CHAPTER I

STUDIES ON 3-HYDROXYCOUMARINS

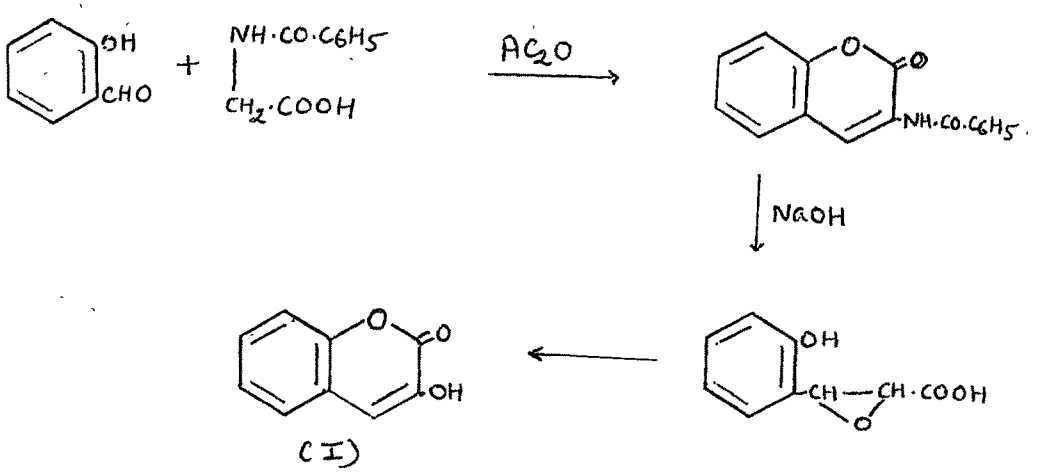
CHAPTER I

Studies on 3-hydroxycoumarins

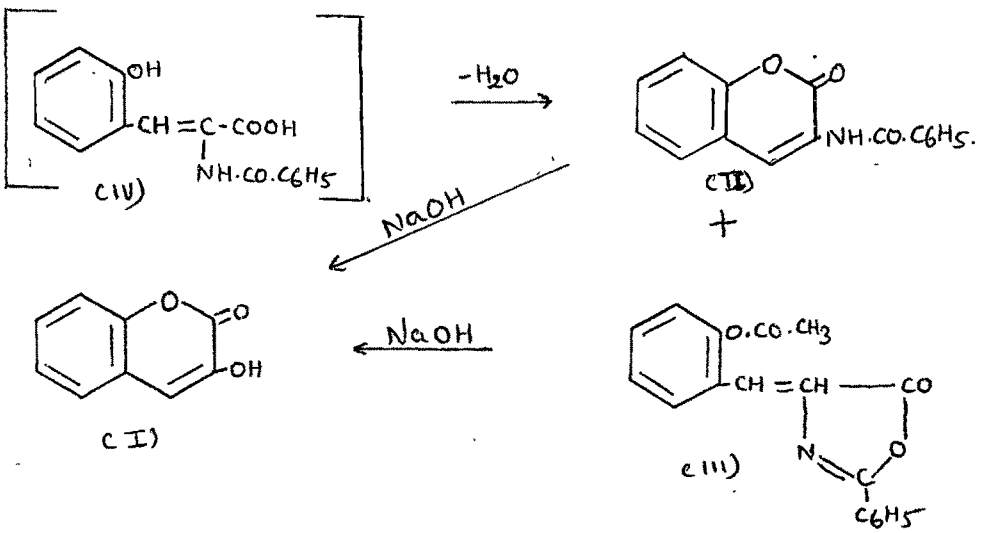
Though 3-hydroxycoumarin (I) was first synthesised as early as 1885 by Plochl and Wolfrum (1), the studies on 3-hydroxycoumarins are relatively few. 3-Hydroxycoumarins have been used for the syntheses of benzo pyrilium salts. Willstatter, Zechmeister and Kindler (2) synthesised pelargonidin-and cyanidin chloride by treating 3:5:7-trimethoxycoumarin with suitable Grignard reagents. Similarly Heilbron, Hill and Walls (3) synthesised 3-methoxy-2-phenyl-benzopyrillium chloride from 3-methoxycoumarin.

Godwin and Taves (4) observed that 3-hydroxycoumarin has an inhibiting effect on the growth of avena roots. Rodighiero and Antonello (5) observed that 3-aminocoumarin derivatives from which 3-hydroxycoumarins can be obtained easily by hydrolysis, are good antibacterial agents against Staphylococcus Pyrogens, Salmonella, Shigella etc.

Plöchl and Wolfrum (1) synthesised 3-hydroxycoumarin (I) by the condensation of salicylaldehyde with hippuric acid in the presence of acetic anhydride through the series of reactions given below:



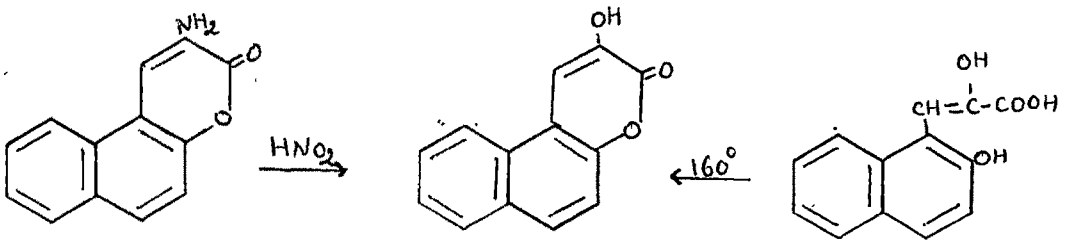
Later, the reaction was modified by Erlenmeyer and Stadlin (6). They heated the reaction mixture on a steam bath with sodium acetate and acetic anhydride when two products : (i) 3-benzoylaminocoumarin (II) and (ii) 2-phenyl-4-o-acetoxybenzylidene-5-oxazolone (III) were obtained probably through the loss of water in two different ways from the primary intermediate product benzoylamino coumarilic acid (IV).



Both the products, on hydrolysis with alkali, gave 3-hydroxycoumarin.

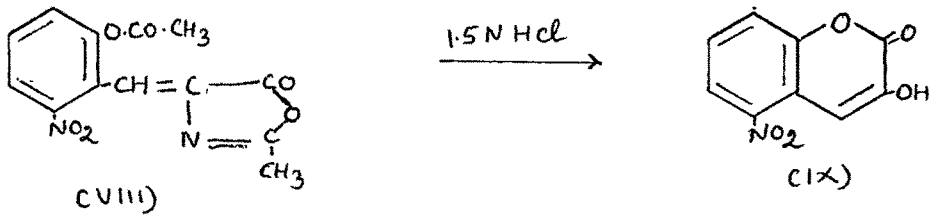
Further modification of the experimental technique such as passing sulphur dioxide after the hydrolysis of azlactone acetate to precipitate benzoic acid was introduced by Offe and Jatzkwitz (7). The same authors also synthesised 7-methoxy-3-hydroxycoumarin in 12 % yield from 2-hydroxy-4-methoxybenzaldehyde.

Dey and Lakshminarayan (8) extended this method to the synthesis of 3-amino-5,6-benzocoumarin (V) which on treatment with nitrous acid gave 3-hydroxy-5,6-benzocoumarin (VI). It was also obtained by heating cis α-hydroxy-β-(2-hydroxynaphthyl)acrylic acid (VII) at 160°.



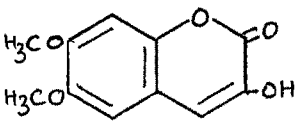
(V) (VI) (VII)

Beer, Clarke, Khorana and Robertson (9) carried out the condensation of 2-nitro-6-hydroxybenzaldehyde with aceturic acid in the presence of acetic anhydride and sodium acetate and obtained 5-keto-4-(2'-nitro-6'-acetoxybenzylidene) 2-methyl-4,5-dihydro-oxazole (VIII) as the only isolable product. This, on hydrolysis with hydrochloric acid, furnished 5-nitro-3-hydroxycoumarin (IX).

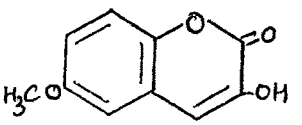


(VIII) (IX)

Using the same procedure, Robertson and his coworkers (10,11) prepared 3-hydroxy-6;7-dimethoxycoumarin (X) and 3-hydroxy-6-methoxycoumarin (XI) from 2-acetoxy-4;5-dimethoxybenzaldehyde and 5-methoxy-2-hydroxybenzaldehyde respectively.



(X)

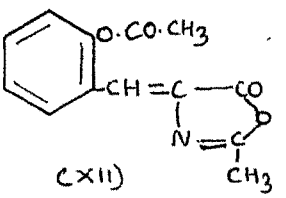


(XI)

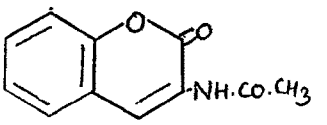
Shaw, McMillan and Armstrong (12) developed the experimental conditions for the synthesis of 3-acetamido- and 3-hydroxycoumarin in optimum yields. Salicyaldehyde was condensed by them with pure acetylglycine in the presence of acetic anhydride and sodium acetate by heating the reaction mixture rapidly to 100° and maintaining it at that temperature for 1.5 hours under dry conditions. The yield of 3-acetamidocoumarin was 25 % . 3-Acetamidocoumarin when refluxed with 3N hydrochloric acid in nitrogen atmosphere gave 3-hydroxycoumarin in 83 % yield.

As stated before Erlenmeyer and Stadlin (6) observed that condensation of salicylaldehyde with

hippuric acid yields a mixture of 3-benzoylaminocoumarin (II) and 2-phenyl-4-o-acetoxybenzylidene-5-oxazolone(III). Dakin (13) reported that 2-methyl-4-(o-acetoxybenzal)-5-oxazolone (XII) is the only product obtained when salicylaldehyde is condensed with acetylglycine in the presence of acetic anhydride and sodium acetate. This difference between the reactivity of hippuric acid and acetylglycine in the course of reaction has been stressed in the reviews by Carter (14) and Baltazzi (15) .



(XII)



(XIII)

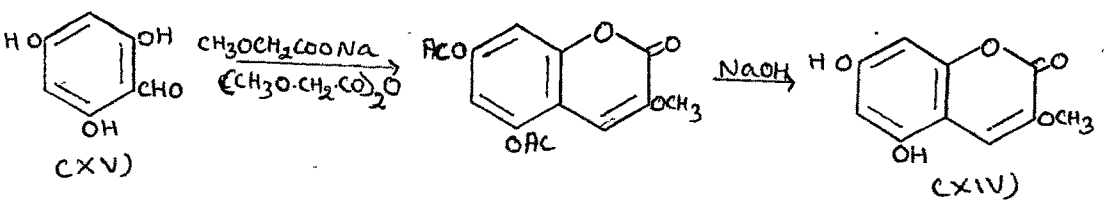
The work of Shaw, McMillan and Armstrong (12) has definitely established that 3-acetamidocoumarin (XIII) is the primary isolable product and that 2-methyl-4-(o-acetoxybenzal)-5-oxazolone (XII) if formed in small quantities remains in the mother liquor.

The marked difference in the products obtained in the condensation of salicylaldehyde with hippuric acid and acetylglycine occurs as a result of two factors according to Shaw et al.(12). In the first place the formation of greater proportion of 2-phenyl-4-o-acetoxybenzylidene-5-oxazolone (III) in the condensation reaction may be expected because of its enhanced resonance stability arising from the conjugation of the two benzene

rings with the oxazolone ring. Secondly, in the reactions with hippuric acid, 2-phenyl-4-o-acetoxybenzylidene-5-oxazolone (III) is less soluble than 3-benzoylaminocoumarin (II) and therefore it is readily isolated. In the reaction with acetylglycine, 3-acetamidocoumarin (XIII) crystallises alone and 2-methyl-4-(o-acetoxybenzal)-5-oxazolone (XII) remains in the mother liquor.

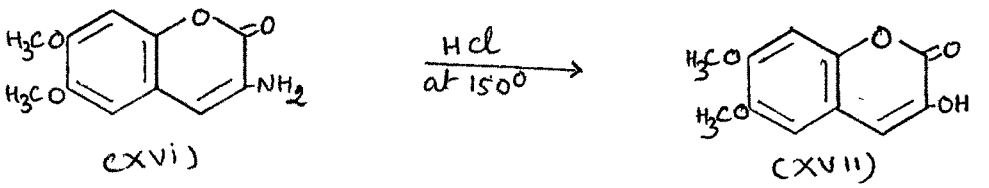
Lambooy (16) also removed a similar confusion between oxazolone and coumarin derivatives in the condensation of 2-hydroxy-3-methoxybenzaldehyde with hippuric acid created by Barltrop (17) and Clemo and Duxbury (18). Robertson and coworkers (9,10,11) obtained oxazolone rather than the 3-acetamidocoumarin derivatives when 2-nitro-6-hydroxybenzaldehyde, 2-acetoxy-4,5-dimethoxybenzaldehyde and 5-methoxy-2-hydroxybenzaldehyde were condensed with aceturic acid in the presence of acetic anhydride and sodium acetate. Gupta (19) also obtained an oxazolone derivative on a similar condensation of 2-acetoxybenzaldehyde with hippuric acid.

Willstatter, Zechmeister and Kindler (2) obtained 5,7-dihydroxy-3-methoxycoumarin (XIV) in the condensation of phloroglucinaldehyde (XV) with the sodium salt of methoxy acetic acid and methoxy acetic anhydride.



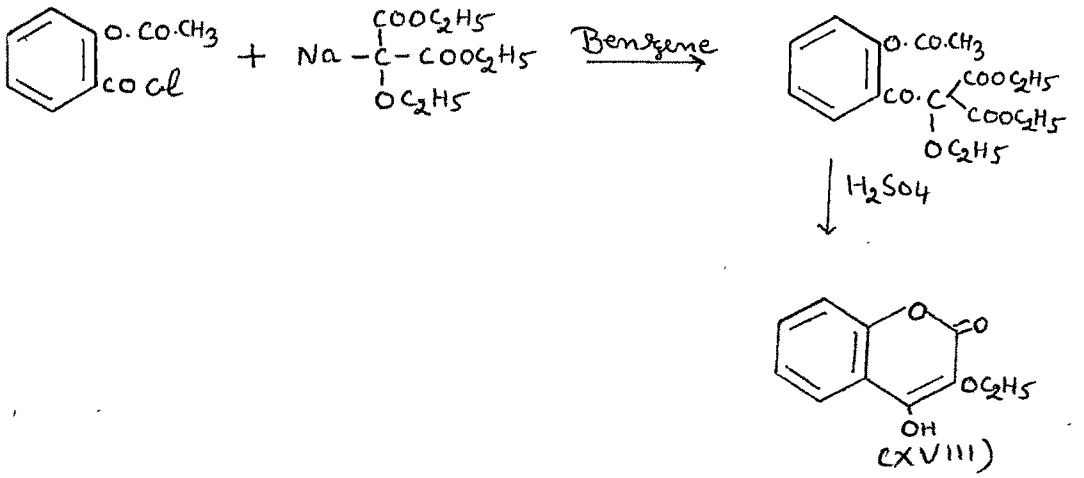
Using this procedure, Heilbron, Hill and Walls (3) prepared 3-methoxycoumarin from salicylaldehyde in good yield.

Spath and Dobrovolny (20) synthesised 3-hydroxy-coumarin derivatives by heating 3-aminocoumarin derivatives with hydrochloric acid. 6,7-Dimethoxy-3-aminocoumarin (XVI) was thus converted into 3-hydroxy-6,7-dimethoxy-coumarin (XVII).



(XVI) (XVII)

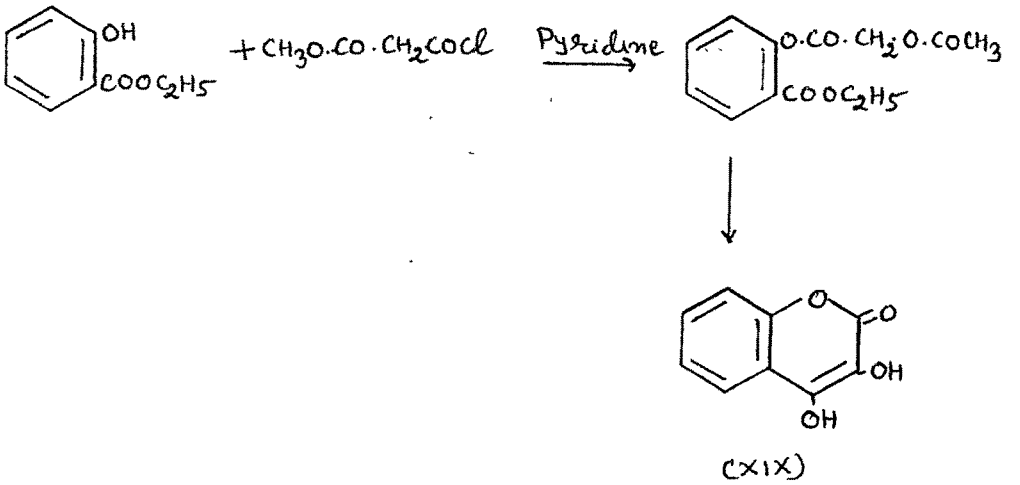
Ghosh (21) condensed a-acetoxy benzoylchloride with the sodium salt of ethoxy malonic ester in dry benzene. The condensation product thus obtained gave, on heating with sulphuric acid 3-ethoxy-4-hydroxycoumarin (XVIII).



(XVIII)

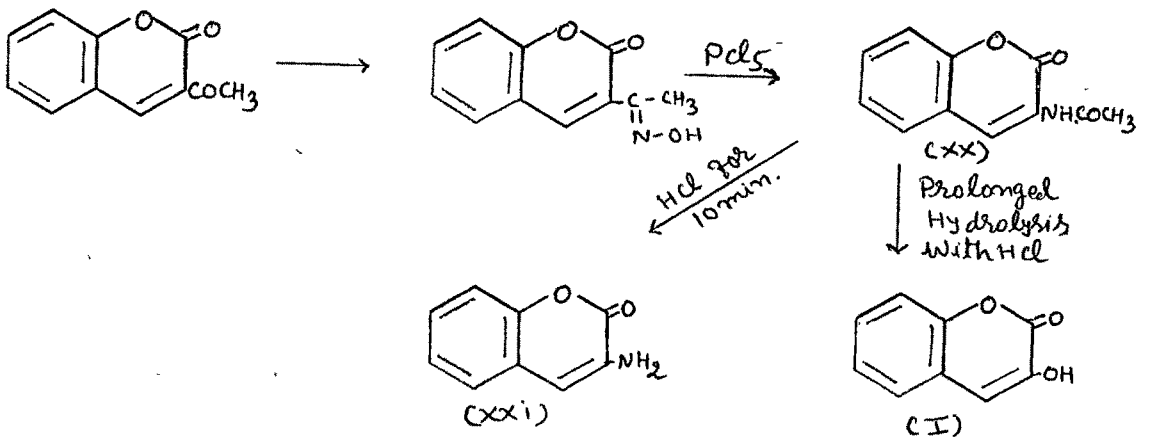
The same author (21) condensed acetoxyacetyl chloride with ethyl salicylate in the presence of pyridine.

The product when refluxed with sodium in benzene gave 3,4-dihydroxycoumarin (XIX) on acidification with sulphuric acid.

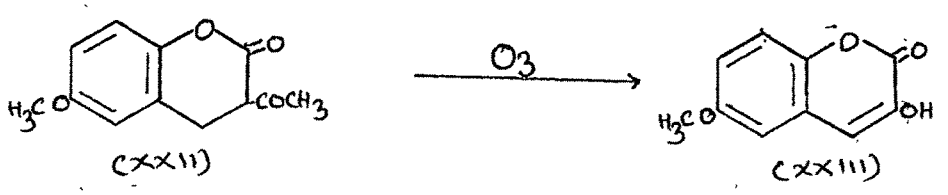


(XIX)

Linch (22) treated the oxime of 3-acetylcoumarin with phosphorous pentachloride when it underwent Beckmann transformation, giving 3-acetylaminocoumarin (XX). Careful hydrolysis with dilute hydrochloric acid gave 3-amino-coumarin (XXI) but prolonged hydrolysis afforded 3-hydroxy-coumarin (I).



Dean, Robertson and Whalley (11) observed that 6-methoxy-3-hydroxycoumarin (XXII) is formed by the action of ozone on 3-acetyl-3,4-dihydrocoumarin (XXIII).



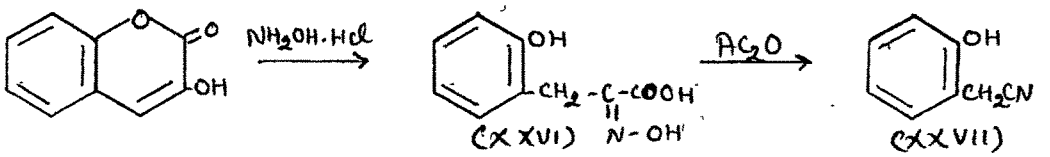
(XXII) (XXIII)

Reactions of 3-hydroxycoumarin

Erlenmeyer and Stadlin (6) prepared the phenylhydrazone (XXIV) of 3-hydroxycoumarin. On condensation with o-phenylenediamine, 3-hydroxycoumarin gave a quinoxaline derivative (XXV). These results indicate that 3-hydroxycoumarin also exhibits ketonic character.

(XXIV) (XXV)

Offe and Jatzkewitz (7) obtained the oxime of o-hydroxyphenylpyruvic acid (XXVI) on heating 3-hydroxycoumarin in alkaline solution with hydroxylamine hydrochloride. This on heating with acetic anhydride gave o-hydroxybenzyl cyanide (XXVII).



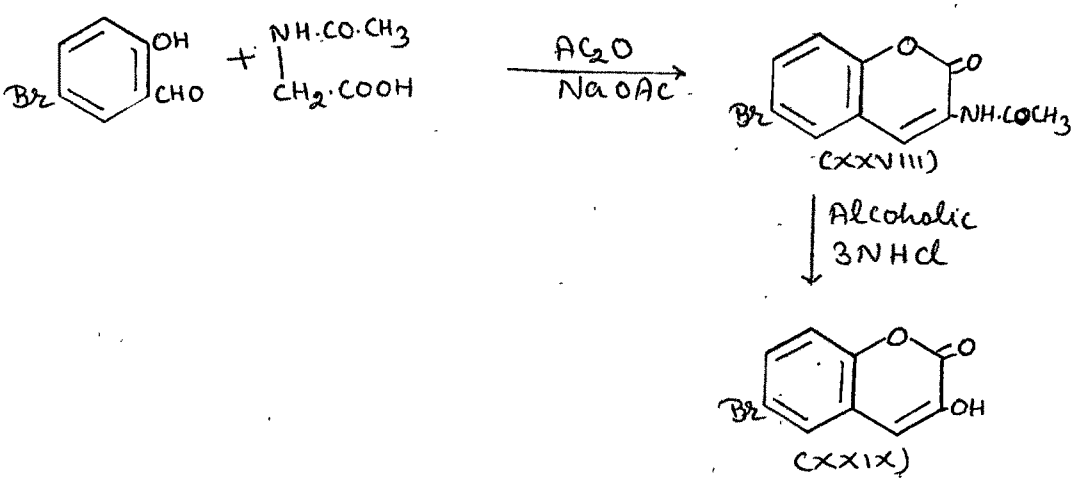
(XXVI) (XXVII)

No other substitution reactions appear to have been attempted.

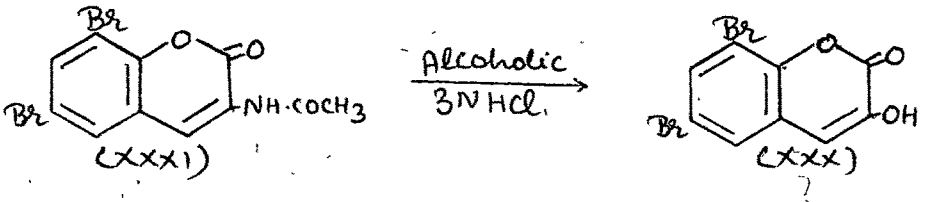
This chapter deals with the synthesis of some substituted 3-hydroxycoumarins by the condensation of substituted salicylaldehydes with acetylglycine and the study of some substitution reactions on 3-hydroxycoumarin.

Synthesis of some 3-hydroxycoumarin derivatives

5-Bromo salicylaldehyde was prepared according to Auwers and Burger (23) by the bromination of salicylaldehyde. This was condensed with acetylglycine in the presence of sodium acetate and acetic anhydride when 6-bromo-3-acetamidocoumarin (XXVIII) was obtained. This was hydrolysed to 6-bromo-3-hydroxycoumarin (XXIX) by refluxing with 3N alcoholic hydrochloric acid. 6-Bromo-3-acetamidocoumarin has been previously prepared by Linch (22) by the Beckmann rearrangement of the oxime of 6-bromo-3-acetylcoumarin. Controlled hydrolysis of this product with dilute sulphuric acid did not give 6-bromo-3-aminocoumarin (m.p. 205°) as reported by Linch but gave 6-bromo-3-hydroxycoumarin (m.p. 252°). Mixed m.p. with the product obtained by hydrolysis with alcoholic hydrochloric acid was not depressed. It gave the characteristic green colouration of 3-hydroxycoumarins with alcoholic ferric chloride solution. It was also soluble in sodium hydroxide solution.

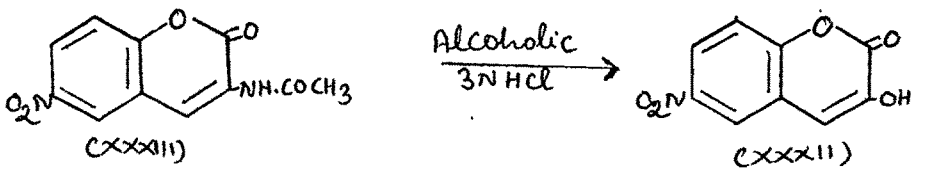


6,8-Dibromo-3-hydroxycoumarin (XXX) was synthesised by the condensation of 3,5-dibromosalicylaldehyde prepared according to Brewston (24) with acetylglycine in the presence of acetic anhydride and sodium acetate and subsequent hydrolysis of 6,8-dibromo-3-acetamidocoumarin (XXXI) formed with alcoholic 3N hydrochloric acid.



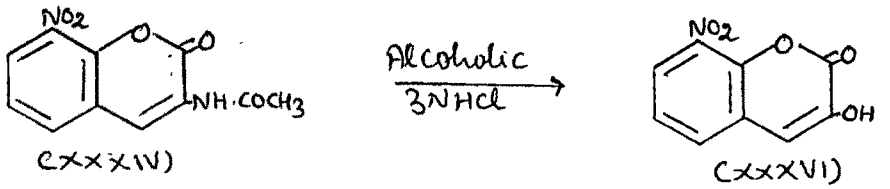
6-Nitro-3-hydroxycoumarin (XXXII) was synthesised by the condensation of 5-nitrosalicylaldehyde, prepared by the nitration of salicylaldehyde according to Miller (25), with acetylglycine in the presence of acetic anhydride and sodium acetate and subsequent hydrolysis of 6-nitro-3-acetamidocoumarin (XXXIII) obtained with 3N hydrochloric

acid.

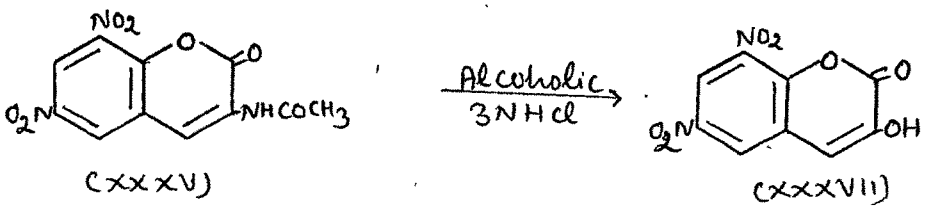


(XXXIII) (XXXII)

3-Nitrosalicylaldehyde prepared by the nitration of salicylaldehyde according to Miller (25) and 3,5-dinitrosalicylaldehyde prepared by the further nitration of the mixture of 3-nitro-and 5-nitrosalicylaldehyde according to Lowett and Roberts (26) on a similar condensation with acetylglycine in the presence of acetic anhydride and sodium acetate gave 8-nitro-3-acetamidocoumarin (XXXIV) and 6,8-dinitro-3-acetamidocoumarin (XXXV) respectively. These were hydrolysed with alcoholic 3N hydrochloric acid to 8-nitro-3-hydroxycoumarin (XXXVI) and 6,8-dinitro-3-hydroxycoumarin (XXXVII) respectively.



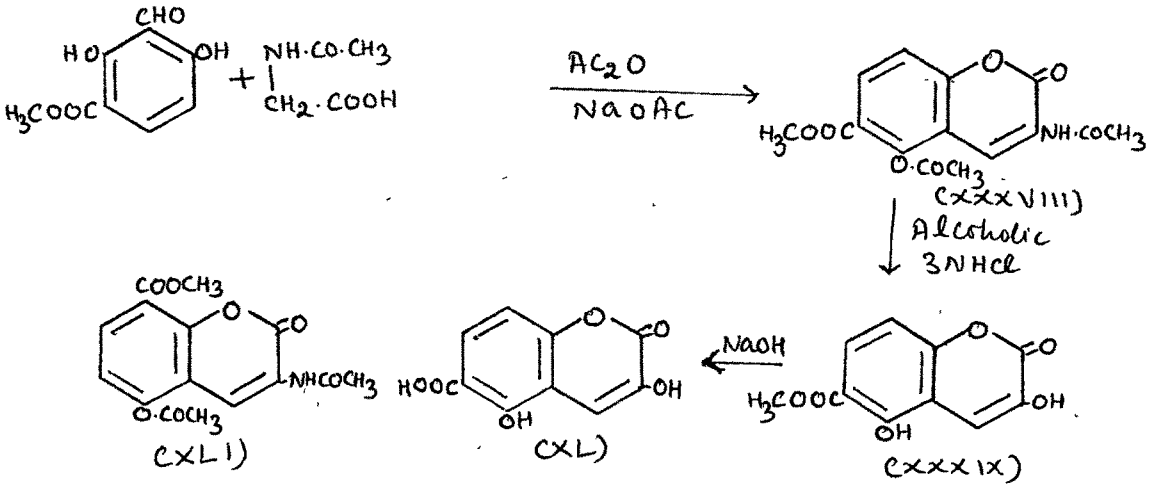
(XXXIV) (XXXVI)



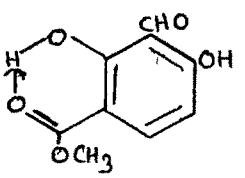
(XXXV) (XXXVII)

Methyl-2,4-dihydroxy-3-formylbenzoate prepared by the modified Gattermann aldehyde synthesis on methyl-β-

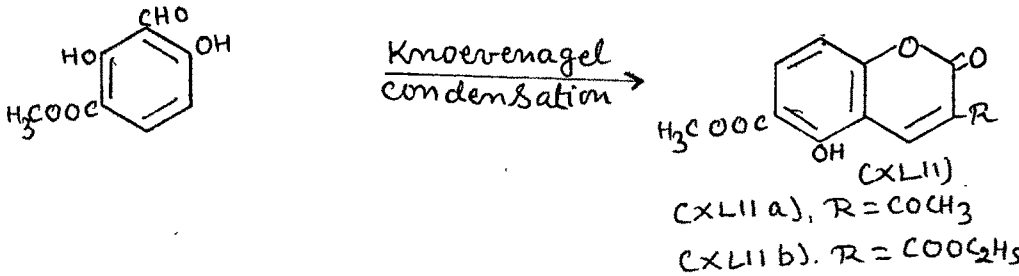
resorcylate according to Shah and Laiwalla (27) was condensed with acetylglycine in the presence of acetic anhydride and sodium acetate as before. 5-Acetoxy-6-carbomethoxy-3-acetamidocoumarin (XXXVIII) thus obtained was hydrolysed with alcoholic 3N hydrochloric acid to 3,5-dihydroxy-6-carbomethoxycoumarin (XXXIX) . It was further hydrolysed to 3,5-dihydroxycoumarin-6-carboxylic acid (XL) by keeping it with 10 % sodium hydroxide solution overnight.



The alternate structure 5-acetoxy-8-carbomethoxy-3-acetamidocoumarin (XLI) for the condensation product does not appear likely because of the chelation between the hydroxyl group and the carbomethoxy group in methyl 2,4-dihydroxy-3-formylbenzoate.



This assumption is supported by the work of Shah and Laiwala (27) who observed that methyl 2,4-dihydroxy-3-formylbenzoate when condensed with ethyl acetoacetate and ethyl malonate in the presence of piperidine gave 5-hydroxy-6-carbomethoxy-3-acetylcoumarin (XLII a) and 5-hydroxy-3,6-dicarbomethoxycoumarin (XLII, b) respectively.

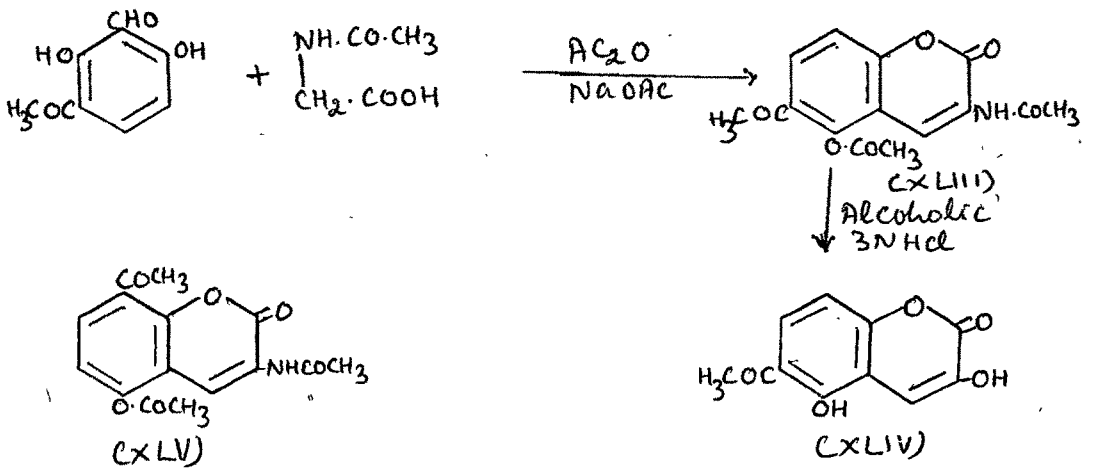


(XLII)

(XLII a), R = $COCH_3$

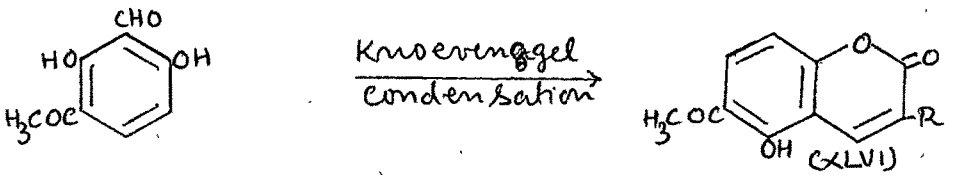
(XLII b), R = $COOC_2H_5$

2,4-Dihydroxy-3-formylacetophenone prepared by modified Gattermann aldehyde synthesis on resacetophenone according to Shah and Shah (28) was condensed with acetylglycine in the presence of acetic anhydride and sodium acetate. 5-Acetoxy-6-acetyl-3-acetamidocoumarin (XLIII) thus obtained was hydrolysed with alcoholic 3N hydrochloric acid to 3,5-dihydroxy-6-acetylcoumarin (XLIV).



The alternate structure 5-acetoxy-8-acetyl-3-acetamidocoumarin (XLV) is precluded for the reasons stated before viz. the possibility of chelation between the hydroxyl group and the acetyl group in the 2,4-dihydroxy-3-formylacetophenone.

Shah and Shah (28) also observed that 2,4-dihydroxy-3-formylacetophone when condensed with ethyl acetoacetate and ethyl malonate in the presence of piperidine gave 5-hydroxy-3,6-diacetylcoumarin (XLVI a) and 5-hydroxy-3-carbomethoxy-6-acetylcoumarin (XLVI b) respectively.



(XLVI a). R = $COCH_3$
(XLVI b). R = $COOC_2H_5$

Screening for antibacterial activity

The following compounds were screened by Messrs. Alembic Chemical Works of Baroda for their antibacterial activity.

(1) 3-Hydroxycoumarin.

(2) 5-Hydroxy-6-acetyl-3-acetamidocoumarin.

(3) 6-Bromo-3-acetamidocoumarin.

(4) 6,8-Dibromo-3-acetamidocoumarin.

(5) 6,8-Dinitro-3-acetamidocoumarin.

The following five micro-organisms were selected, each one to represent a separate type.

(1) Staphylococcus aurens (Gram positive)

(2) Bacillus subtilis (Gram positive, spore-former)

(3) Escherichia coil (Gram negative)

(4) Saccharomyces cerevisiae (Yeast)

(5) Penicillium chrysogenum (Filamentous fungus)

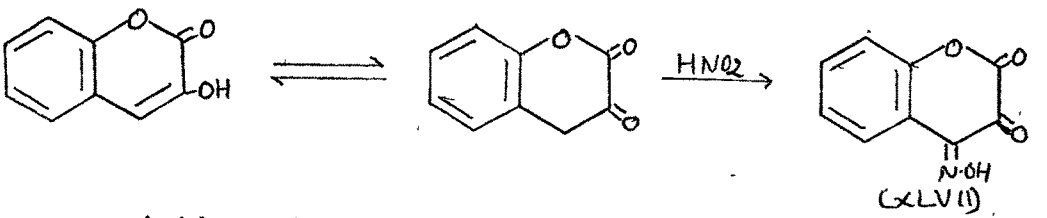
None of the substances was however found to possess any antimicrobial activity even at the concentration of 10 mg. per ml. Penicillin for antibacterial activity and griseofulvin for antifungal activity were used as standards for comparison.

Study of the reactions on 3-hydroxycoumarins

On reviewing the literature it was found that very little work has been done on the study of the reactivity of 3-hydroxycoumarin. So it was thought of interest to study different reactions such as bromination, iodination, Friedel-Crafts acetylation and Fries migration on 3-hydroxycoumarin.

Action of nitrous acid on 3-hydroxycoumarin

With a view to follow up the studies of Erlenmeyer and Stadlin (6) who obtained a phenylhydrazone and a quinoxaline derivative from 3-hydroxycoumarin as stated earlier, it was thought of interest to see if the same pattern of behaviour viz. the presence of ketonic structure in 3-hydroxycoumarin resulting in the presence of a reactive methylene group would be shown with nitrous acid. This was found to be the case and 3-hydroxycoumarin gave with nitrous acid an isonitroso derivative(XLVII).

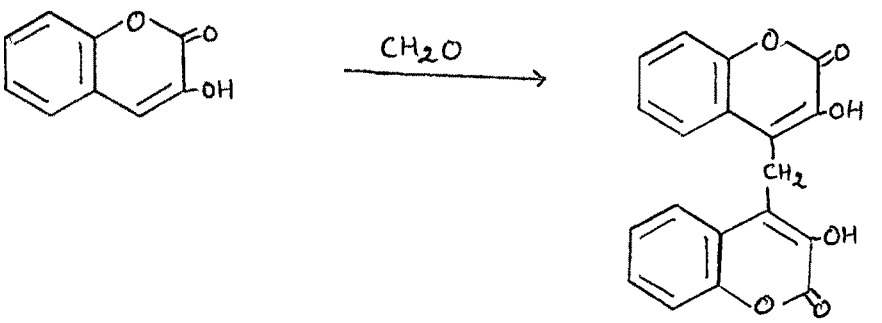


(XLVII)

Action of formaldehyde on 3-hydroxycoumarin

Synthesis of 4,4'-methylenebis-(3-hydroxycoumarin)

In view of the fact that 4-hydroxycoumarin when reacted with formaldehyde gave 3,3'-methylenebis-(4-hydroxycoumarin), it was thought of interest to study the effect of formaldehyde on 3-hydroxycoumarin. When 3-hydroxycoumarin was refluxed with formaldehyde in alcoholic solution 4,4'-methylenebis-(3-hydroxycoumarin) (XLVIII) was obtained in good yield.

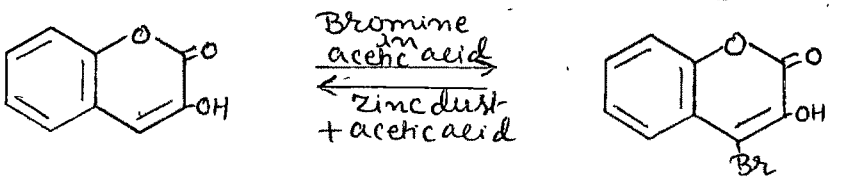


(XLVIII)

When 3-hydroxycoumarin was reacted with benzaldehyde under similar experimental condition, no condensation took place and 3-hydroxycoumarin was recovered unchanged.

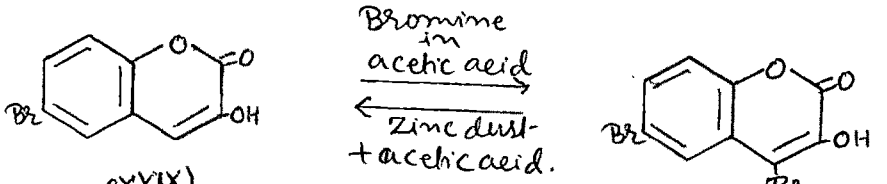
Bromination of 3-hydroxycoumarin derivatives

3-Hydroxycoumarin with bromine in acetic acid gave a monobromo derivative in good yield to which the 4-bromo structure (XLIX) has been assigned. On reduction with zinc dust and acetic acid it gave 3-hydroxycoumarin indicating that the bromine must have entered the pyrone part of the coumarin molecule and the 4-position is the only available position in the pyrone part.

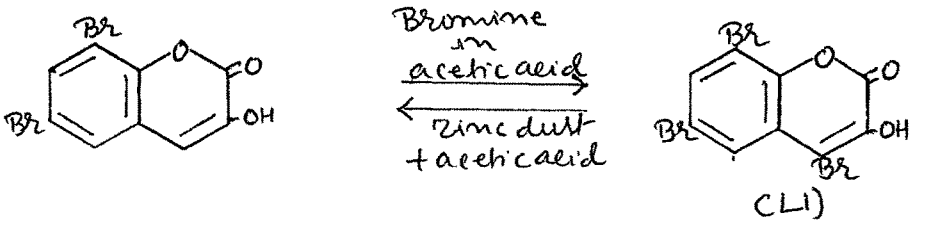


(XLIX)

Attempts to brominate 3-hydroxycoumarin with two or more moles of bromine in acetic acid met with failure to get a dibromo derivative. The 4,6-dibromo-(L) and the 4,6,8-tribromo-3-hydroxycoumarin (LI) were however synthesised by the bromination of the 6-bromo-and 6,8-dibromo-3-hydroxycoumarin respectively. The structures 4,6-dibromo-and 4,6,8-tribromo-3-hydroxycoumarin were assigned to them as they gave the original coumarins back on reduction with zinc dust and acetic acid.



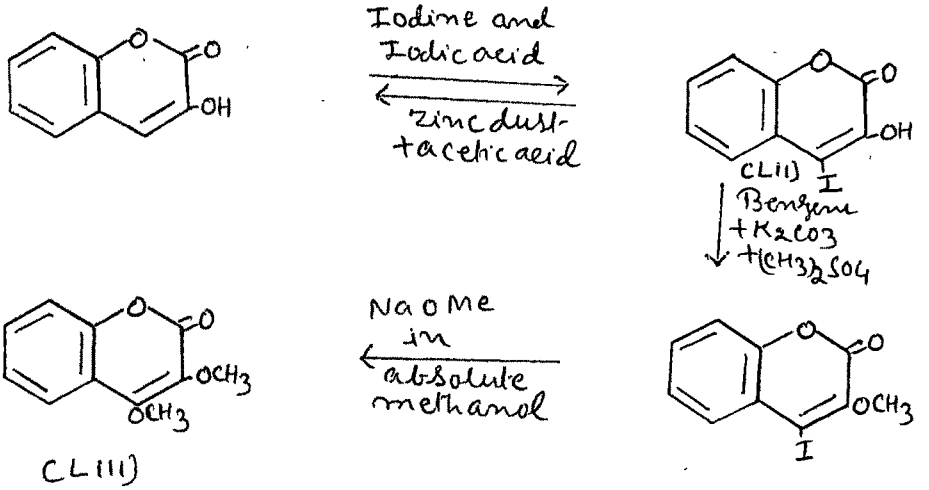
(XXIX) (L)



CLI)

Iodination of 3-hydroxycoumarin

3-Hydroxycoumarin, on iodination with iodine and iodic acid gave a mono iodo derivative. 4-Iodo-3-hydroxycoumarin (LII) structure was assigned to it as it gave 3-hydroxycoumarin back on reduction with zinc dust and acetic acid. Further, on methylation and treatment with sodium methoxide in absolute methylalcohol, the iodo derivative gave the known 3,4-dimethoxycoumarin (LIII) (29).

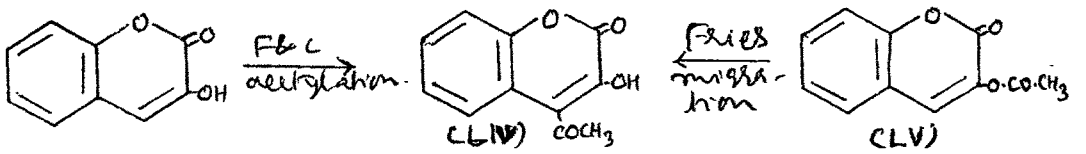


CLIII)

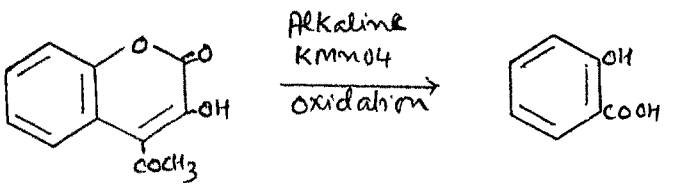
Friedel-Crafts acetylation of 3-hydroxycoumarin and Fries migration of 3-acetoxycoumarin

3-Hydroxycoumarin, on Friedel-Crafts acetylation with acetic anhydride and anhydrous aluminium chloride

gave 4-acetyl-3-hydroxycoumarin (LIV) in very poor yield.

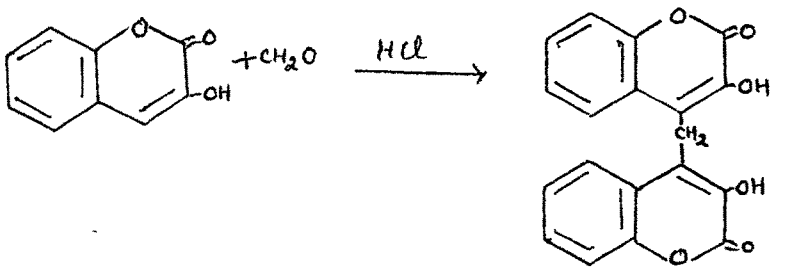


The same product was obtained in poor yield in the Fries migration of 3-acetoxycoumarin (LV) at 140°. It gave the characteristic green colouration in alcoholic ferric chloride solution. It gave salicyclic acid on oxidation with alkaline permanganate solution, which indicated that the acetyl group had not gone to the benzene part of the coumarin molecule.



Chloromethylation of 3-hydroxycoumarin

When 3-hydroxycoumarin was subjected to chloromethylation, it gave a chlorine free product. Its mixed m.p. with 4,4' -methylenebis-(3-hydroxycoumarin) described earlier (p. 22) was not depressed and hence this structure has been assigned to the product.



Some attempted reactions

Formylation : 3-Hydroxycoumarin, when subjected to the action of hexamine gave a complex nitrogenous product which could not be hydrolysed to the formyl derivative. Attempt was also made to formylate it by heating it with N-methylformanilide in the presence of phosphorus oxychloride using chlorobenzene as solvent. Only the original coumarin could be isolated from the reaction mixture.

Nitration : No definite product was isolated when 3-hydroxyccumarin was subjected to nitration.

EXPERIMENTAL

3-Hydroxycoumarin was prepared as follows according to Shaw et al. (12).

3-Acetamidocoumarin

Salicylaldehyde (3.05 g. ; 0.025 mole), acetylglycine (2.92 g. ; 0.025 mole) freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride (10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. The product obtained on pouring the reaction mixture in water crystallised from acetic acid in colourless needles, m.p. 206°. Yield 1.0 g.

3-Hydroxycoumarin

3-Acetamidocoumarin (1.0 g.) was dissolved in minimum quantity of alcohol and refluxed with 3N hydrochloric acid (25 ml.) for 3 to 4 hr. The 3-hydroxy-coumarin obtained on cooling on repeated crystallisation from alcohol (charcoal) gave colourless needles. M.P. 153-54°. It gave a characteristic green colouration with alcoholic ferric chloride solution and was soluble in sodium hydroxide solution in cold.

6-Bromo-3-acetamidocoumarin

5-Bromo salicylaldehyde required for this reaction was prepared by the bromination of salicylaldehyde according to the method of Auwers and Burger (23).

5-Bromo salicylaldehyde (7.5 g. ; 0.025 mole), acetylglycine (2.92 g. ; 0.025 mole) freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride

(10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. The product obtained on dilution of the reaction mixture with water crystallised from acetic acid in colourless needles, m.p. 261-62°. Yield 1.5 g. Linch (22) reported m.p. 266°.

Analysis :

21.24 mg. of the substance gave 14.26 mg. of silver bromide.

Found : Br = 28.57 %.

$C_{11}H_8O_3NBr$ requires : Br = 28.36 %.

6-Bromo-3-hydroxycoumarin

6-Bromo-3-acetamidocoumarin (1.0 g.) was dissolved in minimum quantity of alcohol and refluxed with 3N hydrochloric acid (25 ml.) for 4 hrs. 6-Bromo-3-hydroxy-coumarin obtained on cooling crystallised from alcohol in colourless needles, m.p. 252°. Yield 0.3 g. It gave a characteristic green colouration with alcoholic ferric chloride solution and was soluble in sodium hydroxide solution in cold. The same product was obtained when the hydrolysis was carried out with dilute sulphuric acid according to Linch (22).

Analysis :

8.772 mg. of the substance gave 6.850 mg. of silver bromide.

Found : Br = 33.23 %.

$C_9H_5O_3Br$ requires : Br = 33.02 %.

6,8-Dibromo-3-acetamidocoumarin

3,5-Dibromosalicylaldehyde (24) (3.8 g. ; 0.01 mole), acetylglycine (1.17 g. ; 0.01 mole), freshly fused sodium acetate (0.8 g. ; 0.01 mole) and acetic anhydride (5 ml. ; 0.05 mole) were heated on a steam bath for 1 hr. The product obtained on dilution of the reaction mixture with water crystallised from acetic acid in colourless needles, m.p. 279°. Yield 0.7 g.

Analysis :

8.998 mg. of the substances gave 9.444 mg. of silver bromide.

Found : Br = 44.66 %.

$C_{11}H_7O_3NBr_2$ requires : Br = 44.32 %.

6,8-Dibromo-3-hydroxycoumarin

6,8-Dibromo-3-acetamidocoumarin (1 g.) was dissolved in minimum quantity of alcohol and refluxed with 3N hydrochloric acid (25 ml.) for 4 hr. 6,8-Dibromo-3-hydroxycoumarin, obtained on cooling, crystallised from alcohol in colourless needles, m.p. 261°. Yield 0.25 g. It gave the characteristic green colouration with alcoholic ferric chloride solution and was soluble in sodium hydroxide solution in cold.

Analysis :

7.782 mg. of the substance gave 9.110 mg. of silver bromide.

Found : Br = 49.82 %.

$C_9H_4O_3Br_2$ requires : Br = 50.00 %.

6-Nitro-3-acetamidocoumarin

5-Nitrosalicylaldehyde (25) (4.2 g. ; 0.025 mole), acetylglycine (2.92 g. ; 0.025 mole), freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride (10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. 6-Nitro-3-acetamidocoumarin obtained on working up as before crystallised from acetic acid in yellow needles, m.p. 278°. Yield 0.7 g.

Analysis :

9.50 mg. of the substance gave 0.951 c.c. of nitrogen at t = 33°C and p=758 mm.

Found : N = 11.10 %.

$C_{11}H_8O_5N_2$ requires : N = 11.30 %.

6-Nitro-3-hydroxycoumarin

6-Nitro-3-acetamidocoumarin (1 g.) dissolved in minimum quantity of alcohol was refluxed with 3N hydrochloric acid (25 ml.) for 4 hr. 6-Nitro-3-hydroxycoumarin obtained on cooling crystallised from alcohol in whitish yellow needles, m.p. 256°. Yield 0.25 g. It gave a characteristic green colouration with alcoholic ferric chloride solution and was soluble in sodium hydroxide solution in cold.

Analysis :

9.7 mg. of the substance gave 0.604 c.c. of nitrogen at t = 30°C and p = 757 mm.

Found : N = 6.98 %.

$C_9H_5O_5N$ requires : N = 6.76 %.

8-Nitro-3-acetamidocoumarin

3-Nitrosalicaldehyde (25) (4.2 g. ; 0.025 mole) acetylglycine (2.92 g. ; 0.025 mole) freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride (10 ml.; 0.1 mole) were heated on a steam bath for 1 hr. The reaction mixture on working up as before gave 8-nitro-3-acetamidocoumarin which crystallised from acetic acid in pale yellow needles, m.p. 268°. Yield 0.6 g.

Analysis :

6.02 mg. of the substance gave 0.634 c.c. of nitrogen at t = 34° and p =756 mm.

Found : N = 11.65 %.

$C_{11}H_8O_5N_2$ requires : N = 11.30 %.

8-Nitro-3-hydroxycoumarin

8-Nitro-3-acetamidocoumarin (1 g.) dissolved in alcohol was refluxed with 3N hydrochloric acid (25 ml.) for 4 hr. 8-Nitro-3-hydroxycoumarin obtained on cooling crystallised from alcohol in yellow needles, m.p. 220°. ~~it~~ 0.2 g. It gave characteristic green colouration with alcoholic ferric chloride solution and was soluble in cold sodium hydroxide solution.

Analysis :

9.610 mg. of the substance gave 0.595 c.c. of nitrogen at t = 30° and p = 757 mm.

Found : N = 6.70 %.

$C_9H_5O_5N$ requires : N = 6.76 %.

6,8-Dintro-3-acetamidocoumarin

3,5-Dintrosalicylaldehyde (26) (5.30 g. ; 0.025 mole) acetylglycine (2.92 g. ; 0.025 mole) freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride (10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. The product obtained on working up as usual crystallised from acetic acid in yellow needles, m.p.225°. Yield 0.6 g.

Analysis :

8.74 mg. of the substance gave 11.14 c.c. of nitrogen at t = 30°C and p = 752 mm.

Found : N = 14.54 %.

$C_{11}H_7O_7N_3$ requires : N = 14.33 %.

6,8-Dinitro-3-hydroxycoumarin

6,8-Dinitro-3-acetamidocoumarin (1 g.) was hydrolysed with alcoholic 3N hydrochloric acid (25 ml.) by heating for 4 hr. as before. The 3-hydroxycoumarin derivative obtained on cooling crystallised from alcohol in yellow needles, m.p. 185°. Yield 0.2 g. It gave the characteristic green colouration with alcoholic ferric chloride solution and was soluble in cold sodium hydroxide solution.

Analysis :

9.47 mg. of the substance gave 0.902 c.c. of nitrogen at t = 29° and p = 752 mm.

Found : N = 10.8 %.

$C_9H_4O_7N_2$ requires : N = 11.1 %.

5-Acetoxy-6-carbomethoxy-3-acetamidocoumarin

Methyl 2,4-dihydroxy-3-formylbenzoate (27) (4.92 g. ; 0.025 mole), acetylglycine (2.92 g. ; 0.025 mole) freshly fused sodium acetate (2 g. ; 0.025 mole) and acetic anhydride (10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. The reaction mixture on working up as before gave 5-acetoxy-6-carbomethoxy-3-acetamidocoumarin which crystallised from acetic acid in colourless needles, m.p. 255°. Yield 0.7 g.

Analysis :

8.68 mg. of the substance gave 0.357 c.c. of nitrogen at t = 33° and p = 757 mm.

Found : N = 4.57 %.

$C_{15}H_{13}O_7N$ requires : N = 4.52 %.

3,5-Dihydroxy-6-carbomethoxycoumarin

5-Acetoxy-6-carbomethoxy-3-acetamidocoumarin (1 g.) in minimum of alcohol was refluxed with 3N hydrochloric acid (25 ml.) for 4 hr. The 3,5-Dihydroxy-6-carbomethoxycoumarin obtained on cooling crystallised from alcohol in colourless needles, m.p.225°. Yield 0.35 g. It gave green colouration with alcoholic ferric chloride solution and was soluble in cold sodium hydroxide solution.

Analysis :

9.28 mg. of the substance gave 18.88 mg. of carbon dioxide and 2.50 mg. of water.

Found : C = 55.52 % ; H = 3.02 %.

$C_{11}H_8O_6$ requires : C = 55.90 % ; H = 3.39 %.

3,5-Dihydroxycoumarin-6-carboxylic acid

3,5-Dihydroxy-6-carbomethoxycoumarin (0.2 g.) was kept with sodium hydroxide solution (10 ml. ; 10 %) for 24 hr. It was then acidified with hydrochloric acid and the product crystallised from alcohol in colourless needles, m.p. 265°. Yield 50 mg. It was soluble in sodium hydrogen carbonate solution with effervescence and gave green colouration with alcoholic ferric chloride solution.

Analysis :

9.5 mg. of the substance gave 18.51 mg. of carbon dioxide and 2.37 mg. of water.

Found : C = 54.90 % ; H = 2.90 %.

$C_{10}H_6O_6$ requires : C = 54.50 % ; H = 2.70 %.

5-Acetoxy-6-acetyl-3-acetamidocoumarin

2,4-Dihydroxy-3-formyl acetophenone (28) (4.52 g. ; 0.025 mole), acetylglycine (2.92 g. ; 0.025 mole), freshly fused sodium acetate (2.0 g. ; 0.025 mole) and acetic anhydride (10 ml. ; 0.1 mole) were heated on a steam bath for 1 hr. 5-Acetoxy-6-acetyl-3-acetamidocoumarin obtained on working up as before crystallised from acetic acid in colourless needles, m.p. 290°. Yield 1 g.

Analysis :

9.44 mg. of the substance gave 0.441 c.c. of nitrogen at t = 30° and p = 758 mm.

Found : N = 4.95 %.

$C_{15}H_{13}O_6N$ requires : N = 4.62 %.

3,5-Dihydroxy-6-acetylcoumarin

5-Acetoxy-6-acetyl-3-acetamidocoumarin (1 g.) in minimum of alcohol was refluxed with 3N hydrochloric acid (25 ml.) for 4 hr. 3,5-Dihydroxy-6-acetylcoumarin obtained on cooling crystallised from alcohol in colourless needles, m.p. 230°. Yield 0.3 g. It gave green colouration with alcoholic ferric chloride solution and was soluble in cold sodium hydroxide solution.

Analysis :

7.04 mg. of the substance gave 15.54 mg. of carbon dioxide and 2.28 mg. of water.

Found : C = 60.24 % ; H = 3.62 %.

$C_{11}H_8O_5$ requires : C = 60.04 % ; H = 3.64 %.

Action of nitrous acid on 3-hydroxycoumarin:

4-Isonitroso-2,3-diketochroman

A mixture of 3-hydroxycoumarin (1 g.) in minimum quantity of acetic acid and concentrated hydrochloric acid (5 ml.) was cooled externally and sodium nitrite solution (0.5 g. ; 5 ml. water) was added dropwise. Sodium hydrogen carbonate solution was then added to neutralise the excess of acids in the mixture and the whole solution was then extracted with ether. The product obtained on removal of ether crystallised from benzene-petrol mixture in stout yellow needles, m.p. 185°. Yield 0.15 g.

Analysis :

10.30 mg. of the substance gave 0.654 c.c. of nitrogen at t = 33° and p = 758 mm.

Found . : N = 7.1 %.

$C_9H_5O_4N$ requires : N = 7.3 %.

Action of formaldehyde on 3-hydroxycoumarin: 4,4'-methylene bis-(3-hydroxycoumarin)

3-Hydroxycoumarin (1.62 g. ; 0.01 mole) and formalin (40 % solution) (3 ml. ; 0.03 mole) in alcohol (25 ml.) were refluxed for 3 hr. The separated product was filtered hot and crystallised from alcohol in colourless needles, m.p. 266°. Yield 0.7 g.

Analysis :

9.62 mg. of the substance gave 23.78 mg. of carbon dioxide and 2.88 mg. of water.

Found : C = 67.40 % ; H = 3.45 %.

$C_{19}H_{12}O_6$ requires : C = 67.85 % ; H = 3.53 %.

Bromination of 3-hydroxycoumarin : 4-Bromo-3-hydroxycoumarin

3-Hydroxycoumarin (1.62 g. ; 0.01 mole) was dissolved in minimum quantity of acetic acid and bromine (1.6 g. ; 0.01 mole) in acetic acid (16 ml.) was added. The reaction mixture was stirred for 0.5 hr. The separated product crystallised from acetic acid in colourless needles, m.p. 210°. Yield 1.5 g.

Analysis :

10.219 mg. of the substance gave 8.016 mg. of silver bromide.

Found : Br = 33.15 %.

$C_9H_5O_3Br$ requires : Br = 33.02 %.

This bromocoumarin (0.5 g.) in acetic acid (25 ml.) when refluxed with zinc dust (1 g.) for 2 hr. gave 3-hydroxycoumarin. Melting point and mixed m.p. was 153°.

Bromination of 6-bromo-3-hydroxycoumarin: 4,6-Dibromo-3-hydroxycoumarin

6-Bromo-3-hydroxycoumarin (2.41 g. ; 0.01 mole) was dissolved in minimum quantity of acetic acid, and bromine (1.6 g. ; 0.01 mole) in acetic acid (16 ml.) was added. The reaction mixture was stirred for 0.5 hr. The separated product crystallised from acetic acid in colourless needles, m.p.273°. Yield 2 g.

Analysis :

11.2 mg. of the substance gave 13.196 mg. of silver bromide.

Found : Br = 50.15 %.

$C_9H_4O_3Br_2$ requires : Br = 50.00 %.

When this dibromocoumarin (0.5 g.) was reduced in acetic acid (25 ml.) with zinc dust (1 g.) as above it gave 6-bromo-3-hydroxycoumarin. Melting point and mixed m.p. was 252°.

Bromination of 6,8-dibromo-3-hydroxycoumarin : 4,6,8-Tribromo-3-hydroxycoumarin

6,8-Dibromo-3-hydroxycoumarin (3.2 g. ; 0.01 mole) was dissolved in minimum quantity of acetic acid and bromine (1.6 g. ; 0.01 mole) in acetic acid (16 ml.) was added. The

reaction mixture was stirred for 0.5 hr. The separated product crystallised from acetic acid in colourless needles, m.p. 230°. Yield 3.0 g.

Analysis :

10.32 mg. of the substance gave 14.49 mg. of silver bromide.

Found : Br = 59.60 %.

$C_9H_3O_3Br_3$ requires : Br = 60.10 %.

The above tribromocoumarin (0.5 g.) when reduced with zinc dust (1 g.) and acetic acid (25 ml.) as before gave 6,8-dibromo-3-hydroxycoumarin. Melting point and mixed m.p. was 261°.

Iodination of 3-hydroxycoumarin: 4-Iodo-3-hydroxycoumarin

3-Hydroxycoumarin (1.62 g. ; 0.01 mole) in alcohol was treated with iodine (1.16g. ; 0.008 mole) followed by iodic acid (0.352 g. ; 0.002 mole). The reaction mixture was stirred for 0.5 hr. The separated product crystallised from alcohol in pale yellow needles, m.p. 223°(dec.). Yield 0.8 g.

Analysis :

19.3 mg. of the substance gave 15.58 mg. of silver iodide.

Found : I = 43.64 %.

$C_9H_5O_3I$ requires : I = 44.04 %.

4-Iodo-3-hydroxycoumarin (0.5 g.) when reduced with zinc dust (1 g.) in acetic acid (25 ml.) by refluxing

for 2 hr. gave 3-hydroxycoumarin. Melting point and mixed m.p. was 153°.

The methyl ether

4-Iodo-3-hydroxycoumarin (1 g.) was refluxed with dimethyl sulphate (1.0 ml.) and anhydrous potassium carbonate (2 g.) in benzene (100 ml.) for 10 hr. Benzene was removed by distillation and the reaction mixture was treated with water. The methyl ether which separated crystallised from alcohol in yellow needles, m.p. 102°. Yield 0.7 g.

Analysis :

14.91 mg. of the substance gave 11.67 mg. of silver iodide.

Found : I = 42.30 %.

$C_{10}H_7O_3I$ requires : I = 42.38 %.

3,4-Dimethoxycoumarin

4-Iodo-3-methoxycoumarin (3.02 g. ; 0.01 mole) was dissolved in minimum quantity of absolute methyl alcohol and the solution was treated with sodium (0.23 g.; 0.01 mole) dissolved in absolute methyl alcohol (25 ml.). The reaction mixture was refluxed on a steam bath for 2 hr. Acidification and subsequent ether extraction gave the 3,4-dimethoxycoumarin, m.p. 80°. Arndt and co-workers(29) report the same m.p.

Analysis :

7.35 mg. of the substance gave 16.72 mg. of carbon dioxide and 3.02 mg. of water.

Found : C = 64.42 % ; H = 4.54 %.

$C_{11}H_{10}O_4$ requires : C = 64.08 % ; H = 4.85 %.

Friedel-Crafts acetylation of 3-hydroxycoumarin : 4-Acetyl-3-hydroxycoumarin

3-Hydroxycoumarin (1.62 g. ; 0.01 mole) was heated with acetic anhydride (2 ml. ; 0.02 mole) and anhydrous aluminium chloride (2.6 g. ; 0.02 mole) on a steam bath for 3 hr. The reaction mixture was cooled and treated with ice and hydrochloric acid and filtered . The product after drying was extracted with hot petroleum ether (60-80°) . On cooling 3-hydroxycoumarin separated. Concentration of mother liquor gave 4-acetyl-3-hydroxycoumarin which crystallised from the same solvent in colourless needles, m.p. 85°. Yield 0.03 g. It gave green colouration with alcoholic ferricchloride solution.

Analysis :

6.28 mg. of the substance gave 14.12 mg. of carbon dioxide and 2.18 mg. of water.

Found : C = 64.84 % ; H = 3.88 %.

$C_{18}H_8O_4$ requires : C = 64.71 % ; H = 3.93 %.

The 2,4-dinitrophenylhydrazone

Prepared as usual, gave m.p. 236-38°(dec.)

Analysis :

9.52 mg. of the substance gave 0.932 c.c. of nitrogen at t = 29° and p = 752 mm.

Found : N = 11.70 %.

$C_{17}H_{11}O_7N_4$ requires : N = 11.59 %.

3-Acetoxycoumarin

Prepared as usual by heating 3-hydroxycoumarin (1.62 g. ; 0.01 mole) with acetic anhydride (2 ml. ; 0.02 mole) and pyridine (1 ml.) on a steam bath for 3 hr. It crystallised from benzene in colourless needles, m.p. 105-06°. Yield 1.5 g. It did not give any colouration with alcoholic ferric chloride solution.

Analysis :

7.42 mg. of the substance gave 17.62 mg. of carbon dioxide and 2.86 mg. of water.

Found : C = 64.81 % ; H = 4.30 %.

$C_{18}H_8O_4$ requires : C = 64.10 % ; H = 3.93 %.

Fries migration of 3-acetoxycoumarin : 4-Acetyl-3-hydroxycoumarin

A mixture of 3-acetoxycoumarin (2.04 g. ; 0.01 mole) and anhydrous aluminium chloride (2.6 g. ; 0.02 mole) was heated in an oil bath at 140° for 2 hr. The reaction mixture was cooled and treated with ice and hydrochloric acid and filtered. The product after drying was extracted with hot petroleum ether 60-80°. On cooling, 3-hydroxycoumarin separated. Concentration of mother liquor gave 4-acetyl-3-hydroxycoumarin which crystallised from the same solvent in colourless needles, m.p.85°. Yield 0.05 g. Mixed m.p. with the product obtained from the Friedel-Crafts acetylation of 3-hydroxycoumarin was not depressed.

Oxidation of 4-acetyl-3-hydroxycoumarin

4-Acetyl-3-hydroxycoumarin (1 g.) was dissolved

in sodium hydroxide solution (10 % ; 10 ml.) and heated with potassium permanganate (0.5 g.) on a steam bath for 3 hr. The product obtained on acidification gave m.p.156°. Mixed m.p. with salicyclic acid was not depressed.

Chloromethylation of 3-hydroxycoumarin

A mixture of 3-hydroxycoumarin (1.62 g. ; 0.01 mole) in glacial acetic acid (10 ml.) and paraformaldehyde (0.3 g.; 0.01 mole) was treated with dry hydrogen chloride at 100° for 1 hr. On cooling the reaction mixture a crystalline product separated. It crystallised from alcohol. M.p. and mixed m.p. with an authentic specimen of 4,4 -methylene bis-(3-hydroxycoumarin) was 266°. Yield 0.5 g.

Formylation of 3-hydroxycoumarin with hexamine

3-Hydroxycoumarin (5 g.),hexamine (10 g.) and acetic acid (50 ml.) were heated on a sand bath for 10 hr. Dilute hydrochloric acid (50 ml. ; 1:1) was then added and the whole reaction mixture was heated on a steam bath for another 5 hr. The reaction mixture was extracted twice with ether and the product obtained on removal of ether gave m.p. > 360° and did not crystallise from any solvent.

Formylation of 3-hydroxycoumarin with N-methyl formanilide and phosphorous oxychloride

To 3-hydroxycoumarin (3 g.) dissolved in chlorobenzene (20 ml.) N-methylformanilide (10 ml.) and phosphorus oxychloride(5 ml.) were added and the reaction mixture was heated on a steam bath for 1 hr. Water was then added and the reaction mixture was steam distilled to remove

chlorobenzene. The product obtained gave m.p. 153° and was found to be 3-hydroxycoumarin.

Nitration

To an ice-cooled solution of 3-hydroxycoumarin (1 g.) in acetic acid (7 ml.), con.nitric acid (2.5 ml.; d. 1.3) was added drop-wise. The reaction mixture was stirred for 1 hr. No product separated even on dilution of the reaction mixture with water. It was therefore extracted with ether. The removal of ether did not give any definite product.

REFERENCES

1. Plöch and Wolfrum, Ber., 18, 1183 (1885).
2. Willstatter, Zechmeister and Kindler, Ber., 57, 1938 (1924).
3. Heilbron, Hill and Walls, J.Chem.Soc., 1931, 1701.
4. Godwin and Taves, Am.J.Botany., 37, 224 (1950).
5. Rodighiero and Antonello, Bull.Chim.Farm., 97, 592 (1958).
6. Erlenmeyer and Stadlin, Ann., 337, 283 (1904).
7. Offe and Jatzkwitz, Ber., 80, 469 (1947).
8. Dey and Lakshminarayan, J.Indian Chem.Soc., 11, 827 (1934).
9. Beer, Clarke, Khorana and Robertson, J.Chem.Soc., 1948, 1605.
10. Robertson and coworkers, J.Chem.Soc., 1949, 562.
11. Dean, Robertson and Whalley, J.Chem.Soc., 1950, 895.
12. Shaw, McMillan and Armstrong, J.Org.Chem., 21, 601 (1956).
13. Dakin, J.Biol.Chem., 82, 439 (1929).
14. Carter, "Azlactone". Organic reactions, 3, 198 (1946).
15. Baltazzi,"The chemistry of 5-oxazolones", Quarterly reviews, 9, 150 (1955).
16. Lambooy, J.Am.Chem.Soc., 76, 133 (1954).
17. Barltrop, J.Chem.Soc., 1946, 958.
18. Clemo and Duxbury, J.Chem.Soc., 1950, 1795.
19. Gupta, J.Sci.and Ind.research., 19B, 117 (1960).
20. Spath and Debrovolny, Ber., 71, 1831 (1938).
21. Ghosh, J.Indian Chem.Soc., 24, 323 (1947).
22. Linch, J.Chem.Soc., 101, 1758 (1912).

23. Auwers and Burger, Ber., 37, 3934 (1904).

24. Brewston, J.Am.Chem.Soc., 46, 2464 (1924).

25. Miller, Ber., 20, 1927 (1887).

26. Lovett and Roberts, J.Chem.Soc., 117, 1978 (1926).

27. Shah and Laiwalla, J.Chem.Soc., 1938, 1828.

28. Shah and Shah, J.Chem.Soc., 1939, 132.

29. Arndt, Loewe, Un and Ayca, Ber., 84, 319 (1951).