NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLIV. New Synthesis of Polyhydroxy Coumarins and A Note on Trimethyl Dihydro-Psoralene

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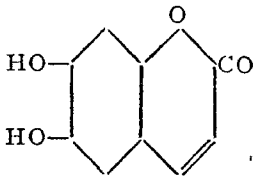
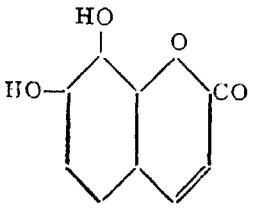
OF the dihydroxy coumarins containing the hydroxyl groups in the benzene ring only three of the six possible arrangements have been known to occur in nature. These are æsculetin (I; 6:7-dihydroxy coumarin), daphnetin (II; 7:8-dihydroxy coumarin) and limettin (III; 5:7-dimethoxy coumarin).



(I)



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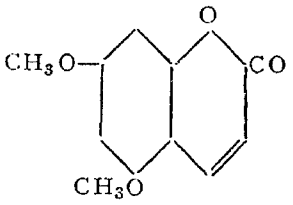
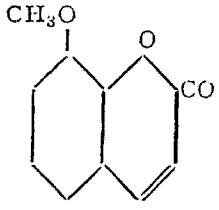


(III)

The other three arrangements, *viz.*, 5:6-, 5:8- and 6:8-, are not so far known to occur in nature. Of these only one has been synthetically prepared earlier, namely, the 6:8-dihydroxy (methoxy) type, by Mauthner[1] who subjected 8-methoxy coumarin (IV) to Elb's persulphate oxidation thus obtaining 8-methoxy-6-hydroxy coumarin (V *a*) which was methylated to give 6:8-dimethoxy coumarin (V *b*).



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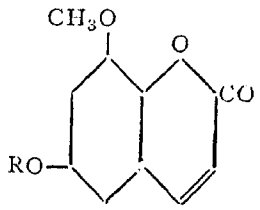


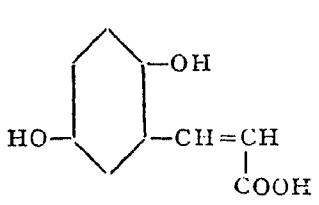
(V)

(*a*) R = H
(*b*) R = CH_3

The other two types, *viz.*, 5:6- and 5:8-dihydroxy coumarins are of interest in connection with the possible occurrence of ring isomerisation, a phenomenon which has been met with in the flavone series. The former has not so far been synthesised. The preparation of the 5:6-dihydroxy coumarins was done in this laboratory during 1950.[2] About the same time

this problem has been studied by Dalvi, Desai and Sethna.[3] They started with 5-methoxy-4-methyl coumarin and subjected it to persulphate oxidation obtaining 6-hydroxy-5-methoxy coumarin which was finally demethylated to give 5: 6-dihydroxy-4-methyl coumarin. Our method of synthesis employs the two stage process of nuclear oxidation and the more readily available 6-hydroxy coumarin (VI *a*) as the starting material. This is made from coumarin itself by persulphate oxidation, a reaction which had already been carried out by Bargellini and Monti.[4] It is now found to be more advantageous to convert coumarin into coumaric acid and subject the latter to persulphate oxidation. The 5-hydroxy coumaric acid (VII) thus obtained is converted into 6-hydroxy coumarin by the action of mercuric chloride. This method follows closely the procedure adopted by Sawhney, Seshadri and Thiruvengadam[5] for the oxidation of 7-methoxy and 7: 8-dimethoxy coumarins. The process can be made continuous giving finally 6-hydroxy coumarin.

6-Hydroxy coumarin undergoes condensation with hexamine to yield the 5-aldehyde (VIII *a*) as a yellow crystalline solid closely resembling in its properties umbelliferone-8-aldehyde.[6] The hydroxy coumarin aldehyde (VIII *a*) undergoes smooth oxidation with alkaline hydrogen peroxide (Dakin's reaction) to yield 5: 6-dihydroxy coumarin (IX *a*). The new dihydroxy coumarin resembles daphnetin (II) and æsculetin (I), dissolving in alkali to give a deep yellow solution and giving a grass green colour with ferric chloride in alcoholic solution. Its dimethyl ether has also been prepared. The dihydroxy compound as well as the dimethyl ether are definitely different from æsculetin and its dimethyl ether.



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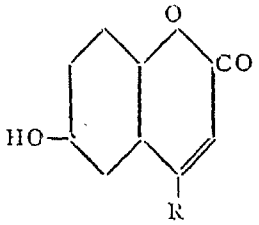

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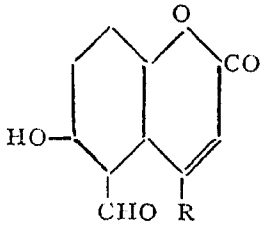

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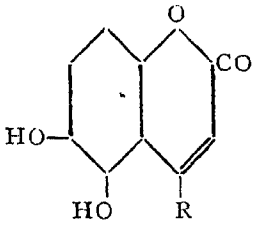
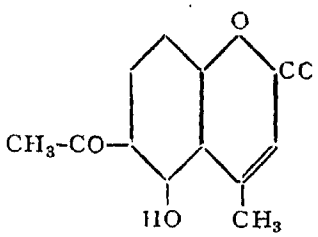


(IX)



(X)

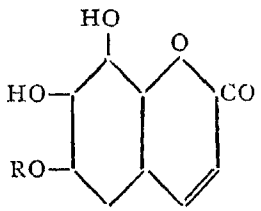
(*a*) R=H
(*b*) R=CH_3

The synthesis of 5: 6-dihydroxy-4-methyl coumarin (IX *b*) has also been effected following a parallel procedure. The starting material 6-hydroxy-4-methyl coumarin (VI *b*) is however made by the condensation of hydroquinone with ethyl acetoacetate in the presence of concentrated sulphuric acid.[7] This method is found to be more convenient than the alternative method involving the persulphate oxidation of 4-methyl coumarin. 5: 6-dihydroxy-4-methyl coumarin (IX *b*) obtained from the corresponding aldehyde (VIII *b*) by this procedure agrees with the description given by Dalvi *et al.*[3] It is definitely different from 4-methyl æsculetin.

Special attention may be drawn here to the activating effect of the 6-hydroxyl group preferentially on the 5-position and not on the 7-position. Similar behaviour has been noticed in the case of the 7-hydroxyl which preferentially activates the 8-position. These observations are explicable on the basis of the tendency of the aromatic double bond to get fixed between 5: 6- and 7: 8-positions. This seems to be a general characteristic of all the benzopyrone (α as well as γ) derivatives.

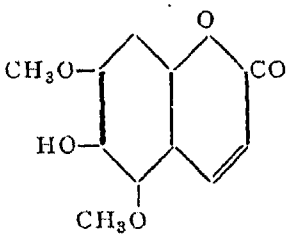
The above aldehyde method of synthesis though much better than the other one involving nuclear oxidation of 5-methoxy-4-methyl coumarin, suffers from the disability that the yield of the aldehyde is poor. A simpler method of obtaining 5: 6-dihydroxy-4-methyl coumarin (IX *b*) is to start with resacetophenone and convert it into 6-acetyl-5-hydroxy-4-methyl coumarin (X) by the method of Sethna, Shah and Shah.[8] This hydroxy coumarin ketone undergoes oxidation with alkaline hydrogen peroxide yielding 5: 6-dihydroxy-4-methyl coumarin (IX *b*).

Of the four possible isomeric trihydroxy coumarins containing the hydroxyl groups in the benzene ring the most commonly occurring in nature is the 6: 7: 8-arrangement of hydroxyl groups. Fraxetin (XI *a*) and its partial methyl ethers fraxidin and isofraxidin belong to this category. The 5: 6: 7-trihydroxy type is met with in fraxinol (XII), and pimpinellin (XIII), a furanocoumarin, may also be considered to be a compound of this type. To the 5: 7: 8-trihydroxy type would belong furanocoumarins like isopimpinellin (XIV), no simpler compound being known. The earlier synthesis of these trihydroxy coumarins followed difficult steps. Recently 6: 7: 8-trihydroxy coumarin (XI *b*) could be obtained more easily from daphnetin dimethyl ether by alkaline persulphate oxidation and subsequent demethylation.[5] Adopting a similar procedure fraxinol (XII) has also been prepared and has been demethylated to 5: 6: 7-trihydroxy coumarin. But the yields in these methods of preparation are poor.[5]



(XI)

(*a*) R=CH_3
(*b*) R=H



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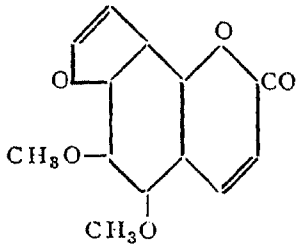

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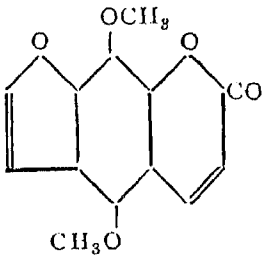
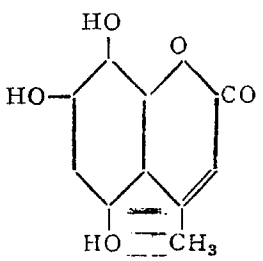


(XIV)

The synthesis of 5:7:8-trihydroxy coumarin and its derivatives does not appear to have been carried out so far. In connection with the study of ring isomerisation in the coumarin series we needed samples of these compounds and have therefore explored convenient methods of their synthesis. 5:7:8-Trihydroxy-4-methyl coumarin (XV) could be prepared from 2:5-dimethoxy resorcinol (XVI)[9] by condensation with acetoacetic ester and subsequent demethylation. The aldehyde (XVII) of this resorcinol also undergoes coumarin condensation with malonic ester. Both these methods work satisfactorily. The aldehyde (XVII) was prepared earlier by Clarke and Robertson[10] using 2:5-dimethoxy resorcinol (XVI) and Gattermann reaction. Recently it has been more conveniently obtained by utilising an earlier intermediate, namely, the dibenzyl derivative of the resorcinol (XVIII)[11] for this purpose and this method has been adopted in the present work. The feasibility of using the dibenzyl derivative directly for the synthesis was first shown by Rao *et al.*,[12] who made from it ω:3:6-trimethoxy-2:4-dihydroxy acetophenone. Subsequently this reaction was studied by Sastri and Seshadri[13] who could also prepare by suitable modifications the 4-benzyl ether of the above ketone. The preparation of the aldehyde (XVII) itself from this dibenzyl ether was described by Sastri in his thesis.[14]

An easier method would be to carry out Dakin's oxidation of 5:7-dihydroxy-8-acetyl-4-methyl coumarin (XIX). In attempting to prepare this ketone it was noticed that Shah and Shah[15] had earlier reported the condensation of phloracetophenone with ethyl acetoacetate in the presence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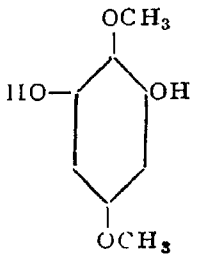
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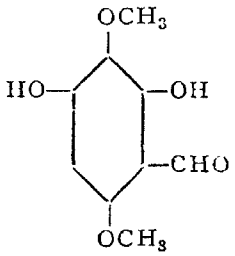
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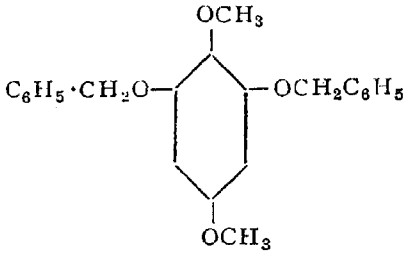
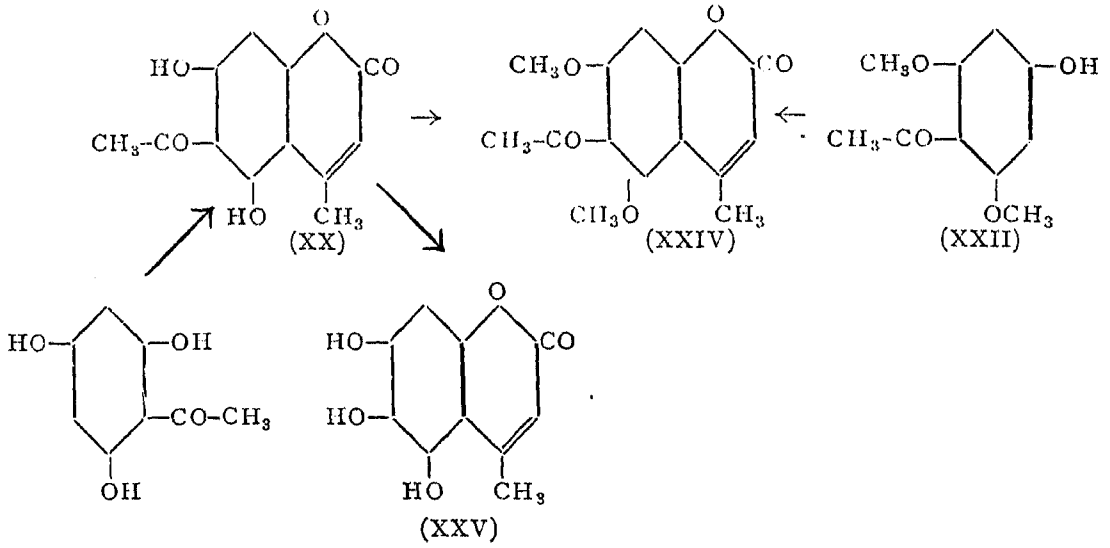
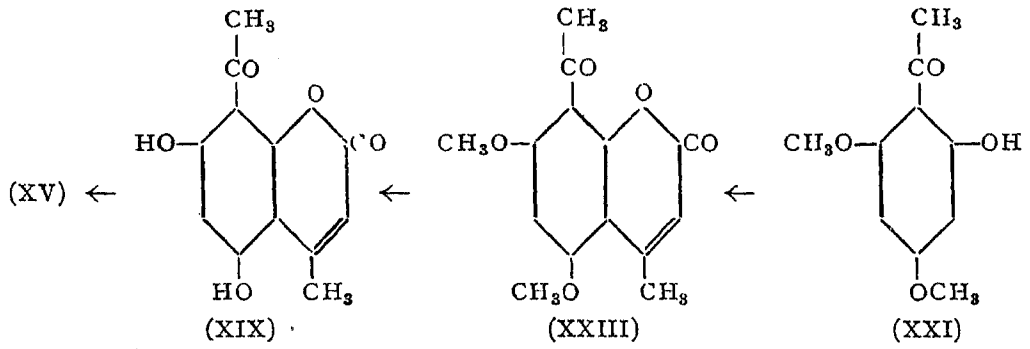

(XVIII)

of concentrated sulphuric acid or anhydrous aluminium chloride. Of the two possibilities for its constitution they felt that it was more likely to be 5: 7-dihydroxy-8-acetyl-4-methyl coumarin (XIX) since it could be readily and completely methylated by methyl iodide in acetone solution in the presence of anhydrous potassium carbonate. This would mean that it is the 2-hydroxyl group of phloracetophenone that takes part in the condensation. But from reactions involving benzoylation,[17a] methylation and benzylation[16] it is known that the 4-hydroxyl group of phloracetophenone is the more reactive one and hence the constitution 5: 7-dihydroxy-6-acetyl-4-methyl coumarin (XX) is more likely to represent the nature of the product obtained by Shah and Shah.[15] In order to settle this issue there was need for unambiguous synthesis of one or both the isomers. For this purpose the two isomeric phloracetophenone dimethyl ethers namely, (i) 2-hydroxy-4: 6-dimethoxy acetophenone (XXI)[17] and (ii) 4-hydroxy-2 : 6-dimethoxy acetophenone (XXII)[17a] are prepared. Each is condensed with ethyl acetoacetate in the presence of concentrated sulphuric acid. The former yields 5: 7-dimethoxy-8-acetyl-4-methyl coumarin (XXIII) which on demethylation with anhydrous aluminium chloride in boiling benzene solution (hydriodic acid could not be used since it produces ununderstandable decomposition of the methoxy ketone) gives rise to 5: 7-dihydroxy-8-acetyl-4-methyl coumarin (XIX) melting at 304–6°. This is different from the compound obtained by the method of Shah and Shah.[15] On the other hand the alternative 2: 6-dimethyl ether of phloracetophenone (XXII) gives rise to 5: 7-dimethoxy-6-acetyl-4-methylcoumarin (XXIV) which is identical with the product obtained by the complete methylation of the dihydroxy ketone

prepared according to the method of Shah and Shah.[15] It is thus clear that the direct condensation of phloracetophenone with ethyl acetoacetate yields only 5:7-dihydroxy-6-acetyl-4-methyl coumarin (XX) and not its isomer (XIX).





The two isomeric dihydroxy coumarin ketones (XIX) and (XX) undergo smooth oxidation with alkaline hydrogen peroxide to yield the two isomeric trihydroxy coumarins, *viz.*, 5:7:8-trihydroxy-4-methyl coumarin (XV) and 5:6:7-trihydroxy-4-methyl coumarin (XXV). They exhibit characteristic difference in their reactions; the former gives with aqueous alkali and sodium carbonate a deep orange colour fading rapidly and finally changing to yellowish green and with ferric chloride a transient green colour changing rapidly to red and also a positive test with *p*-benzoquinone, whereas the latter gives a bright yellow colour with aqueous alkali and sodium carbonate which slowly changes to yellowish green on standing, a blue colour slowly changing to olive brown with ferric chloride and no reaction with *p*-benzoquinone. Thus the production of the trihydroxy coumarins could also be used for establishing the constitution of the corresponding dihydroxy coumarin ketones.

Another point that should be mentioned here is the absence of isomeric change when the dimethyl and trimethyl ethers of 5:7:8-trihydroxy-4-methyl coumarin (XV) are subjected to demethylation with hydriodic acid. The product has all the properties of the 5:7:8-arrangement of hydroxyl groups and is identical with the one obtained by the Dakin's reaction. Even the reverse isomeric change does not occur since the demethylation with hydriodic acid[5] of 4-methyl fraxinol yields a product identical with 5:6:7-trihydroxy-4-methyl coumarin (XXV) obtained independently by the Dakin's method. It is therefore clear that the α-pyrone ring is stable in the presence of hot acids and does not undergo the isomeric change. Ring opening will certainly occur in the presence of excess of alkali but the isomerisation in alkaline conditions could not be studied since the compounds are unstable under these conditions as is evident from the rapid colour change they suffer in alkaline solutions.

Experimental

6-*Hydroxy coumarin* (*VI a*)

Persulphate oxidation through coumaric acid.—Coumarin (12 g.) was dissolved in aqueous sodium hydroxide (12 g. in 15 c.c. of water) yellow mercuric oxide (1·5 g.) was added and the solution shaken vigorously with cooling till all the coumarin dissolved. The solution was filtered and to the resulting filtrate (greenish-yellow fluorescence) sodium hydroxide solution (8 g. in 40 c.c. of water) was added. A saturated solution of potassium persulphate (8 g. in 140 c.c. of water) was added to the above solution cooled in ice-water, with vigorous stirring during the course of 3 hours. After the addition was complete the solution was left overnight and then neutralised with hydrochloric acid (congo red) whereby the unchanged coumaric acid was precipitated. It was filtered off and the filtrate extracted twice with ether to remove any traces of unchanged coumaric acid present. Concentrated hydrochloric acid (100 c.c.) was added to the solution followed by sodium bisulphite (1·5 g.) and it was heated in a boiling water-bath for half an hour. It was then cooled and extracted repeatedly with ether. The dark-brown residue of 4-hydroxy coumaric acid obtained on distilling the ether (3 g.) was dissolved in water (50 c.c.), mercuric chloride (0·5 g.) added and the solution boiled under reflux for an hour. It was then cooled and extracted repeatedly with ether. The ether solution was dried over anhydrous sodium sulphate and the ether distilled off when a pale brown crystalline residue of 6-hydroxy coumarin was obtained. On recrystallisation from alcohol it was obtained as almost colourless needles melting at 248–50°. Yield, 2 g.

6-Hydroxy-coumarin-5-aldehyde (VIII a)

A mixture of 6-hydroxy coumarin (3·5 g.), hexamine (7·2 g.) and glacial acetic acid (30 c.c.) was heated for 8 hours in a boiling water-bath, after which a boiling solution of hydrochloric acid (40 c.c. in 40 c.c. of water) was added to it while hot. The solution was left overnight and then distilled under reduced pressure to remove the solvent. The residue was extracted twice with alcohol (20 c.c. each time) and the alcoholic extract concentrated to about 10 c.c. The first two fractions that separated were discarded. 6-Hydroxy coumarin-5-aldehyde could be obtained by concentrating the mother liquor (Yield, 0·5 g.). It was purified by recrystallisation from alcohol and was obtained as almost colourless clusters of rectangular prisms tapering towards the edges, melting at 212–3°. It dissolved in aqueous sodium hydroxide to give a yellow solution and gave a deep pink colour with ferric chloride (Found: C, 62·9; H, 2·9; $C_{10}H_6O_4$ requires C, 63·2; H, 3·2%).

5: 6-Dihydroxy coumarin (IX a)

6-Hydroxy-coumarin-5-aldehyde (1 g.) was dissolved in aqueous sodium hydroxide (0·3 g. in 25 c.c. of water) and pyridine (5 c.c.) with cooling. To the solution was added hydrogen peroxide (6 c.c., 6%) dropwise with cooling. After the addition was complete the solution was left aside for 2 hours, then acidified, saturated with sodium chloride and extracted with ether repeatedly. The ether solution was washed successively with dilute hydrochloric acid and water and dried over anhydrous magnesium sulphate. On distilling the ether 5: 6-dihydroxy coumarin was obtained as an yellow solid. When recrystallised from ethyl acetate it separated as clusters of yellow needles melting at 256–8°. Yield, 0·8 g. The recorded melting point of æsculetin (6: 7-dihydroxy coumarin) is 270°. It dissolved in aqueous sodium hydroxide to give a bright yellow solution and gave a grass green colour with ferric chloride in alcoholic solution (Found: C, 60·3; H, 2·9; $C_9H_6O_4$ requires C, 60·7; H, 3·4%).

5: 6-Dimethoxy coumarin

5: 6-Dihydroxy coumarin (0·5 g.) was methylated by refluxing in acetone (30 c.c.) with dimethyl sulphate (0·6 c.c.) and anhydrous potassium carbonate (2 g.) for 8 hours. 5: 6-Dimethoxy coumarin thus obtained crystallised from methyl alcohol as long colourless rectangular rods melting at 132–3°. (The melting point of 6: 7-dimethoxy coumarin has been reported to be 144°.) It did not dissolve in cold aqueous alkali and gave no colour with ferric chloride (Found: C, 64·0; H, 4·6; $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

6-Hydroxy-4-methyl coumarin-5-aldehyde (VIII b)

A mixture of 6-hydroxy-4-methyl coumarin (4 g.), hexamine (8 g.) and glacial acetic acid (32 c.c.) was heated in a boiling water-bath for 8 hours, after which a boiling solution of hydrochloric acid (40 c.c. in 40 c.c. of water) was added to it while hot. The solution was left overnight and then distilled under reduced pressure. The residue was extracted with boiling alcohol twice (25 c.c. each time) and the alcoholic solution concentrated. The first two fractions that crystallised out consisted of unchanged 6-hydroxy-4-methyl coumarin. 6-Hydroxy-4-methyl coumarin-5-aldehyde was obtained from the alcoholic mother-liquor by further concentration. It was purified by recrystallisation from alcohol and was obtained as clusters of yellow stout rectangular prisms melting at 202-3°. It gave a deep pink colour with ferric chloride and dissolved in aqueous sodium hydroxide to give an yellow solution. Yield, 0·4 g. (Found: C, 64·3; H, 4·4; $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%).

5: 6-Dihydroxy-4-methyl coumarin (IX b)

6-Hydroxy-4-methyl coumarin-5-aldehyde (1 g.) was dissolved in aqueous sodium hydroxide (0·3 g. in 25 c.c. of water) and pyridine (5 c.c.) with cooling. The well-cooled solution was treated with hydrogen peroxide (6·5 c.c., 6%) added dropwise. The solution was worked up as in the case of 5: 6-dihydroxy coumarin. The 5: 6-dihydroxy-4-methyl coumarin which was obtained as an yellow solid on distilling off ether crystallised from ethyl acetate as thin rectangular rods melting at 248–50°. It dissolved in aqueous sodium hydroxide to give a deep yellow solution and gave a grass green colour with ferric chloride in alcoholic solution. It agrees in all its properties with the report of Dalvi *et al.*[3]

5: 6-Dimethoxy-4-methyl coumarin

5: 6-Dihydroxy-4-methyl coumarin (0·3 g.) was methylated by refluxing in acetone (25 c.c.) with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) for 8 hours. 5: 6-Dimethoxy-4-methyl coumarin crystallised from alcohol as colourless elongated rectangular prisms melting at 127–8°.[3] (Found: C, 65·9; H, 5·4; $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%.)

5: 6-Dihydroxy-4-methyl coumarin (IX b) by the Dakin's oxidation of 6-acetyl-5-hydroxy-4-methyl coumarin (X)

6-Acetyl-5-hydroxy-4-methyl coumarin[8] (2 g.) was dissolved in sodium hydroxide solution (12 c.c., 4%) with cooling and to the ice-cold solution hydrogen peroxide (1·8 c.c., 30%, 2 moles) was added dropwise. A little pyridine was added to keep the solution clear and it was set aside at 0° for

2 hours. It was then acidified with ice-cold hydrochloric acid (1 : 1), the solid that was precipitated was filtered and washed with a little ice-cold water. On crystallising twice from ethyl acetate the product was obtained as pale yellow thin rectangular rods melting at 248–9°. It gave a bright green colour with ferric chloride in alcoholic solution and dissolved in sodium hydroxide to give an yellow solution. It was identical in its reactions with 5: 6-dihydroxy-4-methyl coumarin and a mixed melting point with the sample described earlier was undepressed. Yield, 1 g.

5: 6-Diacetoxy-4-methyl coumarin obtained by the acetylation of the dihydroxy compound using acetic anhydride and pyridine crystallised from ethyl acetate as colourless needles and melted at 175–6°.

7-Hydroxy-5: 8-dimethoxy-4-methyl coumarin

To a mixture of 2: 5-dimethoxy resorcinol (1 g.) and ethyl acetoacetate (1 g.), cooled in ice, was added twice the weight of ice-cold concentrated sulphuric acid. After leaving overnight, the mixture was poured on crushed ice and the solid that separated was filtered, washed well with water and crystallised from alcohol. 7-Hydroxy-5: 8-dimethoxy-4-methyl coumarin formed rectangular prisms from alcohol on slow crystallisation and elongated needles when crystallised quickly and melted at 218–9°. It gave no colour with ferric chloride in alcoholic solution. Its solution in concentrated sulphuric acid did not exhibit any fluorescence in daylight. The coumarin dissolved readily in sodium hydroxide but the solution exhibited no fluorescence. Yield, 0·8 g. (Found: C, 60·9; H, 5·3; $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%).

5: 7-Dimethoxy-8-acetyl-4-methyl coumarin (XXIII)

To a mixture of phloracetophenone-4: 6-dimethyl ether[13] (2 g.) and ethyl acetoacetate (2 g.) cooled to 0° in ice, ice-cold concentrated sulphuric acid (15 c.c.) was added taking care to see that the temperature does not rise above 5° and the mixture left in an ice-bath for 24 hours. The deep yellow solution was then poured into crushed ice (200 g.) with stirring when a very pale yellow solid separated. It was filtered, washed with cold aqueous sodium hydroxide (5%), hot water, and finally hot dilute alcohol. On crystallising twice from alcohol 5: 7-dimethoxy-8-acetyl-4-methyl coumarin separated as colourless rectangular prisms and rods melting at 178–80°. It gave no colour with ferric chloride in alcoholic solution and was insoluble in aqueous alkali. Yield, 0·4 g. (Found: C, 63·7; H, 5·8; $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%).

5 : 7-*Dihydroxy*-8-*acetyl*-4-*methyl coumarin* (*XIX*)

A benzene solution (80 c.c.) of 5 : 7-dimethoxy-8-acetyl-4-methyl coumarin (2 g.) was refluxed with anhydrous aluminium chloride (5 g.) for 2 hours. The solvent was then distilled off, the residue treated with ice and hydrochloric acid (20 c.c.) and left overnight. The colourless solid that separated was filtered, washed with ice-cold dilute hydrochloric acid and then with water. 5 : 7-Dihydroxy-8-acetyl-4-methyl coumarin crystallised from alcohol as colourless tiny prisms and melted at 304–6°. It gave a pink colour with ferric chloride and dissolved readily in aqueous sodium carbonate. Yield, 1·2 g. (Found: C, 61·9; H, 4·7; $C_{12}H_{10}O_5$ requires C, 61·6; H, 4·3%).

5 : 7 : 8-*Trihydroxy*-4-*methyl coumarin* (*XV*)

(i) *Dakin's oxidation of* 5 : 7-*dihydroxy*-8-*acetyl*-4-*methyl coumarin.*—To an ice-cold solution of 5 : 7-dihydroxy-8-acetyl-4-methyl coumarin (1 g.) in aqueous sodium hydroxide (9 c.c., 4%, 2 moles) hydrogen peroxide (1 c.c., 30%) was added dropwise and the solution kept clear by the addition of a few drops of pyridine. After 2 hours the deep brownish yellow solution was acidified with ice-cold hydrochloric acid when a pale yellow solid separated. It was filtered, washed with water and dried. On crystallising from ethyl acetate it separated as pale yellow small needles and prisms melting at 273–5°. It gave a very transient green colour changing rapidly to red with ferric chloride. It dissolved in aqueous sodium hydroxide and carbonate to give initially a deep orange colour which faded rapidly and finally changed to a yellowish green. With *p*-benzoquinone in absolute alcoholic solution it gave a red colour.

The acetate obtained by heating with acetic anhydride and pyridine crystallised from ethyl acetate-petrol mixture as colourless rectangular rods melting at 148–9°.

(ii) *Demethylation of* 7-*hydroxy*-5 : 8-*dimethoxy*-4-*methyl coumarin.*—7-Hydroxy-5 : 8-dimethoxy-4-methyl coumarin (0·6 g.) was dissolved in acetic anhydride (5 c.c.) and heated with hydriodic acid (8 c.c., d. 1·7) and the mixture refluxed (oil-bath) at 140° for 3 hours. The mixture was then poured into water saturated with sulphur dioxide when the trihydroxy coumarin separated as a pale yellow solid. Yield 0·3 g. It was filtered, washed and crystallised twice from alcohol. It came out as pale yellow small needles and prisms and was identical in all its reactions and properties with the trihydroxy compound described in the previous experiment (mixed m.p. 273–5°) (Found: C, 57·5; H, 4·0; $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%).

(iii) *Demethylation of* 5:7:8-*trimethoxy*-4-*methyl coumarin.*—The trimethoxy coumarin described below (0·2 g.) was demethylated in acetic anhydride solution (2 c.c.) with hydriodic acid (5 c.c.) and the product worked up as in the above experiment. On crystallising from alcohol it was obtained as pale yellow tiny prisms and needles melting at 273–5°. It was identical with 5:7:8-trihydroxy-4-methyl coumarin and mixed melting point with the two samples described in the experiments (i) and (ii) was undepressed.

5:7:8-*Trimethoxy*-4-*methyl coumarin*

(i) 5:7:8-Trihydroxy-4-methyl coumarin (0·2 g.) obtained by the Dakin's oxidation was refluxed in acetone solution (50 c.c.) with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) for 6 hours. The trimethyl ether crystallised from alcohol as colourless stout rectangular prisms melting at 173–4°. It gave no colour with ferric chloride and was insoluble in aqueous alkali (Found: C, 62·6; H, 5·8; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·8%).

(ii) 7-Hydroxy-5:8-dimethoxy-4-methyl coumarin described earlier (0·2 g.) was methylated with excess dimethyl sulphate as in the above experiment; the trimethyl ether was identical with the product described above (m.p. and mixed melting point 173–4°).

5:7-*Dimethoxy*-6-*acetyl*-4-*methyl coumarin* (*XXIV*)

(i) *From* 2:6-*dimethoxy*-4-*hydroxy acetophenone.*—This was prepared by the same method as was used for the corresponding-8-acetyl compound described earlier, starting with 2:6-dimethoxy-4-hydroxy acetophenone.[17a] The product crystallised from alcohol as fine needles melting at 173–4° and gave no colour with ferric chloride. A mixed melting point with a sample of 5:7-dimethoxy-8-acetyl-4-methyl coumarin was considerably depressed (140–3°).

(ii) *Methylation of the product* (*XX*) *obtained from phloracetophenone and ethyl acetoacetate.*—The dihydroxy-acetyl-4-methyl coumarin obtained by the method of Shah and Shah[15] was methylated by refluxing it (0·5 g.) in acetone solution (100 c.c.) with dimethyl sulphate (0·5 c.c., excess) and anhydrous potassium carbonate (1·5 g.). The methyl ether was obtained from alcohol as colourless long rectangular prisms and needles melting at 173–5° (Shah and Shah reported the melting point as 165–6°). It was insoluble in cold aqueous sodium hydroxide and gave no colour with ferric chloride. It was identical with 5:7-dimethoxy-6-acetyl-4-methyl coumarin and a mixed melting point with the synthetic sample described above was

undepressed while that with 5: 7-dimethoxy-8-acetyl-4-methyl coumarin was considerably depressed (143°).

5: 6: 7-*Trihydroxy-4-methyl coumarin* (*XXV*)

Dakin's oxidation of 5: 7-dihydroxy-6-acetyl-4-methyl coumarin (*XX*).—5: 7-Dihydroxy-6-acetyl-4-methyl coumarin (1 g.) dissolved in sodium hydroxide solution (4 c.c., 4%, 2 moles) was cooled in ice and treated with hydrogen peroxide (1 c.c., 30%) a little pyridine being added to get a clear solution. The initial yellow colour changed to yellowish-brown. After keeping in an ice-bath for 2 hours the solution was acidified with hydrochloric acid and the solid obtained was filtered and washed with water. After drying it was crystallised from ethyl acetate twice when it separated as pale yellow thin plates melting at 278–80°. (Parikh and Sethna[5] reported the same melting point). Ether extraction of the aqueous solution gave some more of the product. Total yield 0·5 g. 5: 6: 7-Trihydroxy-4-methyl coumarin gave a blue colour changing rapidly to green and finally olive-brown colour with ferric chloride. It dissolved readily in aqueous sodium hydroxide and carbonate to give a bright yellow solution changing to yellowish green. The mixture with 5: 7: 8-trihydroxy-4-methyl coumarin melted at 230°.

The triacetate crystallised from ethyl acetate as colourless mass of woolly needles melting at 159–60°. A mixture with 5: 7: 8-triacetoxy-4-methyl coumarin melted at 130°.

The trimethyl ether obtained by methylation with excess dimethyl sulphate and anhydrous potassium carbonate in acetone solution crystallised from alcohol as colourless rectangular prisms and melted at 115–6°.[5]

7-*Hydroxy*-5: 8-*dimethoxy*-3-*carbethoxy coumarin*

2: 4-Dihydroxy-3: 6-dimethoxy benzaldehyde (0·5 g.) was added to malonic ester (0·5 g.) and then treated with a few drops of piperidine with cooling under the tap. The deep reddish brown mixture was allowed to stand at laboratory temperature for 24 hours and then gently warmed on the water-bath for 10 minutes. Ice-water containing a few c.c. of hydrochloric acid was added, when the carbethoxy-coumarin was precipitated as a crystalline solid. It was collected, washed and recrystallised from alcohol. The 3-carbethoxy-coumarin was obtained as big rectangular plates from alcohol on slow crystallisation and clusters of needles when rapidly crystallised and melted at 230–2°. Yield almost quantitative. It dissolved in aqueous sodium hydroxide to give a deep yellow solution which showed no fluorescence and gave no colour with ferric chloride in alcoholic solution. Its solution in concentrated sulphuric acid exhibited no fluorescence in daylight (Found: C, 57·4; H, 4·7; $C_{14}H_{14}O_7$ requires C, 57·2; H, 4·8%).

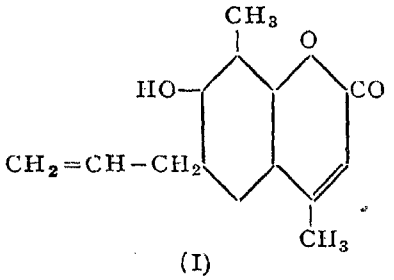
SUMMARY

6-Hydroxy coumarin and 6-hydroxy-4-methyl coumarin are condensed with hexamine to yield the corresponding 5-aldehydes, which undergo Dakin's oxidation smoothly yielding the corresponding 5:6-dihydroxy coumarins. The 6-hydroxyl group activates predominantly the 5-position. 5:6-Dihydroxy-4-methyl coumarin is more conveniently prepared by the Dakin's oxidation of the readily available 6-hydroxy-5-acetyl-4-methyl coumarin.

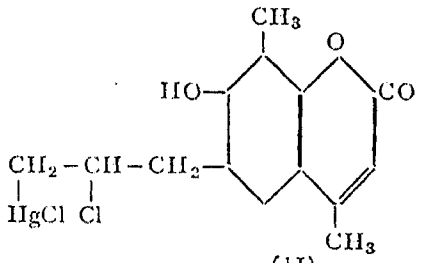
5:7:8-Trihydroxy coumarin derivatives are obtained from (1) 2:5-dimethoxy resorcinol by Pechmann condensation, (2) from the aldehyde of the above resorcinol by malonic ester condensation, and (3) by Dakin's oxidation of 5:7-dihydroxy-8-acetyl-4-methyl coumarin. The 8-acetyl compound required for this purpose is made from 4:6-dimethyl phloracetophenone by condensation with ethyl acetoacetate and final demethylation with anhydrous aluminium chloride. It is shown that direct condensation of phloracetophenone with acetoacetic ester yields the isomeric 5:7-dihydroxy-6-acetyl-4-methyl coumarin which on oxidation yields 5:6:7-trihydroxy-4-methyl coumarin. No isomeric change is noticed when the methyl ethers of these trihydroxy coumarins are boiled with hydriodic acid.

A Note on the Synthesis of α:4:8-*Trimethyl dihydro-psoralene*

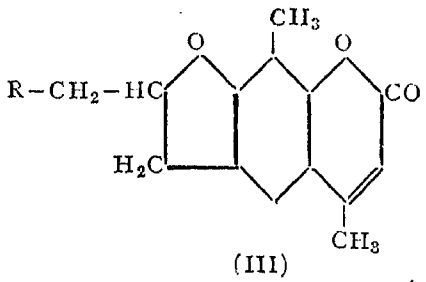
With a view to compare the toxic properties of angular coumarinofuran derivatives with the corresponding linear ones the abovementioned compound has been prepared using the method of Adams *et al.*,[18] with the modifications adopted by Krishnaswamy and Seshadri.[19] Since in many reactions of 7-hydroxy coumarins the 8-position is far more reactive than



(I)



(II)



(III)

(*a*) R=I
(*b*) R=H

the 6-position the former has to be blocked by means of an alkyl group in order to obtain the linear coumarino-furan derivative. 7-Hydroxy-6-allyl-4 : 8-dimethyl coumarin (I) had already been reported by Rangaswami and Seshadri.[20] This is treated with mercuric chloride in methyl alcoholic solution; the addition product (II) yields the α-iodomethyl dihydro furan (III *a*) on treatment with a solution of iodine in potassium iodide. When this is reduced by sodium and alcohol α : 4 : 8-trimethyl dihydro-psoralene (III *b*) is obtained.

EXPERIMENTAL

7-Hydroxy-4 : 8-dimethyl-6-allyl coumarin (I)

The following modification of the original method[20] gave better yields of the pure product. The reaction is carried out at a lower temperature and under reduced pressure.

7-Allyloxy coumarin (1·5 g.) was heated in a test-tube at 195–200° under reduced pressure (water pump) using an oil-bath for 2 hours. After cooling the brown mass was extracted with hot alcohol and filtered hot through animal charcoal. The crystalline solid that separated was again crystallised from dilute alcohol, when 7-hydroxy-6-allyl-4 : 8-dimethyl coumarin was obtained in the form of star-like clusters of short needles and rectangular plates melting at 168–9°. Yield 1·2 g. It dissolved in aqueous sodium hydroxide giving blue fluorescence and gave no colour with ferric chloride in alcoholic solution.

Mercuric chloride addition compound (II)

The allyl coumarin (1 g.) dissolved in a slight excess of methyl alcohol, was treated with a clear cold saturated solution of mercuric chloride (1·5 g.) in the same solvent and the clear mixture allowed to stand at the laboratory temperature. It gradually deposited a crystalline solid in about an hour; after 48 hours the colourless addition product was collected, washed well with hot methyl alcohol in which it was sparingly soluble and dried. Yield, 1·75 g. It appeared as elongated rectangular prisms and decomposed at 265° with previous sintering at 245°. It was difficultly soluble in aqueous sodium hydroxide and the alkali when kept in contact with the solid for some time developed a weak blue fluorescence (Found: Cl, 13·9; $C_{14}H_{14}O_3 HgCl_2$ requires Cl, 14·2%).

4 : 8-Dimethyl coumarino-α-iodomethyl dihydro-7 : 6-furan (III a)

The mercuric chloride addition product (1·5 g.) was added in small quantities at a time to a fairly concentrated solution of iodine in potassium iodide (20 c.c.) with stirring and heated in the water-bath for an hour. The solid was then collected, washed well with water and a little alcohol. It was

dissolved in excess of alcohol and filtered from a small quantity of unchanged material. The alcoholic filtrate on concentration and allowing to stand, deposited the iodo-compound as a crystalline solid which was collected and recrystallised from alcohol. It was obtained as fine needles melting at 144–5° and was insoluble in aqueous sodium hydroxide. Yield, 1·3 g. (Found: C, 47·1; H, 4·0; $C_{14}H_{13}O_3I$ requires C, 47·2; H, 3·7%).

α: 4: 8-*Trimethyl coumarino-dihydro*-7: 6-*furan* (*III b*)

The α-iodomethyl compound (1 g.) was dissolved in absolute alcohol (40 c.c.) and small pieces of sodium metal (2 g.) were pressed to the bottom of the container by means of a glass rod, the addition of sodium was continued till the reaction became slack. The solution was then diluted with water (100 c.c.) and acidified with concentrated hydrochloric acid, when the α-methyl dihydro furan separated out as a crystalline solid. It was collected, washed with water and recrystallised from alcohol. It was obtained as broad plates tapering at the ends on slow crystallisation and short needles when crystallised quickly, and melted at 230–1°. It was insoluble in hot dilute sodium hydroxide solution and gave no colour with ferric chloride in alcoholic solution. Yield, 0·15 g. (Found: C, 73·1; H, 5·9; $C_{14}H_{14}O_3$ requires C, 73·0 H, 6·1%).

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