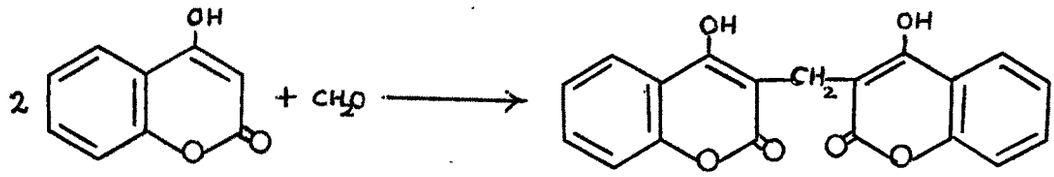
CHAPTER IV

REACTIONS ON 4-HYDROXY-5,6-BENZOCOUMARIN

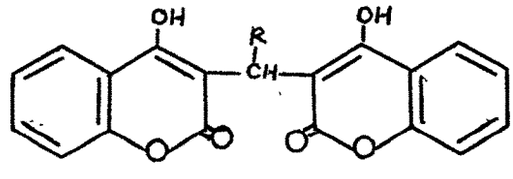
Reactions on 4-hydroxy-5,6-benzocoumarin

Cattle, feeding on spoiled sweet clover hay, suffer from a condition characterised by a sharp increase of the blood clotting time. The pathogenic hemorrhagic principle of sweet clover hay was found to be 3,3'-methylene bis-(4-hydroxycoumarin) (1), popularly called 'Dicoumarol'[1]. Dicoumarol is synthesised by reacting formaldehyde with 4-hydroxycoumarin and it is a good anticoagulant of blood.



(1)

Since this discovery the chemistry of 4-hydroxy-coumarins has assumed importance. Tromexan (2a) the analogous compound with a $-COOC_2H_5$ group in the methylene carbon bridge, has been developed to give more rapid onset of the recovery from anticoagulant symptoms[2].



(2)

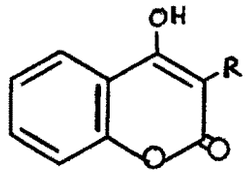
(a) R = $-COOC_2H_5$ (b) R = $-CH_2OCH_3$ (c) R = CH_3

Many attempts to vary the structure of dicoumarol and thereby prepare more active anticoagulant drugs have been made. (2b) obtained by reacting 4-hydroxycoumarin with β-methoxy propionaldehyde[3] is another such compound with anticoagulant properties similar to that of dicoumarol.

Mentzer, Meunier, Buu-Hoi and Cagniant[4] tested the compounds in which hetero oxygens of dicoumarol were replaced either by sulphur or nitrogen and found them to be feebly active compounds. The former had one-tenth and the latter had one-fiftieth activity of dicoumarol.

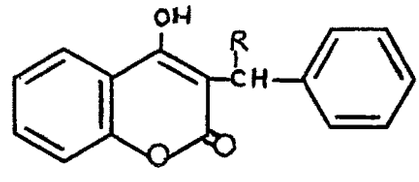
Lehmann[5] showed that the replacement of bridge $-CH_2-$ by ethylidene bridge $-CH-CH_3-$ gave compound (2c) which possessed higher anticoagulant properties than dicoumarol.

Meunier et al.[6] observed that 3-methyl-4-hydroxycoumarin (3a) possesses coagulant properties like Vitamin K while the corresponding 3-bromo (3b) and 3-chloro-4-hydroxycoumarins (3c) have slight anticoagulant properties.



(3)

(a) R=CH_3 (b) R=Br
(c) R=Cl (d) R=naphthyl
(e) R=$-CH_2-C_6H_5$



(4)

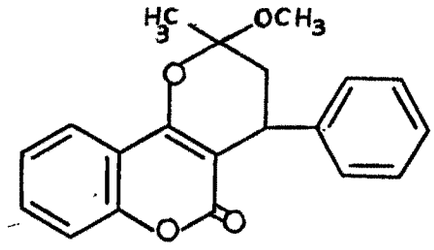
(a) R=$-CH_2COCH_3$
(b) R=C_2H_5

α or β?

Moraux et al.[7] have prepared 3-naphthyl-4-hydroxy-coumarin (3d) which is equal to dicoumarol in activity and is less toxic.

3-Benzyl-4-hydroxycoumarin (3e) has slight activity, but the acetonyl derivative, Warfarin (4a) is a powerful anticoagulant and rodenticide and shows a remarkable specificity for rats in which the action of minute doses has fatal results[8].

Link et al.[9] prepared cyclocoumarol or 3,4-(2'-methyl-2'-methoxy-4'-phenyl)dihydro-pyranocoumarin (5) by treating Warfarin with 4 % hydrogen chloride in methanol and found that it possessed greater activity than dicoumarol.



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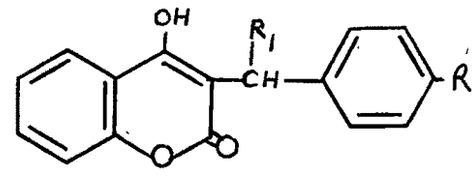


(6)

(a) R=Cl ; R_1=$-CH_2-CO-CH_3$

(b) R=NO_2 ; R_1=$-CH_2-CO-CH_3$

Other compounds which are related to Warfarin and possess anticoagulant property are coumarchlor (6a), sintron (6b) and marcoumar (4b).

Link et al.[10] prepared different esters of dicoumarol and found that the activity of these compounds is less than that of dicoumarol.

Arora and Mathur[11] reported that coumarino (3',4',5,6)-4-methyl-3-phenyl-α-pyrone possesses anti-coagulant activity comparable to that of dicoumarol.

Recently K.S.K.Krishna Mohan Rao and N.V. Subbarao[12] synthesised different 3-amino-4-hydroxycoumarins and coumarino (3,4)oxazoles and found that they are bacteriostatic and fungistatic active.

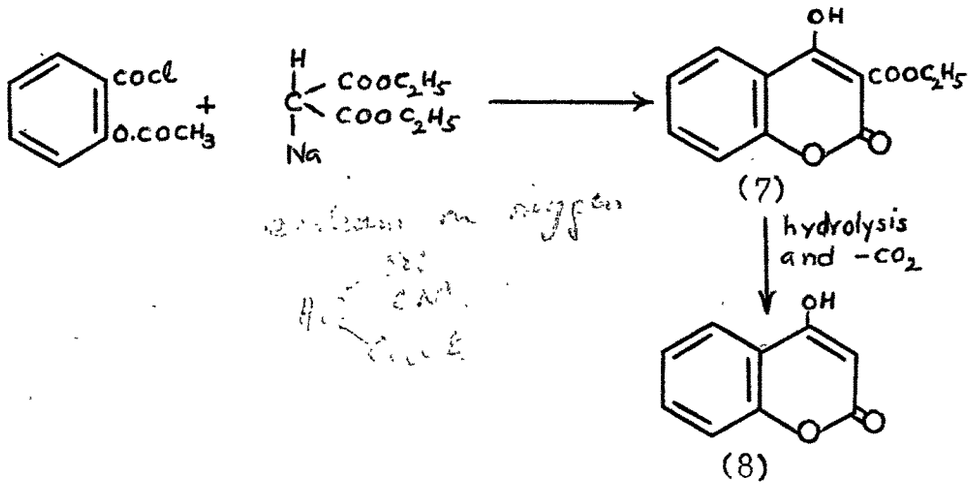
From their studies of various 4-hydroxycoumarin derivatives, Link and coworkers[8] put forward the minimum structural requirements for a substance to possess anti-coagulant properties. The first essential condition is that there should be an intact 4-hydroxycoumarin residue and that the 3-position must be substituted by a C residue. Every compound fulfiling this requirement is active. For high activity a bis-4-hydroxycoumarin structure is specially required. An alteration in this structure results in decrease of activity. Compounds containing one 4-hydroxy-coumarin residue with an alkyl or aryl group in 3-position show diminished activity.

A number of methods are available for the synthesis of 4-hydroxycoumarin derivative.

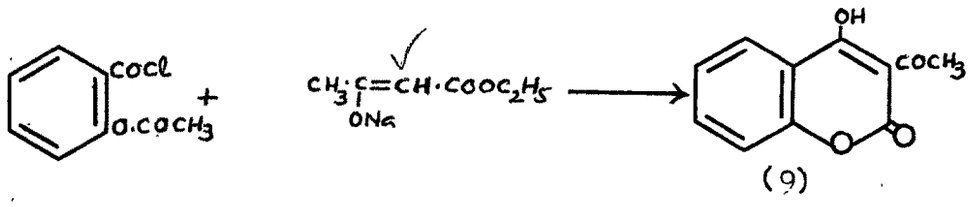
Methods for the synthesis of 4-hydroxycoumarin

Anschutz[13] condensed sodium salt of malonic ester with O-acetoxy benzoylchloride and obtained 3-carboethoxy-4-hydroxycoumarin (7). The ester thus obtained on hydrolysis

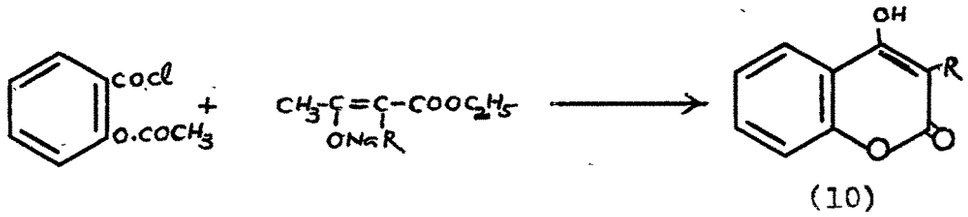
and decarboxylation gave 4-hydroxycoumarin (8).



A similar condensation of the sodium salt of acetoacetic ester with o-acetoxy benzoylchloride in etheral solution gave 3-acetyl-4-hydroxycoumarin (9)[14].

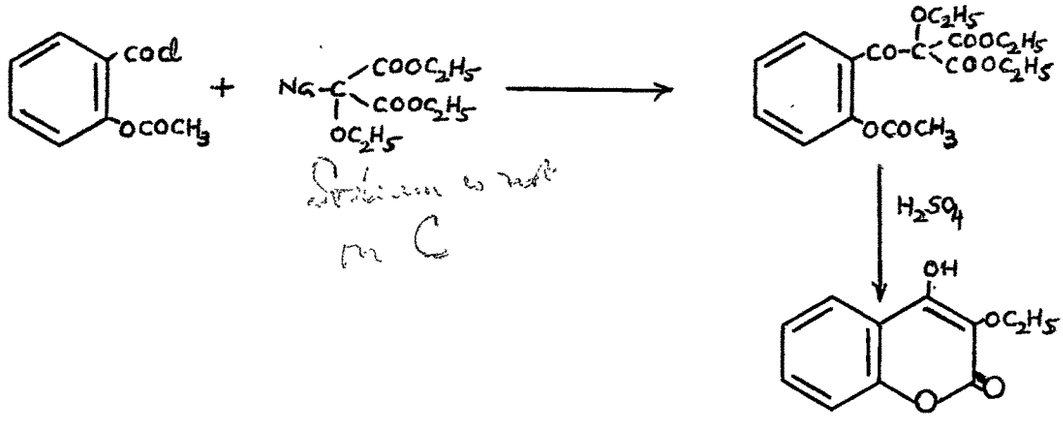


Heilbron and Hill[15] extended this method and condensed the sodium salt of α-substituted acetoacetic ester and obtained 3-methyl-, 3-benzoyl-, and 3-benzyl-4-hydroxycoumarin derivatives (10). The acetyl group was eliminated during the condensation.



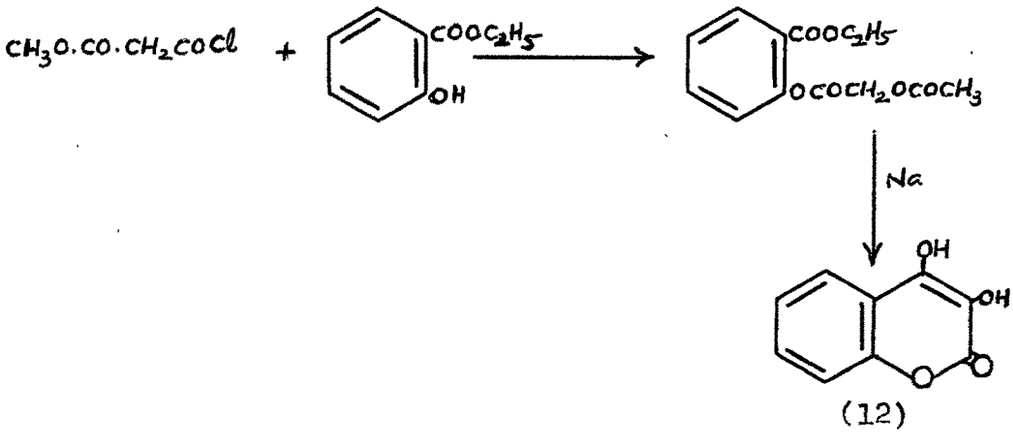
R=CH_3, COC_6H_5, $-CH_2-C_6H_5$

Ghosh[16] condensed o-acetoxy benzoylchloride with the sodium salt of ethoxy malonic ester in dry benzene. The condensation product thus obtained gave on heating with sulphuric acid, 3-ethoxy-4-hydroxycoumarin(11).



(11)

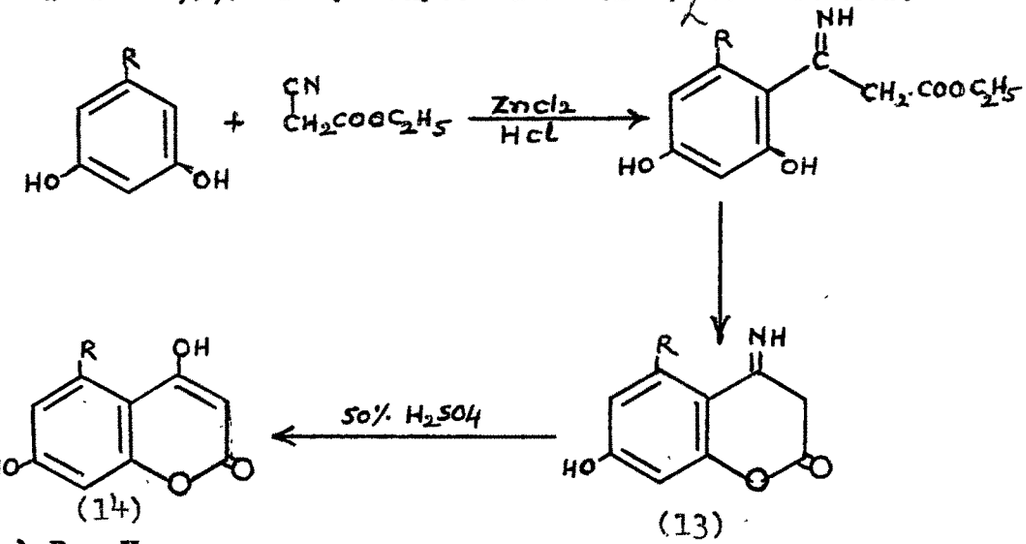
The same author[16] condensed acetoxy acetylchloride with ethyl salicylate in the presence of pyridine. The product obtained, on refluxing with sodium in dry benzene, gave 3,4-dihydroxycoumarin (12) after acidification with sulphuric acid.



(12)

Sonn[17] and Bauer and Schoder[18] applied the Hoesch synthesis[19] to the preparation of 4-hydroxycoumarin derivatives. By condensing cyano-acetic ester with

resorcinol and phlòroglucinol in the presence of hydrochloric acid and zinc chloride followed by the hydrolysis of the intermediate ketimine (13), 4,7-dihydroxy- (14a) and 4,5,7-trihydroxycoumarin (14b) were formed.

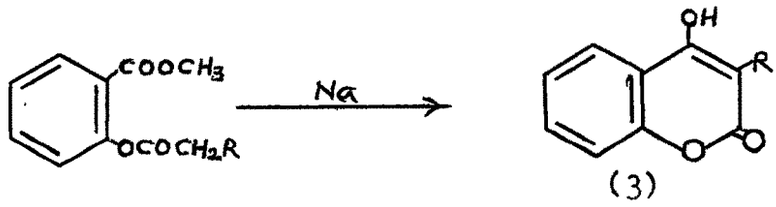


(a) R = H

(b) R = OH

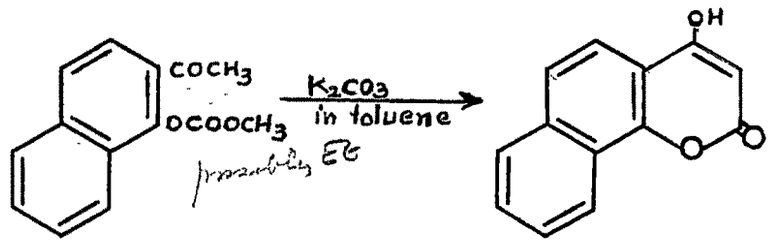
This method is applicable mainly to m-dihydric phenols and their derivatives.

Pauly and Lockemann[20] synthesised 4-hydroxy-coumarin derivatives (3) from methyl acetyl salicylate by adding metallic sodium to the molten ester.



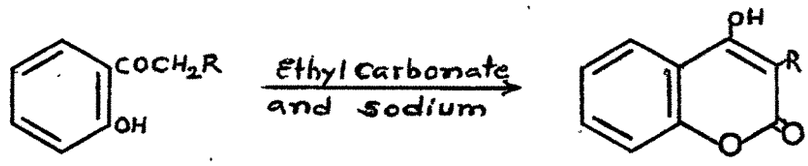
This method involves condensation with sodium at high temperatures. This procedure was re-investigated by Jensen and Jensen[21] and they did not obtain the yields given by Pauly and Lockemann[20]. Stahmann, Wolff and Link[22] reported that the optimum temperature for the condensation is 240-50°.

Anand and Venkataraman[23] synthesised 4-hydroxy-7,8-benzocoumarin (15) by the internal condensation of ethyl 2-acetyl-1-naphthyloxy-acetate o-carboethoxy-2-acetyl-1-naphthol (16), in the presence of sodamide, anhydrous potassium carbonate, metallic sodium or sodium ethoxide in appropriate solvents.



(16) (15)

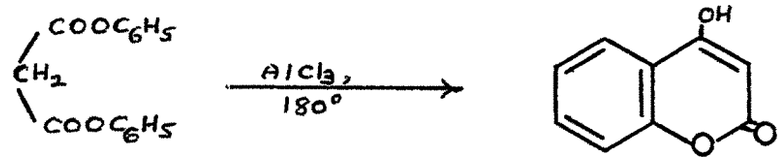
Boyd and Robertson[24] found that o-hydroxy acetophenones and its w-substituted derivatives readily condensed with ethyl carbonate in the presence of sodium to give 4-hydroxycoumarin derivatives in good yields.



(3)

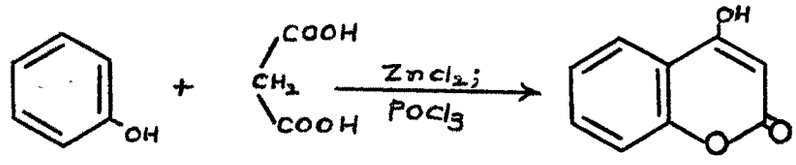
This is a very convenient method for the synthesis of 4-hydroxycoumarins and its scope has been demonstrated by its application to a variety of o-hydroxy acetophenones.

Ziegler and Junek[25] obtained 4-hydroxycoumarin derivatives by the cyclisation of diaryl malonates in the presence of anhydrous aluminium chloride at 180°.



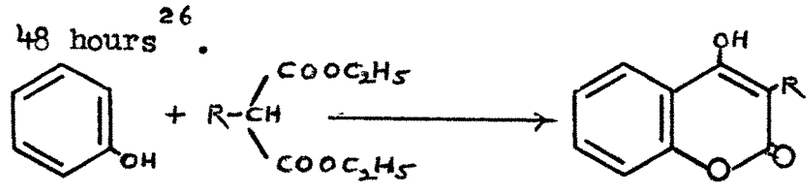
(8)

Shah, Bose and Shah[26] have prepared 4-hydroxy-coumarin derivatives in good yields by the condensation of phenols with malonic acid in the presence of freshly fused zinc chloride and phosphorus oxychloride.



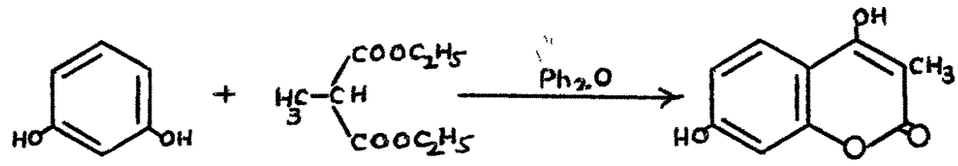
(8)

3-Alkyl-4-hydroxycoumarins have been prepared by heating phenol with ethyl monoalkyl malonates at 200-40° for 48 hours[26].



R=CH_3, C_6H_5, $CH_2C_6H_5$

Trivedi[27] prepared 3-methyl-(17) and 3-benzyl-4-hydroxycoumarin (18) derivatives by the condensation of different phenols with ethyl methyl malonate or ethyl benzyl malonate in refluxing diphenyl ether. He observed that in the case of reactive phenols such as resorcinol, phloroglucinol and α-naphthol the yields are over 60 %, but they are poor in the case of less reactive phenols such as phenol and β-naphthol.



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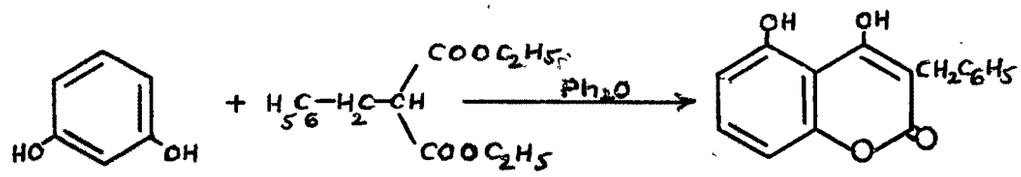


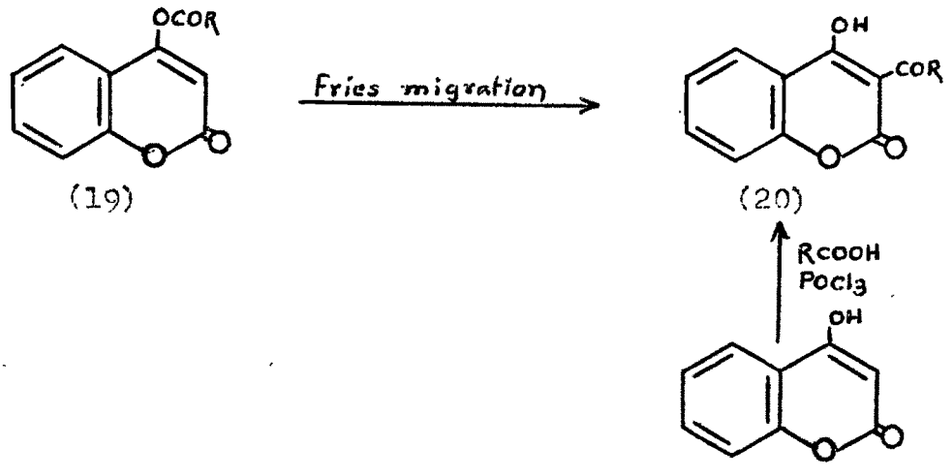
(18)

As the present work deals with the reactions on 4-hydroxy-5,6-benzocoumarin, it will be of interest to review a few known reactions on 4-hydroxycoumarin derivatives.

Fries migration and Friedel Crafts reaction

Klosa[28] studied the Fries migration of 4-acyloxycoumarins (19) in the presence of several metal halides and obtained the corresponding 3-acyl derivatives (20). These were also obtained by condensing

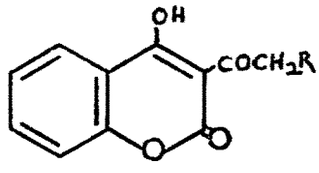
4-hydroxycoumarin with various organic acids in the presence of phosphoryl chloride.



(19) (20)

Claisen condensation

Mustafa et al.[29] prepared β-dicarbonyl compounds (22,b-c) obtained by the Claisen condensation of 4-hydroxy-3-acetylcoumarin (22a) and cyclised them to the corresponding substituted benzopyranyl (3,2-c)pyran-2,10-diones (23 a-b) in the presence of sulphuric acid.



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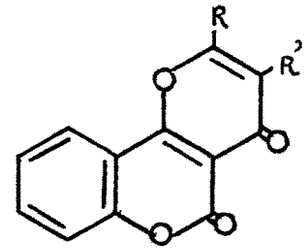


(23)

(a) R = H

(b) R = $COCH_3$

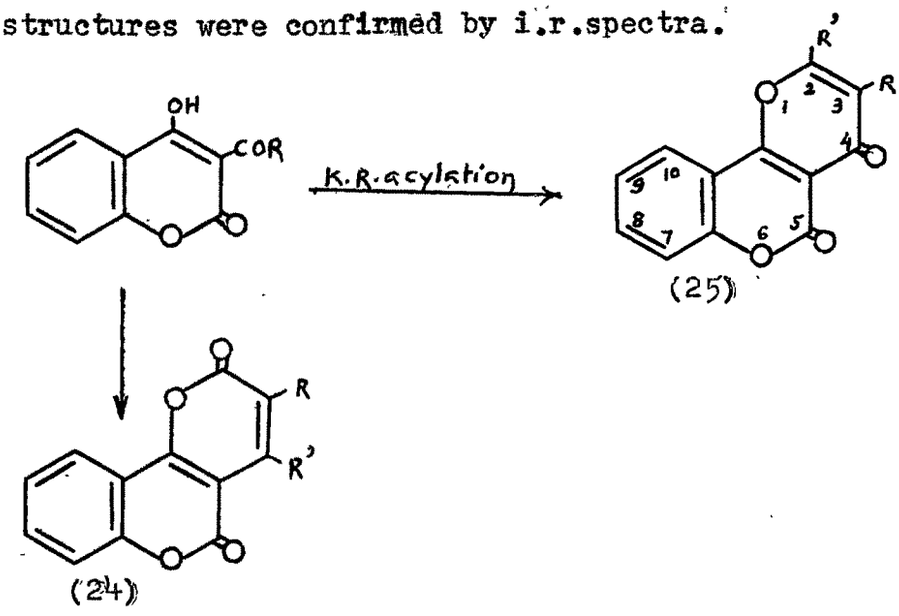
(c) R = COC_6H_5

(a) R = CH_3 ; R' = H

(b) R = C_6H_5 ; R' = H

Kostanecki-Robinson acylation

The Kostanecki-Robinson acylation of 3-acyl-4-hydroxycoumarins using the acid anhydride and salts of the corresponding acids, has been studied by Cook and McIntyre[30]. They showed that if the acyl side chain has an α-CH_2 group or not, 2H,5H-pyrano(4,3-b) pyran-2,5-diones (24) or 4H,5H-pyrano(4,3-b)pyran-4,5-diones (25) were isolated from the reaction mixture. The latter derivatives were prepared by other methods and the structures were confirmed by i.r.spectra.



Chalkone synthesis

Mustafa et al.[29] prepared chalkones by the condensation of 3-acetyl-4-hydroxycoumarin and substituted aldehydes. Attempts to synthesise flavones from these chalkones by selenium dioxide oxidation in dry alcohol or by dehydrobromination of their dibromides with selenium dioxide in amyl alcohol were unsuccessful.

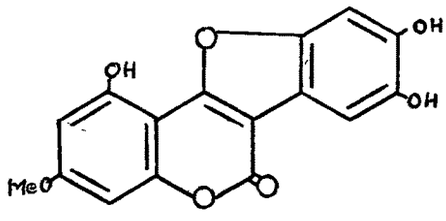
Bicoumarinyls

Huebner and Link[31] reported the formation of the bicoumarinyl derivatives from 3-bromo-4-methoxycoumarin when subjected to Ullmann reaction. They reported that the substance responsible for producing hemorrhage in cattle feeding on spoiled sweet clover hay is 3,3'-methylene-bis(4-hydroxycoumarin) and can be synthesised by reacting formaldehyde with 4-hydroxycoumarin.

Several other aldehydes have been used in place of formaldehyde[32] and also substituted 4-hydroxycoumarin derivatives have been used instead of simple 4-hydroxy-coumarin[33] but these changes have not led to a better coagulant.

Coumaronocoumarins

Coumestrol, Wedelolactone, trifoliol, medicagol and psoralidin are the naturally occuring compounds. These coumaronocoumarins are of structural interest in that they are related to the coumaranochromans and the 3-aryl-coumarins. Wanzlick et al.[34] prepared wedelolactone (26) by dehydrogenative coupling of catechol with 4,5-dihydroxy-7-methoxycoumarin and potassium ferricyanide. Similarly the



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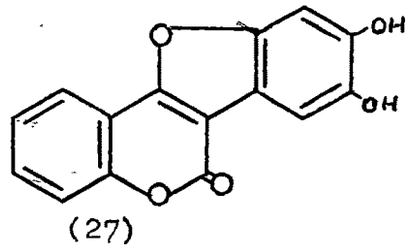
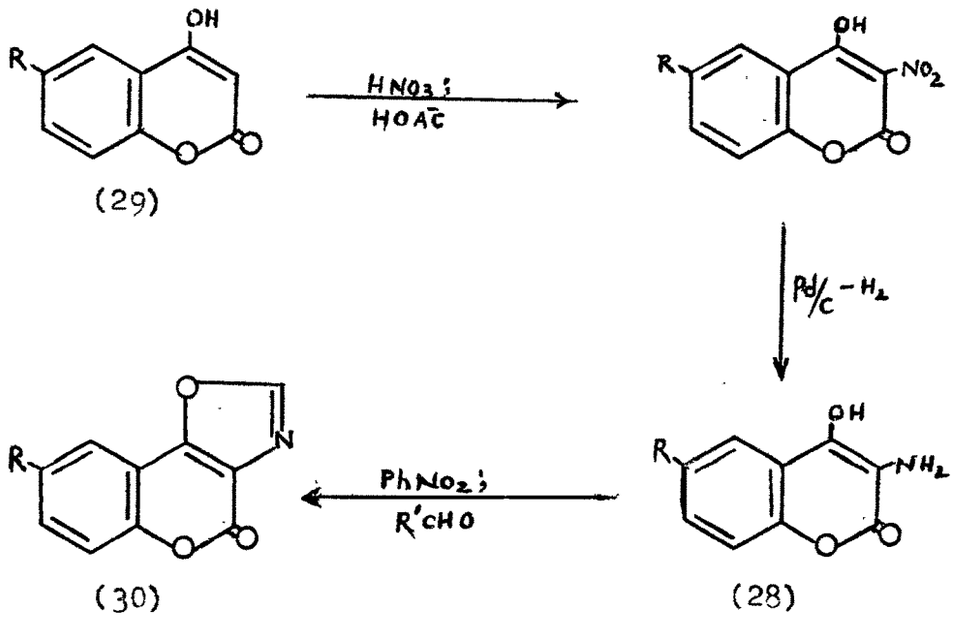


(27)

angular coumaronocoumarin (27) was obtained by dehydrogenative coupling of catechol with 4-hydroxy-coumarin in the presence of potassium iodate[34].

Nitration

The nitration of 4-hydroxycoumarin gave the 3-nitro and 3,6-dinitro derivatives[31]. SubbaRao et al.[35] synthesised some 3-amino-4-hydroxycoumarins and coumarino(3:4)oxazoles. 3-Amino-4-hydroxycoumarins (28) were prepared by first subjecting 4-hydroxycoumarin (29) to nitration followed by reduction with hydrogen in the presence of palladised charcoal. The amino hydroxycoumarins (28) were converted into the corresponding (3:4)oxazoles(30) by condensation with aromatic aldehydes. The authors also studied the bacteriostatic and fungistatic properties of these compounds.



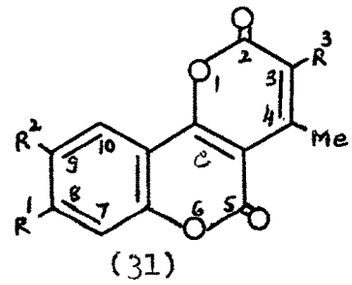
(29) (28) (30)

The present work deals with the study of some reactions on 4-hydroxy-5,6-benzocoumarin and its pattern of substitution towards different reagents.

4-Hydroxy-5,6-benzocoumarin was prepared according to Shah et al.[36] by heating β-naphthol, malonic acid, phosphorus oxychloride and anhydrous zinc chloride at 70-75° for 9 hours.

Pechmann condensation of 4-hydroxycoumarin and 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate : 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran(31b) and 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran (34)

Arora and Mathur[11] reported that a methyl-dioxophenylpyranobenzopyran (31a) possesses anticoagulant activity comparable to that of dicoumarol. It was thought of interest to prepare α-and γ-pyrones having fused benzene ring in the benzenoid part of the coumarin ring system and to study their anticoagulant activity.



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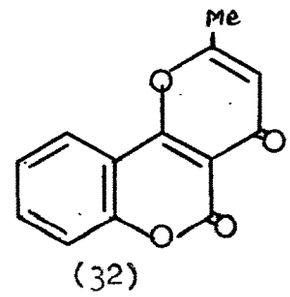


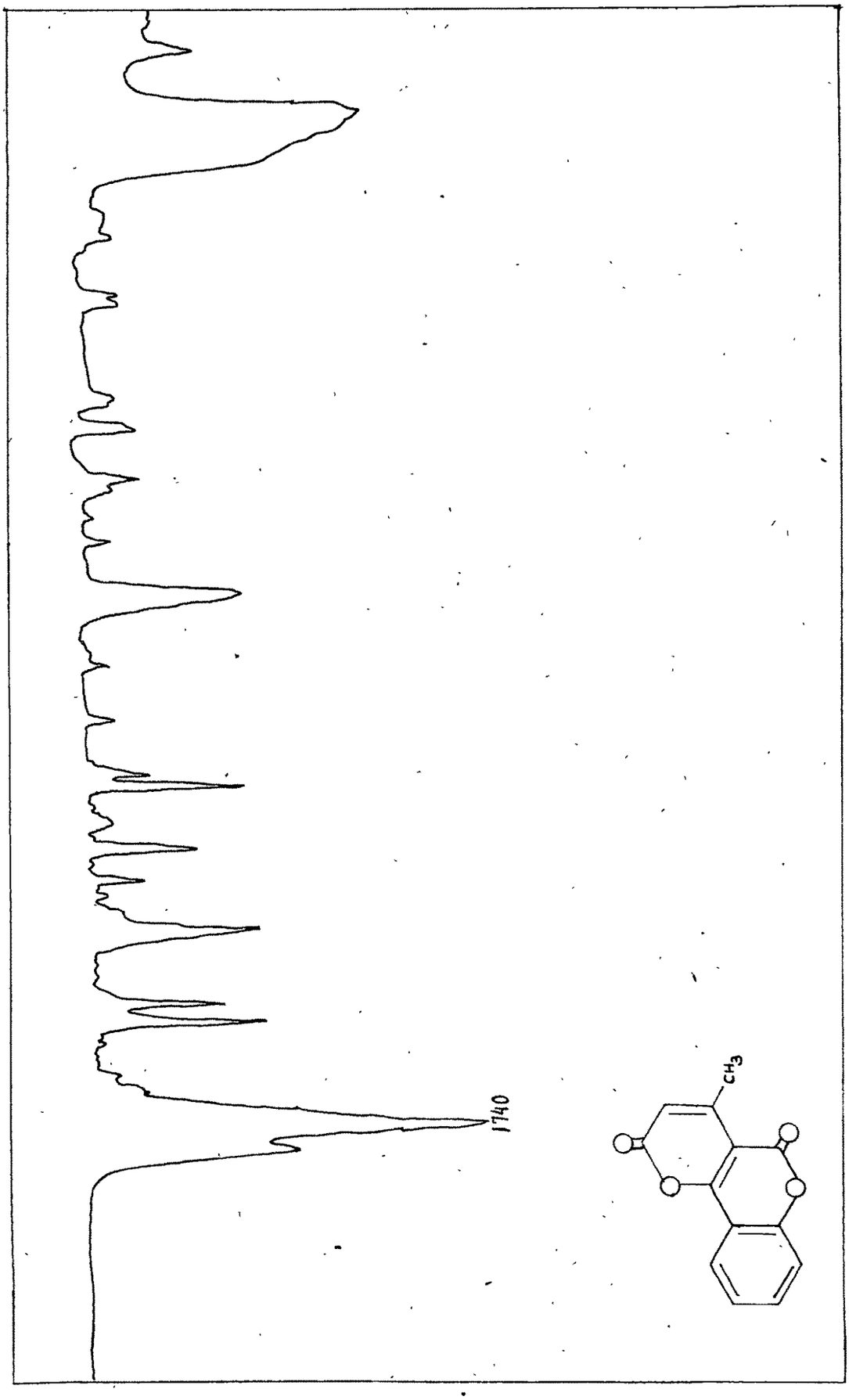
(32)

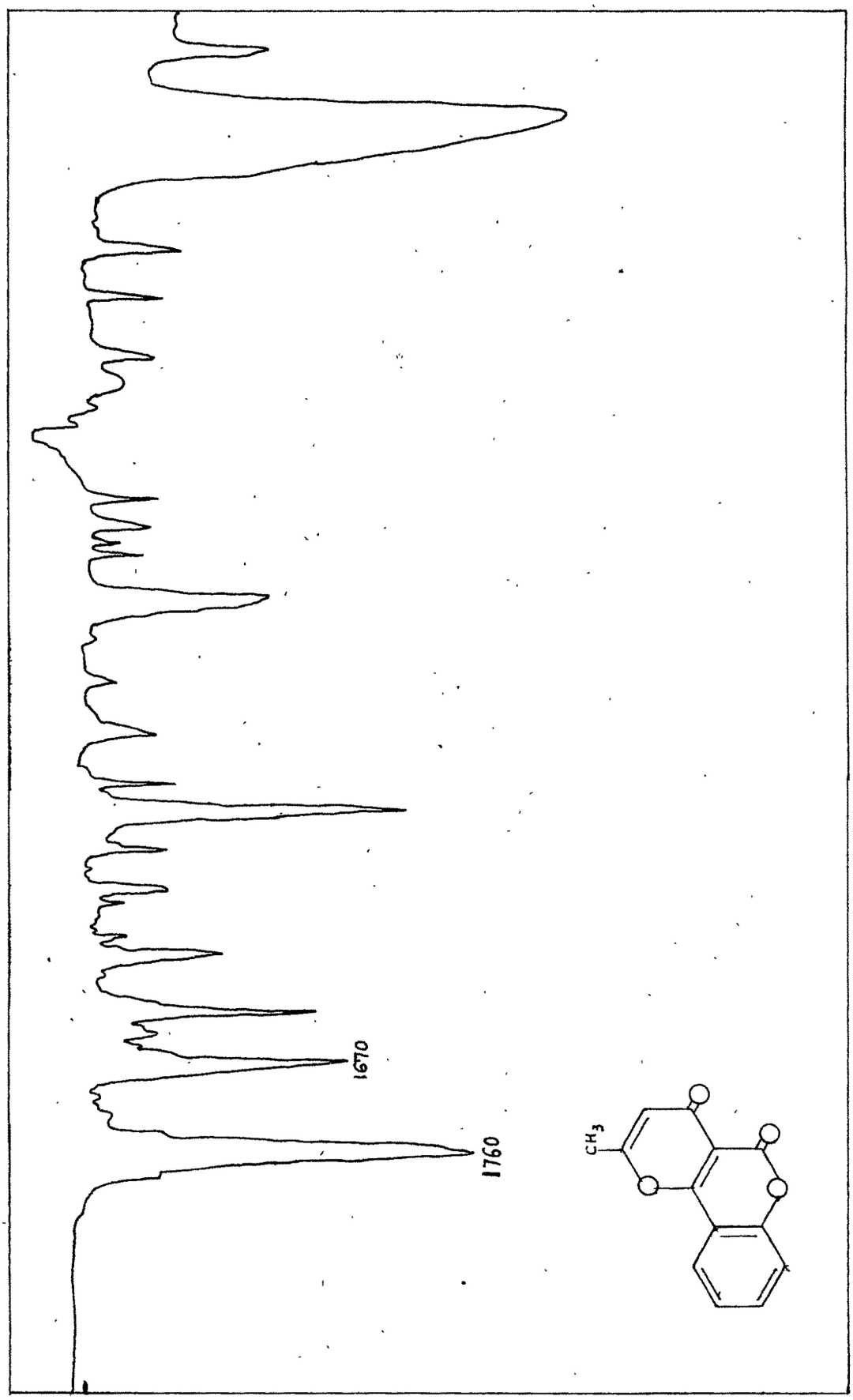
(a) R^1 = H ; R^2 = H ; R^3 = Ph

(b) R^1 = H ; R^2 = H ; R^3 = H

Woods[37] condensed 4-hydroxycoumarin with ethyl acetoacetate in the presence of trifluoroacetic acid and claimed to have obtained 2-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran (32), m.p. 252°, principal absorption bands in the i.r. region, 3344, 1727, 1631, 1613 cm^{-1}. Mustafa et al.[38] synthesised (32), yellow crystals, m.p. 246°, carbonyl stretching frequencies, 1754 cm^{-1} and 1667 cm^{-1}, by different routes and claimed that it was identical in all respects with the compound prepared according to Woods[37]. On repeating Woods's work, it was found that 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo-pyran (31b), colourless crystals, m.p. 243°, carbonyl stretching frequency in the i.r. region, 1740 cm^{-1}, was the only isolable product when the condensation was carried out in the presence of trifluoroacetic acid. The mixed m.p. with an authentic sample of (31b) prepared by using either concentrated sulphuric acid[38,39] or anhydrous aluminium chloride[39] was not depressed; but the mixed m.p. with an authentic sample of (32), yellow crystals, m.p. 246°, carbonyl stretching frequencies in the i.r. region, 1760 cm^{-1} and 1670 cm^{-1}, prepared according to Mustafa et al.[38] was depressed by 20°.

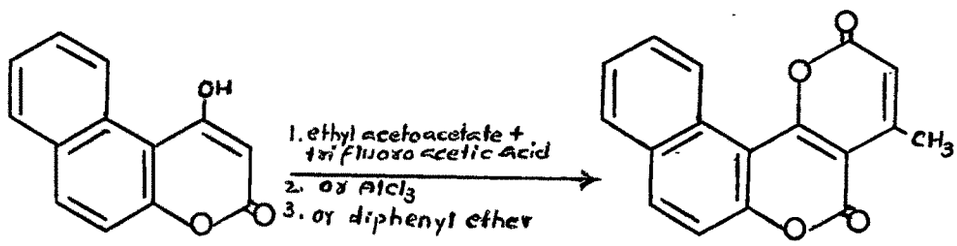
Desai, Trivedi and Sethna[40] condensed different phenols with β-ketonic esters in the presence of refluxing diphenyl ether and obtained benzo-γ-pyrones. When 4-hydroxycoumarin was condensed with ethyl acetoacetate in the presence of refluxing diphenyl ether, only 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzopyran(31b)


1740
CH3


1670
1760
CH3

was obtained and not the expected 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (32). This was also confirmed by mixed m.p. and i.r.spectra which showed carbonyl stretching frequency 1740 cm^{-1}.

This observation was further supported when 4-hydroxy-5,6-benzocoumarin (33) was condensed with ethyl acetoacetate in the presence of trifluoroacetic acid : it gave the same known compound (34) which was obtained by

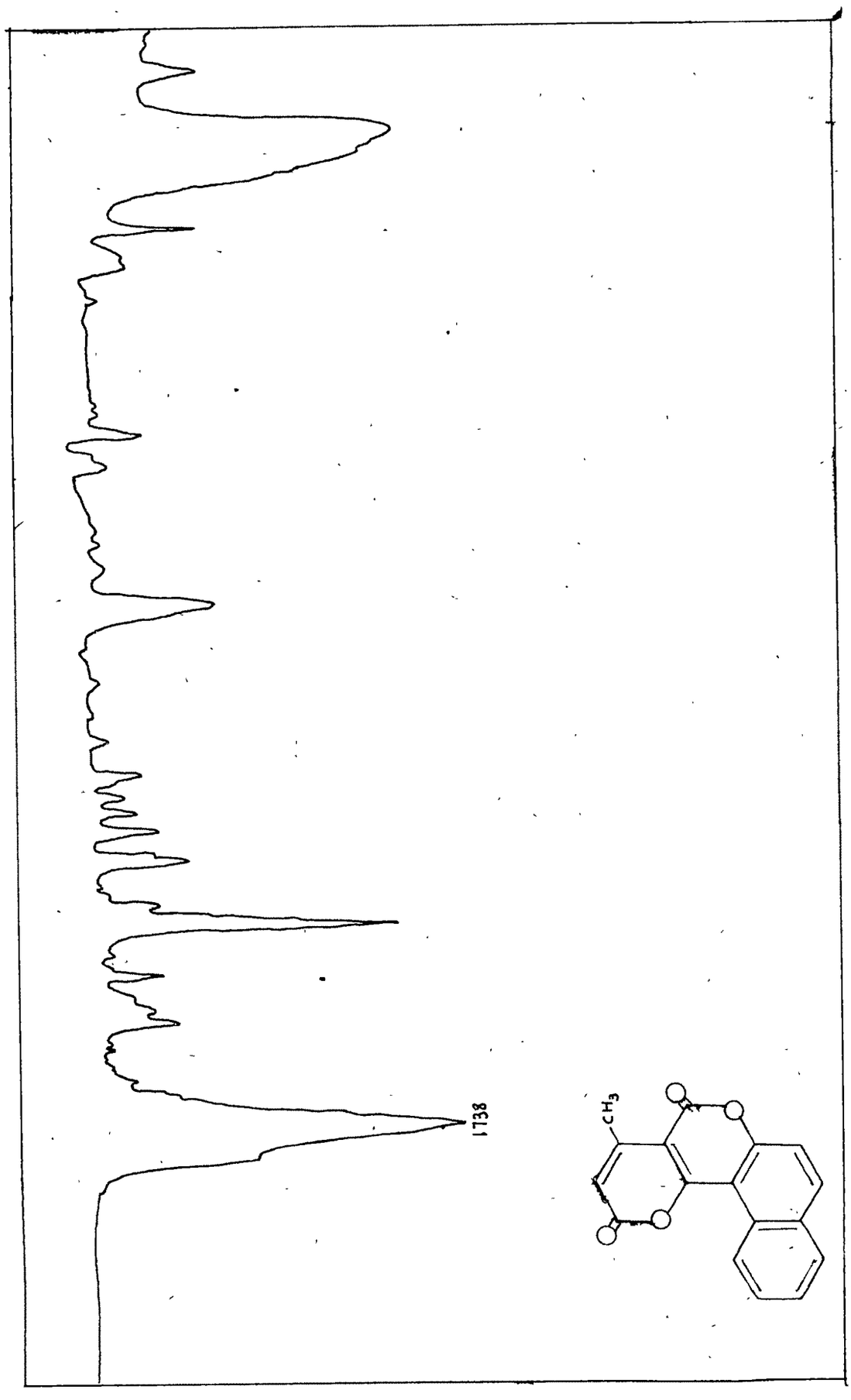


(33) (34)

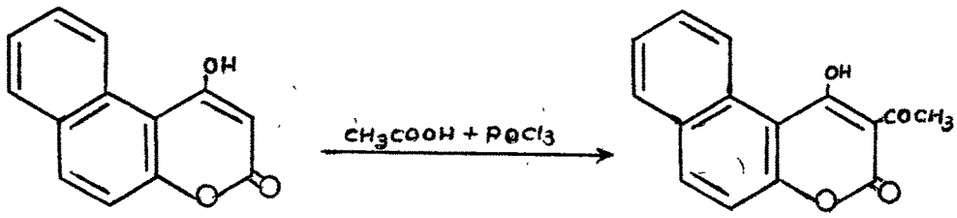
using anhydrous aluminium chloride as condensing agent. The structure was further confirmed by taking its i.r. spectra which showed the carbonyl stretching frequency 1738 cm^{-1}. 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran (34) differed considerably from the corresponding (37) in the i.r.spectra and melting point (page no.160)

The Friedel-Crafts acetylation of 4-hydroxy-5,6-benzocoumarin : 3-Acetyl-4-hydroxy-5,6-benzocoumarin (35)

4-Hydroxy-5,6-benzocoumarin on condensation with glacial acetic acid in the presence of phosphorus oxychloride afforded 3-acetyl-4-hydroxy-5,6-benzocoumarin(35). The structure was confirmed by the analytical data and the


1738
CH3

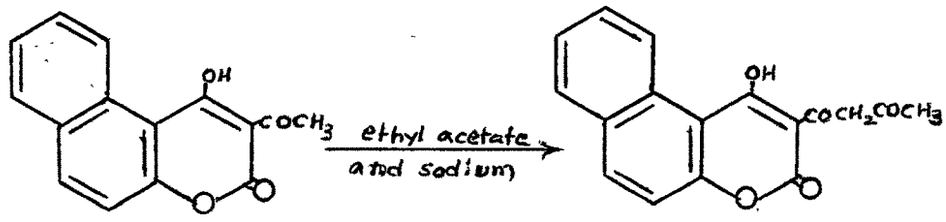
characteristic alcoholic ferric chloride colouration of the hydroxy ketone. As there was a strong chelation between hydroxy group with the neighbouring acetyl group, the compound was found to be insoluble in alkali.



(35)

Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethylacetate : 3-Acetoacetyl-4-hydroxy-5,6-benzocoumarin (36)

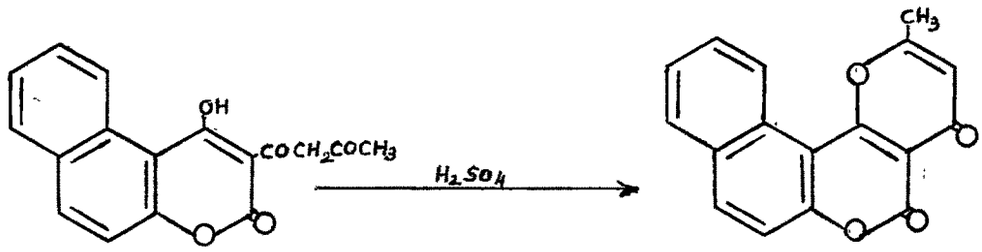
3-Acetyl-4-hydroxy-5,6-benzocoumarin on condensation with ethylacetate and sodium gave the product to which 3-acetoacetyl-4-hydroxy-5,6-benzocoumarin (36) structure was assigned.



(36)

Cyclisation of 3-acetoacetyl-4-hydroxy-5,6-benzocoumarin to 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran (37)

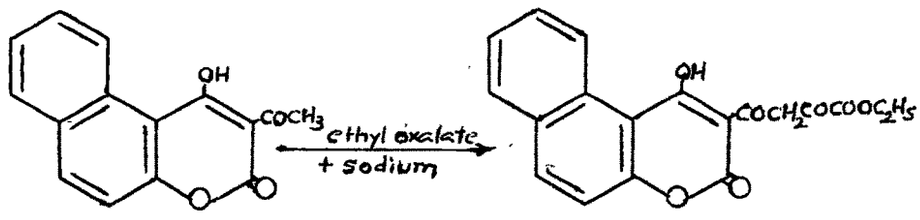
3-Acetoacetyl-4-hydroxy-5,6-benzocoumarin on cyclisation with 25 % sulphuric acid gave the product to which the structure 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran (37) has been assigned. The carbonyl stretching frequencies in the i.r. region are 1760 and 1670 cm^{-1}.



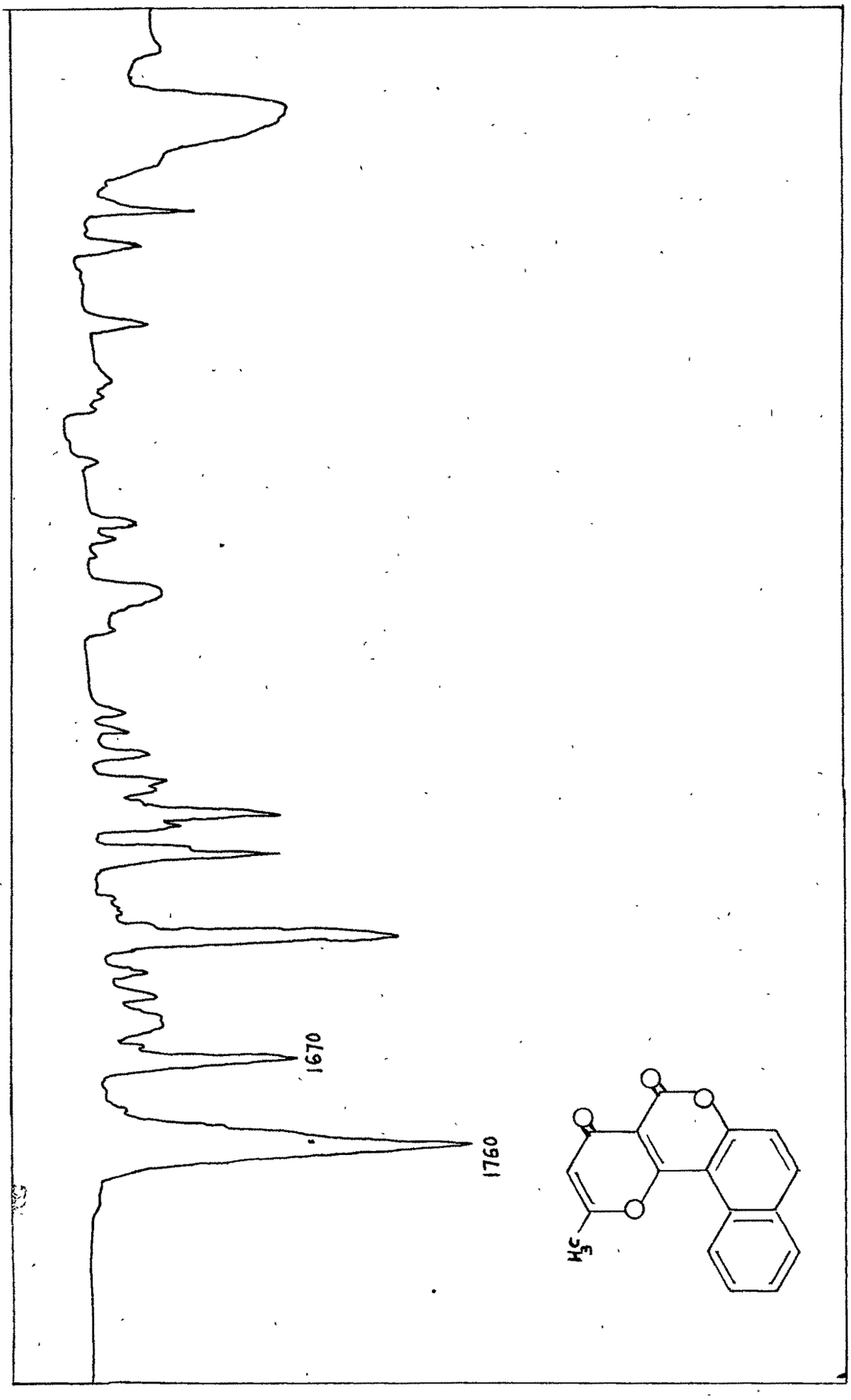
(37)

Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl oxalate : 3-Aceto-oxalyl-4-hydroxy-5,6-benzocoumarin(38)

3-Acetyl-4-hydroxy-5,6-benzocoumarin when condensed with ethyl oxalate in the presence of sodium gave the product to which 3-aceto-oxalyl-4-hydroxy-5,6-benzocoumarin structure (38) was assigned.



(38)

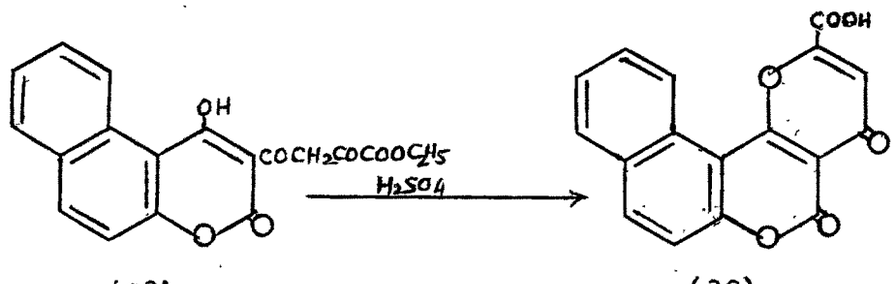

1670
1760
H3C

Cyclisation of the above β-dicarbonyl compound to 2-carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f) benzopyran (39)

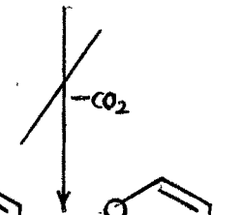
3-Aceto-oxalyl-4-hydroxy-5,6-benzocoumarin on cyclisation with 50 % sulphuric acid gave the product which was assigned the structure, 2-carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran (39)

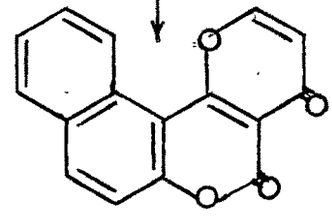
Attempted decarboxylation of 2-carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran to 4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran (40)

The above acid on refluxing with copper and quinoline or heating above its melting point gave an unworkable product.



(38) (39)





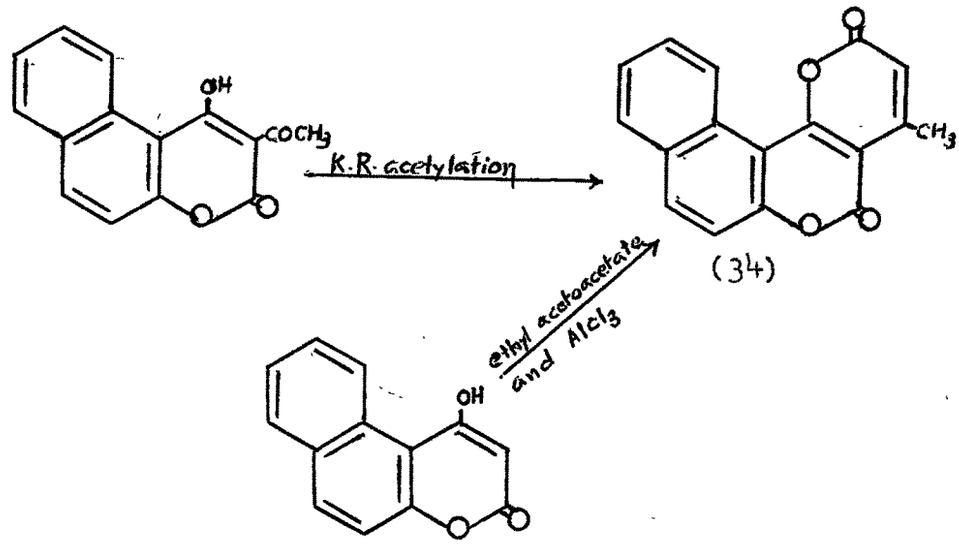
(40)

Attempted Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl benzoate

3-Acetyl-4-hydroxy-5,6-benzocoumarin on condensation with ethyl benzoate in the presence of sodium at high temperature or heating for longer period gave the original product back.

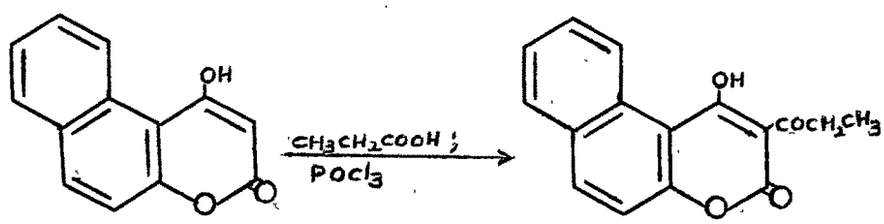
Kostanecki-Robinson acetylation of 3-acetyl-4-hydroxy-5,6-benzocoumarin : 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c) benzo(f)benzopyran (34)

3-Acetyl-4-hydroxy-5,6-benzocoumarin on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate gave the product which did not develop any colouration with alcoholic ferric chloride solution and to which 4-methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f) benzopyran (34) structure was assigned. The mixed m.p. with an authentic sample prepared by the Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate as described earlier was not depressed.



Friedel-Crafts propionylation of 4-hydroxy-5,6-benzocoumarin : 3-Propionyl-4-hydroxy-5,6-benzocoumarin (41)

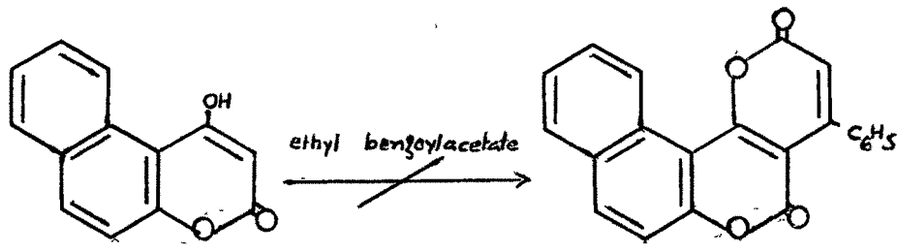
4-Hydroxy-5,6-benzocoumarin when condensed with propionic acid and phosphorus oxychloride afforded the product which gave red colouration with alcoholic ferric chloride solution. On the basis of this property and analytical data it was assigned 3-propionyl-4-hydroxy-5,6-benzocoumarin structure (41).



(41)

Attempted Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with ethyl benzoylacetate to 4-phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran (42)

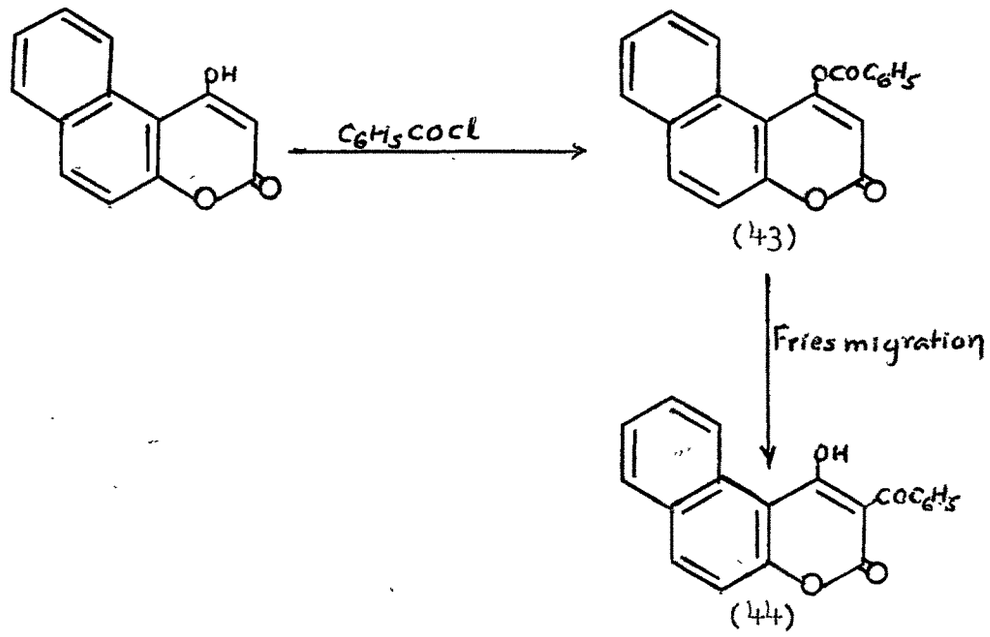
4-Hydroxy-5,6-benzocoumarin when condensed with ethyl benzoylacetate in the presence of concentrated sulphuric acid or anhydrous aluminium chloride did not give the expected α-pyrone (42). Only the original product was obtained. The reaction also failed when the mixture was refluxed for long time in diphenyl ether.



(42)

Fries migration of 4-benzoyloxy-5,6-benzocoumarin (43): 3-Benzoyl-4-hydroxy-5,6-benzocoumarin (44)

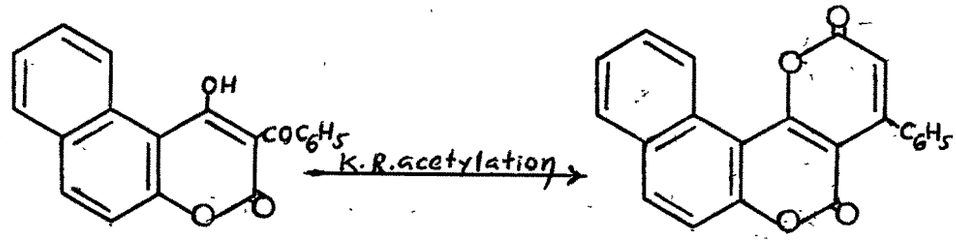
4-Hydroxy-5,6-benzocoumarin when mixed with benzoyl chloride in presence of pyridine and piperidine gave the alkali insoluble product which was assigned the structure 4-benzoyloxy-5,6-benzocoumarin (43). This on heating with anhydrous aluminium chloride afforded the



alkali soluble product which gave the characteristic red colouration with alcoholic ferric chloride solution. On the basis of these properties and analytical data it was assigned 3-benzoyl-4-hydroxy-5,6-benzocoumarin structure(44).

Kostanecki-Robinson acetylation of 3-benzoyl-4-hydroxy-5,6-benzocoumarin : 4-Phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran (45)

3-Benzoyl-4-hydroxy-5,6-benzocoumarin on Kostanecki-Robinson acetylation with acetic anhydride and sodium acetate gave an alkali insoluble product which did not develop any colouration with alcoholic ferric chloride solution. On the basis of these properties and i.r.spectra which showed carbonyl absorption 1730 cm^{-1} (lactonyl >C=O group) it was assigned 4-phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran structure(45).

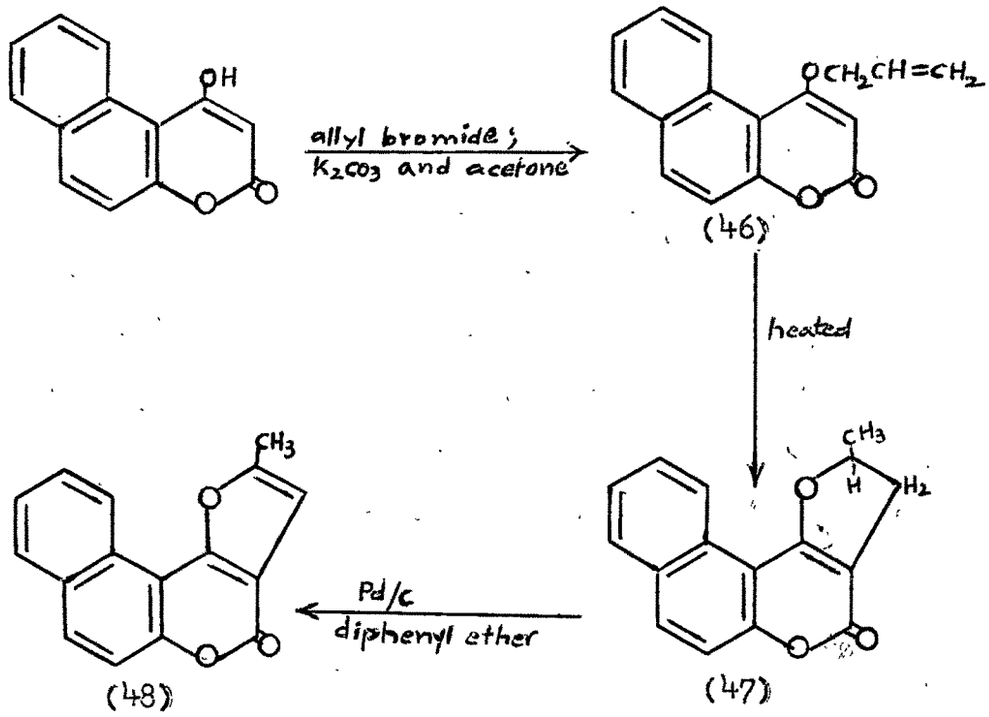


(45)

Synthesis of 2-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran (48)

4-Hydroxy-5,6-benzocoumarin on allylation with allyl bromide in the presence of anhydrous potassium carbonate in acetone gave the alkali insouble product 4-allyloxy-5,6-benzocoumarin (46), which on Claisen

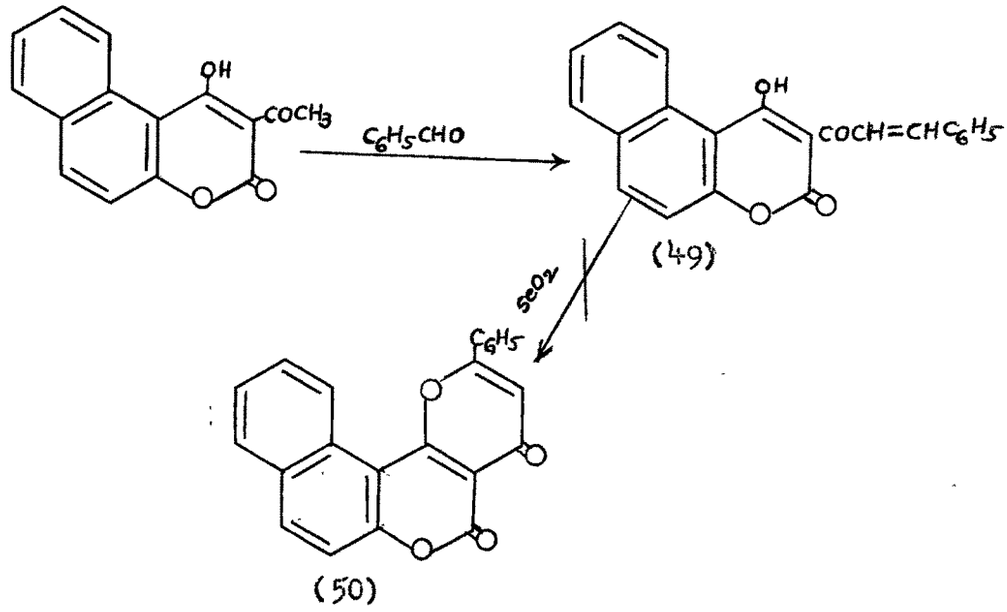
rearrangement by heating at 200°C afforded 2-methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran (47) and not 3-allyl-4-hydroxy-5,6-benzocoumarin. (47) on dehydrogenation by refluxing it with diphenyl ether in the presence of palladised charcoal yielded 2-methyl-4-oxo-4H-furo(3,2-c)benzo(f)benzopyran (48).



Chalkone synthesis : Condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with benzaldehyde : 3-Cinnamoyl-4-hydroxy-5,6-benzocoumarin (49)

3-Acetyl-4-hydroxy-5,6-benzocoumarin when condensed with benzaldehyde in the presence of ethanolic potassium hydroxide solution gave the product which was

assigned 3-cinnamoyl-4-hydroxy-5,6-benzocoumarin structure (49).



Attempted cyclisation of the chalkone to the corresponding flavone (50)

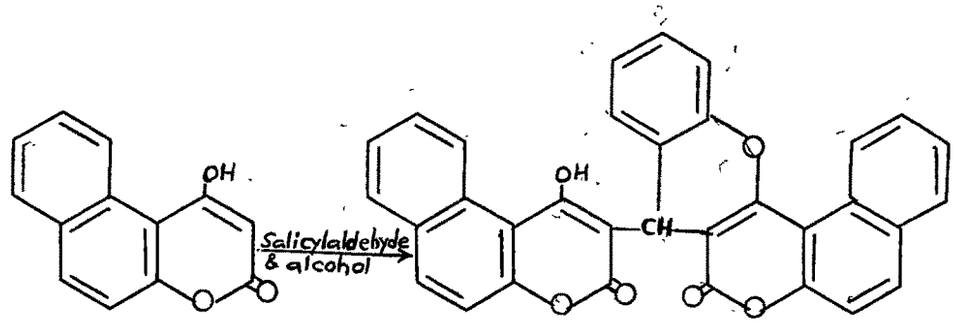
The above chalkone when refluxed with selenium dioxide in amyl alcohol gave only the original product. The reaction did not proceed even on heating for a longer period.

Condensation of 4-hydroxy-5,6-benzocoumarin with salicylaldehyde :

Arora et al[32] studied the structure and anti-coagulant activity of bridge-substituted dicoumarols. They synthesised various 3,3'-benzylidene bis-4-hydroxycoumarins

by condensing 4-hydroxycoumarin with substituted benzaldehyde.

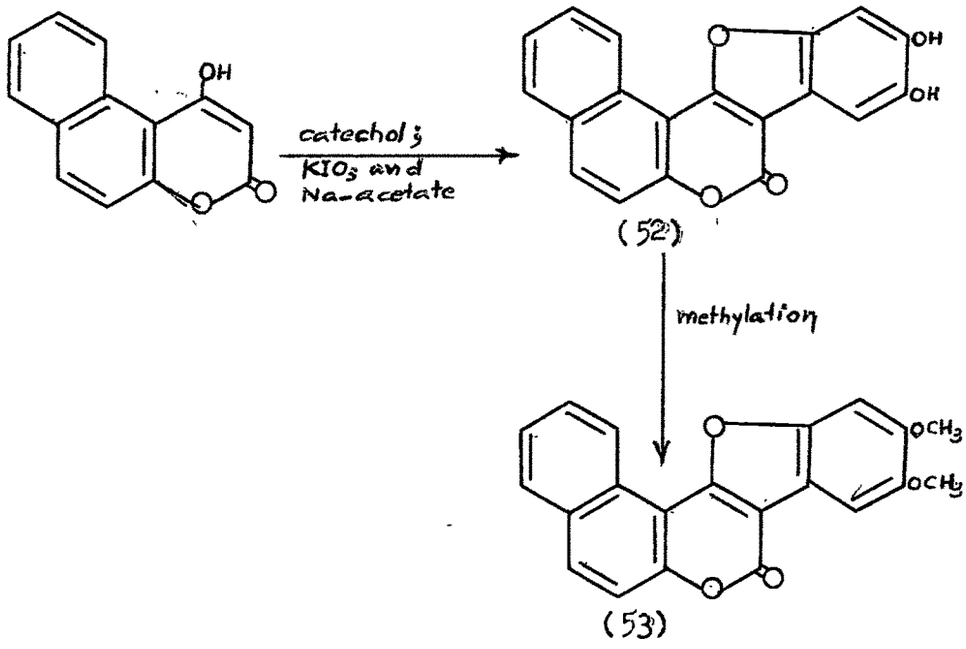
4-Hydroxy-5,6-benzocoumarin on similar condensation with salicylaldehyde gave the product which was assigned the structure (51).



(51)

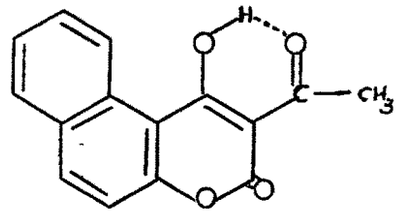
Condensation of 4-hydroxy-5,6-benzocoumarin with catechol

4-Hydroxy-5,6-benzocoumarin was condensed with catechol in the presence of sodium acetate and potassium iodate. The dihydroxy product (52) gave characteristic green colouration with ferric chloride solution. Because of its insolubility in common organic solvents it was therefore methylated with dimethyl sulphate in the presence of potassium carbonate in acetone whereby it afforded the alkali insoluble compound to which the structure (53) has been assigned.



Attempted condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethylbromoacetate

An attempt to condense 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethylbromoacetate to build up the furan ring in the 3-4 position of α-pyrone was met with failure. The reaction did not take place even on boiling



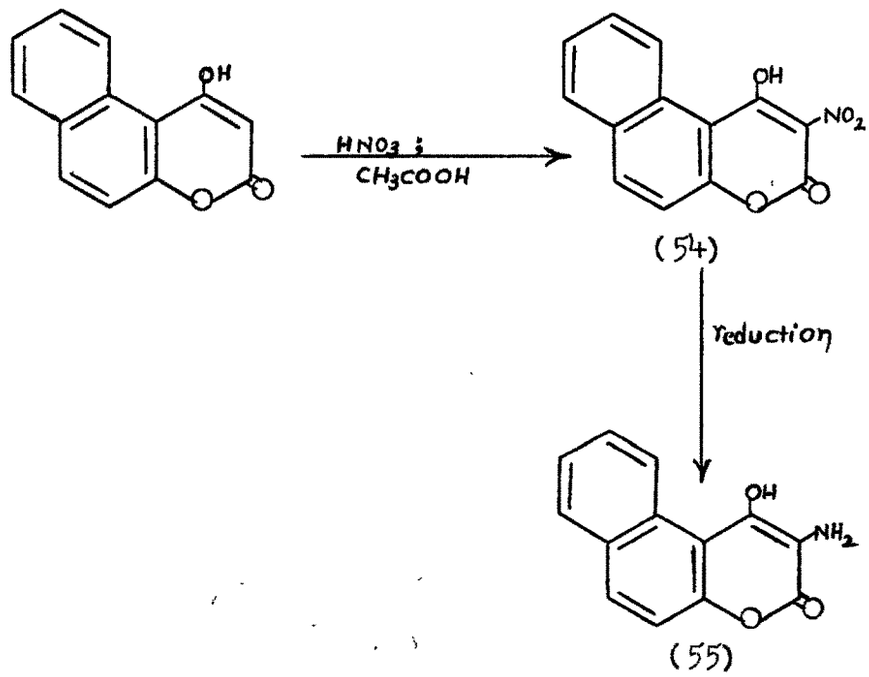
the mixture for 70 hours. Only the original compound was obtained back. This may be because of the strong chelation of the hydroxy group with the neighbouring acetyl group in the ortho position.

Nitration of 4-hydroxy-5,6-benzocoumarin : 3-Nitro-4-hydroxy-5,6-benzocoumarin (54)

4-Hydroxy-5,6-benzocoumarin was nitrated with concentrated nitric acid in glacial acetic acid. The reaction took place immediately and the product was assigned the structure 3-nitro-4-hydroxy-5,6-benzocoumarin (54).

Reduction of 3-nitro-4-hydroxy-5,6-benzocoumarin : 3-Amino-4-hydroxy-5,6-benzocoumarin (55)

The above nitro compound on reduction with sodium bisulphite in alcohol gave the compound which was assigned the structure 3-amino-4-hydroxy-5,6-benzocoumarin (55).



EXPERIMENTAL

4-Hydroxy-5,6-benzocoumarin

4-Hydroxy-5,6-benzocoumarin was prepared according to Shah et al.[36] as follows :

A mixture of β-naphthol (1 M), malonic acid (1 M), phosphorus oxychloride (2-3 M) and anhydrous zinc chloride (2-3 M) was heated with stirring for 9 hours at 70-75°. It was then cooled, decomposed with ice-water and allowed to stand. The crude product was taken in sodium bicarbonate solution and acidified. The compound on crystallisation from acetic acid gave m.p. 285°.

4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)-benzopyran

4-Hydroxy-5,6-benzocoumarin (1 g.) was heated with ethyl acetoacetate (1 ml.) in trifluoroacetic acid (8 ml.) on a sand bath for 15 hours. After the completion of the reaction, a few millilitres of ethanol were added and the mixture kept overnight. The product which separated was filtered off and washed with sodium bicarbonate solution. The residue was crystallised from benzene in yellowish needles, yield 0.6 g. M.P. and mixed m.p. with an authentic sample obtained by using anhydrous aluminium chloride as condensing agent was 246°. The carbonyl stretching frequency in the i.r. region is 1745 cm^{-1}.

Analysis : Found : C,73.38 ; H,3.23 %.

$C_{17}H_{10}O_4$ requires : C,73.38 ; H,3.62 %.

The same compound was also prepared by refluxing the mixture of 4-hydroxy-5,6-benzocoumarin (1 g.), ethyl acetoacetate (2 ml.) and diphenyl ether (8 ml.) for 5 to 6 hours. The mixture was cooled and the separated product was washed with petroleum ether (60-80°). It was then treated with sodium bicarbonate solution and the residue was crystallised from benzene in yellowish needles, m.p. 246°. Yield 0.5 g. M.P. and mixed m.p. with the above product was not depressed.

The Friedel-Crafts acetylation of 4-hydroxy-5,6-benzocoumarin : 3-Acetyl-4-hydroxy-5,6-benzocoumarin

4-Hydroxy-5,6-benzocoumarin (1 g.) was dissolved in acetic acid (5 ml.) and phosphorus oxychloride (2 ml.) was added to it. The reaction mixture was gently refluxed for 40 minutes. It was then cooled and added to ice-water. The product after drying, was crystallised from acetic acid in shining needles, m.p. 201°. Yield 0.7 g. It developed a red colouration with alcoholic ferric chloride solution.

Analysis : Found : C,70.38 ; H,4.12 %.

$C_{15}H_{10}O_4$ requires : C,70.86 ; H,3.96 %.

Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl acetate : 3-Acetoacetyl-4-hydroxy-5,6-benzocoumarin

3-Acetyl-4-hydroxy-5,6-benzocoumarin (1 g.) was dissolved in freshly distilled ethyl acetate (30 ml.) by gentle warming. The solution was slowly added to pulverized

sodium (1.2 g.) with shaking. The reaction mixture was then heated on a water-bath for 6 hours and decomposed with ice. The mixture was extracted with ether and the aqueous layer was acidified. The product was filtered, dried and crystallised from benzene in shining yellow needles, m.p. 166°. Yield 0.4 g.

Analysis : Found : C, 68.96 ; H, 4.50 %.

$C_{17}H_{12}O_5$ requires : C, 68.92 ; H, 4.10 %.

2-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)-benzopyran

A solution of 3-acetoacetyl-4-hydroxy-5,6-benzocoumarin (0.8 g.) in 50 ml. dilute sulphuric acid (25 %.) was heated on a sand-bath for 2 hours. The cooled reaction mixture was neutralised with sodium carbonate solution and the separated product was crystallised from acetic acid in yellow needles, m.p. 282°. Yield 0.2 g.

Analysis : Found : C, 73.07 ; H, 3.94 %.

$C_{17}H_{10}O_4$ requires : C, 73.38 ; H, 3.62 %.

Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl oxalate : 3-Aceto-oxalyl-4-hydroxy-5,6-benzocoumarin

3-Acetyl-4-hydroxy-5,6-benzocoumarin (1 g.) was dissolved in ethyl oxalate (25 ml.) by warming and this warm solution was added slowly with shaking to pulverized sodium (1 g.). The mixture was heated on a steam-bath for 6 to 7 hours with occational shaking and decomposed with

ice-water. The separated product was washed several times with water and dried. It was crystallised from large quantity of acetic acid in yellow needles, m.p. 202°C. Yield 0.6 g. The filtrate in the above reaction mixture was ether extracted to remove unreacted ethyl oxalate and the aqueous solution was acidified. No product was separated from the filtrate.

Analysis : Found : C,64.52 ; H,4.05 %.

$C_{19}H_{14}O_7$ requires : C,64.40 ; H,3.95 %.

2-Carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)-benzopyran (39)

3-Aceto-oxalyl-4-hydroxy-5,6-benzocoumarin (0.5 g.) was mixed with 30 ml. of sulphuric acid (50 %) and the mixture was refluxed on a sand-bath for 4 hours. It was then poured into ice-cold water and filtered. The residue was purified by taking into bicarbonate solution and acidified. The product after drying was crystallised from large quantity of acetic acid in colourless crystals, m.p. 285°.

Analysis : Found : C,66.55 ; H,2.62 %.

$C_{17}H_7O_6$ requires : C,66.45 ; H,2.28 %.

$C_{17}H_8O_6$ 66.23 2.60

Attempted decarboxylation of the above acid to 4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)benzopyran

2-Carboxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzo(f)-benzopyran (0.5 g.) was dissolved in freshly distilled quinoline (4 ml.) and it was refluxed with copper bronze(0.2 g.)

The mixture was decomposed with ice-cold hydrochloric acid and ether extracted. On evaporation of the ether only unworkable product was obtained. Attempt to decarboxylate the acid by heating above its melting point also met with failure.

Attempted Claisen condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl benzoate

3-Acetyl-4-hydroxy-5,6-benzocoumarin (1 g.) was dissolved in ethyl benzoate (25 ml.) and the hot solution was added to pulverized sodium (1 g.). The reaction mixture on heating on a steam-bath or at a higher temperature (180-90°) gave the original product only.

K.R.Acetylation of 3-acetyl-4-hydroxy-5,6-benzocoumarin: 4-Methyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran

A mixture of 3-acetyl-4-hydroxy-5,6-benzocoumarin (2 g.),freshly fused sodium acetate (2 g.) and acetic anhydride (4 ml.) was refluxed at 135° for 2 hours. It was cooled and poured into water. The brown solid was filtered and after 2-3 crystallisations from acetic acid it gave yellowish crystals in poor yield, m.p. 245°. The mixed m.p. with an authentic sample prepared by the Pechmann condensation of 4-hydroxy-5,6-benzocoumarin with ethyl acetoacetate was 245°.

Friedel-Crafts propionylation of 4-hydroxy-5,6-benzocoumarin : 3-Propionyl-4-hydroxy-5,6-benzocoumarin

A mixture of 4-hydroxy-5,6-benzocoumarin (1 g.)

propionic acid (5 ml.) and phosphorus oxychloride (2 ml.) was gently refluxed on a sand-bath for 2 hours. The cold mixture was poured into ice-water, filtered, washed and crystallised from acetic acid in shining needles, m.p.193°. Yield 0.5 g. It gave the red colouration with alcoholic ferric chloride solution.

Analysis : Found : C,71.60 ; H,4.32 %.

$C_{16}H_{12}O_4$ requires : C,71.64 ; H,4.47 %.

Attempted Pechmann condensation of 4-Hydroxy-5,6-benzocoumarin with ethyl Benzoylacetate to 4-Phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran

4-Hydroxy-5,6-benzocoumarin (1 g.) was heated with ethyl benzoylacetate (2 ml.), anhydrous aluminium chloride (1.2 g.) and nitrobenzene (6 ml.) in an oil bath at 130° for 4 to 5 hours. On working out the reaction mixture as usual the original compound was obtained back.

4-Hydroxy-5,6-benzocoumarin (1 g.) was refluxed with ethyl benzoylacetate (1 ml.) and diphenyl ether (5 ml.) for 20 hours. The reaction mixture was cooled and on working out as usual the original product was recovered.

Fries migration of 4-benzoyloxy-5,6-benzocoumarin : 3-Benzoyl-4-hydroxy-5,6-benzocoumarin :

4-Benzoyloxy-5,6-benzocoumarin

4-Hydroxy-5,6-benzocoumarin (1.5 g.) was dissolved in pyridine (10 ml.) and piperidine (2-3 drops) was added to it. The mixture was kept at 0° and

benzoyl chloride (3 ml.) was slowly added with constant stirring. It was kept in ice-bath for 5 minutes and then decomposed with ice and hydrochloric acid. The separated product was washed with dilute alkali and crystallised from acetic acid in shining needles, m.p. 206°. Yield 1 g.

Analysis : Found : C,75.79 ; H,4.18 %.

$C_{20}H_{12}O_4$ requires : C,75.94 ; H,3.82 %.

3-Benzoyl-4-hydroxy-5,6-benzocoumarin

An intimate mixture of 4-benzoyloxy-5,6-benzocoumarin (1 g.) and anhydrous aluminium chloride (3 g.) was heated in an oil bath at 140-50° for 1 hour. The cold mixture was decomposed with ice and hydrochloric acid and the product was purified by taking it in sodium bicarbonate solution. It was crystallised from benzene in yellow shining needles, m.p. 204°. Yield 0.5 g. It developed a red colouration with alcoholic ferric chloride solution.

Analysis : Found : C,75.67 ; H,3.64 %.

$C_{20}H_{12}O_4$ requires : C,75.94 ; H,3.82 %.

Kostanecki-Robinson acetylation of 3-benzoyl-4-hydroxy-5,6-benzocoumarin : 4-Phenyl-2,5-dioxo-2H,5H-pyrano(3,2-c)benzo(f)benzopyran

3-Benzoyl-4-hydroxy-5,6-benzocoumarin (1 g.) was mixed with freshly fused sodium acetate (3 g.) and acetic anhydride (35 ml.). It was heated in an oil bath at 150-60° for 6 to 8 hours and decomposed with water. The product was filtered, washed with bicarbonate solution

and crystallised from acetic acid in reddish crystals, m.p. 280°. Yield 0.4 g.

Analysis : Found : C,78.07 ; H,3.20 %.

$C_{22}H_{12}O_4$ requires : C,77.64 ; H,3.53 %.

Synthesis of 2-methyl-4-oxo-4H-furo(3,2-c)benzo(f)-benzopyran : 4-Allyloxy-5,6-benzocoumarin

A mixture of 4-hydroxy-5,6-benzocoumarin (1 g.), allyl bromide (0.8 ml.), anhydrous potassium carbonate (2 g.) and dry acetone (100 ml.) was refluxed for 20 hours. The acetone was distilled off and the product was washed with dilute alkali solution and then with petroleum ether. It was dissolved in benzene and the dried benzene solution was allowed to percolate through a short column of activated alumina and eluted with hexane. The elugte on evaporation yielded the product which crystallised from benzene-petroleum ether as yellowish needles, m.p.146°. Yield 0.2 g.

Analysis : Found : C,76.14 ; H,4.70 %.

$C_{16}H_{12}O_3$ requires : C,76.19 ; H,4.76 %.

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

4-Allyloxy-5,6-benzocoumarin (0.5 g.) was heated at 195-200° (temperature of reaction mixture) in an oil bath for 1 hour. The dark brown mass was washed with bicarbonate solution and on crystallisation from benzene-petroleum ether it gave the colourless shining needles, m.p. 154°. Yield 0.2 g.

Analysis : Found : C,75.84 ; H,4.58 %.

$C_{16}H_{12}O_3$ requires : C,76.19 ; H,4.76 %.

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

2-Methyl-2,3-dihydro-4-oxo-4H-furo(3,2-c) benzo(f)benzopyran (0.2 g.) was dissolved in diphenyl ether (2 ml.) and refluxed with palladised charcoal (0.2 g. ; 10 %) for 6 to 8 hours. It was filtered hot and cooled. The separated crystals were washed with petroleum ether,dried and crystallised from acetic acid in shining needles, m.p. 246°. Yield 0.05 g.

Analysis : Found : C,76.33 ; H,3.88 %.

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

Chalkone synthesis : 3-Cinnamoyl-4-hydroxy-5,6-benzocoumarin

3-Acetyl-4-hydroxy-5,6-benzocoumarin (1 g.) was dissolved in ethanol by warming and to this solution benzaldehyde (1 ml.) and potassium hydroxide solution (10 ml. ; 100 %) were added. The mixture was kept at the room temperature for 3 days. The clear solution was diluted with water and ether extracted. The aqueous solution on acidification gave the product which was crystallised from acetic acid in yellow needles, m.p. 176°. Yield 0.4 g.

Analysis : Found : C,77.05 ; H,4.08 %.

$C_{22}H_{14}O_4$ requires : C,77.20 ; H,4.09 %.

Attempted cyclisation of the chalkone to the flavone derivative

3-Cinnamoyl-4-hydroxy-5,6-benzocoumarin (0.5 g.), amyl alcohol (5 ml.) and selenium dioxide (0.5 g.) were heated at 140-50° for 20 hours. The mixture was filtered and the separated product on crystallisation from acetic acid was found to be unchanged 3-cinnamoyl-4-hydroxy-5,6-benzocoumarin.

Condensation of 4-hydroxy-5,6-benzocoumarin with salicylaldehyde

4-Hydroxy-5,6-benzocoumarin (0.5 g.) was dissolved in alcohol (80 to 90 ml.) by boiling. To the clear solution salicylaldehyde (2 ml.) was added and the reaction mixture was refluxed for 3 to 4 hours. The separated product was filtered and crystallised from large quantity of benzene in yellowish crystals, m.p. 291°. Yield 0.2 g.

Analysis : Found : C,77.67 ; H,3.66 %.

$C_{33}H_{18}O_6$ requires : C,77.64 ; H,3.55 %.

Condensation of 4-hydroxy-5,6-benzocoumarin with catechol

4-Hydroxy-5,6-benzocoumarin (0.5 g.), catechol (0.3 g.) and sodium acetate (2 g.) were mixed in acetone-water (50 ml. 1:1). To the clear solution potassium iodate (0.3 g.) and sodium acetate (0.5 g.) in water (15 ml.) were added slowly with shaking. After 15 minutes the separated product was filtered and dried. It developed green

colouration with alcoholic ferric chloride solution. Because of its insolubility in many organic solvents it was methylated with dimethyl sulphate (1 ml.), anhydrous potassium carbonate (2 g.) and acetone by refluxing the mixture for 6 hours. On evaporation of the solvent the product was washed with dilute alkali and crystallised from benzene in yellow crystals, m.p. 277°. Yield 0.2 g.

Analysis : Found : C,72.70 ; H,3.94 %.

$C_{21}H_{14}O_5$ requires : C,72.83 ; H,4.05 %.

Attempted condensation of 3-acetyl-4-hydroxy-5,6-benzocoumarin with ethyl bromoacetate

A mixture of 3-acetyl-4-hydroxy-5,6-benzocoumarin (1 g.), anhydrous potassium carbonate (2 g.), ethyl bromoacetate (1 ml.) and dry acetone (100 ml.) was refluxed for 70 hours. Acetone was distilled off and the product on crystallisation from acetic acid gave the yellowish needles melting at 201°. Mixed m.p. with the original product was not depressed.

3-Nitro-4-hydroxy-5,6-benzocoumarin

4-Hydroxy-5,6-benzocoumarin (1 g.) was dissolved in glacial acetic acid (5 ml.). To this hot solution concentrated nitric acid (0.5 ml.) in acetic acid (3 ml.) was added and the reaction mixture was warmed in a water bath at 80° for few minutes. The mixture was immediately cooled and the separated product was filtered off. It was washed with minimum quantity of alcohol and crystallised

from acetic acid in yellow needles, m.p. 171° (decomp.), yield 0.4 g.

Analysis	: Found	: C,60.56 ; H,2.68 ; N,5.25 %.
$C_{13}H_7O_5N$	requires	: C,60.71 ; H,2.74 ; N,5.45 %.

3-Amino-4-hydroxy-5,6-benzocoumarin

3-Nitro-4-hydroxy-5,6-benzocoumarin (0.5 g.) was dissolved in alcohol (5 ml.) and to the warm solution, sodium bisulphite (1.5 g.) was added slowly with shaking. The compound dissolved but immediately separated out. The mixture was then refluxed on a water-bath for 30 minutes. It was filtered hot and on evaporation of the solvent the separated product was washed with minimum quantity of water and filtered. The compound was dried and crystallised from acetic acid in colourless crystals. M.P. 245° (decomp.).

Analysis	: Found	: C,68.51 ; H,3.84 ; N,6.55 %.
$C_{13}H_9O_3N$	requires	: C,68.72 ; H,3.99 ; N,6.17 %.

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