CHAPTER II

STUDIES ON 4-HYDROCYCOUMARINS

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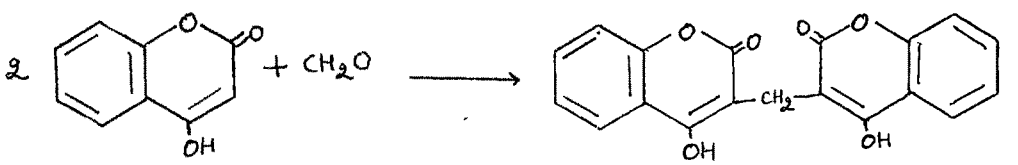
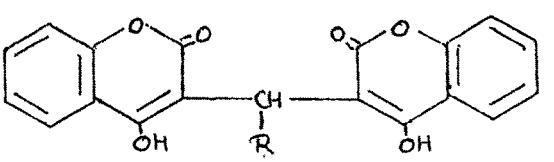
Studies on 4-hydroxycoumarins

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)(I), popularly called 'Dicoumarol'(1). Dicoumarol is synthesised by reacting formaldehyde with 4-hydroxycoumarin and it is a good anticoagulant of blood.



(I)

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



(II)

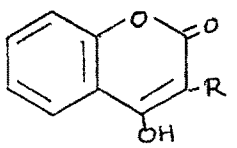
(a) $R = -COOC_2H_5$. (b). $R = -CH_2OCH_3$ (c) $R = CH_3$.

Many attempts to vary the structure of dicoumarol and thereby prepare more active anticoagulant drugs have been made. (II b) 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.

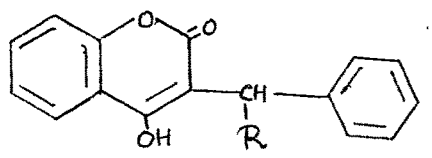
Lehmann (5) showed that the replacement of bridge $-CH_2-$ by ethylidene bridge $-CH-CH_3-$ gave a compound (II c) which possessed higher anticoagulant properties than dicoumarol.

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



(III)

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



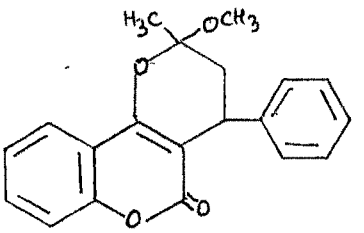
(IV)

(a) R = $-CH_2CO\,CH_3$
(b) R = C_2H_5

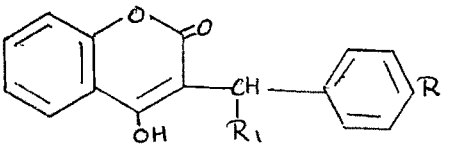
Moraux et al. (7) have prepared 3-naphthyl-4-hydroxycoumarin (III d) which is equal to dicoumarol in activity and is less toxic.

3-Benzyl-4-hydroxycoumarin (III e) has slight activity, but the acetonyl derivative, Warfarin (IV a) 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 (V) by treating Warfarin with 4% hydrogen chloride in methanol and found that it possessed greater activity than dicoumarol.



(V)



(VI)

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

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

Other compounds which are related to warfarin and possess anticoagulant property are coumachlor (VI a) sintron (VI b) and marcoumar (IV b)

Link et al. (10) prepared different esters of dicoumarol and found that the activity of these compounds is

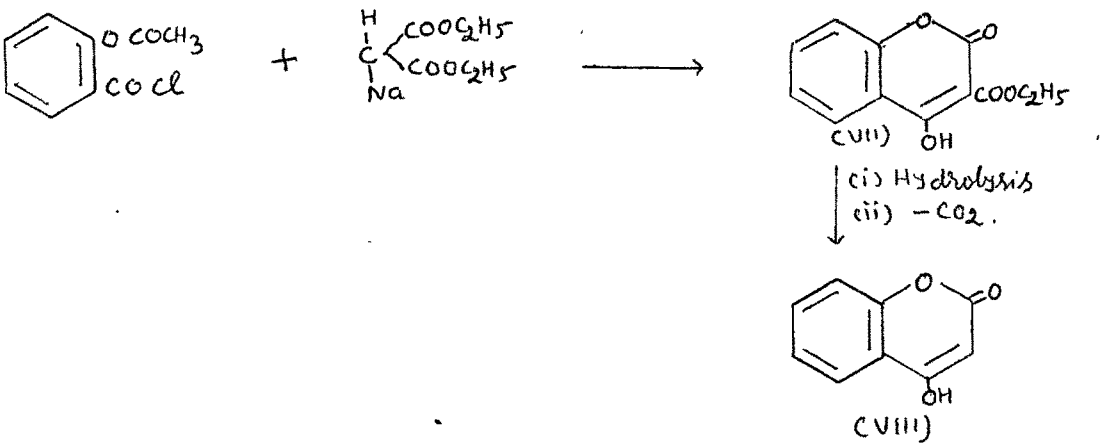
less than that of dicoumarol.

From their studies of various 4-hydroxycoumarin derivatives, Link and coworkers (8) ~~have~~ put forward the minimum structural requirements for a substance to possess anticoagulant 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.

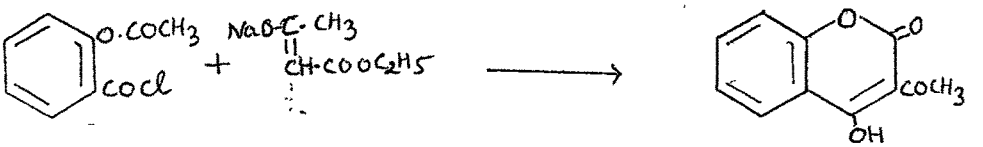
A number of methods are available for the synthesis of 4-hydroxycoumarin derivative.

Methods for the synthesis of 4-hydroxycoumarin

Anschutz (11) condensed sodium salt of malonic ester with o-acetoxy benzoylchloride and obtained 3-carboethoxy-4-hydroxycoumarin (VII). The ester thus obtained on hydrolysis and decarboxylation gave 4-hydroxycoumarin (VIII).

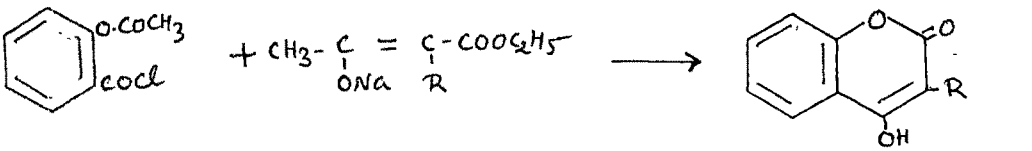


A similar condensation of the sodium salt of aceto acetic ester with o-acetoxy benzoylchloride in etheral solution gave 3-acetyl-4-hydroxycoumarin (IX) (12)



(IX)

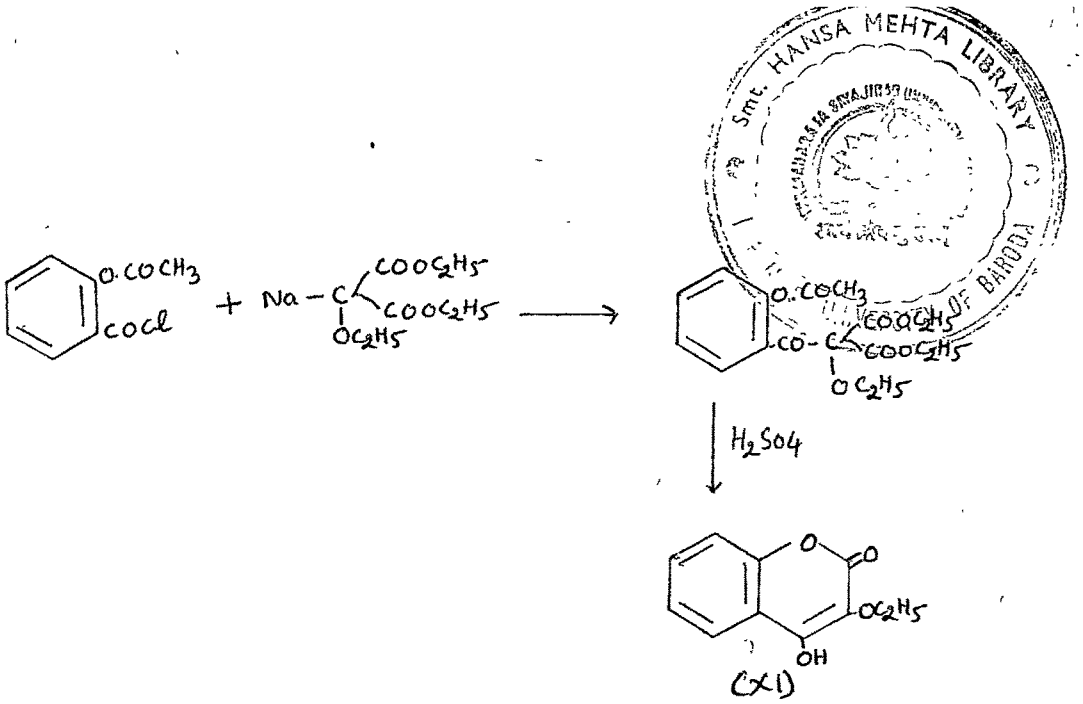
Heilbron and Hill (13) extended this method and condensed the sodium salt of α-substituted aceto acetic ester and obtained 3-methyl-,3-benzoyl-, and 3-benzyl-4-hydroxy-coumarin derivatives (X). The acetyl group was eliminated during the condensation.



(X)

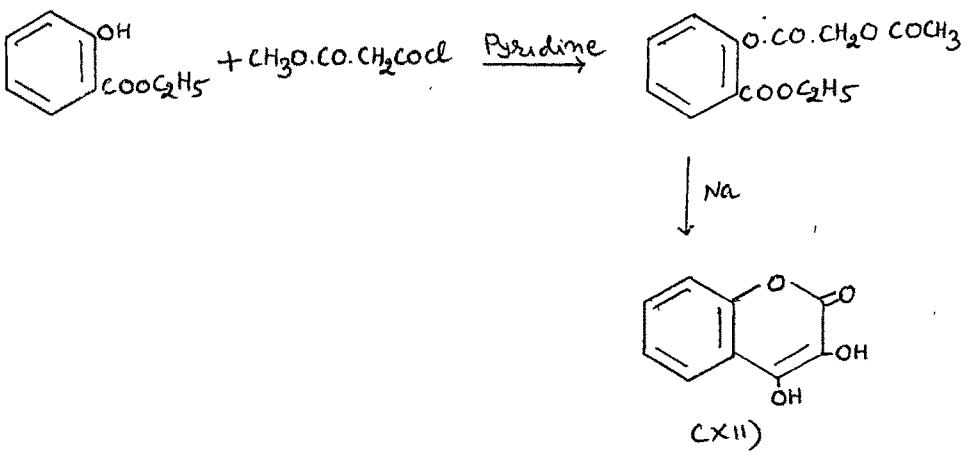
R = CH_3, COC_6H_5, $-CH_2.C_6H_5$.

Ghosh (14) 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 (XI)



(XI)

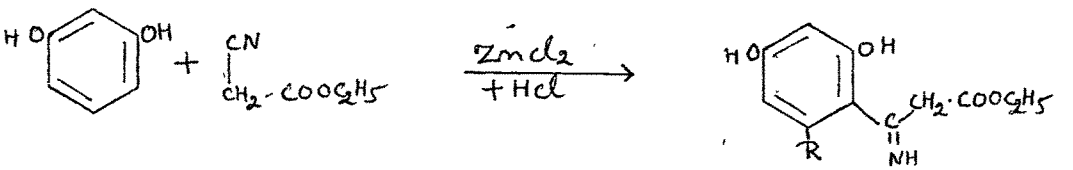
The same author (14) condensed acetoxy acetylchloride with ethyl salicylate in the presence of pyridine. The product obtained, on refluxing with sodium in dry benzene, gave 3,4-dihydroxycoumarin (XII) after acidification with sulphuric acid.

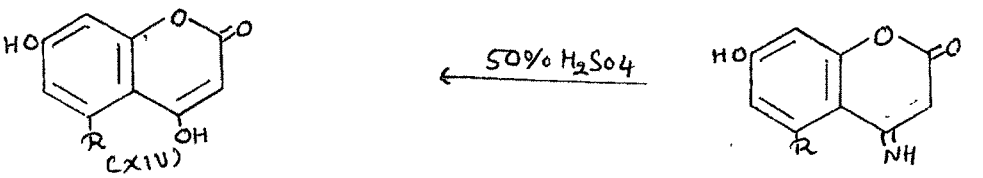


(XII)

Sonn (15) and Bauer and Schoder (16) applied the Hoesch synthesis (17) to the preparation of 4-hydroxycoumarin derivatives. By condensing cyano acetic ester with resorcinol

and phloroglucinol in the presence of hydrochloric acid and zinc chloride followed by the hydrolysis of the intermediate ketimine (XIII), 4,7-dihydroxy-(XIV a) and 4,5,7-trihydroxy-coumarin (XIV b) were formed.



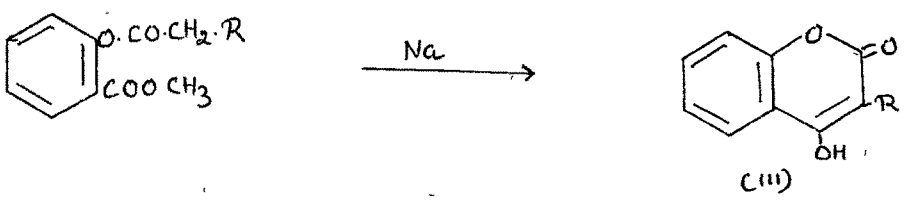


(XIV)
(a) R = H
(b) R = OH

(XIII)

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

Paulfy and Lockemann (18) synthesised 4-hydroxycoumarin derivatives (III) from methyl acetyl salicylate by adding metallic sodium to the molten ester.

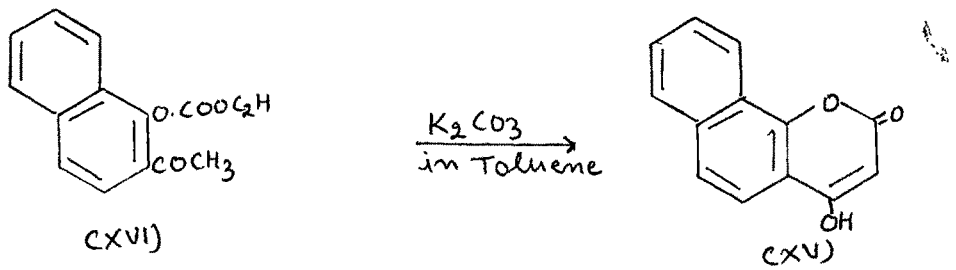


(III)

This method involves condensation with sodium at high temperatures. This procedure was re-investigated by Jensen and Jensen (19) and they did not obtain the yields given by Paulfy and Lockemann (18). Stahmann, Wolff and Link (20) state that the optimum temperature for the condensation

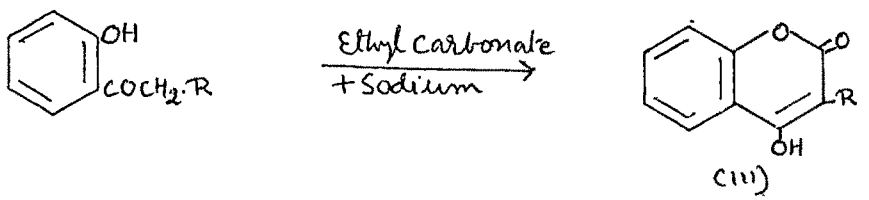
is 240-50°.

Anand and Venkataraman (21) synthesised 4-hydroxy-7,8-benzocoumarin (XV) by the internal condensation of o-carboethoxy-2-acetyl-1-naphthol (XVI) in the presence of sodamide, anhydrous potassium carbonate, metallic sodium or sodium ethoxide in appropriate solvents.



(XVI) (XV)

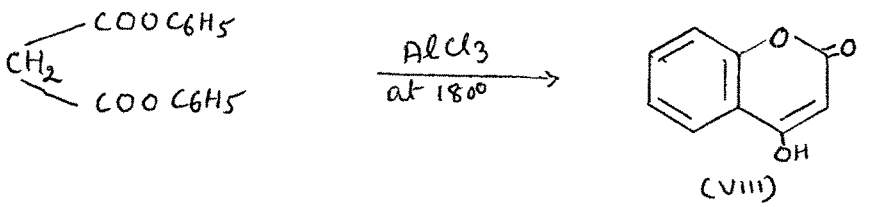
Boyd and Robertson (22) found that o-hydroxy acetophenones and its ω-substituted derivatives readily condensed with ethyl carbonate in the presence of sodium to give 4-hydroxycoumarin derivatives in good yields.



(III)

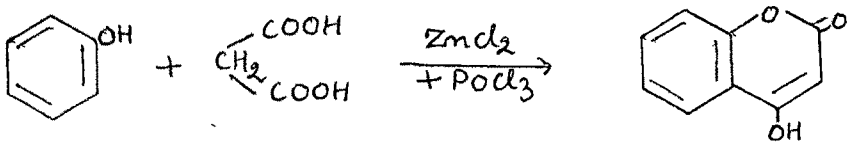
This is a very convenient method for the synthesis of 4-hydroxycoumarins and its scope has been demonstrated by its application to a variety of o-hydroxy acetophenones.

Ziegler and Junek (23) obtained 4-hydroxycoumarin derivatives by the cyclisation of diaryl malonates in the presence of anhydrous aluminium chloride at 180°.



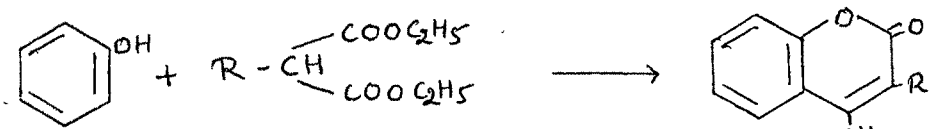
(VIII)

Shah, Bose and Shah (24) 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.



(VIII)

3-Alkyl-4-hydroxycoumarins have been prepared by heating phenol with ethyl monoalkyl malonates at 200-40° for 48 hrs. (24).



R = CH_3, C_6H_5, $-CH_2-C_6H_5$. (III)

Interest has been created in 3-methyl-and 3-benzyl-4-hydroxycoumarins. Maunier et al. (6) observed that 3-methyl-4-hydroxycoumarin possesses coagulant properties like vitamin K. It has been also observed by Lacharme et al. (26) that it inhibits growth and germination of plants. While Link and coworkers (8) observed that

3-benzyl-4-hydroxycoumarin possesses slight anticoagulent property. Ukita (27) has observed that 3-alkyl-4-hydroxy-coumarins possess slight antibacterial properties. The present work deals with the synthesis of various 3-methyl- and 3-benzyl-4-hydroxycoumarin derivatives.

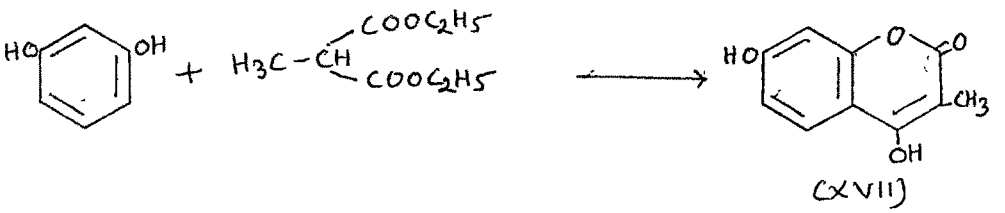
Mentzer and coworkers (25,28,29) observed that phenols can be condensed with substituted malonic esters by heating at temperatures ranging from 200-280° for 2 to 4 days and 3-substituted -4-hydroxycoumarin derivatives obtained. It is now found that if the condensation is carried out in refluxing diphenyl ether, the reaction time is 4 hr. in the case of reactive phenols such as resorcinol, phloroglucinol α-naphthol etc. and 8 hr. in the case of less reactive phenols such as phenol and β-naphthol. The yield is improved in some cases and the products obtained are cleaner and do not require vacuum sublimation as was found necessary by Mentzer and his coworkers. It has been observed that in the case of reactive phenols yields are more than 60%, but they are poor in the case of less reactive phenols.

Diethyl malonate when condensed with different phenols in refluxing diphenyl ether however gave only dark red amorphous solids such as the one obtained by refluxing diethyl malonate alone in diphenyl ether.

4,7-Dihydroxy-3-methylcoumarin

Equimolecular quantities of resorcinol and diethyl methyl malonate when refluxed in diphenyl ether for 4 hr. gave 4,7-dihydroxy-3-methylcoumarin (XVII). The same product

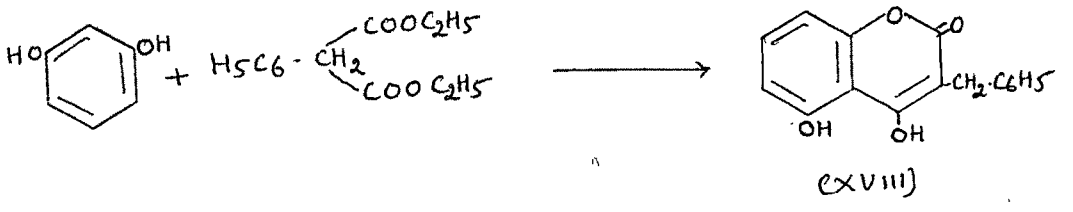
was obtained earlier by Mentzer and coworkers (25).



(XVII)

4,5-Dihydroxy-3-benzylcoumarin and 4,5-dihydroxycoumarin

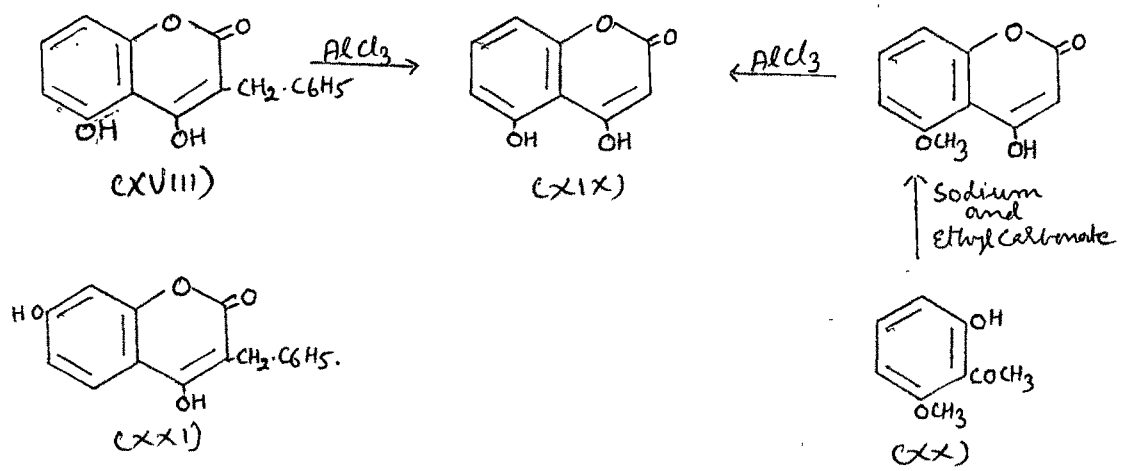
Resorcinol condensed with ethyl benzyl malonate when refluxed with diphenyl ether to give 4,5-dihydroxy-3-benzylcoumarin (XVIII). It gave a bluish violet colouration with alcoholic ferric chloride solution which is characteristic of 4,5-dihydroxycoumarin derivatives (30)



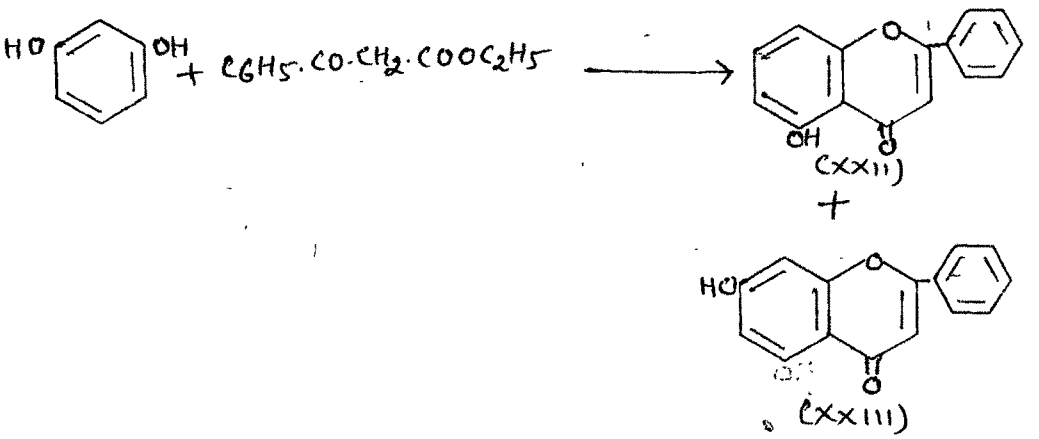
(XVIII)

Rigorous proof of the structure of this compound was supplied by its conversion to 4,5-dihydroxycoumarin (XIX). When 4,5-dihydroxy-3-benzylcoumarin was heated with anhydrous aluminium chloride at 200°C for 15 minutes, debenzylation took place and 4,5-dihydroxycoumarin was obtained. Mixed m.p. with an authentic specimen of 4,5-dihydroxycoumarin prepared by condensing 2-hydroxy-6-methoxy acetophenone (XX) with sodium and ethyl carbonate followed by demethylation with anhydrous aluminium chloride according to Desai and Sethna (30)

was not depressed.



Mentzer et al. (31) have carried out the thermal condensation of resorcinol with ethyl benzyl malonate and obtained 4,7-dihydroxy-3-benzylcoumarin ((XXI). It is quite surprising that the course of reaction is changed by merely heating the reactants in diphenyl ether at its boiling point. Another observation of interest in this connection is that the reaction is taking place totally at the γ-position in resorcinol which is unusual. A few cases are known where the substitution takes place partly in the β-position and partly in the γ-position in resorcinol or its derivatives. For example, Desai,Trivedi and Sethna (32) obtained 5-hydroxyflavone (XXII) along with the 7-hydroxy isomer (XXIII) when resorcinol was condensed with ethyl benzoyl acetate in refluxing diphenyl ether.

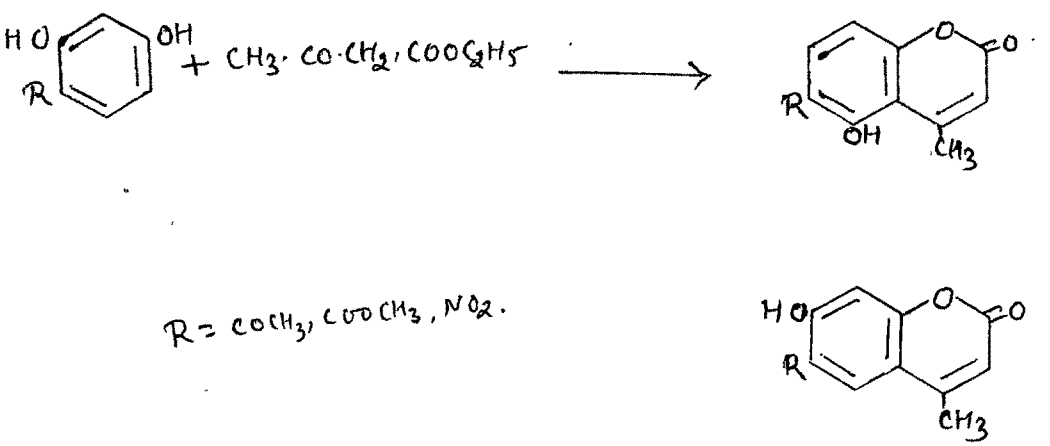


(XXIII)

+

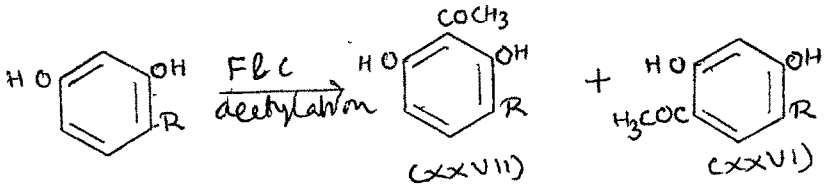
(XXIV)

Sethna, Shah and Shah (33) condensed resacetophenone and methyl- β-resorcylate with ethyl acetoacetate in the presence of anhydrous aluminium chloride and obtained the 5-hydroxycoumarin derivative (XXIV) exclusively in the case of resacetophenone and a mixture of 5-and 7-hydroxy isomers (XXV) in the case of methyl- β-resorcylate. Parekh and Shah also(34) observed that in the condensation of 4-nitroresorcinol with ethyl acetoacetate the condensation takes place in the γ- positions.



R = $COCH_3$, $COOCH_3$, NO_2.

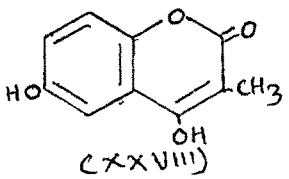
Trivedi and Sethna (35) carried out the Friedel-Crafts acetylation of resacetophenone and methyl-β - resorcylate and obtained a mixture of β - and γ - substituted products (XXVI, XXVII).

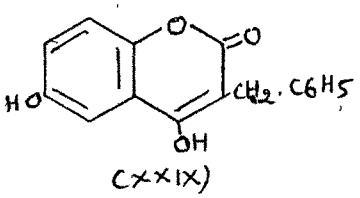


R = $COCH_3$, $COOCH_3$.

4,6-Dihydroxy-3-methylcoumarin and 4,6-dihydroxy-3-benzylcoumarin

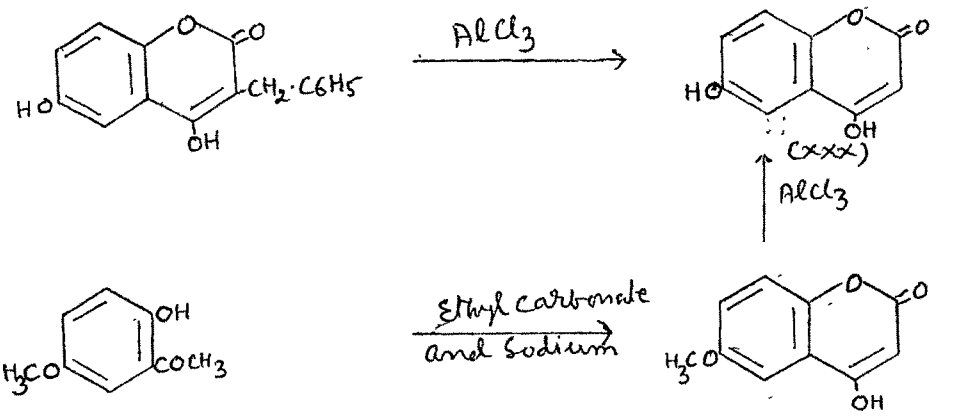
Hydroquinone on condensation with diethyl methyl malonate in boiling diphenyl ether gave a product to which the 4,6-dihydroxy-3-methylcoumarin (XXVIII) structure has been assigned. Similarly the condensation product from hydroquinone and ethyl benzyl malonate obtained under the above conditions is assigned the 4,6-dihydroxy-3-benzylcoumarin structure (XXIX).





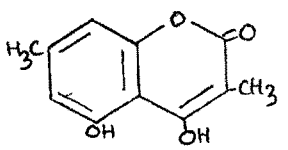
When 4,6-dihydroxy-3-benzylcoumarin was heated with anhydrous aluminium chloride, 4,6-dihydroxycoumarin (XXX) was obtained in poor yield. It was identical with an authentic

specimen of 4,6-dihydroxycoumarin prepared according to Desai and Sethna (30)

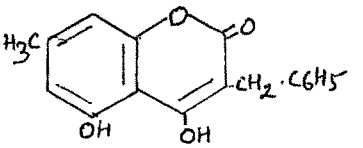


3,7-Dimethyl-4,5-dihydroxycoumarin and 3-benzyl-4,5-dihydroxy-7-methylcoumarin

When orcinol was condensed with diethyl methyl malonate by refluxing in diphenyl ether a product was obtained which gave a bluish violet colouration with alcoholic ferric chloride solution and also gave yellow colour with sodium hydroxide solution. Hence it was assigned 3,7-dimethyl-4,5-dihydroxycoumarin (XXXI) structure. Pechmann condensation of orcinol with β-ketonic ester also gives 5-hydroxycoumarin derivatives (31). On a similar condensation of orcinol with ethyl benzyl malonate a product was obtained which gave a bluish violet colouration with alcoholic ferric chloride solution and a yellow colouration with sodium hydroxide solution and hence 3-benzyl-4,5-dihydroxy-7-methylcoumarin (XXXII) structure has been assigned to it.



(XXXI)

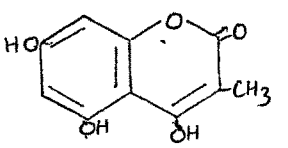


(XXXII)

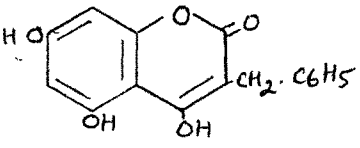
Attempts to debenzylate 3-benzyl-4,5-dihydroxy-7-methylcoumarin with anhydrous aluminium chloride did not succeed. Only the original coumarin was obtained.

4,5,7-Trihydroxy-3-methylcoumarin and 4,5,7-trihydroxy-3-benzylcoumarin

Equimolecular quantities of phloroglucinol and diethyl methyl malonate when refluxed in diphenyl ether for 3 hr. gave a product to which 4,5,7-trihydroxy-3-methylcoumarin (XXXIII) structure has been assigned. Similarly, equimolecular quantities of phloroglucinol and ethyl benzyl malonate gave 4,5,7-trihydroxy-3-benzylcoumarin (XXXIV).



(XXXIII)

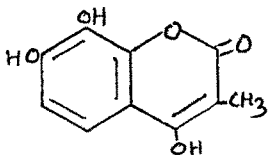


(XXXIV)

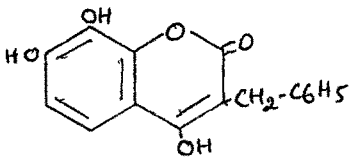
On heating with anhydrous aluminium chloride with a view to see whether debenzylation took place a black product with indefinite melting point was obtained.

4,7,8-Trihydroxy-3-methylcoumarin and 4,7,8-trihydroxy-3-benzylcoumarin

Pyrogallol also condensed with diethyl methyl malonate and ethyl benzyl malonate in boiling diphenyl ether to give 4,7,8-trihydroxy-3-methyl- (XXXV) and 4,7,8-trihydroxy-3-benzylcoumarin (XXXVI).



(XXXV)

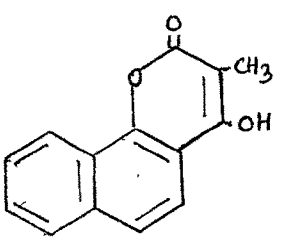


(XXXVI)

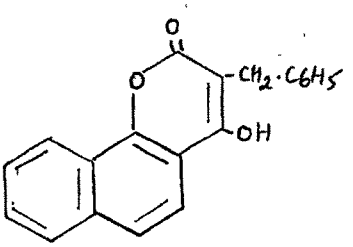
The latter on heating with anhydrous aluminium chloride gave a black product with indefinite melting point.

3-Methyl-4-hydroxy-7,8-benzocoumarin and 3-benzyl-4-hydroxy-7,8-benzocoumarin

α-Naphthol similarly condensed with diethyl methyl malonate and ethyl benzyl malonate to give 3-methyl-4-hydroxy-7,8-benzocoumarin (XXXVII) and 3-benzyl-4-hydroxy-7,8-benzocoumarin (XXXVIII) respectively. The latter gave only the original coumarin on heating with anhydrous aluminium chloride.



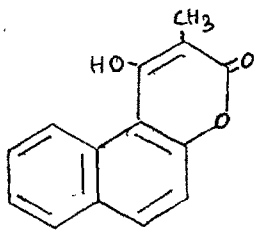
(XXXVII)



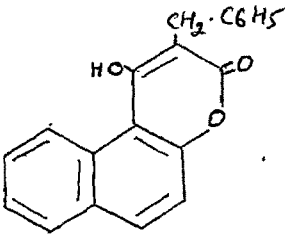
(XXXVIII)

3-Methyl-4-hydroxy-5,6-benzocoumarin and 3-benzyl-4-hydroxy-5,6-benzocoumarin

β-Naphthol on a similar condensation with diethyl methyl malonate and ethyl benzyl malonate gave 3-methyl-4-hydroxy-5,6-benzocoumarin (XXXIX) and 3-benzyl-4-hydroxy-5,6-benzocoumarin (XL) respectively. The latter on heating with anhydrous aluminium chloride gave the original coumarin.



(XXXIX)



(XL)

Testing for the physiological properties

These 4-hydroxycoumarin derivatives have been sent to Messrs. Alembic Chemical Works Ltd., Baroda for testing of their physiological properties. Unfortunately, the results have not been available by the date fixed for the submission of this thesis.

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

4,7-Dihydroxy-3-methylcoumarin

A mixture of resorcinol (5.5 g. ; 0.05 mole), diethyl methyl malonate (8.7 g. ; 0.05 mole) and diphenyl ether (25 ml.) was allowed to reflux for 4 hr in a flask fitted with a short air condenser which allowed the alcohol formed to escape. The product which separated on cooling was filtered and washed several times with petroleum ether (60-80°). It crystallised from alcohol in colourless needles, m.p. 303°. Yield 7 g. Mentzer et al.(25) report the same m.p.

Analysis :

4.718 mg. of the substance gave 10.756 mg. of carbon dioxide anddl.84 mg. of water.

Found : C = 62.22 % ; H = 4.37 %.

$C_{10}H_8O_4$ requires : C = 62.50 % ; H = 4.20 %.

4,5-Dihydroxy-3-benzylcoumarin

A mixture of resorcinol (2.75 g. ; 0.025 mole) ethyl benzyl malonate (6.25 g. ; 0.025 mole) and diphenyl ether (25 ml.) was refluxed for 3 hr. The separated product was treated as above and crystallised from alcohol in colourless tubes, m.p.259-60°. Yield 6.0 g. It gave bluish violet colouration with alcoholic ferric chloride solution and a yellow colouration with sodium hydroxide solution.

Analysis :

10.60 mg. of the substance gave 27.96 mg. of carbon dioxide and 4.32 mg. of water.

Found : C = 71.99 % ; H = 4.60 %.

$C_{16}H_{12}O_4$ requires : C = 71.64 % ; H = 4.48 %.

Debenzylation : 4,5-dihydroxycoumarin

An intimate mixture of the above coumarin (1 g.) and anhydrous aluminium chloride (2 g.) was heated in an oil bath at 200° for 15 minutes. Ice and hydrochloric acid were added and the separated product crystallised from very dilute alcohol in colourless needles, m.p. 221°. Yield 0.1 g. Mixed melting point with an authentic specimen of 4,5-dihydroxycoumarin (Desai and Sethna) (30) was not depressed.

4,6-Dihydroxy-3-methylcoumarin

A mixture of hydroquinone (5.5 g. ; 0.05 mole) diethyl methyl malonate (8.7 g. ; 0.05 mole) and diphenyl ether (25 ml.) was allowed to reflux for 8 hr. No product separated on cooling the reaction mixture so large quantity of petroleum ether (100 ml.) was added. The separated product was filtered and washed several times with petroleum ether. It crystallised from alcohol in colourless needles, m.p. 270°. Yield 2.0 g.

Analysis :

4.94 mg. of the substance gave 10.30 mg. of carbon dioxide and 1.69 mg. of water.

Found : C = 62.57 % ; H = 4.22 %.

$C_{10}H_8O_4$ requires : C = 62.50 % ; H = 4.20 %.

4,6-Dihydroxy-3-benzylcoumarin

A mixture of hydroquinone (2.75 g. ; 0.025 mole) ethyl benzyl malonate (6.25 g. ; 0.025 mole) and diphenyl

ether (25 ml.) was refluxed for 8 hr. The product which separated on cooling crystallised from alcohol in colourless needles, m.p. 210°. Yield 0.9 g.

Analysis :

4.56 mg. of the substance gave 11.95 mg. of carbon dioxide and 1.90 mg. of water.

Found : C = 71.53 % ; H = 4.67 %.

$C_{16}H_{12}O_4$ requires : C = 71.63 % ; H = 4.51 %.

Debenzylation : 4,6-dihydroxycoumarin

An intimate mixture of 4,6-dihydroxy-3-benzylcoumarin (0.5 g.) and anhydrous aluminium chloride (1 g.) was heated in an oil bath at 200° for 15 minutes. The product obtained on working up as before crystallised from hot water in colourless needles, m.p.261°. Yield 0.05 g. Mixed m.p. with an authentic specimen of 4,6-dihydroxycoumarin was not depressed. (Desai and Sethna) (30).

4,7,8-Trihydroxy-3-methylcoumarin

A mixture of pyrogallol (3.15 g. ; 0.025 mole) diethyl methyl malonate (4.4 g. ; 0.025 mole) and diphenyl ether (25 ml.) was refluxed for 3 hr. The product obtained on cooling crystallised from dilute alcohol in colourless needles, m.p. 245°. Yield 3.0 g.

Analysis :

4.50 mg. of the substance gave 9.58 mg. of carbon dioxide and 1.47 mg. of water.

Found : C = 58.10 % ; H = 3.67 %.

$C_{10}H_8O_5$ requires : C = 57.69 % ; H = 3.87 %.

4,7,8-Trihydroxy-3-benzylcoumarin

A mixture of pyrogallol (1.55 g. ; 0.012 mole) and ethyl benzyl malonate (3.1 g. ; 0.012 mole) in diphenyl ether (25 ml.) was refluxed for 3 hr. The product obtained crystallised from alcohol in colourless needles, m.p. 259°. Yield 1.1 g.

Analysis :

3.91 mg. of the substance gave 9.63 mg. of carbon dioxide and 1.53 mg. of water.

Found : C = 67.21 % ; H = 4.38 %.

$C_{16}H_{12}O_5$ requires : C = 67.60 % ; H = 4.26 %.

On heating the above coumarin with anhydrous aluminium chloride at 200° for 15 minutes only a black product with indefinite m.p. was obtained.

4,5,7-Trihydroxy-3-methylcoumarin

A mixture of phloroglucinol (3.15 g. ; 0.025 mole) and diethyl methyl malonate (4.4 g. ; 0.025 mole) in diphenyl ether (25 ml.) was refluxed for 3 hr. The product crystallised from hot water in pink needles, m.p.289°. Yield 3.0 g. It gave a bluish violet colouration with alcoholic ferric chloride solution.

Analysis :

4.36 mg. of the substance gave 9.18 mg. of carbon dioxide and 1.56 mg. of water.

Found : C = 57.42 % ; H = 4.00 %.

$C_{10}H_8O_5$ requires : C = 57.69 % ; H = 3.87 %.

4.5.7-Trihydroxy-3-benzylcoumarin

A mixture of phloroglucinol (1.55 g. ; 0.012 mole) and ethyl benzyl malonate (3.1 g. ; 0.012 mole) in diphenyl ether (25 ml.) was refluxed for 3 hr. The product obtained crystallised from very dilute alcohol in pink needles, m.p. 260°. Yield 1.0 g. It gave a bluish violet colouration with alcoholic ferric chloride solution.

Analysis :

4.63 mg. of the substance gave 11.54 mg. of carbon dioxide and 1.83 mg. of water.

Found : C = 67.99 % ; H = 4.44 %.

$C_{16}H_{12}O_5$ requires : C = 67.60 % ; H = 4.26 %.

Attempt to debenzylate this product with anhydrous aluminium chloride resulted in a dark mass with an indefinate m.p.

4.5-Dihydroxy-3.7-dimethylcoumarin

A mixture of orcinol (2.48 g. ; 0.02 mole) and diethyl methyl malonate (3.48 g. ; 0.02 mole) in diphenyl ether (25 ml.) was refluxed for 4 hr. The product crystallised from alcohol in colourless tubes, m.p. 259°. Yield 2.7 g. It gave a bluish violet colouration with alcoholic ferric chloride solution and gave a yellow colouration with sodium hydroxide solution.

Analysis :

4.00 mg. of the substance gave 9.38 mg. of carbon dioxide and 1.84 mg. of water.

Found : C = 64.01 % ; H = 5.16 %.

$C_{11}H_{10}O_4$ requires : C = 64.07 % ; H = 4.89 %.

4.5-Dihydroxy-3-benzyl-7-methylcoumarin

A mixture of orcinol (2.48 g. ; 0.2 mole) and ethyl benzyl malonate (5.0 g. ; 0.02 mole) in diphenyl ether (25 ml.) was refluxed for 4 hr. The product crystallised from alcohol in colourless needles, m.p. 247-48°. Yield 3.0 g. It gave a bluish violet colouration with alcoholic ferric chloride solution and a yellow colouration with sodium hydroxide solution.

Analysis :

4.38 mg. of the substance gave 11.83 mg. of carbon dioxide and 1.99 mg. of water.

Found : C = 73.57 % ; H = 5.10 %.

$C_{17}H_{14}O_4$ requires : C = 73.33 % ; H = 5.00 %.

It remained unchanged on heating with anhydrous aluminium chloride.

3-Methyl-4-hydroxy-7,8-benzocoumarin

A mixture of α-naphthol (4.32 g. ; 0.03 mole) and diethyl methyl malonate (5.2 g. ; 0.03 mole) in diphenyl ether (25 ml.) was refluxed for 4 hr. The product which separated on cooling crystallised from acetic acid in colourless needles, m.p. 258°. Yield 4.5 g.

Analysis :

4.17 mg. of the substance gave 11.32 mg. of carbon dioxide and 1.62 mg. of water.

Found : C = 73.99 % ; H = 4.35 %.

$C_{14}H_{10}O_3$ requires : C = 74.33 % ; H = 4.46 %.

3-Benzyl-4-hydroxy-7,8-benzocoumarin

A mixture of α-naphthol (2.88 g. ; 0.02 mole) and

ethyl benzyl malonate (5 g. ; 0.02 mole) in diphenyl ether (25 ml.) was refluxed for 4 hr. The separated product crystallised from acetic acid in colourless needles, m.p. 257°. Yield 3.5 g.

Analysis :

4.27 mg. of the substance gave 12.40 mg. of carbon dioxide and 1.75 mg. of water.

Found : C = 79.10 % ; H = 4.59 %.

$C_{20}H_{14}O_3$ reqmires : C = 79.47 % ; H = 4.63 %.

It remained unchanged on heating with anhydrous aluminium chloride.

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

A mixture of β -naphthol (4.32 g. ; 0.03 mole) and diethyl methyl malonate (5.2 g. ; 0.03 mole) in diphenyl ether (25 ml.) was refluxed for 8 hr. The product obtained on addition of large quantities of petroleum ether crystallised from acetic acid in yellow shining plates, m.p.234°. Yield 1.0 g.

Analysis :

4.67 mg. of the substance gave 11.69 mg. of carbon dioxide and 1.94 mg. of water.

Found : C = 74.16 % ; H = 4.66 %.

$C_{14}H_{10}O_3$ requires : C = 74.33 % ; H = 4.46 %.

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

A mixture of β -naphthol (2.88 g. ; 0.02 mole) and ethyl benzyl malonate (5.0 g. ; 0.02 mole) in diphenyl ether

was refluxed for 8 hr. The product obtained on large addition of petroleum ether crystallised from acetic acid in yellow needles, m.p. 199°. Yield 1.5 g.

Analysis :

4.41 mg. of the substance gave 12.84 mg. of carbon dioxide and 1.96 mg. of water.

Found : C = 79.23 % ; H = 4.98 %.

$C_{20}H_{14}O_3$ requires : C = 79.47 % ; H = 4.63 %.

The product remained unchanged on heating with anhydrous aluminium chloride.

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