

SYNTHESIS OF 6:7-DIHYDROXY-FLAVONOLS

Part I. 6:7:3':4'-Tetra-hydroxy-flavonol

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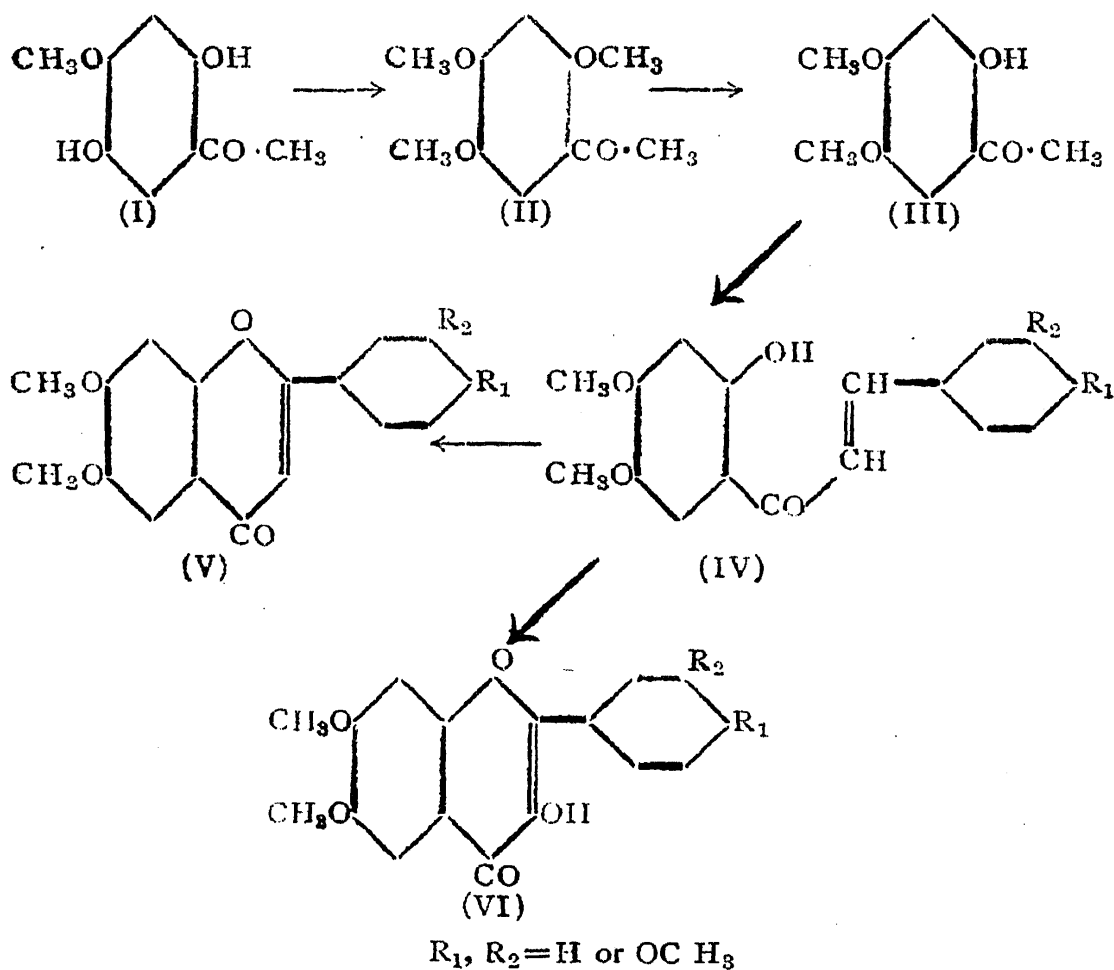
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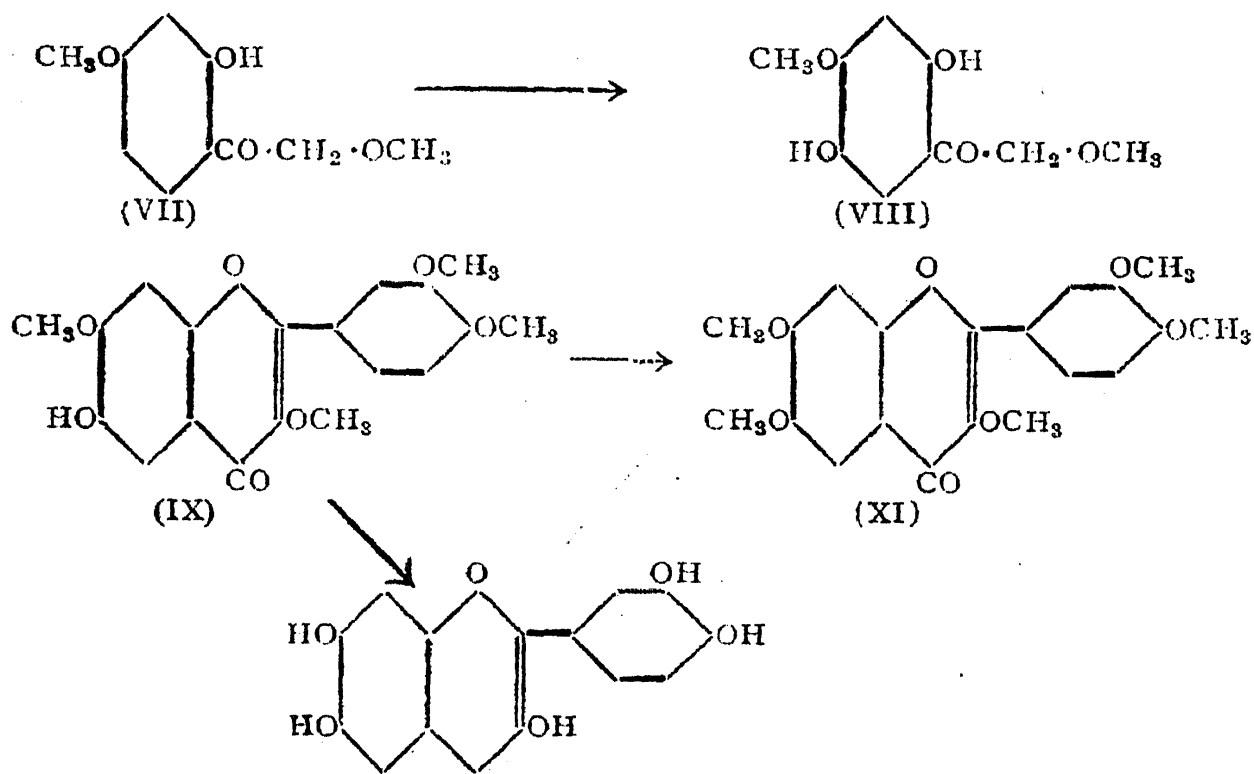
IN connection with the constitution of patuletin¹ it has been found necessary to prepare 6:7-dihydroxy-flavonols and study their properties. That there should be some relation between patuletin and quercetagenin is based on the fact that they are present in closely related plants. It has recently been shown that 5:6:3':4'-tetra-hydroxy-flavonol² is not identical with patuletin. The possibility of its having a 6:7-combination of hydroxyl groups is not altogether excluded though most of its reactions favour the 5:6-combination. The present paper describes the synthesis of 6:7:3':4'-tetra-hydroxy-flavonol and its derivatives.

Bargellini and Bettolo³ have recently reported the preparation of 6:7-dihydroxy-flavones and flavonols. They oxidised peonol with alkaline persulphate to obtain 4-methoxy-2:5-dihydroxy-acetophenone (I). This was completely methylated and the product (II) partially demethylated by boiling with concentrated hydrochloric acid (d. 1.18) to yield 2-hydroxy-4:5-dimethoxy-acetophenone (III). Condensation with benzaldehyde, anisaldehyde and veratraldehyde yielded chalcones (IV). They were converted into flavones (V) by boiling with selenium dioxide in iso-amyl alcohol solution whereas by their oxidation with hydrogen peroxide in the presence of alcoholic potash flavonols (VI) were produced. Information regarding this work has been so far available only in abstract form and hence full details are not yet known. Further only partially methylated compounds seem to have been prepared. Neither the completely methylated flavonols, nor the products of complete demethylation are described. Hence comparison with patuletin and its known derivatives could not be effected.

The procedure adopted in the present synthesis is different from that of previous workers, the starting material being ω :4-dimethoxy-2-hydroxy-acetophenone⁴ (VII). On oxidation with alkaline persulphate it yields ω :4-dimethoxy-2:5-dihydroxy-acetophenone (VIII). By partial methylation of this substance a trimethoxy compound with a free hydroxyl ortho to the carbonyl grouping and by complete methylation, a tetramethoxy compound have been obtained. The constitution of the oxidation product (VIII) is based on analogy with compounds prepared in a similar manner such as



4-methoxy-2:5-dihydroxyacetophenone³ (I) and 6-methoxy-2:5-dihydroxyacetophenone⁵ and several others. The reactions of the new ketone also support it. In alcoholic solution it gives an olive green colour with ferric chloride and forms no precipitate with lead acetate. The second property



is considered to indicate the absence of vicinal hydroxyls. It may be mentioned here that this is the first time an ω -methoxy-acetophenone derivative has been subjected to nuclear oxidation in this manner. Though the reaction is smooth, the yields are not good as when the ω -methoxyl group is absent.

On condensing the new dihydroxy ketone (VIII) with veratric anhydride and sodium veratrate according to the method of Allan and Robinson, 3:7:3':4'-tetramethoxy-6-hydroxy-flavone (IX) is obtained in good yield. It undergoes demethylation with hydriodic acid yielding 3:6:7:3':4'-penta-hydroxy-flavone (X) which forms a pentaacetate and a pentamethyl ether (XI). The latter is also obtained by directly methylating (IX).

A comparison of 6:7:3':4'-tetrahydroxy-flavonol (X) and its derivatives with patuletin shows that they are not identical. The following table gives the comparative data. The constitution of patuletin is under investigation.

	Patuletin	6:7:3':4'-Tetrahydroxy-flavonol
1. The flavonol	M.P. 261-262°	Does not melt below 310° but darkens between 315-320°.
2. Penta-acetate	M.P. 174-176°	M.P. 223-224°.
3. Penta-methyl-ether	M.P. 159-160° No fluorescence in alcoholic solution.	M.P. 186-187°. Exhibits green fluorescence in alcoholic solution.

EXPERIMENTAL

ω :4-Dimethoxy-resacetophenone

Though this compound could be prepared according to the method of Slater and Stephen⁴ the following modification improved the yield and the product was directly obtained pure enough for further use without any crystallisation.

ω -Methoxy-resacetophenone (4.5 g.) was dissolved in anhydrous benzene (500 c.c.) and treated with dimethyl sulphate (3.0 g.) and anhydrous potassium carbonate (50 g.). The mixture was refluxed on a water-bath for 12 hours and while still hot the potassium salts were separated by filtration and washed with hot benzene. The filtrate was extracted after cooling, with 5% aqueous sodium hydroxide (20 c.c. at a time) thrice. The alkaline solution was then acidified with hydrochloric acid while cooling under the tap. A white crystalline solid quickly separated out and was almost pure. It crystallised from water acidified with hydrochloric acid in the form of clusters of fine needles melting at 69-70°; yield—4.0 g. A small amount

of the trimethyl ether could be invariably isolated as an oil from the alkali-extracted benzene solution.

ω : 4-Dimethoxy-2: 5-dihydroxy-acetophenone

The oxidation was effected by means of potassium persulphate in alkaline solution according to the method of Bargellini⁶.

To a solution of ω : 4-dimethoxy-2-hydroxy-acetophenone (5 g.) in aqueous sodium hydroxide (5 g. in 100 c.c.) a solution of potassium persulphate (14 g. in 150 c.c.) and a solution of sodium hydroxide (10 g. in 50 c.c. of water) were added alternately in small quantities while stirring vigorously. Throughout the addition the reaction mixture was kept between 30-40° by cooling in a water-bath. The addition was made slowly during the course of an hour and a half. The mixture was further stirred for 15 minutes and left aside for 36 hours. The solution was then rendered neutral to litmus by the addition of hydrochloric acid, when the unchanged ketone separated out in the form of an emulsion. It was removed by shaking twice with ether; on evaporating the ether extract 0.5 g. of the substance was recovered.

After ether extraction, the aqueous solution was rendered strongly acidic with 30 c.c. of concentrated hydrochloric acid and then heated to 90° on a water-bath. It was then rapidly filtered through animal charcoal. The filtrate was reddish brown in colour and was quite clear. On cooling under the tap, pale yellow woolly crystals (about 1 g.) separated out. But it was better to leave the filtrate in the ice-chest over-night. When the crystalline solid was filtered and washed with a small quantity of water it melted at 142° with sintering at 98-100°. A second crystallisation from hot water yielded colourless broad rectangular plates melting at 145-146°. (Found: C 45.3; H 6.6; OCH₃ 23.2; C₁₀H₁₂O₅, 3H₂O requires C 45.1; H 6.8; and OCH₃ 23.3%). When dried at 110-120° *in vacuo*, the substance sublimed and hence the presence of water of hydration could not be checked by drying.

The substance dissolved in alkali with a pale brown colour which gradually intensified to dark brown. With ferric chloride the alcoholic solution gave a green colour at first but changed rapidly to reddish brown.

Methylation of ω : 4-dimethoxy-2: 5-dihydroxy-acetophenone

A solution of ω : 4-dimethoxy-2: 5-dihydroxy-acetophenone (0.5 g.) in anhydrous benzene (50 c.c.) was refluxed with anhydrous potassium carbonate (2.0 g.) and dimethyl sulphate (0.3 g.) for 12 hours. The hot mixture was then filtered and the residue washed repeatedly with warm benzene (25 c.c.). The benzene solution was then extracted with aqueous sodium

hydroxide (5% solution). On acidifying the alkaline layer, the trimethoxy compound (about 0.2 g.) separated out in a crystalline condition. It crystallised from aqueous alcohol in the form of rectangular plates melting at 90-91°. It gave a dark brown colour with ferric chloride in alcoholic solution and was readily soluble in aqueous alkali yielding a pale yellow solution. (Found: C 58.8; H 6.1; OCH₃ 41.6; C₁₁H₁₄O₅ requires C 58.4; H 6.2; and OCH₃ 41.2%).

After extraction with alkali, the benzene layer was evaporated when the tetramethoxy compound (0.1 g.) was obtained as a crystalline solid. It crystallised from aqueous alcohol in the form of rectangular plates melting at 131-132°. It was insoluble in alkali and gave no colour with ferric chloride in alcoholic solution. (Found: C 59.8; H 6.4; OCH₃ 51.3; C₁₂H₁₆O₅ requires C 60.0; H 6.7; and OCH₃ 51.7%).

3:7:3':4'-Tetramethoxy-6-hydroxy-flavone

An intimate mixture of ω :4-dimethoxy-2:5-dihydroxy-acetophenone (1.5 g., 1 mol.) veratric anhydride (12.5 g., 5 mols.) and sodium veratrate (6.0 g., 4 mols.) was heated under reduced pressure at 180° for four hours in an oil-bath. The dark brown product was treated with alcoholic potash (150 c.c., 5%) and refluxed for 30 minutes. The alcohol was then distilled off under reduced pressure the temperature being allowed to rise to 60°. The semi-solid residue was treated with water (about 150 c.c.) and filtered. There was little insoluble residue and all went into solution. It was then saturated with carbon dioxide. A dark brown resinous solid separated out. Since it could not be crystallised from any solvent, it was rejected. The filtrate was subsequently extracted with ether several times. On evaporating the ether solution a yellowish brown solid separated out. It was crystallised twice from dilute acetic acid from which it separated in the form of short pale yellow needles and plates melting at 219-220°. (Found: C, 64.1; H 5.4; OCH₂ 35.0; C₁₉H₁₈O₇ requires C 63.7; H 5.0; and OCH₃ 34.6%). Yield: 0.9 g.

An alcoholic solution of the substance gave a bright green fluorescence. It gave a light brown colour with ferric chloride. The substance was soluble in aqueous sodium hydroxide forming stable orange-yellow solution. It dissolved in concentrated sulphuric acid giving a bright yellow solution which developed feeble green fluorescence after some time.

3:6:7:3':4'-Pentahydroxy-flavone

A cold solution of 3:7:3':4'-tetramethoxy-6-hydroxy-flavone (0.5 g.) in acetic anhydride (5 c.c.) was treated with hydriodic acid (d. 1.7, 10 c.c.) drop by drop. During the first stages of addition there was considerable

evolution of heat and the addition of hydriodic acid was made cautiously. In the later stages hydriodic acid could be added more rapidly. After refluxing for 3 hours, the solution was diluted to about 50 c.c. and sulphur dioxide passed through the solution. A pale yellow solid separated out. It was crystallised twice from dilute acetic acid using a small quantity of animal charcoal whereby it was obtained as pale yellow narrow rectangular plates. Yield: 0.2 g. It did not melt below 310° and darkened between 315 and 320° . (Found in air-dried sample: C 53.6; H 4.0; $C_{15}H_{10}O_7$, $2H_2O$ requires C 53.3; H 4.1; loss on drying at $110-120^{\circ}$ *in vacuo* for 3 hours, 9.97%; $C_{15}H_{10}O_7$, $2H_2O$ requires 10.7%. Found in oven-dried sample C 59.6; H 3.3; $C_{15}H_{10}O_7$ requires C 59.6 and H 3.3%).

An alcoholic solution of the flavonol exhibited bright green fluorescence. With ferric chloride, it developed a dark olive green colour in alcoholic solution. It was easily soluble in aqueous sodium hydroxide yielding a stable bright orange-yellow solution. In concentrated sulphuric acid, the solution was bright yellow with green fluorescence. Lead acetate gave a heavy orange-red precipitate from an alcoholic solution of the flavonol.

3:6:7:3':4'-Pentamethoxy-flavone

First method.—A solution of 3:7:3':4'-tetramethoxy-6-hydroxy-flavone (0.1 g.) in acetone (20 c.c.) was treated with aqueous sodium hydroxide (2 c.c., 5%) and dimethyl sulphate (0.2 c.c.). On shaking, the solution became warm and the golden yellow colour became pale yellow. Again dimethyl sulphate (0.2 c.c.) and sodium hydroxide (2 c.c.) were added successively and shaking continued. The operation was repeated till a total of 1 c.c. dimethyl sulphate was added. Finally the liquid was rendered definitely alkaline by adding a further quantity (5 c.c.) of aqueous sodium hydroxide. During the course of an hour and a half, the insoluble pentamethyl ether separated out as fine crystals which were filtered and crystallised from alcohol. It was obtained in the form of colourless, elongated, narrow rectangular plates melting at $186-187^{\circ}$. (Found: C 64.7; H 5.3; $C_{20}H_{20}O_7$ requires C 64.5; H 5.4%).

The pentamethyl ether was insoluble in alkali and gave no colour with ferric-chloride in alcoholic solution. Its alcoholic solution showed bluish violet fluorescence resembling that given by umbelliferone in alkaline solution though much less in intensity.

Second method.—6:7:3':4'-Tetra-hydroxy-flavonol (0.1 g.) was dissolved in anhydrous acetone (50 c.c.) and then treated with freshly ignited potassium carbonate (2 g.) and dimethyl sulphate (1.0 c.c.). The mixture was refluxed for 30 hours, the potassium salts were filtered off and washed well

with warm acetone. The acetone layer on evaporation deposited fine colourless crystals of the pentamethoxy-flavone. It crystallised from alcohol in the form of narrow rectangular plates melting at 186-87°. It did not depress the melting point of the sample obtained by the first method.

3:6:3':4'-Penta-acetoxy-flavone.

3:6:7:3':4'-Pentahydroxy-flavone (0.1 g.) was refluxed with acetic anhydride (5.0 c.c.) and freshly fused sodium acetate (1 g.) for 3 hours. The mixture was then cooled and poured into cold water to decompose the excess of acetic anhydride. After a few hours a white crystalline solid separated out. It was crystallised twice from alcohol using once a small quantity of animal charcoal. It was obtained as colourless rectangular plates melting at 223-24°. Yield: 0.1 g. (Found: C 58.4; H 4.2; $C_{25}H_{20}O_{12}$ requires C 58.6 and H 3.9%).

SUMMARY

The synthesis and properties of 6:7:3':4'-tetrahydroxy-flavonol and of its derivatives are described. ω : 4-Dimethoxy-2-hydroxy-acetophenone is oxidised with persulphate in alkaline medium to yield ω : 4-dimethoxy-2:5-dihydroxy-acetophenone which is then condensed with veratric anhydride and sodium veratrate. The new flavonol and its methyl and acetyl derivatives differ from patuletin and its derivatives.

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