

## STUDIES IN ELBS PERSULPHATE OXIDATION. PART I. OXIDATION OF SOME COUMARIN DERIVATIVES

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4-Methylcoumarin, 7-methoxy-4-methylcoumarin, 5-methoxy-4:7-dimethylcoumarin, 5:7-dimethoxy-4-methylcoumarin and 7:8-dimethoxy-4-methylcoumarin have been oxidised with potassium persulphate in alkaline solution and the corresponding 6-hydroxycoumarin derivatives are obtained in good yields. The methyl ethers have been demethylated and the hitherto unknown 5:6-dihydroxy-4:7-dimethyl-, 5:6:7-trihydroxy-4-methyl-, and 6:7:8-trihydroxy-4-methylcoumarins have been obtained. The completely methylated coumarins are dissolved by opening out the  $\alpha$ -pyrone ring by warming on a steam-bath and then oxidised with potassium persulphate. In actual practice therefore it is the *o*-hydroxycinnamic acid derivative which is oxidised in each case, the coumarin ring being formed again when the reaction mixture is acidified.

Elbs (*J. prakt. Chem.*, 1893, 48, 179) oxidised *o*-nitrophenol to nitroquinol by the action of ammonium persulphate in presence of alkali. Later, potassium persulphate was substituted for ammonium persulphate and the reaction extended to other substituted phenols (D.R.P., 81,068; 81,297; 81,298. Chemische Fabrik Auf Aktien-vorm. E. Schering. See Friedländer, "Fortschritte der Teerfarben Fabrikation", 1894-1897, Part IV, pp. 126, 127 and 121 respectively).

This reaction has been successfully applied by a number of workers to various derivatives of phenols like aldehydes, ketones and acids (Neubauer and Flatow, *Z. physiol. Chem.*, 1907, 52, 375; Bargellini and Aureli, *Atti. R. Accad. Lincei*, 1911, 20, 118; Bargellini, *Gazzetta*, 1915, 45, 90; Hodgson and Beard, *J. Chem. Soc.*, 1927, 2339; Baker and co-workers, *ibid.*, 1938, 1602; 1939, 959, 1922; 1941, 667, 669; and others). Baker and Brown (*J. Chem. Soc.*, 1948, 2303) have worked out the general reaction conditions and have also suggested a mechanism for this reaction. Seshadri and his co-workers (*Proc. Ind. Acad. Sci.*, 1947, 28A, 417, 427, 432, 444 *et seq.*) have in recent years successfully applied this method extensively to the flavones and synthesised a large number of natural flavones. The oxidation in all these cases is found to take place in the *para* position to the hydroxyl group if that position is free, and in the *ortho* position, if the *para* position is occupied. In the latter case the yields are very poor.

As a part of the systematic study of the reactivity of coumarin derivatives, which is being actively pursued in these laboratories, it was thought of interest to study systematically the application of this reaction to coumarin derivatives.

Only a few coumarins have been previously subjected to this reaction. Bargellini and Monti (*Gazzetta*, 1915, 45, 90) oxidised coumarin and 7-methoxycoumarin. Wessely and Demmer (*Ber.*, 1929, 62, 120) oxidised 7:8-dimethoxycoumarin and 7-methoxy-8-ethoxycoumarin, and Mauthner (*J. prakt. Chem.*, 1939, 182, 23) oxidised 8-methoxycoumarin. In all the cases 6-hydroxycoumarin derivatives were obtained. The reaction has now been applied to a number of coumarin derivatives. Preliminary investigations

carried out with hydroxycoumarins showed that generally pasty uncrystallisable products were obtained and wherever a definite product could be isolated, the yield of the oxidation product was very poor. As the oxidation is carried out in alkaline medium the  $\alpha$ -pyrone ring is likely to open out and the additional hydroxy group, so formed, may not only help general oxidation, but it may also lead to a mixture of different products in oxidation. In view of this it was decided to first study the oxidation of completely methylated coumarin derivatives.

4-Methylcoumarin, 7-methoxy-4-methylcoumarin, 5-methoxy-4:7-dimethylcoumarin, 5:7-dimethoxy-4-methylcoumarin and 7:8-dimethoxy-4-methylcoumarin have been oxidised, the oxidation being carried out in all cases according to the general reaction method given by Baker and Brown (*loc.cit.*).

4-Methylcoumarin on oxidation gave the known 6-hydroxy-4-methylcoumarin as shown by direct comparison with an authentic specimen prepared by the Pechmann method. 7-Methoxy-4-methylcoumarin gave 6-hydroxy-7-methoxy-4-methylcoumarin which on demethylation with hydriodic acid gave the known 6:7-dihydroxy-4-methylcoumarin which was also obtained in a very poor yield by the oxidation of 7-hydroxy-4-methylcoumarin. That the oxidation has taken place in the 6 position is shown by the fact that the dihydroxy compound obtained on demethylation has m.p. 275°, identical with the known 6:7-dihydroxy-4-methylcoumarin (Appel, *J. Chem. Soc.*, 1935, 1031). The isomeric 7:8-dihydroxy-4-methylcoumarin has m.p. 235° (Pechmann and Duisberg, *Ber.*, 1883, 16, 2122); Bargellini and Martegiani (*Gazzetta*, 1911, 41, 612) obtained on methylation of 6:7-dihydroxy-4-methylcoumarin, the dimethyl ether (m.p. 130-34°) and a monomethyl ether (m.p. 173-75°) to which the constitution was not assigned. As 6-hydroxy-7-methoxy-4-methylcoumarin obtained in this work has m.p. 209°, the monomethyl ether of Bargellini and Martegiani is very likely 6-methoxy-7-hydroxy-4-methylcoumarin. Baker and Evans (*J. Chem. Soc.*, 1938, 374), however, give m.p. 213° for this compound. 5-Methoxy-4:7-dimethylcoumarin, 7:8-dimethoxy-4-methylcoumarin and 5:7-dimethoxy-4-methylcoumarin on oxidation gave products to which the structures of 5-methoxy-6-hydroxy-4:7-dimethylcoumarin, 7:8-dimethoxy-6-hydroxy-4-methylcoumarin and 5:7-dimethoxy-6-hydroxy-4-methylcoumarin respectively have been assigned by analogy with the previous work. All these coumarin derivatives are found to give a deep yellow solution with caustic alkalis as given by the known 6-hydroxycoumarin derivatives. The methoxycoumarins have been demethylated with hydriodic acid and the hitherto unknown 5:6-dihydroxy-4:7-dimethyl-, 6:7:8-trihydroxy-4-methyl-, and 5:6:7-trihydroxy-4-methylcoumarins have been obtained. In the case of 5-hydroxycoumarins the hydroxy compounds were again methylated and compared with the completely methylated coumarins and were found to be the same. This was done in order to find out if the ring had opened out and closed again in the other direction, as it sometimes happens in the case of flavones.

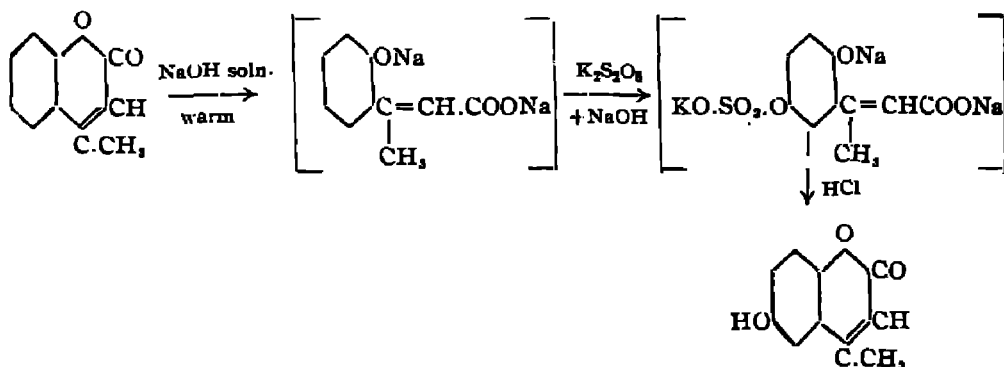
The completely methylated coumarins are naturally not soluble in cold alkali and the reaction does not proceed when they are merely suspended in alkali. It has been found that if the methoxycoumarins are warmed on a steam-bath with 10% alkali for some time, they go into solution, presumably because the  $\alpha$ -pyrone ring opens out and an  $\alpha$ -hydroxycinnamic acid derivative is formed. The position *para* to the hydroxy group

formed by the opening of the ring is the 6 position in the original coumarin and therefore oxidation takes place in this position. In actual practice therefore, it is the *o*-hydroxycinnamic acid derivative which is oxidised, the coumarin ring being formed again when the reaction mixture is acidified. The successful oxidation of the coumarin derivatives therefore depends on this technique of opening out the  $\alpha$ -pyrone ring of the methoxycoumarin derivatives. The following table gives the yields of the oxidation products.

TABLE I

	Starting material recovered.	Yield of the oxidation product. % of the theoretical	
		on the basis of the starting material.	allowing for the recovery.
1. 4-Methyl-	25%	41.7	45.4
2. 7-Methoxy-4-methyl-	31.3	17.3	25.2
3. 5-Methoxy-4 : 7-dimethyl-,	12.1	40	53.9
4. 5 : 7-Dimethoxy-4-methyl-	25	24.7	33.6
5. 7 : 8-Dimethoxy-4-methyl-	20.5	25.4	32

The work is being extended to the synthesis of several unknown and natural coumarins.



### EXPERIMENTAL

*Oxidation of 4-Methylcoumarin : 6-Hydroxy-4-methylcoumarin.*—4-Methylcoumarin (2.4 g.), prepared according to Woodruff ("Organic Synthesis", Vol. 24, p. 69) was dissolved in sodium hydroxide (3 g. in 30 c.c. water) by heating on a steam-bath. The solution was then cooled and potassium persulphate (4.5 g. in 100 c.c.) was added gradually from a separating funnel during 3 hours. The solution was mechanically stirred and the temperature was not allowed to rise above 10°. After the addition was complete the reaction mixture was stirred for half an hour more and left overnight. Next day it was just acidified with concentrated hydrochloric acid when some product (0.4 g.)

separated which was found to be the original coumarin. The filtrate was extracted with ether when a further quantity (0.2 g.) of the original coumarin was obtained. To the aqueous layer more hydrochloric acid (conc., 50 c.c.) was added and the solution heated on a steam-bath for 40 minutes. The solution was cooled and the product which separated out was filtered and crystallised from rectified spirit in plates (0.9 g.), m.p. 242°. Mixed m.p. with an authentic specimen of 6-hydroxy-4-methylcoumarin, prepared by the Pechmann method from quinol (Borsche, *Ber.*, 1907, 40, 2732), was not depressed. The filtrate was extracted with ether and the ethereal layer gave a further quantity (0.2 g.) of the oxidised product. The oxidation product dissolved in sodium hydroxide to give a deep yellow solution.

*Oxidation of 7-Methoxy-4-methylcoumarin*: 6-Hydroxy-7-methoxy-4-methylcoumarin.—7-Hydroxy-4-methylcoumarin (Pechmann and Duisberg, *Ber.*, 1883, 16, 2122) was methylated according to Limaye and Bhide (*Rasayanam*, 1938, 138). 7-Methoxy-4-methylcoumarin (6.4 g.) was dissolved in sodium hydroxide (7 g. in 70 c.c. of water) by heating on a steam-bath and oxidised with potassium persulphate (9.9 g. in 200 c.c. of water). The reaction mixture was worked up as before. The product (2 g.) which came down on just acidifying the solution was found to be the original coumarin. The product which was obtained after heating with excess of hydrochloric acid (conc., 150 c.c.) was crystallised from dilute alcohol in needles (1.2 g.), m.p. 208-209°. (Found: C, 64.3; H, 4.7.  $C_{11}H_{10}O_4$  requires C, 64.1; H, 4.9 per cent). The substance dissolves in sodium hydroxide to give a deep yellow solution.

6:7-Dimethoxy-4-methylcoumarin.—The above coumarin (0.5 g.) was dissolved in dry acetone (50 c.c.) and refluxed for 20 hours with methyl iodide (3 c.c.) and anhydrous potassium carbonate (1 g.). The reaction mixture was then filtered and the product obtained on removal of acetone was crystallised from very dilute alcohol in needles (0.3 g.), m.p. 133-34°. (Found: C, 65.5; H, 5.0. Calc. for  $C_{12}H_{12}O_4$ : C, 65.5; H, 5.5 per cent). Bargellini and Martegiani (*loc. cit.*) give m.p. 130-34°.

6:7-Dihydroxy-4-methylcoumarin.—6-Hydroxy-7-methoxy-4-methylcoumarin (0.5 g.) was heated with acetic anhydride (5 c.c.) and hydriodic acid (*d* 1.7, 5 c.c.) in an oil-bath at 130°-140° for 2 hours and the reaction mixture poured in cold sodium bisulphite solution. The product obtained was crystallised from rectified spirit in needles (0.3 g.), m.p. 275°. (Found: C, 62.4; H, 4.2. Calc. for  $C_{10}H_8O_4$ : C, 62.5; H, 4.1 per cent). Appel (*loc. cit.*) gives the same m.p. Bargellini and Martegiani (*loc. cit.*) give m.p. 269°. The product dissolves in sodium hydroxide to give an orange solution and it gives a green colour with alcoholic ferric chloride. This coumarin was also obtained in a very poor yield by the oxidation of 7-hydroxy-4-methylcoumarin (4.4 g.) in sodium hydroxide (5 g. in 50 c.c. of water) solution with potassium persulphate (7 g. in 150 c.c. of water) and working up the reaction mixture as usual.

*Oxidation of 5-Methoxy-4:7-dimethylcoumarin*: 6-Hydroxy-5-methoxy-4:7-dimethylcoumarin.—5-Hydroxy-4:7-dimethylcoumarin (Pechmann and Cohen, *Ber.*, 1884, 17, 2187) (6 g.) was methylated in acetone solution with methyl iodide (10 c.c.) in presence of potassium carbonate as usual by refluxing for 20 hours, m.p. 147°, yield 5.8 g. Collie and Chrystall (*J. Chem. Soc.*, 1907, 91 1805) give m.p. 146°.

5-Methoxy-4:7-dimethylcoumarin (5 g.) was dissolved in sodium hydroxide (5 g. in 50 c.c. of water) solution by warming on a steam-bath and oxidised as before with potassium persulphate (7.4 g. in 160 c.c. of water). On working up the reaction mixture the product, which came down on just acidification of the mixture, was found to be the starting material (0.7 g.). The product obtained on heating with excess of hydrochloric acid (conc., 150 c.c.) was crystallised from rectified spirit in tiny needles (2.5 g.), m.p. 175°. (Found: C, 65.0; H, 5.5.  $C_{12}H_{12}O_4$  requires C, 65.5; H, 5.5 per cent). It dissolves in alkali to give a deep yellow solution.

5:6-Dimethoxy-4:7-dimethylcoumarin.—The above coumarin (0.5 g.) was dissolved in acetone and refluxed for 24 hours with methyl iodide (3 c.c.) and anhydrous potassium carbonate (2 g.). The product obtained on working up the reaction mixture as before was crystallised from methyl alcohol in plates (0.3 g.), m.p. 96°. (Found: C, 66.5; H, 5.8.  $C_{12}H_{14}O_4$  requires C, 66.7; H, 6.0 per cent).

5:6-Dihydroxy-4:7-dimethylcoumarin.—6-Hydroxy-5-methoxy-4:7-dimethylcoumarin (0.6 g.) was dissolved in acetic anhydride (5 c.c.) and hydriodic acid (*d* 1.7, 5 c.c.) was added. The reaction mixture was heated in an oil-bath between 135° and 140° for 2 hours. The product, obtained on pouring the reaction mixture in sodium bisulphite solution, was crystallised from rectified spirit in tiny needles (0.4 g.), m.p. 260°. (Found: C, 63.8; H, 4.4.  $C_{11}H_{10}O_4$  requires C, 64.1; H, 4.9 per cent). It gives a deep red solution with alkali and a brownish coloration with alcoholic ferric chloride. This hydroxy-coumarin was methylated again by the methyl iodide-potassium carbonate method when 5:6-dimethoxy-4:7-dimethylcoumarin was obtained, as seen by direct comparison.

Oxidation of 5:7-Dimethoxy-4-methylcoumarin: 6-Hydroxy-5:7-dimethoxy-4-methyl coumarin.—5:7-Dihydroxy-4-methylcoumarin (Pechmann and Cohen, *loc. cit.*) was methylated with dimethyl sulphate and alkali (Head and Robertson, *J. Chem. Soc.*, 1931, 1258). The dimethoxycoumarin (10 g.) was dissolved in sodium hydroxide (9 g. in 90 c.c. of water) by heating on a steam-bath and oxidised with potassium persulphate (13 g. in 260 c.c. of water) as before. The product (2.5 g.) which came down on just acidification was found to be the starting material. The product, obtained on heating with excess of hydrochloric acid (conc., 200 c.c.), was crystallised from dilute alcohol in square plates (2.65 g.), m.p. 195°. (Found: C, 61.3; H, 5.0.  $C_{12}H_{12}O_5$  requires C, 61.0; H, 5.1 per cent). It dissolves in alkali to give a deep yellow solution.

5:6:7-Trimethoxy-4-methylcoumarin was prepared from the above coumarin (0.8 g.), methyl iodide (5 c.c.) and anhydrous potassium carbonate (1.5 g.) as usual and was crystallised from dilute alcohol in thin plates (0.6 g.), m.p. 115-16°. (Found: C, 62.5; H, 5.3.  $C_{13}H_{14}O_6$  requires C, 62.4; H, 5.6 per cent).

5:6:7-Trihydroxy-4-methylcoumarin.—6-Hydroxy-5:7-dimethoxy-4-methylcoumarin (0.5 g.) was heated with acetic anhydride (5 c.c.) and hydriodic acid (*d* 1.7, 4 c.c.) at 135°-140° for 3 hours. The product, obtained on pouring the reaction mixture in sodium bisulphite solution, was crystallised from rectified spirit in needles (0.3 g.), m.p. 278°. (Found: C, 57.8; H, 3.9.  $C_{10}H_8O_6$  requires C, 57.6; H, 3.8 per cent). It dissolves in alkali to give a brown solution with intense green fluorescence and gives a violet colour with alcoholic ferric chloride.

This hydroxycoumarin was methylated again by the methyl iodide-potassium carbonate method when 5:6:7-trimethoxy-4-methylcoumarin was obtained, as seen by direct comparison.

*Oxidation of 7:8-Dimethoxy-4-methylcoumarin: 6-Hydroxy-7:8-dimethoxy-4-methylcoumarin.*—7:8-Dihydroxy-4-methylcoumarin (Pechmann and Duisberg, *loc. cit.*) was methylated by the methyl iodide-potassium carbonate method and the dimethyl ether, m.p. 135°, was obtained. Sakai and Chotar (*J. Pharm. Soc. Japan*, 1935, 55, 691; *Chem. Abs.*, 1935, 29, 7311) give m.p. 132°.

The dimethoxycoumarin (4.4 g.) was dissolved in sodium hydroxide (4.0 g. in 40 c.c. of water) by warming and oxidised as before with potassium persulphate (5.9 g. in 125 c.c. of water). On working up the reaction mixture as before 0.9 g. of the original product was recovered. The oxidation product obtained was crystallised from alcohol in needles (1.2 g.), m.p. 179°. (Found: C, 60.9; H, 4.6.  $C_{12}H_{12}O_5$  requires C, 61.0; H, 5.1 per cent). It dissolves in alkali to give a deep yellow solution.

*6:7:8-Trimethoxy-4-methylcoumarin.*—The above coumarin (0.5 g.) was methylated with methyl iodide (3 c.c.) and potassium carbonate (1 g.) in acetone solution as usual and the product obtained was crystallised from dilute alcohol in square plates (0.35 g.), m.p. 113°. (Found: C, 61.8; H, 5.2.  $C_{13}H_{14}O_5$  requires C, 62.4; H, 5.6 per cent).

*6:7:8-Trihydroxy-4-methylcoumarin.*—6-Hydroxy-7:8-dimethoxy-4-methylcoumarin (0.7 g.) was heated with acetic anhydride (5 c.c.) and hydriodic (d 1.7, 5 c.c.) in an oil-bath at 135°-140° for 2 hours. The product obtained on working up as usual was crystallised from rectified spirit in needles (0.5 g.), m.p. 274-76°. (Found: C, 53.3; H, 4.3.  $C_{10}H_8O_6$ , 1  $H_2O$  requires C, 53.1; H, 4.4 per cent). It dissolves in alkali to give a deep orange solution and gives a deep blue coloration with alcoholic ferric chloride.

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