

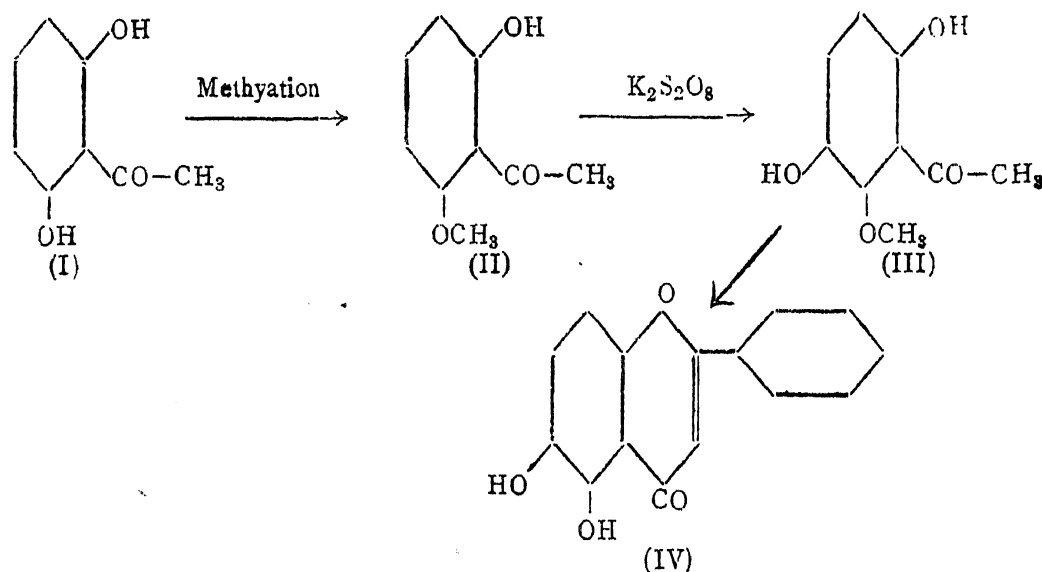
# SYNTHESIS OF 5:6-DIHYDROXYFLAVONOLS—PART I

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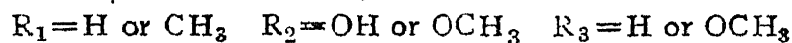
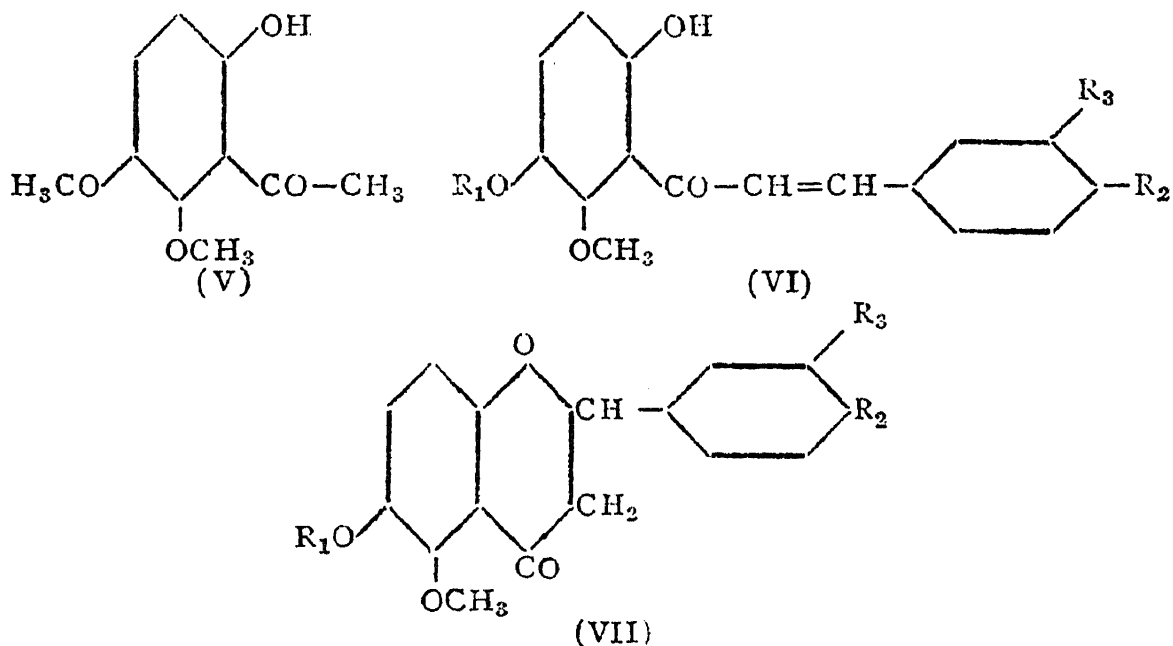
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5:6-DIHYDROXYFLAVONOLS have not so far been synthesised. In connection with the constitution of patuletin it is now found necessary to prepare them and study their properties and reactions. 5:6-Dihydroxy-flavone (IV) was made by Baker<sup>1</sup> in the course of his study of primetin; starting from 2:6-dihydroxy-acetophenone (I) the various stages of his synthesis are represented below:



Since the  $\omega$ -methoxy derivative of (III) is not available the method of Allan and Robinson cannot be used for the synthesis of the flavonols. Consequently the original procedure of Kostanecki has been adopted. This paper records the condensation of ketone (III) with vanillin and of 5:6-dimethoxy-2-hydroxyacetophenone (V) with veratric aldehyde and anisaldehyde to obtain the corresponding chalcones (VI). The conditions for getting the best yields were worked out initially using resacetophenone and its 4-methyl ether. Addition of an excess of the aldehyde component, and the use of strong aqueous alcoholic potash were found to be advantageous. It was noted that in all the cases reported here, some quantity of the flavanones (VII) accompanied the corresponding chalcones.

The conversion of the chalcones (VI) to the flavanones (VII) was carried out by means of aqueous alcoholic sulphuric acid. Even here the products



were mixtures, a portion of the original chalcones remaining unchanged. 5:6:3':4'-Tetramethoxy-flavanone was first obtained by methylating 5:3'-dimethoxy-6:4'-dihydroxy-flavanone using methyl iodide and potassium carbonate in acetone medium. The identity of the compound was established by synthesis directly from (V) and veratric aldehyde. This is rather remarkable since in other cases of flavanones like naringin and hesperidin the methylation of the hydroxyl groups is accompanied by the opening of the flavanone ring and final methylation of the hydroxyl thus set free. The factors that contribute to this difference are not quite clear.

The chalcones described in this paper are bright red in colour whereas the flavanones are colourless. Only the former yield colour with ferric chloride whereas the latter alone give red colour when reduced with magnesium and hydrochloric acid, the colour being definitely weaker with the fully methylated flavanones. In general the chalcones are markedly less soluble.

The synthesis of the flavonols from the flavanones and their study will be reported later.

### Experimental

*2:5:4'-Trihydroxy-6:3'-dimethoxy chalcone.* (VI.  $R_1 = \text{H}$ ,  $R_2 = \text{OH}$ ,  $R_3 = \text{OCH}_3$ ).—2:5-Dihydroxy-6-methoxy acetophenone<sup>1</sup> (4.0 g.) and vanillin (8.0 g.) were dissolved in alcohol (40 c.c.). To this solution aqueous potassium hydroxide (75 g. in 100 c.c. water) was added with stirring and the mixture refluxed on a water-bath for about 15 minutes. While still hot, the flask was corked tight and allowed to stand for about 24 hours. The reddish-brown liquid was then diluted to about 200 c.c. with water and acidified with hydrochloric acid with cooling under the tap, when an orange-red precipitate separated out. On crystallising it twice from alcohol deep-red

needles melting at 167–8° C. were obtained. Further crystallisation did not raise the melting point. Yield: 3.0 g.

The chalkone dissolved in concentrated sulphuric acid yielding an orange-red solution. With aqueous alkali a bright yellow solution was obtained. Alcoholic ferric chloride gave a brownish-red colouration with a solution of the chalkone in alcohol. (Found: C, 64.2; H, 5.4; OCH<sub>3</sub>, 19.2; C<sub>17</sub>H<sub>16</sub>O<sub>6</sub> requires C, 64.6; H, 5.1, and OCH<sub>3</sub>, 19.6%.)

The alcoholic mother liquors from the crystallisation of the chalkone were largely diluted with water when a brown powder was deposited. On recrystallisation twice from alcohol it came out as glistening colourless plates melting at 185–186° C. (Yield: about 0.3 g.). This product was found to be identical with the flavanone described below (VII).

*5:3'-Dimethoxy-6:4'-dihydroxy-flavanone.* (VII. R<sub>1</sub> = H, R<sub>2</sub> = OH, R<sub>3</sub> = OCH<sub>3</sub>).—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 orange yellow solution was boiled under reflux for 24 hours. The liquid was then concentrated *in vacuo* until crystals appeared, cooled and filtered. The solid consisted mainly of the unchanged chalkone (0.5 g.) and some resin. The filtrate on further concentration *in vacuo* and cooling deposited a pale yellow powder. When crystallised twice from aqueous alcohol it was obtained as glistening colourless rectangular plates melting at 186–87° C. Yield: 0.8 g.

The substance gave an orange red solution with concentrated sulphuric acid and a yellow solution with alkali. It gave no colour with ferric chloride in alcoholic solution. It was readily soluble in alcohol and acetone, and sparingly in ether and chloroform. With magnesium powder and concentrated hydrochloric acid it produced a bright red colour in alcoholic solution. (Found: C, 64.5; H, 5.2; OCH<sub>3</sub>, 19.9; C<sub>17</sub>H<sub>16</sub>O<sub>6</sub> requires C, 64.6; H, 5.1 and OCH<sub>3</sub>, 19.6%.)

*5:6:3':4'-Tetramethoxy flavanone.* (VII. R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = R<sub>3</sub> = OCH<sub>3</sub>).—A solution of 5:3'-Dimethoxy-6:4'-dihydroxy flavanone (0.5 g.) in anhydrous acetone (80 c.c.) was treated with anhydrous potassium carbonate (3.0 g.) and methyl iodide (4.0 g.). The mixture was refluxed on a water-bath for about 12 hours, during which time small quantities of methyl iodide were added at intervals to make up for losses. The solvent was then distilled off and excess of water was added to the residue. The methyl ether separated out as a pale yellow solid which on crystallisation from alcohol was obtained in the form of colourless hexagonal prisms melting at 137–38°. Yield, 0.3 g. The substance was insoluble in cold

aqueous alkali and gave an orange red solution with concentrated sulphuric acid. With magnesium powder and concentrated hydrochloric acid, a weak red colour was obtained in alcoholic solution. (Found:  $\text{OCH}_3$ , 33.5.  $\text{C}_{19}\text{H}_{20}\text{O}_6$  requires  $\text{OCH}_3$ , 33.1%.)

*2-Hydroxy-5:6:3':4'-tetramethoxy chalcone*. (VI.  $R_1 = \text{CH}_3$ ,  $R_2 = R_3 = \text{OCH}_3$ ).—A solution of 5:6-dimethoxy-2-hydroxy-acetophenone<sup>1</sup> (3.0 g.) and veratric aldehyde (3.5 g.) in alcohol (20 c.c.) was slowly treated with strong aqueous potash (20 g. in 25 c.c.) and then refluxed on a water-bath for 15 minutes. In some experiments two layers separated out, but this did not decrease the yield of the chalcone. While still hot the flask was corked tight and left overnight. The reddish-brown liquid was then diluted with water and extracted with ether in order to remove the unreacted veratric aldehyde. On acidification with hydrochloric acid, a dark-red gummy solid separated out. When crystallised twice from alcohol bright-red prismatic crystals melting at 135–136° C. were obtained. Yield: 2.0 g. It gives a reddish-brown colour with ferric chloride in alcoholic solution. It is easily soluble in ether, alcohol and acetone. (Found: C, 65.8; H, 5.5;  $\text{C}_{18}\text{H}_{20}\text{O}_6$  requires C, 65.3; and H, 6.0%.) From the alcoholic mother liquors the corresponding flavanone was isolated in a very small yield.

*5:6:3':4'-Tetramethoxy flavanone*. (VII.  $R_1 = \text{CH}_3$ ;  $R_2 = R_3 = \text{OCH}_3$ ).—This was obtained from the above chalcone by boiling with aqueous alcoholic sulphuric acid as already once described. The resulting solution was concentrated under reduced pressure when an orange-brown solid separated out. It was treated with a weak solution of aqueous alkali, ground up well and filtered. The residue (about 1.5 g. from 2.0 g. of the chalcone) was pale-brown in colour and when crystallised from alcohol was obtained as white glistening hexagonal prisms melting at 136–137°, a second crystallisation raising it only to 137–38°. Further crystallisation effected no change. The alkaline filtrate on acidification deposited reddish-orange crystals of the unconverted chalcone (0.3 g.).

The above colourless sample did not depress the melting point of 5:6:3':4'-tetramethoxy flavanone obtained previously by methylation and it gave identical colour reactions.

*5:6:4'-Trimethoxy-2-hydroxy chalcone*. (VI.  $R_1 = \text{CH}_3$ ,  $R_2 = \text{OCH}_3$  and  $R_3 = \text{H}$ ).—A solution of 5:6-dimethoxy-2-hydroxy-acetophenone (3.0 g.) and anisaldehyde (4.0 g.) in alcohol (20 c.c.) was cooled in ice and treated slowly with an ice-cold solution of potassium hydroxide (30 g. in 24 c.c. of water) with vigorous shaking. The flask was corked tight and allowed to stand for four days. Heating had to be avoided as otherwise

considerable amount of anisic acid was produced and the yield of chalkone was reduced. The mixture was then diluted with water (100 c.c.), extracted thrice with ether to remove any anisaldehyde left unreacted and acidified with hydrochloric acid. A dark red crystalline precipitate separated out. It was filtered and macerated with sodium-bicarbonate solution to remove any anisic acid that might have formed during the process of condensation. The red coloured product was filtered, washed with water and crystallised from alcohol. A bright red substance (long needles and rectangular plates tapering at the ends) melting at 102-103° C. was obtained. Yield: 1.3 g. With ferric chloride, the chalkone produced a deep-brown colour in alcoholic solution. (Found: C, 69.2; H, 5.9;  $C_{18}H_{18}O_5$  requires C, 68.8; and H, 5.7%.) The yield of the flavanone recovered from the mother liquors was very small (about 0.1 g.).

5:6:4'-Trimethoxy flavanone. (VII.  $R_1 = CH_3$ ,  $R_2 = OCH_3$ , and  $R_3 = H$ ).—This compound was obtained from the foregoing chalkone. The unchanged chalkone was separated with the help of a very dilute solution of sodium hydroxide. The flavanone (0.5 g. from 1 g. of the chalkone) crystallised from alcohol in the form of colourless large rectangular plates melting at 154-155° C. It gave no colour with ferric chloride in alcoholic solution. On reduction with magnesium and hydrochloric acid only a weak red colour was obtained in alcoholic solution. (Found: C, 69.3; H, 6.0;  $C_{18}H_{18}O_5$  requires C, 68.8; and H, 5.7%.)

#### Summary

Methyl ethers of 5:6-dihydroxy-chalkones and flavanones have been prepared. 2:5-Dihydroxy-6-methoxy acetophenone has been condensed with vanillin and 5:6-dimethoxy-2-hydroxy-acetophenone with veratric aldehyde and anisaldehyde; the resulting chalkones have been converted into the flavanones. In the above reactions mixtures of chalkones and flavanones result.

#### REFERENCE