CHAPTER VI

STUDIES ON 6,7-DIHYDROXY-4-METHYLCOUMARIN AND ITS METHYL ETHERS

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Studies on 6,7-dihydroxy-4-methylcoumarin and its methyl ethers

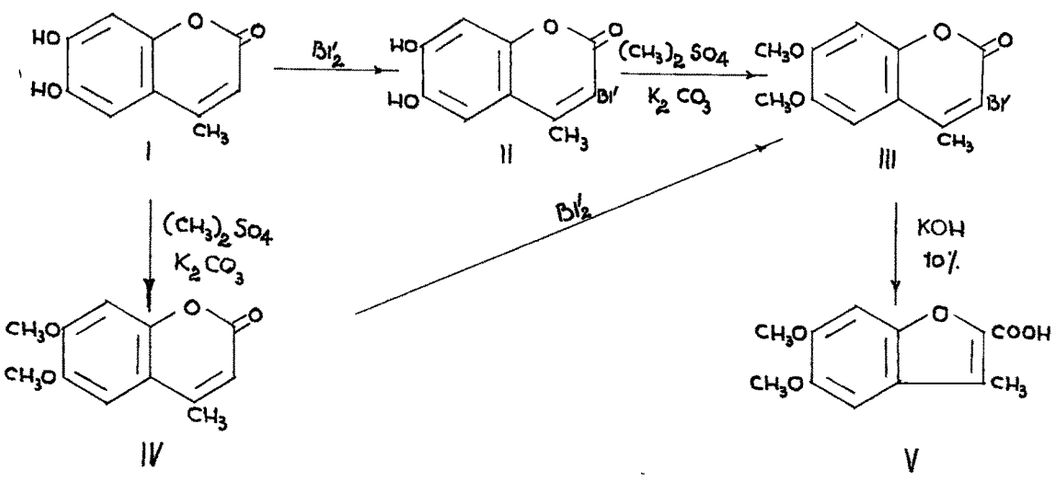
Considerable work has been done on the reactivity of various mono- and dihydroxycoumarins, but the data regarding the reactivity of 6,7-dihydroxycoumarin is meagre. 6,7-dihydroxycoumarin derivatives occur in nature and are therefore of interest. King et al. (J. Chem. Soc., 1954, 1392) and Gurbaksh Singh et al. (Chem. and Ind., 1954, 1294) as a part of their studies on certain plant products brominated 6,7-dimethoxycoumarin and obtained the 3-bromo derivative. Spath and Dobrovonly (Ber., 1938, 71B, 1831) nitrated 6,7-dimethoxy- and 6-methoxy-7-hydroxycoumarin and obtained the 3-nitro derivatives.

The present work deals with the systematic study of the pattern of substitution in 6,7-dihydroxy-4-methylcoumarin as both 5- and 8-positions are capable of substitution in this compound if there is a fixation of double bond as shown in (I). It was therefore of interest to see which one is more reactive, or whether both the positions would be deactivated in view of the presence of a hydroxyl group in meta position. The reactivity of this coumarin in various reactions such as (i) bromination (ii) nitration (iii) iodination (iv) Friedel-Crafts and Fries reaction and (v) chloromethylation has been studied.

Bromination of 6,7-dihydroxy-4-methylcoumarin and its dimethyl ether

6,7-Hydroxy-4-methylcoumarin required for the present work was prepared by passing dry hydrochloric acid gas in a solution of quinone triacetate in absolute alcohol and ethylacetoacetate (Gilman and Blatt, Org. Synthesis Collective Vol., I , 360)

6,7-Dihydroxy-4-methylcoumarin (I) was brominated using one mole of bromine in acetic acid solution at room temperature. The product obtained was found to be 6,7-dihydroxy-3-bromo-4-methylcoumarin (II) as its dimethyl ether (III) on hydrolysis with hot alcoholic alkali gave a coumarilic acid derivative (V). The dimethyl ether was found to be identical with the product obtained on the bromination of 6,7-dimethoxy-4-methylcoumarin with one mole of bromine.

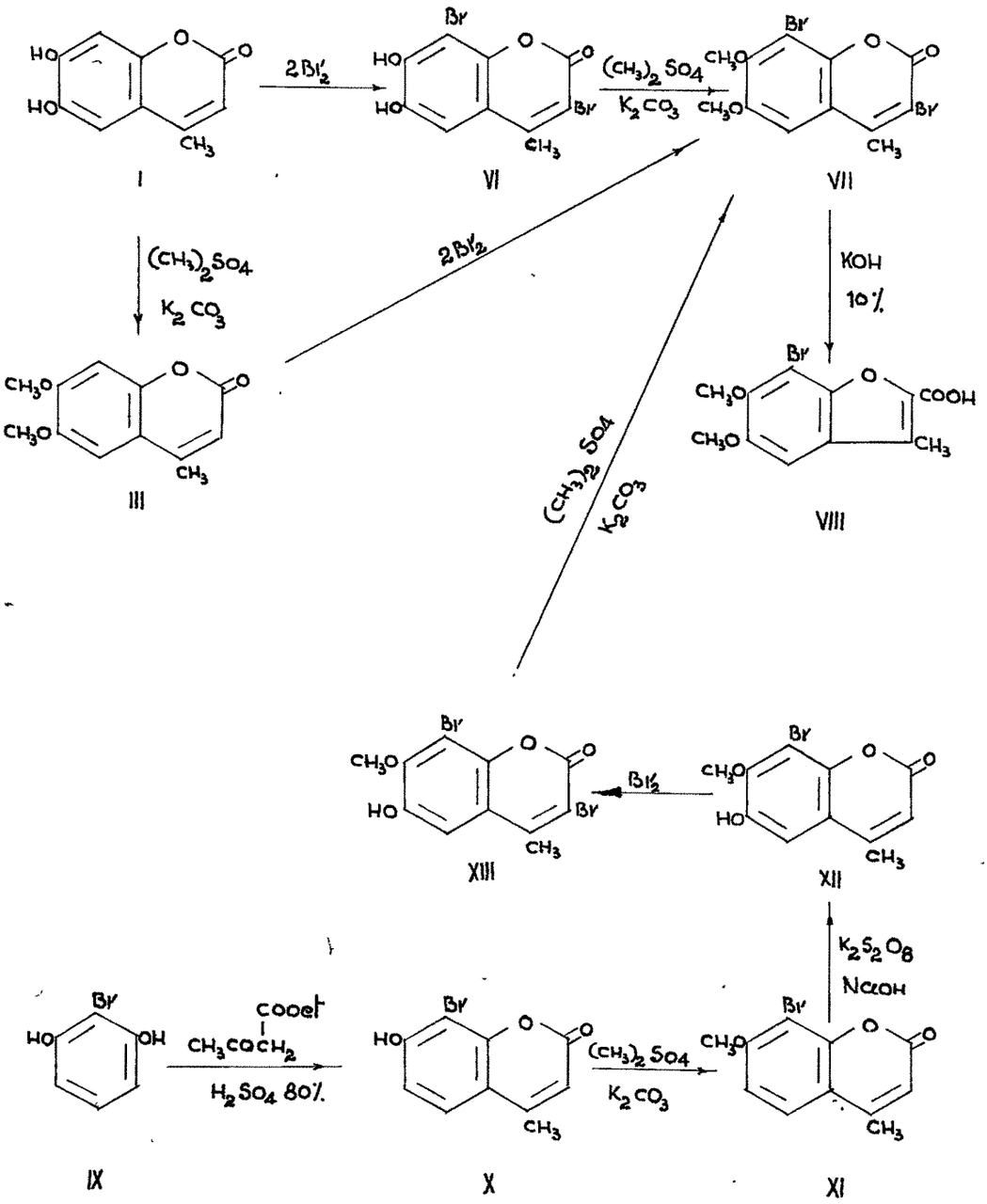


With two moles of bromine 6,7-dihydroxy-4- methylcoumarin (I) gave a dibromo derivative (VI) to which the 3,8-dibromo structure has been assigned as its dimethyl ether gave a mono bromocoumarilic acid derivative and the dimethyl ether was found to be identical on direct comparison with an authentic specimen of 6,7-dimethoxy-3,8-dibromo-4-methylcoumarin synthesised as follows :

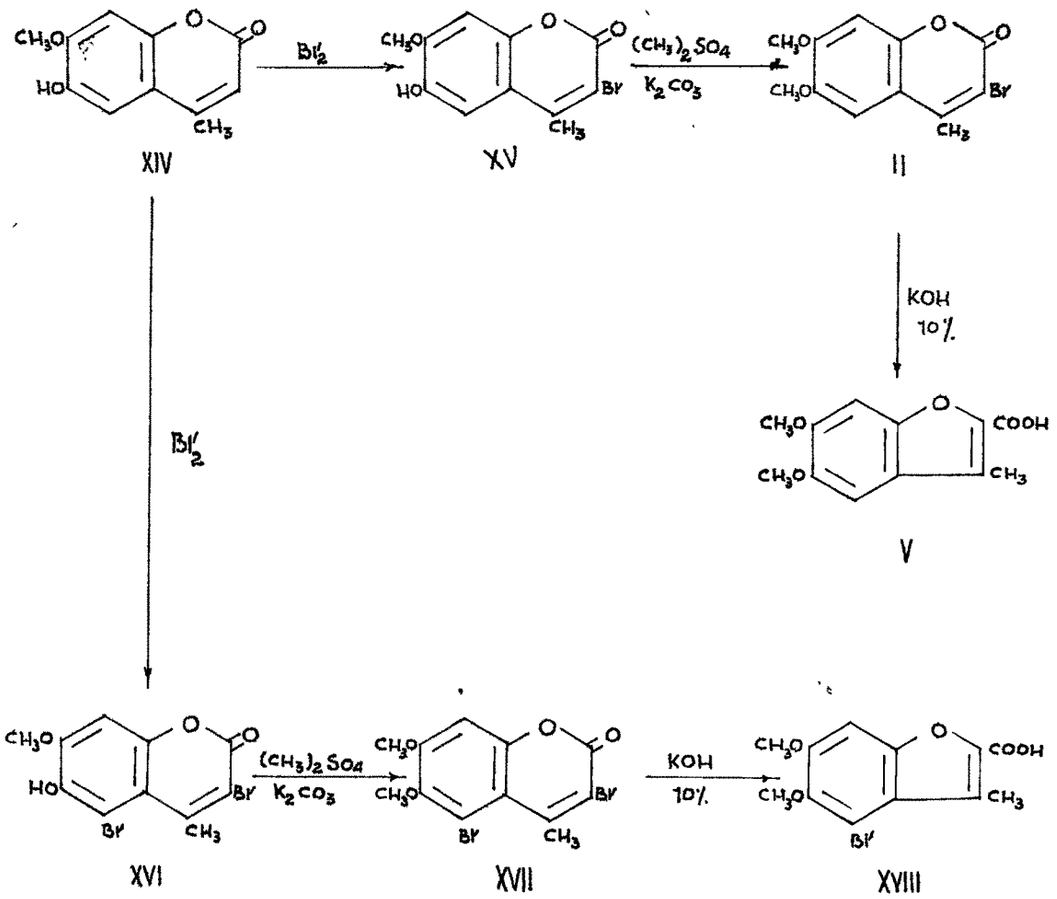
2-Bromo resorcinol (IX) was condensed with ethylacetoacetate in presence of sulphuric acid and 7-hydroxy-8-bromo-4-methylcoumarin (X) was obtained. This was obtained previously by Chakravarti and Mukerjee (J. Ind. Chem. Soc., 1937, 14, 729) from 7-hydroxy-8-nitro-4-methylcoumarin by diazotization and treatment with cuprous bromide. The hydroxy bromocoumarin (X) was methylated to 7-methoxy-8-bromo-4-methylcoumarin (XI). This was subjected to Elbs Persulphate Oxidation when 7-methoxy-6-hydroxy-8-bromo-4-methylcoumarin (XII) was obtained. On bromination with one mole of bromine it gave a dibromo derivative. Its methyl ether was identical with the dimethyl ether of the dibromo compound obtained above. The same dibromo derivative was obtained on bromination of 6,7-dimethoxy-4-methylcoumarin. It gave the monobromocoumarilic acid (VIII) on hydrolysis the same as that described above.

Bromination of 7-methoxy-6-hydroxy-4-methylcoumarin (XIV) with one mole of bromine in acetic acid at room temperature gave 7-methoxy-6-hydroxy-3-bromo-4-methylcoumarin (XV). On methylation and hydrolysis with hot alcoholic alkali it gave the coumarilic acid derivative (V) described above. With two moles of bromine in acetic acid at the temperature of boiling water bath a dibromo derivative was obtained. Its methyl ether was different from

6,7-dimethoxy-3,8-dibromo-4-methylcoumarin described above, and hence it must have the alternate structure 6,7-dimethoxy-3,5-dibromo-4-methylcoumarin (XVI)



On hydrolysis with hot alcoholic alkali it gave a monobromocoumarilic acid isomeric with the 5,6-dimethoxy-7-bromo-3-methylcoumarilic acid (VIII) described above.



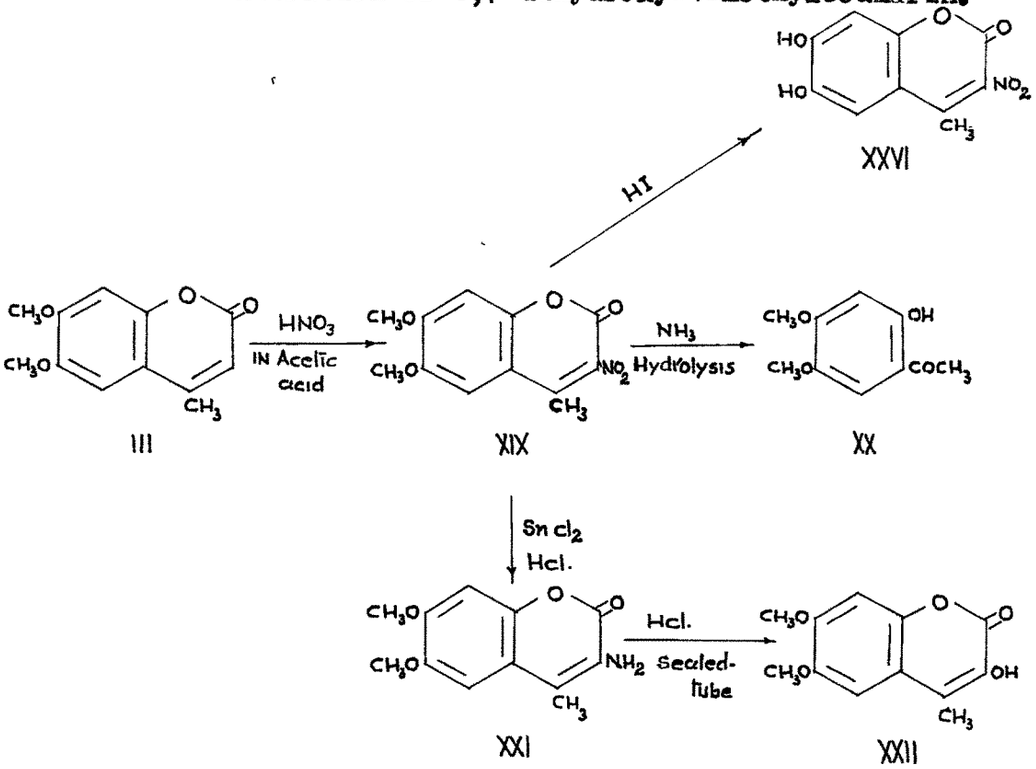
Nitration of 6,7-dimethoxy-4-methylcoumarin

6,7-Dimethoxy-4-methylcoumarin (III) was nitrated with concentrated nitric acid in acetic acid. The product obtained has been assigned 6,7-dimethoxy-3-nitro-4-methylcoumarin (XIX) structure as on hydrolysis with liquor ammonia it yielded 2-hydroxy-4,5-dimethoxy acetophenone (XX) identical

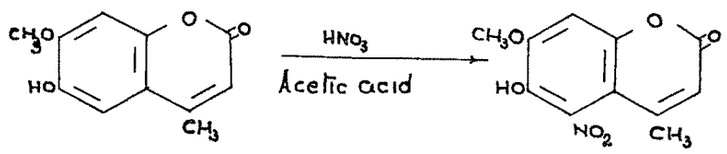
with an authentic specimen obtained according to Bargellini and Aureli (Atti. R. Accade. Lincei., 1911, V, 20, 118).

The nitroderivative (XIX) was reduced with stannous chloride in hydrochloric acid to the corresponding 3-aminocoumarin (XXI) and this was hydrolysed in a sealed tube with hydrochloric acid to the corresponding 3-hydroxy-coumarin derivative (XXII). 6,7-Dimethoxy-3-nitrocoumarin was demethylated with hydriodic acid in acetic anhydride to 6,7-dihydroxy-3-nitro-4-methylcoumarin (XXVI).

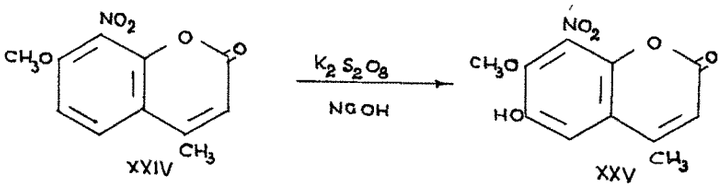
No product could be isolated from the reaction mixture in the nitration of 6,7-dihydroxy-4-methylcoumarin.



7-Methoxy-6-hydroxy-4-methylcoumarin (XIV) with nitric acid and acetic acid gave a mononitro derivative to which 7-methoxy-6-hydroxy-5-nitro-4-methylcoumarin (XXIII) structure has been assigned as it remained unchanged with liquor ammonia and it was different from the 7-methoxy-6-hydroxy-8-nitro-4-methylcoumarin derivative (XXV) obtained by the Elbs Persulphate Oxidation of 7-methoxy-8-nitro-4-methylcoumarin (XXIV).



XIV XXIII



XXIV XXV

Other attempted reactions

Iodination

Iodination of 6,7-dihydroxy-4-methylcoumarin with (i) iodine and iodic acid (ii) iodine and ammonia and (iii) iodine monochloride did not succeed. 6-Hydroxy-7-methoxy-4-methylcoumarin on iodination with iodine monochloride gave a chloro-iodo product which was not investigated. Iodination of 6-hydroxy-7-methoxy-4-methylcoumarin with iodine and iodic acid and iodine and ammonia also did not succeed.

Formylation

Formylation of 6,7-dihydroxy-4-methylcoumarin with hexamethylene tetramine in acetic acid did not succeed. However 6-hydroxy-7-methoxy-4-methylcoumarin gave a formyl derivative to which 5-formyl structure has been assigned as it gave a violet colouration with alcoholic ferric chloride. 6,7-Dimethoxy-4-methylcoumarin on formylation gave a product m.p. 325° which was found to be identical with the chlorine free product obtained in the chloromethylation of 6,7-dimethoxy-4-methylcoumarin (described below). On the basis of this observation and the analysis results the product has been assigned ? ? methylene bis (6,7-dimethoxy-4-methylcoumarin) structure.

Friedel-Crafts reaction

The Friedel-Crafts acetylation of 6,7-dihydroxy-4-methylcoumarin and 6-hydroxy-7-methoxy-4-methylcoumarin under varying conditions did not succeed. Fries migration of 6-acetoxy-7-methoxy-4-methylcoumarin also did not succeed.

Chloromethylation

Chloromethylation of 6,7-dihydroxy-4-methylcoumarin resulted in a polymeric product which did not melt on a spatula. Chloromethylation of 6-hydroxy-7-methoxy-4-methylcoumarin gave an unworkable pasty product. 6,7-Dimethoxy-4-methyl-coumarin gave a chlorine free product, m.p. 325° discussed above under formylation.

EXPERIMENTAL

Bromination of 6,7-dihydroxy-4-methylcoumarin : 6,7-Dihydroxy-3-bromo-4-methylcoumarin.

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in acetic acid (200 ml.) by warming and bromine (10 % ; 16 ml.; 0.01 mole) in acetic acid was added drop-wise. The reaction mixture was kept at room temperature for 30 minutes after the addition was complete. The solid which separated crystallised from acetic acid in needles, m.p. 244-245° . Yield 1.8 g.

Analysis :

13.2 mg. of the substance gave 9.34 mg. of silver bromide.

Found : Br = 30.11 %.

$C_{10}H_7O_4Br$ requires : Br = 29.52 %.

6,7-Dimethoxy-3-bromo-4-methylcoumarin.

The above monobromo derivative (2.7 g.) was refluxed in acetone (250 ml.) with dimethyl sulphate (2.5 ml.) and anhydrous potassium carbonate (7 g.) for 10 hours. The residue remaining after the removal of acetone was washed with sodium hydroxide solution. It crystallised from acetic acid in needles, m.p. 205-206°.

Analysis :

16.25 mg. of the substance gave 10.08 mg. of silver bromide.

Found : Br = 26.39 %.

$C_{12}H_{11}O_4Br$ requires : Br = 26.75 %.

The same product was obtained when 6,7-dimethoxy-4-methylcoumarin (2.2 g. ; 0.01 mole) was dissolved in acetic acid (30 ml.) and brominated with bromine in acetic acid (10 % ; 16 ml. ; 0.01 mole).

5,6-Dimethoxy-3-methylcoumarilic acid.

6,7-Dimethoxy-3-bromo-4-methylcoumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 15 ml.) for 2 hours on a steam bath. The product obtained on acidification with hydrochloric acid was purified through sodium bicarbonate solution. It crystallised from acetic acid in needles, m.p. 220°.

Analysis :

3.210 mg. of the substance gave 7.226 mg. of carbon dioxide and 1.518 mg. of water.

Found : C = 61.43 % ; H = 5.29 %.

$C_{12}H_{12}O_5$ requires : C = 61.01 % ; H = 5.08 %.

6,7-Dihydroxy-3,8-dibromo-4-methylcoumarin.

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in acetic acid by warming. Bromine (10 % ; 32 ml. ; 0.02 mole) in acetic acid was added drop-wise and the reaction mixture kept over-night. The solid obtained was crystallised from dilute alcohol in needles, m.p. 267°. Yield 2.0 g.

Analysis :-

20.88 mg. of the substance gave 22.12 mg. of silver bromide.

Found : Br = 45.10 %.

$C_{10}H_6O_4Br_2$ requires : Br = 45.71 %.

6,7-Dimethoxy-3,8-dibromo-4-methylcoumarin.

The above dibromo coumarin was methylated by refluxing its acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate as usual. m.p. 215-216°. Mixed m.p. with an authentic specimen of 6,7-dimethoxy-3,8-dibromo-4-methylcoumarin synthesised as described later (p 192) was not depressed.

Analysis :

12.018 mg. of the substance gave 12.090 mg. of silver bromide.

Found : Br = 42.81 %.

$C_{12}H_{10}O_4Br_2$ requires : Br = 42.33 %.

The same product was obtained when to 6,7-dimethoxy-4-methylcoumarin (2.2 g. ; 0.01 mole) in acetic acid (30 ml.) bromine (10 % ; 32 ml. ; 0.02 mole) in acetic acid was added drop-wise and the mixture was heated on a water bath for 4 hours.

5,6-Dimethoxy-7-bromo-3-methylcoumarilic acid

6,7-Dimethoxy-3,8-dibromo-4-methylcoumarin (0.2 g.) was refluxed with alcoholic potassium hydroxide (10 % ; 30 ml.) for 2 hours on a steam bath. The product which separated on acidification was purified through sodium

bicarbonate solution. It crystallised from dilute alcohol in needles, m.p. 270-272°.

Analysis :

8.314 mg. of the substance gave 4.990 mg. of silver bromide.

Found : Br = 25.54 %.

$C_{12}H_{11}O_5Br$ requires : Br = 25.40 %.

7-Methoxy-6-hydroxy-3-bromo-4-methylcoumarin

7-Methoxy-6-hydroxy-4-methylcoumarin (2.06 g. ; 0.01 mole) was dissolved in acetic acid (100 ml.) and to this solution, bromine in acetic acid (10 % ; 16 ml. ; 0.01 mole) was added. The mixture was stirred at room temperature for 2 hours and the solid which separated crystallised from alcohol in needles, m.p. 237-238°. Yield 2.1 g.

Analysis :

9.82 mg. of the substance gave 6.60 mg. of silver bromide.

Found : Br = 28.60 %.

$C_{11}H_9O_4Br$ requires : Br = 28.06 %.

The above brompcoumarin was methylated by refluxing its acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate as usual when 6,7-dimethoxy-3-bromo-4-methylcoumarin described before was obtained.

7-Methoxy-6-hydroxy-3,5-dibromo-4-methylcoumarin

7-Methoxy-6-hydroxy-4-methylcoumarin (2.06 g. ; 0.01 mole) was dissolved in acetic acid (200 ml.) and

bromine in acetic acid (10 % ; 64 ml. ; 0.04 mole) was added. The reaction mixture was heated on a steam bath for 4 hours. The product which separated on keeping the reaction mixture over-night in a refrigerater crystallised from alcohol in needles, m.p. 200°. Yield 0.5 g.

Analysis :

14.30 mg. of the substance gave 14.88 mg. of silver bromide.

Found : Br = 44.28 %.

$C_{11}H_8O_4Br_2$ requires : Br = 43.96 %.

6,7-Dimethoxy-3,5-dibromo-4-methylcoumarin

The above dibromocoumarin (0.5 g.) in benzene (100 ml.) was refluxed with anhydrous potassium carbonate (2 g.) and dimethyl sulphate (0.7 ml.) on a steam bath for 10 hours. The product obtained on removal of benzene was crystallised from benzene-petroleum ether (40-60°) mixtured in needles, m.p. 195-196°.

Analysis :

11.186 mg. of the substance gave 11.292 mg. of silver bromide.

Found : Br = 42.95 %.

$C_{12}H_8O_4Br_2$ requires : Br = 42.33 %.

5,6-Dimethoxy-4-bromo-3-methylcoumarilic acid

The above dibromo coumarin (0.2 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 20 ml.) for 2 hours on a steam bath. The product obtained on acidification crystallised from acetic acid in needles,

m.p. 240-245° (decomp.).

Analysis :

14.14 mg. of the substance gave 8.38 mg. of silver bromide.

Found : Br = 25.22 %.

$C_{12}H_{11}O_5Br$ requires : Br = 25.40 %.

7-Hydroxy-8-bromo-4-methylcoumarin

To a mixture of 2-bromoresorcinol (1.9 g. ; 0.01 mole) prepared according to Davis and Herrington (J. Am. Chem. Soc., 1934, 56, 129) and ethylacetoacetate (1.6 ml. ; 0.012 mole), sulphuric acid (80 % ; 10 ml.) was slowly added. The reaction mixture was allowed to stand over-night. The solid which separated on pouring the reaction mixture over crushed ice was purified through sodium hydroxide solution. It crystallised from acetic acid in needles, m.p. 255-257°. Yield 1.9 g. Chakravarti and Mukerjee (J. Ind. Chem. Soc., 1937, 14, 729) give m.p. 251-252°. This bromocoumarin was very sparingly soluble in acetic acid and alcohol.

Analysis :

10.374 mg. of the substance gave 7.630 mg. of silver bromide.

Found : Br = 31.37 %.

$C_{10}H_7O_3Br$ requires : Br = 31.30 %.

7-Methoxy-8-bromo-4-methylcoumarin

The above bromocoumarin (1 g.) was methylated in acetone solution with dimethyl sulphate (1 g.) in presence of anhydrous potassium carbonate (2 g.) as usual. It crystallised from dilute acetic acid in needles, m.p. 206-208°.

Analysis :

10.130 mg. of the substance gave 7.142 mg. of silver bromide.

Found : Br = 30.00 %.

$C_{11}H_9O_3Br$ requires : Br = 29.74 %.

7-Methoxy-6-hydroxy-8-bromo-4-methylcoumarin

7-Methoxy-8-bromo-4-methylcoumarin (2.7 g. ; 0.01 mole) was dissolved in sodium hydroxide solution (10 % ; 30 ml.) by warming on a steam bath. The solution was then cooled and potassiun persulphate solution (3 g. in 60 ml. of water) was added drop-wise during 2 hours. The product obtained on working up as usual was crystallised from dilute alcohol, m.p. 220-221°. Yield 0.5 g.

Analysis :

10.036 mg. of the substance gave 6.650 mg. of silver bromide.

Found : Br = 28.20 %.

$C_{11}H_9O_4Br$ requires : Br = 28.06 %.

7-Methoxy-6-hydroxy-3,8-dibromo-4-methylcoumarin

To 7-methoxy-6-hydroxy-8-bromo-4-methylcoumarin (0.3 g. ; 0.001 mole) in acetic acid (10 ml.) bromine in acetic acid (10 % ; 2 ml. ; 0.001 mole) was added. The solid which separated on keeping for a few hours crystallised from alcohol as yellow needles, m.p. 253-254°. Yield 0.2 g.

Analysis :

9.450 mg. of the substance gave 9.868 mg. of silver bromide.

Found : Br = 44.50 %.

$C_{11}H_8O_4Br_2$ requires : Br = 43.96 %.

The above dibromocoumarin (0.5 g.) was methylated as usual with dimethyl sulphate (0.5 ml.) in presence of anhydrous potassium carbonate (2 g.) . It crystallised from acetic acid in needles, m.p. 215-216°.

Nitration of 6,7-dimethoxy-4-methylcoumarin : 6,7-dimethoxy-3-nitro-4-methylcoumarin.

6,7-Dimethoxy-4-methylcoumarin (2.2 g. ; 0.01 mole) was dissolved in acetic acid (15 ml.) and a mixture of concentrated nitric acid (1 ml.) and acetic acid (6 ml.) was added with stirring. A yellow crystalline product separated within 20 minutes. The reaction mixture was stirred for one hour and then poured over crushed ice. The solid obtained crystallised from acetic acid in yellow needles, m.p. 215-217°. Yield 2.0 g.

Analysis :

7.822 mg. of the substance gave 0.347 ml. of nitrogen at 35.4° and 760 mm.

Found : N = 4.92 % .

$C_{12}H_{11}O_6N$ requires : N = 5.20 %.

6,7-Dihydroxy-3-nitro-4-methylcoumarin

6,7-Dimethoxy-3-nitro-4-methylcoumarin (1 g.) was dissolved in acetic anhydride (10 ml.) and the solution cooled. To this cooled solution hydriodic acid (10 ml. ; d. 1.7) was added cautiously drop-wise. The reaction mixture

was heated in an oil bath at 130-140° for 2 hours and then poured in saturated solution of sodium bisulphite. The solution was then extracted with ether and the residue obtained after removal of ether crystallised from dilute acetic acid in needles, m.p. 229-230°. It gave a green colouration with alcoholic ferric chloride.

Analysis :

9.260 mg. of the substance gave 0.505 ml. of nitrogen at 34° and 756 mm.

Found : N = 6.03 %.

$C_{10}H_7O_6N$ requires : N = 5.91 %.

Hydrolysis of 6,7-dimethoxy-3-nitro-4-methylcoumarin with liquor ammonia : 2-Hydroxy-4,5-dimethoxy acetophenone.

6,7-Dimethoxy-3-nitro-4-methylcoumarin (1 g.) was heated under reflux with liquor ammonia (60 ml.) for 2 hours on a steam bath. The mixture was cooled and acidified with concentrated hydrochloric acid. The product from the ether extraction of the reaction mixture was further purified from benzene. It crystallised from water in needles, m.p. 112-114°. Mixed m.p. with an authentic specimen synthesised according to Bargellini and Aureli (Atti-R. Accadφ. Lincei, 1911, V, 20, 118) was not depressed. It gave a violet colouration with alcoholic ferric chloride.

6,7-Dimethoxy-3-amino-4-methylcoumarin

6,7-Dimethoxy-3-nitro-4-methylcoumarin (2.6 g. ; 0.01 mole) and stannous chloride (14 g.) was heated with concentrated hydrochloric acid (100 ml.) on a wire-gauze

for 3 hours. The solution was basified with liquor ammonia. The emulsion obtained was extracted with ether. The solid obtained on removal of ether crystallised from benzene - petroleum ether (40-60°) mixture in fine silky needles, m.p. 164-165°. Yield 1.3 g.

Analysis :

8.46 mg. of the substance gave 0.426 ml. of nitrogen at 34° and 757 mm.

Found : N = 5.57 %.

$C_{12}H_{13}O_4N$ requires : N = 5.96 %.

6,7-Dimethoxy-3-hydroxy-4-methylcoumarin

To 6,7-dimethoxy-3-amino-4-methylcoumarin (1.2 g.) hydrochloric acid (4 ml.) and water (24 ml.) was added. This solution was heated in a sealed tube at 150-160° for 4 hours. The brown needles which separated on cooling recrystallised from alcohol in cubes m.p. 210-212°. Yield 0.6 g. The substance gave a green colouration with alcoholic ferric chloride.

Analysis :

4.818 mg. of the substance gave 10.758 mg. of carbon dioxide and 2.076 mg. of water.

Found : C = 60.93 % ; H = 4.82 %.

$C_{12}H_{12}O_5$ requires : C = 61.00 % ; H = 5.08 %.

Nitration of 7-methoxy-6-hydroxy-4-methylcoumarin :

7-Methoxy-6-hydroxy-5-nitro-4-methylcoumarin.

7-Methoxy-6-hydroxy-4-methylcoumarin (2.1 g. ; 0.01 mole) was suspended in acetic acid (40 ml.) and a mixture of concentrated nitric acid (1 ml.) and acetic acid

(6 ml.) was added drop-wise at room temperature and the reaction mixture stirred for 2 hours. Reddish brown needles separated. These were recrystallised from alcohol in needles, m.p. 220-222° (decomp.)

Analysis :

7.136 mg. of the substance gave 0.337 ml. of nitrogen at 35° and 760 mm.

Found : N = 5.23 %.

$C_{11}H_9O_6N$ requires : N = 5.57 %.

The above nitrocoumarin (1 g.) could not be hydrolysed by boiling with liquor ammonia (60 ml.) on a steam bath for 2 hours.

Elbs Persulphate Oxidation of 7-methoxy-8-nitro-4-methylcoumarin : 7-Methoxy-6-hydroxy-8-nitro-4-methylcoumarin.

7-Methoxy-8-nitro-4-methylcoumarin (1 g.) was dissolved in sodium hydroxide solution (10 % ; 20 ml.) by warming. The solution was cooled and potassium persulphate (2 g. in 40 ml. water) was added drop-wise with stirring for 3 hours. Next day it was worked up as usual. The product obtained crystallised from dilute alcohol. It started decomposing at 235° and finally melted at 260° with effervescence.

Analysis :

8.160mg. of the substance gave 0.416 ml. of nitrogen at 34° and 757 mm.

Found : N = 5.65 %.

$C_{11}H_9O_6N$ requires : N = 5.57 %.

Formylation of 6-hydroxy-7-methoxy-4-methylcoumarin : 6-Hydroxy-5-formyl-7-methoxycoumarin

6-Hydroxy-7-methoxy-4-methylcoumarin (2.06 g. ; 0.01 mole) dissolved in acetic acid (20 ml.) was treated with hexamine (4 g.). It was gently heated on a steam bath for 4 hours and then treated with hydrochloric acid (1 : 1 ; 75 ml.) and further heated for 1 hour. Next day it was diluted with water and extracted with ether. On removal of ether a yellow solid was obtained. This crystallised from dilute alcohol in greenish yellow needles, m.p. 240°. It gave violet colouration with alcoholic ferric chloride.

Analysis :

4.092 mg. of the substance gave 9.276 mg. of carbon dioxide and 1.552 mg. of water.

Found : C = 61.86 % ; H = 4.24 %.

$C_{12}H_{10}O_5$ requires : C = 61.55 % ; H = 4.27 %.

The 2,4-dinitrophenyl hydrazone

It was prepared as usual and crystallised from alcohol as reddish brown needles, m.p. 250-255° (decomp.)

Analysis :

6.52 mg. of the substance gave 0.758 ml. of nitrogen at 30° and 762 mm.

Found : N = 13.14 %.

$C_{18}H_{14}O_8N_4$ requires : N = 13.53 %.

Some other attempted reactions

Iodination of 6,7-dihydroxy-4-methylcoumarin and its mono methylether

(a) With iodine and ammonia

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) dissolved in ammonia (22 % ; 10 ml.) and water (35 ml.) was treated drop-wise with iodine (2.54 g. ; 0.01 mole) in potassium iodide (5 g.) solution with vigorous stirring of the reaction mixture for 15 minutes. It was then poured into ice cold dilute sulphuric acid. No product could be isolated from this solution.

(b) With iodine and iodic acid

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in warm alcohol (40 ml.) and iodine crystals (1.01 g. ; 0.004 mole) were added. To this clear solution iodic acid (0.35 g.) dissolved in minimum quantity of water was then added and the mixture stirred for 3 hours. The solution on dilution did not give any product.

(c) With iodine monochloride

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) in acetic acid (20 ml.) and hydrochloric acid (10 ml. d. 1 : 1) was treated with iodine monochloride (1.62 g. ; 0.01 mole) and the reaction mixture left over-night at 60° in an oven. It was then diluted with water. The separated product was found to be the original coumarin.

Attempts to iodinate 6-hydroxy-7-methoxy-4-methyl-coumarin under the same conditions as (a), (b) and (c) above did not succeed. In (a) and (b) the original coumarin was

obtained and in (c) a chloro (→ iodo) derivative which has not been investigated further.

Attempted chloromethylation of 6,7-dihydroxy-4-methylcoumarin and its mono and dimethyl ethers

(a) 6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in acetic acid (20 ml.) by warming. Paraformaldehyde (0.3 g.) was added and the clear solution was saturated with hydrogen chloride for 2 hours at room temperature. The product which separated on cooling the reaction mixture was sparingly soluble in organic solvents such as acetone, benzene, alcohol and acetic acid. It did not melt on a spatula.

(b) 6-Hydroxy-7-methoxy-4-methylcoumarin on chloromethylation under the above conditions gave a paste from which no pure product could be obtained.

(c) ?.?- Methylene-bis-(6,7-dimethoxy-4-methylcoumarin

6,7-Dimethoxy-4-methylcoumarin (2.2 g. ; 0.01 mole) was dissolved in acetic acid (10 ml.) and treated with paraformaldehyde (0.3 g. ; 0.01 mole) and the solution saturated with dry hydrogen chloride for 1 hour. Needles separated within a short time. Recrystallised from acetic acid in needles, m.p. 325°. Yield 1.5 g. This may be a methylene-bis-(6,7-dimethoxy-4-methylcoumarin) compound as it did not contain any chlorine and gave the following analysis.

Analysis :

4.254 mg. of the substance gave 10.316 mg. of carbon dioxide and 1.970 mg. of water.

Found : C = 66.18 % ; H = 5.18 %.

$C_{25}H_{24}O_4$ requires : C = 66.37 % ; H = 5.31 %.

Friedel-Crafts acetylation of 6,7-dihydroxy-4-methylcoumarin and its monomethyl ether

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in nitrobenzene (20 ml.) and treated with acetic anhydride (1.02 ml. ; 0.01 mole). Aluminium chloride (1.6 g. ; 0.012 mole) in nitrobenzene (10 ml.) was then added and the reaction mixture heated at 120° for 4 hours. The mixture was treated with dilute ice cold hydrochloric acid (1 : 1) and nitrobenzene was steam distilled. The separated product was found to be the original coumarin. No C-acetyl derivative was obtained even when the reaction was carried out at 180°.

Friedel-Crafts reaction on 6-hydroxy-7-methoxy-4-methylcoumarin under the above conditions gave 6,7-dihydroxy-4-methylcoumarin.

Fries migration of 6-acetoxy-7-methoxy-4-methylcoumarin

6-Acetoxy-7-methoxy-4-methylcoumarin (2.48 g. ; 0.01 mole) was mixed with aluminium chloride (1.6 g. ; 0.01 mole) and heated at 120° for 2 hours. It was then treated with hydrochloric acid (1 : 1). The solid obtained was found to be 6-hydroxy-7-methoxy-4-methylcoumarin.

When the above reaction was carried out in nitro benzene solution the same product was obtained.

Attempted formylation of 6,7-dihydroxy-4-methylcoumarin

6,7-Dihydroxy-4-methylcoumarin (1.92 g. ; 0.01 mole) was dissolved in acetic acid (30 ml.) and treated with hexamine (4 g.). Then it was gently heated on a water bath for 4 hours. Hydrochloric acid (1 : 1 ; 75 ml.) was added and it was further heated on a steam bath for 1 hour. Next day it was poured in water and extracted with ether, the solid obtained was found to be the original coumarin.

Attempted formylation of 6,7-dimethoxy-4-methylcoumarin

6,7-Dimethoxy-4-methylcoumarin (2.2 g. ; 0.01 mole) dissolved in acetic acid (10 ml.) was treated with hexamine (4 g.). It was gently heated on a steam bath when needles which separated crystallised from acetic acid m.p. 325°. Yield 0.8 g. Mixed m.p. with the product obtained in the chloromethylation of 6,7-dimethoxy-4-methylcoumarin described above was not depressed.