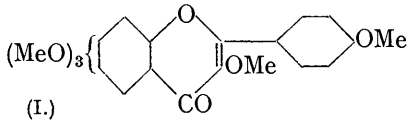
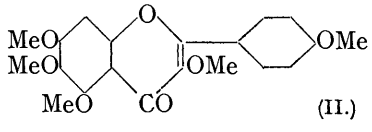
11. *A Synthesis of Tangeritin.*

By L. J. Goldsworthy and Robert Robinson.

Tangeritin, a pentamethoxyflavone, was isolated by Nelson (*J. Amer. Chem. Soc.*, **1934**, **56**, 1392) from the oil expressed from the peel of tangerine oranges (*Citrus nobilis deliciosa*) and its constitution was all but completely elucidated. On hydrolysis with aqueous alcoholic potassium hydroxide, anisic acid and tangeretol, an isomeride of gossypitol tetramethyl ether, $C_6H(OMe)_3(OH)(CO{\cdot}CH_2{\cdot}OMe)$, were obtained. The position of the extra-nuclear methoxyl in the last-named substance was not deduced as the result of further degradation but from the fact that the pentahydroxyflavone obtained by demethylating tangeritin was found to exhibit the general character of a flavonol. For these reasons tangeritin was considered to be best represented by the expression (I).



(I.)



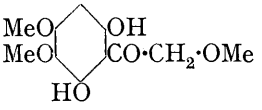
(II.)

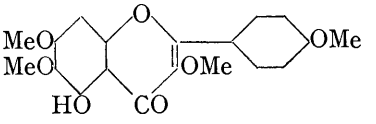
As the gossypetin-type orientation of the tetrahydroxybenzene nucleus may be tentatively excluded, it appeared that the most probable formula for tangeritin would be (II), which is structurally similar to quercetagetin, baicalein and scutellarein. Hence tangeretol should be quercetagetol tetramethyl ether and in order to correlate tangeritin and quercetagetin we tried to obtain tangeritol from *O*-hexamethylquercetagetin. The experiment was necessary because A. G. Perkin (J., **1913**, **103**, 209) used *O*-hexaethylquercetagetin in his work on the constitution of the flavonol. Owing to the small quantity of quercetagetin available, the derived *O*-tetramethylquercetagetol oxime could not be

obtained quite pure, but a mixture with tangeretol oxime had a higher melting point and there is no doubt that the two specimens were identical.

The synthesis of tangeritin was effected several months before the period of the above experiment and it followed the lines of that of quercetagetin and its pentamethyl ether (Baker, Nodzu, and Robinson, J., 1929, 76), anisic acid derivatives being substituted for those of veratric acid previously employed.

It may be recalled that the intermediate in this synthesis was a ketone obtained by coupling 4 : 5-dimethoxyresorcinol with methoxyacetonitrile in a Hoesch reaction. On grounds of analogy this was at first thought to be 4 : 6-dihydroxy-ω : 2 : 3-trimethoxyacetophenone, but this view was discarded in favour of the constitution (III) (2 : 6-dihydroxy-ω : 2 : 3-trimethoxyacetophenone) partly on account of the properties of the synthetic quercetagetin pentamethyl ether and partly as the result of further work in the same field (Baker and Robinson, J., 1929, 156).

(III.) 



(IV.)

Naturally, if (III) had the alternative constitution, there would be no ambiguity about the orientation of hydroxyl groups in the flavones resulting from it. In the case of (III), however, there is some dubiety, resolved so far as quercetagetin is concerned by the independent unambiguous synthesis of gossypetin. In the present instance we rely on the same evidence; we assume that the direction of ring-closure using anisic anhydride with (III) will be the same as that observed when veratric anhydride was used, and we are confirmed in our view by the character of the pentahydroxyflavone produced on demethylation of the synthetic product, since this resembles quercetagetin and differs from gossypetin in its properties.

Fusion of (III) with anisic anhydride and sodium anisate, followed by hydrolysis, is accordingly considered to give *5-hydroxy-3 : 6 : 7 : 4′-tetramethoxyflavone* (IV) and on further methylation tangeritin was obtained. Through the kindness of Dr. E. K. Nelson, to whom we are greatly indebted, we have been able to make a direct comparison of the natural and the synthetical specimen, which proved to be identical.

We have taken the opportunity to prepare and more closely to characterise 3 : 5 : 6 : 7 : 4′-pentahydroxyflavone, as it would be surprising if this substance were not a natural product. The isomeric 3 : 5 : 7 : 8 : 4′-pentahydroxyflavone is being synthesised for comparison and in order to strengthen the argument bearing on the structure. We are informed by Dr. T. R. Seshadri that the flavonol herbacetin isolated by him may have this gossypetin-like constitution.

Experimental.

5-Hydroxy-3 : 6 : 7 : 4′-tetramethoxyflavone (IV).—An intimate mixture of 2 : 6-dihydroxy-ω : 3 : 4-trimethoxyacetophenone (0·5 g.), prepared essentially according to the methods described by Chapman, Perkin, and Robinson (J., 1927, 3031) and by Baker and Robinson (*loc. cit.*), anisic anhydride (2·0 g.), and sodium anisate (1·0 g.) was heated for 3 hours at 180—185° (oil-bath) under diminished pressure (20 mm.). The product of the reaction was hydrolysed by heating with alcohol (15 c.c.), water (1 c.c.), and potassium hydroxide (2·0 g.) on the steam-bath for 30 minutes, and the flavonol derivative precipitated from the cooled solution, after dilution with water (100 c.c.), by carbon dioxide; the washed and dried material (0·66 g.) had m. p. 145—150°. Two crystallisations from alcohol afforded well-defined rectangular yellow plates, m. p. 171° (Found in material dried at 120°: C, 64·0; H, 5·1. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). The yellow solution of the *substance* in concentrated sulphuric acid is non-fluorescent; the ferric reaction in alcoholic solution is olive-green. The low melting point of the substance before recrystallisation suggested that it might be a mixture of the two theoretically possible products of the condensation, *viz.*, 5-hydroxy-3 : 6 : 7 : 4′-tetramethoxy- and 5-hydroxy-3 : 7 : 8 : 4′-tetramethoxy-flavone. This seemed probable in view of the fact that Baker, Nodzu, and Robinson (*loc. cit.*) obtained evidence that the analogous condensation of 2 : 6-dihydroxy-ω : 3 : 4-trimethoxyacetophenone with veratric anhydride and sodium veratrate

gave a mixed product. Accordingly an attempt was made to obtain an isomeride of the compound, m. p. 171°, from the alcoholic mother-liquors. Although various solvents, including acetic acid, ethyl acetate, acetone, mixtures of alcohol and water, and acetic acid and water were tried, all attempts to obtain a pure substance from the material derived from the mother-liquors were unsuccessful. In some cases the crystallised product melted over a range of only a few degrees, and in others over a range of 10° or more. A specimen having m. p. 145—148° (Found: C, 63·6; H, 5·2%) was probably of the nature of a eutectic mixture. The material contained in these mother-liquors was also per-methylated and gave a product, m. p. 130—137°, not appreciably raised by crystallisation from ethyl acetate. Further recrystallisations resulted in the separation of a little crude tangeritin, m. p. 150—151°, but the isomeride could not be isolated.

3 : 5 : 6 : 7 : 4′-*Pentamethoxyflavone* (*Tangeritin*).—As the hydroxyl group in position 5 is known to resist methylation, the methylation of 5-hydroxy-3 : 6 : 7 : 4′-tetramethoxyflavone was carried out by the method applied by Baker and Robinson (J., 1928, 3115) to the case of 5-hydroxy-7 : 4′-dimethoxy-2-styryl*iso*flavone. Methyl sulphate (2 c.c.) and aqueous sodium hydroxide (2 c.c. of 20%) were added to a solution of 5-hydroxy-3 : 6 : 7 : 4′-tetramethoxyflavone (0·2 g.) in acetone (10 c.c.), and the mixture was shaken vigorously at about 50°. When the acetone layer, at first orange, became pale yellow, methyl sulphate (1 c.c.) and aqueous sodium hydroxide (1 c.c. of 20%) were added and the shaking was continued. On further shaking with an additional quantity of aqueous sodium hydroxide (2 c.c. of 20%) and subsequent addition of water (12 c.c.), the methylated product separated as fine white needles (m. p. 153—154°). The substance crystallised from ethyl acetate as well-defined rods and needles, m. p. 154° (Found in material dried at 100°: C, 64·4; H, 5·4. Calc. for $C_{20}H_{20}O_7$: C, 64·5; H, 5·4%) alone, or mixed with the pure specimen of tangeritin supplied by Dr. E. K. Nelson. Its solubility properties in solvents and reagents, the formation of yellow needles of an oxonium salt with concentrated hydrochloric acid, the development of a blood-red colour with concentrated nitric acid, and other characters were found on direct comparison to tally with the corresponding properties of naturally occurring tangeritin.

The synthetic product was demethylated by heating at 135° with hydriodic acid (*d* 1·7) and phenol. The yellow microcrystalline substance precipitated on the addition of sulphurous acid rapidly acquired a greenish tinge when exposed to the air.

Like the flavonol from natural tangeritin, the synthetic flavonol developed a pinkish-red colour when reduced with magnesium ribbon in an acidified alcoholic solution. Addition of an alcoholic solution of lead acetate to its alcoholic solution gave an orange-coloured precipitate, which gradually became greenish-brown. In the case of the pentahydroxy-compound from natural tangeritin this colour change is described as taking place at once. With ferric chloride an alcoholic solution of the synthetic flavonol gave a dark olive-green colour. In the case of demethylated natural tangeritin the colour is described as bluish-green. These details are given in this place because they complete the comparison of our synthetic tangeritin with the substance isolated by Nelson (*loc. cit.*). Other properties of pure 3 : 5 : 6 : 7 : 4′-pentahydroxyflavone are mentioned below.

3 : 5 : 6 : 7 : 4′-*Pentahydroxyflavone*.—A mixture of 5-hydroxy-3 : 6 : 7 : 4′-tetramethoxyflavone (0·5 g.), hydriodic acid (7·5 c.c., *d* 1·7), and phenol (2·0 g.) was heated at 135—140° for 1½ hours. The yellow needles of the hydriodide which separated were collected, triturated with sulphurous acid, and then digested for 1 hour with 50% acetic acid. Well-defined, yellow, microscopic needles were obtained in this way (Found in material dried in a vacuum: C, 59·9; H, 3·7. $C_{15}H_{10}O_7$ requires C, 59·6; H, 3·3%). On heating, the substance darkened at 270° and began to melt at about 314°; at 320° the colour was almost black and fusion was not complete.

The colour changes which accompany the oxidation of the flavonol in alkaline buffered solutions showed a general resemblance to those characteristic of quercetagetin under similar conditions (cf. Baker, Nodzu, and Robinson, *loc. cit.*), thus affording further evidence of the parallel course of the synthesis herein described and that of quercetagetin. The solutions were prepared with the aid of the " B.D.H. Universal Buffer " mixtures and were aerated before the introduction of the flavonol.

At p_H 9·8 the yellow colour of the solution changed within a few minutes to greenish-yellow and within 12 minutes to bright green; 5 minutes later the green had a distinct olive tinge, which slowly deepened and then changed to yellowish-brown, after which no further colour change occurred during 2 days.

At p_H 10·4 the same series of colour changes occurred with much greater rapidity. The

change from yellow to bright green took place in 3 minutes and within 10 minutes the colour was dark olive-green. The yellow-brown colour finally attained after several hours remained unchanged after 2 days.

At p_H 11·0 precisely similar colour changes occurred; within 6 minutes the shade of olive-green was darker than the shade observed at p_H 10·4 after 10 minutes.

The flavonol is a weaker adjective dye than quercetagetin, giving duller but generally similar shades on mordanted cotton, and the colours observed were the following: With a weak aluminium mordant, a very poor dull yellow; strong aluminium, canary-yellow; weak iron, brownish greenish grey; strong iron, deep brown; iron with aluminium, khaki.

Tangeretol Oxime from Quercetagetin.—A mixture of *O*-hexamethylquercetagetin (0·3 g.), alcohol (10 c.c.), water (7 c.c.), and potassium hydroxide (5 g.) was refluxed for 6 hours. Hydroxylamine hydrochloride (6 g.) was then introduced, and the alcohol removed by distillation; water (about 30 c.c.) was added during this process. The solution was acidified and extracted with a relatively large volume of light petroleum. The residue after removal of the solvent was a colourless viscous liquid; it was taken up in a little hot carbon disulphide, leaving a small insoluble portion, mixed with light petroleum, and on keeping in the ice-chest the solution deposited first an oil and then a small quantity of soft, colourless needles, m. p. 85—87°. The melting point was a degree higher on admixture with tangeretol oxime prepared as described by Nelson (*loc. cit.*).

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