6:7-DIHYDROXY-FLAVONOLS: PART II

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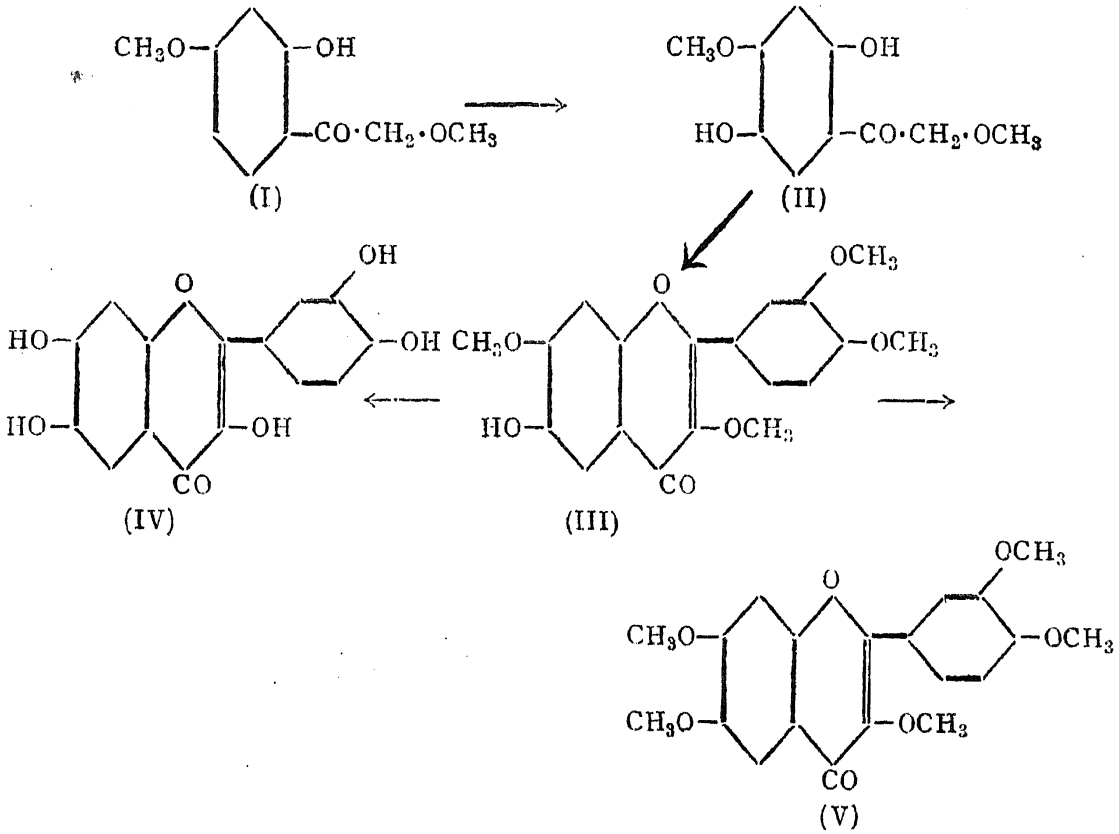
Received October 11, 1945

In Part I[1] was described the preparation of 3:6:7:3′:4′-pentahydroxy-flavone using the following series of reactions:



Following the same procedure and using the sodium salts and anhydrides of benzoic, anisic and trimethyl gallic acids for condensation with the ketone (II), the other flavonols of the series with 0, 1 and 3 hydroxyl groups in the side-phenyl nucleus have now been prepared and their properties and those of their derivatives are described in this paper. Certain interesting similarities and gradations in properties have been observed among them and they are discussed below.

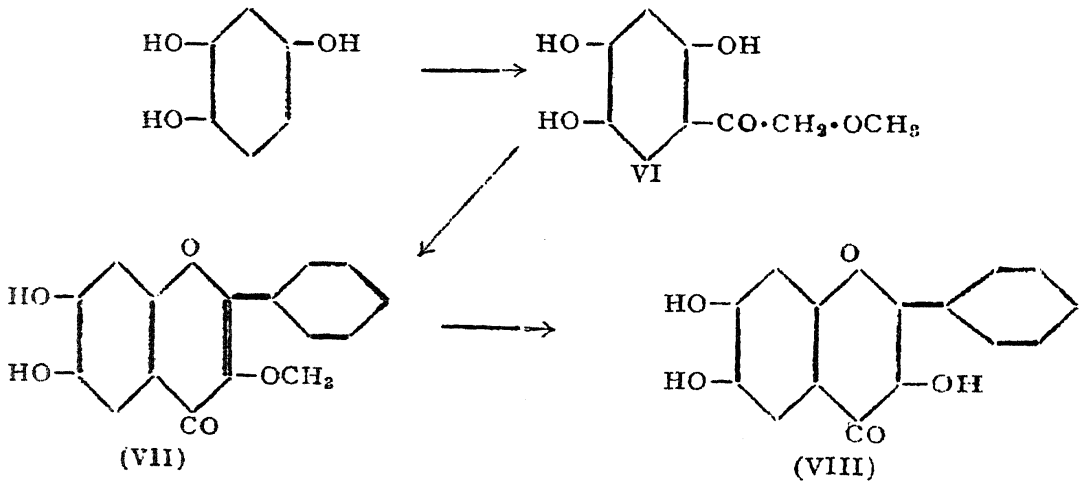
Those corresponding to (III) having one free hydroxyl group in position 6, are soluble in aqueous alkali giving stable yellow coloured solutions. Their alcoholic solutions exhibit greenish blue fluorescence and give only

a feeble colour with ferric chloride. There is decreasing intensity in the colour of the solid substance with increasing number of methoxyls in the side-phenyl nucleus. 3:7:4'-Trimethoxy-6-hydroxy flavone is bright yellow in colour, the next higher member only pale yellow and the last member is quite colourless.

The poly-hydroxy compounds corresponding to (IV) are pale yellow substances sparingly soluble in alcohol. Their alcoholic solutions exhibit bright green fluorescence and give deep greenish brown colour with ferric chloride. The colour changes exhibited by the earlier members in solutions of alkaline pH are not prominent; but the highest member quickly changes its colour in dilute alkali from yellow to pink, violet, blue and finally brown. They all exhibit bright bluish green fluorescence in concentrated sulphuric acid.

Among the completely methylated compounds (Type V) the hexa- and penta-methoxy flavones exhibit pale blue fluorescence in alcoholic solution, but the lower members do not. However, all of them give bright bluish-green fluorescence in concentrated sulphuric acid solution.

An alternative method of preparing the above-mentioned 6:7-dihydroxy-flavonols would be to start with hydroxy-quinol and proceed as indicated below:



6:7-Dihydroxy-flavone [2,3] itself was prepared in the past by a similar procedure employing 2:4:5-tri-hydroxy acetophenone or its methyl ether. There has been some difference of opinion regarding the exact constitution of the ketone obtained from hydroxy-quinol. Chada and Venkataraman[3] have given satisfactory arguments in support of its constitution as 2:4:5-tri-hydroxy-acetophenone. Based on similar considerations the product of the condensation of methoxy acetonitrile with hydroxy-quinol should have the constitution (VI). This has now been independently supported by

methylating the compound completely and comparing the resulting product with *w* : 2: 4: 5-tetra-methoxy-aceto-phenone prepared by Row and Seshadri[1] by a different method. The two ketones are found to be identical. The preparation of the ω-methoxy-ketone (VI) was first made by Healy and Robinson[4] who converted it into 2-methyl-3-methoxy-6:7-dihydroxy-chromone. The ketone normally comes as a monohydrate and melts low; the anhydrous substance melts at 150°.

Though the second method given above may look simpler, there are difficulties of experimental technique particularly in regard to the preparation of pure samples of hydroxy-quinol and of its conversion into the ω-methoxy-ketone (VI). Attempts to simplify the synthesis by using the more easily available triacetate of hydroxy-quinol were not successful. The acetate does not undergo deacetylation or condensation with acetonitrile under the conditions of Hoesch reaction. Consequently the earlier method adopted by Row and Seshadri for preparing these flavonols seems to be more convenient.

Experimental

ω-Methoxy-2: 4: 5-trihydroxy-acetophenone (VI):—As reported by Healy and Robinson[4] the yield of this ketone is very low under the ordinary conditions of Hoesch reaction. Even under these conditions it could be raised to about 30% by employing purified hydroxy-quinol and hydrolysing the ketimine hydrochloride in an atmosphere of carbon dioxide. The product is a coloured oil which does not solidify and could not be crystallised directly. But on treatment with saturated sodium bisulphite solution it rapidly turns into a mass of crystals (colourless needles) and can be subsequently crystallised from acetone or acetone-benzene mixture. It first comes as a monohydrate and melts at 110–11°; but crystallisation from anhydrous acetone-benzene mixture yields the anhydrous form melting at 150–51°. (Found: C, 54·3; H, 4·9; $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%.)

ω: 2 : 4 : 5-Tetramethoxy-acetophenone:—ω-Methoxy-2: 4: 5-trihydroxy-acetophenone (VI) (0·15 g.) was dissolved in dry acetone (25 c.c.) and treated with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (1 g.). The mixture was refluxed for 12 hours. After removing the acetone, water was added to dissolve the potassium salts and the mixture extracted with ether. The ether solution was shaken with aqueous alkali to remove any partially methylated ketone. It was then washed with water and evaporated; a colourless crystalline solid was obtained and it was purified by crystallising twice from alcohol. It came out as colourless, long, transparent rectangular plates melting at 133–34°. It was insoluble in alkali and gave no colour with ferric chloride. Mixed melting point with

the substance prepared by methylating ω : 4-dimethoxy-2 : 5-dihydroxy acetophenone by Row and Seshadri was not depressed. (Found : C, 60·0; H, 6·9; $C_{12}H_{16}O_5$ requires C, 60·0 and H, 6·7%.)

6 : 7-*Dihydroxy-3-methoxy-flavone* (*VII*):—An intimate mixture of ω-methoxy-2 : 4 : 5-tri-hydroxy-acetophenone (VI) (0·9 g.), benzoic anhydride (9 g.) and sodium benzoate (4 g.) was heated *in vacuo* at 170–80° in an oil-bath for four hours. The pale brown solid was broken up with a glass-rod and refluxed with alcohol (25 c.c.) for 10 minutes. Alcoholic potash (8 g. of potash in 55 c.c.) was slowly introduced through the condenser and the refluxing continued for 20 minutes more. The solvent was then distilled under reduced pressure keeping the temperature as low as possible. Water (40 c.c.) was added to the residue and the clear solution obtained was saturated with carbon dioxide when a brown solid separated out. It was filtered and washed with water. The filtrate was repeatedly extracted with ether (5 times) and some more substance recovered by evaporating the ethereal extract. The two lots were combined and purified by crystallisation from alcohol. Two crystallisations were found sufficient to give the compound in a state of purity. 6 : 7-Dihydroxy-3-methoxy-flavone was thus obtained in the form of very pale yellow rectangular plates melting at 242–44°. With alcoholic ferric chloride it gave an olive green colour. It readily dissolved in alkali forming a bright yellow solution. In concentrated sulphuric acid, an yellow solution with blue fluorescence was obtained. Yield 0·45 g. (Found : C, 68·0; H, 4·2; $C_{16}H_{12}O_5$ requires C, 67·6 and H, 4·2%.)

3 : 6 : 7-*Trimethoxy-flavone*: *First Method*:—6 : 7-Dihydroxy-3-methoxy flavone (VII) (0·1 g.) was treated with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (1 g.) in anhydrous acetone (25 c.c.). After refluxing the mixture for 12 hours, the solvent was removed by evaporation, the residue treated with water and the mixture extracted twice with ether. The ether extract was first shaken with a weak solution of alkali and then twice with water. It was then evaporated to dryness and the colourless crystalline solid thus obtained, was crystallised from alcohol. The trimethoxy flavone crystallised in the form of colourless long needles melting at 175–76°. It gave no colour with ferric chloride in alcoholic solution and was insoluble in alkali. (Found : C, 69·2; H, 4·7; $C_{18}H_{16}O_5$ requires C, 69·2 and H, 5·0%.)

Second Method:—ω : 4-Dimethoxy-2 : 5-dihydroxy-acetophenone (II) (0·25 g.) was condensed with benzoic anhydride (2·0 g.) and sodium benzoate (0·5g.) according to the method of Allan and Robinson. After hydrolysis, the product was crystallised from alcohol, when 3 : 7-dimethoxy-6-hydroxy-flavone was obtained in the form of narrow rectangular plates and needles

melting at 198–200°. This was methylated using dimethyl sulphate, anhydrous acetone and anhydrous potassium carbonate as in the first method. The trimethyl ether was crystallised twice from alcohol and obtained in the form of colourless long needles melting at 175–176°. The mixed melting point with the sample from the first method was not depressed.

3 : 6 : 7-*Trihydroxy-flavone* (*VIII*) :—6 : 7-Dihydroxy-3-methoxy-flavone (VII)(0·3 g.) was dissolved in acetic anhydride (5 c.c.) by warming and the solution treated with hydriodic acid (7 c.c., *d* 1·7) slowly with stirring and cooling in ice water. The solution was then gently boiled under reflux for an hour; water was then added to the cooled solution and the mixture treated with a current of sulphurdioxide. The solid product was filtered and washed well with water. It was purified by crystallising twice from alcohol when it was obtained in the form of elongated rectangular prisms. It darkened at about 300° and melted completely at 312–315°. Yield 0·2. g. It was sparingly soluble in cold alcohol and the solution exhibited a feeble blue fluorescence. With ferric chloride it gave a dark greenish-brown colour. (Found: C, 66·5; H, 3·6; $C_{15}H_{10}O_5$ requires C, 66·7 and H, 3·7%.)

The triacetate of the above flavonol was prepared by refluxing it with acetic anhydride and anhydrous sodium acetate for an hour and a half. It crystallised from alcohol (amimal charcoal) in the form of colourless triangular prisms melting at 191–192°. (Found: C, 63·6; H, 4·0; $C_{21}H_{16}O_8$ requires C, 63·6 and H, 4·1%.)

3 : 7 : 4′-*Trimethoxy-6-hydroxy-flavone.*—ω : 4-Dimethoxy-2 : 5-dihydroxy acetophenone (II) was condensed with anisic anhydride (8 g.) and sodium anisate (2 g.) in the usual manner. The product obtained after hydrolysis and neutralisation of the alkali with carbon dioxide was purified by crystallisation from glacial acetic acid. It came out in the form of yellow glistening crystals melting at about 220°. A second crystallistion from alcohol gave the pure compound in the form of bright yellow rectangular plates and prisms melting at 225–26°. Yield, 0·9 g. It was sparingly soluble in alcohol; the alcoholic solution exhibited a feeble green fluorescence and did not give any colour with ferric chloride. It was readily soluble in aqueous alkali giving a bright yellow colour. (Found: C, 65·3; H, 4·6; $C_{18}H_{16}O_6$ requires C, 65·9 and H, 4·9%.)

3 : 6 : 7 : 4′-*Tetra-methoxy-flavone* was obtained by methylating the above flavone with dimethyl sulphate and anhydrous potassium carbonate in anhydrous acetone medium as before. After two crystallisations from alcohol it was obtained as colourless narrow rectangular plates melting at 164–65°. It did not dissolve in alkali and developed no colour with ferric chloride

in alcoholic solution. (Found: C, 66·9; H, 5·7; $C_{19}H_{18}O_6$ requires C, 66·9 and H, 5·3%.)

3 : 6 : 7 : 4′-*Tetra-hydroxy-flavones*:—The demethylation of 3 : 7 : 4′-trimethoxy-6-hydroxy-flavone was effected with hydriodic acid (*d.* 1·7) in the usual manner. The product was sparingly soluble in alcohol and acetic acid. It was, however, crystallised from glacial acetic acid-acetone-ethyl acetate mixture from which it came out as yellow thin rectangular plates. It did not melt below 320° and darkened above that temperature. An alcoholic solution of the substance exhibited a greenish blue fluorescence and gave a deep olive green colour with ferric chloride. The substance was readily soluble in dilute alkali giving a bright yellow coloured solution. (Found: C, 59·3; H, 3·5; $C_{15}H_{10}O_6$, H_2O requires C, 59·2 and H, 3·9%.)

The tetra-hydroxy-flavone was acetylated using acetic anhydride and sodium acetate. The acetate crystallised from alcohol in the form of thin rectangular plates melting at 193–95°. (Found: C, 60·6; H, 3·7; $C_{23}H_{18}O_{10}$ requires C, 60·8 and H, 4·0%.)

3 : 7 : 3′ : 4′ : 5′-*Pentamethoxy-6-hydroxy-flavone*:—ω : 4-Dimethoxy-2 : 5-dihydroxy-acetophenone (II) (1 g.) was condensed in the usual manner with O-trimethyl gallic anhydride (12 g.) and sodium O-trimethyl gallate (4 g.). The condensation product was collected after hydrolysis and neutralisation of the alkali with carbon dioxide and was crystallised from alcohol. It was obtained in the form of colourless narrow, rectangular prisms melting at 203–04°. Yield, 0·8 g. It was easily soluble in alcohol and gave no characteristic colour with ferric chloride. In aqueous sodium hydroxide it dissolved readily forming an yellow coloured solution. (Found: C, 62·1; H, 5·4; $C_{20}H_{20}O_8$ requires C, 61·9 and H, 5·2%.)

3:6:7:3′:4′:5′-*Hexamethoxy-flavone* was prepared by methylating the above compound with dimethyl sulphate and anhydrous potassium carbonate in anhydrous acetone medium. It crystallised from alcohol in the form of broad rectangular plates melting at 204–05°. It gave no colour with ferric chloride and did not dissolve in aqueous alkali. It exhibited a blue fluorescence in alcoholic solution. The mixed melting point with the 6-hydroxy compound was considerably depressed (180–85°) showing that they were not identical. (Found: C, 62·9; H, 5·5; $C_{21}H_{22}O_8$ requires C, 62·7 and H, 5·5%.)

3 : 6 : 7 : 3′ : 4′ : 5′-*Hexahydroxy-flavone*:—The above pentamethoxy-6-hydroxy flavone was demethylated using hydriodic acid (*d.* 1·7). The yellow solid obtained was sparingly soluble in alcohol, acetic acid, acetone and ethyl acetate. It was crystallised from aqueous pyridine from which it

came out as star-like clusters of needles. It did not melt below 330°. An alcoholic solution of the flavonol exhibited a green fluorescence and developed a dark greenish brown colour with ferric chloride. In dilute aqueous alkali it dissolved readily to give an yellow solution which quickly changed from yellow to pink, violet, blue and finally to brown. (Found: C, 50·7; H, 4·0; $C_{15}H_{10}O_8$, 2 H_2O requires C, 50·9 and H, 4·0%.)

The acetate of the pentahydroxy flavonol was prepared in the usual manner by refluxing the flavonol with acetic anhydride and anhydrous sodium acetate for about an hour and a half. It crystallised from alcohol in the form of silky narrow rectangular plates melting at 227–29°. (Found C, 56·4; H, 4·1; $C_{27}H_{22}O_{14}$ requires C, 56·8 and H, 3·9%.)

Summary

Starting from ω-methoxy-resacetophenone and adopting the procedure described in Part I, 6 : 7-dihydroxy flavonols with 0, 1 and 3 hydroxyls in the side-phenyl nucleus have been prepared. The characteristic properties of the group with reference to the hydroxy-compounds and their partial and complete methyl ethers are described. An alternative method starting with hydroxy-quinol has also been investigated and the simplest member of the group prepared by this method also.

References

1. Row and Seshadri .. *Proc. Ind. Acad. Sci.*, 1945, **21 A**, 155.
2. Reigrodsky and Tambor .. *Ber.*, 1910, **43**, 1964.
3. Chada and Venkataraman .. *J. C. S.*, 1933, 1073.
4. Healy and Robinson .. *Ibid.*, 1934, 1628.