

SYNTHESIS OF 5:6-DIHYDROXY-FLAVONOLS

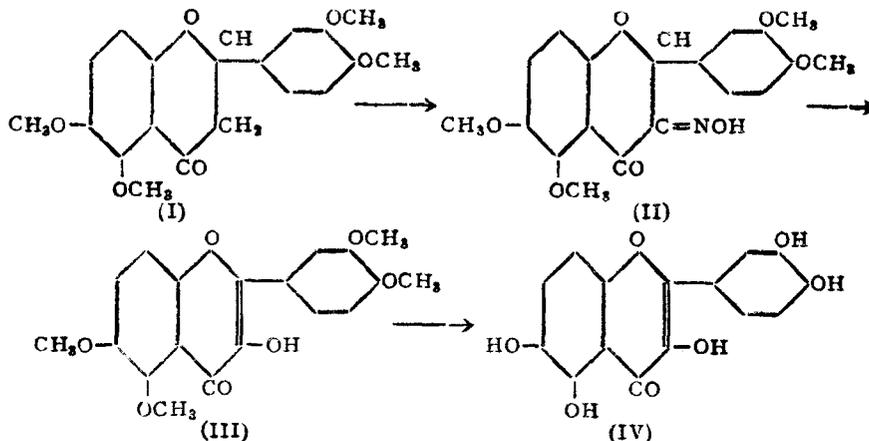
Part II. 3:5:6:3':4'-Pentahydroxy-flavone

BY L. RAMACHANDRA ROW AND T. R. SESHADRI

(From the Department of Chemistry, Andhra University)

Received February 12, 1945

IN Part I¹ the preparation and properties of 5:6:3':4'-tetramethoxy flavanone (I) and related compounds were described. The conversion of this substance into its 3-iso-nitroso-compound (II) and further into the corresponding flavonol (III) could be readily effected by adopting the procedure of Kostanecki. It is now found to be more advantageous to carry out the preparation of the flavonol in one operation without isolating the isonitroso-compound as the intermediate stage. This is possible if excess of hydrochloric acid is employed and the treatment is carried out for a longer period. Better yield of a purer product is obtained readily by this modification. Demethylation of (III) gave rise to 3:5:6:3':4'-pentahydroxy-flavone (IV) and methylation of (III) yielded the pentamethyl-ether readily. Demethylation with hydriodic acid has been stated to cause conversion of 5:8- and 5:7:8-hydroxy-flavones into their isomers.² No isomeric change takes place in the present case (*i.e.*) from 5:6- to 5:8 arrangement of hydroxyl groups, since the product does not give the gossypetone reaction which is characteristic of the 5:8-dihydroxy compounds.



It is remarkable that the tetramethoxy-flavonol (III) and its methyl ether give marked fluorescence in alcoholic solution and not in sulphuric acid whereas the pentahydroxy compound does not exhibit fluorescence under both conditions. From the data presented in Table I it is clear that

patuletin³ is not the same as 3:5:6:3':4': pentahydroxy flavone and it should have a different constitution. This subject is being further studied.

TABLE I

	5:6:3':4'-Tetrahydroxy flavonol	Patuletin ³
1. Flavonol ..	M.P. 318-320°	M.P. 261-262°
2. Acetyl derivative ..	M.P. 195-196°	M.P. 171-172°
3. Methyl ether ..	M.P. 121-122°	M.P. 159-160°
	Exhibits bright green fluorescence in alcoholic solution	No fluorescence in alcoholic solution

EXPERIMENTAL

5:6:3':4'-Tetramethoxy-3-isonitroso-flavanone

A solution of 5:6:3':4'-tetra-methoxy-flavanone¹ (0.5 g.) in alcohol (40 c.c.) was kept slowly boiling, and treated alternately in small quantities with isoamyl nitrite (3 c.c.) and concentrated hydrochloric acid (6 c.c.) with shaking. The solution gradually turned deep red. After the addition was over, the solution was cooled and diluted to about 50 c.c. with water. A heavy reddish orange oil collected at the bottom and it showed no signs of crystallising even after leaving it in an ice-chest for 24 hours. It was therefore extracted with ether and from the ethereal solution, the isonitroso compound was taken up into aqueous alkali. This procedure separated the isonitroso-derivative from the unchanged flavanone and amyl alcohol that are also extracted by the ether. The alkali solution was acidified with hydrochloric acid and as no solid or oil separated, it was immediately extracted with ether. On removal of ether, a dark brown crystalline solid (0.10 g.) was obtained. It was crystallised twice from benzene when it was obtained as orange coloured, elongated rectangular prisms melting at 172-73°. (Found: C, 60.9; H, 5.4; C₁₉H₁₉O₇N requires C, 61.1 and H, 5.1%.)

5:6:3':4'-Tetramethoxy-3-hydroxy-flavone

(a) *Hydrolysis of the iso-nitroso compound.*—To a boiling solution of the iso-nitroso compound (0.1 g.) in alcohol (5 c.c.) concentrated hydrochloric acid (d. 1.19, 3 c.c.) was added slowly with stirring. The liquid was left aside for 2 hours and then diluted with water (25 c.c.). As no appreciable amount of solid came down the mixture was extracted with ether. From the ether extract on evaporation, light brown shining crystals of the tetramethoxy-flavonol separated out. It was crystallised once from alcohol and then from dilute acetic acid, when it was obtained as shining brownish-yellow, rhombic plates melting at 194-6°. Yield 50 mg. It was sparingly soluble in aqueous alkali yielding a bright yellow solution. With ferric chloride, an alcoholic

solution of the flavonol gave a dull brown colour. It exhibited bright green fluorescence in methyl and ethyl alcoholic solutions. It was soluble in benzene, acetic acid and ether. With concentrated sulphuric acid a bright yellow solution was obtained and it did not exhibit any fluorescence. (Found: C, 63.7; H, 5.3; $C_{14}H_{18}O_7$ requires C, 63.7 and H, 5.0%.)

(b) *From 5:6:3':4'-tetramethoxy-flavanone directly.* — 5:6:3':4'-Tetramethoxy-flavanone (0.5 g.) was dissolved in alcohol (40 c.c.) and while the solution was boiling gently over a small flame, iso-amyl nitrite (3 c.c.) and concentrated hydrochloric acid (30 c.c., d. 1.19) were added alternately in small quantities at a time with stirring. The solution turned bright yellow at first and finally bright reddish orange. The hot solution was allowed to cool slowly and to stand for 2 hours with occasional stirring. It was then diluted to about 200 c.c. with cold water. Within a few minutes bright shining yellow plates began to separate out. After an hour, the crystalline precipitate was filtered and washed. It crystallised from alcohol as bright yellow shining, rhombic plates melting at 194–196°. Yield about 0.1 g. It was found to be identical with the flavonol obtained in the previous experiment.

The mother-liquor from the flavonol was repeatedly extracted with ether and the ethereal solution was extracted with aqueous sodium hydroxide several times. The alkaline layer on acidification deposited droplets of a reddish brown oil which showed no tendency to crystallise. It was, therefore, treated with a mixture of glacial acetic acid and concentrated hydrochloric acid (1:1, 10 c.c.) and heated on the water-bath for 30 minutes. On diluting the solution a small quantity of brown powder was obtained. It was filtered and crystallised from alcohol when it came out in the form of shining yellow plates and was identical with 5:6:3':4'-tetramethoxy-3-hydroxy-flavone (50 mg.).

3:5:6:3':4'-Pentamethoxy-flavone

5:6:3':4'-tetramethoxy-3-hydroxy-flavone (0.2 g.) was dissolved in acetone (20 c.c.) and treated with aqueous sodium hydroxide (5%, 5 c.c.) and dimethyl sulphate (0.5 c.c.). The mixture was shaken vigorously until the initial rise in temperature was brought down. When the solution was cool, more alkali (3 c.c.) was added and then dimethyl sulphate (5 c.c.). Once again the contents were shaken vigorously. After an hour, the excess of dimethyl sulphate was destroyed by keeping the mixture in a boiling water-bath for about 15 minutes. It was then cooled and acidified with hydrochloric acid. Not much solid separated out. So the mixture was extracted with ether; on evaporating the ether solution a pale yellow semi-solid separated out. It crystallised from aqueous alcohol in the form of pale yellow

rhombic prisms melting at 121-122°. After a second crystallisation from aqueous alcohol, the melting point was unaffected.

The compound was freely soluble in alcohol, ether, acetone, benzene and chloroform. It exhibited a bright green fluorescence in alcoholic solution. (Found: C, 64.6; H, 5.6; $C_{20}H_{20}O_7$ requires C, 64.5 and H, 5.4%.)

5:6:3':4'-Tetrahydroxy-flavonol

A cold solution of 5:6:3':4'-tetra-methoxy-3-hydroxy-flavone (0.5 g.) in acetic anhydride (5 c.c.) was treated drop by drop with hydriodic acid (d. 1.7, 10 c.c.). At first there was considerable evolution of heat and consequently the addition was made slowly with stirring and cooling. Towards the end the acid could be added rapidly. The mixture was then refluxed on a wire-gauze for 3 hours. In the course of the first half hour a pale yellow solid separated out and caused bumping. After 3 hours, the solution was diluted to about 50 c.c. and decolourised by passing sulphur dioxide into it when a yellow solid separated out. It was filtered and crystallised from aqueous pyridine. It was thus obtained as yellow rectangular plates which sintered at 310° and finally melted at 318-320°. Yield: 0.25 g. (Found: C, 53.2; H, 4.3; $C_{15}H_{10}O_7$, $2H_2O$ requires C, 53.3 and H, 4.1%.) It was sparingly soluble in alcohol and glacial acetic acid. Its alcoholic solution was yellow and showed no fluorescence. In concentrated sulphuric acid, a bright yellow solution was obtained exhibiting no fluorescence. It did not respond to the "gossypetone reaction" and gave a dark olive green with alcoholic ferric chloride.

3:5:6:3':4'-Penta-acetoxy-flavone

The pentahydroxy-flavone (0.1 g.) was acetylated by refluxing with freshly distilled acetic anhydride (10 c.c.) and freshly fused sodium acetate (1 g.) for 4 hours. On pouring the mixture into cold water and stirring, a colourless white solid separated out. After crystallising twice from alcohol, it came out as long rectangular plates melting at 196°. (Found: C, 58.8; H, 4.3; $C_{25}H_{20}O_{12}$ requires C, 58.6 and H, 3.9%.)

SUMMARY

The preparation of 3:5:6:3':4'-pentahydroxy-flavone by Kostanecki's method and its properties are described. Its methyl ether and acetate have been prepared and characterised. These differ from patuletin and its derivatives.

REFERENCES

- | | |
|---------------------|---|
| 1. Row and Seshadri | .. <i>Proc. Ind. Acad. Sci., A</i> , 1944, 20 , 274. |
| 2. Baker | .. <i>J. C. S.</i> , 1939, 956. |
| 3. Rao and Seshadri | .. <i>Proc. Ind. Acad. Sci., A</i> , 1941, 14 , 643. |