

SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

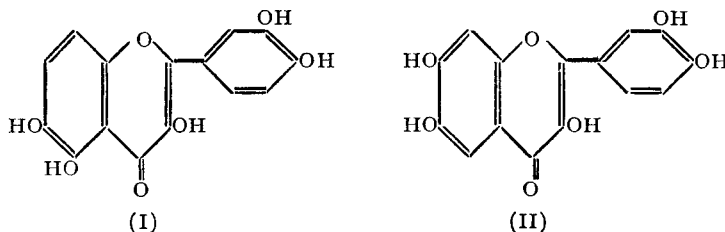
Part XXX. A Synthesis of 3 : 5 : 8 : 3' : 4'-Pentahydroxyflavone and Its Non-identity with Ponderosin

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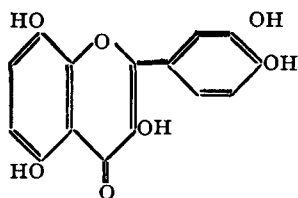
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KURTH and HUBBARD¹ isolated from *Ponderosa* pine bark a bright yellow colouring matter, to which we propose to assign the name ponderosin. It was soluble in acetone and alcohol, slightly soluble in water and insoluble in benzene, hexane and ethyl acetate; crystallization from acetone, ether and alcohol gave a material melting at 305–07° with decomposition. Reduction with magnesium and hydrochloric acid gave a pink colour and the test with Wilson's boric acid reagent² was positive. Molecular weight determination by the ebullioscopic method in ethyl alcohol gave values of 305 and 314, and the elementary analysis corresponded to $C_{15}H_{10}O_7$. A pentacetate with a m.p. of 237–39° was obtained on treatment with acetic anhydride and sodium acetate. The pentamethyl ether, m.p. 198–99°, was prepared by methylation with diazomethane in dry ether containing a trace of methanol till the methoxyl content did not increase; the product was insoluble in aqueous caustic soda and gave no colour with ferric chloride. Oxidation of the pentamethyl ether with hot alkaline potassium permanganate gave veratric acid. Fusion of ponderosin with caustic potash and methylation of the products with dimethyl sulphate gave veratrole and 1 : 2 : 4-trimethoxybenzene. Ponderosin thus appeared to be one of three pentahydroxyflavones: 3 : 5 : 6 : 3' : 4' (I), 3 : 6 : 7 : 3' : 4' (II), or 3 : 5 : 8 : 3' : 4' (III).



The structure (III) was then assigned, since (I) and (II) synthesized by Row and Seshadri³ had properties different from those of ponderosin; (II) was



(III)

also ruled out because a positive Wilson's boric acid test indicates a 5-hydroxyl group in a flavone.

3:5:8:3':4'-Pentahydroxyflavone (III) has now been synthesized and found to be different from ponderosin by a direct comparison. The properties of the pentahydroxyflavones (I), (II), (III) and ponderosin are shown in Table I.

In the course of our studies in Raney nickel reductions⁴ a method⁵ was developed for reducing 5:7-dihydroxyflavones to 5-hydroxyflavones by the action of Raney nickel and hydrogen on the 7-tosyl ester (*cf.* Kenner and Murray).⁶ This reaction has many interesting synthetic possibilities and has now been used for the synthesis of the flavone (III). 5:7-Dihydroxy-3:3':4'-trimethoxyflavone (IV)⁷ readily gave the 7-tosyl ester (V) on treatment with a molar proportion of *p*-toluenesulphonyl chloride and anhydrous potassium carbonate in boiling acetone. The hydrogenolysis of this derivative (V) with Raney nickel and hydrogen was carried out under controlled conditions leaving a part of the tosyl derivative unreacted in order to avoid reduction beyond the desired stage. The crude reaction product was

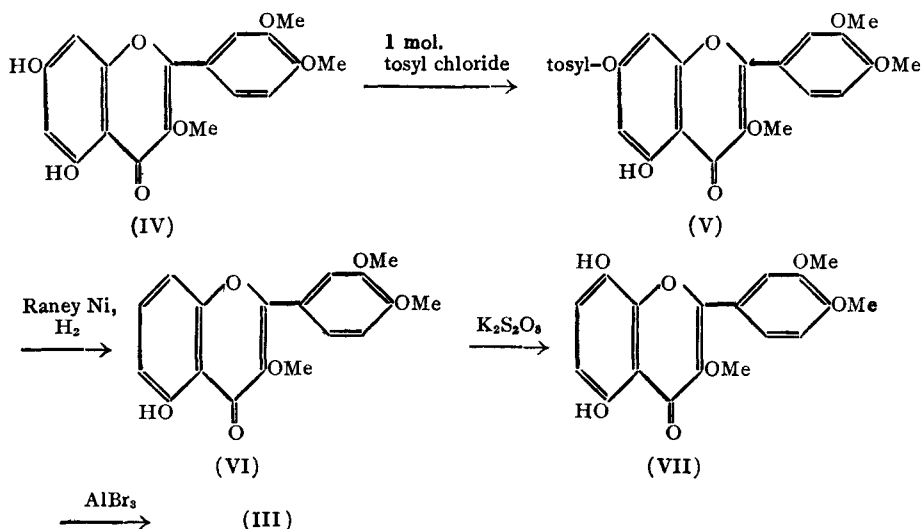


TABLE I
Properties of 3:5:6:3':4'-, 3:6:7:3':4'-, and 3:5:8:3':4'-pentahydroxyflavones and of ponderosin

Pentahydroxyflavone	m.p. ° C.	Fluorescence in alcoholic solution	Colour in aqueous caustic soda	Colour in potassium carbonate solution	Colour in concentrated sulphuric acid	Ferric chloride colouration	Lead acetate	M.P. of pentacetate ° C.	M.P. of pentamethyl ether ° C.
3:5:6:3':4'	Sinters 310 318-20	None			Bright yellow, no fluo- rescence	Dark olive green		196	121-2
3:6:7:3':4'	Does not melt below 310, darkens 315-20	Bright green	Bright stable orange- yellow		Bright yellow, green fluo- rescence	Dark olive green	Heavy orange- red preci- pitate	223-4	186-7
3:5:8:3':4'	270-71	None	Yellow- orange, turning pink	Yellow- orange, turning pink	Bright yellow, no fluo- rescence	Dark green	Heavy orange- red preci- pitate	236-7	165
Ponderosin	305-07		Green	Dark green	Bright orange	Dark green	Orange colouration	237-9	198-99 (diazomethane) 173 (dimethyl sulphate)

treated with alcoholic caustic potash to hydrolyse the unreacted tosyl derivative. From the resulting mixture of hydroxyflavones (IV and VI), 5-hydroxy-3:3':4'-trimethoxyflavone (VI) was extracted with cold benzene and purified further by chromatography on Florex. Oxidation of (VI) with potassium persulphate according to Rao and Seshadri⁸ yielded 5:8-dihydroxy-3:3':4'-trimethoxyflavone (VII).

Demethylation of the trimethyl ether (VII) with hydriodic acid gave a product which melted over a range and was difficult to crystallize. Aluminium chloride as a demethylating agent is free from the complication of rearrangement of flavones with hydroxyl groups in the 5:8-positions to the corresponding 5:6-compounds.⁹ Briggs and Locker¹⁰ found in connection with their work on meliternatin that, when aluminium chloride in nitrobenzene at 100° was used as the dealkylating agent, an aluminium lake was formed from which the metal could not be removed. Under milder conditions, using aluminium chloride in boiling ether, only partial dealkylation took place with the formation of a flavonol still containing one methoxyl group and giving a positive methylenedioxy test. Seshadri and co-workers¹¹ have reported failure in their attempt to demethylate "the higher members of the norwogonin series" with aluminium chloride. By using aluminium bromide which is readily soluble in benzene, the ether (VII) has now been smoothly demethylated to the pentahydroxy compound (III). The 5:8-orientation of the hydroxyl groups in the fused benzene ring was shown by the positive gossypetone reaction. The pentahydroxyflavone (III) dissolved in 0.1 N caustic soda and in potassium carbonate solution to yellow-orange solutions changing to pink, unlike ponderosin which gave a green colour with these reagents; (III) was soluble in ethyl acetate unlike ponderosin. The m.p. of (III) was depressed by mixing with ponderosin. Acetylation of (III) with acetic anhydride and pyridine gave the pentacetate, m.p. 236–37° which was depressed to 210–12° on admixture with the pentacetate prepared from ponderosin. The pentamethyl ether obtained by treatment of (VII) with dimethyl sulphate and anhydrous potassium carbonate in boiling acetone melted at 155°. For the purpose of comparison, ponderosin was methylated by the same method and the pentamethyl ether had m.p. 173°, while the product obtained by Kurth and Hubbard by means of diazomethane melted at 198–99°.

3:5:8:3':4'-Pentamethoxyflavone is being prepared by a second method involving the reduction of 3:5:8:3':4'-pentamethoxy-7-tosyloxyflavone.

EXPERIMENTAL

5-Hydroxy-3:3':4'-trimethoxy-7-tosyloxyflavone (V)

5:7-Dihydroxy-3:3':4'-trimethoxyflavone (14 g.) was dissolved in dry acetone (1,400 c.c.); *p*-toluenesulphonyl chloride (7.8 g., 1 mol.) and anhydrous potassium carbonate (45 g.) were added and the mixture was refluxed for 3 hours. Acetone was distilled off, the residue taken up in water and acidified. The precipitate was filtered, washed with water and dried; it crystallized from alcohol in yellow plates (15.1 g.), m.p. 157° (Found: C, 60.4; H, 4.5. $C_{25}H_{22}O_9S$ requires C, 60.2; H, 4.4%). The substance gives with aqueous caustic soda a sparingly soluble yellow sodium salt and with alcoholic ferric chloride a brown colour.

Reduction of 5-hydroxy-3:3':4'-trimethoxy-7-tosyloxyflavone

The tosyl ester (14 g.) was dissolved in alcohol (10 l.), Raney nickel prepared according to the method of Mazingo (140 g.) added, and the mixture agitated for one hour while a steady stream of hydrogen was led in. The mixture was then filtered and concentrated to a small bulk. The nickel residue was deactivated under hydrochloric acid, filtered, washed with water and the residue extracted with hot alcohol. The extract was added to the above concentrate, potassium hydroxide (7 g.) dissolved in a small amount of water added, and the solution refluxed for one hour. The alcohol was distilled off, the residue taken up in water and acidified. The precipitate (7.6 g.) was extracted with cold benzene and the benzene extract chromatographed on Florex. The yellow percolate on removal of the solvent gave a yellow substance which crystallized from methanol in pale yellow needles (4.2 g.), m.p. 153° (Found: C, 65.9; H, 5.1. $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9%). The substance, *5-hydroxy-3:3':4'-trimethoxyflavone (VI)*, gives a difficultly soluble yellow sodium salt with aqueous caustic soda and with alcoholic ferric chloride a green colour.

The residue undissolved by cold benzene (2.6 g.), after crystallization from alcohol, was identified as 5:7-dihydroxy-3:3':4'-trimethoxyflavone by m.p. and mixed m.p.

5-Acetoxy-3:3':4'-trimethoxyflavone

This was prepared by acetylation of (VI) (0.1 g.) by acetic anhydride (1 c.c.) and a drop of pyridine. It crystallized from methanol in long colourless silky needles, m.p. 157° (Found: C, 64.8; H, 5.2. $C_{20}H_{18}O_7$ requires C, 64.9; H, 4.9%).

5:8-Dihydroxy-3:3':4'-trimethoxyflavone (VII)

To a mechanically stirred solution of 5-hydroxy-3:3':4'-trimethoxyflavone (VI) (3.0 g.) in pyridine (75 c.c.) and potassium hydroxide solution (5 g. in 125 c.c. water), a solution of potassium persulphate (5 g. in 250 c.c. water) was added slowly in the course of two hours. The brown solution was allowed to stand for 24 hours and acidified, when unchanged 5-hydroxy-3:3':4'-trimethoxyflavone separated and was filtered off. The filtrate was extracted twice with ether to remove the last traces of the unreacted compound. The quantity of (VI) recovered was 0.6 g. After ether extraction, the clear brown aqueous layer was treated with sodium sulphite (10 g.) and conc. hydrochloric acid (100 c.c.) and heated on a boiling water-bath for 30 minutes. It was then cooled, and the yellow product which separated was filtered and washed with water. The filtrate on ether extraction gave more of the substance, but this was less pure. The product was first crystallized from ethyl acetate using a little Florex for removing the impurities, and then from methanol; the yellow needles (1.4 g.) had m.p. 212–13° (Found: C, 63.2; H, 4.9. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%). The substance dissolves in aqueous caustic soda to give a pinkish red solution; with alcoholic ferric chloride a brown colour is produced. On treatment with *p*-benzoquinone in alcoholic solution a dull red solid separates slowly (the gossypetone reaction).

The dihydroxy compound (VII) (0.1 g.) was acetylated with acetic anhydride (1.5 c.c.) and two drops of pyridine. The diacetate crystallized from alcohol in colourless needles, m.p. 190–91° (Found: C, 61.8; H, 4.8. $C_{22}H_{20}O_9$ requires C, 61.7; H, 4.7%).

3:5:8:3':4'-Pentahydroxyflavone (III)

5:8-Dihydroxy-3:3':4'-trimethoxyflavone (0.4 g.) was dissolved in hot benzene (400 c.c.) and anhydrous aluminium bromide (2.4 g.), dissolved in benzene, was added slowly. A red precipitate of the complex was immediately formed. The mixture was refluxed for 3 hours and the benzene then distilled off. The residue was taken up in crushed ice and hydrochloric acid and, after the complete decomposition of the complex, the yellow product was filtered and washed. It was dissolved in acetone and carefully diluted with water when an oily material was thrown out. This impurity was removed, and the precipitate obtained by further dilution was crystallized thrice from aqueous acetone; the yellow needles (0.24 g.) had m.p. 270–71° (Found: C, 59.7; H, 3.6. $C_{15}H_{10}O_7$ requires C, 59.6; H, 3.3%). The mixed m.p. with ponderosin is 250–55°. The substance dissolves in 0.1 N aqueous caustic soda to a yellow-orange solution turning slightly pink. It

gives the same colour with aqueous potassium carbonate solution. The alcoholic ferric chloride colouration is green. The gossypetone reaction (with *p*-benzoquinone) yields a red solution.

3 : 5 : 8 : 3' : 4'-Pentacetoxyflavone

The pentahydroxyflavone (0.1 g.) was acetylated with acetic anhydride (2 c.c.) and a few drops of pyridine. The acetyl derivative crystallized from alcohol in colourless rectangular plates, m.p. 236–37° (Found: C, 58.7; H, 4.0. $C_{25}H_{20}O_{12}$ requires C, 58.6; H, 3.9%). On admixture with the pentacetate prepared from ponderosin, the m.p. was depressed to 210–12°.

3 : 5 : 8 : 3' : 4'-Pentamethoxyflavone

A mixture of (VII) (0.1 g.), acetone (10 c.c.), dimethyl sulphate (0.16 c.c.) and anhydrous potassium carbonate (1.0 g.) was refluxed for 12 hours. The mixture was cooled, filtered and the residue washed with a little acetone. The solvent was distilled off, the oily residue treated with 5% sodium carbonate solution (20 c.c.), and heated on a water-bath for one hour. The solution was cooled and the colourless needles which separated were filtered, washed and dried. Recrystallization from benzene-hexane gave colourless needles, m.p. 155° (Found: C, 64.3; H, 5.3. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%).

Methylation of ponderosin

A mixture of ponderosin (20 mg.), acetone (2 c.c.), anhydrous potassium carbonate (0.5 g.) and dimethyl sulphate (0.06 c.c.) was refluxed for 15 hours. The mixture was cooled, filtered and the residue washed with a little acetone. The product, obtained after the evaporation of acetone, crystallized from aqueous methanol in colourless needles, m.p. 173° (Found: C, 63.9; H, 5.8. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%).

SUMMARY

By Raney nickel hydrogenolysis of the 7-tosyl ester (V), 5:7-dihydroxy-3:3':4'-trimethoxyflavone (IV) has been converted into 5-hydroxy-3:3':4'-trimethoxyflavone (VI). Persulphate oxidation of (VI) gave 5:8-dihydroxy-3:3':4'-trimethoxyflavone (VII), which was demethylated to 3:5:8:3':4'-pentahydroxyflavone (III) by means of aluminium bromide in benzene. This pentahydroxyflavone was different in its properties from ponderosin, the yellow colouring matter of *Ponderosa* pine bark.

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