# NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

## Part XXXII. Some Coumarin Derivatives

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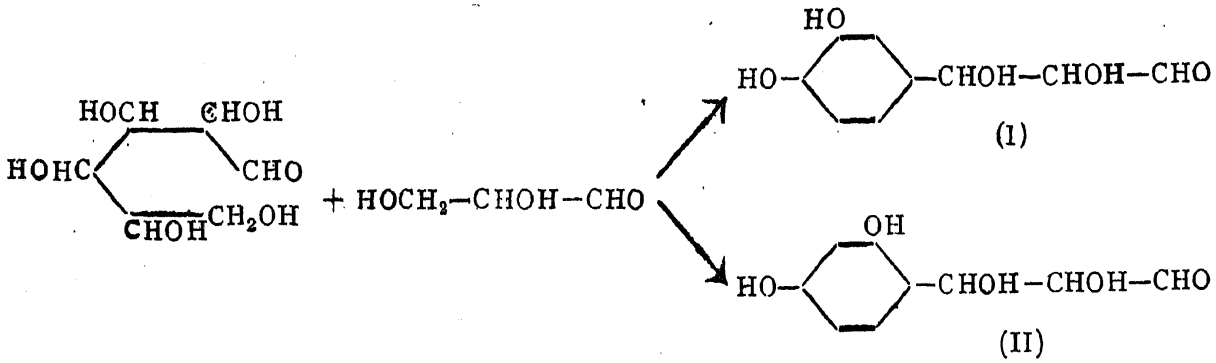
Received September 19, 1950

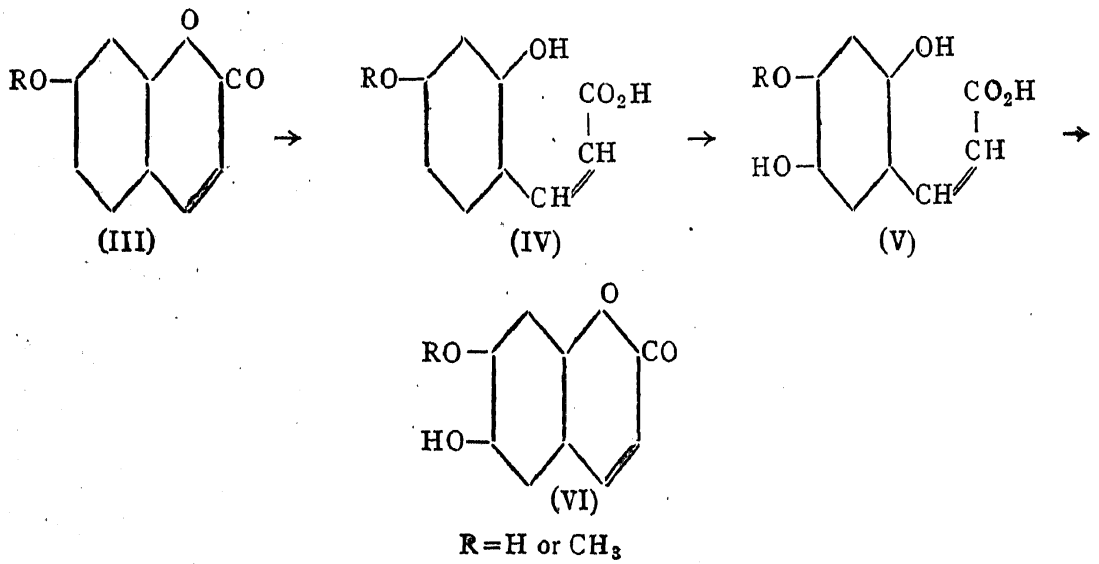
THE $C_6-C_3$ unit is not only present as a component of anthoxanthin and anthocyanin molecules, but it also exists in the form of a large number of simpler compounds. The $C_3$ side chain takes every possible form, amino acid in phenyl alanine derivatives, allyl and propenyl chains in components of essential oils, and other unsaturated forms in cinnamic acids, aldehydes and alcohols; phenyl propane derivatives are present in lignins. The lignane group of compounds represent combinations of two $C_6-C_3$ units. In all these there is a general resemblance in the nature and location of the substituents, hydroxyl and methoxyl groups in the benzene ring. According to Robinson[1] the catechol (3 : 4-dihydroxy phenyl) form (I) is the most fundamental and the others are derived from it by stages involving oxidation or reduction. As far as oxidation is concerned the validity of this suggestion has been supported by laboratory experiments with flavonols and allyl and propenyl benzene derivatives.[2]

There are however cases of anthoxanthins having the hydroxyl groups of the side phenyl nucleus in the 2′ and 4′ positions, *e.g.*, morin, cyanomaclurin, pterocarpin and homopterocarpin. Even rotenone may be considered to be derived from such a side phenyl nucleus. It was therefore suggested in one of our earlier publications[3] that as a less common alternative the resorcinol derivative (II) is also produced by the condensation of a hexose and triose and this undergoes changes in the same way as the catechol derivative. If the side chain gets transformed into a cinnamic acid, a coumarin will result. On this basis umbelliferone will represent the simplest member of the group and the others should be derived from it by processes involving oxidation and reduction. This idea appears to fit in with the common occurrence of 6 : 7 and 7 : 8-dihydroxy substituted compounds in coumarins, types which are not met with in the anthocyanin and anthoxanthin series. It is therefore developed here using laboratory experiments in support.

Bargellini[4] showed that umbelliferone methyl ether (III, $R = CH_3$) can be oxidised by means of alkaline persulphate to yield 7-methoxy-6-hydroxy



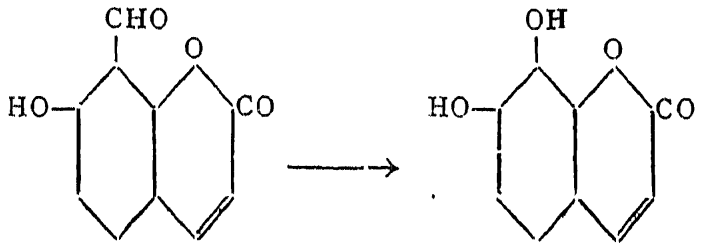

coumarin (VI). He did not give the yield; in our experiments about 20% yield is obtained. Obviously the reaction involves the formation of a coumarinic acid (IV) and its oxidation in the position *para* to the liberated hydroxyl group. In nature a stabler form in which the pyrone ring is open should be involved in this *para* oxidation. Consequently experiments have now been carried out employing the corresponding coumaric acid (umbellic acid methyl ether) for oxidation. The yield (about 25%) is not appreciably different. Umbelliferone (III, R = H) itself could be directly oxidised by this method to yield æsculetin (VI, R = H). Though the yield is rather low, this method is handy for getting free æsculetin readily.




Parallel series of experiments have now been carried out with 4-methyl umbelliferone and its methyl ether with ver similar results. That geometrical inversion takes place more readily in 4-methyl substituted coumarins has been pointed out earlier by Murti, Rao and Seshadri[5] and this knowledge has been used in our experiments. It may be mentioned here that 4-methyl æsculetin was subjected to partial methylation by Bargellini and Martegiani[6] who considered that the resulting monomethyl ether having m.p. 173–75° might be either the 7 or 6-monomethyl ether. No derivatives were described. The above authors used methyl iodide and methyl alcoholic potash at 100°. More recently Velluz and Amiard[7] have employed for this

partial methylation, dimethyl sulphate and aqueous sodium carbonate solution. They consider the product to be the 7-monomethyl ether and report its melting point as 208–9°, the acetate melting at 200–01°. We have been able to repeat their experiments and confirm their results. The product of oxidation of 4-methyl-7-methoxy coumarin melts also at 208–9° and yields an acetate melting at 199–200°; the mixed melting points were undepressed. Since on further methylation both yield 4-methyl æsculetin-dimethyl ether there is no doubt that they are correctly represented as 4-methyl-æsculetin-7-methyl ether.

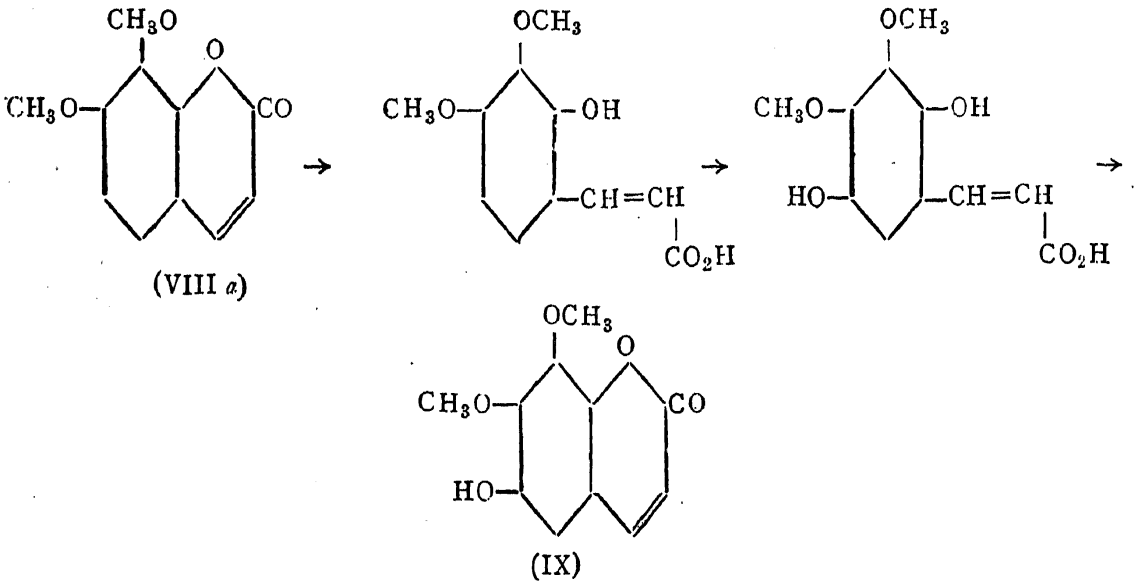
No experiment seems to have been made in the past to get daphnetin from umbelliferone. This has now been accomplished by adopting the two stage process of *ortho* nuclear oxidation. Umbelliferone condenses with hexamine to yield the 8-aldehyde (VII)[8] which undergoes smooth oxidation with alkaline hydrogen peroxide to give high yields of daphnetin (VIII). Similarly from 4-methyl-umbelliferone-8-aldehyde, 4-methyl daphnetin is made. These experiments suggest the possible biogenesis of æsculetin, daphnetin and their derivatives from umbelliferone by *para-* and *ortho-*oxidation respectively.




(VII) (VIII)

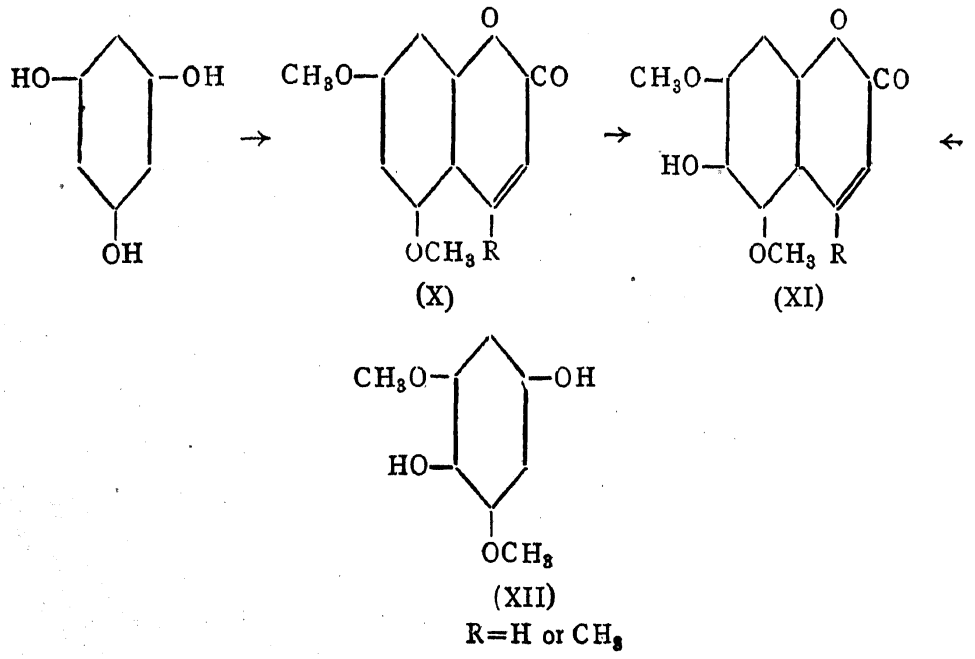
As compared with the anthocyanins and anthoxanthins, compounds containing the 6:7:8 arrangement of hydroxyl and methoxyl groups are markedly common in the coumarin group and are represented by fraxetin, fraxidin and isofraxidin. There are two ways in which they could be derived (i) *ortho* oxidation of æsculetin and its derivatives and (ii) *para* oxidation of daphnetin and its derivatives. Process (i) using scopoletin should be feasible and it is being studied. On the other hand, process (ii) using daphnetin dimethyl ether (VIII *a*) has already been examined by Bargellini.[9] He has recorded a yield of 10% of (IX). In our experiments using direct oxidation the yield was 15%, and introducing conversion to coumaric acid as an intermediate stage the yield was about 30%. On methylation it yields fraxetin dimethyl ether. The dimethyl ether of 4-methyl daphnetin gives similar yields of the oxidation product, 4-methyl-7:8-dimethoxy-6-hydroxy coumarin.

It should however be mentioned here that limettin (X, R=H) (5:7-dimethoxy coumarin) and derived compounds do not fall into line with the



(VIII *a*) (IX)

above scheme since no direct method of obtaining them from umbelliferone is known. They should therefore indicate the existence of an alternative process of evolution based on phloroglucinol and triose units. In laboratory synthesis they are obtained starting from phloroglucinol. On this basis fraxinol (XI, R = H) could be considered to be directly obtained from limettin by *para* oxidation in the 6-position. Though it is possible to obtain 5:6:7-trihydroxy (methoxy) coumarins from 6:7-dihydroxy compounds by partial methylation in the 7-position and *ortho*-oxidation in the 5-position, the structure of fraxinol with a free hydroxyl in the 6-position would support its biogenetic relationship with limettin. Experiments carried out on the direct *p*-oxidation of 4-methyl-limettin (X, R= $CH_3$) in alkaline solution gave only poor yields of the oxidation product. But when preliminary conversion is effected to produce the coumaric acid (4-methyl limettic acid) and then oxidation carried out, fair yields (20%) of 4-methyl fraxinol (XI,

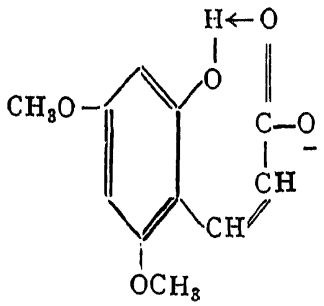


(X) (XI) (XII)

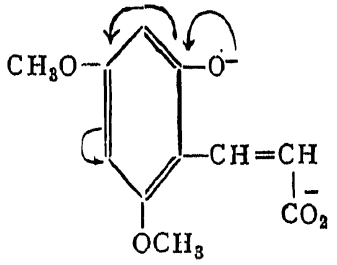
R=H or $CH_3$

R = $CH_3$) are obtained. It is most convenient to carry out the conversion, oxidation of the coumaric acid and final reconversion into coumarin all in one continuous operation. For purposes of comparison 4-methyl-fraxinol is now also synthesised using 2:6-dimethoxy-quinol (XII) and acetoacetic ester.

The yield of the pure products in the persulphate oxidation is generally poor in the coumarin series though in some cases the crude yields may be high. This seems to be partly due to the formation of coloured by-products. The difference in the behaviour of the *cis* and *trans* acids is marked in the case of disubstituted coumarins particularly when the 5- and 7-positions are occupied. A possible explanation of this observation may be the existence of hydrogen bond in the *cis* form (XIII) which will reduce the ionisation of the phenolic hydroxyl and the development of strong anionoid (nucleophilic) activity in the required *para* position.




(XIII)




(XIV)

## Experimental

Para- *oxidation of umbelliferone and 4-methyl umbelliferone*

To a stirred solution of umbelliferone (5 g.) in aqueous sodium hydroxide (4 g. in 100 c.c.), cooled in ice-water, was added dropwise with stirring a solution of sodium persulphate (7·2 g.) in water (100 c.c.) in the course of two hours. After twenty-four hours, the solution was just acidified with hydrochloric acid (congo red) when unchanged umbelliferone (1·5 g.) was precipitated. It was filtered and the filtrate extracted twice with ether to remove any traces of umbelliferone remaining in solution. Concentrated hydrochloric acid (60 c.c.) and sodium bisulphite (1 g.) were then added to the aqueous solution which was heated in a boiling water-bath for half an hour. On cooling the solution æsculetin was obtained as a dark brown precipitate. It was filtered and purified by repeated crystallisations from aqueous alcohol when it was obtained as pale yellow needles melting at 267–8°. It was soluble in aqueous sodium hydroxide and sodium carbonate and gave a grass green colour with alcoholic ferric chloride. Mixed melting point with an authentic sample of æsculetin was not depressed. Its diacetate

was prepared by refluxing with acetic anhydride and a drop of pyridine. It crystallised from ethyl acetate as colourless needles melting at 135–6°.

Under the same conditions 4-methyl umbelliferone yielded 4-methyl æsculetin crystallising from alcohol as clusters of pale yellow prisms melting at 269–70°. It was identical with a sample prepared by the method of Pechmann and Krafft.[10] The diacetate crystallised from ethyl acetate in the form of colourless needles and melted at 134–5°.

The yield of the pure oxidation product in both cases was about 10%. Changing the conditions such as working up soon after the completion of the addition of persulphate and using a lower temperature for hydrolysing the sulphate did not improve the yield.

p-*Oxidation of 7-methoxy coumarin*

This was originally carried out by Bargellini and Monti[4] with alkaline potassium persulphate in the presence of ferrous sulphate. The yield was not reported. Omitting ferrous sulphate we were able to obtain a yield of 20%. Experiments were made preparing the corresponding coumaric acid, subjecting it to oxidation with alkaline persulphate and converting the product into the coumarin. Eventually a continuous process was adopted as follows:

The methoxy coumarin was converted into the corresponding coumaric acid (4-*O*-methyl-umbellic acid) by treatment with aqueous alkali and mercuric oxide according to the method of Rao and Seshadri.[14] Mercuric oxide was filtered off and the alkaline solution treated with potassium persulphate. After the completion of the addition (with or without allowing to stand overnight) the solution was rendered just acid and extracted with ether to remove the unoxidised material. Then it was acidified strongly after adding some sodium bisulphite and heated to hydrolyse the sulphate ester. The product was extracted with ether repeatedly and the ether extract evaporated. The residue was treated with a small amount of alcohol and mercuric chloride (0·1 g. for 1 g. of the coumaric acid) and heated at 100° for 2 hours. Towards the end strong hydrochloric acid (1 c.c.) was added and the mixture allowed to cool. The final product came out as a solid, but it was extracted with ether and the ether solution evaporated; the residue crystallised from alcohol or ethyl acetate as colourless rectangular prisms melting at 184–5°. The yield was about 25%.

p-*Oxidation of* 4-*methyl*-7-*methoxy coumarin to* 4-*methyl*-7-*methoxy*-6-*hydroxy-coumarin*

4-Methyl-7-methoxy coumarin (5 g.) was dissolved in hot sodium hydroxide (100 c.c., 10%), cooled in ice-water and oxidised with potassium per-

sulphate (11·5 g.). The product crystallised from ethyl acetate as colourless elongated rectangular prisms melting at 208–9°. Yield 1·2 g. (Found: C, 63·8, H, 4·9; $C_{11}H_{10}O_4$ requires C, 64·0, H, 4·9%).

The acetate was prepared by refluxing it with acetic anhydride and a drop of pyridine. It could be crystallised from ethyl acetate as colourless shining rectangular prisms melting at 199–200° (Found: C, 63·4, H, 5·1; $C_{13}H_{12}O_5$ requires C, 62·9, H, 4·8%).

Methylation was effected by means of dimethyl sulphate and potassium carbonate in dry acetone solution. The product crystallised from ethyl acetate as colourless rectangular prisms melting at 143–44°. The mixed melting point with an authentic sample of 4-methyl æsculetin dimethyl ether was undepressed.

4-Methoxy-β-methyl coumaric acid[5] produced from 7-methoxy-4-methyl-coumarin (5 g.) was oxidised with alkaline sodium persulphate in the same way as in a previous experiment. After hydrolysis, the oxidation product was directly converted into the coumarin without being isolated. 7-Methoxy-6-hydroxy-4-methyl coumarin thus obtained (1·7 g.) crystallised from ethyl acetate in the form of elongated rectangular prisms melting at 208–9°, agreeing in every respect with the product obtained directly from 4-methyl-7-methoxy coumarin. Mixed melting point with the product of partial methylation of 4-methyl-æsculetin was undepressed.

*Dakin's oxidation of umbelliferone-8-aldehyde*

Umbelliferone-8-aldehyde[8] (1 g.) was dissolved in pyridine (5 c.c.) and the solution was added to aqueous sodium hydroxide (0·3 g. in 25 c.c. of water) with cooling. The mixed solution was treated with hydrogen peroxide (6 c.c., 6%) dropwise and with cooling when the temperature appreciably exceeded the room temperature. After addition it was left aside for 2 hours, then acidified, saturated with sodium chloride and extracted with ether 4 times. The ether solution was washed successively with dilute hydrochloric acid and water. On distilling the ether, daphnetin was left behind as a crystalline solid. It crystallised from ethyl acetate in the form of pale yellow rectangular prisms melting at 257-8°. It gave a grass green colour with alcoholic ferric chloride. Yield 0·6 g. Mixed melting point with an authentic sample of daphnetin prepared from pyrogallol and malic acid was undepressed. The dimethyl ether crystallised from boiling water to give colourless needles melting at 119–20°. Mixed melting point with an authentic sample of daphnetin dimethyl ether was undepressed.

*Dakin's oxidation of 4-methyl umbelliferone-8-aldehyde*

The oxidation was carried out in the same way as in the case of umbelliferone-8-aldehyde. 4-Methyl daphnetin thus obtained crystallised from alcohol in the form of pale yellow rectangular prisms melting at 235–6°. Mixed melting point with a sample prepared according to the method of Pechmann and Duisberg[11] was undepressed. Yield 0·8 g. of 4-methyl daphnetin from 1 g. of 4-methyl umbelliferone-8-aldehyde.

The dimethyl ether crystallised from ethyl acetate as colourless rectangular plates melting at 132–3°. Mixed melting point with an authentic sample was undepressed.

*Methylenation*

This was carried out by refluxing 4-methyl daphnetin (5 g.) in acetone solution (500 c.c.) with methylene iodide (10·5 g., 1·5 moles) and anhydrous potassium carbonate (10 g.) for 16 hours. The solution was then filtered and the potassium salts washed with hot acetone. The combined filtrate and washings was then distilled to remove the solvent; the residue crystallised from alcohol as pale yellow plates melting at 226–27°. (Yield 1 g., about 20%. Earlier Baker and Savage[12] carried out this methylenation using aqueous alkali, acetone and methylene sulphate and the yield was 8%.

p-*Oxidation of 4-methyl-daphnetin-dimethyl ether*

(i) The dimethyl ether (5 g.) was dissolved in aqueous sodium hydroxide (100 c.c., 10%) by warming and also adding a few drops of pyridine. A saturated solution of potassium persulphate (12 g.) was added drop by drop and with constant stirring, to the above solution cooled in ice-water. After 24 hours, the product was worked up as usual. 6-Hydroxy-7: 8-dimethoxy-4-methyl coumarin crystallised from ethyl acetate to give colourless tiny prisms melting at 173–4°. Some more of it could be obtained by extracting the filtrate with ether. Total yield 0·8 g.

(ii) 7: 8-Dimethoxy-4-methyl coumarin (5 g.) was dissolved in hot aqueous potassium hydroxide (100 c.c., 10%). The solution was cooled, yellow mercuric oxide (2 g.) added and the mixture stirred for 2 hours. The solution was maintained below 10° C. The mercuric oxide was then filtered off and more aqueous potassium hydroxide (25 c.c., 10%) was added. Potassium persulphate (12 g.) was then added under conditions described in previous experiments. After 24 hours, the solution was saturated with hydrogen sulphide, acidified with hydrochloric acid and the dark brown precipitate filtered. The filtrate was extracted with ether.

The sulphate present in the aqueous solution was then hydrolysed with concentrated hydrochloric acid (40 c.c.) at 80° for thirty minutes. The mixture was cooled and shaken with mercuric chloride (0·5 g.). The solid that separated was filtered. Some more of it was obtained when the filtrate was saturated with sodium chloride, extracted with ether and the ether solution evaporated. Total yield 1·5 g. 7: 8-Dimethoxy-6-hydroxy-4-methyl coumarin thus obtained was crystallised from ethyl acetate to give colourless tiny prisms melting at 173–4° (Found: C, 61·1, H, 5·1; $C_{12}H_{12}O_5$ requires C, 61·0, H, 5·1%).

The above product (0·5 g.) was methylated by refluxing in acetone solution (50 c.c.) with dimethyl sulphate (0·5 g.) and potassium carbonate (5 g.) for 6 hours. It was filtered and the filtrate distilled to remove the solvent. The trimethyl ether crystallised from ethyl acetate to give colourless thin rectangular prisms melting at 108–9° (Found: C, 62·1, H, 5·6; $C_{13}H_{14}O_5$ requires C, 62·4, H, 5·6%).

p-*Oxidation of daphnetin-dimethyl ether*

Daphnetin dimethyl ether (2 g.) was dissolved in aqueous potassium hydroxide (50 c.c., 10%) and was stirred with yellow mercuric oxide (1 g.) for two hours. It was filtered, the coumaric acid solution oxidised with potassium persulphate (5 g.) and the product worked up as described for the oxidation of umbelliferone-methyl-ether. 7: 8-Dimethoxy-6-hydroxy coumarin came out as colourless rectangular plates melting at 184–85°; yield 0·6 g. Bargellini[9] reported a melting point of 184° for this compound.

4-*Methyl fraxinol*

(i) *Direct oxidation of* 4-*methyl limettin.*—4-Methyl limettin (5 g.) was dissolved in aqueous sodium hydroxide (100 c.c., 10%) by warming and also adding a few drops of pyridine. A saturated solution of potassium persulphate (12 g.) was added to the above solution, cooled in ice-water, drop by drop and with constant stirring. After 24 hours the product was worked up as usual. It crystallised from ethyl acetate to give colourless stout prisms melting at 193–4°. Yield 5% (Found: C, 61·3, H, 5·4; $C_{12}H_{12}O_5$ requires, C, 61·0, H, 5·1%).

(ii) *Oxidation through coumaric acid.*—5: 7-Dimethoxy-4-methyl coumarin (5 g.) was dissolved in hot aqueous potassium hydroxide (100 c.c., 10%). The solution was cooled, yellow mercuric oxide (2 g.) added and the mixture stirred for two hours. The solution was maintained below 10°. The mercuric oxide was then filtered off and more aqueous potassium hydroxide

(25 c.c., 10%) was added. Potassium persulphate (12 g.) was then added slowly and the product worked up as described under 4-methyl daphnetin. 4-Methyl fraxinol thus obtained crystallised from ethyl acetate to give colourless stout prisms melting at 193–4°, identical with the sample described above; yield 20%.

Methylation was carried out by refluxing 4-methyl fraxinol (0·5 g.) in acetone solution (50 c.c.) with dimethyl sulphate (0·5 g.) and potassium carbonate (5 g.) for 6 hours. The mixture was filtered and the filtrate distilled to remove the solvent. The methyl ether of 4-methyl fraxinol crystallised from ethyl acetate as colourless thick rhombic plates melting at 113–14°.

The acetate crystallised from ethyl acetate as colourless broad rectangular plates melting at 167–8°.

(iii) *Synthesis.*—2:6-Dimethoxy quinol was prepared by the method of Spath and Jerzmanowska-Sienkiewiczowa.[13] 2:6-Dimethoxy quinol (2 g.) was made into a thin paste with ethyl acetoacetate (1·5 g.) and slowly added to concentrated sulphuric acid (5 c.c.) cooled in ice and stirred well. It was left in the refrigerator overnight, and then poured into 50 c.c. of ice-water. The precipitated solid was filtered after keeping for 2 hours, washed with a little water and dried. It crystallised from dry ethyl acetate in the form of colourless stout prisms melting at 193–4°. It agreed in every respect with the nuclear oxidation product of 4-methyl limettin and the mixed melting point was undepressed. The methyl ether of the synthetic product melted also at 113–14° and the acetate at 167–68° and these were identical with the methyl ether and acetate of the nuclear oxidation product.

## Summary

It is suggested that umbelliferone is a fundamental compound in the biogenesis of coumarins and that other important hydroxycoumarins involve further stages of oxidation. In support of this idea experiments are described for the preparation from umbelliferone of æsculetin by *p*-oxidation and daphnetin by *ortho*-oxidation. From either of these dihydroxycoumarins, 6:7:8-trihydroxycoumarin can be prepared. Limettin would, however, appear to have a different origin. The possible evolution of fraxinol from limettin by *p*-oxidation is supported by persulphate oxidation experiments using 4-methyl limettin. 4-Methyl fraxinol has also been synthesised from 2:6-dimethoxyquinol and acetoacetic ester.

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