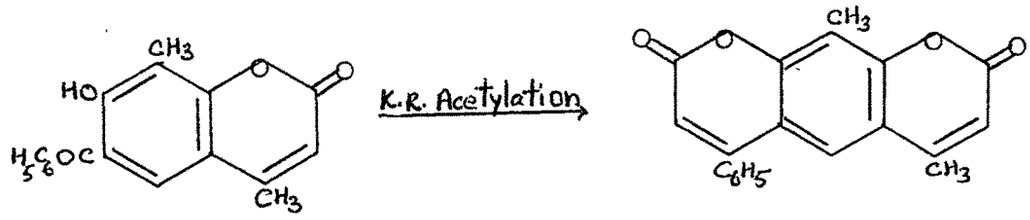


LXXVIII



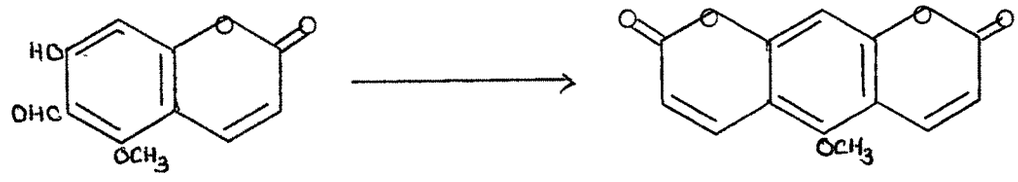
LXXIX

Trivedi and co-workers[52] synthesised 4-methyl-4'-phenylcoumarino-(7,6 : 6',5')-α-pyrone (LXXXI) by carrying out Kostanecki-Robinson acetylation of 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin (LXXX). The structure of this coumarino-α-pyrone was established by spectral data.



LXXX LXXXI

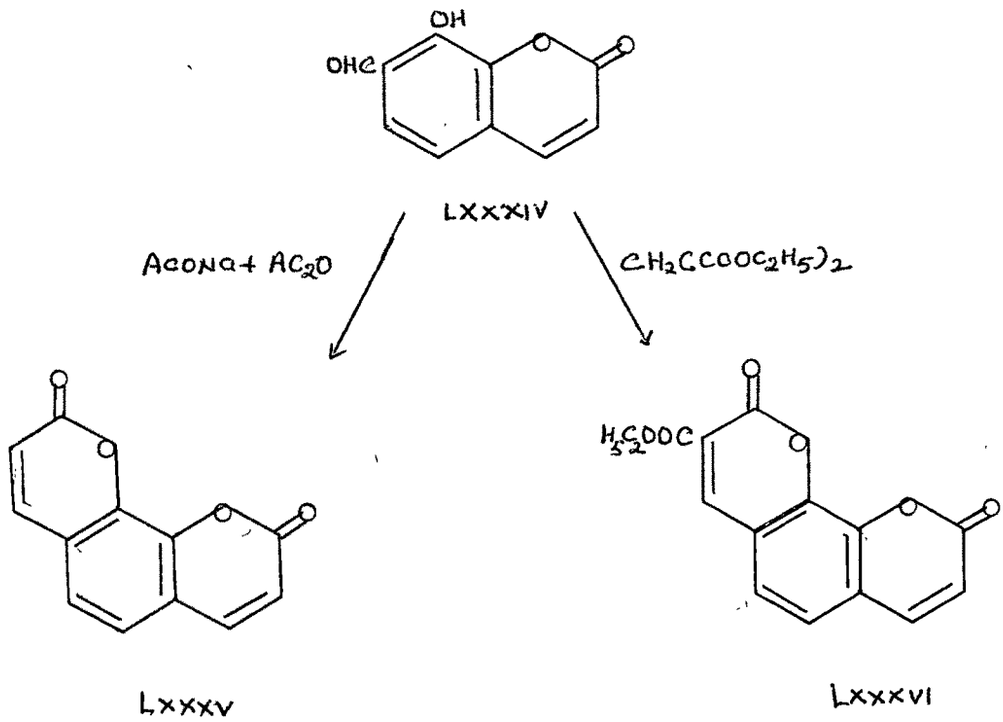
Similarly they prepared 4,8-dimethyl-4'-phenylcoumarino-(7,6 : 6',5')-α-pyrone from 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin. Mustafa, Starkovsky and Zaki[53] prepared 5-methoxycoumarino-(7,6 : 6',5')-α-pyrone (LXXXIII) by Perkin acetylation of 5-methoxy-7-hydroxy-6-formylcoumarin (LXXXII).



LXXXII LXXXIII

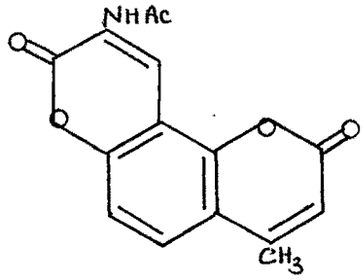
Mehta[54] carried out Perkin acetylation and Knoevenagel reaction on 8-hydroxy-7-formylcoumarin (LXXXIV)

and obtained coumarino-(8,7 : 6',5')-α-pyrone (LXXXV) and 3'-carbethoxycoumarino-(8,7 : 6',5')-α-pyrone (LXXXVI).

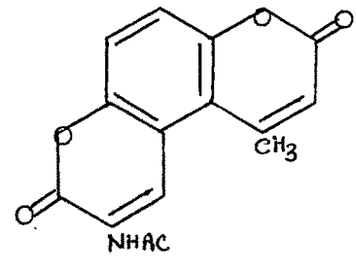


Chakravarti and co-workers[55] condensed 7-hydroxy--8-formyl-4-methyl- and 6-hydroxy-5-formyl-4-methylcoumarin with glycine and obtained 3'-acetamido-4-methylcoumarino-(7,8 : 6',5')-α-pyrone ((LXXXVIII) and 4-methyl-3'-acetamido-coumarino-(6,5 : 6',5')-α-pyrone (LXXXIX).

Shaikh and Trivedi[56] synthesised 3'-acetamido-coumarino-(7,8 : 6',5')-α-pyrone, 4-methyl-3'-acetamido-



LXXXVIII



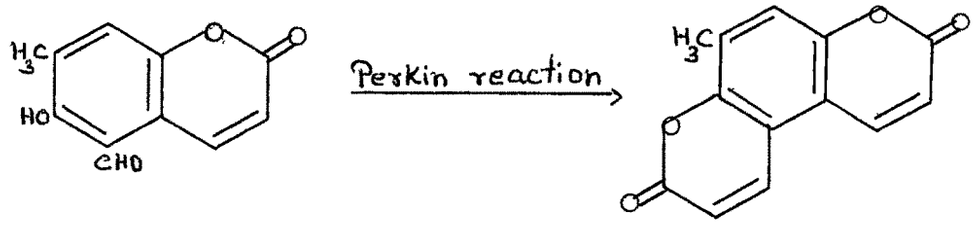
LXXXIX

coumarino-(7,8 : 6',5')-α-pyrone and 4-methyl-8-hydroxy-3'-acetamidocoumarino-(7,6 :6',5')-α-pyrone through a similar procedure.

The present work deals with the synthesis of linear and angular isomers of coumarino-α-pyrone with a methyl group at 7- or 5-position respectively.

Synthesis of 7-methylcoumarino-(6,5 : 6',5')-α-pyrone

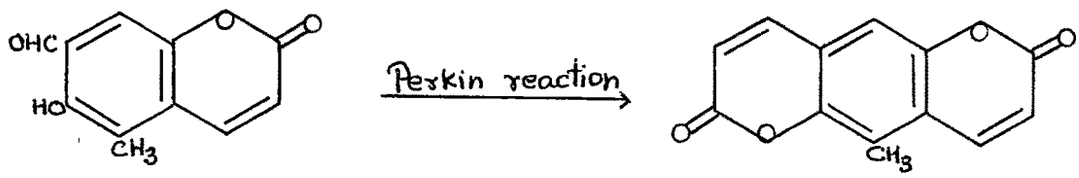
7-Methyl-6-hydroxy-5-formylcoumarin described earlier was subjected to Perkin acetylation with acetic anhydride and fused sodium acetate, when a product was obtained which was insoluble in sodium hydroxide solution and so was assigned the structure 7-methylcoumarino-(6,5 : 6',5')-α-pyrone (XC).



XC

Synthesis of 5-methylcoumarino(6,7 : 6',5')-α-pyrone

5-Methyl-6-Hydroxy-7-formylcoumarin obtained as described earlier (p.43), on Perkin acetylation gave a product which was insoluble in sodium hydroxide and it was assigned the structure 5-methylcoumarino(6,7 : 6',5')-α-pyrone (XCI).



XCI

Coumarino-γ-pyrones

A number of methods are available for the synthesis of γ-pyrone derivatives. In the present work three methods mentioned below have been used :-

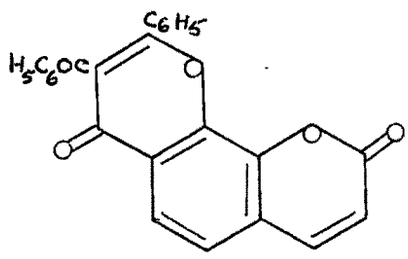
(1) The Chalkone method which consists in the condensation of a formylcoumarin with suitably substituted o-hydroxyphenyl ketone to give a Chalkone which is cyclised into a phenyl-γ-pyrone by the treatment with iso-amyl alcohol or conc. sulphuric acid, (2) by Baker-Venkataraman transformation of an o-benzoyloxy acetophenone and the cyclisation of the β-diketone thus obtained and (3) Kostanecki-Robinson acylation of an o-hydroxy-acetyl derivative with the appropriate acid anhydride and its sodium salt. This

method has been extensively used for the synthesis of various 2-phenylcoumarino-γ-pyrones.

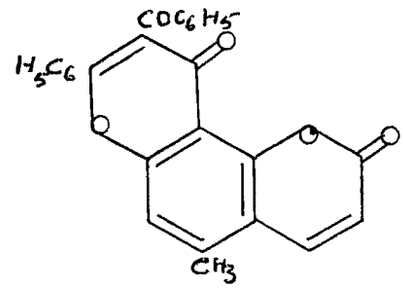
The formation of a mixture of α-pyrone and γ-pyrone and the 3'-acetyl- or benzoyl derivative of the latter is a common feature observed in Kostanecki-Robinson acylation.

Limaye and Ghate[57] obtained 4'-dimethyl-8-ethylcoumarino(7,6 : 6',5')-α-pyrone and 2',4-dimethyl-8-ethyl--3'-acetylcoumarino-γ-pyrone from 7-hydroxy-8-ethyl-6-acetyl--4-methylcoumarin by Kostanecki-Robinson acetylation.

Mehta[58] prepared 2'-phenyl-3'-benzoylcoumarino-(8,7 : 6',5')-γ-pyrone (XCII) from 8-hydroxy-7-acetylcoumarin and 2'-phenyl-3'-benzoyl-5-methylcoumarino(7,8 : 6',5')-γ-pyrone (XCIII) from 7-hydroxy-8-acetyl-5-methylcoumarin by Kostanecki-Robinson benzoylation.



XCII

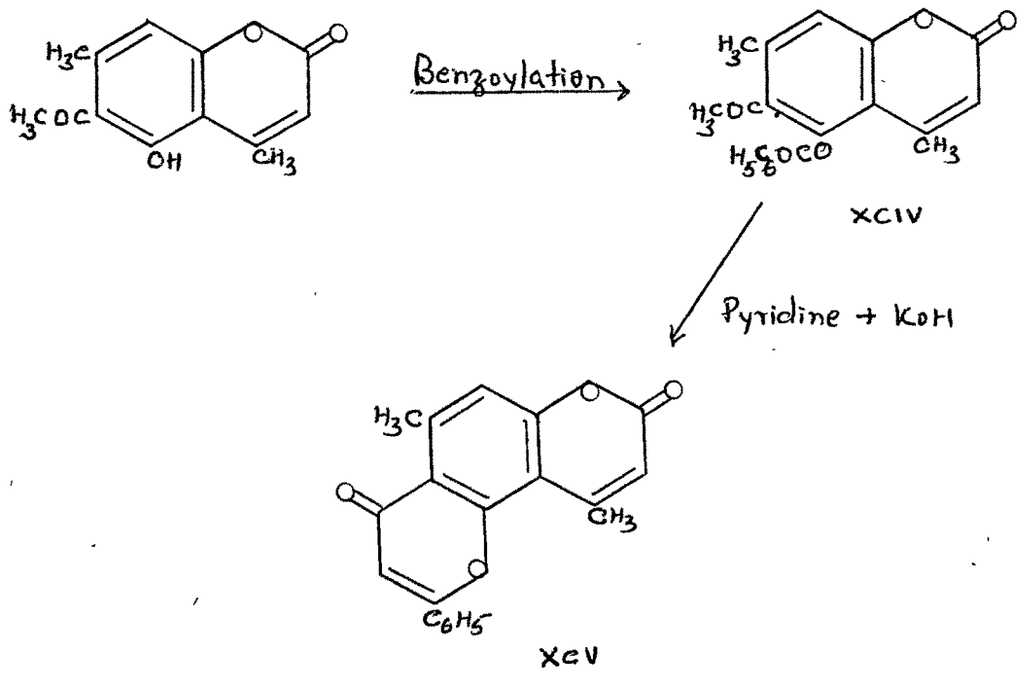


XCIII

Synthesis of 2'-phenyl-4,7-dimethylcoumarino-(5,6 : 6',5')-γ-pyrone

The 5-hydroxy-6-acetyl-4,7-dimethylcoumarin was benzoylated and the benzoyl derivative (XCIV) was subjected

to Baker-Venkataraman transformation with solid potassium hydroxide in pyridine to get β-diketone but it directly gave a cyclised product which was found to be 2'-phenyl--4,7-dimethylcoumarino(5,6 : 6',5')-γ-pyrone (XCV).



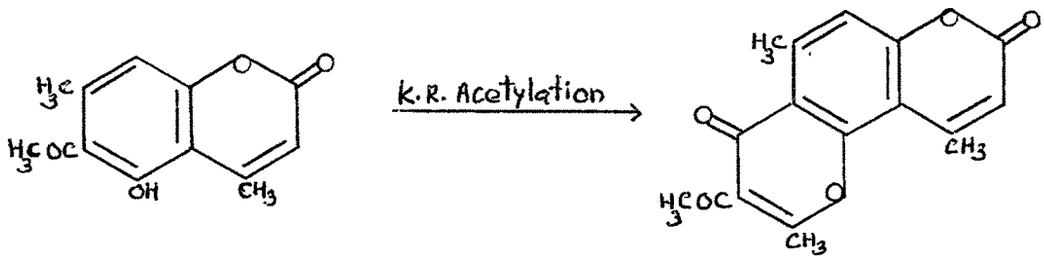
XCIV

XCV

Synthesis of 3'-acetyl-2',4,7-trimethylcoumarino-(5,6 : 6',5')-γ-pyrone

5-Hydroxy-6-acetyl-4,7-dimethylcoumarin was subjected to Kostanecki-Robinson acetylation when a product insoluble in alkali was obtained. On the basis of the analysis and the previous work in this field the 3'-acetyl--2',4,7-trimethylcoumarino(5,6 : 6',5')-γ-pyrone structure(XCVI)

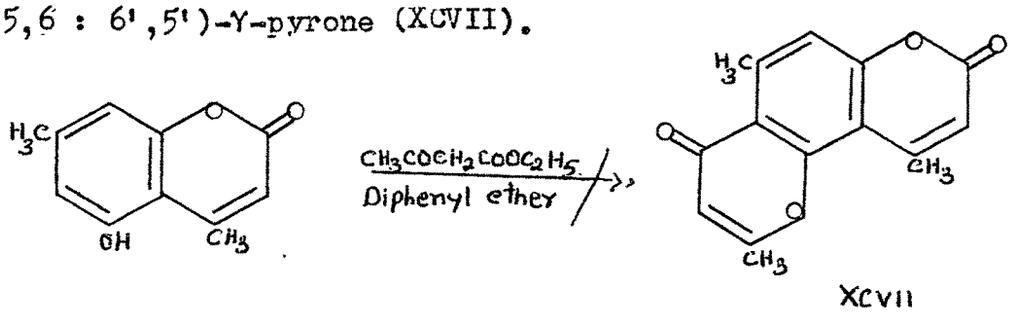
has been assigned to this product. Attempts to deacetylate it by heating with alcoholic potassium hydroxide did not succeed.



XCVI

Attempted synthesis of 2',4,7-trimethylcoumarino-(5,6 : 6',5')-γ-pyrone

Phenols are known to condense with β-ketonic esters either on prolonged heating at high temperature or on refluxing in a high boiling solvent to give chromones[59]. 5-Hydroxy-4,7-dimethylcoumarin was therefore refluxed with ethyl acetoacetate in diphenyl ether for 6 hours. On removal of the solvent a product was obtained which was found to be insoluble in alkali. Its analysis, however, did not agree with that of the desired 2',4,7-trimethylcoumarino-(5,6 : 6',5')-γ-pyrone (XCVII).



XCVII

EXPERIMENTAL

6-Acetyl-5-carbethoxymethoxy-4,7-dimethylcoumarin (XLVIII) :

6-Acetyl-5-hydroxy-4,7-dimethylcoumarin (1.0 g.) was refluxed with ethylbromoacetate (0.5 g.) and anhydrous potassium carbonate (5.0 g.) in dry acetone on a steam bath for 2 hr. The product obtained on removal of the acetone and on addition of water was crystallised from alcohol. M.p. 180°. Yield 0.7 g.

Analysis : Found : C, 64.60 ; H, 5.52 %

$C_{17}H_{18}O_6$: requires : C, 64.15 ; H, 5.66 %.

6-Acetyl-5-carboxymethyl-4,7-dimethylcoumarin (XLIX) :

The above ester (1.5 g.) was heated on a steam bath for 15 min. with 5 % sodium hydroxide solution and then kept overnight. The solid obtained on acidification was purified by sodium carbonate.

4,7,3'-Trimethylfuro(5',4' : 5,6)coumarin (L) :

The above acid was directly refluxed on a wire gauze with freshly fused sodium acetate (3.0 g.) and acetic anhydride (10 ml.) for 4 hr. The product obtained on pouring the reaction mixture in water crystallised from dilute alcohol. M.p. 235°. IR in nujol : 1720 cm^{-1} (δ lactone); 870 cm^{-1} (furan ring breathing). UV in methanol : λ max 250 nm; 300 nm.

Analysis : Found : C, 73.82 ; H, 5.02 %

$C_{12}H_{12}O_3$ requires : C, 73.68 ; H, 5.26 %.

7-Methyl-6-hydroxy-5-formylcoumarin (LI) :

A mixture of 7-methyl-6-hydroxycoumarin (1.0 g.) and hexamine (3.0 g.) in glacial acetic acid (50 ml.) was refluxed for 30 min. Hydrochloric acid (20 ml. ; 1:1) was then added and heating continued for further 10 min. The reaction mixture was then added to cold water and the product obtained crystallised from acetic acid in pale yellow needles, (0.8 g.), m.p. 246°. IR in nujol : 1745 cm^{-1} (CHO) ; 1655 cm^{-1} (δ lactone).

Analysis : Found : C, 65.01 ; H, 4.07 %

$C_{11}H_8O_4$ requires : C, 64.70 ; H, 3.92 %.

7-Methyl-6-carbethoxymethoxy-5-formylcoumarin (LII) :

A solution of 7-methyl-6-hydroxy-5-formylcoumarin (1.0 g.) in dry acetone was refluxed with anhydrous potassium carbonate (3.0 g.) and ethyl bromoacetate (3 ml.) on a steam bath for 3 hr. The solid obtained on removal of acetone was treated with water. The separated product crystallised from benzene-petroleum ether in white needles (1.0 g.), m.p. 185°.

Analysis : Found : C, 62.34 ; H, 4.65 %

$C_{15}H_{15}O_6$ requires : C, 61.92 ; H, 5.15 %.

7-Methyl-6-carboxymethoxy-5-formylcoumarin (LIII) :

The above ester (1.0 g.) was dissolved in acetic acid (20 ml.) and hydrochloric acid (20 ml.) was then added and the mixture was refluxed for 4 hr. The solid obtained on dilution with water was treated with sodium bicarbonate

solution which on acidification with hydrochloric acid afforded a product which crystallised from alcohol in clusters of needles (0.8 g.), m.p. 255° (effer.).

Analysis : Found : C, 59.27 ; H, 3.59 %

$C_{13}H_{10}O_6$ requires : C, 59.54 ; H, 3.82 %.

7-Methyl-furo(5',4' : 6,5')coumarin (LIV) :

The above acid (0.8 g.) was refluxed with sodium acetate (2.0 g.) and acetic anhydride (20 ml.) for 3 hr. The product obtained by dilution of the reaction mixture with water was insoluble in sodium bicarbonate. It then crystallised from alcohol in small needles (0.5 g.),m.p. 208°. IR in nujol : 1720 cm^{-1} (δ lactone) ; 865 cm^{-1} (furan ring breathing). UV in methanol : λ max 318 nm.

Analysis : Found : C, 71.62 ; H, 4.10 %

$C_{12}H_8O_3$ requires : C, 72.00 ; H, 4.00 %.

5-Methyl-6-carbomethoxy-7-formylcoumarin (LXVI) :

A solution of 5-methyl-6-hydroxy-7-formylcoumarin (1.0 g.) in dry acetone was refluxed with anhydrous potassium carbonate (3.0 g.) and ethyl bromoacetate (3 ml.) on a steam bath until the solution became colourless. The solid obtained on removal of acetone was treated with water. The separated product crystallised from acetic acid. M.p. 156°. Yield 0.6 g.

Analysis : Found : C, 62.01 ; H, 4.73 %

$C_{15}H_{14}O_4$ requires : C, 62.07 ; H, 4.83 %.

5-Methyl-6-carboxymethoxy-7-formylcoumarin (LXVII) :

The above ester (0.5 g.) was mixed with sodium hydroxide solution (15 ml.; 10 %) and kept for 24 hr. This was then diluted and acidified. The separated solid was extracted with sodium bicarbonate solution and the bicarbonate extract on acidification afforded the acid which crystallised from acetic acid. M.p. 202°. The analysis agreed with molecule of water.

Analysis : Found : C, 56.25 ; H, 4,27 %

$C_{13}H_{10}O_6.H_2O$ requires : C, 55.71 ; H, 4.29 %.

Attempted synthesis of 5-methylfuro(5',4' : 6,7)coumarin :

The above acid (0.2 g.) was heated with fused sodium acetate and acetic anhydride in an oil bath at 170-80° for 8 hr. After pouring the reaction mixture in water a product was obtained which was insoluble in sodium bicarbonate. Because of the low yield it could not be purified either by crystallisation or by chromatography.

7-Methylcoumarino(6,5 : 6',5')-α-pyrone (XC) :

6-Hydroxy-7-methyl-5-formylcoumarin (1.0 g.) was refluxed with sodium acetate (2.5 g.) and acetic anhydride (20 ml.) at 170-80° for 4 hr. The reaction mixture was poured in water and the solid obtained was washed with sodium bicarbonate solution and then distilled water. It crystallised from alcohol in short thick needles (0.6 g.), m.p. 290°.

Analysis : Found : C, 68.58 ; H, 3.71 %

$C_{13}H_8O_4$ requires : C, 68.49 ; H, 3.50 %.

5-Methylcoumarino(6,7 : 6',5')-α-pyrone (XCI) :

7-Formyl-6-hydroxy-5-methylcoumarin (0.5 g.) prepared as before (P.53) was heated with sodium acetate (1.5 g.) and acetic anhydride (10 ml.) in an oil bath at 170-80° for 12 hr. The reaction mixture was poured in water. The product separated was washed with sodium bicarbonate and then water. It separated from dilute acetic acid as fine powder (0.2 g.), m.p. 270°.

Analysis : Found : C, 67.97 ; H, 3.74 %

$C_{13}H_8O_4$ requires : C, 68.49 ; H, 3.50 %.

6-Acetyl-5-benzyloxy-4,7-dimethylcoumarin (XCIV) :

6-Acetyl-5-hydroxy-4,7-dimethylcoumarin (1.0 g.) was refluxed with benzoyl chloride (0.5 g.) and anhydrous potassium carbonate (4.0 g.) in dry acetone for 6 hr. The solid obtained on removal of acetone was washed with water and crystallised from dilute alcohol. M.p. 185°. Yield 0.7 g.

Analysis : Found : C, 71.50 ; H, 4.62 %

$C_{20}H_{16}O_5$: requires : C, 71.44 ; H, 4.76 %.

Synthesis of 2'-phenyl-4,7-dimethylcoumarino(5,6 : 6',5') γ-pyrone by Baker-Venkataraman transformation (XCV) :

A solution of the above benzoyloxy derivative (1.5 g.) in pyridine was mixed with powdered potassium hydroxide (10.0 g.). After keeping the reaction mixture at

room temperature overnight, hydrochloric acid (1:1) in ice-cold water was added. The product separated was insoluble in sodium hydroxide and was found to be 2'-phenyl -4,7-dimethyl-γ-pyrono(6',5' : 5,6)coumarin. The intermediate 6-benzoylacetyl-5-hydroxy-4,7-dimethylcoumarin could not be isolated. M.p. 275°. It was crystallised from acetic acid.

Analysis : Found : C, 75.02 ; H, 3.96 %

$C_{20}H_{14}O_4$ requires : C, 75.44 ; H, 4.40 %.

IR in nujol 1740 $cm.^{-1}$ (δ lactone) ; 1645 $cm.^{-1}$ (γpyrone).

3'-Acetyl-2',4,7-trimethylcoumarino(5,6 : 6',5')-γ-pyrone (XCVI) :

5-Hydroxy-6-acetyl-4,7-dimethylcoumarin (1.0 g.) was heated with fused sodium acetate (3.0 g.) and acetic anhydride (20 ml.) in an oil bath at 180-90° for 12 hr. The solid obtained on dilution of the mixture with water was washed with sodium bicarbonate solution. It crystallised from glacial acetic acid in tiny needles (0.5 g.), m.p. 272°.

Analysis : Found : C, 68.62 ; H, 4.69 %

$C_{17}H_{14}O_5$ requires : C, 69.30 ; H, 4.69 %.

Attempted deacetylation :

The above coumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 10 ml.) for 2 hr. The product obtained on acidification of the reaction mixture crystallised from dilute acetic acid into needles. M.p. 272°. Mixed m.p. with the original chromonylcoumarin was not depressed.

Attempted synthesis of 2',4,7-trimethylcoumarino(5,6 : 6',5')--γ-pyrone (XCVII) :

A solution of 5-hydroxy-4,7-dimethylcoumarin (1.0 g.) in diphenyl ether (10 ml.) was refluxed with ethyl acetoacetate (1.0 g.) for 8 hr. The product obtained on removal of the solvent was the original coumarin.

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