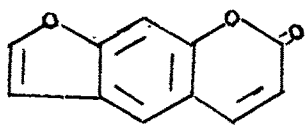
CHAPTER I

PART I

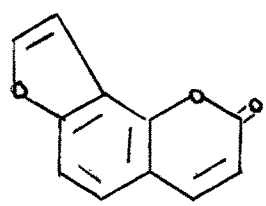
STUDIES ON THE SYNTHESIS OF FUROCOUMARINS

Studies on the synthesis of 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)



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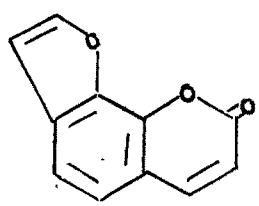

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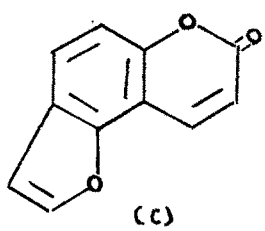

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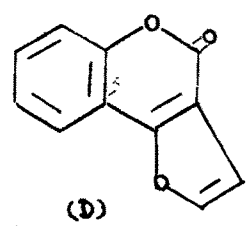


(D)

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 (1) but it is relatively non-toxic to mammals. Schonberg and Latif (2)

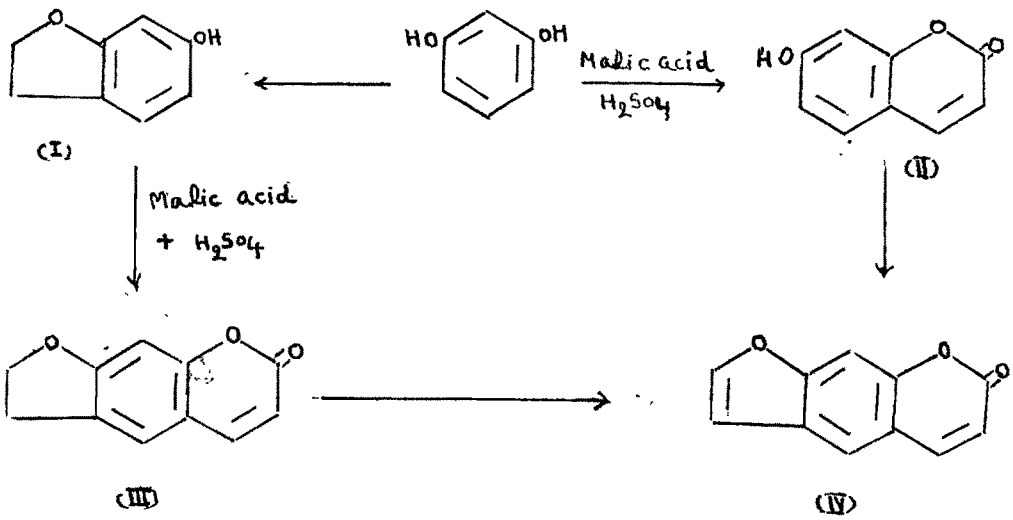
observed that it possesses molluscicidal activity. It was demonstrated by Elwi (3) that it produces fatty degeneration of liver and adrenal hemorrhage if it is administered in large doses to mammals. In the case of human beings the compound has found medical acceptance for the treatment of leukoderma (4). 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 (5). There is some evidence that xanthotoxin under certain conditions may be carcinogenic(6).

Pathak and Fellman (7) 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.

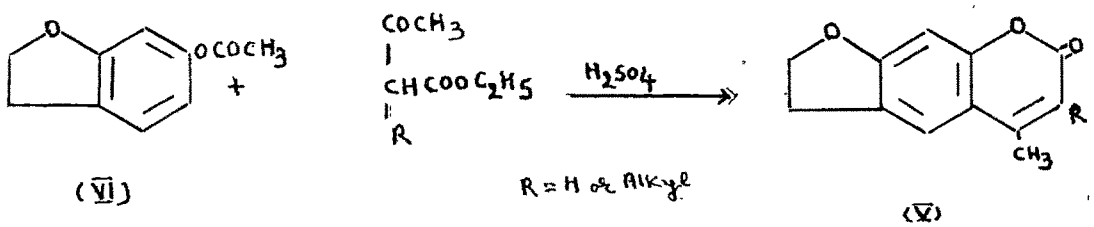
The methods of synthesis of furocoumarins are briefly reviewed here. Two routes are available for the synthesis of psoralenes, either (a) through 6-hydroxycoumaran (I) or (b) through umbelliferone (II).

Spath and Pailer (8) carried out the condensation of 6-hydroxycoumaran with malic acid in the presence of conc. sulphuric acid and obtained 2,3-dihydropsoralene (III)

which on dehydrogenation gave psoralene (IV).

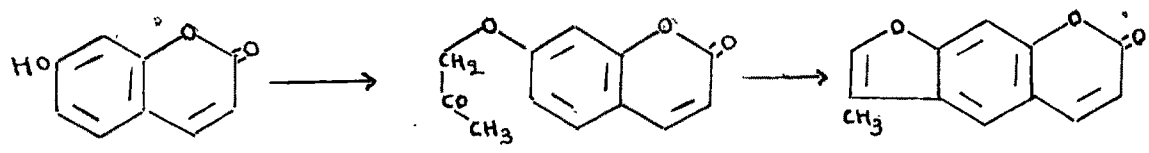


Later on Horning and Reisner (9) prepared different 5-substituted -2,3-dihydropsoralenes (V) by condensing 6-acetoxycoumaran (VI) with a variety of β-ketonic esters in the presence of sulphuric acid. This reaction has been further extended by Erse and Christensen (10) to obtain 6-alkyl-2,3-dihydro-5-methylpsoralenes by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxycoumaran.



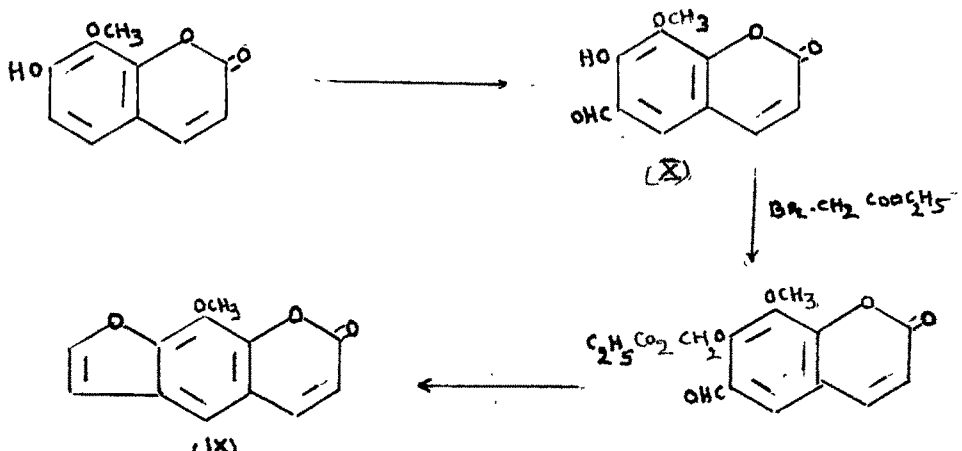
Ray, Shilooja and Vaid (11) have approached the problem of furocoumarin synthesis by starting with umbelliferone. In this procedure, they carried out the

cyclization of 7-acetonyloxycoumarin (VII), obtained by treating umbelliferone with chloracetone, in the presence of sodium ethoxide to 3-methylpsoralene (VIII).



(VII) (VIII)

Rodighero and Antonello (12) synthesised xanthotoxin (IX) by first preparing 7-hydroxy-8-methoxy-6-formylcoumarin (X) and then treating it with ethyl bromo-acetate, followed by hydrolysis, cyclization and decarboxylation.

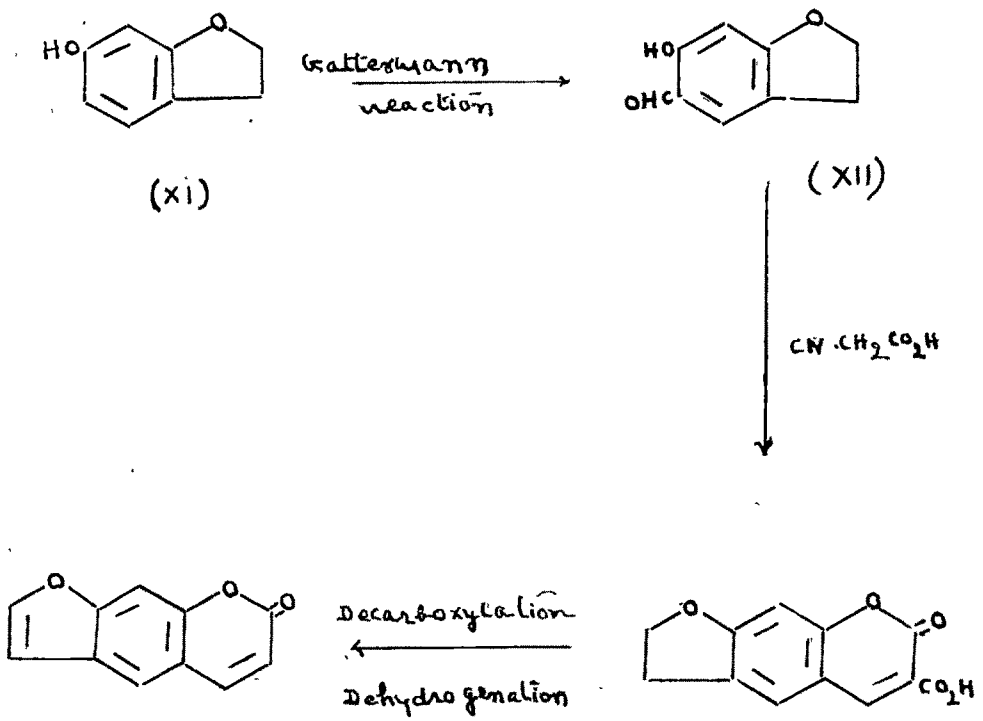


(X) (IX)

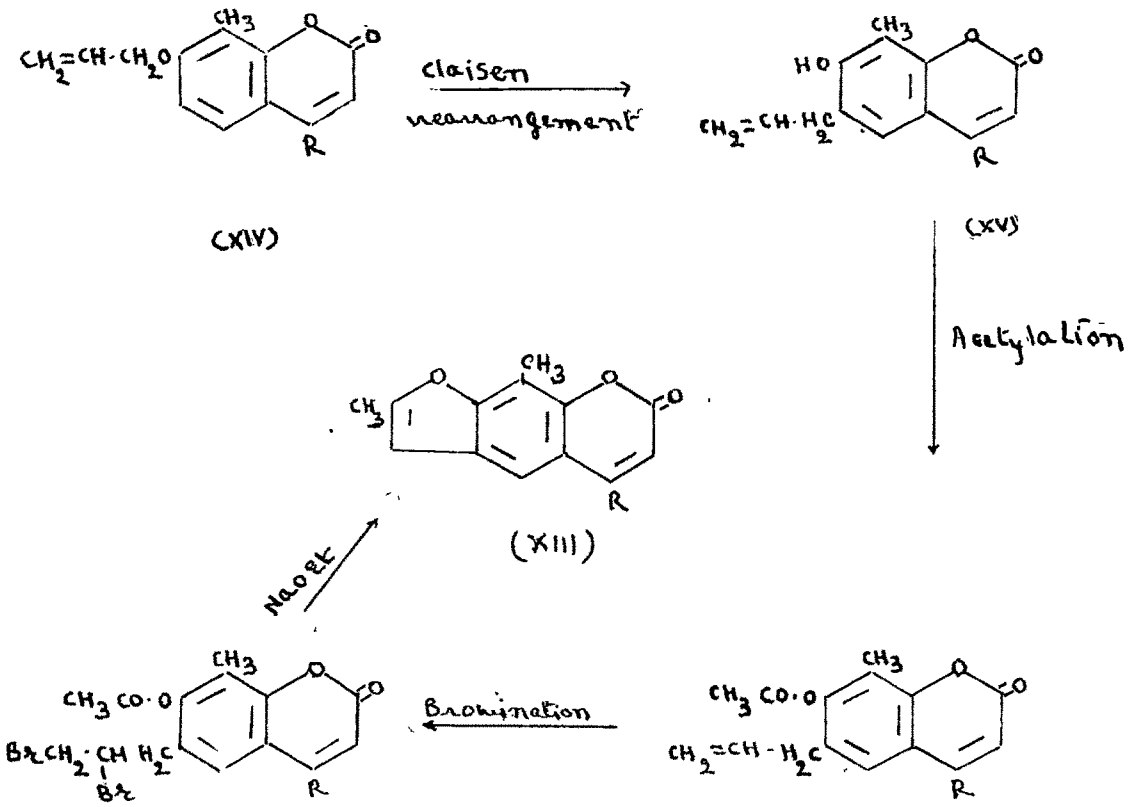
Limaye and Gangal (13) synthesised 3,4'-dimethyl-7,6-furocoumarin from 7-hydroxy-6-acetyl-4-methylcoumarin using the same procedure.

Robinson et al. (14) synthesised psoralene by first subjecting 6-hydroxycoumaran (XI) to Gattermann aldehyde synthesis and then condensing the 6-hydroxy-5-

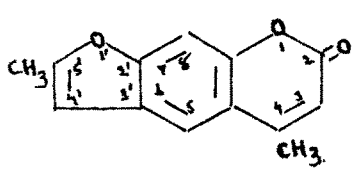
formylcoumaran (XII) with cyanoacetic acid followed by decarboxylation and dehydrogenation.



Recently Kaufman (15) has prepared 4,5',8-trimethylpsoralene (XIII) (a) and 5',8-dimethylpsoralene (XIII) (b) by first carrying out the Claisen rearrangement of 7-allyloxy-4,8-dimethyl-(XIV) (a) and 7-allyloxy-8-methylcoumarin (XIV) (b) to 7-hydroxy-6-allyl-4,8-dimethyl-(XV) (a) and 7-hydroxy-6-allyl-8-methylcoumarin (XV) (b) respectively. These were then acetylated, brominated and cyclised to obtain psoralene derivatives.



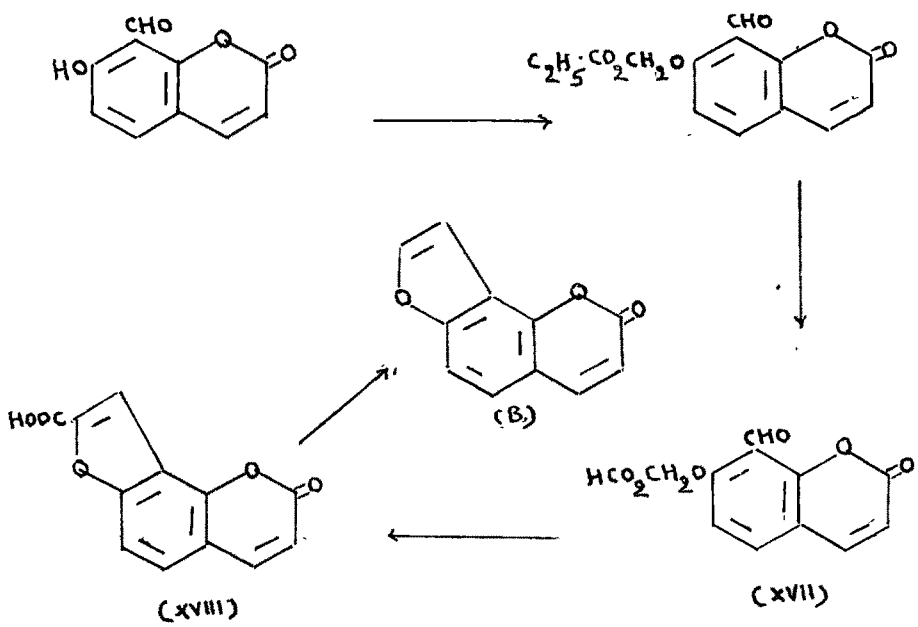
Using a similar procedure Kaufman synthesised 4,5',4'-dimethylpsoralene (XVI).



(XVI) (Numbering according to Kaufman)

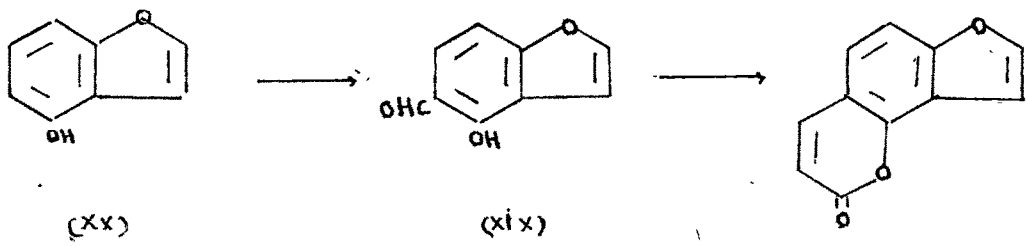
Angelicin is a naturally occuring furocoumarin of type (B) and is synthesised by Spath and Pailer (16) by condensing sodium salt of β-formylumbelliferone with iodoacetic ester under pressure and the product obtained

subjected to hydrolysis followed by cyclisation. Naik and Thakor (17) repeated the whole process using ethyl bromoacetate in acetone in the first step. They observed that the melting point of 7-(8-formylcoumarinoxy)-acetic acid (XVII) was 248-9° instead of 178-81° as reported by Spath and Pailer (16). They also observed that on cyclisation of this product, angelicin-2'-carboxylic acid (XVIII) which was not isolated by Spath and Pailer was obtained and it underwent decarboxylation when heated with copper and quinoline to angelicin.



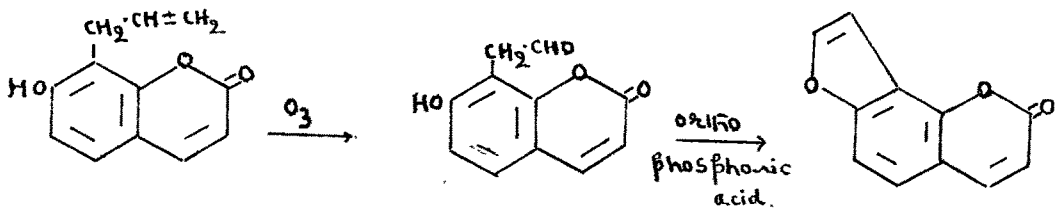
Using the above method Shah and Shah (18) synthesised furano-3'-methyl-4',5',7',8-coumarin from 7-hydroxy-8-acetylcoumarin.

Limaye (19) synthesised angelicin by preparing 4-hydroxy-5-formylcoumarin (XIX) from 4-hydroxycoumarin (XX) and then subjecting it to Perkin reaction.



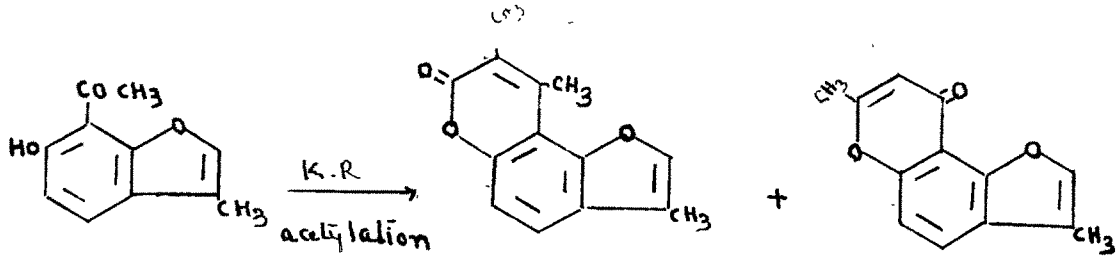
(XX) (XIX)

Aneja, Mukerjee and Seshadri (20) synthesised angelicin by subjecting first 7-hydroxy-8-allylcoumarin (XXI) to ozonolysis and subsequent cyclisation of 7-hydroxy-coumarin-8-acetaldehyde (XXII) with ortho phosphoric acid.



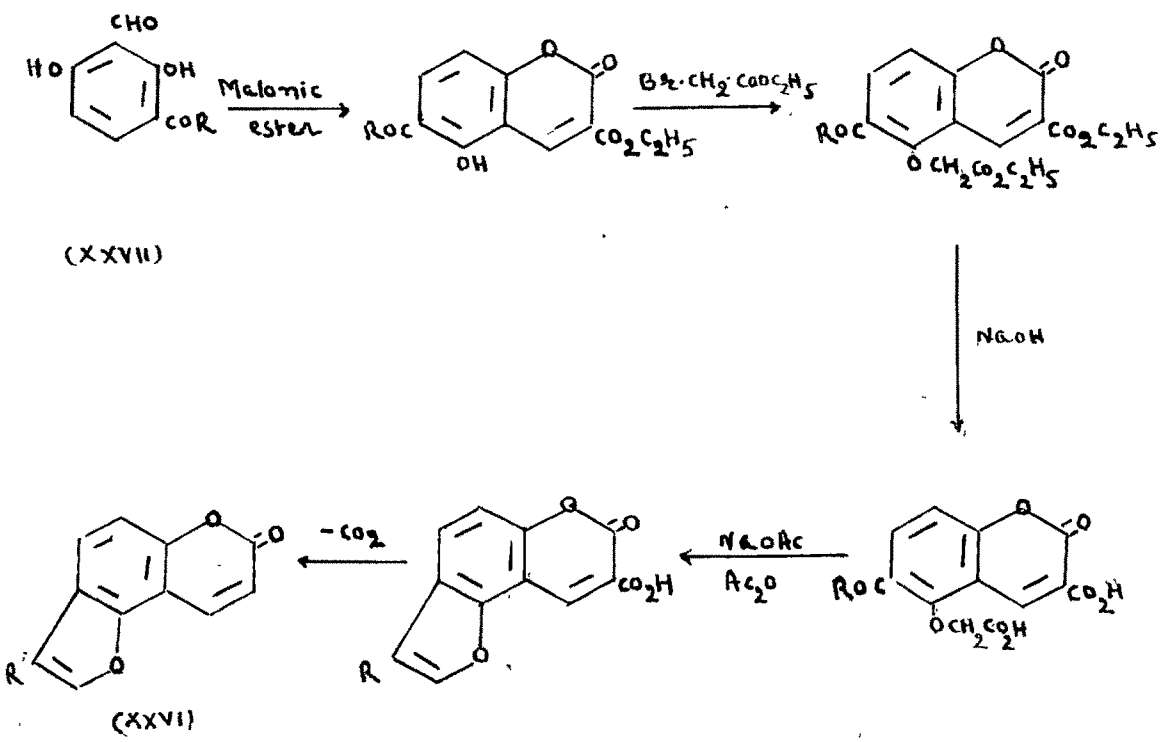
(XXI) (XXII)

Furocoumarins of type (C) have been synthesised by several workers. Limaye and Sathe (21) subjected 6-hydroxy-7-acetyl-3-methylcoumarone (XXIII) to Kostanecki-Robinson acetylation and obtained furo-3',4'-dimethyl-4',5'-7,6,5,6-coumarin (XXIV) in poor yield along with furo-2,3'-dimethyl-4',5'-7,6,5,6-chromone (XXV).



(XXIII) (XXIV) (XXV)

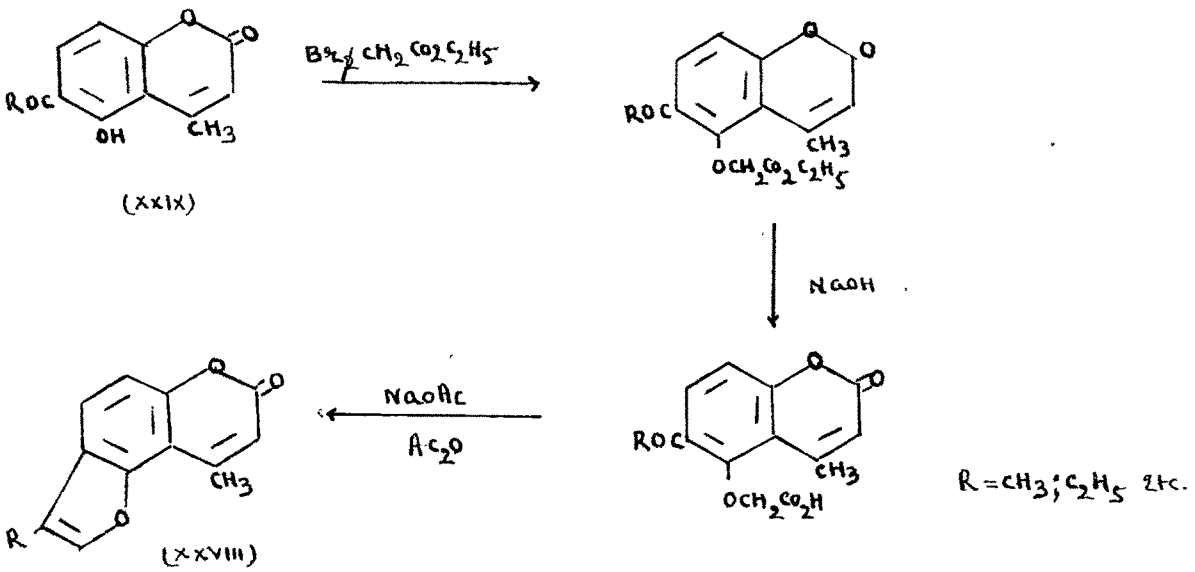
Shah and Shah (22) synthesised 3'-alkyl-furo-4',5'-6,6-coumarin (XXVI) by first condensing 2,4-dihydroxy-3-formylacetophenone (XXVII) with malonic ester and then carrying out the condensation with ethyl bromoacetate followed by hydrolysis, subsequent cyclisation and decarboxylation.



(XXVII)

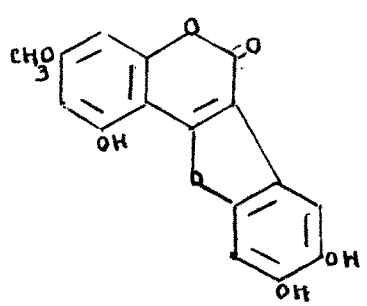
(XXVI)

Chudger and Shah (23) synthesised several 3'-alkyl-4-methyl-furo-4',5',6,5-coumarin (XXVIII) by condensing 5-hydroxy-6-acyl-4-methylcoumarin (XXIX) with ethyl bromoacetate followed by hydrolysis and subsequent cyclisation.

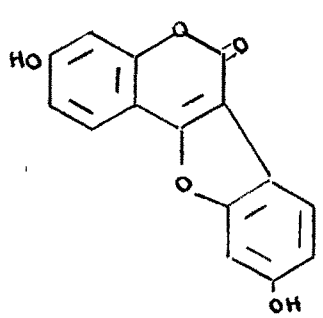


(XXIX) (XXVIII)

Furocoumarins of type (D) have recently assumed great importance as they occur in nature and also possess estrogenic properties. For example, Govindachari et al.(24) found that Wedelolactone isolated from Wedelia Calendulacea had the structure (XXIXa)



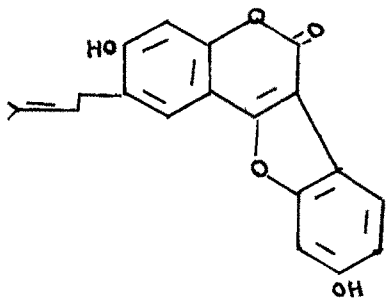
(XXIXa)



(XXIXb)

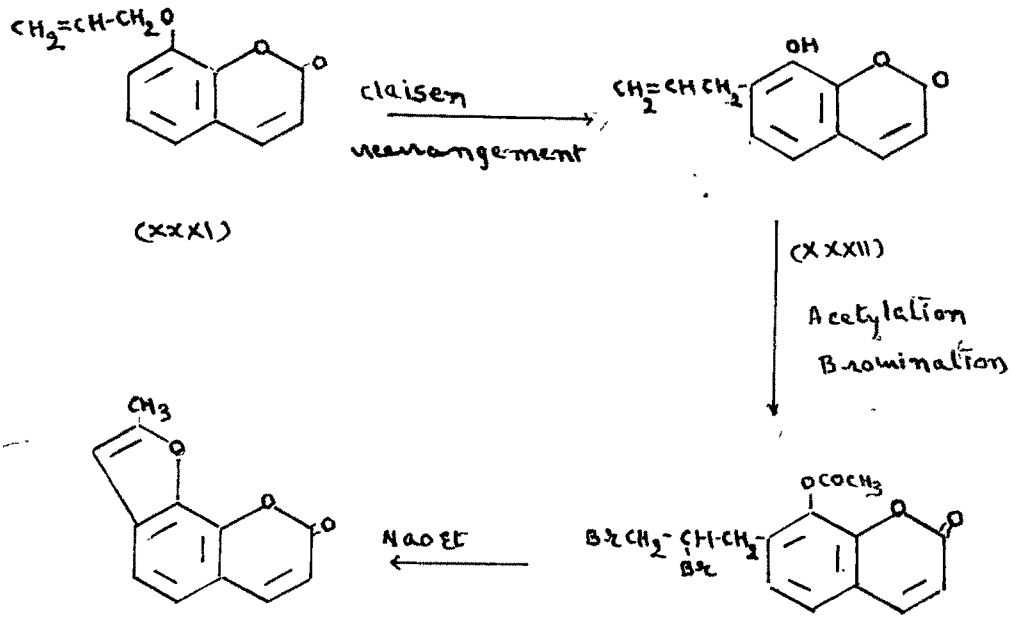
Further, Blickoff, Booth and their associates (25) who isolated the estrogen coumestrol from ladinoclover and alfalfa found that it had the structure (XXIX)

Recently Khastgir, Duttagupta and Sengupta (26) have isolated a phenolic coumarin-psoralidin from Psoralea Corylifolia and established its structure as 6-(3-methylbut-2-enyl)-coumestrol (XXX).



(XXX)

Furocoumarin of type (E) has been recently synthesised by Kaufman and Russey (27) . They carried out the Claisen rearrangement of 8-allyloxycoumarin (XXXI) and obtained 7-allyl-8-hydroxycoumarin (XXXII), the acetyl derivative of which was brominated. This product (XXXIII) underwent cyclisation to 2'-methyl-furo-4',5'-8,7-coumarin (XXXIV) when refluxed with sodium ethoxide in absolute ethanol.



(XXXI) (XXXII) (XXXIII) (XXXIV)

The present work deals with the synthesis of the following furocoumarins.

(a) Furo-2'-carboxy-(4',5'-7,8)-coumarin

(b) Furo-3'-methyl-(4',5'-7,8)-coumarin

(c) Furo-3',5-dimethyl-(5',4'-7,8)-coumarin

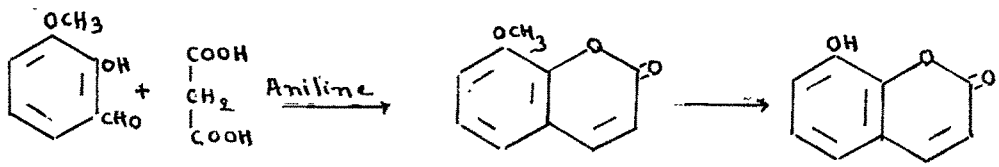
(d) Furo-3',8-dimethyl-(4',5'-6,7)-coumarin

(e) 3'-Methyl benzofurano-(6',7'-8,7)-4-methylcoumarin

(a) For the synthesis of (a) the starting material required was 8-hydroxy-7-formylcoumarin and for the synthesis of (b) 8-hydroxy-7-acetylcoumarin both of which ~~are~~ were hitherto unknown. Though several mono and di-hydroxy-coumarins have been subjected to various substitution reactions little work has been done on the 8-hydroxycoumarin

probably because this coumarin derivative is not easily accessible.

The 8-hydroxycoumarin (XXXV) required in the present work was synthesised from o-vanillin by the method of Cingolani (28) as shown below.

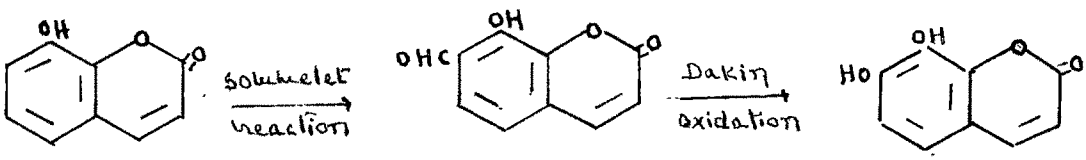


(XXXV)

8-hydroxy-7-formylcoumarin was synthesised from 8-hydroxy-coumarin by formylation with hexamethylenetetramine. The monoformyl derivative gave a brown ferric chloride colouration. On Dakin oxidation it afforded the known 7,8-dihydroxycoumarin (29) which established its structure.

The 8-hydroxy-7-formylcoumarin (XXXVI) on condensation with ethylbromoacetate gave ethyl-7-formyl-8-coumarinoxyacetate. This ester was hydrolysed by treatment with alkali to 7-formyl-8-coumarinoxyacetic acid. Furo-2'-carboxy-(4',5'-7,8)-coumarin (XXXVII) was obtained on heating the acid with sodium acetate and acetic anhydride. Decarboxylation with quinoline-copper powder did not give a pure product.

(b) Furo-3-methyl-(4',5'-7,8)-coumarin was synthesised from 8-hydroxy-7-acetylcoumarin (XXXVIII). This derivative was prepared by the Friedel-Crafts acetylation of 8-hydroxy-coumarin. The same acetyl derivative was obtained on Fries migration of 8-acetoxycoumarin. Its structure has been established by Dakin oxidation when the known 7,8-dihydroxy-



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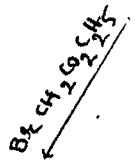
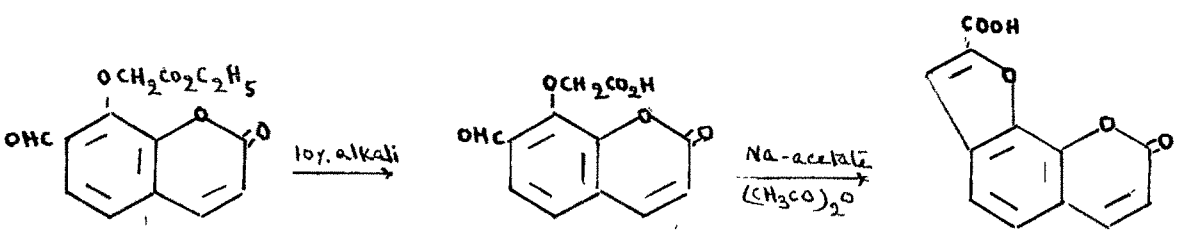
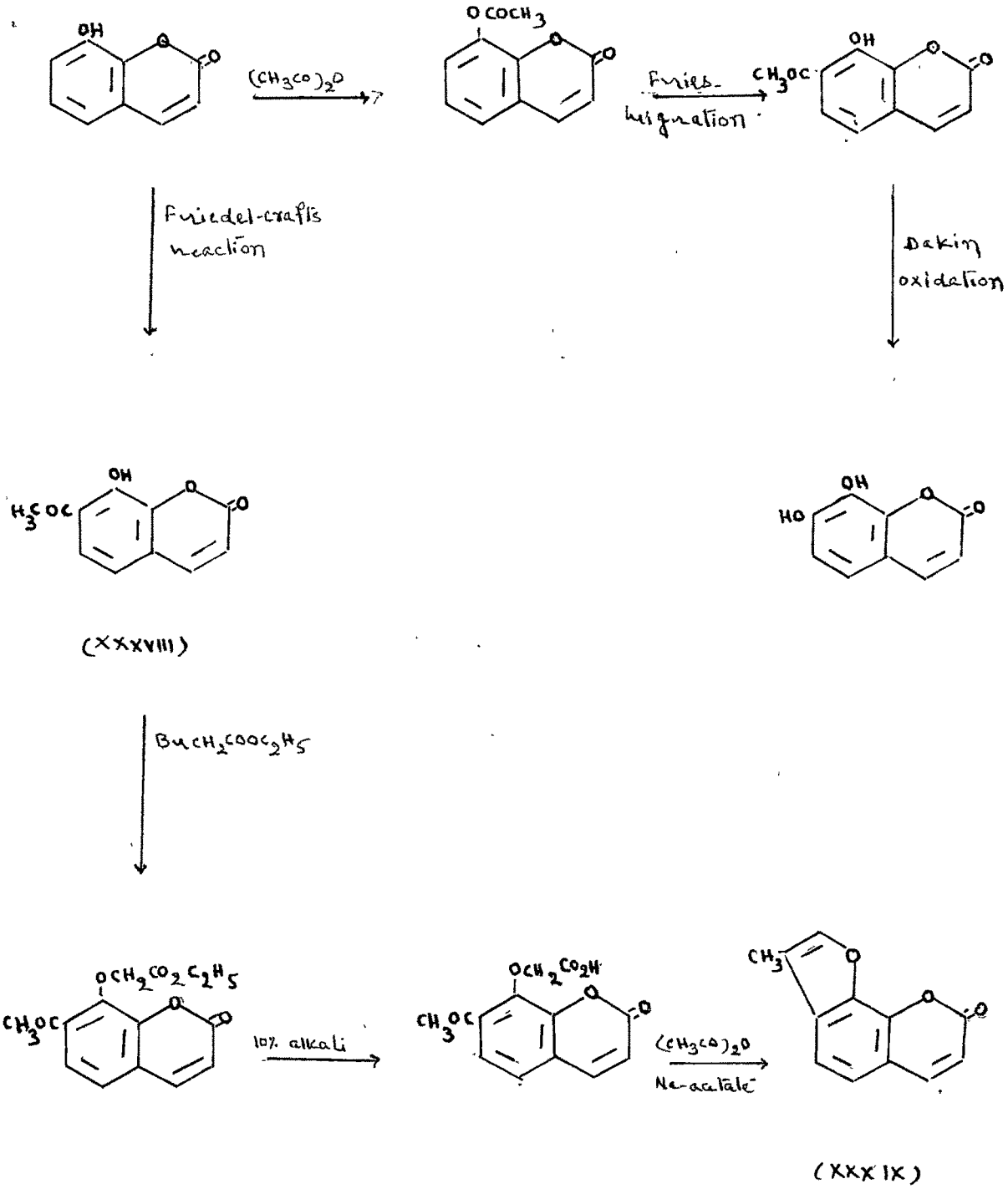




(XXXVII)


OH
O
O
$(CH_3CO)_2O$
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Fries-
migration
CH_3OC
Friedel-crafts
reaction
Dakin
oxidation
H_3COC
HO
(XXXVIII)
$BuCH_2COOC_2H_5$
$OCH_2CO_2C_2H_5$
10% alkali
OCH_2CO_2H
$(CH_3CO)_2O$
Na-acetate
CH_3
(XXXIX)

coumarin was obtained, ~~on Dakin oxidation~~.

8-Hydroxy-7-acetylcoumarin was condensed with ethylbromoacetate when ethyl-7-acetyl-8-coumarin-oxyacetate was obtained. This ester was hydrolysed by treatment with alkali to 7-acetyl-8-coumarin-oxyacetic acid. The cyclisation of this acid was effected by refluxing it with acetic anhydride and freshly fused sodium acetate. Simultaneous decarboxylation took place and furo-3'-methyl-(4',5'-7,8)-coumarin was obtained.

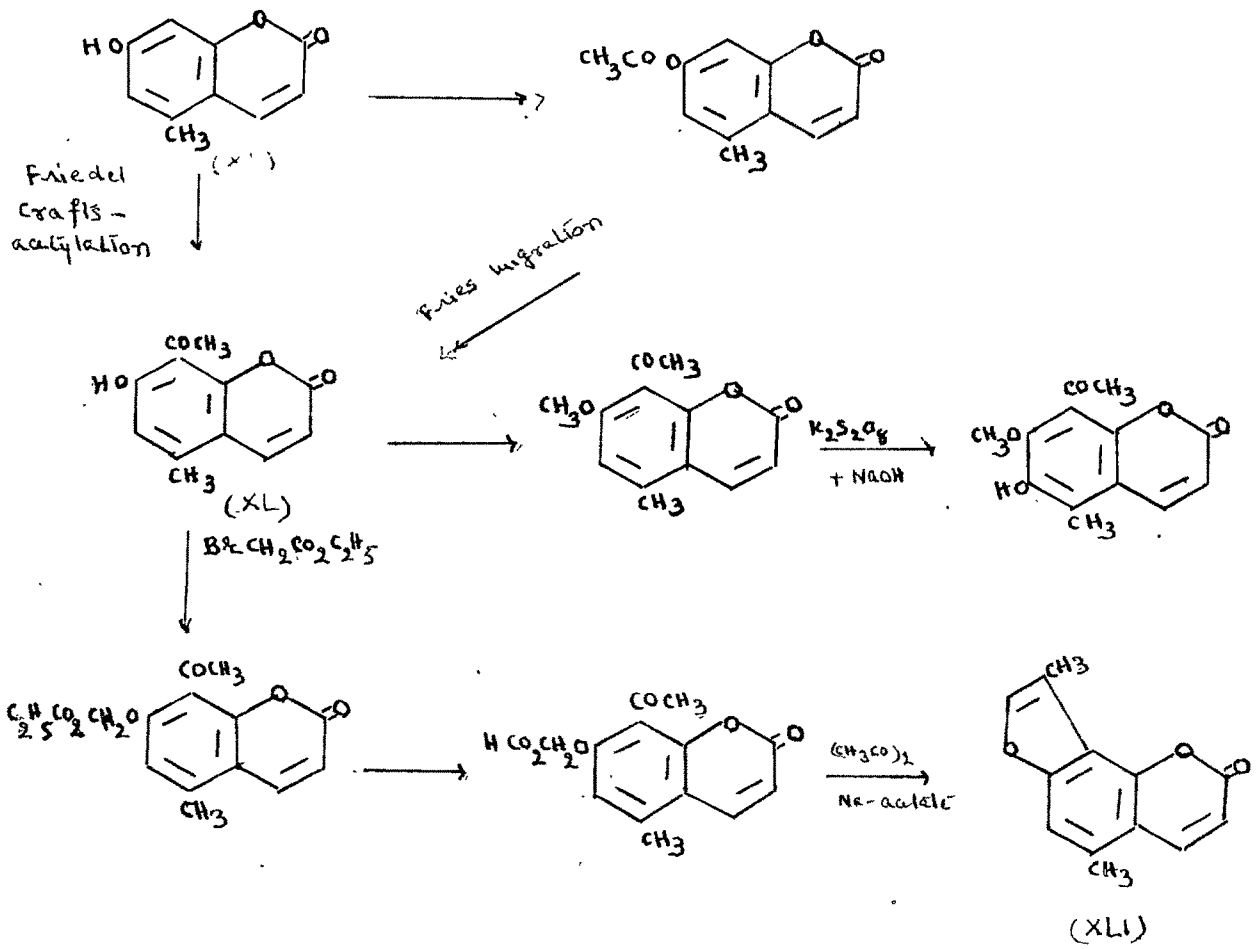
(c) Furo-3',5-dimethyl-(5',4',7,8)-coumarin was prepared from 7-hydroxy-5-methyl-8-acetylcoumarin.

~~The~~ 7-Hydroxy-5-methylcoumarin (30) on Friedel-Crafts acetylation gave 7-hydroxy-5-methyl-8-acetylcoumarin. The above structure has been assigned because its methyl ether underwent Elbs persulphate oxidation to give 7-methoxy-6-hydroxy-5-methyl-8-acetylcoumarin. Sethna and his co-workers(34) have used this as a diagnostic test for finding out whether the 6-position in a coumarin is substituted or not. If the 6-position is substituted no reaction takes place because the oxidation in the 8-position is very difficult. The same 8-acetyl derivative was obtained on Fries-migration of 7-acetoxy-5-methylcoumarin.

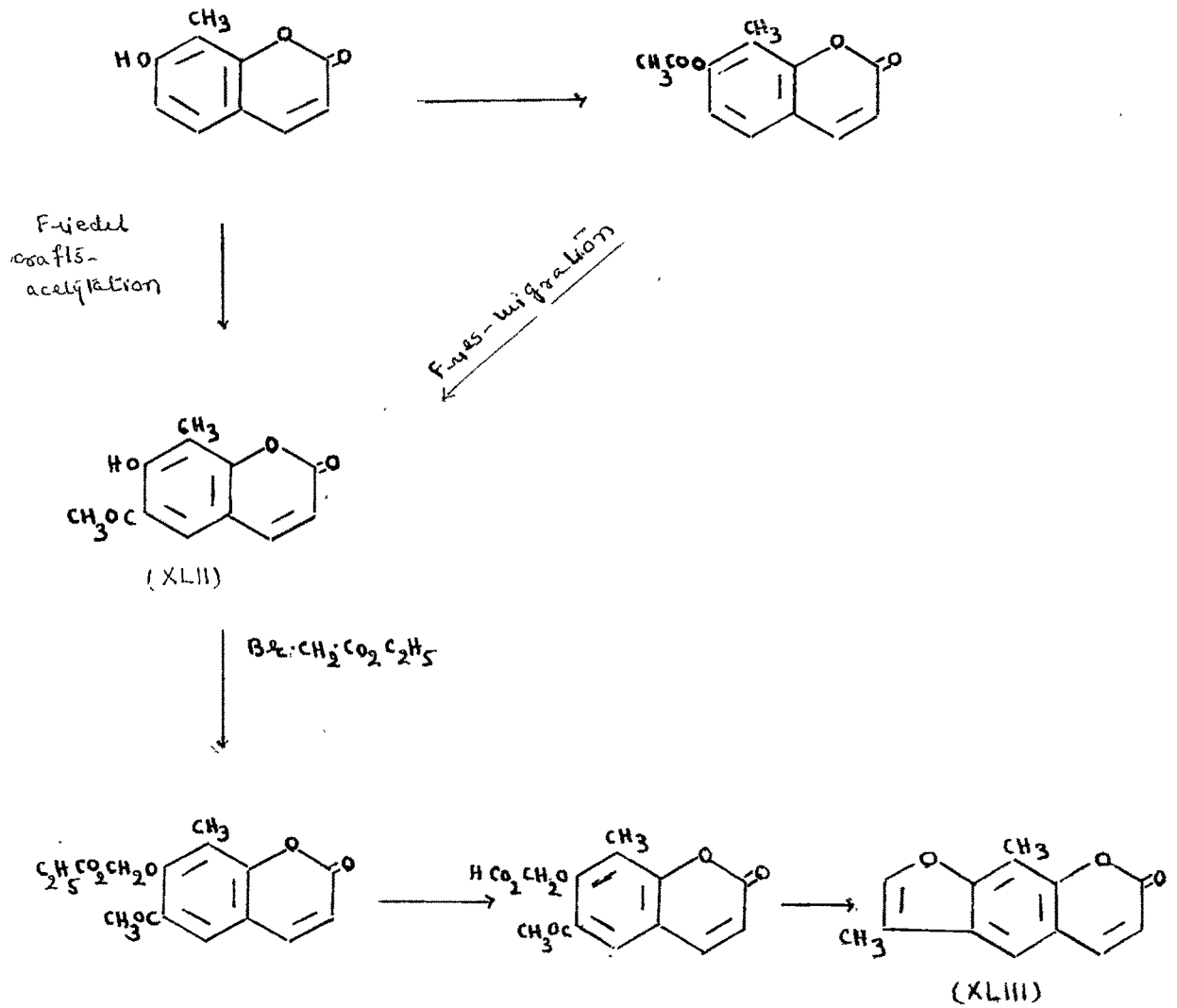
7-Hydroxy-5-methyl-8-acetylcoumarin (XLX) was condensed with ethyl bromoacetate in boiling acetone in the presence of anhydrous potassium carbonate when ethyl-5-methyl-8-acetyl-7-coumarin-oxyacetate was obtained. On hydrolysis with alkali it gave 5-methyl-8-acetyl-7-coumarin-oxyacetic acid. The cyclisation of this acid was

affected by refluxing it with acetic anhydride and freshly fused sodium acetate. Simultaneous decarboxylation and ring closure took place and furo-3',5-dimethyl (4',5',7,8) coumarin (XLII) was obtained.

(d) Furo-3',8-dimethyl (4',5',6,7)-coumarin (XLIII) was synthesised from 7-hydroxy-6-acetyl-8-methylcoumarin (XLIV). This acetyl derivative was derived from 7-hydroxy-8-methylcoumarin (31) by Friedel-Crafts acetylation. It gave purple brown colouration with alcoholic ferric chloride and as there is no other position where the acetyl group can migrate, 7-hydroxy-6-acetyl-8-methylcoumarin structure has been assigned. The same 6-acetyl derivative was obtained on Fries-migration of 7-acetoxy-8-methylcoumarin.



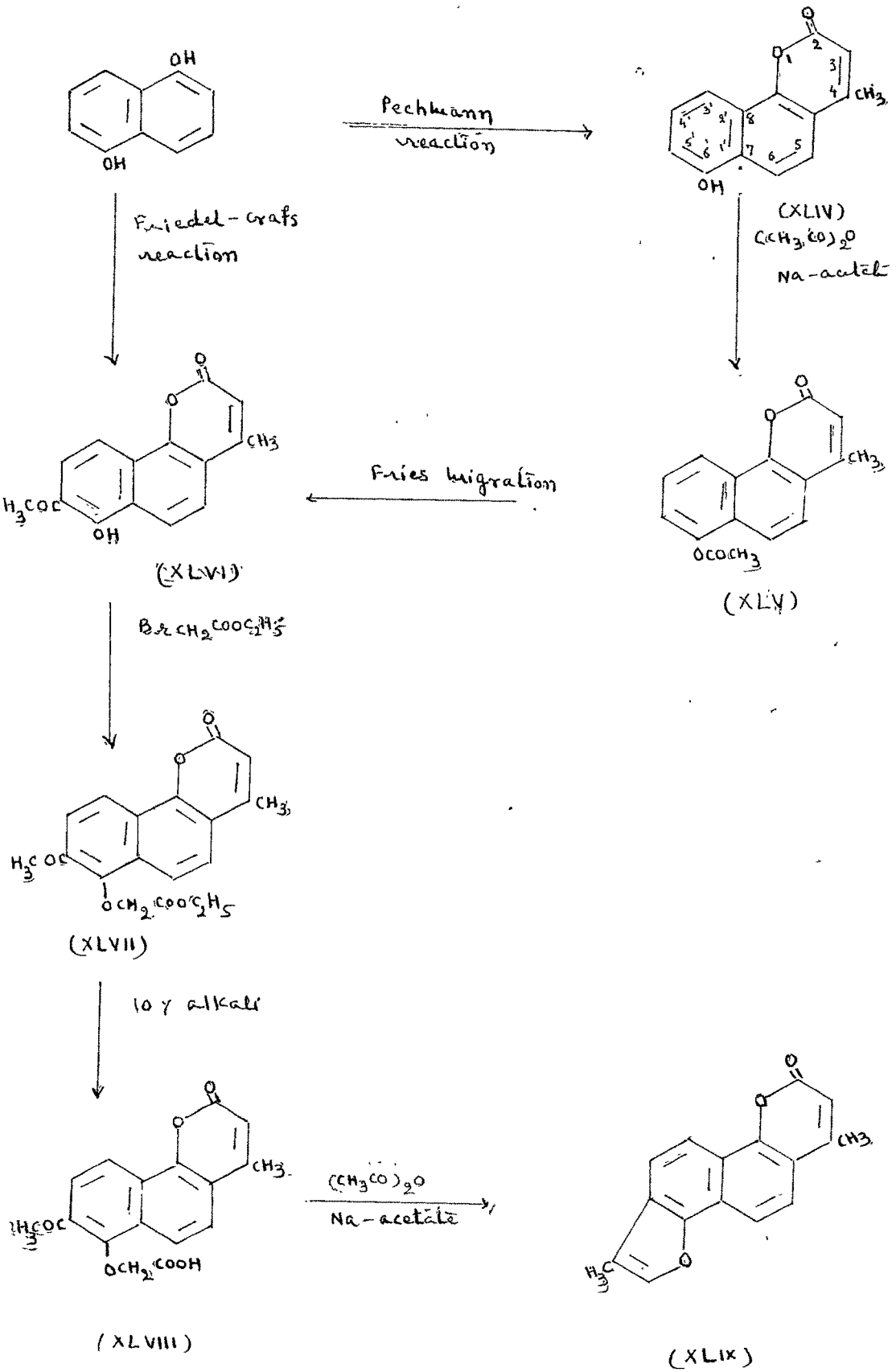
7-Hydroxy-6-acetyl-8-methylcoumarin on condensation with ethyl bromoacetate under the same conditions described before gave ethyl-8-methyl-6-acetyl-7-coumarinoxyacetate. The ester was hydrolysed with alkali to 6-acetyl-8-methyl-7-coumarinoxyacetic acid. Furo-3',8-dimethyl-4',5'-6,7-coumarin was obtained on heating the acid with sodium acetate and acetic anhydride.



(e) Although a number of furocoumarins have been synthesised, there does not appear to have been any instance of the building up of a furan ring on a benzocoumarin. The reason for this probably is that the required hydroxy benzocoumarins are not readily available. The only dihydroxy naphthalene which appears to have been condensed with ethylacetoacetate is the 1,5-dihydroxynaphthalene (32). This gives 6'-hydroxy-4-methyl-7,8-benzocoumarin in fairly good yield. In the present work this coumarin derivative has been made the starting material for the synthesis of 3'-methyl benzofurano-(6',7'-8,7)-4-methylcoumarin.

The above furocoumarin was synthesised from 6'-hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin. This acetyl derivative was derived from 6'-hydroxy-4-methyl-7,8-benzocoumarin (XLIV) by Friedel-Crafts acetylation. It gave light brown colouration with alcoholic ferric chloride. Further, on Kostanecki-Robinson benzoylation, it gave a flavone derivative. On these basis the 5'-acetyl structure has been assigned to the product of Friedel-Crafts reaction. The same 5'-acetyl derivative was obtained on Fries-migration of 6'-acetoxy-4-methyl-7,8-benzocoumarin (XLV).

6'-Hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin (XLVI) was condensed with ethyl bromoacetate when ethyl-5'-acetyl-6'-(4-methyl-7,8-benzocoumarin)-oxyacetate (XLVII) was obtained. This ester was hydrolysed by treatment with alkali to the corresponding acid (XLVIII).


OH
OH
Pechmann reaction
Friedel-Crafs reaction
(XLIV)
$(CH_3CO)_2O$
Na-acetate
Fries migration
(XLVI)
(XLV)
$BrCH_2COOC_2H_5$
(XLVII)
10% alkali
$(CH_3CO)_2O$
Na-acetate
(XLVIII)
(XLIX)

The cyclisation of this acid was effected by refluxing it with acetic anhydride and freshly fused sodium acetate, simultaneous decarboxylation took place and 3'-methylbenzofurano-(6',7'-8,7)-4-methylcoumarin (~~XXXXIX~~ XLIX) was obtained.

E X P E R I M E N T A L

Synthesis of furo-coumarins

(a) Synthesis of furo-2',4',5',7,8-coumarin :

8-Hydroxy-7-formylcoumarin

8-Hydroxycoumarin (1.62 g. ; 0.01 M) and hexamethylene tetramine (5.62 g. ; 0.04 M) in glacial acetic acid (30 ml.) were heated on a steam bath for 7 hrs. Hydrochloric acid (1 : 1) was then added and the heating continued for further 2 hrs. The product obtained on extraction with ether, crystallised from glacial acetic acid in yellow needles, m.p. 238-40°.

Analysis : Found : C=63.5 % ; H=3.2 %.

$C_{10}H_6O_4$ requires : C=63.1 % ; H=3.1 %.

Dakin oxidation of 8-hydroxy-7-formylcoumarin :

7,8-Dihydroxycoumarin

Hydrogen peroxide (6 % ; 0.5 ml.) was dropwise added with stirring to a solution of 8-hydroxy-7-formyl-coumarin (0.5 g.) in sodium hydroxide solution (5 % ; 10 ml.) at 0°. After keeping for 3 hrs. in a refrigerator it was acidified. The crude product was crystallised from alcohol in yellow needles, m.p. 255-6°. Mixed m.p. with the known 7,8-dihydroxycoumarin was not depressed.

Ethyl-7-formyl-8-coumarinoxyacetate

8-Hydroxy-7-formylcoumarin (1.9 g. ; 0.01 M) bromoacetic ester (1.6 g. ; 0.01 M) and potassium carbonate (1.3 g. ; 0.01 M) were refluxed in acetone for 4 hrs. The

product obtained was crystallised from ethanol in needles, m.p. 120-1°.

Analysis : Found : C=61.4 % ; H=4.6 %.

$C_{14}H_{12}O_6$ requires : C=60.8 % ; H=4.4 %.

7-Formyl-8-coumarinoxyacetic acid

The above ester on hydrolysis by heating with sodium hydroxide (10 cc. ; 5 %) on a steam bath for 3 hrs. gave 7-formyl-8-coumarinoxyacetic acid which crystallised from acetic acid, m.p. 193-5°.

Analysis : Found : C=58.1 % ; H=3.2 %.

$C_{12}H_8O_6$ requires : C=58.3 % ; H=3.2 %.

Furo-2'-carboxy-4',5'-7,8-coumarin

The above acid (2 g. ; 0.01 M) was heated with sodium acetate (1 g. ; 0.01 M) and acetic anhydride (3 ml. ; 0.02 M) on a wire gauze for 30 minutes. The product obtained on pouring the reaction mixture in ice-cold water, crystallised from ethanol in white crystals, m.p. 365-7°.

Analysis : Found : C=62.5 % ; H=2.7 %.

$C_{12}H_6O_5$ requires : C=62.6 % ; H=2.6 %.

Synthesis of furo-3'-methyl-4',5'-7,8-coumarin :

8-Hydroxy-7-acetylcoumarin

(i) By the Friedel-Crafts acetylation of 8-hydroxycoumarin : 8-Hydroxycoumarin (1.62 g. ; 0.01 M) mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and acetic anhydride (3 ml.) was heated in an oil bath at

140-50° for 2 hrs. The product obtained on working up as usual crystallised from ethanol in yellow needles, m.p. 201-02°.

Analysis : Found : C=64.7 % ; H=3.9 %.

$C_{11}H_8O_4$ requires : C=64.7 % ; H=3.9 %.

(ii) The same compound described above was obtained by the Fries migration of 8-acetoxycoumarin as follows: 8-Acetoxycoumarin (2.04 g. ; 0.01 M) (32) was mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and heated at 125° and then slowly to 170° during 2 hrs. Dilute hydrochloric acid (1 : 1) was added and the mixture was again heated on a steam bath for 30 minutes. The crude product was crystallised from alcohol, m.p. 201-02°. Mixed m.p. of this with 8-hydroxy-7-acetylcoumarin described above was not depressed.

The 2,4-dinitrophenyl hydrazone

Prepared by refluxing phenylhydrazine (0.1 g.) and 8-hydroxy-7-acetylcoumarin (0.1 g.) in glacial acetic acid for 30 minutes. It was crystallised from glacial acetic acid in shining needles, m.p. 241-3°

Analysis : Found : N=14.3 %.

$C_{17}H_{12}O_7N_4$ requires : N=14.5 %.

Dakin oxidation of 8-hydroxy-7-acetylcoumarin : 7,8-Dihydroxycoumarin

The oxidation of 7-acetyl derivative was carried out as described before, m.p. 255-6°. Mixed m.p. with the known 7,8-dihydroxycoumarin ~~did~~ was not depressed.

Ethyl-7-acetyl-8-coumarinoxyacetate

8-Hydroxy-7-acetylcoumarin (2 g. ; 0.01 M) ethyl bromoacetate (1.6 g. ; 0.01 M) and potassium carbonate (1.3 g. ; 0.01 M) were refluxed in acetone for 4 hrs. The product obtained was crystallised from ethanol, m.p. 145-8°.

Analysis : Found : C=62.2 % ; H=5.0 %.

$C_{15}H_{14}O_6$ requires : C=62.0 % ; H=4.8 %.

7-Acetyl-8-coumarinoxyacetic acid

The above ester on hydrolysis by heating with 5 % sodium hydroxide on a steam bath for 3 hrs. gave 7-acetyl-8-coumarinoxyacetic acid which crystallised from ethanol in white plates, m.p. 235-6°.

Analysis : Found : C=59.4 % ; H=3.9 %.

$C_{13}H_{10}O_6$ requires : C=59.5 % ; H=3.8 %.

Furo-3'-methyl-4',5'-7,8)-coumarin

The above acid (2.6 g. ; 0.01 M) was heated with sodium acetate (1 g. ; 0.01 M) and acetic anhydride (3 ml. ; 0.02 M) on a wire gauge for 30 minutes. The product obtained on pouring the reaction mixture in ice-cold water, crystallised from ethanol in white shining plates, m.p. 146-8°

Analysis : Found : C=71.7 % ; H=4.1 %.

$C_{12}H_8O_3$ requires : C=72.0 % ; H=4.0 %.

(c) Synthesis of furo-3',5-dimethyl-(5',4'-7,8)-coumarin : 7-Hydroxy-8-acetyl-5-methylcoumarin

(i) By the Friedel-Crafts acetylation of 7-hydroxy-5-methylcoumarin : 7-Hydroxy-5-methylcoumarin (1.76 g. ; 0.01 M) mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and acetic anhydride (3 ml.) was heated in an oil bath at 140-50° for 2 hrs. The product obtained on working up as usual crystallised from ethanol in needles, m.p. 190-1°.

Analysis : Found : C=66.5 % ; H=4.6 %.
$C_{12}H_{10}O_4$ requires : C=66.0 % ; H=4.6 %.

(ii) The same compound was obtained on Fries rearrangement of 7-acetoxy-5-methylcoumarin.

7-Acetoxy-5-methylcoumarin

7-Hydroxy-5-methylcoumarin (2.86 g. ; 0.01 M) and acetic anhydride (5.72 g. ; 0.01 M) were refluxed for 1 hr. The product obtained on working up as usual crystallised from acetic acid, m.p. 115-6°.

Analysis : Found : C=66.4 % ; H=4.6 %.
$C_{12}H_{10}O_4$ requires : C=66.0 % ; H=4.6 %.

7-Acetoxy-8-methylcoumarin (2.18 g. ; 0.01 M) was mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and heated at 125° and then slowly to 170° during 2 hrs. The product obtained on working up as usual crystallised from acetic acid, m.p. 190-1°

Analysis : Found : C=66.5 % ; H=4.5 %.

$C_{12}H_{10}O_4$ requires : C=66.0 % ; H=4.6 %.

7-Methoxy-8-acetyl-5-methylcoumarin

7-Hydroxy-8-acetyl-5-methylcoumarin (1.76 g.; 0.01 M), dimethyl sulphate (2.4 g. : 0.02 M) and potassium carbonate (4.8 g. ; 0.04 M) were refluxed in boiling acetone for 8 hrs. The product obtained on working up as usual was crystallised from alcohol, m.p. 174-5°.

Analysis : Found : C=67.4 % ; H=5.2 %.

$C_{13}H_{12}O_4$ requires : C=67.2 % ; H=5.1 %.

Elbs Persulphate Oxidation of 7-methoxy-8-acetyl-5-methylcoumarin : 7-Methoxy-6-hydroxy-8-acetyl-5-methylcoumarin : 7-Methoxy-8-acetyl-5-methylcoumarin (0.2 g.) was dissolved in sodium hydroxide (10 % ; 10 ml.) by warming on a steam bath. The solution was then cooled and potassium persulphate (0.8 g. ; 10 ml. water) was added gradually from a separating funnel during 2 hrs. The solution was mechanically stirred and the temperature was not allowed to rise above 10°. The reaction mixture was kept overnight. The following day it was just acidified with hydrochloric acid, when the original 7-methoxy-8-acetyl-5-methylcoumarin was obtained. This was filtered and the filtrate was twice extracted with ether. The aqueous layer was then heaated on a boiling water bath with con.hydrochloric acid (10 ml.) for about an hour. The product separated was crystallised from acetic acid, m.p. 226-8°.

Analysis : Found : C=62.4 % ; H=4.6 %.
$C_{13}H_{12}O_5$ requires : C=62.9 % ; H=4.8 %.

Ethyl-8-acetyl-5-methyl-7-coumarinoxyacetate

7-Hydroxy-8-acetyl-5-methylcoumarin (2.18 g. ; 0.01 M), ethyl bromoacetate (1.6 g. ; 0.01 M) and potassium carbonate (1.3 g. ; 0.01 M) were refluxed in acetone for 4 hrs. The product obtained on working up as usual was crystallised from ethanol, m.p. 130-2°.

Analysis : Found : C=62.8 % ; H=5.0 %.
$C_{16}H_{16}O_6$ requires : C=63.1 % ; H=5.2 %.

8-Acetyl-5-methyl-7-coumarinoxyacetic acid

The above ester on hydrolysis with 5 % sodium hydroxide on a water bath for 1 hr. gave 8-acetyl-5-methyl-7-coumarinoxyacetic acid which crystallised from acetic acid in needles, m.p. 225-7°.

Analysis : Found : C=60.4 % ; H=3.9 %.
$C_{14}H_{17}O_6$ requires : C=60.8 % ; H=4.4 %.

Furo-3',5-dimethyl-5',4'-7,8)-coumarin

The above acid (1.6 g. ; 0.01 M) was heated with sodium acetate (1 g. ; 0.01 M) and acetic anhydride (3 ml.; 0.02 M) on a wire-gauze for 45 minutes. The product obtained on pouring the reaction mixture in ice-cold water, crystallised from ethanol in needles, m.p. 169-70°.

Analysis : Found : C=73.1 % ; H=4.7 %.
$C_{13}H_{10}O_3$ requires : C=72.9 % ; H=4.7 %.

Synthesis of furo-3',8-dimethyl-4',5'-6,7-coumarin :

7-Hydroxy-6-acetyl-8-methylcoumarin

(i) By the Friedel-Crafts acetylation of 7-hydroxy-8-methylcoumarin : 7-Hydroxy-8-methylcoumarin (1.76 g. ; 0.01 M) mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and acetic anhydride (3 ml.) was heated in an oil bath at 140-50° for 2 hrs. The product obtained on working up as usual crystallised from acetic acid, m.p. 207-08°.

Analysis : Found : C=65.9 % ; H=4.3 %.

$C_{12}H_{10}O_4$ requires : C=66.0 % ; H=4.6 %.

(ii) The same coumarin derivative was obtained by Fries rearrangement of 7-acetoxy-8-methylcoumarin as follows :

7-Acetoxy-8-methylcoumarin

Prepared from 7-hydroxy-8-methylcoumarin (2.86 g.; 0.01 M) and acetic anhydride (5.72 g. ; 0.01 M) by refluxing for 1 hr. The product obtained on working up as usual, crystallised from acetic acid, m.p. 130-2°.

Analysis : Found : C=66.4 % ; H=4.7 %.

$C_{12}H_{10}O_4$ requires : C=66.0 % ; H=4.6 %.

7-Acetoxy-8-methylcoumarin (2.18 g. ;0.01 M) was mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and heated at 125° and then slowly to 170° during 2 hrs. The product obtained on working up as usual, crystallised from acetic acid, m.p. 207-08°. Mixed m.p. with 7-hydroxy-6-acetyl-

8-methylcoumarin described above was not depressed.

Ethyl-6-acetyl-8-methyl-7-coumarinoxyacetate

7-Hydroxy-6-acetyl-8-methylcoumarin (2.18 g. ; 0.01 M), ethylbromoacetate (1.6 g. ; 0.01 M) and potassium carbonate (1.3 g. ; 0.01 M) were refluxed in acetone for 3 to 4 hrs. The product obtained was crystallised from dilute acetic acid, m.p. 106-07°.

Analysis : Found : C=63.0 % ; H=5.2 %.
$C_{16}H_{16}O_6$ requires : C=63.1 % ; H=5.2 %.

6-Acetyl-8-methyl-7-coumarinoxyacetic acid

The above ester on hydrolysis with 5 % sodium hydroxide on a water bath for 1 hr. gave 6-acetyl-8-methyl-7-coumarinoxyacetic acid which crystallised from acetic acid in needles, m.p. 165-7°.

Analysis : (After heating at 120° under vaccum)
Found : C=60.6 % ; H=4.5 %.
$C_{14}H_{12}O_6$ requires : C=60.8 % ; H=4.3 %.

Furo-3',8-dimethyl-4',5',6,7-coumarin

The above acid (1.6 g. ; 0.01 M) was heated with sodium acetate (1 g. ; 0.01 M) and acetic anhydride (3 ml. ; 0.02 M) on a wire gauge for 2 hrs. The product obtained on working up as usual crystallised from acetic acid in shining plates, m.p. 188°. (~~Softens at 183°~~).

Analysis : Found : C=72.5 % ; H=4.6 %.
$C_{13}H_{10}O_3$ requires : C=72.8 % ; H=4.7 %.

(e) Synthesis of 3'-methyl benzofurano-(6',7'-8,7)-4-methylcoumarin : 6'-Hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin

(i) By the Friedel-Crafts acetylation of 6'-hydroxy-4-methyl-7,8-benzocoumarin : 6'-Hydroxy-4-methyl-7,8-benzocoumarin (2.6 g. ; 0.01 M) was mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and acetic anhydride (3 ml.) and heated in an oil bath at 140-50° for 2 hrs. The product obtained on heating the reaction mixture with hydrochloric acid crystallised from acetic acid in yellow crystals. M.P. 315-17°.

Analysis : Found : C = 71.2 % ; H = 4.3 %.

$C_{16}H_{12}O_4$ requires : C = 71.6 % ; H = 4.4 %.

(ii) The same compound was obtained on Fries rearrangement of 6'-acetoxy-4-methyl-7,8-benzocoumarin.

6'-Acetoxy-4-methyl-7,8-benzocoumarin

6'-Acetoxy derivative was prepared by refluxing 6'-hydroxy-4-methyl-7,8-benzocoumarin (2.6 g. ; 0.01 M) and acetic anhydride (5 ml. ; 0.05 M) for 2 hrs. on a wire gauze. The product crystallised from acetic acid in white crystals, m.p. 207-09°.

Analysis : Found : C = 71.5 % ; H = 4.2 %.

$C_{16}H_{12}O_4$ requires : C = 71.6 % ; H = 4.4 %.

6'-Acetoxy-4-methyl-7,8-benzocoumarin (2.6 g. ; 0.01 M) was mixed with anhydrous aluminium chloride (5.2 g. ; 0.04 M) and heated at 125° and then slowly to 170° during the period of 2 hrs. Dilute hydrochloric acid

(1 : 1) was added and the mixture was again heated on a steam bath for 30 minutes. The crude product was crystallised from acetic acid m.p. 315-17°. Mixed m.p. of this with the product obtained from Friedel-Crafts reaction was not depressed. It also gave light brown colouration with alcoholic ferric chloride.

Ethyl-5'-acetyl-6'-(4-methyl-7,8-benzocoumarinyl)-oxyacetate

6'-Hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin (2.6 g. ; 0.01 M) bromoacetic ester (1.6 g. ; 0.01 M) and potassium carbonate (1.3 g. ; 0.01 M) were refluxed in acetone for 4 hrs. on a water bath. The product obtained on working up as usual crystallised from acetic acid. M.P. 138-39°.

Analysis : Found : C = 67.8 % ; H = 5.0 %.

$C_{20}H_{18}O_6$ requires : C = 67.7 % ; H = 5.1 %.

5'-Acetyl-6'-(4-methyl-7,8-benzocoumarinyl)-oxyacetic acid

The above ester on hydrolysis by heating with sodium hydroxide (5 %) on a water bath for one hour gave 5'-acetyl-6'-(4-methyl-7,8-benzocoumarinyl) oxyacetic acid which was crystallised from acetic acid, m.p. 220-22°.

Analysis : Found : C = 65.9 % ; H = 4.0 %.

$C_{18}H_{14}O_6$ requires : C = 66.2 % ; H = 4.3 %.

3'-Methyl benzofurano-(6',7'-8,7)-4-methylcoumarin

The above acid (1.5 g.) was heated with sodium acetate (1 g.) and acetic anhydride (3 ml.) on a wire gauze

for 45 minutes. The product obtained on pouring the reaction mixture in ice cold water was crystallised from acetic acid, m.p. 252-53°.

Analysis	: Found	: C = 77.8 % ; H = 4.2 %.
$C_{17}H_{12}O_3$	requires	: C = 77.3 % ; H = 4.5 %.

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