CHAPTER III

STUDIES ON THE SYNTHESIS OF COUMARINO-α-PYRONES AND FUROCOUMARINS

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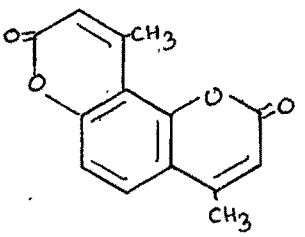
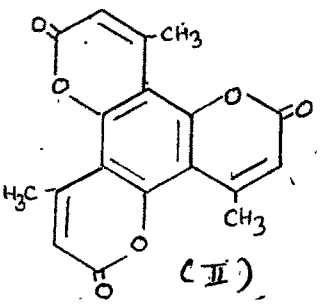
Coumarino-α-pyrones

Hantzsch and Zurcher (1) condensed resorcinol and phloroglucinol with 2 and 3 moles of ethyl acetoacetatei in the presence of sulphuric acid and obtained coumarino-α-pyrones (I) and (II) respectively in poor yields.

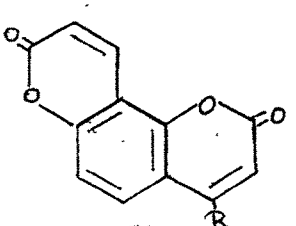


(I)

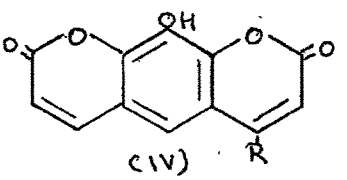


(II)

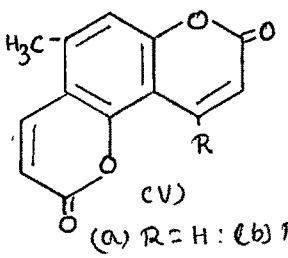
Sen and Chakravarti (2) condensed umbelliferone, 4-methylumbelliferone, daphnetin, 4-methyldaphnetin, homoumbelliferone and 4-methylumbelliferone with malic acid in the presence of sulphuric acid and obtained coumarino-7,8-α-pyrone (III a), 4-methylcoumarino-7,8-α-pyrone (III b), 8-hydroxycoumarino-7,6-α-pyrone (IV a), 4-methyl-8-hydroxy-coumarino-7,6-α-pyrone (IV b), 7-methylcoumarino-5,6-α-pyrone (V a), and 4,7-dimethylcoumarino-5,6-α-pyrone (V b) respectively.



(III)
(a). R=H ; (b) R=CH$_3$

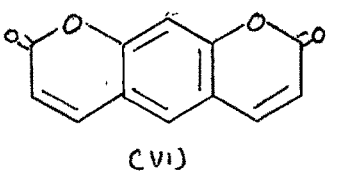


(IV)
(a). R=H ; (b). R=CH$_3$.



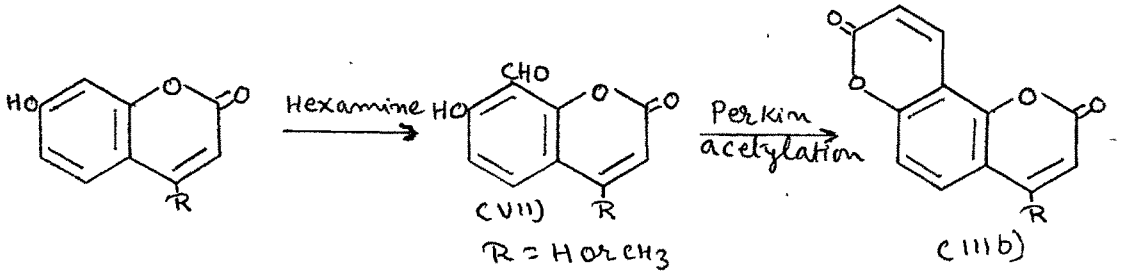
(V)

(a) R = H : (b) R = CH_3.



(VI)

They however did not prove the structures of the coumarino-α-pyrones formed. Rangaswami and Seshadri (3) showed that when umbelliferone is condansed with malic acid both the angular (III a) and the linear (VI) coumarino-α-pyrones are formed but the latter is obtained in poor yield. Under the same experimental conditions 4-methylumbelliferone gives only the angular coumarino-α-pyrone (III b). They proved the structure of coumarino-7,8-α-pyrone by its synthesis from 7-hydroxy-8-formylcoumarin (VII) by Perkin reaction. In a similar way the constitution of 4-methylcoumarino-7,8-α-pyrone was also proved.

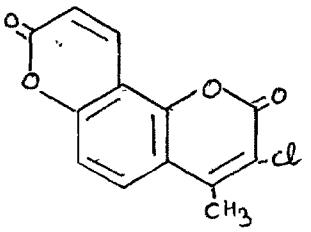


(VII) R = H or CH_3

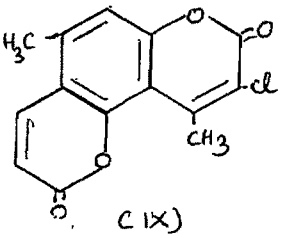
(III b)

Biswas (4) condensed 7-hydroxy-3-chloro-4-methyl-, 5-hydroxy-3-chloro-4,7-dimethyl-, and 7,8-dihydroxy-3-chloro-4-methylcoumarin with malic acid and obtained the corresponding 3-chloro-4-methylcoumarino-7,8-α-pyrone(VIII),

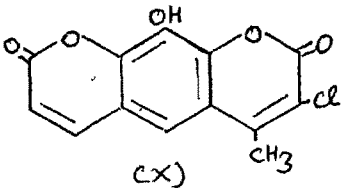
3-chloro-4,7-dimethylcoumarino-5,6-α-pyrone (IX) and 3-chloro-4-methyl-8-hydroxycoumarino-7,6-α-pyrone (X).



(VIII)

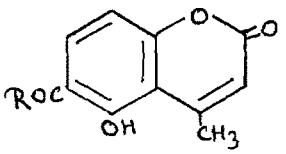


(IX)



(X)

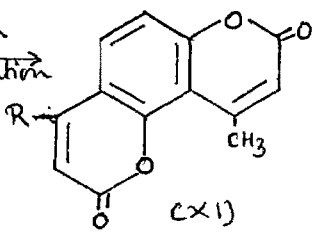
Shah and coworkers (5) synthesised several coumarino-α-pyrones (XI) and coumarino-γ-pyrones (XII) by subjecting 6-acyl-5-hydroxycoumarins (XIII) to Kostanecki-Robinson acylation.



(XIII)

R = Alkyl or Aryl.

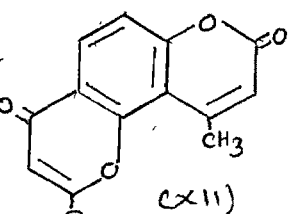
K-R acetylation



(XI)

R = Aryl

or

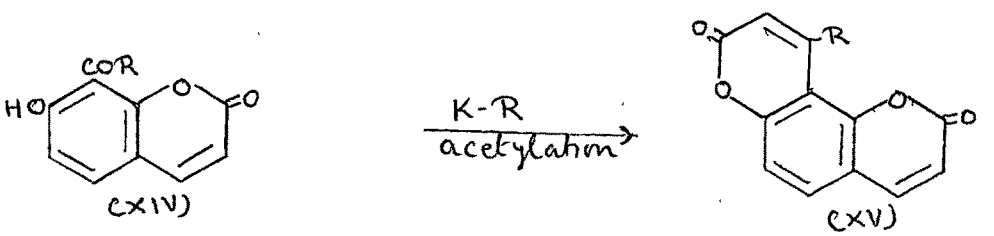


(XII)

R = Alkyl

Shah and Contractor (6) carried out the Kostanecki-Robinson acylation of 7-hydroxy-8-propionyl-(XIV a) and

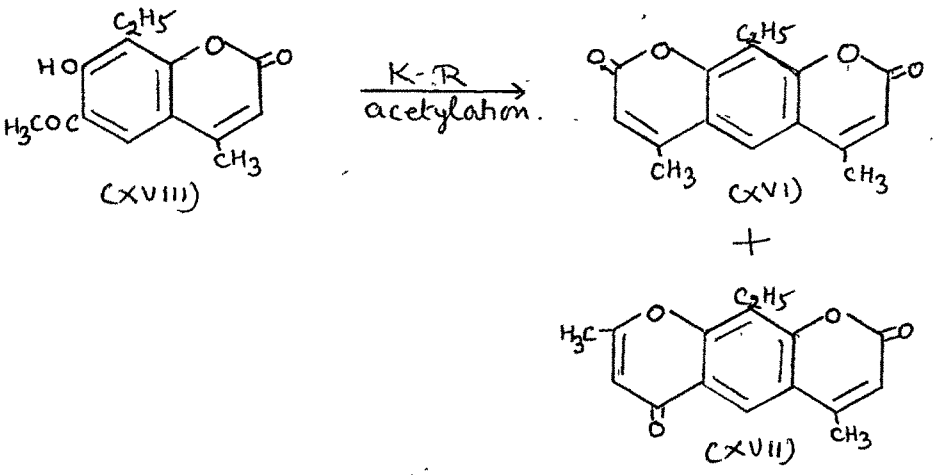
7-hydroxy-8-butyrylcoumarin (XIV b) and assigned the 4'-ethylcoumarino-7,8-α-pyrone (XV a) and 4'-propylcoumarino-7,8-α-pyrone (XV b) structures to the products obtained.



(XIV)
(a). R = C_2H_5
(b). R = C_3H_7

(XV)
(a) R = C_2H_5
(b) R = C_3H_7

Limaye and Ghate (7) obtained 4,4'-dimethyl-8-ethylcoumarino-7,6-α-pyrone (XVI) and 2',4-dimethyl-8-ethyl-3'-acetylcoumarino-γ- pyrone (XVII) from 7-hydroxy-8-ethyl-6-acetyl-4-methylcoumarin (XVIII) by Kostanecki-Robinson acetylation.

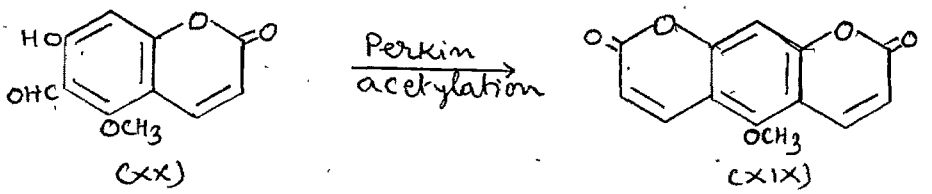


(XVIII)

(XVI)

(XVII)

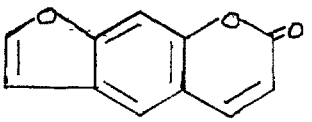
Mustafa, Štrkovsky and Zaki (8) prepared 5-methoxy-coumarino-7,6-α-pyrone(XIX) by Perkin acetylation of apoxanthoxyletin (XX).



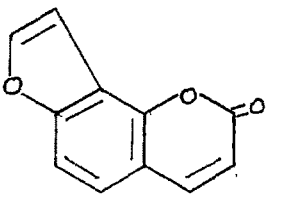
(XX) (XIX)

Furocoumarins

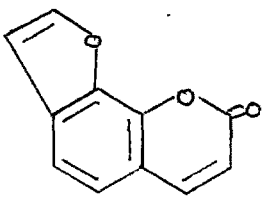
If the furan ring is built on a suitably substituted coumarin derivative, it leads to the synthesis of furocoumarins. Alternately, one can start with an appropriate coumarone derivative and build up the α-pyrone ring on it. Five isomeric forms of furocoumarins are found in the literature.



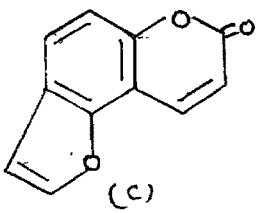
(A)



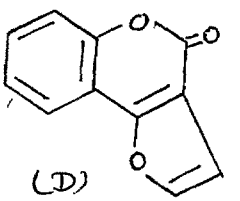
(B)



(E)



(C)



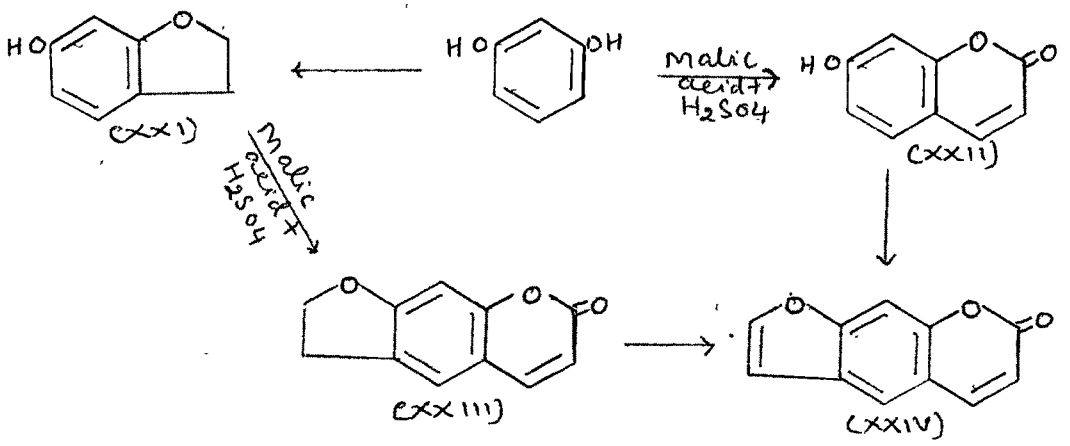
(D)

In recent years furocoumarins of the type (A) i.e. psoralene type have received considerable attention on account of their therapeutic properties. Xanthotoxin or

9-methoxypsoralene is a fish poison (9) but it is relatively non-toxic to mammals. Schönberg and Latif (10) observed that it possesses molluscicidal activity. It was demonstrated by Elwi (11) that it produces fatty degeneration of liver and adrenal hemorrhage 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 leukodermia (12). 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-burn (13). There is some evidence that xanthotoxin under certain conditions may be carcinogenic (14).

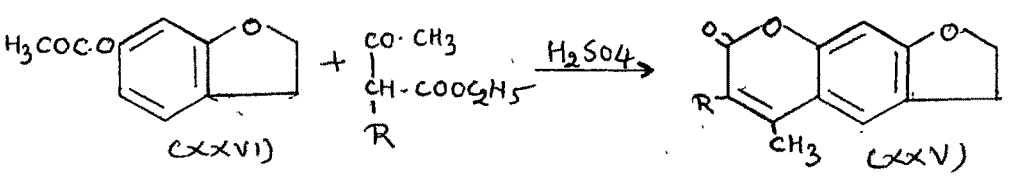
Pathak and Fellman (15) have recently studied the activating and fluorescent wave-lengths of 37 furocoumarins and their biological photosensitising action was also investigated. Furocoumarins which induced definite photosensitised erythermal response on mammalian skin showed activation peaks in the region of 340-380 mμ and concomitantly 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.

The methods of synthesis of furocoumarins are briefly reviewed here. Two routes are available for the synthesis of psoralenes, either (a) via conversion to 6-hydroxycoumaran (XXI) or (b) through umbelliferone (XXII)



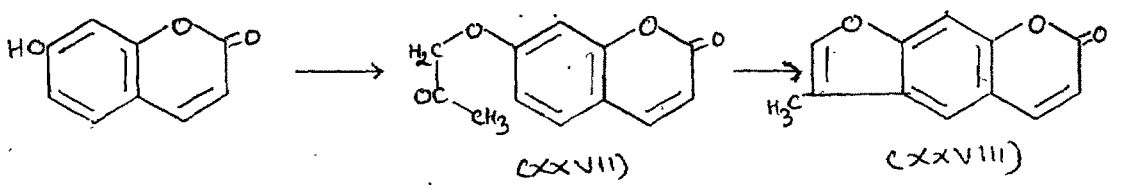
Spath and Pailer (16) carried out the condensation of 6-hydroxycoumaran with malic acid in the presence of conc. sulphuric acid and obtained 2,3-dihydropsoralene (XXIII) which on dehydrogenation gave psoralene(XXIV).

Later on Horning and Reisner (17) prepared different 5-substituted -2,3-dihydropsoralenes (XXV) by condensing 6-acetoxycoumaran (XXVI) with a variety of β-ketonic esters in the presence of sulphuric acid. This reaction has been further extended by Erse and Christensen (18) to obtain 6-alkyl-2,3-dihydro-5-methylpsoralenes by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxycoumaran.



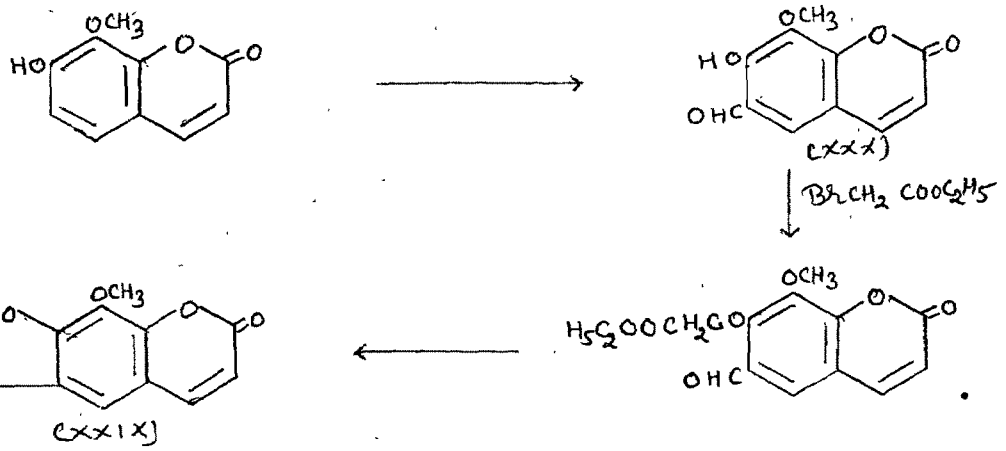
R = H or Alkyl

Ray, Shilooja and Vaid (19) have approached the problem of furocoumarin synthesis by starting with umbelliferone. In this procedure, they carried out the cyclisation of 7-acetonyloxycoumarin (XXVII), obtained by treating umbelliferone with chloracetone, in the presence of sodium ethoxide to 3-methylpsoralene (XXVIII).



(XXVII) (XXVIII)

Rodighiero and Antonello (20) synthesised xanthotoxin (XXIX) by first preparing 7-hydroxy-8-methoxy-6-formylcoumarin (XXX) and then treating it with ethyl bromoacetate, followed by hydrolysis, cyclization and decarboxylation.

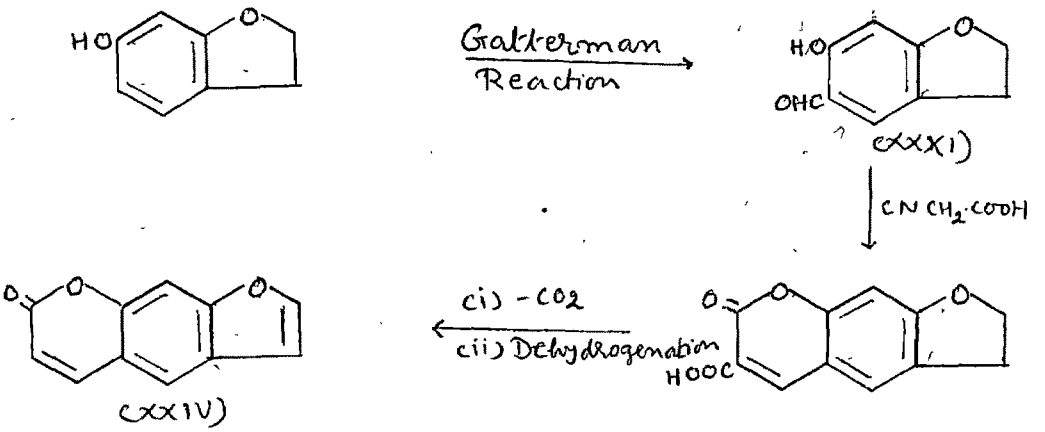


(XXX)

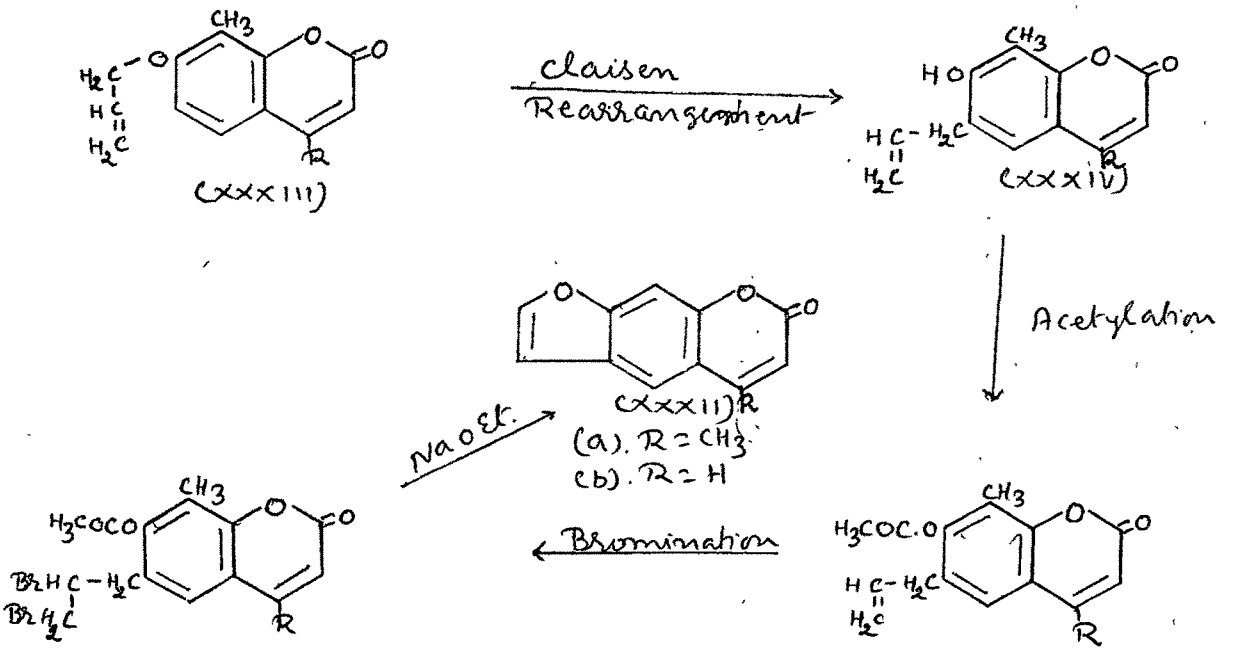
(XXIX)

Limaye and Gangal (21) synthesised 3,4'-dimethyl-7,6-furocoumarin from 7-hydroxy-6-acetyl-4-methylcoumarin using the same procedure.

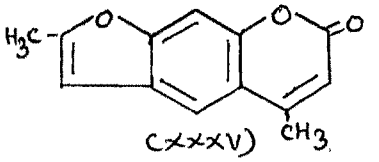
Robinson et al (22) synthesised psorelene by first subjecting 6-hydroxycoumaran (XXI) to Gatterman aldehyde synthesis and then condensing the 6-hydroxy-5-formylcoumaran (XXXI) with cyanoacetic acid followed by decarboxylation and dehydrogenation.



Recently Kaufman (23) has prepared 4,5',8-trimethylpsoralene (XXXII a) and 5',8-dimethylpsoralene (XXXII b) by first carrying out the Claisen rearrangement of 7-allyloxy-4,8-dimethyl-(XXXIII a) and 7-allyloxy-8-methylcoumarin (XXXIII b) to 7-hydroxy-6-allyl-4,8-dimethyl-(XXXIV a) and 7-hydroxy-6-allyl-8-methylcoumarin (XXXIV b) respecively. These were then acetylated, brominated and cyclised to obtain psoralene derivatives.

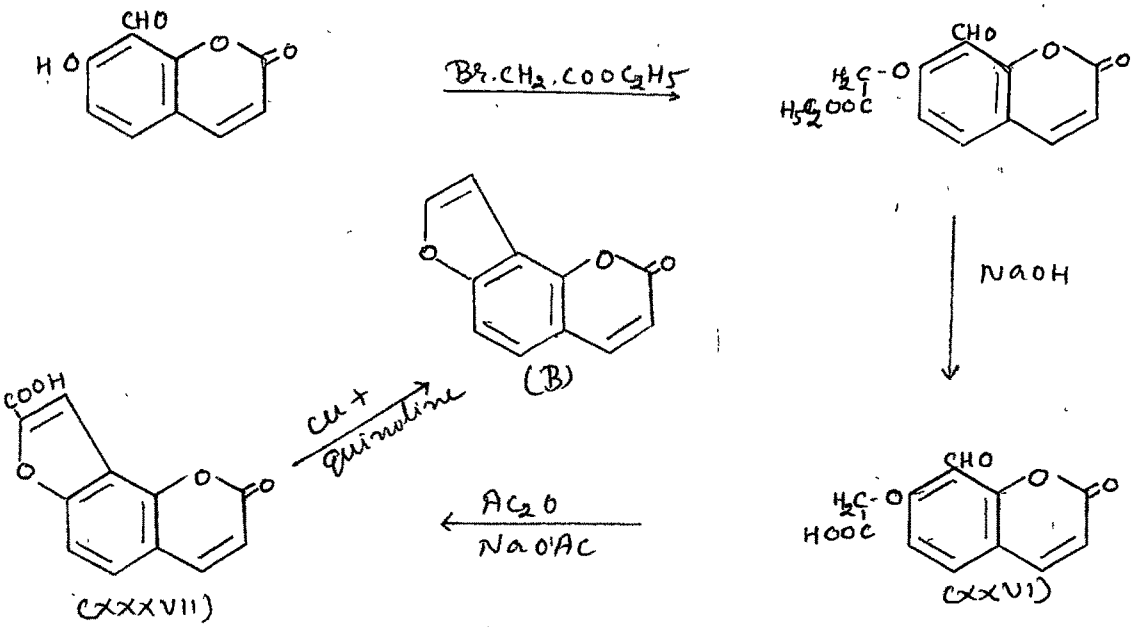


Using a similar procedure Kaufman synthesised 4,5'-dimethylpsoralene (XXXV).



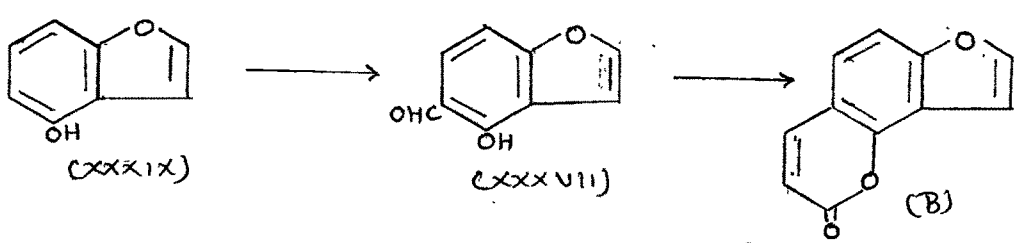
Angelicin is a naturally occuring furocoumarin of type (B) and is synthesised by Spath and Pailer(24) by condensing sodium salt of 8-formylumbelliferone with iodoacetic ester under pressure and the product obtained subjected to hydrolysis followed by cyclisation. Naik and Thakore (25) repeated the whole process using ethyl bromo-acetate in acetone in the first step. They observed that the melting point of 7-(8-formylcoumarinoxy) acetic acid (XXXVI) was 248-49^{0} instead of 178-81^{0} as reported by Spath and Pailer (24). They also observed that on cyclisation of this

product,angelicin-2'-carboxylic acid (XXXVII) which was not isolated by Spath and Pailer was obtained and it underwent decarboxylation when heated with copper and quinoline to angelicin.

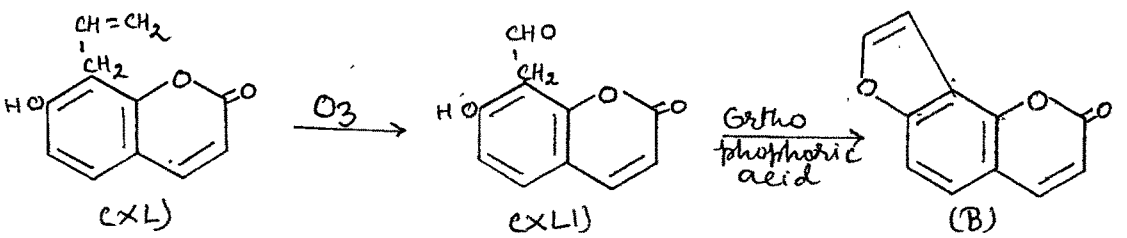


Using the above method Shah and Shah (26) synthesised furano-3'-methyl-4',5',7,8-coumarin from 7-hydroxy-8-acetyl-coumarin.

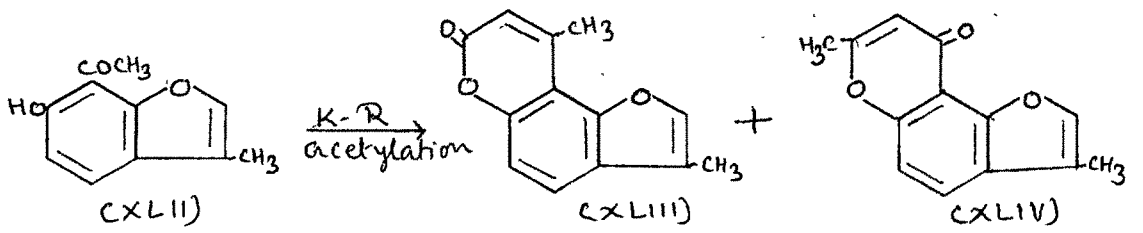
Limaye (27) synthesised angelicin by preparing 4-hydroxy-5-formylcoumarine(XXXVIII) from 4-hydroxycoumarine (XXXIX) and then subjecting it to Perkin reaction.



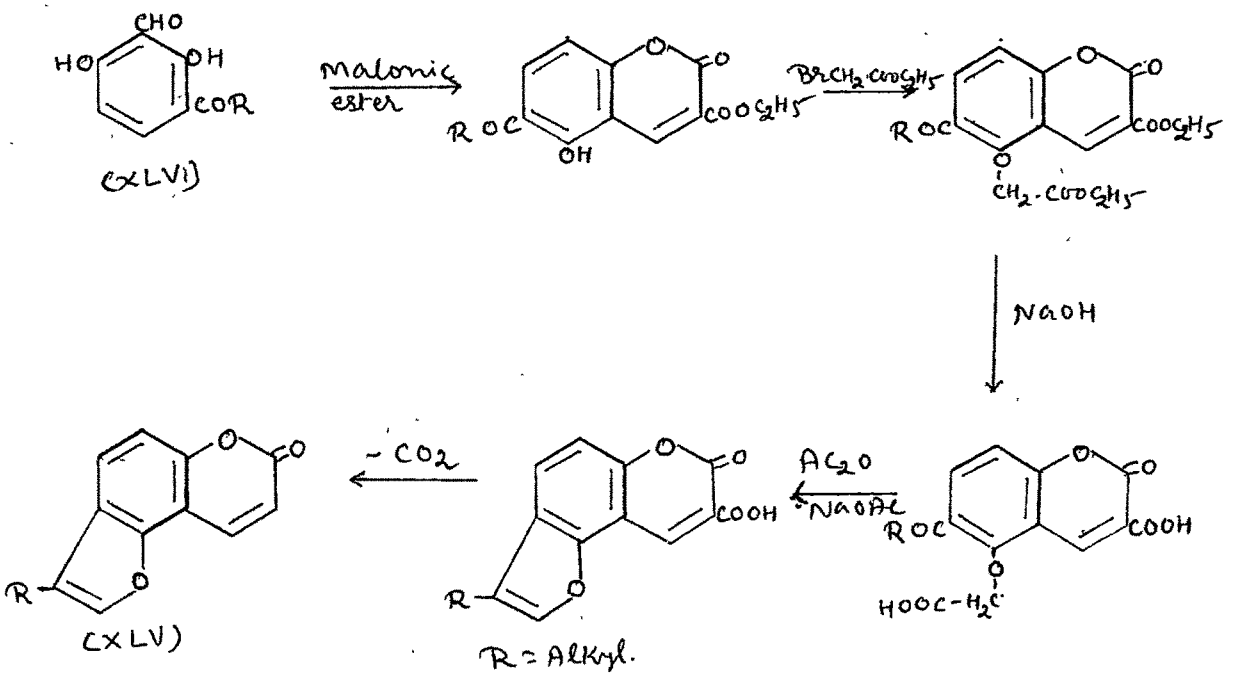
Aneja, Mukerjee and Seshadri (28) synthesised angelicin by subjecting first 7-hydroxy-8-allylcoumarin (XL) to ozonolysis and subsequent cyclisation of 7-hydroxycoumarin 8-acetaldehyde (XLI) with ortho phosphoric acid.



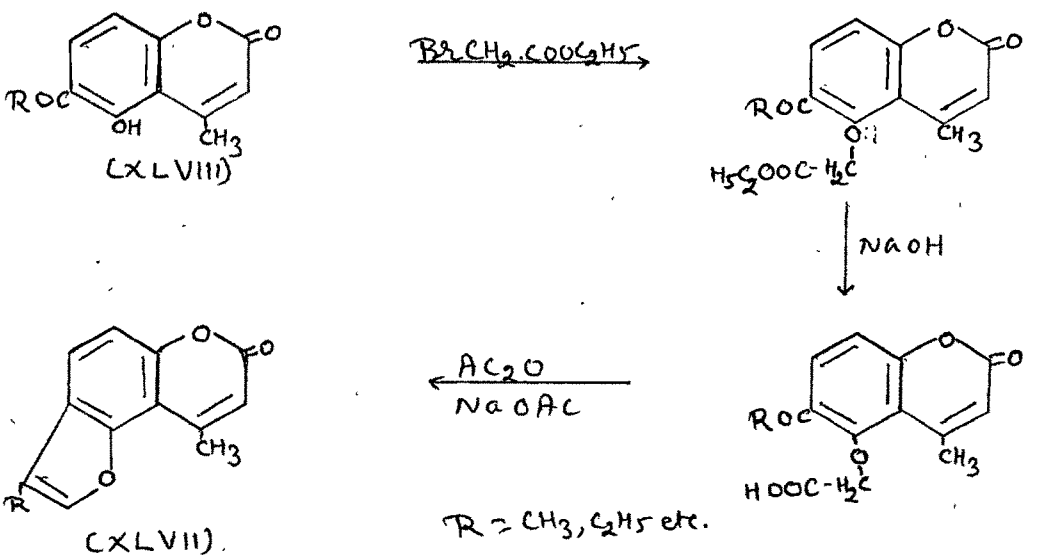
Furocoumarins of type (C) have been synthesised by several workers. Limaye and Sathe (29) subjected 6-hydroxy-7-acetyl-3-methylcoumarone (XLII) to Kostanecki-Robinson acetylation and obtained furo-3',4-dimethyl-4',5',5,6-coumarin (XLIII) in poor yield along with furo-2,3'-dimethyl-4',5',5,6-chromone (XLIV).



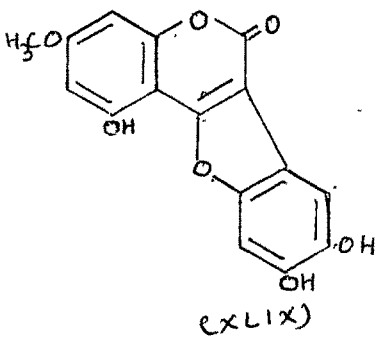
Shah and Shah (30) synthesised 3'-alkyl-furo-4',5',5,6-coumarin (XLV) by first condensing 2,4-dihydroxy-3-formylacetophenone (XLVI) with malonic ester and then carrying out the condensation with ethyl bromoacetate followed by hydrolysis, subsequent cyclisation and decarboxylation.



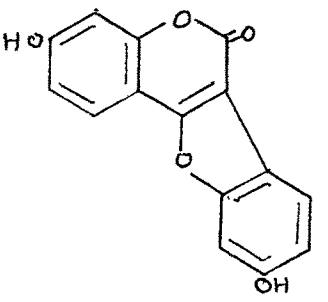
Chudger and Shah (31) synthesised several 3'-alkyl-furo-4',5',5,6-4-methylcoumarin (XLVII) by condensing 5-hydroxy-6-acyl-4-methylcoumarin (XLVIII) with ethyl bromo-acetate followed by hydrolysis and subsequent cyclisation.



Furocoumarins of type (D) have recently assumed great importance as they occur in nature and also possess estrogenic properties. For example, Govindachari et al (32) found that Wedelolactone isolated from Wedelia Calendulacea had the structure (XLIX).



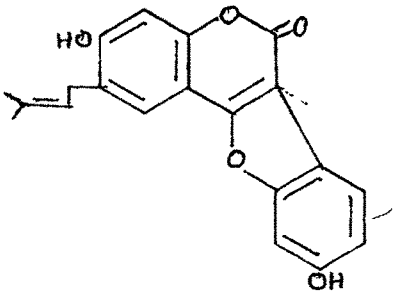
(XLIX)



(L)

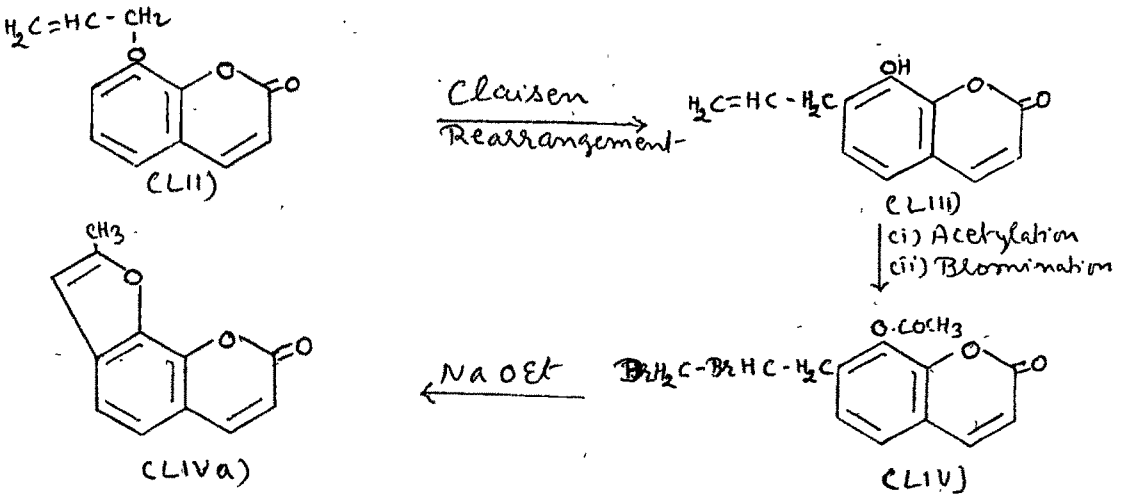
Further, Blickoff, Booth and their associates (33) who isolated the estrogen coumestrol from ladinoclover and alfalfa found that it had the structure (L).

Recently Khastgir, Duttagupta and Sengupta (34) have isolated a phenolic coumarin-psoralidin from Psoralea Corylifolia and established its structure as 6-(3-methylbut-2-enyl)-coumestrol (LI).



(LI)

Furocoumarin of type (E) has been recently synthesised by Kaufman and Russey (35) . They carried out the Claisen rearrangement of 8-allyloxycoumarin (LII) and obtained 7-allyl-8-hydroxycoumarin (LIII), the acetyl derivative of which was brominated. This product (LIV) underwent cyclisation to 2'-methyl-furo-4',5',8,7-coumarin (LIVa) when refluxed with sodium ethoxide in absolute ethanol.

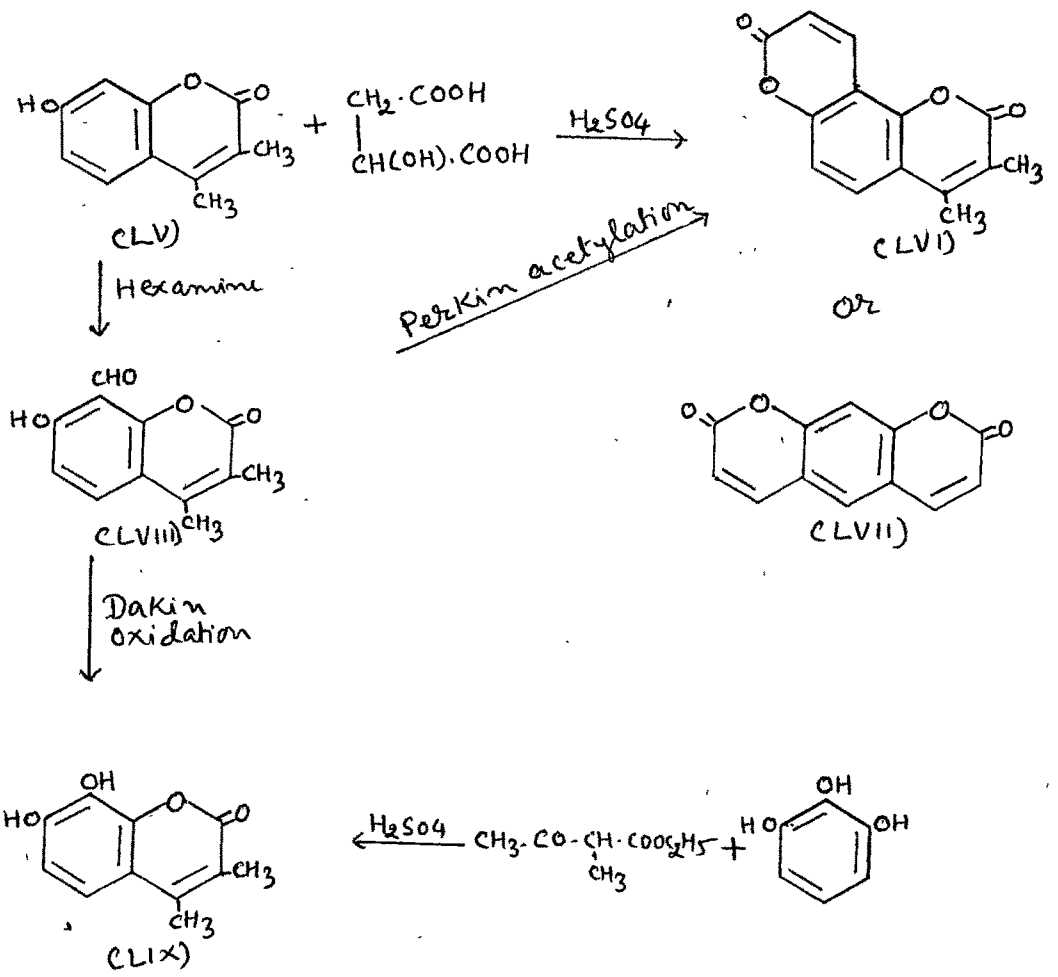


(LII) (LIII) (LIV) (LIVa)

The present work deals with the syntheses of some coumarino-α-pyrones and furocoumarins.

Pechmann condensation of 7-hydroxy-3,4-dimethylcoumarin with malic acid : 3,4-dimethylcoumarino-7,8-α-pyrone

7-Hydroxy-3,4-dimethylcoumarin (LV) prepared according to Pechmann and Duisberg (36) was condensed with malic acid in the presence of sulphuric acid. The product was assigned the structure: 3,4-dimethylcoumarino-7,8-α-pyrone (LVI) and not the linear 3,4-dimethylcoumarino-7,6-α-pyrone (LVII) on the basis of the following series of reactions.



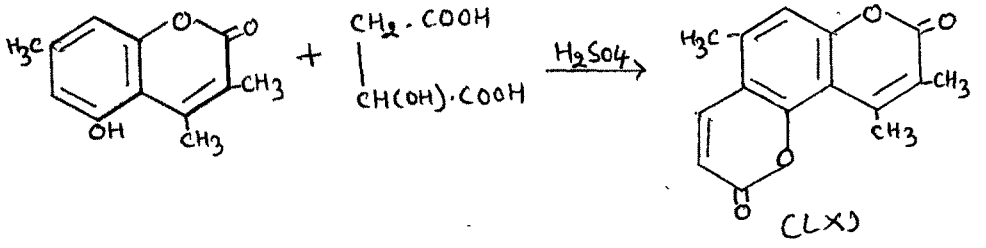
7-Hydroxy-3,4-dimethylcoumarin was formylated with hexamine when 8-formyl-7-hydroxy-3,4-dimethylcoumarin(LVIII)

was obtained which on Dakin oxidation with hydrogen peroxide gave the 7,8-dihydroxy-3,4-dimethylcoumarin (LIX) identical with the product obtained from the condensation of pyragallol with ethyl-α-methylacetoacetate in the presence of sulphuric acid.

7-Hydroxy-8-formyl-3,4-dimethylcoumarin was then subjected to Perkin acetylation which gave a product identical with 3,4-dimethylcoumarino-7,8-α-pyrone obtained by the Pechmann condensation of 7-hydroxy-3,4-dimethylcoumarin with malic acid.

Pechmann condensation of 5-hydroxy-3,4,7-trimethylcoumarin with malic acid : 3,4,7-Trimethylcoumarino-5,6-α-pyrone

5-Hydroxy-3,4,7-trimethylcoumarin prepared by the condensation of orcinol with ethyl-α-methylacetoacetate according to Chakravarti (37) was condensed with malic acid in the presence of sulphuric acid. The product obtained is assigned 3,4,7-trimethylcoumarino-5,6-α-pyrone (LX) structure.

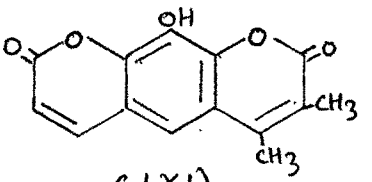


(LX)

Pechmann condensation of 7,8-dihydroxy-3,4-dimethylcoumarin with malic acid : 3,4-Dimethyl-8-hydroxycoumarino-7,6-α-pyrone

7,8-Dihydroxy-3,4-dimethylcoumarin prepared according

to Canter et al. (38) was condensed with malic acid in the presence of concentrated sulphuric acid. The product obtained is assigned 3,4-dimethyl-8-hydroxycoumarino-7,6-α-pyrone (LXI) structure.



(LXI)

Attempted Pechmann condensation of 7-hydroxy-4,6-dimethylcoumarin and 7-hydroxy-4,8-dimethylcoumarin with malic acid

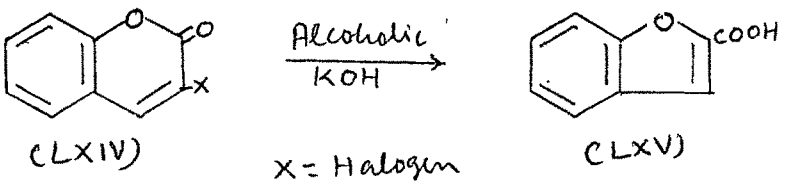
As 7-hydroxy-3,4-dimethylcoumarin condensed with malic acid, it was thought of interest to study the effect of a methyl group in the 6- and the 8-position of the 7-hydroxy-4-methylcoumarin. 7-Hydroxy-4,6-dimethylcoumarin (39) however, did not condense with malic acid. 7-Hydroxy-4,8-dimethylcoumarin (40) also did not condense with malic acid. Original coumarins were obtained back in both the cases. These results indicate that the methyl group in the 6- and 8-position hinders the course of Pechmann reaction.

Pechmann condensation of 7-hydroxy-3-bromo-4-methylcoumarin with malic acid : 3-Bromo-4-methylcoumarino-7,8-α-pyrone

7-Hydroxy-3-bromo-4-methylcoumarin (LXII) prepared according to Dalvi and Sethna (41) was condensed with malic acid in the presence of sulphuric acid. The product obtained was assigned the 3-bromo-4-methylcoumarino-7,8-α-pyrone(LXIII)

structure, as it was identical with the product obtained on the bromination of 4-methylcoumarino-7,8-α-pyrone (III b) with bromine in acetic acid.

It has been observed by several workers that when 3-halogen substituted coumarin derivatives (LXIV) are refluxed with alcoholic potassium hydroxide or sodium hydroxide solution the corresponding coumarilic acids (LXV) are obtained.

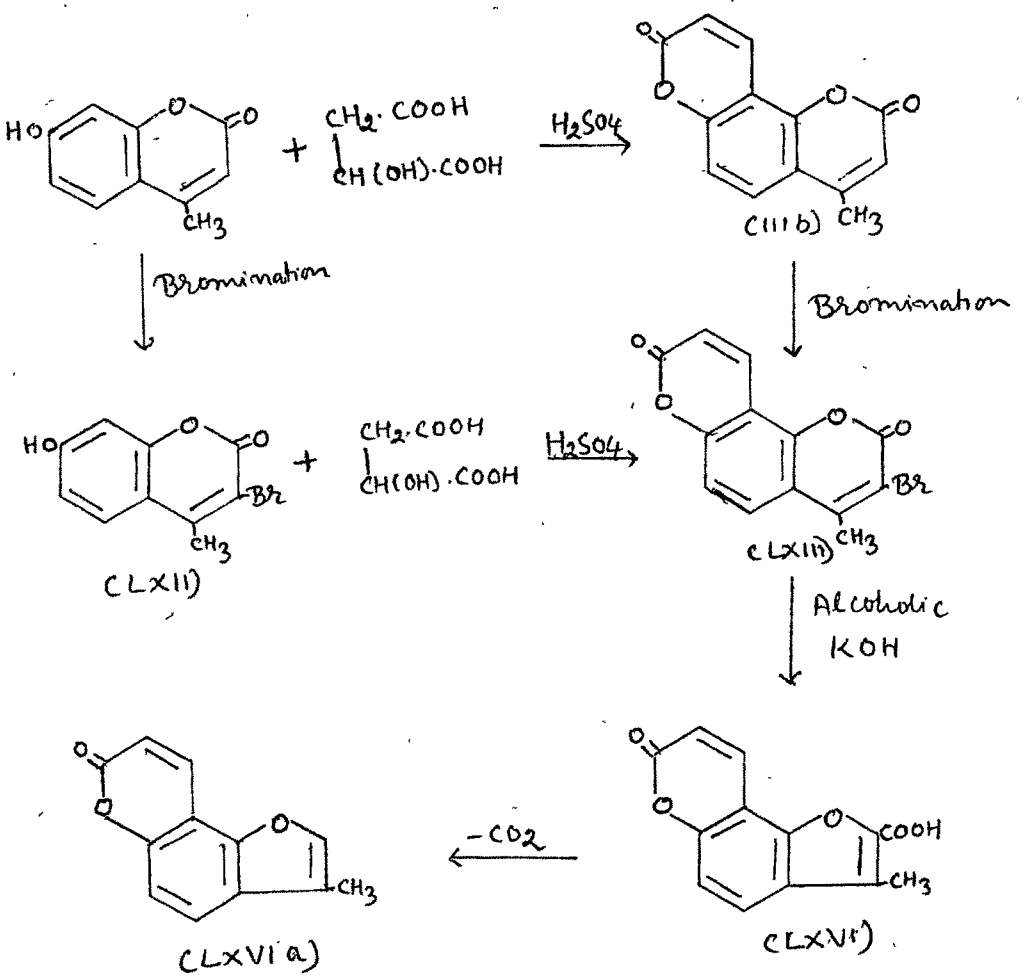


It was therefore thought of interest to study the hydrolysis of 3-halogen substituted coumarino-α-pyrones with alcoholic potassium hydroxide solution with a view to synthesise the corresponding furocoumarins.

Furo-3'-methyl-4',5',5,6-coumarin-2"-carboxylic acid and furo-3'-methyl-4',5',5,6-coumarin

The above 3-bromo-4-methylcoumarino-7,8-α-pyrone was refluxed with 10 % potassium hydroxide solution. On acidification, furo-3'-methyl-4',5',5,6-coumarin-2'-carboxylic acid (LXVI) was obtained. This on decarboxylation with quinoline and copper powder afforded furo-3'-methyl-4',5',5,6-coumarin (XLVI a). The same furocoumarin was prepared previously by Shah and Shah (30). This is a new approach to the synthesis of furocoumarins.

The above series of reactions are represented in the following chart.



Attempted Pechmann reaction of 7-hydroxy-3,6-dibromo-4-methylcoumarin and 7-hydroxy-3,8-dibromo-4-methylcoumarin with malic acid

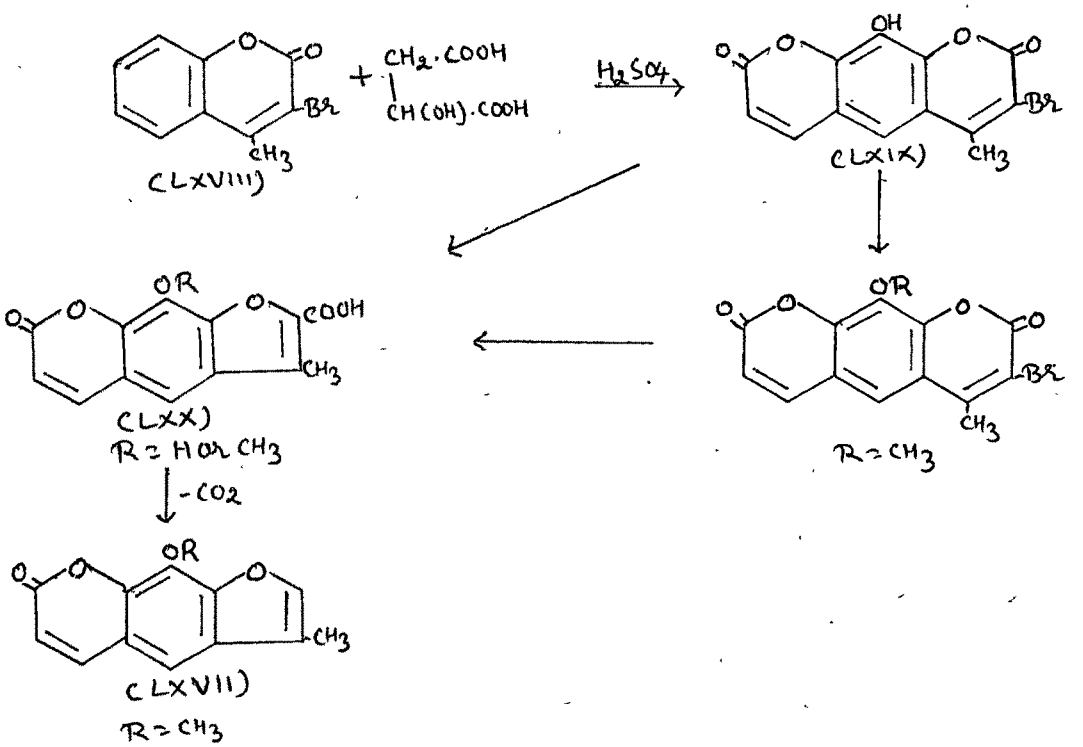
In view of the above synthesis of furocoumarin it was thought of interest to study the Pechmann reaction on 7-hydroxy-3,6-dibromo-4-methylcoumarin and 7-hydroxy-3,8-dibromo-4-methylcoumarin (41) and subsequent hydrolysis and

of the product formed
decarboxylation to bromo furocoumarins. But the Pechmann reaction of the above coumarins with malic acid in the presence of sulphuric acid did not succeed.

Attempted synthesis of 3-methylxanthotoxin

Pechmann condensation of 7,8-dihydroxy-3-bromo-4-methylcoumarin with malic acid : 3-Bromo-4-methyl-8-hydroxy-coumarino-7,6-α-pyrone

It was thought of interest to see if the above reaction could be utilised to synthesise 3-methylxanthotoxin (LXVII), a member of the psoralene group of furocoumarins according to the following scheme.



CLXVIII)

CLXIX)

CLXX)
R = H or CH3

R = CH3

CLXVII)
R = CH3

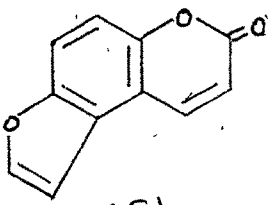
7,8-Dihydroxy-3-bromo-4-methylcoumarin (LXVIII) prepared according to Sakai and Kato (42) was condensed with malic acid in the presence of sulphuric acid and the 3-bromo-4-

methyl-8-hydroxycoumarino-7,6-α-pyrone (LXIX) was obtained in good yield. It was insoluble in common organic solvent and possessed m.p. > 360°. Attempt to methylate this compound by refluxing it in either acetone or benzene with dimethyl sulphate met with failure. Attempt to methylate it with dimethyl sulphate and alkali in cold as well as on a steam-bath also failed.

Attempts to convert it to 3-methylxanthotoxol-2'-carboxylic acid (LXX) by the action of alcoholic potassium hydroxide or with 5 % sodium carbonate solution gave black tarry mass.

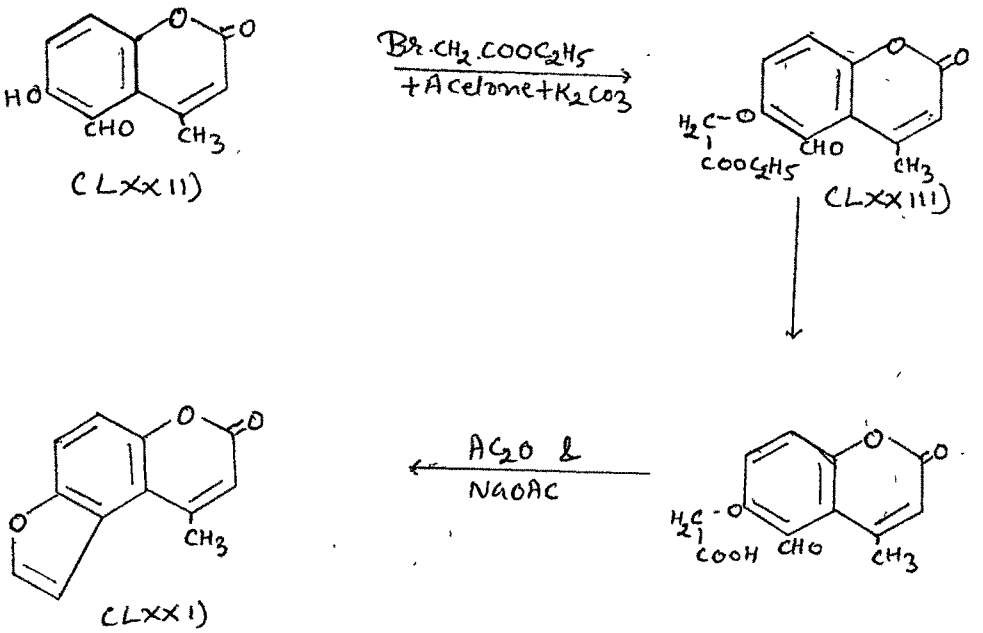
Attempted synthesis of 4-methyl-furo-4',5',6,5-coumarin

On reviewing the literature it was found that the following type of furocoumarin (F) is not still synthesised.



(F)

Attempt was therefore made to synthesise the its 4-methyl-analogue (LXXI) according to the following scheme.



6-Hydroxy-5-formyl-4-methylcoumarin (LXXII) was prepared by subjecting 6-hydroxy-4-methylcoumarin to the action of hexamine according to Naik and Thakore (43). The 5-formyl derivative on condensation with ethyl bromoacetate in acetone solution however, gave a deep yellow paste which did not give any pure product on treatment with common organic solvents. It was then chromatographed over alumina whereby pure 6-(5-formylcoumarinoxy) acetic ester (LXXIII) was isolated. Attempts to hydrolyse it with hot and cold sodium hydroxide solution gave a polymerised product, m.p. > 400° which gave negative reactions for an aldehyde group. Hydrolysis with sulphuric acid also gave an unworkable mass. It was heated with acetic anhydride and sodium acetate to obtain directly the furocoumarin but it also met with failure.

Attempted reactions on coumarino-α-pyrones

On reviewing the literature it was found that no reactions have been tried on coumarino-α-pyrones. In the present work 4-methylcoumarino-7,8-α-pyrone was subjected to bromination and 3-bromo-4-methylcoumarino-7,8-α-pyrone was obtained as seen by direct comparison with the product obtained on the Pechmann condensation of 7-hydroxy-3-bromo-4-methylcoumarin(P. 92). Attempts to brominate it further by using excess of bromine in acetic acid or liquid bromine did not succeed.

Attempt to iodinate 4-methylcoumarino-7,8-α-pyrone with either iodine and iodic acid or under different experimental condition also did not succeed. Only the original coumarino-α-pyrone was obtained.

Attempts to chloromethylate 4-methylcoumarino-7,8-α-pyrone by passing dry hydrogen chloride gas in its solution in glacial acetic acid containing paraformaldehyde met with failure. The use of anhydrous zinc chloride or concentrated sulphuric acid as catalysts did not bring about the condensation, the original coumarino-α-pyrone was recovered.

Friedel-Crafts acetylation of 4-methylcoumarino-7,8-α-pyrone with acetic anhydride in the presence of anhydrous aluminium chloride with or without nitrobenzene by heating at 120° or 200° for 4 hr. were tried but only the original coumarino-α-pyrone was obtained.

Elbs Persulphate Oxidation of 4-methylcoumarino-7,8-α-pyrone also failed, only unworkable black tarry product was obtained.

Attempted Pechmann condensation of 7-hydroxy-2-methylchromone,7-hydroxyflavone,7-hydroxy-6-acetyl-4-methyl-, 7-hydroxy-6-nitro-4-methyl- and 7-hydroxy-6-carbomethoxy-4-methylcoumarin with malic acid

With a view to synthesise chromono-α-pyrones and furochromones, this reaction was extended to 7-hydroxy-2-methylchromone and 7-hydroxyflavone. When 7-hydroxy-2-methylchromone and 7-hydroxyflavone were condensed with malic acid in the presence of sulphuric acid, only the original compounds were recovered.

Pechmann condensation of 7-hydroxy-6-acetyl-4-methyl-, 7-hydroxy-6-nitro-4-methyl- and 7-hydroxy-6-carbomethoxy-4-methylcoumarin with malic acid also met with failure.

Attempted condensation of 7-hydroxy-4-methylcoumarin with ethyl acetoacetate in the presence of phosphorus pentoxide

It has been observed that only the reactive phenols condense with malic acid yielding coumarin derivatives. 7-hydroxy-4-methylcoumarin reacts with malic acid to give good yield of 4-methylcoumarino-7,8-α-pyrone but it gives poor yield of 4,4'-dimethylcoumarino-7,8-α-pyrone when reacted with ethyl acetoacetate in the presence of sulphuric acid. This is a peaculiar case where 7-hydroxy-4-methylcoumarin behaves as a reactive phenol in the condensation with malic acid but behaves as a less reactive phenol in the condensation with ethyl acetoacetate. Condensation of 7-hydroxy-4-methylcoumarin with ethyl acetoacetate in the presence of phosphorus

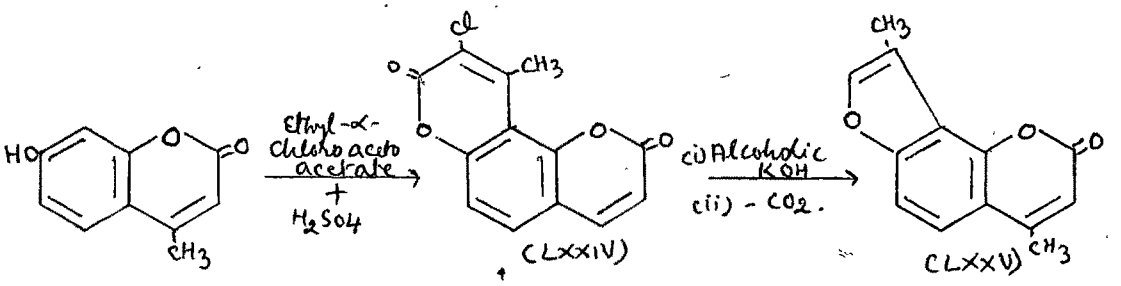
pentoxide was then tried but it met with failure. Attempt was also made to carry out the thermal condensation of 7-hydroxy-4-methylcoumarin with ethyl acetoacetate in refluxing diphenyl ether but it also failed.

Attempted Pechmann condensations of 5-hydroxy-4-methylcoumarin with malic acid and ethyl acetoacetate

5-Hydroxy-4-methylcoumarin prepared according to Sethna, Shah and Shah (44) was condensed with malic acid in the presence of sulphuric acid but only original coumarin was recovered. Attempts were also made to condense it with ethyl acetoacetate in the presence of sulphuric acid, phosphorus pentoxide or in refluxing diphenyl ether but all met with failure.

Attempted Pechmann condensation of 7-hydroxy-4-methylcoumarin with ethyl-α-chloroacetoacetate

Application of the above reaction to the synthesis of furocoumarins of angelicin group was next tried. Attempt was made to synthesise 3'-chloro-4,4'-dimethylcoumarino-7,8-α-pyrone (LXXIV), an intermediate for the synthesis of 3',4-dimethylangelicin (LXXV) by the condensation of ethyl-α-chloroacetoacetate with 7-hydroxy-4-methylcoumarin in the presence of sulphuric acid according to the Scheme given below but the reaction did not take place and only the original coumarin was isolated.



EXPERIMENTAL

Condensation of 7-hydroxy-3,4-dimethylcoumarin with malic acid : 3,4-Dimethylcoumarino-7,8-α-pyrone

7-Hydroxy-3,4-dimethylcoumarin was prepared according to Pechmann and Duisberg (36)

A mixture of 7-hydroxy-3,4-dimethylcoumarin(5 g.) malic acid (5 g.) and con.sulphuric acid (25 ml.) was heated on a steam bath till the effervescence of carbon monoxide ceased (about 4 to 5 hr.). The reaction mixture was added to crush ice and filtered. The separated product was treated with ammonia and filtered. The residue crystallised from acetic acid in colourless cubes, m.p. 285-87°. Yield 1.5 g.

Analysis :

4.016 mg. of the substance gave 10.240 mg. of carbon dioxide and 1.418 mg. of water.

Found : C = 69.58 % ; H = 3.95 %.

$C_{14}H_{10}O_4$ requires : C = 69.42 % ; H = 4.16 %.

7-Hydroxy-8-formyl-3,4-dimethylcoumarin

A mixture of 7-hydroxy-3,4-dimethylcoumarin (10 g.) hexamethylenetetramine (10 g.) and glacial acetic acid (100 ml.) were gently refluxed on a sand bath for 10 hr. Dilute hydrochloric acid (100 ml. ; 1 : 1) was then added and the whole reaction mixture was heated on a steam bath for 5 hr. It was cooled and extracted with ether. The product obtained on removal of ether and acetic acid were found to consist of the formyl derivative and original coumarin. The mixture was triturated with hot alcohol and

filtered. The filtrate on dilution with water gave a product which crystallised from very dilute alcohol in yellow needles, m.p. 185-86°. Yield 0.5 g. It gave deep red colouration with alcoholic ferric chloride solution. The residue contained the original coumarin.

Analysis :

4.192 mg. of the substance gave 10.102 mg. of carbon dioxide and 1.644 mg. of water.

Found : C = 65.76 % ; H = 4.38 %.

$C_{12}H_{10}O_4$ requires : C = 66.08 % ; H = 4.62 %.

2,4-Dinitrophenylhydrazone

Prepared as usual, gave m.p. 290° (dec.)

Analysis :

6.574 mg. of the substance gave 0.841 c.c. of nitrogen at t = 27°C and p = 756 mm.

Found : N = 14.48 %.

$C_{18}H_{14}O_7N_4$ requires : N = 14.06 %.

7,8-Dihydroxy-3,4-dimethylcoumarin

To a solution of 7-hydroxy-8-formyl-3,4-dimethyl-coumarin (.5 g.) in sodium hydroxide solution (10 ml.; 2 %) at 0°. Hydrogen peroxide (3 ml. ; 6 %) was added drop-wise the reaction mixture was stirred at 0° for an hour. It was then acidified with hydrochloric acid and the product which separated crystallised from alcohol in colourless cubes, m.p. 272°. Yield 0.4 g. Mixed m.p. with an authentic specimen of 7,8-dihydroxy-3,4-dimethylcoumarin prepared according to Canter et al. (38) was not depressed.

Perkin reaction on 7-hydroxy-8-formyl-3,4-dimethyl coumarin : Synthesis of 3,4-dimethylcoumarino-7,8-α-pyrone

A mixture of 7-hydroxy-8-formyl-3,4-dimethyl-coumarin (0.82 g. ;0.004 mole) freshly fused sodium acetate (0.66 g.; 0.008 mole) and acetic anhydride (2 ml.; 0.016 mole) was heated in an oil bath kept at 180° for 8 to 10 hr. The product which separated on pouring the reaction mixture in water crystallised from acetic acid in colourless cubes, m.p. 286°. Yield 0.3 g. Mixed m.p. with 3,4-dimethylcoumarino-7,8-α-pyrone described above was not depressed.

Pechmann condensation of 5-hydroxy-3,4,7-trimethyl-coumarin with malic acid : 3,4,7-Trimethylcoumarino-5,6-α-pyrone

5-Hydroxy-3,4,7-trimethylcoumarin prepared by the condensation of orcinol with ethyl-α-methylacetoacetate according to Chakravarti (37). A mixture of 5-hydroxy-3,4,7-trimethylcoumarin (4 g.), malic acid (4 g.) and concentrated sulphuric acid (20 ml.) was heated on a steam bath till the effervescence ceased (4 to 5 hr.). The product obtained on adding the reaction mixture to crushed ice crystallised from acetic acid in colourless needles, m.p. 262°. Yield 1 g.

Analysis :

4.362 mg. of the substance gave 11.03 mg. of carbon dioxide and 1.930 mg. of water.

Found : C = 69.93 % ; H = 4.55 %.

$C_{15}H_{12}O_4$ requires : C = 70.30 % ; H = 4.72 %.

Pechmann condensation of 7,8-dihydroxy-3,4-dimethylcoumarin with malic acid : 3,4-Dimethyl-8-hydroxy-coumarino-7,6-α-pyrone

A mixture of 7,8-dihydroxy-3,4-dimethylcoumarin (4 g.) (38), malic acid (4 g.) and concentrated sulphuric acid (20 ml.) was heated on a steam bath till the effervescence ceased (4 to 5 hr.). The cooled reaction mixture was added to crushed ice and filtered. The separated product was refluxed with large quantity of absolute alcohol and filtered to remove the original coumarin. The residue crystallised from pyridine, m.p. > 400°. Yield 0.7 g.

Analysis :

4.914 mg. of the substance gave 11.752 mg. of carbon dioxide and 1.880 mg. of water.

Found : C = 65.26 % ; H = 4.28 %.

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

Attempted Pechmann condensation of 7-hydroxy-4,6-dimethylcoumarin with malic acid

A mixture of 7-hydroxy-4,6-dimethylcoumarin(3 g.) (39), malic acid (3 g.) and sulphuric acid (25 ml.) was heated on a steam bath till the effervescence ceased (4 to 5 hr.). On working of the reaction mixture as before only the original coumarin was obtained.

Attempted condensation of 7-hydroxy-4,8-dimethyl coumarin with malic acid

A mixture of 7-hydroxy-4,8-dimethylcoumarin(3 g.) (40), malic acid (3 g.) and concentrated sulphuric acid

(15 ml.) was heated on a steam bath as before. On working up the reaction mixture as before, the original coumarin was obtained.

Pechmann condensation of 7-hydroxy-3-bromo-4-methylcoumarin with malic acid : 3-Bromo-4-methylcoumarino-α-pyrones

7-Hydroxy-3-bromo-4-methylcoumarin (4 g.)(41) and malic acid (4 g.) and concentrated sulphuric acid (25 ml.) was heated on a steam bath till the effervescence ceased. The product was then treated with ammonia and filtered. It crystallised from large quantities of acetic acid in tiny brownish red needles, m.p.335°. Yield 0.5 g.

Analysis :

13.256 mg. of the substance gave 8.238 mg. of silver bromide.

4.212 mg. of the same substance gave 7.818 mg. of carbon dioxide and 0.994 mg. of water.

Found : C = 50.65 % ; H = 2.64 % ; Br = 26.44 %.

$C_{13}H_7O_4Br$ requires : C = 50.08 % ; H = 2.28 % ; Br = 26.07 %.

The same product was obtained when 4-methylcoumarino-7,8-α-pyrone (0.46 g. ; 0.002 mole) (2) in hot acetic acid (125 ml.) was treated with bromine (1.3 g. ; 0.008 mole) in glacial acetic acid (13 ml.). The reaction mixture was left over-night at room temperature. Yield 0.2 g.

Furo-3'-methyl-4',5',5,6-coumarin-2'-carboxylic acid

4-Methyl-3-bromocoumarino-7,8-α-pyrone(0.5 g.) was dissolved in hot alcoholic potassium hydroxide solution (10 ml.; 10 %) and gently refluxed for 4 hr. The cooled

reaction mixture was acidified and filtered. The dried product was extracted with benzene. The product obtained on evaporation of benzene crystallised from small quantity of the same solvent (charcoal) in white needles, m.p. 293°. Yield 0.1 g.

Analysis :

4.55 mg. of the substance gave 10.65 mg. of carbon dioxide and 1.462 mg. of water.

Found : C = 63.87 % ; H = 3.59 %.

$C_{13}H_8O_5$ requires : C = 63.94 % ; H = 3.3 %.

Decarboxylation : Furo-3'-methyl-4',5',5,6-coumarin

A mixture of furo-3'-methyl-4',5',5,6-coumarin-2'-carboxylic acid (0.5 g.) copper powder (1 g.) and quinoline (10 ml.) was refluxed for 4 to 5 hr. The product obtained on pouring the reaction mixture in dilute hydrochloric acid crystallised from dilute alcohol in tiny colourless needles, m.p. 134°. Yield .05 g. Shah and Shah (30) reports melting point 138-40°.

Analysis :

4.610 mg. of the substance gave 12.160 mg. of carbon dioxide and 1.704 mg. of water.

Found : C = 71.98 % ; H = 4.13 %.

$C_{11}H_8O_3$ requires : C = 71.99 % ; H = 4.03 %.

Attempted Pechmann condensation of 3,6-dibromo-4-methylcoumarin with malic acid

A mixture of 7-hydroxy-3,6-dibromo-4-methylcoumarin (3 g.) (41), malic acid (3 g.) and concentrated sulphuric acid

(15 ml.) was heated on a steam bath till the effervescence ceased (4 to 5 hr.). The reaction mixture was added to crushed ice. The separated product was treated with ammonia and filtered. No residue was obtained. The filtrate on acidification gave the original coumarin.

Attempted Pechmann condensation of 3,8-dibromo-4-methylcoumarin with malic acid

A mixture of 3,8-dibromo-4-methylcoumarin(3 g.) (41), malic acid (3 g.) and concentrated sulphuric acid (15 ml.) was heated on a steam bath till the effervescence ceased (4 to 5 hr.). The reaction mixture on working up as above gave the original coumarin.

Pechmann condensation of 7,8-dihydroxy-3-bromo-4-methycoumarin with malic acid : 3-Bromo-4-methyl-8-hydroxy-coumarino-7,6-α-pyrone

7,8-Dihydroxy-3-bromo-4-methylcoumarin (4 g.) prepared by the bromination of 7,8-dihydroxy-4-methylcoumarin according to Sakai and Kato (42) and malic acid (4 g.) was heated with concentrated sulphuric acid (20 ml.) on a steam bath till the effervescence ceased (4 to 5 hr.). The reaction mixture was added to crushed ice and filtered. The separated product was refluxed with large quantities of absolute alcohol and filtered to remove the original coumarin. The product crystallised from pyridine m.p. > 400°. Yield 0.5 g. It is practically insoluble in common organic solvent. It was soluble in sodium hydroxide solution.

Analysis :

4.330 mg. of the substance gave 7.712 mg. of carbon dioxide and 0.978 mg. of water.

10.128 mg. of the same substance gave 5.786 mg. of silver bromide.

Found : C = 48.6 % ; H = 2.52 % ; Br = 24.31 %.

$C_{13}H_7O_5Br$ requires : C = 48.3 % ; H = 2.16 % ; Br = 24.76 %.

Attempted methylation of 3-bromo-4-methyl-8-hydroxycoumarino-7,6-α-pyrone

(a) 3-Bromo-4-methyl-8-hydroxycoumarino-7,6-α-pyrone (0.3 g.) was suspended in acetone (100 ml.) and dimethyl sulphate (1 ml.) was added. The reaction mixture was refluxed for 72 hr. The product obtained on working up the reaction mixture was found to be the original coumarin.

Substitution of benzene in place of acetone gave the same result.

(b) Attempt to methylate it (0.3 g.) by dissolving it in sodium hydroxide solution (25 ml. ; 10 ml.) and then adding dimethyl sulphate (1 ml.) and heating the reaction mixture on a steam bath for 10 hr. also met with failure.

Action of alkali on 3-bromo-4-methyl-8-hydroxy-coumarino-7,6-α-pyrone

3-Bromo-4-methyl-8-hydroxycoumarino-7,6-α-pyrone (0.5 g.) was dissolved in alcoholic potassium hydroxide solution (20 ml. ; 10 %) and the reaction mixture refluxed on a steam bath for 4 hr. It was then cooled, acidified and extracted with ether. On evaporation of ether

a black paste was obtained from which no pure product could be isolated.

Refluxing the above coumarino-α-pyrone (0.3 g.) with sodium carbonate solution (25 ml. ; 5 %) on a sand bath for 4 hr. also gave a similar unworkable product.

Attempted ~~the~~ synthesis of 4-methylfuro-4',5', 6,5-coumarin

6-Hydroxy-5-formyl-4-methylcoumarin was prepared according to Naik and Thakore (43). But in the last stage the product was extracted with hot benzene instead of triturating with alcohol. Benzene has got an advantage over alcohol in this case as the product is soluble in benzene while 6-hydroxy-4-methylcoumarin is springly soluble in it.

A mixture of 6-hydroxy-5-formyl-4-methylcoumarin (0.87 g. ; 0.04 mole), ethyl bromoacetate (0.67 g. ; 0.04 mole) and potassium carbonate (2 g.) in acetone (75 ml.) was refluxed on a steam bath for 8 hr. The reaction mixture was filtered hot and on evaporation of the acetone a bright yellow liquid paste was obtained. It could not be solidified either by treatment with common organic solvent or by keeping it in a vacuum dessicator for a week. The paste was then dissolved in benzene and chromatographed over alumina. It was eluted with benzene and several fractions were collected. On evaporating the solvent, a yellow viscous oil was obtained which solidified on keeping in a vacuum dessicator. The product was treated with alcohol and filtered. It was washed

with dilute sodium hydroxide solution and finally crystallised from dioxane-petrol mixture in colourless tiny needles, m.p. 85°. Yield 0.3 g.

Analysis :

5.004 mg. of the substance gave 11.37 mg. of carbon dioxide and 2.17 mg. of water.

Found : C = 62.00 % ; H = 4.90 %.

$C_{15}H_{14}O_6$ requires : C = 62.06 % ; H = 4.82 %.

Ethyl-6-(5-formylcoumarinoxy) acetate (0.3 g.) was subjected to hydrolysis with sodium hydroxide solution (10 ml. ; 10 %) by keeping over-night at room temperature. On acidification a polymeric product which was soluble in sodium hydrogen carbonate solution was obtained m.p.> 400°. It showed negative reactions for aldehyde group. The same product was obtained when the reaction mixture was heated on a steam bath for 2 hr.

On hydrolysis with concentrated sulphuric acid by keeping it over-night at room temperature a black paste was obtained. Attempts to solidify this met with failure. It was then treated with sodium hydrogen carbonate solution. On acidification a similar type of polymeric product was obtained which did not give any tests for formyl group.

It was also heated with acetic anhydride and freshly fused sodium acetate to obtain directly the furocoumarin but it also met with failure.

Attempted iodination of 4-methylcoumarino-7,8-α-pyrone

4-Methylcoumarino-7,8-α-pyrone (0.57 g. ; 0.0025 mole) was dissolved in hot alcohol (200 ml.), iodine (0.25 g. ; 0.02 mole) and iodic acid (0.088 g. ; 0.0006 mole) dissolved in water (2 ml.) was added and the reaction mixture was stirred for 8 hr. The reaction mixture was added to a dilute sodium bi-sulphite solution. The separated product was found to be the original coumarin. Attempts to iodinate it with iodine monochloride also failed.

Attempted chloromethylation of 4-methylcoumarino-7,8-α-pyrone

4-Methylcoumarino-7,8-α-pyrone (0.57 g. ; 0.0025 mole) was dissolved in glacial acetic acid (100 ml.) and para formaldehyde (0.075 g. ; 0.0025 mole) was added. The reaction mixture was kept in a water bath at 80°C and dry hydrogen chloride gas was passed for 3 hr. The reaction mixture was cooled and the separated product was found to the original coumarin.

Attempt to chloromethylate the compound by increasing the moles of paraformaldehyde in the presence of either anhydrous zinc chloride or concentrated sulphuric acid also failed.

Attempted Friedel-Crafts acetylation of 4-methyl-coumarino-7,8-α-pyrone

A mixture of 4-methylcoumarino-7,8-α-pyrone (0.57 g.; 0.0025 mole), acetic anhydride (0.51 g. ; 0.005 mole) and anhydrous aluminium chloride (0.66 g. ; 0.005 mole) was heated

on a oil bath at 120° for 4 hr. On working up the reaction mixture as usual only the original coumarin was obtained back. Attempts to carry out the reaction at 180° by using nitro benzene also did not succeed.

Attempted Elbs Persulphate Oxidation of 4-methylcoumarino-7,8-α-pyrone

Potassium persulphate solution (2.7 g. in 50 ml. water ; 0.01 mole) was added drop-wise to a cooled solution (obtained after boiling) of 4-methylcoumarino-7,8-α-pyrone (2.28 g. ; 0.01 mole) in sodium hydroxide solution (25 ml.; 10 %) and the reaction mixture stirred for 6 hr. Next day the reaction mixture worked up as usual from which no pure product could be isolated.

Attempted Pechmann condensation of 7-hydroxy-2-methylchromone,7-hydroxyflavone,7-hydroxy-6-acetyl-4-methyl-, 7-hydroxy-6-nitro-4-methyl- and 7-hydroxy-6-carbomethoxy-4-methylcoumarin with malic acid

7-Hydroxy-2-methylchromone (45) (3 g.), malic acid (3 g.) and sulphuric acid (15 ml.) were heated on a steam-bath for 4 hr. On working up the reaction mixture as before only the original chromone was recovered.

Similar condensation of 7-hydroxyflavone(49)(3 g.) 7-hydroxy-6-acetyl-4-methylcoumarin (46).(3 g.), 7-hydroxy-6-nitro-4-methylcoumarin (47) (3 g.) and 7-hydroxy-6-carbomethoxy-4-methylcoumarin (48) with malic acid (3 g.) in the presence of sulphuric acid (15 ml.) met with failure. Only the original compounds were obtained back.

Attempted condensation of 7-hydroxy-4-methylcoumarin with ethyl acetoacetate in the presence of phosphorus pentoxide

To a mixture of 7-hydroxy-4-methylcoumarin (5.5 g.; 0.05 mole), ethyl acetoacetate (6.5 g.; 0.05 mole) and absolute alcohol (10 ml.), phosphorus pentoxide (15 g.) was added and the reaction mixture heated on a steam-bath for 2 hr. It was then added to crushed ice. The separated product crystallised from alcohol m.p. 185°. The product was identical with 7-hydroxy-4-methylcoumarin as seen by its direct comparison.

7-Hydroxy-4-methylcoumarin (5.5 g. ; 0.05 mole) and ethyl acetoacetate (6.5 g. ; 0.05 mole) were refluxed in diphenyl ether (25 ml.) for 8 hr. On cooling the reaction mixture 7-hydroxy-4-methylcoumarin was recovered.

Attempted condensations of 5-hydroxy-4-methyl-coumarin with malic acid and ethyl acetoacetate

5-Hydroxy-4-methylcoumarin (44) (3 g.), malic acid (3 g.) and sulphuric acid (15 ml.) were heated on a steam-bath for 4 hr. On working up the reaction mixture 5-hydroxy-4-methylcoumarin was obtained back.

Attempts to condense 5-hydroxy-4-methylcoumarin with ethyl acetoacetate in the presence of sulphuric acid, phosphorus pentoxide or in refluxing diphenyl ether met with failure.

Attempted condensation of 7-hydroxy-4-methylcoumarin with ethyl-α-chloroacetoacetate in the presence of sulphuric acid.

To a mixture of 7-hydroxy-4-methylcoumarin (3.5 g.; 0.02 mole) and ethyl-α-chloroacetoacetate(3.3 g.; 0.02 mole) and sulphuric acid (20 ml.) was added dropwise with external cooling. The reaction mixture was kept at room temperature for 4 days. On working up the reaction mixture as usual, only the original coumarin was isolated.

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