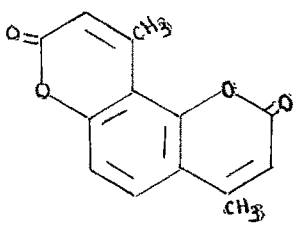
CHAPTER I

PART II

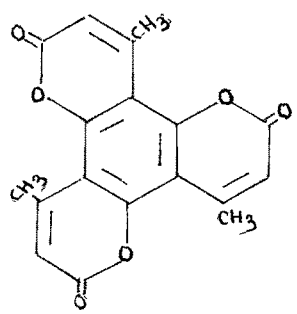
SYNTHESIS OF COUMARINO-α-AND -γ-PYRONES

Synthesis of coumarino-α-and γ-pyrones

The benzo-α-pyrones or coumarins and the 2-phenyl benzo-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 (I)and (II) respectively in poor yields.

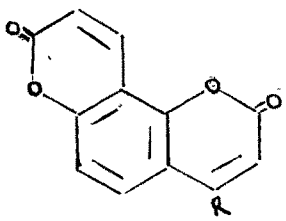


(I)



(II)

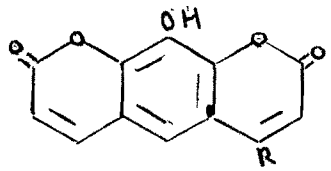
Sen and Chakravarti (3) condensed umbelliferone, 4-methylumbelliferone, daphnetin,4-methyldaphnetin, homoumbelliferone and 4-methylumbelliferone with malic acid in the presence of sulphuric acid and obtained coumarino-7,8-α-pyrone (III a), 4-methylcoumarino-7,8-α-pyrone (III b), 8-hydroxycoumarino-7,6-α-pyrone (IV a), 4-methyl-8-hydroxycoumarino-7,6-α-pyrone (IV b), 7-methylcoumarino-5,6-α-pyrone (V a), and 4,7-dimethyl-coumarino-5,6-α-pyrone (V b) respectively.



(III)

(a) ≠ R = H

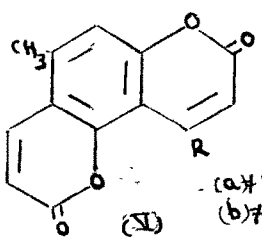
(b) R = CH_3



(IV)

(a) ≠ R = H

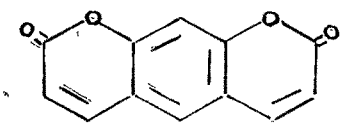
(b) ≠ R = CH_3



(V)

(a) ≠ R = H

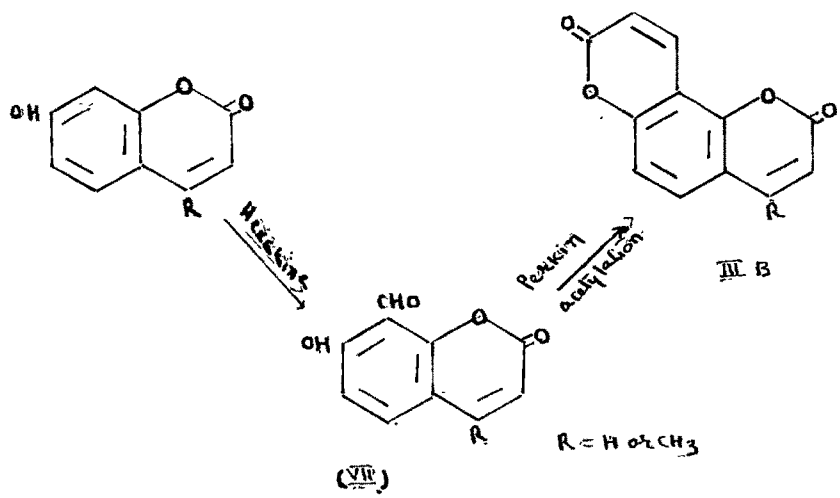
(b) ≠ R = CH_3



(VI)

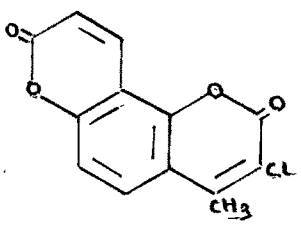
They however did not prove the structures of the coumarino-α-pyrones formed. Rangaswami and Seshadri (4) showed that when umbelliferone is condensed with malic acid both the angular (III a) and the linear (VI) coumarino-α-pyrones are formed but the latter is obtained in poor yield. Under the same experimental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

Biswas (5) condensed 7-hydroxy-3-chloro-4-methyl-, 5-hydroxy-3-chloro-4,7-dimethyl-, and 7,8-dihydroxy-3-chloro-4-methylcoumarin with malic acid and

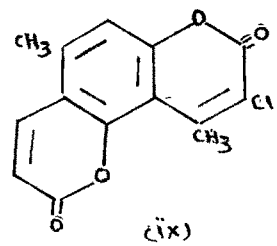


(VII)

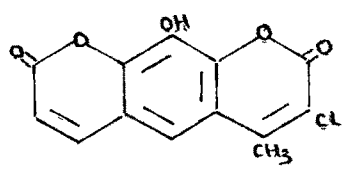
obtained the 3-chloro-4-methylcoumarino-7,8-α-pyrone (VIII), 3-chloro-4,7-dimethylcoumarino-5,6-α-pyrone (IX) and 3-chloro-4-methyl-8-hydroxycoumarino-7,6-α-pyrone (X) respectively.



(VIII)

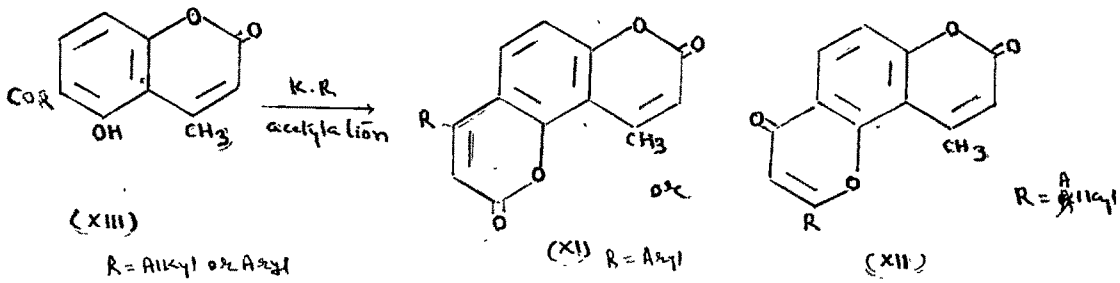


(IX)



(X)

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



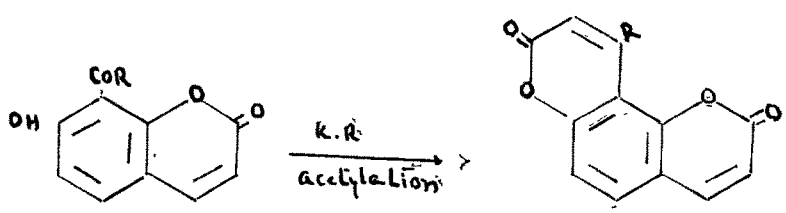
(XIII)

R = Alkyl or Aryl

(XI) R = Aryl

(XII)

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



(XIV)

(a) $R = C_2H_5$

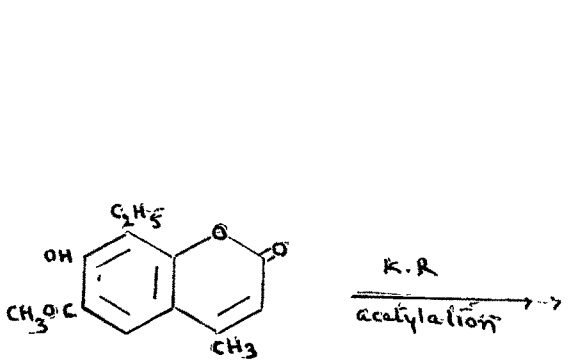
(b) $R = C_3H_7$

(XV)

(a) $R = C_2H_5$

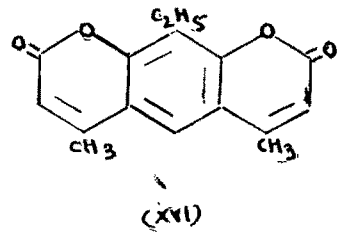
(b) $R = C_3H_7$

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



(XVIII)

K.R acetylation



(XVI)

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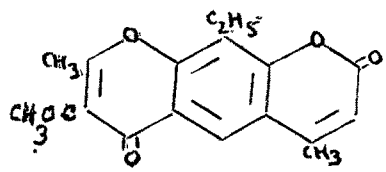
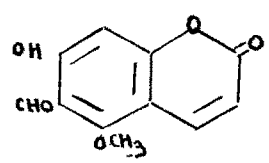


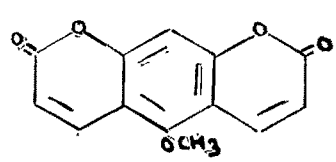
(XVII)

Mustafa, Starkovsky and Zaki (9) prepared 5-methoxy-coumarino-7,6-α-pyrone (XIX) by Perkin acetylation of apoxanthoxyletin (XX).



(XX)

Perkin acetylation



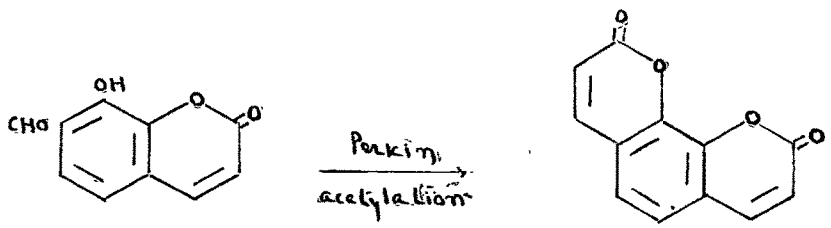
(XIX)

The work has been extended to the synthesis of coumarino-α-and γ-pyrones by the application of Perkin, Knoevenagel, and Kostanecki-Robinson acylation reactions to some other formyl and acyl 8-~~hydroxy~~coumarin derivatives.

The present work may now be described.

Perkin acetylation of 8-hydroxy-7-formylcoumarin : α-pyrono-(5',6'-7,8)-coumarin

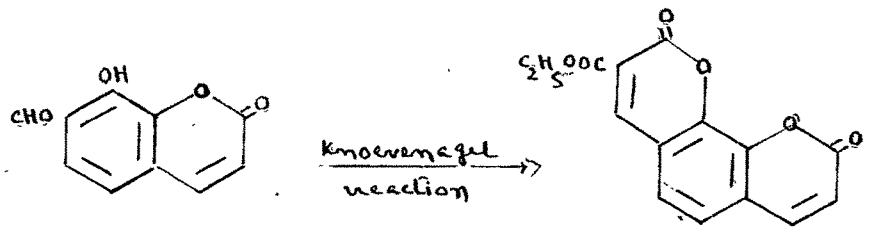
8-Hydroxy-7-formylcoumarin (XXI) on Perkin acetylation with acetic anhydride and sodium acetate gave a product which was insoluble in cold dilute alkali and did not give alcoholic ferric chloride colouration. On the basis of these properties and the analytical results it has been assigned the α-pyrono-(5',6'-7,8)-coumarin (XXII).



(XXI) (XXII)

Knoevenagel condensation of 8-hydroxy-7-formylcoumarin : 3'-carbethoxy-α-pyrono-(5',6'-7,8)-coumarin

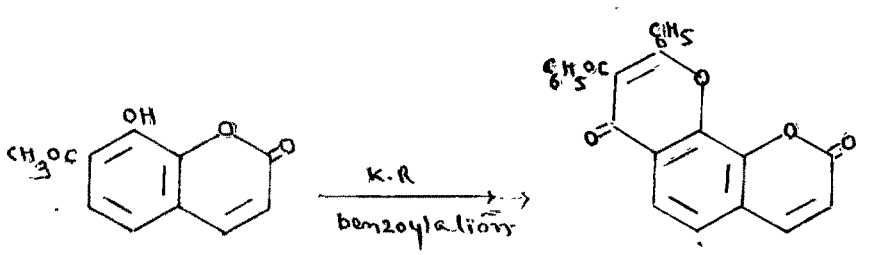
8-Hydroxy-7-formylcoumarin on condensation with diethyl malonate in the presence of a few drops of mixture of piperidine and pyridine furnished a product which was insoluble in cold dilute alkali and did not give a colouration with alcoholic ferric chloride. On the basis of these observations and the analysis it has been assigned 3'-carbethoxy-α-pyrono-(5',6'-7,8)-coumarin(XXIII)



(XXI) (XXIII)

Kostanecki-Robinson benzoylation of 8-hydroxy-7-acetylcoumarin : 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-7,8)-coumarin

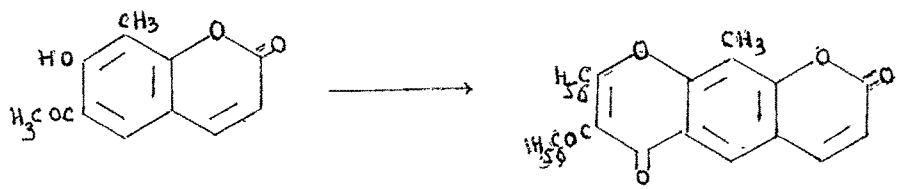
8-Hydroxy-7-acetylcoumarin (XXIV) on Kostanecki-Robinson benzoylation gave a product which was insoluble in cold dilute alkali which has been assigned the 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-7,8)-coumarin structure(XXV).



(XXIV) (XXV)

Kostanecki-Robinson benzoylation of 7-hydroxy-6-acetyl-8-methylcoumarin : 2'-Phenyl-3'-benzoyl-γ-pyrono-(5',6'-6,7)-8-methylcoumarin

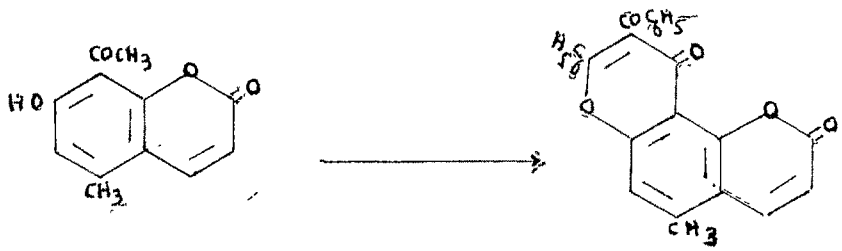
7-Hydroxy-6-acetyl-8-methylcoumarin (XXVI) (p. 25) was subjected to Kostanecki-Robinson benzoylation. The product obtained on working up as usual, was crystallised from acetic acid in needles. It did not give ferric chloride colouration. It has been assigned 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-6,7)-8-methylcoumarin structure (XXVII).



(XXVI) (XXVII)

Kostanecki-Robinson benzoylation of 7-hydroxy-8-acetyl-5-methylcoumarin : 2'-Phenyl-3'-benzoyl-γ-pyrono-(5',6'-8,7)-5-methylcoumarin

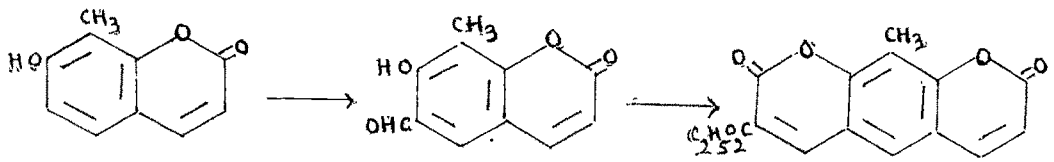
7-Hydroxy-8-acetyl-5-methylcoumarin (XXVIII) (p. 24) on Kostanecki-Robinson benzoylation with benzoic anhydride and sodium benzoate furnished a product which was insoluble in cold dilute alkali and did not give ferric chloride colouration. On the basis of this and from analytical data it has been assigned the 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-8,7)-5-methylcoumarin structure (XXIX)



(XXVIII) (XXIX)

Knoevenagel Condensation of 7-hydroxy-6-formyl-8-methyl coumarin with diethyl malonate : 3'-Carbethoxy-α-pyrono-(5',6'-6,7)-8-methylcoumarin

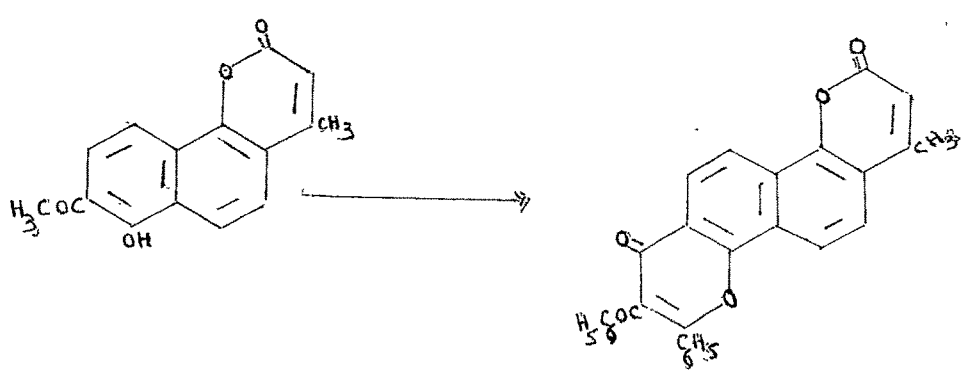
The 7-hydroxy-6-formyl-8-methylcoumarin (XXX) was subjected to Knoevenagel reaction with diethylmalonate and the product obtained has been assigned the 3'-carbethoxy-α-pyrono-(5',6'-6,7)-8-methylcoumarin (XXXI) structure. It did not give ferric chloride colouration and was also insoluble in cold dilute alkali. The above formyl derivative is hitherto unknown. It was prepared by direct formylation of 7-hydroxy-8-methylcoumarin with hexamethylenetetramine. It gave purple colouration with alcoholic ferric chloride and also underwent Knoevenagel reaction as above, therefore it has been assigned 7-hydroxy-6-formyl-8-methylcoumarin structure.



(XXX) (XXXI)

Kostanecki-Robinson benzoylation of 6'-hydroxy-5-acetyl-4-methyl-7,8-benzocoumarin:

6'-Hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin (XXXII) (p. 27) on Kostanecki-Robinson benzoylation gave a product which was insoluble in cold dilute alkali and it did not give colouration with alcoholic ferric chloride. It has been assigned 4-methyl-3'-benzoyl flavono-(7',8'-8,7)-coumarin (XXXIII)



(XXXII) (XXXIII)

EXPERIMENTAL

Perkin acetylation of 8-hydroxy-7-formylcoumarin : Synthesis of α-pyrono-(5',6'-7,8)-coumarin

A mixture of 8-hydroxy-7-formylcoumarin (1.9 g.; 0.01 M) acetic anhydride (10 g. ; 0.1 M) and sodium acetate (4 g. ; 0.05 M) was heated for 7 hrs. at a temperature of 180-90° in an oil bath.

The solid reaction mixture was then poured in ice cold water and the product which separated on keeping was crystallised from acetic acid, m.p. > 350°

Analysis : Found : C=66.2 % ; H=3.7 %.
$C_{12}H_6O_4$ requires : C=65.7 % ; H=3.2 %.

Knoevenagel condensation of 8-hydroxy-7-formylcoumarin with diethylmalonate : Synthesis of 3'-carbethoxy-α-pyrono-(5',6'-7,8)-coumarin

8-Hydroxy-7-formylcoumarin (1.9 g. ; 0.01 M) was mixed with diethylmalonate (1.6 g. ; 0.01 M) and a few drops of pyridine were added and the reaction mixture was kept overnight. It was then decomposed by dil. hydrochloric acid and the solid obtained crystallised from dil.acetic acid in shining plates, m.p. 255-6°.

Analysis : Found : C=63.1 % ; H=3.7 %.
$C_{15}H_{10}O_6$ requires : C=62.9 % ; H=3.5 %.

Kostanecki-Robinson benzoylation of 8-hydroxy-7-acetylcoumarin : Synthesis of 2',3'-benzoyl-γ-pyrono-(5',6'-7,8)-coumarin

A mixture of 8-hydroxy-7-acetylcoumarin (2.2 g. ; 0.01 M) , benzoic anhydride (10 g. ; 0.05 M) and sodium benzoate (2.8 g. ; 0.02 M) was heated for 9 hrs. at a temperature of 180-90° in an oil bath. The solid reaction mixture was then washed with hot water several times and finally with sodium bicarbonate. This was then crystallised from methanol in fine yellowish brown needles, m.p. 253-4°.

Analysis : Found : C = 76.1 % ; H = 3.4 %.
$C_{25}H_{14}O_5$ requires : C = 76.1 % ; H = 3.5 %.

Kostanecki-Robinson benzoylation of 7-hydroxy-6-acetyl-8-methylcoumarin : Synthesis of 2',3'-benzoyl-γ-pyrono-(5',6'-6,7)-8-methylcoumarin

A mixture of 7-hydroxy-6-acetyl-8-methylcoumarin (2.18 g. ; 0.01 M) benzoic anhydride (6.6 g. ; 0.03 M) and sodium benzoate (2.8 g. ; 0.02 M) was heated for 8 hours at a temperature of 180-90° in an oil bath. The reaction mixture was then poured in ice-water. The product obtained on working up as usual crystallised from acetic acid in buff-needles, m.p. 255-57°.

Analysis : Found : C = 76.3 % ; H = 3.8 %.
$C_{26}H_{16}O_5$ requires : C = 76.4 % ; H = 3.9 %.

Kostanecki-Robinson benzoylation of 7-hydroxy-8-acetyl-5-methylcoumarin : Synthesis of 2'-phenyl-3'-benzoyl-γ-pyrono-(5',6'-8,7)-5-methylcoumarin

7-Hydroxy-8-acetyl-5-methylcoumarin (2.18 g. ; 0.01 M) benzoic anhydride (6.6 g. ; 0.03 M) and sodium benzoate were mixed and heated in an oil bath at 180-90° for 8 to 9 hrs. The product obtained on working up as usual was crystallised from acetic acid in brown-needles, m.p. 228-30°.

Analysis : Found : C = 76.1 % ; H = 4.1 %.

$C_{26}H_{16}O_5$ requires : C = 76.4 % ; H = 3.9 %.

Knoevenagel condensation of 7-hydroxy-6-formyl-8-methylcoumarin :

7-Hydroxy-6-formyl-8-methylcoumarin : 7-Hydroxy-8-methylcoumarin (1.76 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 hours. Hydrochloric acid (1 : 1) was then added and the heating continued for further two hours. The product obtained on extraction with ether crystallised from glacial acetic acid in needles, m.p. 191-92°.

Analysis : Found : C = 65.1 % ; H = 4.3 %.

$C_{11}H_8O_4$ requires : C = 64.7 % ; H = 3.8 %.

Synthesis of 3'-carbethoxy-α-pyrono-(5',6'-6,7)-8-methyl-coumarin

7-Hydroxy-6-formyl-8-methylcoumarin (2.04 g. ; 0.01 M) was mixed with diethylmalonate (1.6 g. ; 0.01 M)

and a drop of piperidine was added and the reaction mixture was kept overnight. It was then decomposed by dilute hydrochloric acid and the solid obtained was crystallised from acetic acid, m.p. 205-06°

Analysis : Found : C = 63.9 % ; H = 3.7 %.
$C_{16}H_{12}O_6$ requires : C = 64.0 % ; H = 4.0 %.

Kostanecki-Robinson benzoylation of 6'-hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin : 4-Methyl-3'-benzoyl-flavono-(7',8'-8,7)-coumarin

A mixture of 6'-hydroxy-5'-acetyl-4-methyl-7,8-benzocoumarin (2.68 g. ; 0.01 M), benzoic anhydride (6.6 g. ; 0.03 M) and sodium benzoate (2.8 g. ; 0.02 M) was heated for 8 hrs. at a temperature of 180-90° in an oil bath. The reaction mixture was then poured in ice water and worked up as usual. The product crystallised from acetic acid in yellow needles, m.p. 311-12°. (softens at 295°).

Analysis: Found : C = 78.3 % ; H = 4.0 %.
$C_{30}H_{18}O_5$ requires : C = 78.5 % ; H = 3.9 %.

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