NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLVI. Synthesis in the Primetin Series

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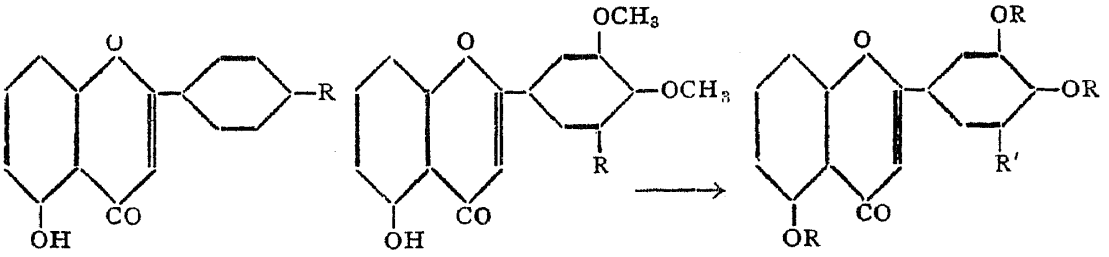
5-Hydroxy flavone (I *a*) occurs along with flavone in the deposits formed on the stalks and blossoms of *Primula imperialis*[1] and also probably in other species of *Primulæ*.[2] It was also synthesised by a number of workers starting from γ-resacetophenone (*see* Rajagopalan, Rao and Seshadri[3] for collected references). 5-Hydroxy-4′-methoxy flavone (I *b*) was prepared by Syed and Wheeler[4] and later by Baker, Flemons and Winter.[5]

The preparation of 5-hydroxy flavones with two and three hydroxyl (methoxyl) groups in the side-phenyl nucleus by Allan-Robinson method has now been investigated with the object of preparing the higher analogues of primetin by nuclear oxidation. The synthesis of 5-hydroxy-3′: 4′: 5′-trimethoxy flavone (II) from γ-resacetophenone by condensation with trimethylgallic anhydride and sodium trimethylgallate was examined under different conditions of hydrolysis. After the usual method of boiling with alcoholic potash for 20 minutes, it was noticed that the 3-acyl compound formed the major product which could later be deacylated to 5-hydroxy-3′: 4′: 5′-trimethoxy flavone by boiling with 10% sodium carbonate solution for 4 hours. In another experiment the product after condensation was directly boiled with 10% aqueous sodium carbonate for 4 hours and a fairly good yield of the free flavone was obtained. It was earlier observed by Baker, Flemons and Winter[5] during the preparation of 5-hydroxy-4′-methoxy flavone that refluxing the product with alcoholic alkali or sodium carbonate led to considerable loss; consequently they adopted a different method for working up the condensation product. It was shaken with ethyl acetate and cold 10% sodium carbonate solution for 18 hours when a good yield of 5-hydroxy-4′-methoxy-3-anisoyl flavone was obtained. But during the next stage when deacylation was attempted with sodium carbonate or sodium hydroxide considerable destruction of the flavone was encountered. In the

present work, the crude product was shaken with ether and 10% sodium carbonate for 24 hours. A mixture of the 3-acyl compound and the free flavone was frequently obtained and their proportions varied considerably in different experiments. They could, however, be separated by taking advantage of the greater solubility of the 3-acyl flavone in a mixture of alcohol and acetone. The yield of the 5-hydroxy-3′ : 4′ : 5′-trimethoxy flavone during these different experiments varied very much and the yields were not consistent.

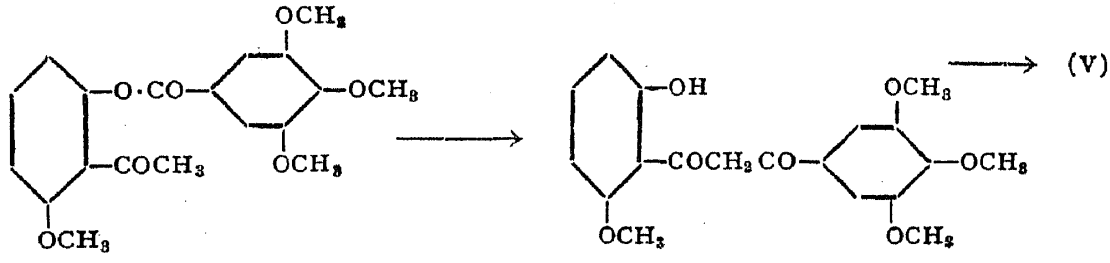


I *a*, R=H
I *b*, R=OCH_3

II, R=OCH_3
VI, R=H

V, R=CH_3, R′=OCH_3
VII, R=CH_3, R′=H
VIII, R=R′=H
IX, R=H; R′=OH

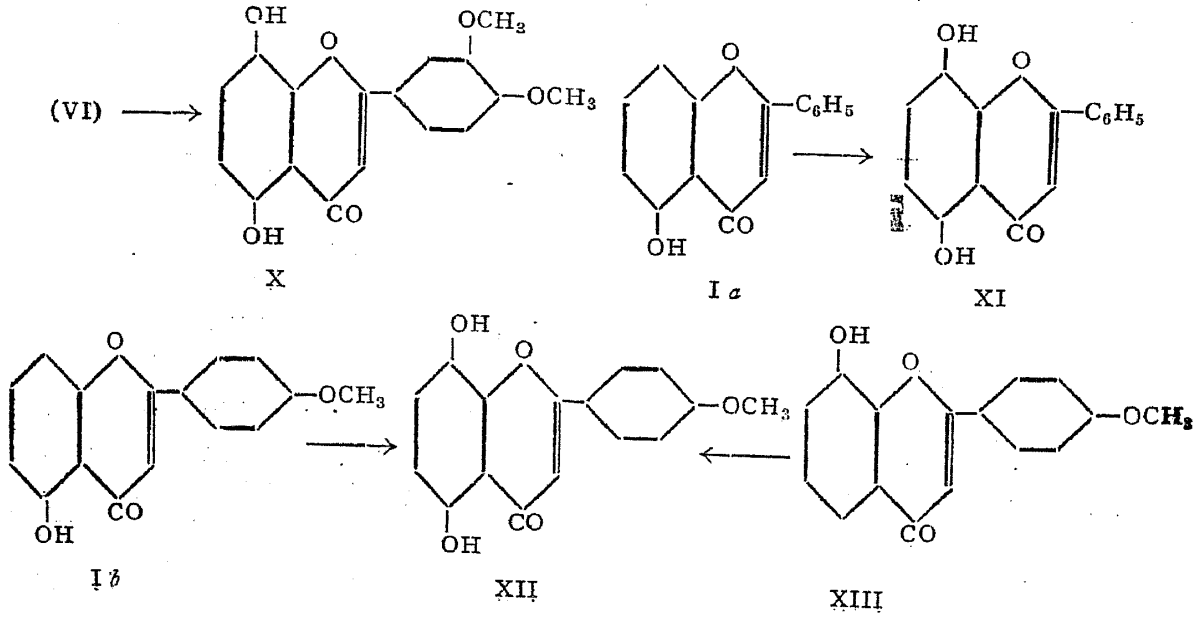
An alternative method was also tried for the preparation of the same flavone. 2-Hydroxy-6-methoxy acetophenone was condensed with trimethylgalloyl chloride in the presence of anhydrous pyridine. Attempts to convert the resulting ester (III) into the dibenzoyl methane (IV) by the use of sodamide in toluene solution were unsuccessful; but success was achieved by the use of powdered potassium hydroxide in dry pyridine.[6] The diketone could be converted into the 5 : 3′ : 4′ : 5′-tetramethoxy flavone (V) by refluxing with fused sodium acetate in glacial acetic acid solution though the yields were not very satisfactory.



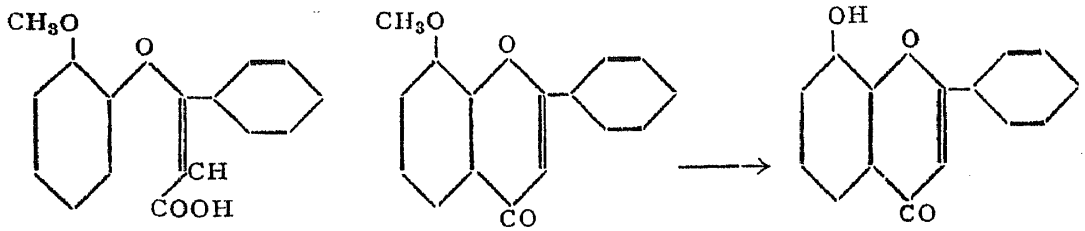
III IV

5-Hydroxy-3′ : 4′-dimethoxy flavone (VI) was also prepared by the Allan-Robinson method. The dimethoxy and the trimethoxy-5-hydroxy flavones were methylated and demethylated by the usual methods and the corresponding methyl ethers (VII and V) and the hydroxy compounds (VIII) and (IX) obtained.

In an attempt to prepare the analogues of primetin, 5-hydroxy-3′: 4′-dimethoxy (VI) and 5-hydroxy-3′: 4′: 5′-trimethoxy (II) flavones have been subjected to oxidation with alkaline persulphate. Owing to the sparing solubility of these compounds in alkali, pyridine is employed to keep them in solution. The yield of the oxidation product (X) is very poor in the case of (VI) while (II) does not undergo any oxidation at all. It may be noted in this connection that 5-hydroxy flavone (I *a*) itself gives fairly good yields of primetin (XI) by nuclear oxidation with alkaline persulphate[3] and 5-hydroxy-4′-methoxy flavone (I *b*) gives about 20% yield of the 5: 8-dihydroxy compound[5] (XII). The reason for the difficulty in the oxidation of the higher members may be that in these compounds the 5-hydroxyl group is not activating adequately the 8-position. It may be mentioned that these substances are sparingly soluble in aqueous alkali because of the chelate bond between the 5-hydroxyl and the carbonyl groups. Though they could be brought into solution by means of pyridine, adequate quantity of the oxide ion is probably not formed and consequently activation of the 8-position is not enough. In the alternative method of preparing members of the primetin series, 8-hydroxy flavones can be used for this nuclear oxidation. Since they are more easily soluble in alkali they could form the oxide ions better and hence the 5-position could be adequately oxidised. Hence it was considered to be of special interest to study the persulphate oxidation of 8-hydroxy flavone derivatives. One such example 8-hydroxy-4′-methoxy flavone (XIII) was investigated by Baker *et al.*[5] and they reported that the yield was poor, about 3%.



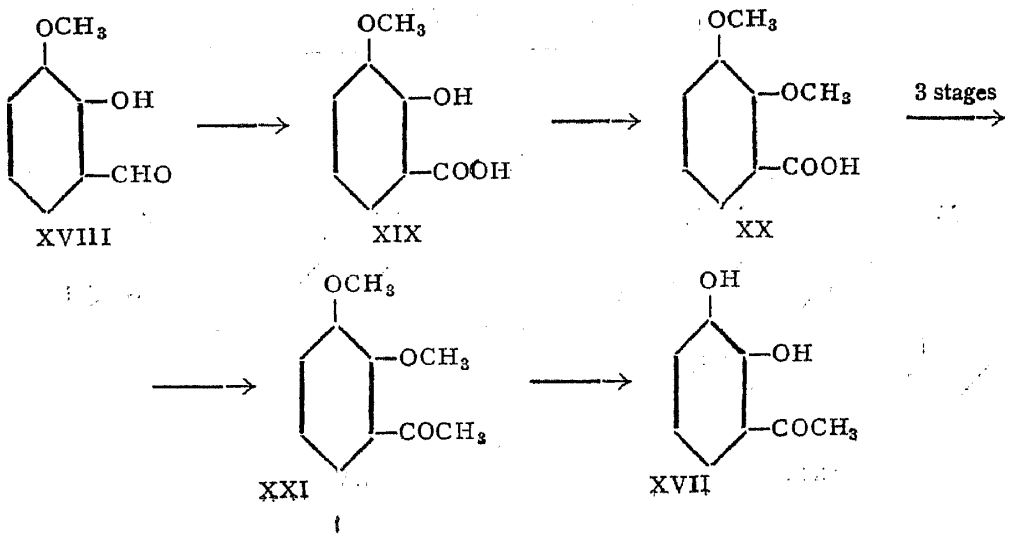
8-Hydroxy flavone (XIV) was first prepared by Ruhemann[7] by cyclisation of β-guiaicoxy cinnamic acid (XV) and subsequent demethylation of the intermediate 8-methoxy flavone (XVI).



XV XVI XIV

8-Hydroxy-4'-methoxy flavone (XIII) was prepared by Baker, Flemons and Winter[5] from 2:3-dihydroxy acetophenone (XVII) employing the Allan-Robinson condensation. The required ketone was obtained by Baker and Smith[8] from 2:3-dimethoxybenzonitrile which was treated with methyl-magnesium iodide and the resulting product decomposed with dilute acetic acid; the dimethoxy acetophenone thus prepared was demethylated by boiling with hydrobromic acid in glacial acetic acid solution. It was also earlier obtained by oxidation of 2:3-dimethoxyphenylmethyl carbinol with chromic acid.[9]

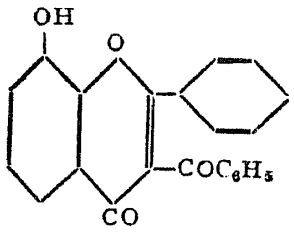
In the present investigation the required ketone (XVII) was obtained from orthovanillin (XVIII) by using the following steps. It was first oxidised to orthovanillic acid (XIX) by fusion with potash[10] and the resulting acid methylated to orthoveratric acid (XX). Its chloride was condensed with acetoacetic ester and sodium alcoholate in dry ether medium. The product formed (2:3-dimethoxybenzoyl acetoacetic ester) was directly hydrolysed by refluxing with 33% sulphuric acid for 10 hours. The resulting dimethoxy acetophenone (XXI) was characterised by its boiling point (143-44° at14 mm.).



XVIII XIX XX XXI XVII

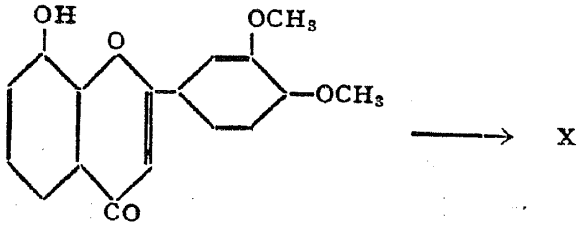
and the preparation of the oxime. The 2: 3-dimethoxy acetophenone was demethylated to 2: 3-dihydroxy acetophenone (XVII) by refluxing with aqueous hydrobromic acid (48%) and glacial acetic acid for 5 hours.[8]

8-Hydroxy flavone (XIV) was now prepared by condensing 2: 3-dihydroxy acetophenone (XVII) with benzoic anhydride and sodium benzoate by the Allan-Robinson method. Hydrolysis was effected by refluxing the reaction product with alcoholic potash (8%) for 20 minutes. The 3-acyl compound (XXII) was deacylated by refluxing with sodium carbonate solution (5%) for 2 hours. 5: 8-Dihydroxy flavone (XI) (primetin) was obtained by the persulphate oxidation of 8-hydroxy flavone and the yield was about (15%).



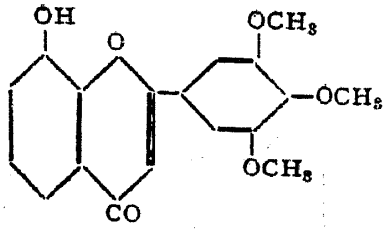
XXII

8-Hydroxy-3′: 4′-dimethoxy (XXIII) and 8-hydroxy-3′: 4′: 5′-trimethoxy flavones (XXIV) were obtained by condensing 2: 3-dihydroxy acetophenone (XVII) with the anhydride and sodium salt of veratric acid and of trimethyl gallic acid respectively. The flavones were oxidised by alkaline persulphate to 5: 8-dihydroxy-3′: 4′-dimethoxy flavone (X) and 5: 8-dihydroxy-3′: 4′: 5′-trimethoxy flavone (XXV) respectively (10% yields). (XXIII) and (XXIV) have been methylated and demethylated by the usual methods and the corresponding methyl ethers and the hydroxy compounds obtained.

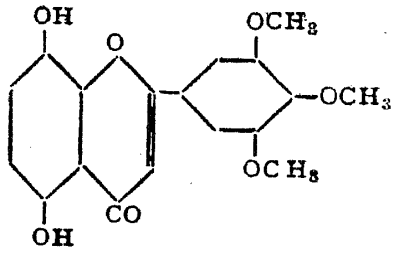


X

XXIII



XXIV



XXV

EXPERIMENTAL

5-Hydroxy-3′ : 4′ : 5′-trimethoxy flavone (II)

An intimate mixture of γ-resacetophenone (3 g.), trimethylgallic anhydride (24 g.) and sodium trimethylgallate (6 g.) was heated under reduced pressure at 180° C. for 4 to 5 hours. The product was then worked up using different conditions for hydrolysis:—

Method (1).—The hydrolysis was carried out by refluxing for 20 minutes with aqueous alcoholic potassium hydroxide (8 g. in 150 c.c.). The alcohol was removed under reduced pressure, the residue taken up in water and carbon dioxide passed through the suspension for 4 hours. The precipitated solid was found to be largely the 3-acyl derivative. It was purified by recrystallisation from alcohol when the 5-hydroxy-3′ : 4′ : 5′-trimethoxy-3-trimethylgalloyl flavone was obtained as pale yellow long thin plates melting at 147–48° C. Yield, 1·5 g. (Found: C, 64·3; H, 5·0. $C_{28}H_{26}O_{10}$ requires C, 64·4; H, 5·1%). The 3-acyl group was removed by boiling this compound with 10% aqueous alcoholic sodium carbonate solution for 4 hours. The free flavone was crystallised from a large volume of alcohol when it was obtained as bright yellow thick rods melting at 194–95°. (Found: C, 66·1; H, 5·0; $C_{18}H_{16}O_6$ requires C, 65·8 and H, 4·9%.)

The substance is insoluble in cold aqueous sodium hydroxide; on boiling it is converted into the bright yellow, sparingly soluble sodium salt. It dissolves to a pale yellow solution in concentrated sulphuric acid which shows no fluorescence but slowly turns brown. The compound gives a pink brown colour with alcoholic ferric chloride which becomes dark brown with excess.

Method (2).—The crude condensation product was broken up, suspended in alcohol (50 c.c.) and refluxed with 10% sodium carbonate solution (100 c.c.) for a period of 4 hours. The mixture which consisted of a suspension of the sparingly soluble, bright yellow sodium salt was acidified with dilute hydrochloric acid and the mixture of flavone and trimethylgallic acid which separated was filtered. It was stirred into an excess of aqueous sodium bicarbonate solution, the undissolved flavone filtered, washed well with water and then crystallised from a large volume of alcohol. 5-Hydroxy-3′ : 4′ : 5′-trimethoxy flavone was obtained as bright yellow thick rods melting at 194-95° C. Yield, 1·1 g.

Method (3).—The product from the Allan-Robinson condensation was broken up and treated with aqueous sodium carbonate (10%, 200 c.c.) and ether (100 c.c.) and the mixture shaken occasionally in the cold for 24 hours.

The ether layer was separated, washed successively with sodium bicarbonate solution and then with water. The solid which was left behind after removal of the solvent was crystallised from alcohol. The composition of the product varied in different experiments and consisted sometimes of the 3-acyl compound and at other times of the free flavone as the major fraction.

5 : 3′ : 4′ : 5′-*Tetramethoxy flavone* (*V*)

5-Hydroxy-3′ : 4′ : 5′-trimethoxy flavone (0·8 g.) was dissolved in 50 c.c. of dry acetone and redistilled dimethyl sulphate (1 c.c.) and freshly ignited potassium carbonate (3 g.) were added. The mixture was gently refluxed on a water-bath and after 15 hours another lot of 0·5 c.c. of dimethyl sulphate was added. The refluxing was continued for a total period of 32 hours after which time the acetone solution was filtered, the inorganic salts washed with warm acetone and the solvent distilled off. An yellowish oil was obtained which quickly solidified on rubbing with a glass rod. It was filtered, washed with water and crystallised twice from dilute alcohol (charcoal) when the tetramethoxy flavone was obtained as long colourless needles melting at 148–49° after drying. (Found: C, 66·8; H, 4·7. $C_{19}H_{18}O_6$ requires C, 66·6 and H, 5·2%.)

5 : 3′ : 4′ : 5′-*Tetrahydroxy flavone* (*IX*)

The trimethoxy flavone (1 g.) was dissolved in acetic anhydride (10 c.c.) by warming and to the solution was added hydriodic acid (15 c.c.; d. 1·7) in small quantities with cooling. The mixture was refluxed in an oil-bath for 2½ hours, cooled and treated with an excess of a saturated solution of sodium bisulphite. The brown solid which separated was filtered and repeatedly extracted with hot acetone, the acetone solution filtered and concentrated when an yellow solid was obtained. When crystallised twice from acetone-alcohol mixture it came out as clusters of yellow prisms turning brown at 290° and decomposing at 310–12° C. Yield, 0·6 g. (Found: C, 62·7, H, 4·0. $C_{15}H_{10}O_6$ requires C, 62·9 and H, 3·5%). The tetra-acetate prepared as usual melted at 225–26°.

2-*Trimethylgalloyloxy-6-methoxy acetophenone* (*III*)

Dry trimethylgallic acid (2 g.) was treated with thionyl chloride (3 c.c.) and the mixture heated on a water-bath for half an hour. The excess of thionyl chloride was then distilled away and monomethyl ether of γ-resacetophenone (0·5 g.) added followed by 6 c.c. of anhydrous pyridine. The mixture was heated on a water-bath for 1 hour and then treated with ice-cold dilute hydrochloric acid. The precipitated solid was extracted with ether and the ethereal solution was successively washed with dilute sodium

hydroxide, dilute hydrochloric acid and water. The ester obtained after removal of the solvent crystallised from alcohol as colourless long thin plates melting at 153–54° C. Yield, 0·5 g. (Found: C, 63·1; H, 5·8. $C_{19}H_{20}O_7$ requires C, 63·3 and H, 5·5%).

2-*Hydroxy*-6 : 3′ : 4′ : 5′-*tetramethoxy dibenzoyl methane* (*IV*)

The above ester (1 g.) was dissolved by warming in 10 c.c. of dry pyridine, then treated with finely powdered potassium hydroxide (1·2 g.) and shaken vigorously. The temperature was maintained at 40° by occasional warming in a water-bath. The solution soon became deep yellow and thick due to the separation of the potassium salt of the diketone. After 15 minutes the mixture was acidified with 100 c.c. of cold 20% acetic acid when a yellow semi-solid separated which soon solidified. It was filtered, washed thoroughly with water and crystallised from benzene-petroleum ether mixture. The diketone was obtained as bright yellow broad prisms and plates melting at 150–51° C. Yield, 0·6 g. (Found: C, 63·5, H, 5·6. $C_{19}H_{20}O_7$ requires C, 63·3 and H, 5·5%.) It gave a pink-brown colour with ferric chloride in alcoholic solution, and turned reddish-brown with excess.

5 : 3′ : 4′ : 5′-*Tetramethoxy flavone*

The diketone (1 g.) was dissolved in frozen and remolten acetic acid (20 c.c.) and fused sodium acetate (3 g.) added and the mixture refluxed for 2 hours. It was then diluted with water, the precipitated solid filtered and recrystallised from dilute alcohol. It melted at 147° and did not depress the melting point of the tetramethoxy flavone prepared earlier. Yield, 0·3 g.

5-*Hydroxy*-3′ : 4′-*dimethoxy flavone* (*VI*)

An intimate mixture of γ-resacetophenone (3 g.), veratric anhydride (24 g.) and sodium veratrate (6 g.) was heated under reduced pressure at 180° for 5 hours. The product was broken up and treated with 10% aqueous sodium carbonate solution (200 c.c.) and ether (100 c.c.) and the mixture occasionally shaken in the cold for 24 hours. The ether layer was worked up as before, and the pale yellow solid was crystallised from alcohol when the 5-hydroxy-3′ : 4′ -dimethoxy-3-veratroyl flavone was obtained as yellow prisms melting at 142-43°. Yield, 1·0 g. (Found: C, 67·7, H, 5·0. $C_{26}H_{22}O_8$ requires C, 67·5 and H, 4·8%.) In a number of experiments, the amount of the free flavone isolated by this method was found to be very little.

The hydrolysis of the 3-acyl group was carried out by boiling with 10% aqueous-alcoholic sodium carbonate and the flavone isolated in the usual manner. It crystallised from alcohol as pale yellow plates and prisms melting

at 165-66°. (Found: C, 68·0, H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4 and H, 4·7%.) The compound dissolves with difficulty in 5% sodium hydroxide to give an yellow solution from which the yellow sodium salt slowly separates. It gives a pink brown colour with alcoholic ferric chloride and turns purple-brown with excess.

5 : 3′ : 4′-*Trimethoxy flavone (VII)*

The dimethoxy flavone (0·25 g.) was methylated by refluxing in anhydrous acetone (50 c.c.) solution with redistilled dimethyl sulphate (2 c.c.) and ignited potassium carbonate (5 g.) for 40 hours. The trimethyl ether crystallised from dilute alcohol as long, colourless needles and thin rods and melted at 139–40° after drying at 100° for 4 hours. The compound dissolves in concentrated sulphuric acid to a bright yellow solution showing no fluorescence. The solution slowly turns brown and then green in 24 hours.

5 : 3′ : 4′-*Trihydroxy flavone (VIII)*

The dimethoxy flavone (2 g.) was demethylated in acetic anhydride (15 c.c.) solution by boiling with hydriodic acid (d. 1·7, 20 c.c.) for 4 hours. The brown solid product was recrystallised from methyl alcohol and the trihydroxy flavone obtained as pale yellow plates darkening at 260° and decomposing at 278–80° C. Yield 0·8 g. In 5% sodium hydroxide the substance dissolves immediately to a deep yellow solution which quickly turns brown on shaking. With ferric chloride it gives a brown colour in alcoholic solution.

5 : 8-*Dihydroxy*-3′ : 4′-*dimethoxy flavone (X)*.—A solution of potassium persulphate (1·2 g. in 100 c.c.) was added dropwise to a mechanically stirred solution of 5-hydroxy-3′ : 4′-dimethoxy flavone (0·8 g.) in a mixture of aqueous potash (2 g. in 25 c.c.) and pyridine (25 c.c.) during 2 hours. The stirring was continued for another 4 hours after which the contents were left for 36 hours. After acidification with hydrochloric acid a small quantity of unchanged flavone was extracted with ether (25 c.c.; thrice); a further amount of concentrated hydrochloric acid (15 c.c.) was added and the mixture kept on a boiling water-bath for 20 minutes. It was then repeatedly extracted with ether and the quinol obtained by removal of the solvent. The yellow solid crystallised from ethyl acetate as bright yellow small plates sintering at 235° and melting with decomposition at 240° C. A mixed melting point determination with a sample prepared by the oxidation of 8-hydroxy-3′ : 4′-dimethoxyflavone showed no depression. Yield, 80 mg.

In aqueous sodium carbonate the quinol dissolves instantly to a red solution which rapidly changes to green and fades off to yellow. In aqueous

sodium hydroxide it gives a greenish solution quickly turning pale pink and fading to brownish-yellow. The compound gives a brown ferric reaction, after the production of an initial green colour.

2 : 3-*Dimethoxybenzoyl acetoacetic ester*

Separate solutions of sodium (2·49 g., 0·3 mole) in absolute alcohol (42 c.c.) and of 2 : 3-dimethoxybenzoyl chloride (10 g., 0·15 mole) in absolute ether (210 c.c.) were prepared. Half of the sodium alcoholate solution (21 c.c.) was mixed with acetoacetic ester (7·01 g., 0·15 mole) and to this half of the ethereal solution of dimethoxybenzoic acid chloride (105 c.c.) was added and the mixture shaken in the cold for half an hour. A mixture of sodium chloride and the sodium salt of the dimethoxybenzoyl acetoacetic ester gradually separated. After half an hour, sodium alcoholate solution (10·05 c.c.) and dimethoxybenzoyl chloride solution (50 c.c.) were added and the shaking continued for another half an hour. The condensation was completed by the addition of the remaining sodium alcoholate solution (10·05 c.c.) and the acid chloride solution (50 c.c.). The reaction flask was then kept overnight in the refrigerator. The salts which separated were filtered, washed with absolute ether and directly put up for hydrolysis with dilute sulphuric acid.

2 : 3-*Dimethoxy acetophenone* (*XXI*)

The sodium salt of 2 : 3-dimethoxybenzoyl acetoacetic ester obtained above was refluxed with excess of 33% sulphuric acid (200 c.c.) for 8 hours. The solution along with the oily material was then cooled and extracted with ether. The ethereal solution was thoroughly washed with 5% alkali to remove any free acid present, then with water and dried over anhydrous sodium sulphate. The solvent was removed and the 2 : 3-dimethoxy acetophenone distilled under reduced pressure (143–44° at 14 mm.). Yield, 4 g.

The oxime was prepared by refluxing a solution of 2 : 3-dimethoxy acetophenone (2·5 g.) in 10 c.c. alcohol with hydroxylamine hydrochloride (3 g. in 5 c.c. water) and sodium acetate (5·1 g.) for 2 hours. After crystallisation from alcohol it melted at 96–97°.

2 : 3-*Dihydroxy acetophenone* (*XVII*)

2 : 3-Dimethoxy acetophenone (1 g.) was demethylated by refluxing with hydrobromic acid (8 c.c., d. 1·5) in acetic acid solution (8 c.c.) for 5 hours according to the method of Baker and Smith.[8] On crystallisation from dilute methanol the dihydroxy acetophenone came out as pale yellow plates melting at 97–98° C. Yield, 0·6 g. It gave a green colour with alcoholic ferric chloride solution.

8-*Hydroxy flavone* (*XIV*)

An intimate mixture of 2:3-dihydroxy acetophenone (3·5 g.), benzoic anhydride (30 g.) and sodium benzoate (8 g.) was heated under reduced pressure at 180–85° for 10 hours. The cake was then broken up, stirred with alcohol (150 c.c.) and refluxed with potassium hydroxide solution (15 g. in 15 c.c. water) for 20 minutes. The alcohol was removed under reduced pressure, the residue dissolved in water (300 c.c.) and the alkaline solution extracted with ether to remove oily impurities. Carbon dioxide was then passed into the solution for 4 hours, the brown mass that separated was filtered and extracted with benzene (8–10 times; 100 c.c. each time). The benzene solution on concentration gave the 3-acyl flavone (XXII). A further quantity was obtained by extracting the mother liquor with benzene. It crystallised from benzene as colourless, thick prisms melting at 223–24° C. Yield, 3·5 g.

The 3-acyl group was removed by refluxing the substance with sodium carbonate solution (100 c.c.; 5%) for 2 hours. The solution was then acidified with hydrochloric acid in the hot and the solid filtered. It was washed with a small quantity of hot water and crystallised from alcohol when the 8-hydroxy flavone was obtained as colourless, stout rods melting at 249-50° C. Ruhemann records the melting point of 8-hydroxy flavone as 250°. Yield, 1·7 g. It dissolved in 5% sodium hydroxide to a brown solution and gave a light brown colour with alcoholic ferric chloride.

8-Acetoxy flavone was prepared by heating 8-hydroxy flavone with acetic anhydride and 2 drops of dry pyridine at 140-50° for 2 hours. The acetate crystallised from a mixture of benzene and petrol as bunches of colourless needles melting at 142-43° C. 8-Methoxy flavone prepared by methylation of 8-hydroxy flavone in acetone solution with methyl sulphate and potassium carbonate crystallised from dilute alcohol as bunches of colourless, long needles and melted at 199–200°.

5:8-*Dihydroxy flavone*: *Primetin* (*XI*)

8-Hydroxy flavone (1·5 g.) was dissolved in sodium hydroxide solution (2·25 g. in 50 c.c. water) and the yellowish-brown solution continuously stirred with a magnetic stirrer. A solution of sodium persulphate (1·5 g. in 40 c.c. water) was then added dropwise during the course of 2 hours, the temperature of the contents being maintained at 15-20° C. throughout the experiment. After the addition was complete, the strirring was continued for another hour and the solution left overnight. It was then acidified to congo red with hydrochloric acid when some of the original product separated. This was filtered and the filtrate extracted with ether. Sodium

bisulphite (0·2 g.) and concentrated hydrochloric acid (25 c.c.) were added and the solution heated on a water-bath at 75–80° for 15 minutes. After cooling it was extracted with ether, the solvent distilled and the brown powder dried and crystallised from a mixture of ethyl acetate and petrol. The product separated as bright yellow plates melting at 227–29° C. Yield, 0·2 g. It gave a green colour with alcoholic ferric chloride solution and agreed in all its properties with primetin.[3] Mixed melting point with an authentic sample was undepressed.

8-*Hydroxy*-3′ : 4′-*dimethoxy flavone* (*XXIII*).—

2 : 3-Dihydroxy acetophenone (5·6 g.), veratric anhydride (50 g.) and sodium salt of veratric acid (10 g.) were thoroughly mixed and heated at 180–85° under diminished pressure for 12 hours. The product was worked up as before and the 3-veratroyl flavone crystallised from a mixture of benzene and ethyl acetate when it separated as colourless, small prisms melting at 134–35° C. Yield, 5·0 g. (Found: C, 67·6; H, 4·9. $C_{26}H_{22}O_8$ requires C, 67·5 and H, 4·7%.) It gave a light brown colour with alcoholic ferric chloride.

Deacylation of the 3-acyl compound was effected by refluxing it with sodium carbonate solution (5%, 150 c.c.) for 2 hours, and the 8-hydroxy-3′ : 4′-dimethoxy flavone was crystallised from a mixture of methyl alcohol and ethyl acetate. It came out as pale brown, short needles melting at 254–55° C. Yield, 2·1 g. (Found: C, 66·7; H, 4·8. $C_{17}H_{14}O_5$, $\frac{1}{2}H_2O$ requires C, 66·4 and H, 4·8%.) It gave a light brown colour with alcoholic ferric chloride solution. An alcoholic solution of the flavone developed an orange colour on reduction with magnesium and hydrochloric acid.

The acetate was prepared by heating with acetic anhydride and a drop of dry pyridine. It crystallised from ethyl alcohol as yellow long thin rods melting at 174–75° C. (Found: C, 67·7; H, 5·2. $C_{19}H_{16}O_6$ requires C, 67·1 and H, 4·7%).

8 : 3′ : 4′-*Trimethoxy flavone*

8-Hydroxy-3′ : 4′-dimethoxy flavone was methylated by refluxing with excess of dimethyl sulphate and anhydrous potassium carbonate in dry acetone solution for 8 hours. The methyl ether crystallised from methyl alcohol as yellow small rectangular prisms melting at 148–49° C.

8 : 3′ : 4′-*Trihydroxy flavone*

To a suspension of 8-hydroxy-3′ : 4′-dimethoxy flavone (0·2 g.) in acetic anhydride (5 c.c.) was added hydriodic acid (5 c.c.; d. 1·7) cautiously

with cooling in ice. The solution was refluxed (147–50°) for 2 hours, diluted with ice-cold water and treated with a saturated solution of sodium bisulphite (20 c.c.). The contents were cooled and the solid that separated was filtered and dried. The trihydroxy flavone crystallised from a mixture of ethyl acetate and acetone (charcoal) as very pale yellow, tiny prisms melting at 275–76° C. Yield, 0·15 g. An alcoholic solution of the compound gave a grass green colour with ferric chloride. (Found: C, 66·2; H, 3·9. $C_{15}H_{10}O_5$ requires C, 66·6 and H, 3·7%).

The triacetate prepared by the usual method was crystallised from a mixture of ethyl acetate and methyl alcohol and was obtained as colourless, long woolly needles, melting at 213–14° C. (Found: C, 63·6; H, 4·0; $C_{21}H_{16}O_8$ requires C, 63·7 and H, 4·1%).

5 : 8-*Dihydroxy*-3′ : 4′-*dimethoxy flavone* (*X*)

8-Hydroxy-3′ : 4′-dimethoxy flavone (1·5 g.) was dissolved in sodium hydroxide solution (1 g. in 50 c.c. water) and to the light-brown solution was added dropwise a solution of sodium persulphate (2·3 g. in 30 c.c. water) during the course of 2½ hours. Throughout the addition the mixture was kept mechanically stirred and the temperature maintained at 15–20°. Stirring was then continued for another hour and the contents left overnight at room temperature. After working up as before the oxidation product was obtained as a brown powder. It was dried and crystallised from a mixture of ethyl acetate and petrol when 5 : 8-dihydroxy-3′ : 4′-dimethoxy flavone separated as small yellow broken plates. It sinters at 230°, melts at 234–35° and decomposes at 240° C. Yield, 0·15 g. Mixed melting-point with a sample prepared by the persulphate oxidation of 5-hydroxy-3′ : 4′-dimethoxy flavone was undepressed. With ferric chloride an alcoholic solution of the compound gave a green colour which changed to brown after some time. (Found: C, 61·7; H, 4·6. $C_{17}H_{14}O_6$, H_2O requires C, 61·4 and H, 4·8%.)

8-*Hydroxy*-3′ : 4′ : 5′-*trimethoxy flavone* (*XXIV*)

An intimate mixture of 2 : 3-dihydroxy acetophenone (3·5 g.), trimethylgallic anhydride (32 g.) and sodium salt of trimethylgallic acid (8 g.) was heated under reduced pressure at 180–85° for 10 hours. The product was worked up as before and was found to consist of only the free flavone with practically no admixture of the 3-acyl compound. On crystallisation from a mixture of ethyl acetate and acetone (charcoal) it separated as pale yellow, short needles melting at 228–30° C. Yield, 1·3 g. It does not give any distinct colour with alcoholic ferric chloride. (Found: C, 65·9; H, 5·3. $C_{18}H_{16}O_6$ requires C, 65·8 and H, 4·9%.)

The acetate crystallised from ethyl acetate as colourless, woolly needles melting at 194–95° C.

8 : 3′ : 4′ : 5′-*Tetramethoxy flavone*

8-Hydroxy-3′ : 4′ : 5′-trimethoxy flavone was methylated in dry acetone solution by refluxing with excess of dimethyl sulphate and anhydrous potassium carbonate for 8 hours. The methyl ether crystallised from methyl alcohol as pale yellow long thin plates melting at 189–90° C. (Found: C, 64·9; H, 5·0; $C_{19}H_{18}O_6$, $\frac{1}{2}H_2O$ requires C, 64·9; H, 5·4%).

8 : 3′ : 4′ : 5′-*Tetrahydroxy flavone*

The demethylation of 8-hydroxy-3′ : 4′ : 5′-trimethoxy flavone (0·15 g.) was carried out by boiling in acetic anhydride (5 c.c.) solution with hydriodic acid (5 c.c., d. 1·7) for 2 hours. The tetrahydroxy flavone crystallised from a mixture of ethyl acetate and methyl alcohol (charcoal) as colourless short prismatic needles melting at 320–22° C. Yield, 0·1 g. It gave a green colour with alcoholic ferric chloride.

The tetra-acetate was prepared by heating with acetic anhydride and a drop of dry pyridine for 2 hours. It crystallised from ethyl acetate as colourless flat needles and plates melting at 200–1° C.

5 : 8-*Dihydroxy*-3′ : 4′ : 5′-*trimethoxy flavone* (*XXV*)

8-Hydroxy-3′ : 4′ : 5′-trimethoxy flavone (1 g.) was dissolved in sodium hydroxide solution (0·5 g. in 15 c.c. water) and the oxidation was carried out with sodium persulphate solution (1·5 g. in 35 c.c. water) as in the previous case. The quinol was crystallised from a mixture of ethyl acetate and acetone (charcoal) when it separated as aggregates of yellow plates. It shrinks at 250° and melts at 255° C. Yield, 0·1 g. The compound gave a green colour with alcoholic ferric chloride solution. (Found: C, 63·0; H, 5·0. $C_{18}H_{16}O_7$ requires C, 62·8 and H, 4·7%.)

SUMMARY

The two higher analogues of 5-hydroxy flavone (primuletin) containing two and three methoxyl groups in the side phenyl nucleus have been synthesised and subjected to persulphate oxidation. 5-Hydroxy-3′ : 4′-dimethoxy flavone gave poor yield of dimethoxy primetin while the higher member could not be oxidised under these conditions. Alternatively, oxidation of 8-hydroxy flavones has been attempted and found to proceed more satisfactorily to yield primetin and its higher members. The required 8-hydroxy flavones

have been made from 2:3-dihydroxy acetophenone for the preparation of which a convenient method has been worked out starting from ortho vanillin.

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