

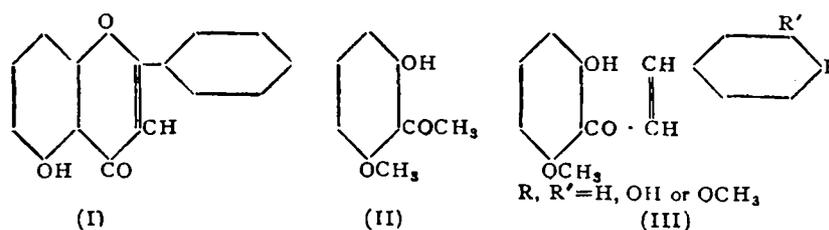
SYNTHESIS OF 5-HYDROXYFLAVONOLS

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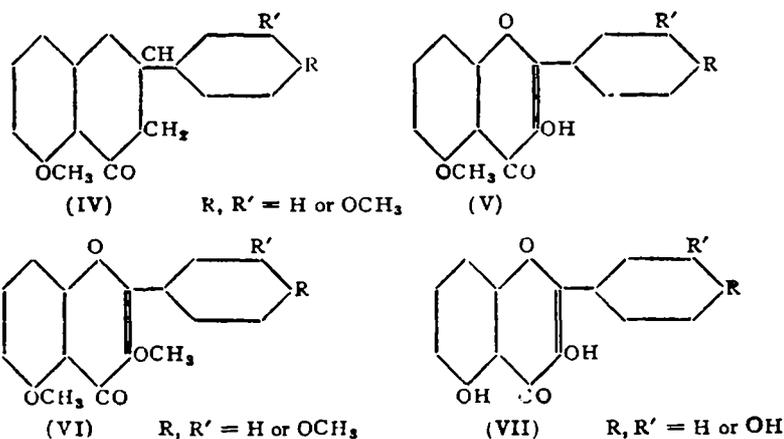
AMONG the naturally occurring flavones and flavonols, the most numerous group contain the 5:7-arrangement of hydroxyl groups in the benzopyrone part¹ and these seem to be the most fundamental of the anthoxanthins from the point of view of biogenesis. There are, however, a few compounds with a single hydroxy group in the 7-position, the 5-position being unsubstituted. The flavone, pratol and the flavonols, fisetin and robinetin belong to this type. On the other hand, till very recently no compound with a hydroxyl only in the 5-position and none in the 7-position was known to occur in nature. 5-Hydroxy-flavone (I) was isolated by Karrer and Schwab² from a deposit on the stalks and blossoms of *Primula imperialis* var. *gracilis* which consisted mainly of simple flavone along with some 5-hydroxy-flavone. The synthesis of this hydroxy-flavone had been accomplished by Sugawara³ several years earlier starting from γ -resacetophenone and adopting the Allan-Robinson method. Improvements in the preparation have recently been described.⁴ The earlier synthesis helped in the identification of the compound in the plant material. The occurrence of flavonols of this type in nature also seems to be possible. It is therefore desirable to have records of the properties of synthetic samples so that their identification in natural products may be easy. With this end in view some members of this group have now been prepared and their properties described in this paper.



For the synthesis of 5-hydroxy flavonols the method of Allan and Robinson is not suitable since the required ω -methoxy- γ -resacetophenone has not yet been made. Hence the older method of Kostanecki has been employed, 2-acetyl resorcinol being the starting material. For the first stage in the synthesis, that is the chalcone condensation, it is found desirable to use an

excess of the aldehyde component and to methylate as far as possible the hydroxyl groups in both the components employed. Thus 2-acetyl resorcinol does not undergo appreciable condensation with vanillin; its condensation with benzaldehyde and veratric and anisaldehydes is better but the yields are poor. Very satisfactory yields of chalcones (III) are obtained by employing these aldehydes and the monomethyl ether of 2-acetyl resorcinol (II). As in many similar cases the products of these condensations contain some quantity of the corresponding flavanones (IV). Further conversion into the flavanones is effected by boiling the chalcones with alcoholic sulphuric acid. Even here the products are mixtures of flavanones and chalcones and have to be separated. The preliminary methylation of hydroxyl groups already mentioned is of advantage for effecting this separation easily by means of cold aqueous alkali, the chalcones being soluble and the flavanones insoluble. The chalcones are coloured, yellow to orange red, whereas the flavanones are colourless. The latter readily yield red solutions in alcohol when reduced with magnesium and hydrochloric acid.

The fully methylated flavanones (IV) are converted into the flavonols (V) in one stage according to the method of Row and Seshadri⁵ in which the yields are better and the products more readily obtained pure. Further methylation yields the methyl ethers (VI) and demethylation the hydroxy compounds (VII).



The 3-hydroxy compounds (V) are yellow substances exhibiting a weak green fluorescence in neutral alcoholic and concentrated sulphuric acid solutions, the colour of the solutions being yellow. They give an olive green colour with alcoholic ferric chloride. The fully methylated compounds (VI) do not exhibit any fluorescence in the above solvents. The hydroxy-flavanols (VII) are yellow in colour and give an olive-green colour

with ferric chloride and do not exhibit fluorescence in solution. In contrast to these the 7-hydroxy flavonols exhibit marked fluorescence. Thus the 5-hydroxyl is inhibitive of fluorescence; conversion of this into the methoxyl gives rise to some weak fluorescence as in compounds of type (V). Similar effects have been noted in the group of pyrylium salts and coumarins also.⁶ In general the 7-hydroxy compounds have markedly higher melting points than the corresponding 5-hydroxy flavonols.

EXPERIMENTAL

2-Hydroxy-6-methoxy-chalkone (III, R, R' = H)

Monomethyl- γ -resacetophenone⁷ (1 g.) and benzaldehyde (3 g.) were dissolved in alcohol (20 c.c.) and to the solution aqueous potassium hydroxide (20 c.c.; 50%) was added with shaking at the laboratory temperature. The mixture was kept in a closed container for about 72 hours. The red solution was then diluted with water, ether extracted to remove the unreacted benzaldehyde and then acidified with dilute hydrochloric acid. The reddish brown viscous liquid that separated out was ether extracted and the ether solution washed with sodium bicarbonate (5%) to remove benzoic acid. On removing the ether, the chalkone was obtained as a viscous red liquid which solidified during the course of several days. Final purification was effected by crystallisation from alcohol when it came out as pale yellow rectangular plates and prisms melting at 127–29°; Yield 1.2 g. The product dissolved easily in dilute alkali giving rise to an orange red solution and gave a dark brown colour with alcoholic ferric chloride (Found: C, 75.5; H, 5.6; C₁₆H₁₄O₃ requires C, 75.6; H, 5.5%).

5-Methoxy-flavanone (IV, R, R' = H)

The above chalkone (III) (2 g.) was dissolved in alcohol (100 c.c. of 50%), treated with concentrated sulphuric acid (3 c.c.) and boiled under reflux for a period of 30 hours. As much of the alcohol as possible was then removed under reduced pressure and the solution diluted with water to about 300 c.c. The liquid that separated out solidified easily on shaking with more water. It was filtered and macerated with dilute sodium hydroxide solution to remove the unreacted chalkone. The pale brown residue was dried and crystallised from ethyl acetate when it came out in the form of colourless rectangular prisms melting at 148–50°. Yield 1.2 g. (Found: C, 75.5; H, 5.8; C₁₆H₁₄O₃ requires C, 75.6; H, 5.5%). It was insoluble in dilute alkali in the cold and did not give any colour with ferric chloride.

5-Methoxy-flavonol (V, R, R' = H)

5-Methoxy-flavanone (IV) (0.5 g.) was dissolved in alcohol (15 c.c.), gently boiled and then treated with amyl nitrite (3 c.c.) and concentrated

hydrochloric acid (30 c.c.; d. 1.19) in small quantities during the course of 15 minutes. The solution assumed rapidly a dark red colour and it was allowed to stand for 2 hours. It was then diluted to 200 c.c. and ether extracted. From the ether extract, the flavanol was taken up in dilute sodium hydroxide (1 N). On acidifying the alkaline solution, it was precipitated as an orange red solid. When dried and crystallised from ethyl acetate twice, it appeared as pale yellow rectangular prisms melting at 170–71°; rapid crystallisation yielded yellow flat needles the melting point being the same; Yield 0.4 g. The substance dissolved in dilute sodium hydroxide to give a yellow solution and with alcoholic ferric chloride gave a deep pink colour changing to brown. It exhibited a green fluorescence with a blue tinge in neutral alcoholic solution, the solution being coloured pale yellow. In concentrated sulphuric acid solution, it gave a pale green fluorescence (Found: C, 71.2; H, 5.3; $C_{18}H_{12}O_3$, H_2O requires C, 71.1; and H, 5.2%).

3: 5-Dimethoxy-flavone (VI, R, R' = H)

The above flavanol (V) was methylated with dimethyl sulphate and anhydrous potassium carbonate in acetone solution by boiling for 10 hours. The product that first separated as a liquid solidified on keeping for about 24 hours and on crystallisation from alcohol appeared as colourless rectangular plates and prisms melting at 160–62°. It was insoluble in dilute alkali and did not give any colour with alcoholic ferric chloride (Found: C, 72.2; H, 5.2; OCH_3 , 21.8; $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0; and OCH_3 , 21.6%). It did not exhibit any fluorescence in alcoholic or concentrated sulphuric acid solutions.

3: 5-Dihydroxy-flavone (VII, R, R' = H)

5-Methoxy-flavanol (V) (0.5 g.) was dissolved in acetic anhydride (10 c.c.), treated with hydriodic acid (10 c.c.; d. 1.7) and boiled under reflux for $\frac{1}{2}$ hour. It was then poured into water and the iodine present removed by sulphur dioxide. The precipitated yellow compound was purified by crystallisation from alcohol when it came out as long yellow rectangular plates and prisms, melting at 145–46°. It gave an olive green colour with alcoholic ferric chloride and did not exhibit any fluorescence in alcoholic or concentrated sulphuric acid solutions (Found: C, 70.2; H, 4.9; $C_{15}H_{10}O_3$, H_2O requires C, 70.3; and H, 4.7%). The flavanol dissolved in alkalis to give a golden yellow colour.

The acetate was prepared by boiling the flavanol with acetic anhydride and a few drops of pyridine. It was crystallised from acetone when it came out as colourless tiny rectangular prisms melting at 148–49° (Found: C, 71.0; H, 4.5; $C_{19}H_{14}O_5$ requires C, 70.8; H, 4.3%).

2: 6-Dihydroxy-4'-methoxy-chalkone

A solution of 2: 6-dihydroxy-acetophenone (1.0 g.) and anisaldehyde (3 g.) in alcohol (20 c.c.) was treated with alkali (20 c.c. of 50% potash) and the red solution heated to boiling on a water-bath for 15 minutes. It was cooled and kept stoppered tightly for 24 hours. On working up as before, the chalkone was obtained as an orange-red crystalline substance. Purified by crystallisation from alcohol, it came out in the form of yellow rectangular plates melting at 185–86°. Yield 0.3 g. It dissolved easily in dilute sodium hydroxide to give a pale yellow solution, and produced a brown colour with alcoholic ferric chloride (Found: C, 71.3; H, 5.4; $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%).

2-Hydroxy-6: 4'-dimethoxy-chalkone (III, R = OCH₃, R' = H)

Monomethyl- γ -resacetophenone (1 g.) and anisaldehyde (3 g.) were dissolved in alcohol (20 c.c.) and to the solution aqueous potassium hydroxide (30 g. of potash and 20 c.c. of water) was added at the laboratory temperature. The mixture was refluxed on a water-bath for about an hour and then kept tightly stoppered for 24 hours. The chalkone obtained by working up the reaction mixture as before was purified by crystallisation first from dilute alcohol and finally from acetic acid when it came out as bright orange-red needle-shaped crystals melting at 114–15°. Yield 0.8 g. The product dissolved easily in dilute alkali giving rise to an orange red solution and gave a dark brown colour with alcoholic ferric chloride (Found: C, 72.0; H, 5.7; $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%). A better yield (1.12 g.) of this chalkone is obtained by heating the above reaction mixture on a water-bath at 50° for a period of 15 minutes and then keeping the solution tightly stoppered for a period of 60 hours.

5: 4'-Dimethoxy-flavanone (IV, R = OCH₃, R' = H)

The above chalkone (III) was converted into the flavanone by boiling a 50% alcoholic solution of the substance with 3% sulphuric acid and worked up as in the previous case. The product was crystallised from ethyl acetate when it came out in the form of colourless flat rectangular plates melting at 115–16°. Yield 0.3 g. (Found: C, 71.4; H, 5.8; $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%). It was insoluble in dilute alkali in the cold, but when boiled with the same, it went into solution giving an orange yellow solution. It did not give any colour with alcoholic ferric chloride.

5: 4'-Dimethoxy-flavonol (V, R = OCH₃, R' = H)

The above flavanone (IV) (1 g.) was converted into the flavonol using amyl nitrite and hydrochloric acid as described already. It was purified by crystallisation from ethyl acetate when it came out as yellow narrow

plates tapering at the ends and melting at 171–72°. Yield 0.2 g. (Found: in air-dried sample: C, 64.4; H, 5.4; loss on drying *in vacuo* at 120° for 2 hours 5.3%; $C_{17}H_{14}O_5$, H_2O requires C, 64.6; H, 5.1 and loss on drying 5.7%). It dissolved in dilute sodium hydroxide giving a yellow solution and with alcoholic ferric chloride gave a deep brown colour. It exhibited a green fluorescence with a blue tinge in neutral alcoholic solution, the solution being coloured pale yellow. In concentrated sulphuric acid solution it gave a pale green fluorescence.

3:5:4'-Trimethoxy-flavone (VI, $R = OCH_3$, $R' = H$)

The above flavonol (V) was methylated with dimethyl sulphate and anhydrous potassium carbonate in acetone solution by boiling for a period of 10 hours. The product was worked up as in similar cases and was purified by crystallisation from dilute alcohol when it came out in the form of colourless rectangular plates melting at 141–42°. It was insoluble in alkali and did not give any colour with alcoholic ferric chloride (Found: C, 69.4; H, 5.3; $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%).

3:5:4'-Trihydroxy-flavone (VII, $R = OH$, $R' = H$)

5:4'-Dimethoxy-flavonol (V) was demethylated using hydriodic acid. The yellow product was purified by crystallisation from alcohol when it came out as yellow rectangular plates melting at 214–15°. It gave an olive green colour with alcoholic ferric chloride and did not exhibit any fluorescence in alcoholic or concentrated sulphuric acid solutions (Found: C, 66.4; H, 4.0; $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%). The flavonol dissolved in alkalies to give a golden-yellow colour.

The acetate was prepared by boiling the flavonol with acetic anhydride using a drop of pyridine. The product obtained was crystallised from acetone when it came out as colourless needles and rectangular plates melting at 179–80° (Found: C, 63.2; H, 4.4; $C_{21}H_{16}O_8$ requires C, 63.4; H, 4.0%).

2:6-Dihydroxy-3':4'-dimethoxy-chalkone

A mixture of 2:6-hydroxy-acetophenone (1 g.) and veratric aldehyde (3 g.) was dissolved in alcohol (20 c.c.), treated with aqueous potash (30 c.c. of 50%) and the mixture boiled for 15 minutes. It was cooled and kept overnight and the chalkone worked up as before. It was finally purified by crystallisation from alcohol when it came out in the form of orange yellow rectangular plates and prisms melting at 187–88°. Yield 0.6 g. (Found: in air-dried sample: C, 64.4; H, 5.6; loss on drying *in vacuo* at 120° for 2 hours 5.6; $C_{17}H_{14}O_5$, H_2O requires C, 64.2; H, 5.7; loss on drying 5.7%). The chalkone was easily soluble in ether, alcohol and acetone but

sparingly in benzene and chloroform. It dissolved readily in dilute alkali giving an orange yellow solution and gave a dark brown colour with alcoholic ferric chloride.

2 : 4'-Dihydroxy-6 : 3'-dimethoxy-chalkone

Mono-methyl- γ -resacetophenone (1 g.) was condensed with vanillin (3 g.) as in the above case. The product was worked up as before and the chalkone was purified by crystallisation from dilute alcohol when it came out in the form of bright orange-red rectangular plates melting at 146–47°. Yield 1.2 g. (Found C, 68.1; H, 5.3; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

2-Hydroxy-6 : 3' : 4'-trimethoxy-chalkone (III, R = R' = OCH₃)

Mono-methyl- γ -resacetophenone (3 g.) was condensed with veratric aldehyde (9 g.) as before and the product obtained was purified by crystallisation from 90% alcohol when it came out as short yellow rectangular plates melting at 131–32°. Yield 4.0 g. (Found: C, 69.0; H, 5.9. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%). It dissolved in alkali giving a deep brown colour and gave a dark reddish brown colour with alcoholic ferric chloride.

5 : 3' : 4'-Trimethoxy-flavanone (IV, R = R' = OCH₃)

The above chalkone (III) (2.0 g.) was converted into the flavanone by boiling with 3% aqueous alcoholic sulphuric acid as in previous cases. The product was first crystallised from alcohol and finally from ethyl acetate when it came out as colourless rectangular prisms melting at 145–47°. Yield 0.3 g. (Found: C, 69.1; H, 6.0; $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%). It was insoluble in cold dilute alkali and did not give any colour with alcoholic ferric chloride. It gave an orange-red solution with concentrated sulphuric acid. It was readily soluble in alcohol and acetone and sparingly in ether and chloroform. With magnesium and alcoholic hydrochloric acid, it produced a bright orange red solution.

5 : 3' : 4'-Trimethoxy-flavonol (V, R = R' = OCH₃)

The above flavanone (IV) was converted into the flavonol as in previous cases. When crystallised from ethyl alcohol it came out in the form of yellow rectangular plates melting at 179–80° (Found: in air-dried sample C, 59.6; H, 5.3; loss on drying at 120° for 3 hours 10.0%; $C_{18}H_{16}O_6, 2H_2O$ requires C, 59.3; H, 5.0 and loss on drying 9.9%). It dissolved in dilute alkali giving a golden yellow solution and with alcoholic ferric chloride it gave a deep brown colour. It exhibited a green fluorescence with a blue tinge in neutral alcoholic solution, which was coloured yellow. In concentrated sulphuric acid solution, it gave a pale green fluorescence, the solution being yellowish brown. The flavonol was easily soluble in ether, acetic acid, alcohol and ethyl acetate and sparingly soluble in benzene and petroleum ether.

3:5:3':4': *Tetra-methoxy-flavone* (VI, $R \stackrel{\Delta}{=} R' = OCH_3$)

The above flavonol (V) was methylated with dimethyl sulphate and anhydrous potassium carbonate in acetone solution and the methyl ether crystallised from alcohol when it came out in the form of colourless rectangular plates melting at 139–40° (Found: C, 66.9; H, 5.7; $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3%). It was easily soluble in alcohol, ether, acetone and ethyl acetate and sparingly in benzene and petroleum ether. It exhibited no fluorescence in neutral alcoholic solution.

3:5:3':4'-*Tetrahydroxy-flavone* (VII, $R = R' = OH$)

The above trimethoxy flavonol was demethylated using hydriodic acid and the product crystallised twice from dilute alcohol when it came out as yellow rectangular plates and prisms melting at 230–32° (Found: C, 63.0; H, 3.9; $C_{16}H_{10}O_6$ requires C, 62.9; H, 3.5%). The substance gave an olive green colour with alcoholic ferric chloride and did not exhibit any fluorescence in alcoholic or concentrated sulphuric acid solutions, the solutions being coloured yellow in both the cases. It was easily soluble in alcohol, acetone and ethyl acetate and sparingly in benzene and petroleum ether.

The acetate was prepared by boiling the above flavonol with acetic anhydride and a drop of pyridine. The product crystallised from acetone in the form of colourless needles and rectangular plates melting at 183–84°.

SUMMARY

The synthesis of some flavonols with only one hydroxy group in the 5-position of the benzo-pyrone part has been effected starting from the mono-methyl ether of 2-acetyl resorcinol and adopting the chalkone method of Kostanecki. The mono-methyl ether of 2-acetyl resorcinol is condensed with benzaldehyde, anisaldehyde and veratric aldehyde and the resulting chalkones converted into flavanones and flavonols. Thus 3:5-dihydroxy-, 3:5:4'-trihydroxy-, and 3:5:3':4'-tetrahydroxy flavones, their methyl ethers and acetates have been prepared and their properties studied. These flavonols differ markedly from the isomeric compounds containing only one hydroxyl group in the 7-position of the benzopyrone part.

REFERENCES

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|--|---|
| 1. Rao and Seshadri | .. <i>Proc. Ind. Acad. Sci., A</i> , 1943, 17, 119. |
| 2. Karrer and Schwab | .. <i>Helv. Chim. Acta.</i> , 1941, 297. |
| 3. Sugasawa | .. <i>J. C. S.</i> , 1934, 1483. |
| 4. Rajagopalan, Rao and Seshadri | .. <i>Proc. Ind. Acad. Sci., A</i> , 1947, 25, 432. |
| 5. Row and Seshadri | .. <i>Ibid.</i> , 1945, 21, 132. |
| 6. Balaiah, Seshadri and Venkateswarlu | .. <i>Ibid.</i> , 1942, 16, 73. |
| Rao and Seshadri | .. <i>Ibid.</i> , 1944, 19, 141. |
| 7. Baker | .. <i>J. C. S.</i> , 1939, 959. |