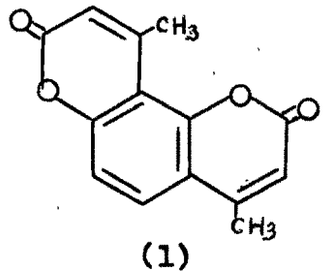
CHAPTER III

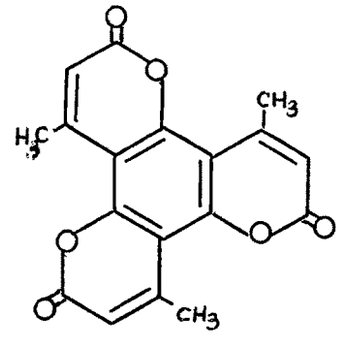
SYNTHESES OF COUMARINO-α-PYRONES AND FUROCOUMARINS

Syntheses of coumarino-α-pyrones and furocoumarins :

The benzo-α-pyrones or coumarins and the 2-phenylbenzo-γ-pyrones or flavones are found in nature in abundance. The α-and γ-pyrone derivatives have also gained importance in recent years because of their important physiological properties. Recently they have been found to have coronary dilating activity[1]. Hantzsch and Zurcher[2] condensed resorcinol and phloroglucinol with 2 and 3 moles of ethyl acetoacetate in the presence of sulphuric acid and obtained coumarino-α-pyrones (1) and (2) respectively,in poor yields.

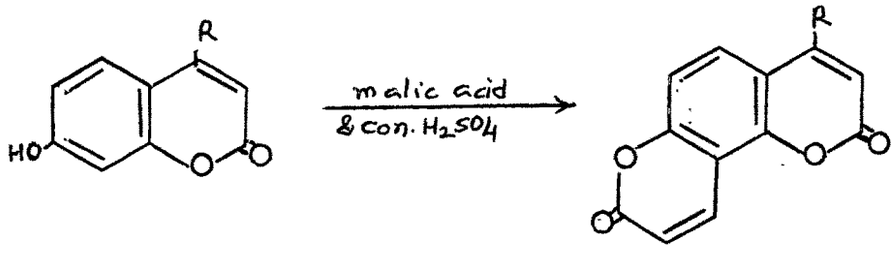


(1)



(2)

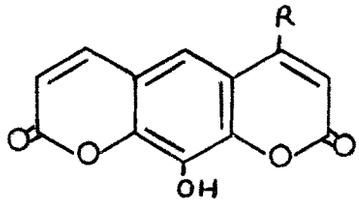
Sen and Chakravarti[3] condensed umbelliferone, 4-methylumbelliferone, daphnetin, 4-methyldaphnetin, homoumbelliferone and 4-methylumbelliferone with malic acid in the presence of sulphuric acid and obtained coumarino-7,8-α-pyrone (3a), 4-methylcoumarino-7,8-α-pyrone (3b), 8-hydroxycoumarino-7,6-α-pyrone (4a), 4-methyl-8-hydroxycoumarino-7,6-α-pyrone (4b),7-methyl-coumarino-5,6-α-pyrone (5a) and 4,7-dimethylcoumarino-5,6-α-pyrone (5b) respectively.[4] (page 52 for detail discussion)



(3)

(a) R=H

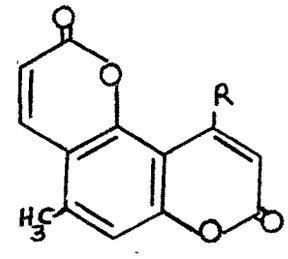
(b) $R=CH_3$



(4)

(a) R = H

(b) $R = CH_3$

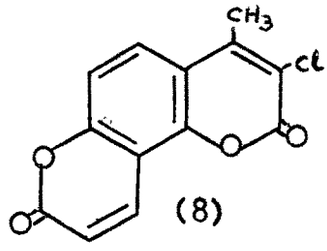


(5)

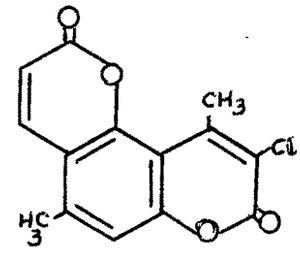
(a) R = H

(b) $R = CH_3$

Biswas[5] 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 3-chloro-4-methylcoumarino-7,8-α-pyrone (8), 3-chloro-4,7-dimethylcoumarino-5,6-α-pyrone (9) and 3-chloro-4-methyl-8-hydroxycoumarino-7,6-α-pyrone (10) respectively.



(8)



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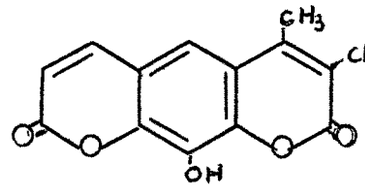
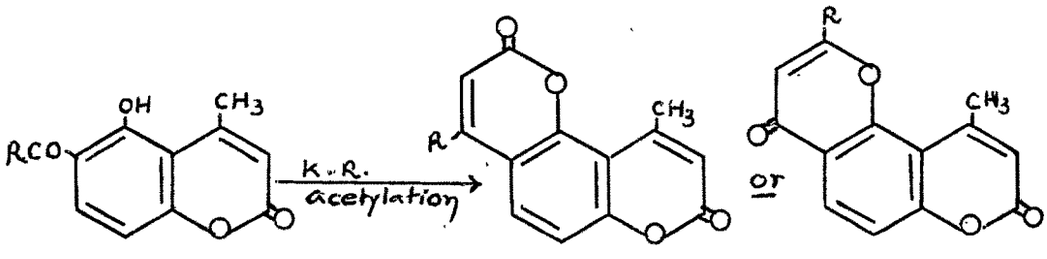


(10)

Shah and coworkers[6] synthesised several coumarino-α-pyrones (11) and coumarino-γ-pyrones (12) by subjecting 5-hydroxy-6-acylcoumarins (13) to Kostanecki-Robinson acylation.

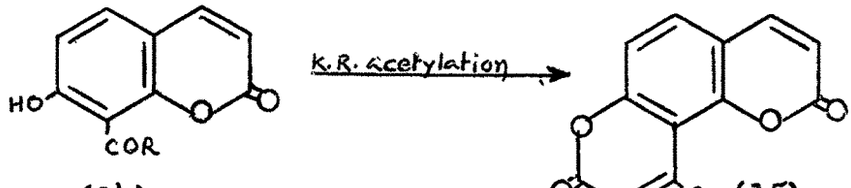


(13)
R = Alkyl or aryl

(11)
R = Aryl

(12)
R = Alkyl

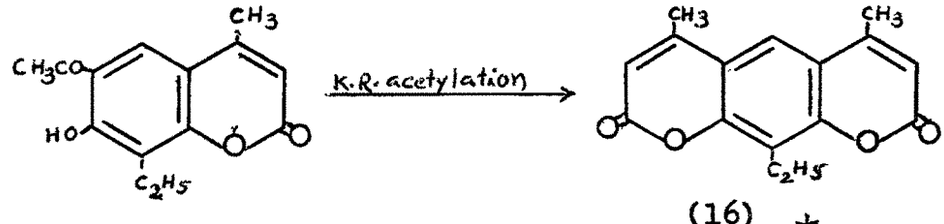
Shah and Contractor[7] carried out the Kostanecki-Robinson acylation of 7-hydroxy-8-propionyl (1^4a) and 7-hydroxy-8-butyrylcoumarin (1^4b) and assigned the 4^1-ethylcoumarino-7,8-α-pyrone (15a) and 4^1-propylcoumarino-7,8-α-pyrone (15b) structures to the products obtained.



(14)
(a) $R = C_2H_5$
(b) $R = C_3H_7$

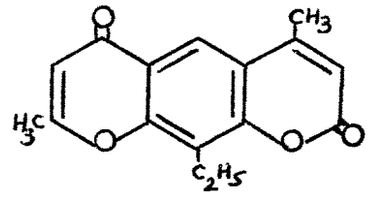
(15)
(a) $R = C_2H_5$
(b) $R = C_3H_7$

Limaye and Ghate[8] obtained $4,4^1$-dimethyl-8-ethylcoumarino-7,6-α-pyrone (16) and $2^1,4$-dimethyl-8-ethyl-3^1-acetylcoumarino-γ-pyrone (17) from 7-hydroxy-8-ethyl-6-acetyl-4-methylcoumarin (18) by Kostanecki-Robinson acetylation.



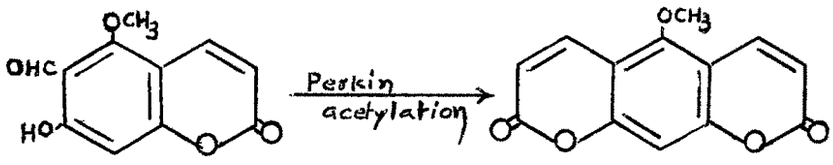
(18)

(16) +



(17)

Mustafa, Starkovsky and Zaki[9] prepared 5-methoxycoumarino-7,6-α-pyrone (19) by Perkin acetylation of apoxanthoxyletin (20).



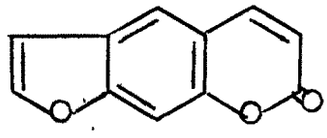
(20) (19)

Trivedi and Sethna[10] prepared 3,4-dimethylcoumarino-7,8-α-pyrone and 3,4,7-trimethylcoumarino-5,6-α-pyrone by the condensation of 7-hydroxy-3,4-dimethylcoumarin and 5-hydroxy-3,4,7-trimethylcoumarin with malic acid. They also synthesised 8-hydroxy-3,4-dimethylcoumarino-7,6-α-pyrone, 3-bromo-4-methylcoumarino-7,8-α-pyrone and 3-bromo-4-methyl-8-hydroxycoumarino-7,6-α-pyrone from 7,8-dihydroxy-3,4-dimethylcoumarin, 7-hydroxy-3-bromo-4-methylcoumarin and 7,8-dihydroxy-3-bromo-4-methylcoumarin respectively. They proved the structures by Perkin acetylation of the corresponding formylated compounds which were degraded to the known coumarin derivatives.

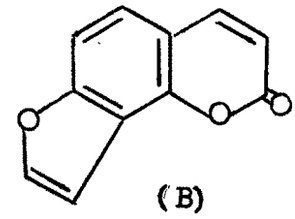
Mehta and Sethna[11] prepared coumarino-α- and γ-pyrones by the application of Perkin, Knoevenagel and Kostanecki-Robinson acylation reactions to some formyl and acyl coumarin derivatives.

Furocoumarins :

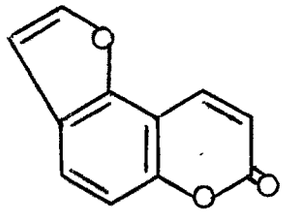
If the furan ring is built on a suitably substituted coumarin derivative, it leads to the synthesis of furocoumarins. Alternately one can start with an appropriate coumarone derivative and build up the α-pyrone ring on it. Seven isomeric forms of furocoumarins are found in the literature.



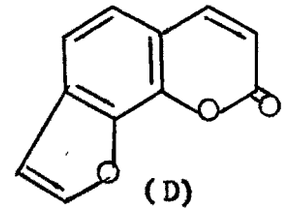
(A)



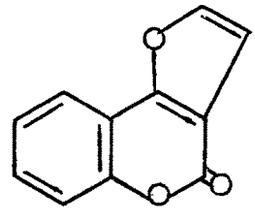
(B)



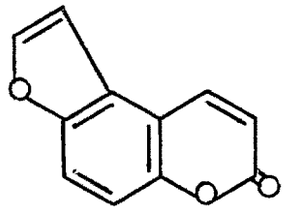
(C)



(D)



(G)



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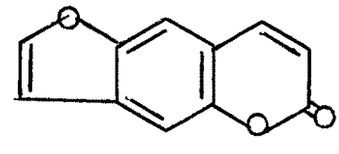


(F)

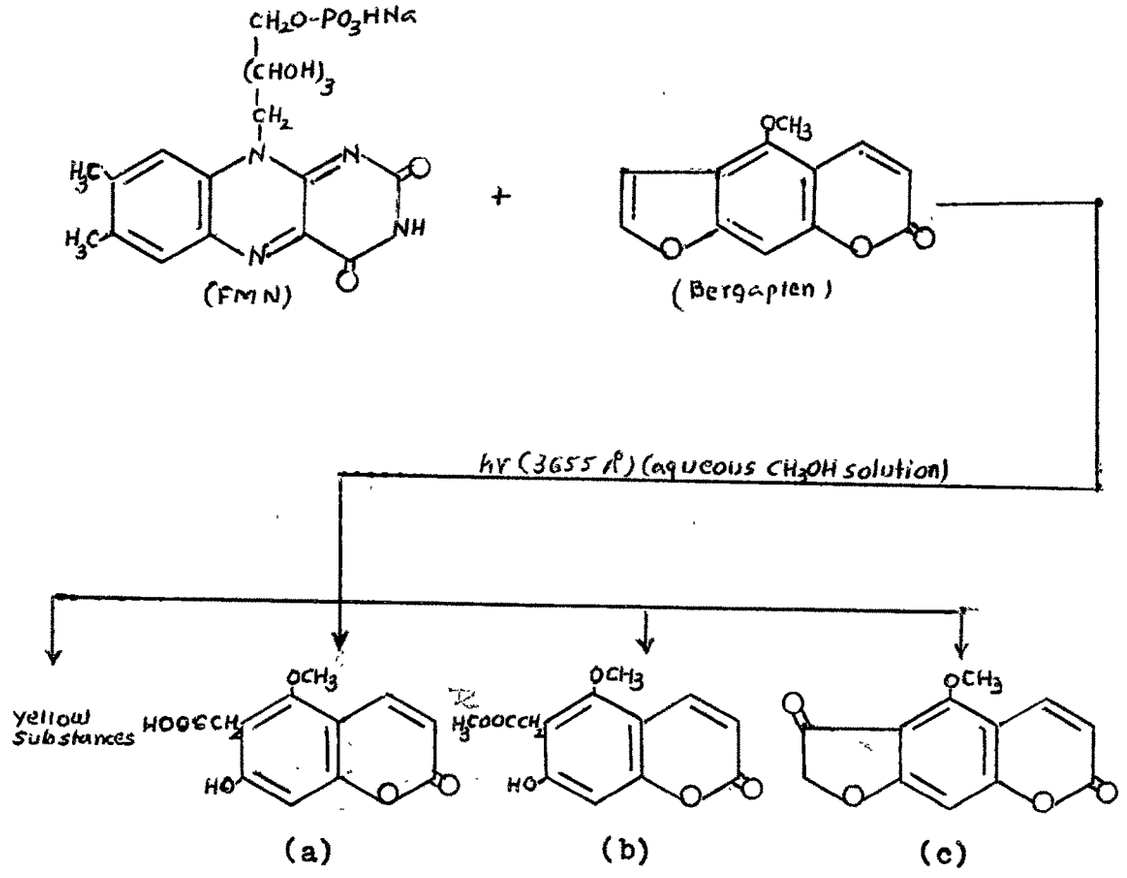
In recent years furocoumarins of the type (A) i.e. psoralene type have received considerable attention on account of their therapeutic properties. Xanthotoxin or 9-methoxypsoralene is a fish poison[12] but it is

relatively non-toxic to mammals. Schonberg and Latif[13] observed that it possesses molluscicidal activity. It was demonstrated by Elwi[14] 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 leukoderma[15]. 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[16]. There is some evidence that xanthotoxin under certain conditions may be carcinogenic[17].

Pathak and Fellman[18] have studied the activating and fluorescent wave-lengths of 37 furocoumarins and their biological photosensitising actions 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.

Recently, Musajo and coworkers[19,20] have observed that flavinmononucleotide (FMN) will react only with the furocoumarins that are photodynamically

active and that the reaction products appear to have been modified mainly in the furan ring. Furthermore, they have demonstrated that FMN in large amounts acts against erythema expected from the psoralene-type molecule. Three new coumarin derivatives have been isolated in the bergapten photoreaction, namely, 7-hydroxy-5-methoxycoumarin-6-acetic acid (a), its methyl or ethyl ester (b) according to the presence of methyl or ethyl alcohol in the irradiated solution, and probably, 4',5'-dihydro-4'-oxo-5-methoxyfurocoumarin (c)

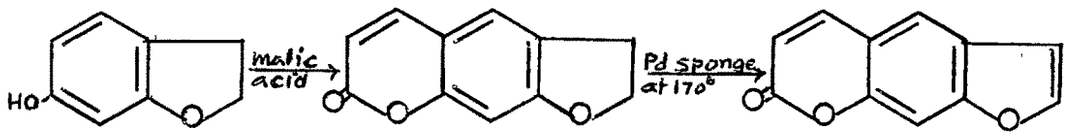


Two substances have been obtained by the photoreaction of FMN and psoralène in a water-methyl alcohol solution, namely the methyl ester of

7-hydroxycoumarin-6-acetic acid and 6-formyl-7-hydroxy-coumarin. No new compounds are formed in the photo-reaction of FMN and xanthotoxin[19].

The methods of synthesis of furocoumarins are briefly reviewed here. Two routes are available for the synthesis of psoralenes, either (a) through 6-hydroxy-coumaran or (b) through umbelliferone.

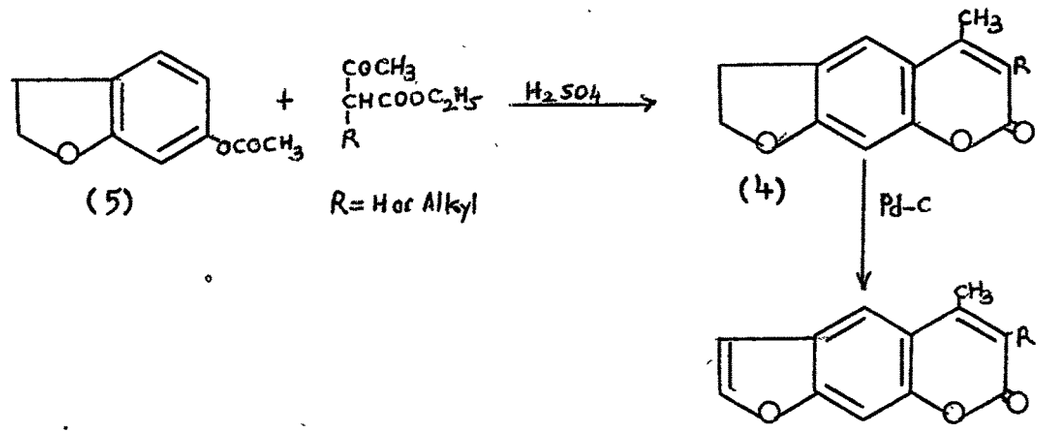
Spath and Pailer[21] carried out the condensation of 6-hydroxycoumaran (1) with malic acid in the presence of concentrated sulphuric acid and obtained 2,3-dihydro-psoralene (2) which on dehydrogenation gave psoralene(3).



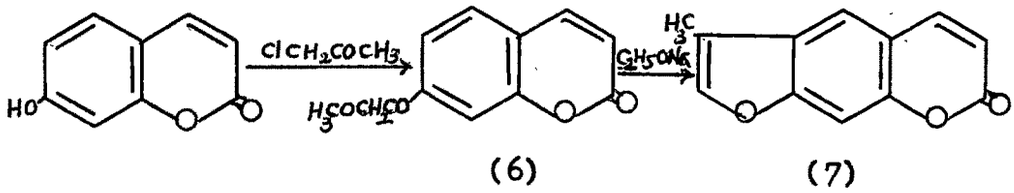
(1) (2) (3)

Later Horning and Reisner[22] prepared different 5-substituted-2,3-dihydropsoralenes by condensing 6-acetoxycoumaran with a variety of β-ketonic esters in the presence of sulphuric acid. This reaction has been further extended by Esse and Christensen[23] to obtain 6-alkyl-2,3-dihydro-5-methylpsoralenes (4) by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxy-coumaran (5). The main drawback in this method is that the dehydrogenation of dihydropsoralene derivatives with palladised charcoal gives poor yields of psoralene

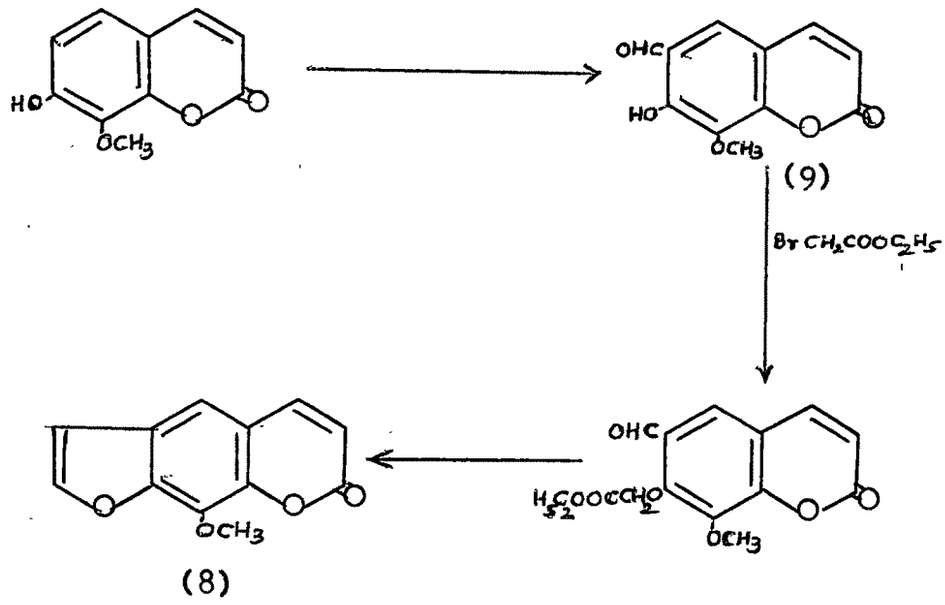
derivatives.



Ray, Silooja and Vaid[24] ~~had~~ approached the problem of psoralene synthesis by starting with umbelliferone. In this procedure, they carried out the cyclisation of 7-acetonyloxycoumarin (6), obtained by treating umbelliferone with chloracetone, in the presence of sodium ethoxide to 3-methylpsoralene (7).

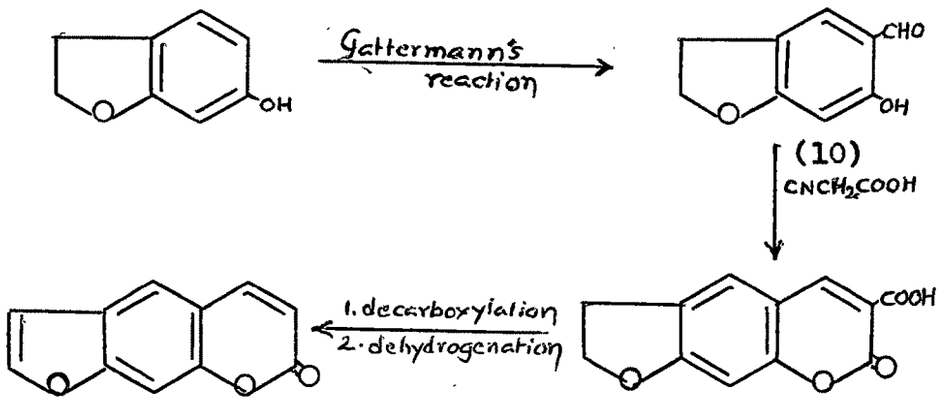


Rodighiero and Antonello[25] synthesised xanthotoxin (8) by first preparing 7-hydroxy-8-methoxy-6-formylcoumarin (9) and then treating it with ethyl bromoacetate, followed by hydrolysis, cyclisation and decarboxylation.

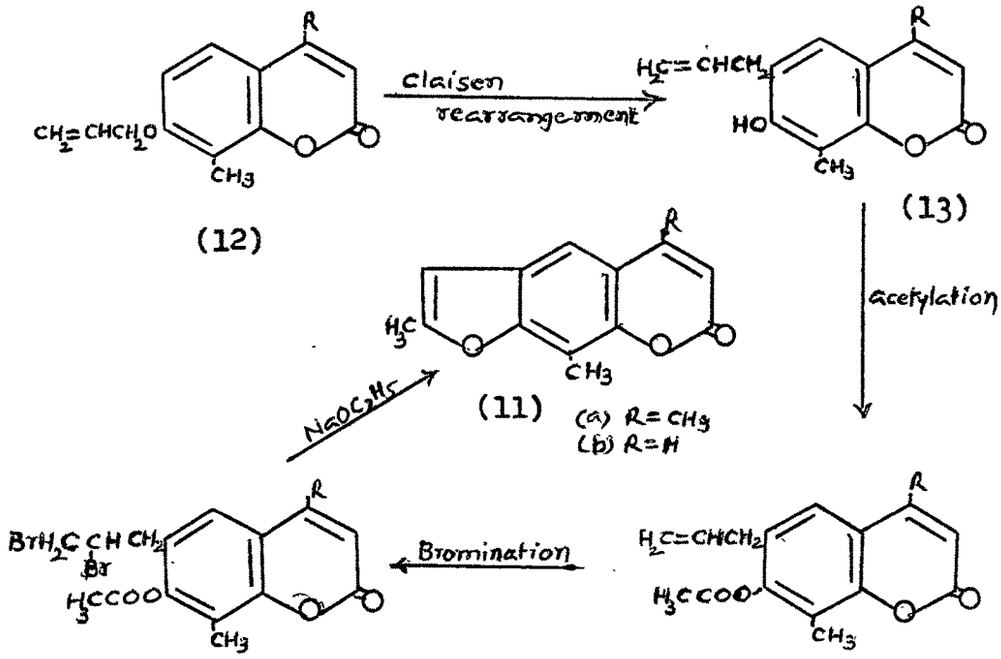


Limaye and Gangal[26] synthesised 3,4'-dimethyl-7,6-furocoumarin from 7-hydroxy-6-acetyl-4-methylcoumarin using the same procedure.

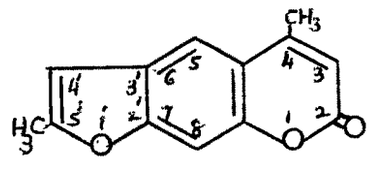
Foster et al.[27] synthesised psoralene by first subjecting 6-hydroxycoumaran to Gattermann aldehyde synthesis and then condensing the 6-hydroxy-5-formyl-coumaran (10) with cyanoacetic acid followed by decarboxylation and dehydrogenation.



Kaufman[28] prepared 4,5',8-trimethylpsoralene (11a) and 5',8-dimethylpsoralene (11b) by first carrying out the Claisen rearrangement of 7-allyloxy-4,8-dimethyl (12a) and 7-allyloxy-8-methylcoumarin (12b) to 7-hydroxy-6-allyl-4,8-dimethyl (13a) and 7-hydroxy-6-allyl-8-methylcoumarin (13b) respectively. These were then acetylated, brominated and cyclised to obtain psoralene derivatives.

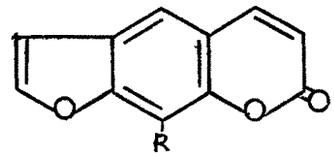


Using a similar procedure Kaufman synthesised 4,5'-dimethylpsoralene (14).



(14)

Kaufman and his co-workers[29] also synthesised psoralene derivatives (15) having different groups such as Cl, Br, CN, $N(CH_3)_2$ etc. in 8-position using 8-amino-psoralene as an intermediate product.

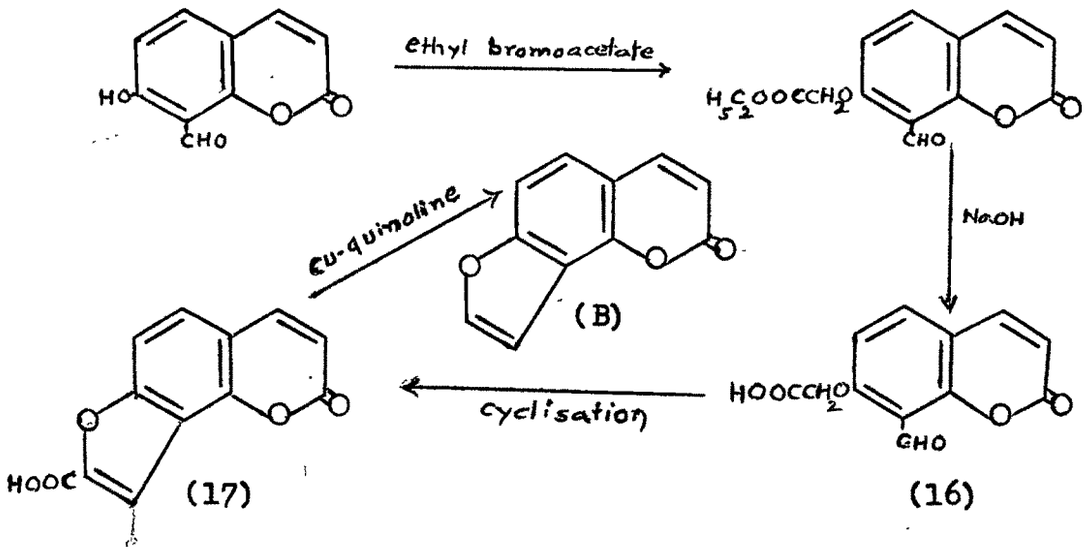


(15)

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

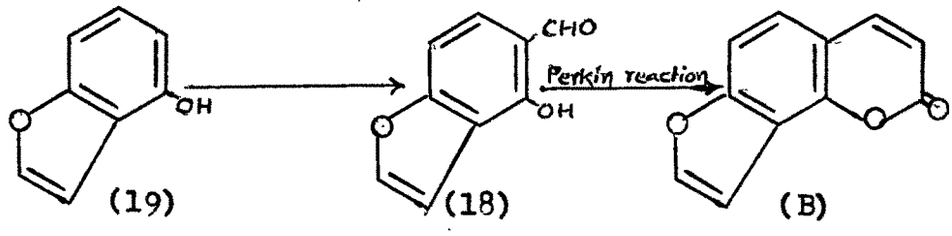
Angelicin is a naturally occurring furocoumarin of type (B) and was synthesised by Spath and Pailer[30] by condensing sodium salt of umbelliferone-8-aldehyde with iodoacetic ester under pressure and the product obtained subjected to hydrolysis followed by cyclisation.

Naik and Thakor[31] repeated this work using ethyl bromoacetate in acetone. They observed that the melting point of 7-(8-formylcoumarinoxy)-acetic acid (16) was 248-49° instead of 178-81° as reported by Spath and Pailer[30]. They also observed that on cyclisation of this product, angelicin-2-carboxylic acid (17) which was not isolated by Spath and Pailer was obtained and it underwent decarboxylation when heated with copper and quinoline to angelicin.

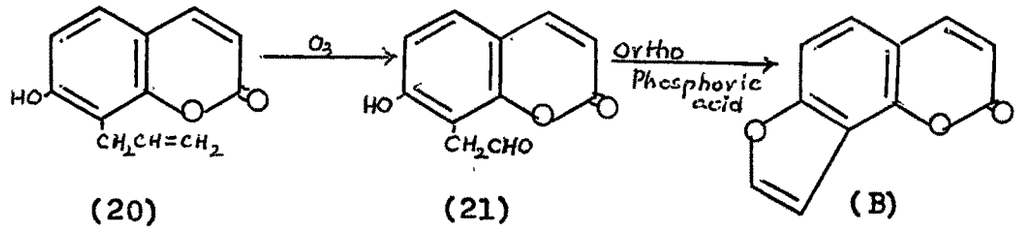


Using the above method Shah and Shah[32] synthesised furano-3'-methyl-4',5',8,7-coumarin from 7-hydroxy-8-acetylcoumarin.

Limaye[33] synthesised angelicin by preparing 4-hydroxy-5-formylcoumarone (18) from 4-hydroxycoumarone (19) and then subjecting it to Perkin reaction.

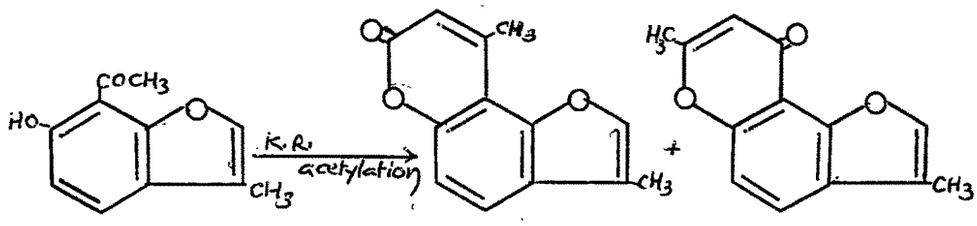


Aneja, Mukerjee and Seshadri[34] synthesised angelicin by subjecting first 7-hydroxy-8-allylcoumarin (20) to ozonolysis and subsequent cyclisation of 7-hydroxycoumarin-8-acetaldehyde (21) with o-phosphoric acid.



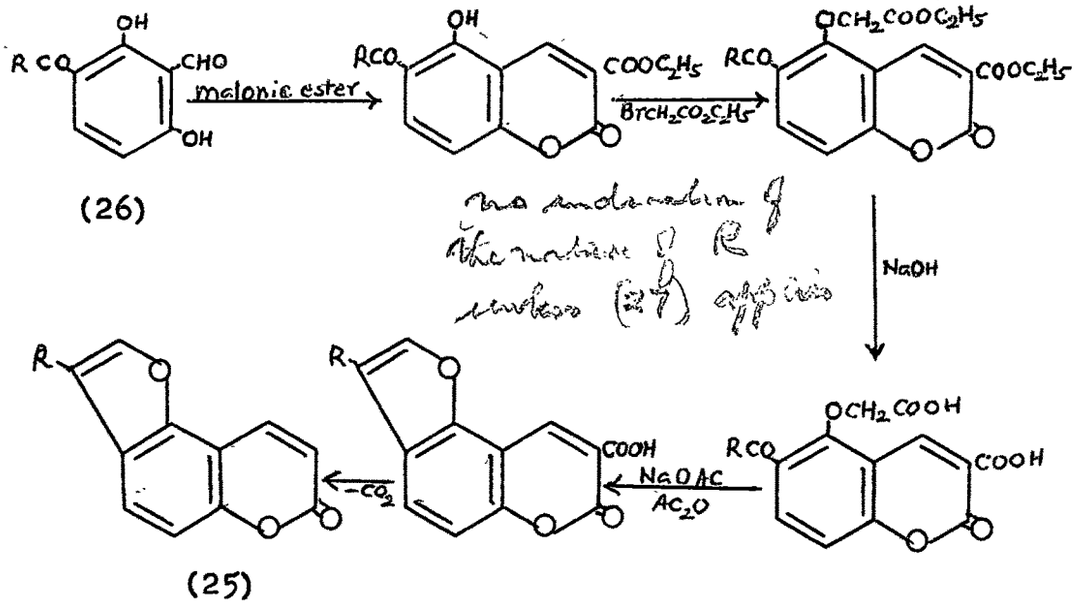
(20) (21) (B)

Furocoumarins of type (C) have been synthesised by several workers. Limaye and Sathe[35] subjected 6-hydroxy-7-acetyl-3-methylcoumarone (22) to Kostanecki-Robinson acetylation and obtained furo-3',4-dimethyl-4',5',6,5-coumarin (23) in poor yield along with furo-2,3'-dimethyl-4',5',6,5-chromone (24).



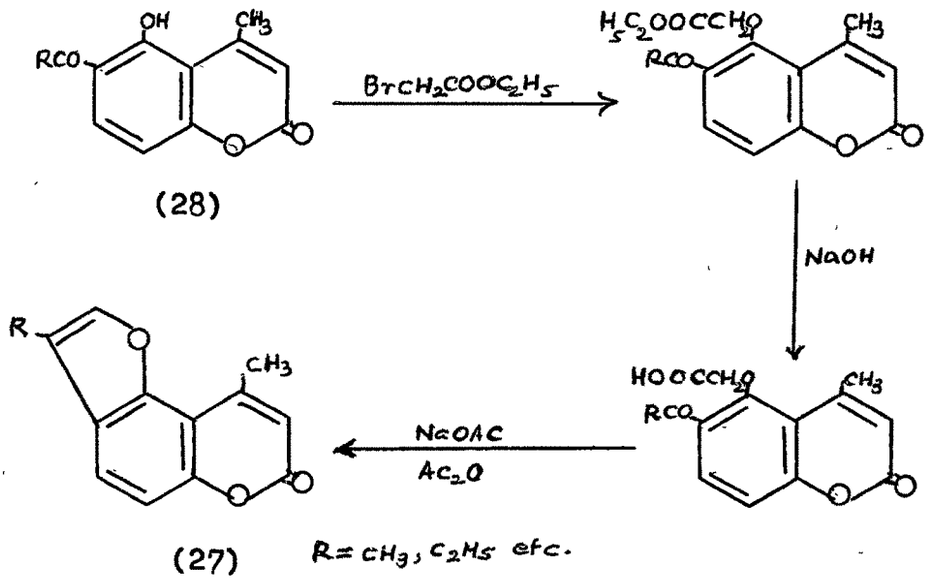
(22) (23) (24)

Shah and Shah[36] synthesised 3'-alkyl-furo-4',5',6,5-coumarin (25) by first condensing 2,4-dihydroxy-3-formylacetophenone (26) with malonic ester and then carrying out the condensation with ethyl bromoacetate followed by hydrolysis, subsequent cyclisation and decarboxylation.



(26) (25)

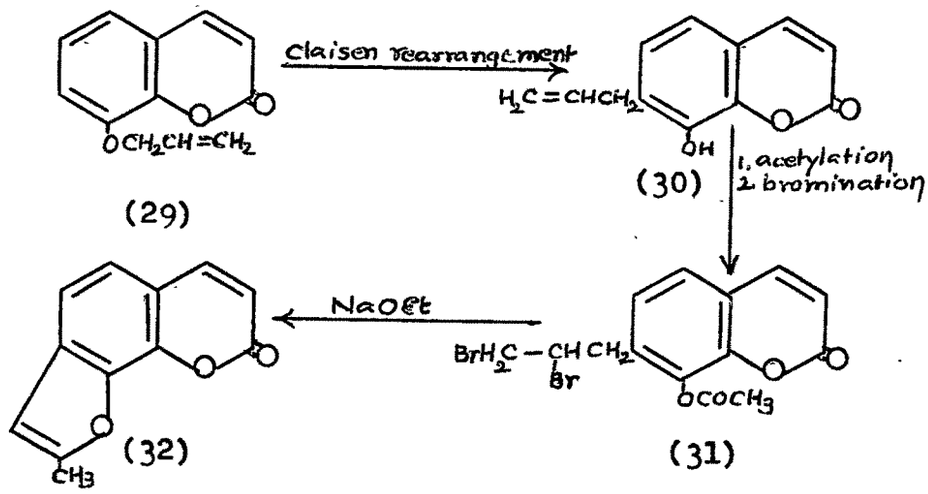
Chudger and Shah[37] synthesised several 3'-alkyl-4-methyl-furo-4',5',6,5-coumarin (27) by condensing 5-hydroxy-6-acyl-4-methylcoumarin (28) with ethyl bromoacetate followed by hydrolysis and subsequent cyclisation.



(28) (27) R = CH3, C2H5 etc.

Mehta[38,39] synthesised furo-3',8-dimethyl-4',5',6,7-coumarin, furo-3',5-dimethyl-5',4',7,8-coumarin and furo-3'-methyl-4',5',7,8-coumarin using the same procedure.

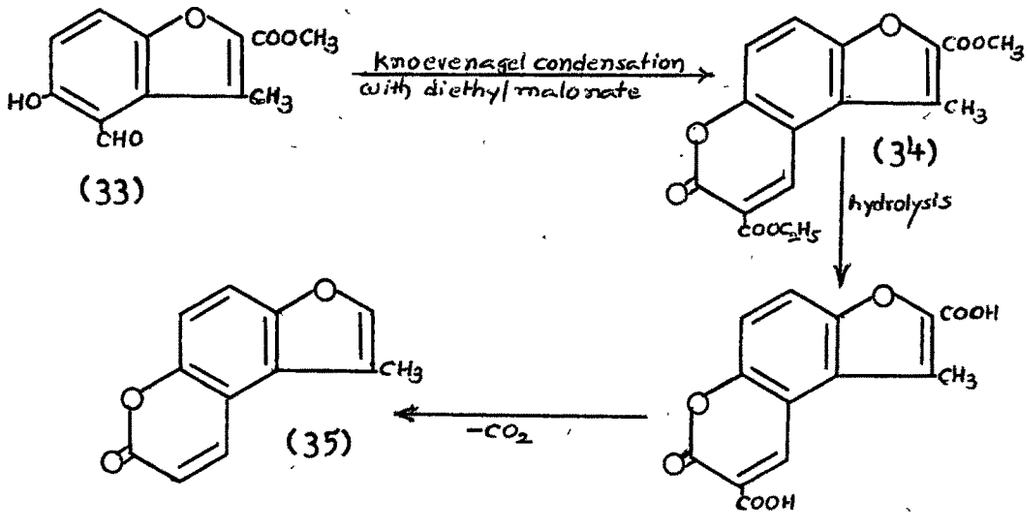
Furocoumarin of type (D) was synthesised by Kaufman and Russey[40]. They carried out the Claisen rearrangement of 8-allyloxycoumarin (29) and obtained 7-allyl-8-hydroxycoumarin (30), the acetyl derivative of which was brominated. This product (31) underwent cyclisation to 2'-methyl-furo-4',5',7,8-coumarin (32) when refluxed with sodium ethoxide in absolute ethanol.



Kaufman et al.[41] synthesised furo-4-methyl-4',5',5,6-coumarin and the corresponding 2-carboxy derivative (type E) by condensing 5-formyl-6-hydroxy-4-methylcoumarin with methyl bromoacetate, followed by hydrolysis and subsequent cyclisation with partial decarboxylation.

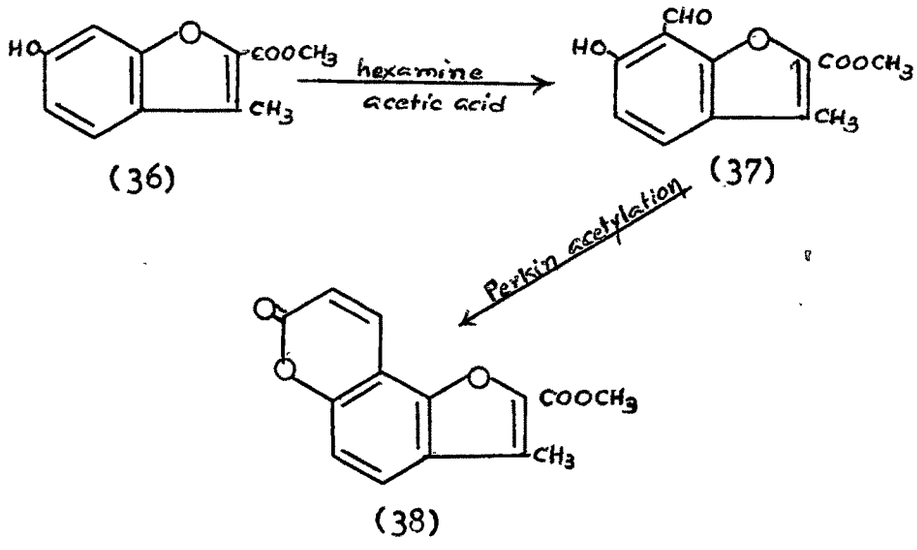
The above authors[41] prepared the same furocoumarin through an alternate route. 6-Hydroxy-4-methylcoumarin was converted to an allyl ether by reaction with allyl bromide and the Claisen rearrangement was carried out by refluxing it with dimethylaniline. The 5-allyl derivative obtained was subjected to ozonolysis, catalytic reduction and then heated with o-phosphoric acid to get the same furocoumarinn of type (E) described above. They also obtained furo-2',4-dimethyl-4',5',5,6-coumarin when 5-allyl-6-hydroxy-4-methylcoumarin was acetylated, brominated and then refluxed with sodium ethoxide in absolute alcohol.

Salvi and Sethna[42] synthesised furocoumarins from various benzofuran derivatives. They formylated the hydroxybenzofurans and then carried out the synthesis of furocoumarins by Perkin or Knoevenagel reaction. They also synthesised the furocoumarin of the type (E) by taking the appropriate benzofuran derivatives. Thus methyl-4-formyl-5-hydroxy-3-methylcoumarilate (33) on reaction with diethyl malonate gave ethyl furo-2'-carbomethoxy-3'-methyl-4',5',5,6-coumarin-3-carboxylate (34) which on hydrolysis and subsequent decarboxylation gave furo-3'-methyl-4',5',5,6-coumarin (35).



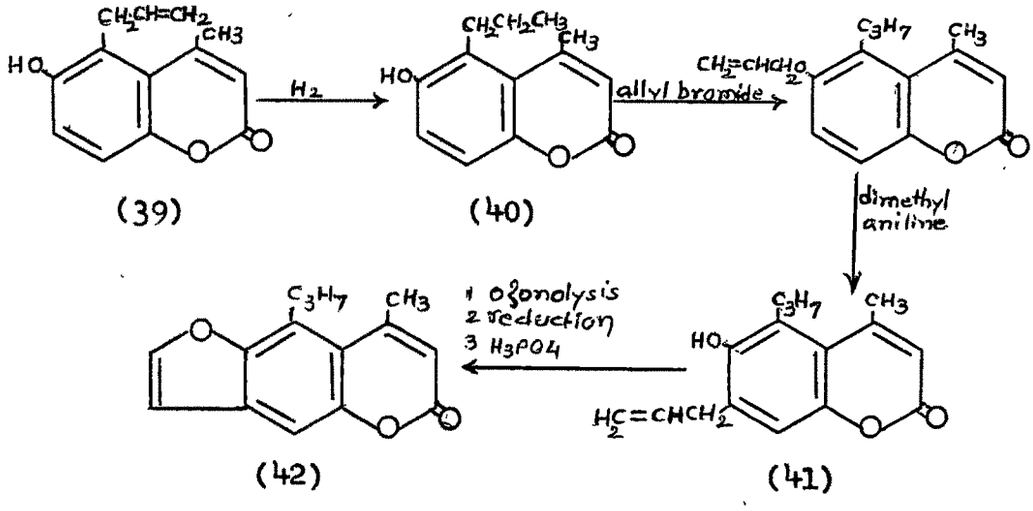
Salvi and Sethna[42] also synthesised furo-coumarin of the type (C) as follows :

Methyl 6-hydroxy-3-methylcoumarilate (36) on reaction with hexamine gave the 7-formyl derivative (37) which on Perkin acetylation gave furo-2'-carbomethoxy-3'-methyl-5',4',5,6-coumarin (38). In a similar manner furo-3'-methyl-4',5',5,6-coumarin was prepared from methyl 5-hydroxy-3-methylcoumarilate.



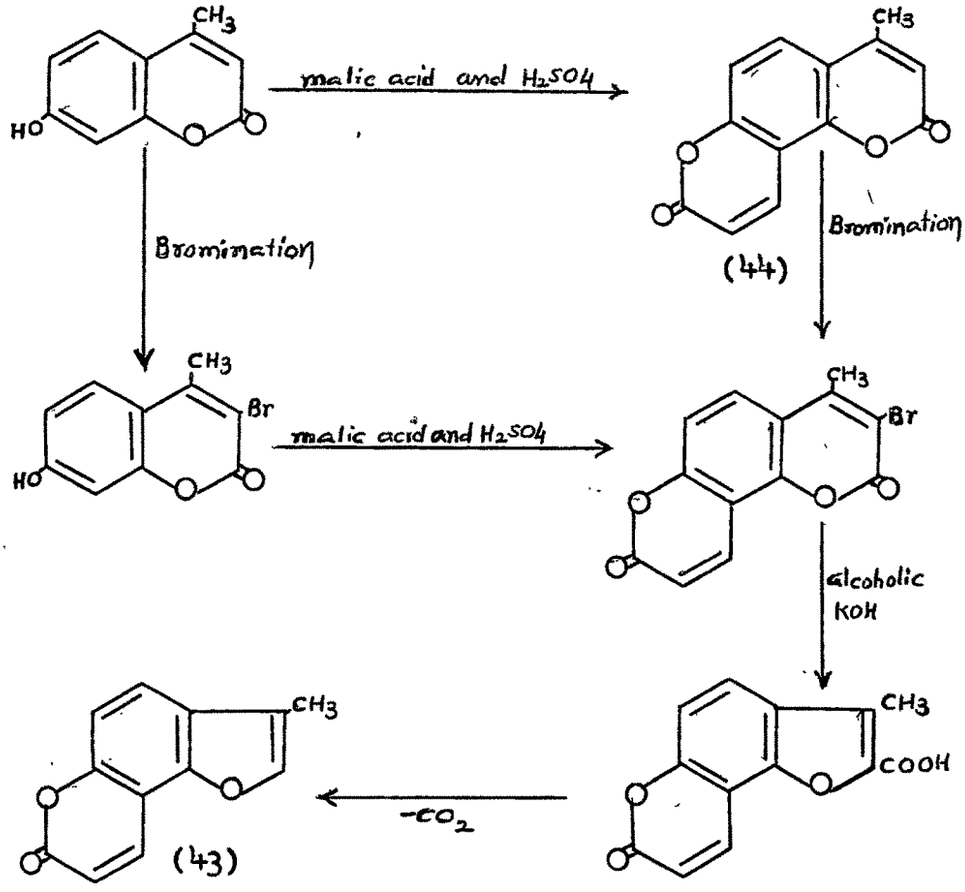
Kaufman et al.[41] prepared the furocoumarin of type (F) as follows :

5-Allyl-6-hydroxy-4-methylcoumarin (39) was catalytically hydrogenated to 6-hydroxy-4-methyl-5-n-propylcoumarin (40), which was converted to an allyl ether by reaction with allyl bromide. Refluxing in diethylaniline caused the Claisen rearrangement and with the 5-position occupied the allyl group was forced to the 7-position giving 7-allyl-6-hydroxy-5-n-propyl-4-methylcoumarin (41). Ozonolysis, catalytic reduction and heating with o-phosphoric acid gave furo-4-methyl-5-n-propyl-5',4',6,7-coumarin (42).



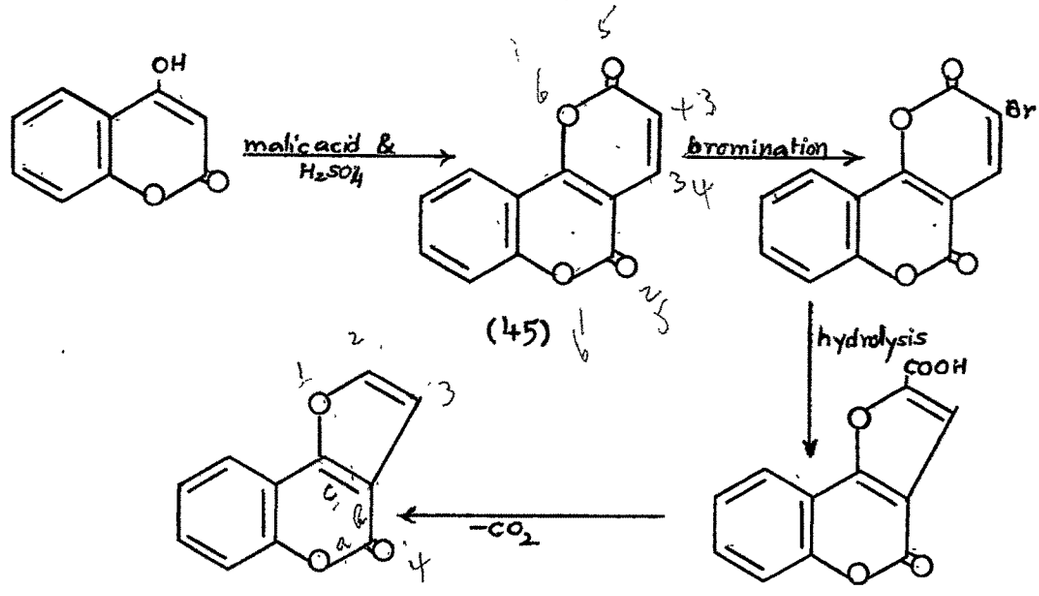
Trivedi and Sethna[43] made new approach to synthesise furocoumarins. They studied the hydrolysis of 3-halogen substituted coumarino-α-pyrones and obtained corresponding furocoumarins. Thus furo-3'-methyl-

5',4',5,6-coumarin (43) was prepared from coumarino-α-pyrone derivative (44) through the following sequence of reactions.



Furocoumarin of type (G) has been recently synthesised by Dholakia and Trivedi[44]. 4-Hydroxycoumarin was condensed with malic acid in the presence of sulphuric acid to give 2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran (45) which was brominated to yield 9-bromo derivative. This on hydrolysis with sodium carbonate furnished 4H-furo (3,2-c)benzopyran-4-one-2-carboxylic acid (46) which was

subsequently decarboxylated to yield 4-H-furo(3,2-c) benzopyran-4-one (47).

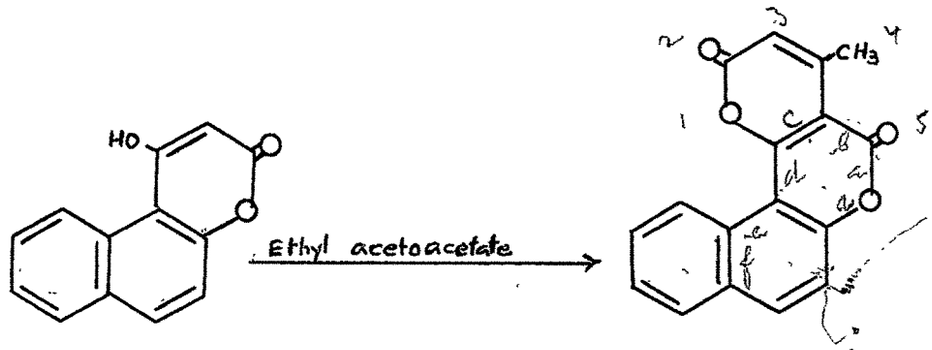


(47) (46)

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

Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate : 4-Methyl-2,5-dioxo-2H,5H-pyrano (3,2-c)benzo(f)benzopyran (48) :

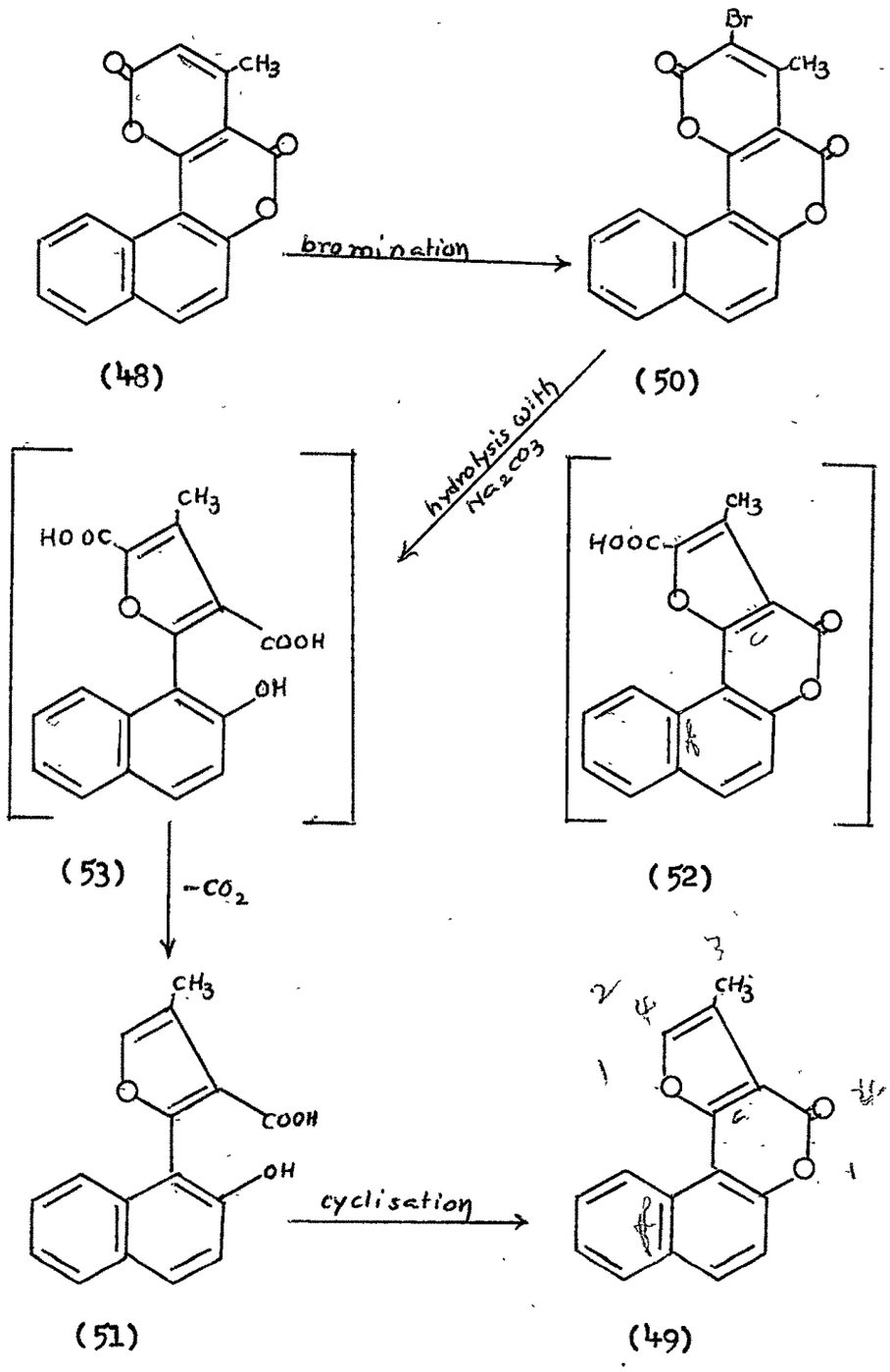
4-Hydroxy-5,6-benzocoumarin on condensation with ethyl acetoacetate in the presence of aluminium chloride and nitrobenzene gave the product to which 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran (48) structure was assigned.[45] The same product was also prepared by refluxing 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate in the presence of trifluoroacetic acid or diphenyl ether. (Vide chapter IV for detail description.)



(48)

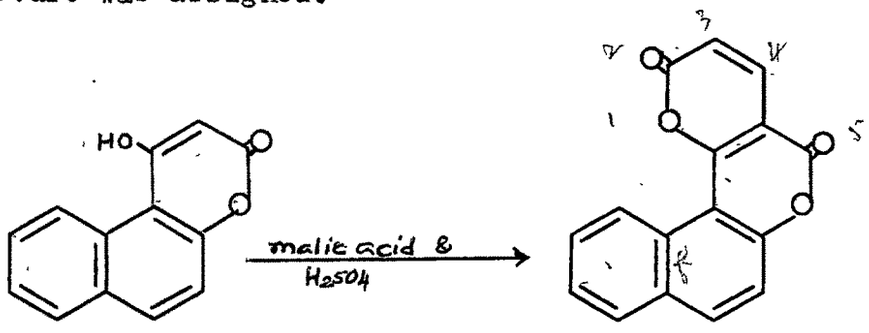
Synthesis of 3-methyl-4-oxo-4H-furo(3,2-c)benzo(f)-benzopyran (49)

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran (48) on bromination with bromine in acetic acid gave 3-bromo-4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzo(f)benzopyran (50) which on hydrolysis with 10 % sodium carbonate solution afforded 2-(o-hydroxy-α-naphthyl)-4-methylfuran-3-carboxylic acid (51) and not 3-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran-2-carboxylic acid (52). The formation of (51) from the expected (52) is shown according to following route through the intermediate (53), which could not be isolated. The acid (51) on cyclisation with ethanolic hydrochloric acid gave 3-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran (49).


CH3
bromination
Br
CH3
(48)
(50)
hydrolysis with
Na2CO3
HO OC
CH3
COOH
OH
HOOC
CH3
(53)
(52)
-CO2
CH3
COOH
OH
cyclisation
CH3
(51)
(49)

Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with malic acid : 2,5-Dioxo-2H,5H-pyrano(3,2-c)benzo(f)-benzopyran (54) :

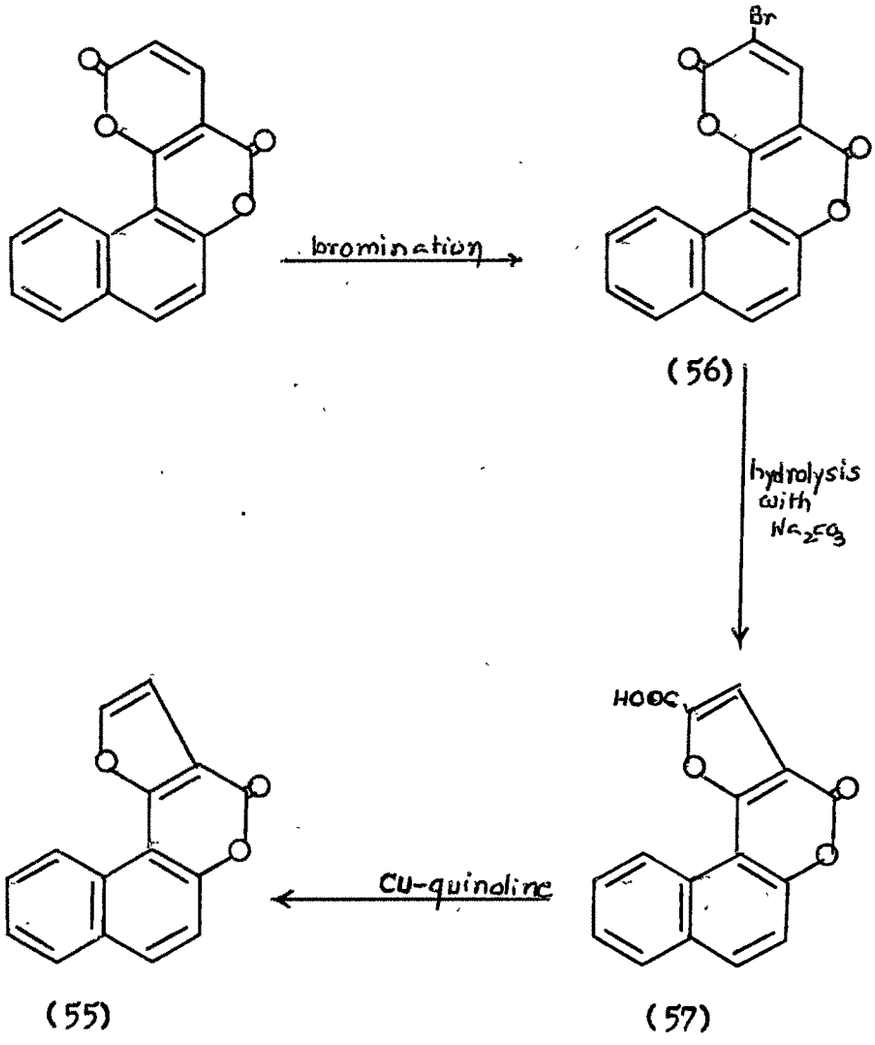
4-Hydroxy-5,6-benzocoumarin on a similar condensation with malic acid in the presence of 80 % sulphuric acid gave an alkali insoluble product to which 2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran (54) structure was assigned.



(54)

Synthesis of 4-oxo-4H-furo(3,2-c)benzo(f)benzopyran (55):

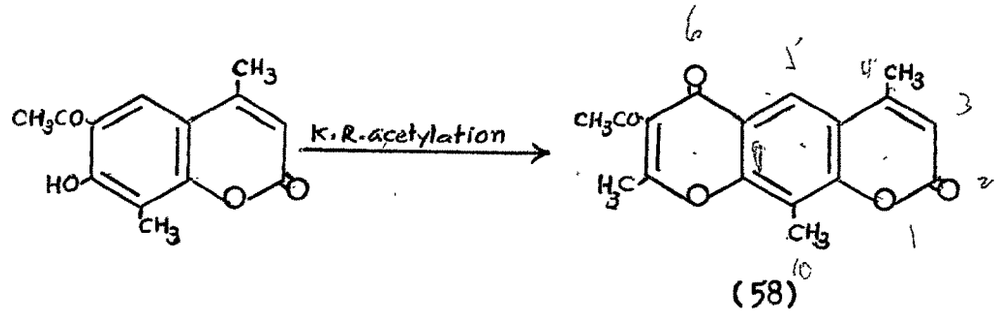
2,5-Dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran (54) on bromination gave 3-bromo-2,5-dioxo-2H,5H-pyrano (3,2-c)benzo(f)benzopyran (56) which on hydrolysis with sodium carbonate solution afforded 4-oxo-4H-furo(3,2-c)-benzo(f)benzopyran-2-carboxylic acid (57). On decarboxylation of the acid (57) with copper and quinoline gave the alkali insoluble product to which 4-oxo-4H-furo(3,2-c)-benzo(f)benzopyran (55) structure was assigned.


Br
bromination
(56)
hydrolysis
with
Na_2CO_3
HOOC
Cu-quinoline
(55)
(57)

The Kostanecki-Robinson acylation of 7-hydroxy-6-acyl-8-methylcoumarin derivatives was carried out to synthesise coumarino-α-pyrones and coumarino-γ-pyrones, the structures of which were established on the basis of their IR spectra.

Kostanecki-Robinson acetylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin : 7-Acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione (58) :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin was prepared according to Rangaswami and Seshadri[46]. This on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate gave a product which was insoluble in cold dilute alkali and did not develop any colouration with ferric chloride solution. The IR spectrum showed three strong bands in the carbonyl region viz. 1750 cm^{-1} (lactonyl >C = O group), 1690 cm^{-1} (γ-pyronyl > C = O group) and 1650 cm^{-1} (acetyl group at position 7). On the basis of the IR spectra and analytical results, the compound has been assigned 7-acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione structure (58).



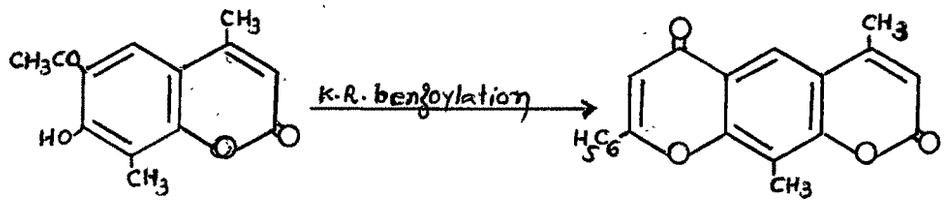
(58)

Attempted deacetylation of 7-acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

Attempt to deacetylate (58) by refluxing with alcoholic anhydrous sodium carbonate or concentrated sulphuric acid did not succeed.

Kostanecki-Robinson benzoylation of 7-hydroxy-6-acetyl 4,8-dimethylcoumarin : 4,10-Dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione (59) :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin on Kostanecki-Robinson benzoylation with benzoic anhydride and sodium benzoate gave the alkali insoluble product to which 4,10-dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione (59) structure was assigned. It showed carbonyl absorption in the IR region 1745 cm^{-1} (lactonyl > C=O group) and 1680 cm^{-1} (γ-pyronyl > C=O) . No 7-benzoyl derivative could be isolated in this case.



(59)

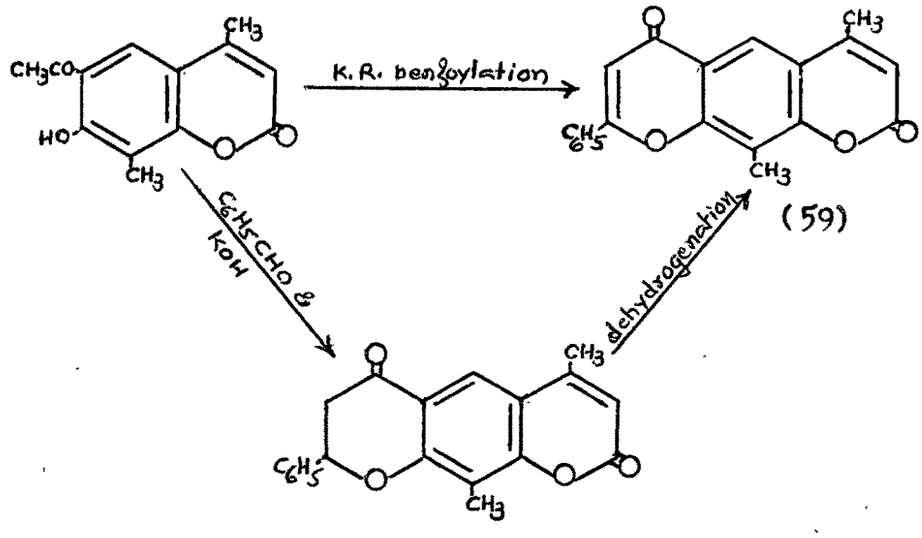
Attempt to prepare the above compound (59) from 7-hydroxy-6-acetyl-4,8-dimethylcoumarin by modified Baker-Venkataraman transformation by refluxing the o-hydroxyketone with benzoyl chloride, potassium carbonate in acetone according to Seshadri et al.[47] gave only the o-benzoyl derivative.

Synthesis of 4,10-dimethyl-8-phenyl-7,8-dihydro-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione (60) :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin on condensation with benzaldehyde in alcoholic potassium hydroxide afforded the alkali insoluble product which did not give any colouration with ferric chloride solution, and to which 4,10-dimethyl-8-phenyl-7,8-dihydro-2H,6H-pyrano (3,2-g)benzopyran-2,6-dione (60) structure was assigned.

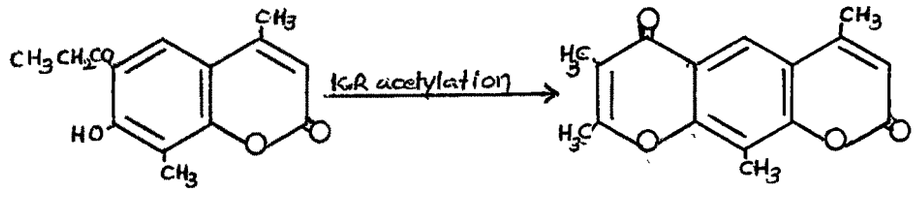
4,10-Dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran 2,6-dione (59) :

The flavanone (60) on dehydrogenation with selenium dioxide in amyl alcohol gave the product which was identical with 4,10-dimethyl-8-phenyl-2H,6H-pyrano (3,2-g)benzopyran-2,6-dione (59) obtained from Kostanecki-Robinson benzoylation of 7-hydroxy-6-acetyl-4,8-dimethyl-coumarin as described earlier.



Kostanecki-Robinson acetylation of 7-hydroxy-6-propionyl-4,8-dimethylcoumarin (61) : 4,7,8,10-Tetramethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione (62) :

7-Hydroxy-6-propionyl-4,8-dimethylcoumarin (61) on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate gave the product which was found to be insoluble in alkali and did not develop any colouration with ferric chloride solution. On the basis of these properties and analytical results it was assigned the structure 4,7,8,10-tetramethyl-2H,6H-pyrano(3,2-g) benzopyran-2,6-dione (62).



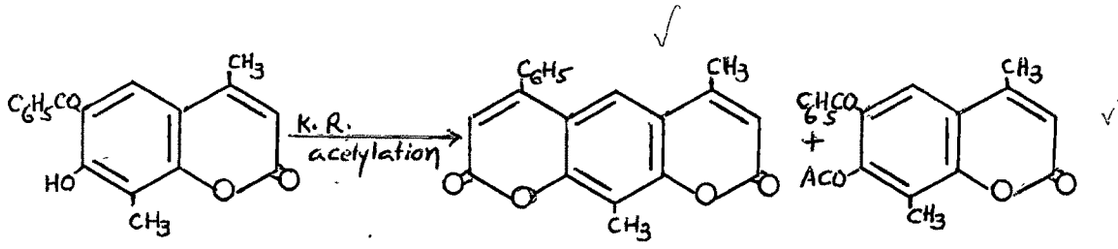
(61) (62)

Kostanecki-Robinson acetylation of 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin (63) : 4,10-Dimethyl-6-phenyl-2H,8H-pyrano(3,2-g)benzopyran-2,8-dione (64) :

7-Hydroxy-6-benzoyl-4,8-dimethylcoumarin (63) when refluxed with acetic anhydride and sodium acetate gave the mixture of two products. The separation of these was affected by the treatment with hot ethanol. The product which remained insoluble in ethanol was found to be 4,10-dimethyl-6-phenyl-2H,8H-pyrano(3,2-g)-

benzopyran-2,8-dione (64). It did not give any colouration with alcoholic ferric chloride solution.

The alcoholic mother liquor on cooling gave the product to which 7-acetoxy-6-benzoyl-4,8-dimethyl-coumarin (65) structure was assigned.



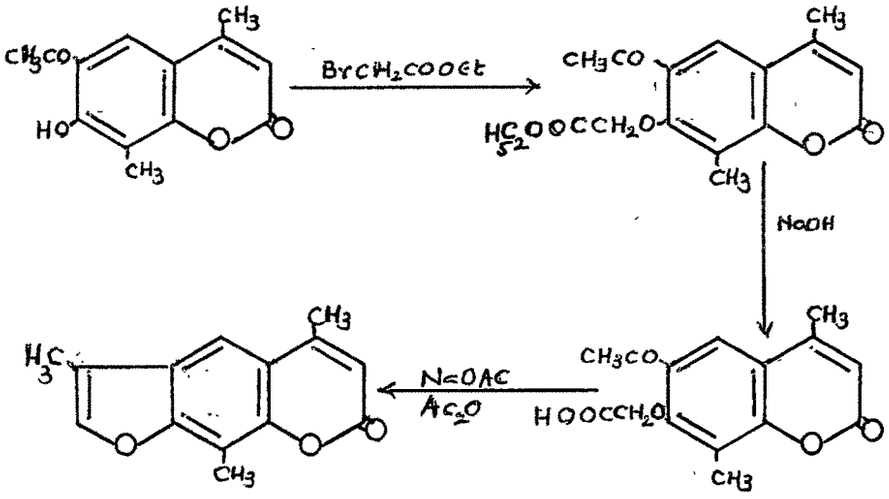
(63) (64) (65)

It has been reported by Pathak et al.[48] that properly located alkyl groups do not decrease the activity of psoralene appreciably and perticularly that 4,5',8-trimethyl psoralene is as active as psoralene in producing an erythermal response on guinea pigs skin irradiated by ultra-violet light. The present work deals with the syntheses of alkyl and aryl psoralene derivatives having substituents in 4',4- and 8-positions.

Synthesis of 4',4,8-trimethyl psoralene (66) :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin was condensed with ethylbromoacetate in boiling acetone in the presence of anhydrous potassium carbonate when ethyl 4,8-dimethyl-6-acetyl-7-coumarinyloxyacetate was obtained. On hydrolysis with alkali it gave 6-acetyl-4,8-dimethyl-7-coumarinyloxyacetic acid. The cyclisation of this acid was affected by refluxing it with acetic anhydride and

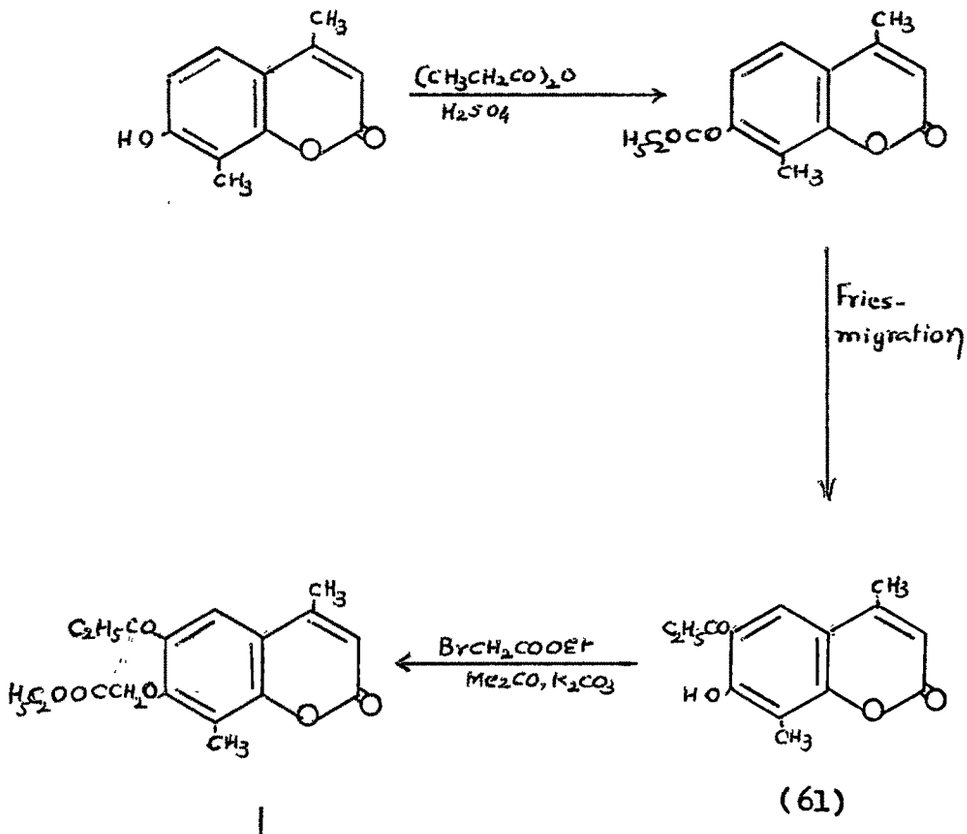
freshly fused sodium acetate. Simultaneous decarboxylation and ring closure took place and 4',4,8-trimethylpsoralene (66) was obtained.



(66)

Synthesis of 4'-ethyl-4,8-dimethylpsoralene (67) :

7-Hydroxy-6-propionyl-4,8-dimethylcoumarin (61) was obtained by Fries migration of 7-propionoxy-4,8-dimethylcoumarin. It gave colouration with alcoholic ferric chloride solution. 7-Hydroxy-6-propionyl-4,8-dimethylcoumarin on condensation with ethyl bromoacetate under the same condition as described before gave ethyl 6-propionyl-4,8-dimethyl-7-coumarinyloxyacetate. The ester was hydrolysed with alkali to 6-propionyl-4,8-dimethyl-7-coumarinyloxyacetic acid. 4'-Ethyl-4,8-dimethylpsoralene (67) was obtained on heating the acid with sodium acetate and acetic anhydride.

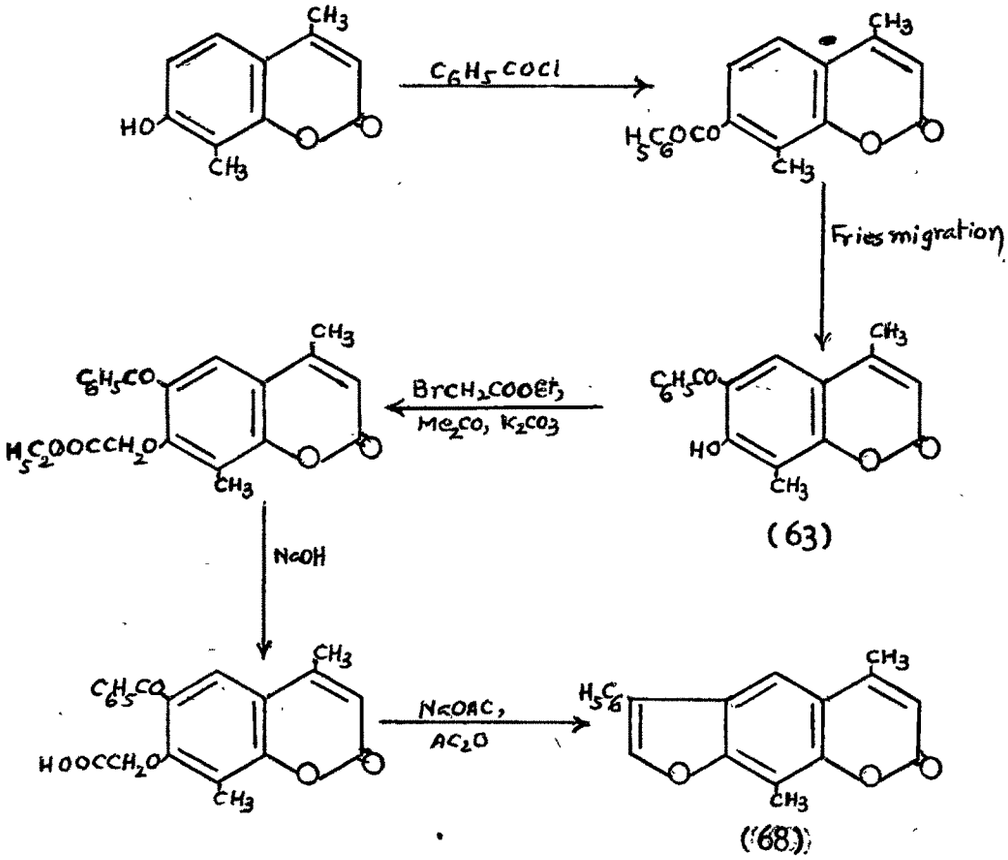

CH3
HO
CH3
(CH3CH2CO)2O
H2SO4
H5C2OCO
CH3
Fries-
migration
C2H5CO
HO
CH3
BrCH2COOEt
Me2CO, K2CO3
C2H5CO
H5C2OOCCH2O
CH3
NaOH
C2H5CO
HOOCCH2O
CH3
NaOAc
Ac2O
H5C2
CH3

(61)

(67)

Synthesis of 4'-phenyl-4,8-dimethylpsoralene (68):

The above furocoumarin was synthesised from 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin (63) which was obtained on Fries migration of 7-benzoyloxy-4,8-dimethylcoumarin. The ketone (63) gave a colouration with alcoholic ferric chloride solution. 7-Hydroxy-6-benzoyl-4,8-dimethylcoumarin was condensed with ethyl bromoacetate when ethyl 6-benzoyl-4,8-dimethyl-7-coumarinyloxyacetate was obtained. This ester was hydrolysed by treatment with alkali to the corresponding acid. The cyclisation of this acid was affected by refluxing it with acetic anhydride and freshly fused sodium acetate. Simultaneous decarboxylation took place and 4'-phenyl-4,8-dimethyl psoralene (68) was obtained.

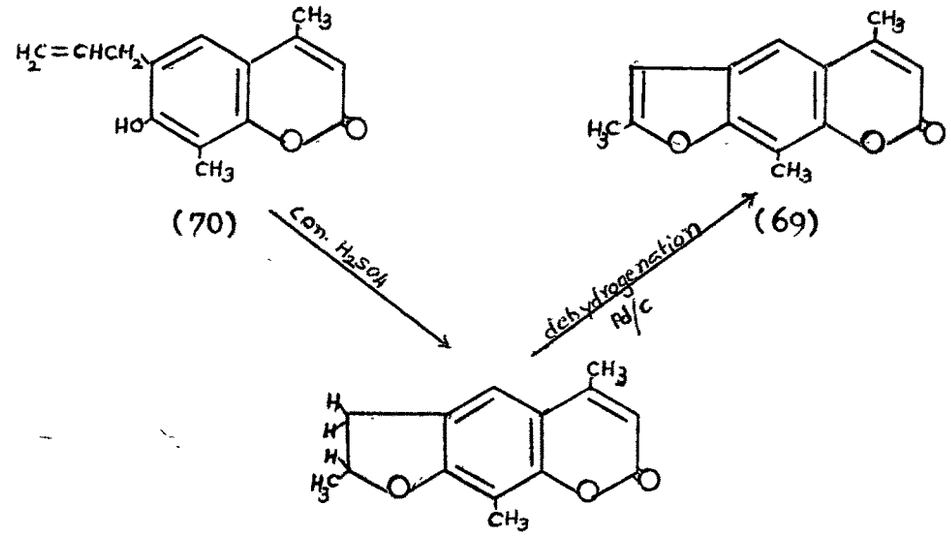


4,5',8-Trimethylpsoralene is a naturally occuring furocoumarin[27a] and was synthesised by Kaufman[28] as described earlier. The present work also deals with the synthesis of 4,5',8-trimethylpsoralene by an another route with the improved yield.

Synthesis of 4,5',8-trimethylpsoralene (69) :

7-Hydroxy-6-allyl-4,8-dimethylcoumarin (70) was triturated with concentrated sulphuric acid for five minutes. The product was found to be insoluble in alkali and it was assigned the structure 4,5',8-trimethyl-4',5'-dihydropsoralene (71). This product was obtained in good yield and was sufficiently pure for further reaction. It was then dehydrogenated by refluxing it with diphenyl ether in the presence of palladised charcoal (10 %) to 4,5',8-trimethylpsoralene (69).

The study of the photodynamic activity of these psoralene derivatives by FMN method developed by Musajo and Rodighiero[20] is in progress.



(71)

EXPERIMENTAL

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

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

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo (f) benzopyran (2.78 g. ; 0.01 M) was dissolved in minimum quantity of acetic acid and bromine dissolved in acetic acid (20 % ; 30 ml. ; 0.04 M) was added slowly with constant stirring and the mixture was heated on a water bath for 3 hours. The separated compound was filtered , dried and crystallised from benzene in yellow shining needles, m.p. 235°. Yield 1.6 g.

Analysis : Found : Br, 22.67 %

$C_{17}H_9O_4Br$ requires : Br, 22.40 %

2-(o-Hydroxy-α-naphthyl)-4-methylfuran-3-carboxylic acid :

3-Bromo-4-methyl-2,5-dioxo-2H,5H-pyrano-(3,2-c) benzo(f)benzopyran (0.8 g.) was refluxed with sodium carbonate solution (10 % ; 15 ml.) for 2 hours. The reaction mixture was allowed to cool and filtered. The filtrate on acidification gave the product which was purified by dissolving it in bicarbonate solution. It was crystallised from hot water in colourless crystals,

m.p. 182°. Yield 0.1 g.

Analysis : Found : C,71.94 ; H,4.75 %.

$C_{16}H_{12}O_4$ requires : C,71.61 ; H,4.48 %.

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

2-(o-Hydroxy-α-naphthyl)-4-methylfuran-3-carboxylic acid (0.5 g.) was dissolved in ethanol and refluxed with hydrochloric acid (5 ml.) for 4 hours. The separated product was filtered and crystallised from acetic acid in shining needles, m.p. 247°. Yield 0.1 g.

Analysis : Found : C,76.30 ; H,4.06 %.

$C_{16}H_{10}O_3$ requires : C,76.79 ; H,4.03 %.

Synthesis of 2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran :

A mixture of 4-hydroxy-5,6-benzocoumarin (4 g.) and malic acid (4 g.) was heated on a steam bath with gradual addition of concentrated sulphuric acid (80 % ; 40 ml.) in 45 minutes period. Heating was continued for further 4 hours. The reaction mixture was added to ice and the product filtered, washed with sodium bicarbonate solution, dried and crystallised from benzene in shining crystals, m.p. 310°. Yield 1 g.

Analysis : Found : C,72.38 ; H,3.31 %.

$C_{16}H_8O_4$ requires : C,72.73 ; H,3.03 %.

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

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

benzopyran (2.64 g. ; 0.01 M) was dissolved in minimum amount of acetic acid and bromine, dissolved in acetic acid (20 % ; 32 ml. ; 0.04 M) was added and the mixture heated on a water bath for 3 hours. The reaction mixture was then added to ice and the bromo derivative was filtered, dried and crystallised from benzene, m.p. 282°. Yield 2 g.

Analysis : Found : Br, 23.68 %.

$C_{16}H_7O_4Br$ requires : Br, 23.32 %.

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

3-Bromo-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran (0.5 g.) was mixed with sodium carbonate solution (10 % ; 10 ml.) and was refluxed for 4 hours. The solution was allowed to cool and filtered. The filtrate on acidification gave the product which was crystallised from acetic acid in yellowish crystals, m.p. 318°. Yield 0.1 g.

Analysis : Found : C,68.47 ; H,2.50 %.

$C_{16}H_8O_5$ requires : C,68.57 ; H,2.85 %.

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

4-Oxo-4H-furo(3,2-c)benzo(f)benzopyran-2-carboxylic acid (0.4 g.) was heated on a sand bath with quinoline (5 ml.) and copper bronze (0.2 g.) for 1 hour. The reaction mixture was filtered hot, acidified with hydrochloric acid and filtered again. The filtrate was

diluted with water and extracted with ether. The product obtained after evaporation of ether was washed with sodium bicarbonate solution and crystallised from dilute acetic acid in colourless needles, m.p. 181°. Yield 0.1 g.

Analysis : Found : C,76.51 ; H,3.16 %.

$C_{15}H_8O_3$ requires : C,76.27 ; H,3.41 %.

Kostanecki-Robinson acetylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin : 7-Acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

A mixture of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin (2.32 g. ; 0.01 M), acetic anhydride (3.5 ml. ; 0.03 M) and freshly fused sodium acetate (1.64 ; 0.02 M) was heated in an oil bath at 180-90° for 9 hours. The reaction mixture was then poured in ice-water. The product was filtered, washed with dilute alkali and crystallised from acetic acid in reddish crystals, m.p. 250°. Yield 0.8 g.

Analysis : Found : C,68.81 ; H,4.97 %.

$C_{17}H_{14}O_5$ requires : C,68.48 ; H,4.70 %.

Attempted deacetylation of 7-acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

7-Acetyl-4,8,10-trimethyl-2H,6H-pyrano(3,2-g)-benzopyran-2,6-dione (0.2 g.) was dissolved in alcohol (65 % ; 50 ml.) and gently refluxed with anhydrous sodium carbonate (1.5 g.) for 2 hours. On working up the reaction mixture no pure product could be isolated.

Attempt to deacetylate by refluxing the compound with concentrated sulphuric acid also did not succeed.

Kostanecki-Robinson benzoylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin : 4,10-Dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

A mixture of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin (2.32 g. ; 0.01 M), benzoic anhydride (6.6 g. ; 0.03 M) and sodium benzoate (2.8 g. ; 0.02 M) was heated in an oil bath at 180-90° for 9 hours. The solid reaction mixture was then washed with hot water several times and finally with sodium bicarbonate solution. This was then crystallised from acetic acid in colourless needles, m.p. 304°. Yield 0.7 g.

Analysis : Found : C,75.26 ; H, 4.34 %.

$C_{20}H_{14}O_4$ requires : C,75.48 ; H,4.40 %.

Attempted Baker-Venkataraman transformation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin : 7-Benzoyloxy-6-acetyl-4,8-dimethylcoumarin :

A mixture of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin (1 g.),benzoyl chloride (1 ml.) and anhydrous potassium carbonate (3 g.) was refluxed in acetone for 35 hours. On working up the reaction mixture as usual, it gave the yellowish product which was crystallised from acetic acid in yellowish needles, m.p.240°. Yield 0.4 g.

Analysis : Found : C,71.90 ; H,4.74 %.

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

Synthesis of 4,10-dimethyl-8-phenyl-7,8-dihydro-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin (1 g.) was dissolved in alcohol and to this cold solution benzaldehyde (2 ml.) and potassium hydroxide solution (100 % ; 10 ml.) was added. The mixture was kept overnight at room temperature. Next day it was diluted with water and ether extracted. The aqueous layer was acidified and the product was filtered, washed and crystallised from benzene in colourless shining crystals, m.p. 209°. The product was found to be insoluble in cold dilute alkali.

Analysis : Found : C,75.50 ; H,4.77 %.

$C_{20}H_{16}O_4$ requires : C,75.00 ; H,5.00 %.

Dehydrogenation of flavanone to 4,10-dimethyl-8-phenyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

The above flavanone (0.3 g.) was mixed with iso-amyl alcohol and selenium dioxide (0.3 g.). The mixture was heated at 140-50° for 8 hours. The hot solution was filtered and the filtrate was kept in a freeze for a day. The separated product was filtered and crystallised from acetic acid in yellowish crystals, m.p. 302-4°. Yield 0.1 g. Mixed m.p. with the the product obtained from K.R.benzoylation of 7-hydroxy-6-acetyl-4,8-dimethylcoumarin was not depressed.

Kostanecki-Robinson acetylation of 7-hydroxy-6-propionyl-4,8-dimethylcoumarin : 4,7,8,10-Tetramethyl-2H,6H-pyrano(3,2-g)benzopyran-2,6-dione :

A mixture of 7-hydroxy-6-propionyl-4,8-dimethylcoumarin (1 g.) ,acetic anhydride (3 ml.) and freshly fused sodium acetate (2 g.)was heated in an oil bath at 180-90° for 8-9 hours. The mixture was cooled and added into ice-water. It was filtered and washed with dilute sodium hydroxide solution. The product was dried and crystallised from dilute acetic acid in colourless needles, m.p. 259°. Yield 0.5 g.

Analysis : Found : C,70.96 ; H,5.21 %.

$C_{16}H_{14}O_4$ requires : C,71.11 ; H,5.18 %.

Kostanecki-Robinson acetylation of 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin : 4,10-Dimethyl-6-phenyl-2H,8H-pyrano(3,2-g)benzopyran-2,8-dione :

7-Hydroxy-6-benzoyl-4,8-dimethylcoumarin (1 g.) was mixed with freshly fused sodium acetate (2 g.) and acetic anhydride (3 ml.). The reaction mixture was heated at 180-90° for 9 hours. It was added to ice-water and filtered. The product was washed with dilute alkali and was taken in minimum amount of ethanol, and filtered. The insoluble product was crystallised from acetic acid in colourless crystals,m.p.258°. Yield 0.3 g.

Analysis : Found : C,75.41 ; H,4.73 %.

$C_{20}H_{14}O_4$ requires : C,75.48 ; H,4.40 %.

7-Acetoxy-6-benzoyl-4,8-dimethylcoumarin :

The alcoholic mother liquor in the above reaction on cooling gave the product which was crystallised from ethanol in shining crystals, m.p. 178°. Yield 0.1 g.

Analysis : Found : C, 71.32 ; H, 4.64 %.

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

Synthesis of 4',4,8-trimethylpsoralene : Ethyl-4,8-dimethyl-6-acetyl-7-coumarinyloxyacetate :

7-Hydroxy-6-acetyl-4,8-dimethylcoumarin (1 g.) was mixed with ethyl bromoacetate (0.8 ml.), dry acetone (50 ml.) and anhydrous potassium carbonate (3 g.). The mixture was refluxed on a water bath for 4-5 hours. After evaporation of acetone the compound was washed with water, filtered and then washed with dilute sodium hydroxide solution. The product was dried and crystallised from acetic acid in colourless needles, m.p. 123°. Yield 0.7 g.

Analysis : Found : C, 64.07 ; H, 6.05 %.

$C_{17}H_{18}O_6$ requires : C, 64.14 ; H, 5.70 %.

6-Acetyl-4,8-dimethyl-7-coumarinyloxyacetic acid :

Ethyl-4,8-dimethyl-6-acetyl-7-coumarinyloxyacetate (1 g.) was hydrolysed with sodium hydroxide solution (10 % ; 25 ml.) by slightly warming and keeping it overnight at the room temperature. Next day it was filtered and the filtrate on acidification with

concentrated hydrochloric acid gave the compound which was purified by taking it in sodium bicarbonate solution. It was crystallised from acetic acid in colourless needles, m.p. 207°. Yield 0.5 g.

Analysis : Found : C,61.63 ; H,4.92 %.

$C_{15}H_{14}O_6$ requires : C,62.06 ; H,4.86 %.

4',4,8-Trimethylpsoralene :

6-Acetyl-4,8-dimethyl-7-coumarinyloxyacetic acid (0.5 g.) was mixed with acetic anhydride (4 ml.) and freshly fused sodium acetate (1 g.). The mixture was then refluxed gently on a sand bath for 2-3 hours. The reaction mixture after cooling was added to ice water. The compound was filtered, washed with sodium bicarbonate solution to remove the acid. The psoralene derivative was crystallised from acetic acid in shining needles, m.p. 183°. Yield 0.25 g. U.V. absorption : λ_{max}^{MeOH} 220, 248 and 298 ($\log\varepsilon$,3.87, 4.63 and 4.28).

Analysis : Found : C,74.11 ; H,5.53 %.

$C_{14}H_{12}O_3$ requires : C,73.67 ; H,5.30 %.

Synthesis of 4'-Ethyl-4,8-dimethylpsoralene :

7-Propionoxy-4,8-dimethylcoumarin :

7-Hydroxy-4,8-dimethylcoumarin (2 g.) was mixed with propionic anhydride (6 ml.) and concentrated sulphuric acid (2-3 drops). The mixture was refluxed on water bath for 4-5 hours. It was then added to ice

water and the separated product was filtered. It was washed with dilute sodium hydroxide solution, dried and crystallised from ethanol in colourless plates, m.p. 129°. Yield 1.5 g.

Analysis : Found : C,68.14 ; H,5.44 %.
$C_{14}H_{14}O_4$ requires : C,68.29 ; H,5.69 %.

7-Hydroxy-6-propionyl-4,8-dimethylcoumarin :

A mixture of 7-propionoxy-4,8-dimethylcoumarin (1 g.) and anhydrous aluminium chloride (4 g.) was heated at 160° for 2 hours. After cooling, the reaction mixture was decomposed with ice cold dilute hydrochloric acid (1:1). The product was filtered and crystallised from dilute acetic acid in colourless crystals, m.p.200°. It gave a red colouration with alcoholic ferric chloride solution. Yield 0.6 g.

Analysis : Found : C,67.89 ; H,5.46 %.
$C_{14}H_{14}O_4$ requires : C,68.29 ; H,5.69 %.

Ethyl 6-propionyl-4,8-dimethyl-7-coumarinyloxyacetate :

7-Hydroxy-6-propionyl-4,8-dimethylcoumarin (1.8 g.), ethyl bromoacetate (2 ml.) and anhydrous potassium carbonate (4 g.) were refluxed on a steam bath for 6 hours. The product was worked out as above, washed with dilute alkali and crystallised from dilute acetic acid in shining needles, m.p.130°. Yield 1.2 g.

Analysis : Found : C,65.55 ; H,6.29 %.
$C_{18}H_{20}O_6$ requires : C,65.05 ; H,6.07 %.

6-Propionyl-4,8-dimethyl-7-coumarinyloxyacetic acid :

Ethyl 6-propionyl-4,8-dimethyl-7-coumarinyloxyacetate (1 g.) was subjected to hydrolysis with sodium hydroxide solution (10 % ; 25 ml.) by keeping the reaction mixture overnight at the room temperature. Next day it was filtered and acidified. The product was dried, and crystallised from dilute acetic acid in colourless crystals, m.p. 184°. Yield 0.6 g.

Analysis : Found : C,62.96 ; H,5.45 %.

$C_{16}H_{16}O_6$ requires : C,63.28 ; H,5.27 %.

4'-Ethyl-4,8-dimethylpsoralene :

A mixture of 6-propionyl-4,8-dimethyl-7-coumarinyloxyacetic acid (0.2 g.), freshly fused sodium acetate (0.2 g.) and acetic anhydride (4 ml.) was heated on a sand bath for 2 hours. The product which separated on pouring the reaction mixture into cold water, was crystallised from dilute ethanol in colourless needles, m.p. 142°. Yield 0.1 g.

U.V. absorption : λ_{max}^{MeOH} 220, 249 and 299 ($\log \epsilon$,3.80, 4.50 and 4.19).

Analysis : Found : C,74.60 ; H,5.97 %.

$C_{15}H_{14}O_3$ requires : C,74.39 ; H,5.78 %.

Synthesis of 4'-Phenyl-4,8-dimethylpsoralene :

7-Benzoyloxy-4,8-dimethylcoumarin :

7-Hydroxy-4,8-dimethylcoumarin (1 g.) was

dissolved in sodium hydroxide solution (10 % ; 15 ml.) and at 0° temperature benzoyl chloride (1 ml.) was added with vigorous shaking. The mixture was kept for 15 minutes at the room temperature, keeping it in alkaline condition. It was then filtered, washed with dilute sodium hydroxide solution and crystallised from acetic acid in colourless crystals, m.p. 213°.
Yield 0.8 g.

Analysis : Found : C,73.11 ; H,4.96 %.
$C_{18}H_{14}O_4$ requires : C,73.48 ; H,4.76 %.

7-Hydroxy-6-benzoyl-4,8-dimethylcoumarin :

A mixture of 7-benzoyloxy-4,8-dimethylcoumarin (1.5 g.) and anhydrous aluminium chloride (6 g.) was heated in an oil bath at 160° for 2 hours. The reaction mixture was cooled, treated with ice and hydrochloric acid and filtered. The product after drying was crystallised from acetic acid in yellowish plates. It gave a red colouration with alcoholic ferric chloride solution, and had m.p. 209°. Yield 0.7 g.

Analysis : Found : C,73.13 ; H,4.81 %.
$C_{18}H_{14}O_4$ requires : C,73.48 ; H,4.76 %.

Ethyl-6-benzoyl-4,8-dimethyl-7-coumarinyl-oxyacetate :

A mixture of 7-hydroxy-6-benzoyl-4,8-dimethylcoumarin (0.5 g.), ethyl bromoacetate (0.5 ml.) and anhydrous potassium carbonate (2 g.) in acetone

was refluxed on a steam bath for 5 hours. The reaction mixture was filtered hot and the acetone was evaporated. The product was washed with dilute sodium hydroxide solution and crystallised from dilute acetic acid in colourless shining needles, m.p. 131°. Yield 0.3 g.

Analysis : Found : C,69.10 ; H,5.80 %.

$C_{22}H_{20}O_6$ requires : C,69.46 ; H,5.30 %.

6-Benzoyl-4,8-dimethyl-7-coumarinyloxyacetic acid :

Ethyl 6-benzoyl-4,8-dimethyl-7-coumarinyloxyacetate (0.3 g.) was hydrolysed with sodium hydroxide solution (10 % ; 15 ml.) by keeping it overnight at the room temperature. It was then filtered and acidified. The product was crystallised from dilute acetic acid in shining needles, m.p. 199°. Yield 0.2 g.

Analysis : Found : C,67.75 ; H,4.85 %.

$C_{20}H_{16}O_6$ requires : C,68.18 ; H,4.58 %.

4'-Phenyl-4,8-dimethylpsoralene :

A mixture of 6-benzoyl-4,8-dimethyl-7-coumarinyloxyacetic acid (0.2 g.), freshly fused sodium acetate (0.2 g.) and acetic anhydride (4 ml.) was heated on a sand bath for 2 hours. The mixture was added to ice water and the filtered product was washed with dilute alkali and crystallised from

alcohol in colourless crystals, m.p. 198°. Yield 0.1 g. U.V. absorption : λ_{max}^{MeOH} 222, 250 and 299 (log ε ,3.89, 4.43 and 4.18).

Analysis : Found : C,78.31 ; H,5.23 %.
$C_{19}H_{14}O_3$ requires : C,78.60 ; H,4.85 %.

Synthesis of 4,5',8-trimethylpsoralene :

4,5',8-Trimethyl-4',5'-dihydropsoralene :

7-Hydroxy-6-allyl-4,8-dimethylcoumarin (0.5 g.) was mixed with concentrated sulphuric acid (1 ml.) with constant shaking for 5 minutes. The clear solution was added to ice-water and the separated product was filtered and washed with dilute alkali. It was crystallised from acetic acid in colourless needles, m.p. 176°. Yield 0.4 g.

Analysis : Found : C,72.96 ; H,5.91 %.
$C_{14}H_{14}O_3$ requires : C,73.02 ; H,6.13 %.

4,5',8-Trimethylpsoralene :

A mixture of 4,5',8-trimethyl-4',5'-dihydropsoralene (0.5 g.), diphenyl ether (4 ml.) and palladised charcoal (10 % ; 0.3 g.) was refluxed for 6 hours, and filtered hot. The reaction mixture was cooled and the separated crystals were washed with petroleum ether and crystallised from alcohol in shining needles, m.p. 232°. Yield 0.35 g. The product was identical with 4,5',8-trimethylpsoralene prepared by Kaufman.

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