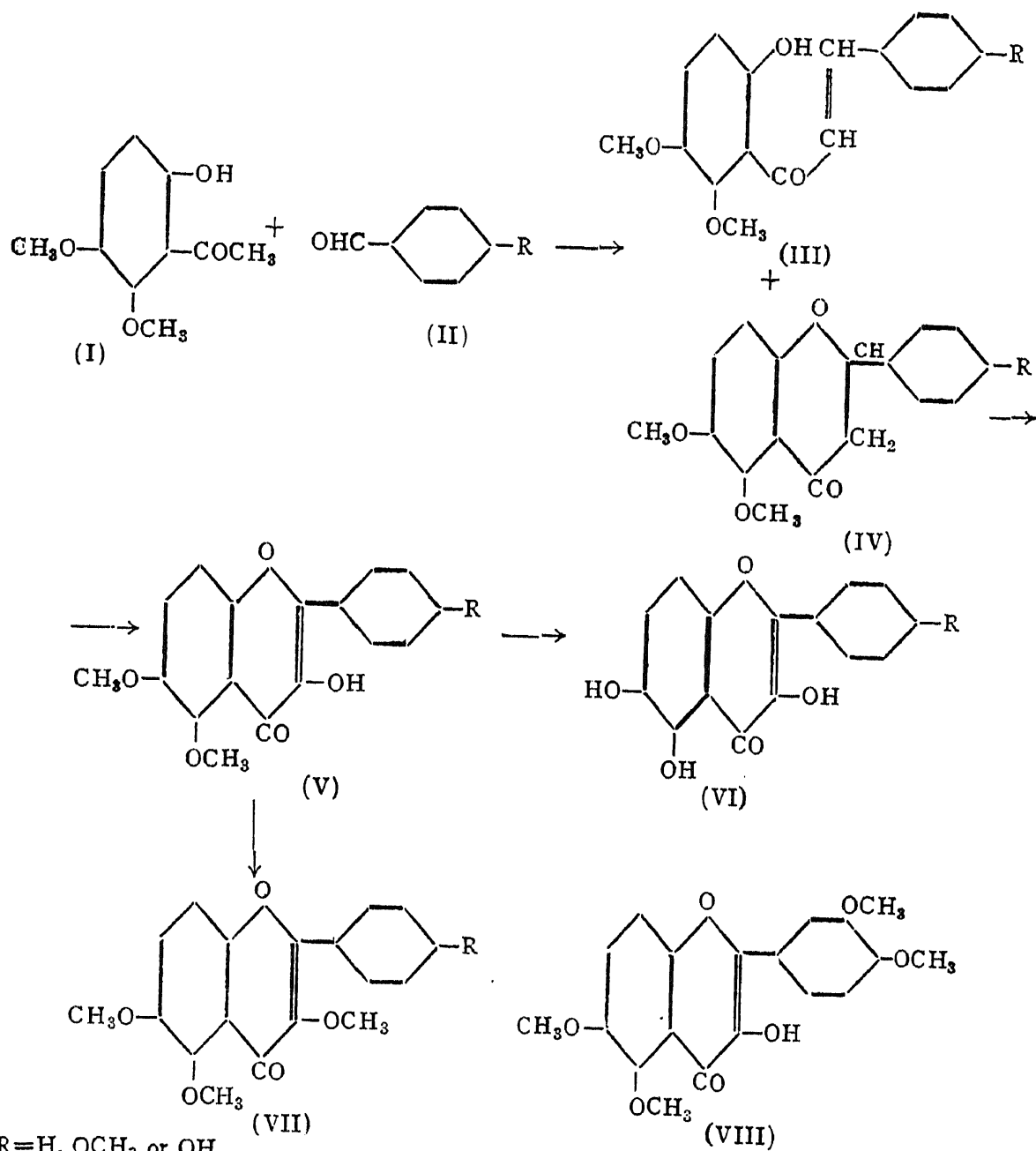


SYNTHESIS OF 5:6-HYDROXY-FLAVONOLS PART III

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Received December 29, 1945

IN Part II¹ the synthesis and study of 3:5:6:3':4'-pentahydroxy-flavone and its derivatives were described. Following the same procedure the two lower members of this series have now been prepared and their properties studied.



Since in the chalcone condensation it is necessary to have the hydroxyl groups protected as far as possible in order to get good yields, 2-hydroxy-

5:6-dimethoxy-acetophenone (I) was employed instead of the more easily available 2:5-dihydroxy ketone and the condensation made with benzaldehyde and anisaldehyde. In each case the product was a mixture of both the chalkone and the corresponding flavanone. Similar mixture resulted even when the chalkone was heated with alcoholic sulphuric acid. The conversion of the flavanone into flavonol was effected directly in one stage since it gives better yields of the products.

The 5:6-hydroxy-flavonols described in the course of this work form a series of compounds lacking a hydroxyl group in the 7-position. There is marked absence of fluorescence as compared with the 7-hydroxy and 5:7-dihydroxy compounds. The importance of the 7-position for this property is thus indicated. They form brownish-red solutions in alkali which rapidly fade on shaking with air. This characteristic seems to be also due to the presence of two hydroxyl groups in the contiguous positions 5 and 6.

The compounds of type (V) having only a hydroxyl group in the 3-position exhibit fluorescence in alcoholic solutions but not in strong sulphuric acid. They also give prominent ferric chloride colour. The fully methylated compounds (type VII) also give some fluorescence in alcohol but none in sulphuric acid.

The possibility of the flavone ring opening and reclosing in a different direction, during demethylation using boiling hydriodic acid, has been shown to be present in the case of the 5:8-hydroxy flavones.³ No definite example is known of 5:6-hydroxy compounds changing in this manner. This point has been examined in one typical case in the course of the present work. 3-Hydroxy-5:6:3':4'-tetra-methoxy-flavone (VIII), was demethylated to the pentahydroxy compound which was again remethylated with dimethyl sulphate and potassium carbonate in acetone solution. The product was found to be identical with that of direct methylation of (VIII) thus showing that no isomeric change is involved during the demethylation.

EXPERIMENTAL

2-Hydroxy-5:6-dimethoxy-chalkone:—To a solution of 2-hydroxy-5:6-dimethoxy-acetophenone (3 g.) and benzaldehyde (5 c.c.) in alcohol (20 c.c.) cooled to 0°, potassium hydroxide (30 g. in 24 c.c. of water) was added in small quantities at a time with shaking. After the addition, the flask was stoppered tight and kept for four days at the laboratory temperature with occasional shaking. The contents were then diluted with water and ether-extracted in order to remove the unreacted aldehyde and then acidified. The product separated in the form of an orange-red liquid which was taken in ether. The ethereal solution was shaken with aqueous sodium bicarbonate

to remove benzoic acid that was also formed during the reaction. On evaporating the ether, a red liquid was obtained which did not solidify even after keeping in the refrigerator for a number of days. The chalkone was soluble in alkali and gave a reddish brown colour with ferric chloride in alcoholic solution. Crystallisation of the product was attempted using benzene, petrol, alcohol and acetone; but in all cases the chalkone was recovered as a liquid. It was therefore directly employed for conversion into the flavanone.

In another experiment, the alkaline solution left after removing the unreacted aldehyde by means of ether, was saturated with carbon dioxide in the hope of obtaining the chalkone in a crystalline condition. A pale brownish yellow solid separated out (0.2 g.). When crystallised from alcohol using animal charcoal, it came out in the form of colourless silky needles melting at 142–44°. It did not depress the melting point of the flavanone obtained from 2-hydroxy-5:6-dimethoxy chalkone. The filtrate from the flavanone on ether-extraction yielded the chalkone in the form of a viscous red liquid.

5:6-Dimethoxy-flavanone.—A solution of the above chalkone (2 g.) in 50% aqueous alcohol (100 c.c.) was treated with concentrated sulphuric acid (3 c.c.) and the resulting solution boiled under reflux for 24 hours. On concentrating the solution, the flavanone separated out in the form of pale yellow silky needles. It was filtered and washed with water. The adhering chalkone was removed by macerating the solid with a weak solution of sodium hydroxide. It then crystallised from alcohol (animal charcoal) in the form of colourless silky needles melting at 142–44° (Found: C, 71.9; H, 5.8; $C_{17}H_{16}O_4$ requires C, 71.8; and H, 5.6%).

5:6-Dimethoxy-3-hydroxy-flavone.—To a gently boiling solution of 5:6-dimethoxy-flavanone (0.5 g.) in alcohol (40 c.c.) were added alternately amyl nitrite (3 c.c.) and concentrated hydrochloric acid (20 c.c.; d., 1.19) little by little with stirring. After the addition, the contents were left for two hours with occasional shaking. The solution was then diluted with water (150 c.c.) and the solid product filtered and washed with water. It was crystallised twice from alcohol when the flavonol was obtained as rhombic plates, melting at 216°. Yield, 0.15 g. It gave a reddish brown colour with alcoholic ferric chloride. When reduced in alcoholic solution with magnesium and hydrochloric acid an orange-red colour was developed. It was soluble in aqueous alkali to give an yellow solution. An alcoholic solution of the flavonol exhibited green fluorescence. It dissolved in concentrated sulphuric acid to yield a yellow solution without fluorescence (Found: C, 68.5; H, 4.7. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%).

3:5:6-Trihydroxy-flavone.—The above dimethoxy flavonol (75 mg.) dissolved in acetic anhydride (3 c.c.) was treated with hydriodic acid (2 c.c.; d., 1.7) with cooling. The solution was refluxed for an hour in an oil-bath kept at 150–55°. After cooling, it was treated with sulphurous acid when a pale yellow crystalline solid separated out. The aqueous solution along with the solid was ether-extracted. On removing ether a pale yellow crystalline solid was obtained. It was crystallised from ethyl acetate when the dihydroxy flavonol came out as stout rectangular rods melting at 183–85°. Yield, 50 mg. It gave a brown ferric chloride colour and exhibited no fluorescence either in concentrated sulphuric acid or in alcoholic solution. It was insoluble in sodium bicarbonate and carbonate solutions but dissolved in aqueous sodium hydroxide to form a brownish red solution; the colour faded slowly to pale yellow, the change being very fast on shaking with air (Found: C, 67.0; H, 3.7; $C_{15}H_{10}O_5$ requires C, 66.7 and H, 3.7%).

3:5:6-Trimethoxy-flavone.—To the above dihydroxy flavonol (40 mg.) in anhydrous acetone (20 c.c.) was added anhydrous potassium carbonate (0.5 g.) and dimethyl sulphate (0.2 c.c.) and the mixture refluxed for 20 hours. The solvent was removed and water added when a very pale yellow solid separated. This was filtered, washed with water and crystallised from benzene-petrol mixture when the trimethyl ether came out as stout rhombohedral prisms melting at 130–32°. It gave no ferric chloride colour in alcoholic solution. It exhibited no fluorescence either in alcohol or in sulphuric acid solution (Found: C, 69.4; H, 4.8; $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%).

5:6:4'-Trimethoxy-3-hydroxy-flavone.—This compound was obtained from the corresponding flavanone² in one operation as in the previous case.

The colourless solution of the flavanone (0.5 g.) in alcohol (40 c.c.) gradually turned reddish orange on treatment with amyl nitrite (3 c.c.) and concentrated hydrochloric acid (30 c.c.; d., 1.19). After 2 hours, the liquid was diluted to 200 c.c. with water. Pale yellow shining flakes separated out after some hours. They were collected and crystallised twice from alcohol. The flavonol was obtained in the form of pale yellow broad rectangular plates melting at 172–73°. Yield, 0.15 g. It gave bright bluish green fluorescence in alcohol, benzene and ether solutions. With alcoholic ferric chloride a light brown colour was obtained. It was sparingly soluble in cold aqueous sodium hydroxide yielding a very pale yellow solution. In concentrated sulphuric acid it dissolved forming an orange coloured liquid with no fluorescence (Found: C, 65.8; H, 5.1; $C_{18}H_{16}O_6$ requires C, 65.9; and H, 4.9%).

3:5:6:4'-Tetramethoxy-flavone.—The trimethoxy flavonol (0.1 g.) was methylated by refluxing it in a solution of anhydrous acetone (50 c.c.) with dimethyl sulphate (0.3 c.c.) and anhydrous potassium carbonate (1 g.) for 8 hours. At the end of the reaction, the potassium salts were filtered and washed with warm acetone. The filtrate was concentrated on the water-bath (2 c.c.) and treated with water (2–3 c.c.). The semi-solid precipitate did not crystallise even after keeping for a long time in the ice-chest. It was, therefore, extracted with ether and the residue obtained after the removal of ether was crystallised twice from alcohol when it was obtained as colourless rectangular plates melting at 147–48°. It gave no colour with ferric chloride in alcoholic solution. Its solution in alcohol exhibited bluish green fluorescence. However, fluorescence was absent in concentrated sulphuric acid (Found: OCH₃, 36.0; C₁₉H₁₈O₆ requires OCH₃, 36.3%).

3:5:6:4'-Tetrahydroxy-flavone.—A solution of 5:6:4'-trimethoxy-3-hydroxy-flavone (0.2 g.) in acetic anhydride was treated with hydriodic acid (d., 1.7; 5 c.c. with cooling.) The resulting solution was refluxed on an oil-bath at 150–55° for 2 hours. It was diluted with water and saturated with sulphur dioxide when an orange coloured precipitate was obtained. When crystallised twice from ethyl acetate, the trihydroxy flavonol was obtained in the form of pale yellow microscopic crystals melting at 305° with slight sintering at 294°. Yield, 0.1 g. With alcoholic ferric chloride a dark olive green colour was obtained. It exhibited no fluorescence either in alcoholic or in strong sulphuric acid solution. It was insoluble in aqueous sodium bicarbonate, but dissolved in carbonate solution giving a fairly stable pale yellow colour. In aqueous sodium hydroxide it formed a brownish red solution which faded slowly to pale brownish yellow; the change was very rapid when shaken with air. It did not show marked colour changes in alkaline buffer solutions; in a solution of pH 12.2, it was bright yellow at first, rapidly turning brown; within 4 minutes it was deep brown, after an hour reddish brown and after 24 hours pale reddish brown (Found: C, 62.8; H, 3.8; C₁₅H₁₀O₆ requires C, 62.9, and H, 3.5%).

SUMMARY

The synthesis of 3:5:6:3':4'-pentahydroxy-flavone was already reported. The lower members of this group of 5:6-hydroxy flavonols with one and no hydroxyl group in the side-phenyl nucleus have now been prepared by Kostanecki's method. The characteristic properties are described.

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