A New Synthesis of Flavonols of the Quercetagetin Series.

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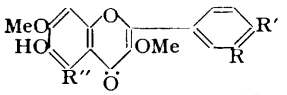
" *ortho*-Oxidation " has been employed for a new synthesis of the flavonols of the quercetagetin series. 6-Hydroxy-3 : 7-dimethoxyflavone yields its 5-aldehyde and thence 5 : 6-dihydroxy-3 : 7-dimethoxyflavone. On methylation it forms the tetramethyl ether of 6-hydroxygalangin. In the same way tangeretin, quercetagetin hexamethyl ether, and melisimplexin have been prepared. Melisimplin has been obtained by partial methylation of the appropriate 5 : 6-dihydroxy-compound.

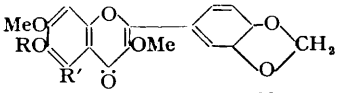
Quercetagetin was synthesised by Baker, Nodzu, and Robinson (*J.*, 1929, 74), from 2 : 6-dihydroxy-ω : 4 : 5-trimethoxyacetophenone, and the same method was later used for the synthesis of tangeretin by Goldsworthy and Robinson (*J.*, 1937, 46). The synthesis was considerably simplified by Row and Seshadri (*Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 24), using the more easily available 2 : 5-dihydroxy-ω : 4 : 6-trimethoxyacetophenone, and they prepared all the members of the series, *i.e.*, 6-hydroxy-derivatives of galangin, kæmpferol, quercetin, and myricetin. Melisimplin and melisimplexin were also synthesised by Briggs and Locker by this procedure (*J.*, 1950, 2379).

Row and Seshadri's method was based on a theory of biogenesis. A purely synthetic

route, using the two-stage "*ortho*-oxidation" of 6-hydroxy-3 : 7-dimethoxyflavones has now been worked out : a 5-aldehyde group is introduced by means of hexamethylenetetramine and then replaced by hydroxyl by treatment with hydrogen peroxide. In the simplest example, 6-hydroxyflavone was earlier converted into 5 : 6-dihydroxyflavone by Seshadri and Viswanadham (*Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 148). The general method is now found to have two advantages over earlier methods : (i) The required intermediates are easily prepared from a cheaper starting material, resorcinol. (ii) The yield of the final product is good and the partial methyl ethers with free 5- and 6-hydroxyl groups are obtained as important intermediates; a compound of this type is oxyayanin-B which was recently isolated by King, King, and Stokes (*J.*, 1954, 4587) from Ayan wood. The compounds listed under the formulæ, and their completely methylated derivatives, have thus been prepared. From the flavone (II; R = H, R′ = OH) partial methylation gives melisimplin (II; R = Me, R′ = OH) and complete methylation gives melisimplexin (II; R = Me, R′ = OMe).



(I) R = R′ = H, R″ = OH
R = H, R′ = OMe, R″ = OH
R = R′ = OMe, R″ = OH



(II) R = H; R′ = OH

Experimental

All the aldehydes and 5 : 6-dihydroxyflavones give the same colour reactions as given for the first examples.

5-Aldehydo-6-hydroxy-3 : 7-dimethoxyflavone (I; R = R′ = H, R″ = CHO).—A solution of 6-hydroxy-3 : 7-dimethoxyflavone (1·9 g.) (Rao, Row, and Seshadri, *Proc. Indian Acad. Sci.*, 1945, **22**, *A*, 30) in glacial acetic acid (75 c.c.) was heated with hexamine (6 g.) on a boiling-water bath for 8 hr. and the resulting reddish solution was further heated with hydrochloric acid (1 : 1; 40 c.c.) for 30 min. After dilution with water and cooling, a pale yellow precipitate separated. It was collected and crystallised from methyl acetate, the *aldehyde* separating as thick yellow plates, m. p. 194—195° (1·5 g.) (Found : C, 66·0; H, 4·0. $C_{18}H_{14}O_6$ requires C, 66·2; H, 4·3%). It gave a reddish-brown colour with ferric chloride and an orange-red colour with concentrated sulphuric acid. Its 2 : 4-dinitrophenylhydrazone separated as orange-yellow needles, m. p. 294° (decomp.), from glacial acetic acid.

5 : 6-Dihydroxy-3 : 7-dimethoxyflavone (I; R = R′ = H, R″ = OH).—To the above aldehyde (1·12 g.), suspended in 6% aqueous sodium hydroxide (12 c.c.), enough pyridine (60 c.c.) was added to yield a clear solution which was cooled to 10°, treated with 6% hydrogen peroxide (5·5 c.c.) in 15 min. with shaking, left at room temperature for 2 hr., then neutralised, and extracted with ether. The residue of *dihydroxyflavone* left on evaporation of the ether solution crystallised from methyl alcohol as yellow rectangular plates, m. p. 171—172° (0·4 g.) (Found : C, 64·9; H, 4·5. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). It gave a brilliant green colour with ferric chloride and a yellow solution with sulphuric acid. With aqueous (5%) sodium hydroxide, it became red and then blue and eventually dissolved to give a golden-yellow solution which exhibited a pale green fluorescence and yielded a brown precipitate when heated. The acetate crystallised from methyl alcohol as colourless rectangular tablets and rods, m. p. 190—191°. Complete methylation was effected by heating the phenol with excess of methyl sulphate and potassium carbonate in acetone until the product gave a negative ferric reaction; 3 : 5 : 6 : 7-tetramethoxyflavone crystallised as colourless flat needles and rectangular plates, m. p. 110—111° (cf. Row and Seshadri, *loc. cit.*).

5-Aldehydo-6-hydroxy-3 : 7 : 4′-trimethoxyflavone (I; R = H, R′ = OMe, R″ = CHO).—6-Hydroxy-3 : 7 : 4′-trimethoxyflavone (Rao, Row, and Seshadri, *loc. cit.*) (2·1 g.) was condensed with hexamine (7·5 g.) in glacial acetic acid (75 c.c.) as in the earlier case. The *aldehyde* crystallised from methyl acetate as yellow prisms, m. p. 211—212° (1·4 g.) (Found : C, 63·7; H, 4·7. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%). The 2 : 4-dinitrophenylhydrazone crystallised from acetic acid as deep red needles, m. p. 296—297° (decomp.).

5 : 6-Dihydroxy-3 : 7 : 4′-trimethoxyflavone (I; R = H, R′ = OMe, R″ = OH).—The preceding aldehyde (1 g.) was oxidised as described above. The *product* crystallised from alcohol as golden-yellow rhombohedral plates, m. p. 176—177° (0·45 g.) (Found : C, 62·3; H, 5·0.

$C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%). The diacetate (prepared by acetic anhydride–pyridine) formed colourless needles, m. p. 170—172°, from ethyl acetate. Methylation yielded 3 : 5 : 6 : 7 : 4′-pentamethoxyflavone (tangeretin) as rectangular plates, m. p. 153—154° (cf. Goldsworthy and Robinson, *loc. cit.*).

5-*Aldehydo*-6-*hydroxy*-3 : 7 : 3′ : 4′-*tetramethoxyflavone* (I; R = R′ = OMe, R″ = CHO).—6-Hydroxy-3 : 7 : 3′ : 4′-tetramethoxyflavone (m. p. 223—224°) (Row and Seshadri, *Proc. Indian Acad. Sci.*, 1945, **21**, *A*, 159) (5 g.) and hexamine (15 g.) were heated in glacial acetic acid (130 c.c.) on a boiling water-bath for 7 hr. After acid-treatment the *product* (2·5 g.) crystallised from methyl acetate as golden-yellow rhombohedral prisms, m. p. 202—203° (Found : C, 61·5; H, 4·6. $C_{20}H_{18}O_8$ requires C, 62·1; H, 4·6%). Its 2 : 4-dinitrophenylhydrazone formed orange-red needles (from acetic acid), m. p. 286—287° (decomp.).

5 : 6-*Dihydroxy*-3 : 7 : 3′ : 4′-*tetramethoxyflavone* (I; R = R′ = OMe, R″ = OH).—The preceding aldehyde (2·3 g.) was subjected to Dakin oxidation; the *product* crystallised from ethyl acetate as orange-yellow rhombohedral prisms, m. p. 220—221° (1·0 g.) (Found : C, 64·2; H, 4·8. $C_{19}H_{18}O_8$ requires C, 64·4; H, 5·1%). The diacetate crystallised from ethyl acetate as rectangular rods and prismatic needles, m. p. 223—224°. The dihydroxy-flavone, when methylated with excess of methyl sulphate and potassium carbonate in acetone for 60 hr., yielded quercetagetin hexamethyl ether as prismatic needles, m. p. 141—142° (cf. Row and Seshadri, *loc. cit.*).

6-*Hydroxy*-3 : 7-*dimethoxy*-3′ : 4′-*methylenedioxyflavone* (II; R = R′ = H).—A mixture of 2 : 5-dihydroxy-ω : 4-dimethoxyacetophenone (4 g.) (Row and Seshadri, *loc. cit.*), piperonylic anhydride (17 g.) (Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 148), and potassium piperonylate (6 g.) was heated in a vacuum at 180° for 4 hr. and the product was refluxed with alcoholic 10% potassium hydroxide (200 c.c.) for 0·5 hr. The solvent was removed under reduced pressure and the residual mixture diluted with water and then saturated with carbon dioxide. The solid *flavone* (3·5 g.) was collected and crystallised from alcohol as needles, m. p. 213—214° (Found : C, 63·2; H, 4·1. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%). It was sparingly soluble in aqueous sodium hydroxide and in common organic solvents. With magnesium and hydrochloric acid it gave a brilliant red colour and with sulphuric acid a yellow solution. The monoacetate crystallised from ethyl acetate–light petroleum as colourless rectangular prisms, m. p. 202°.

5-*Aldehydo*-6-*hydroxy*-3 : 7-*dimethoxy*-3′ : 4′-*methylenedioxyflavone* (II; R = H, R′ = CHO).—The foregoing flavone (2·1 g.) was condensed with hexamine (6·3 g.) in acetic acid; the *aldehyde* (1·2 g.) crystallised from alcohol as pale yellow needles, m. p. 248—249° (Found : C, 61·4; H, 4·2. $C_{19}H_{14}O_8$ requires C, 61·6; H, 3·8%). It readily yielded a 2 : 4-dinitrophenylhydrazone as small red prisms, m. p. 299—300° (decomp.).

5 : 6-*Dihydroxy*-3 : 7-*dimethoxy*-3′ : 4′-*methylenedioxyflavone* (II; R = H, R′ = OH).—The aldehyde (0·9 g.) was subjected to Dakin oxidation; the *dihydroxy-compound* crystallised from methyl acetate as pale yellow needles, m. p. 218—219° (Found : C, 60·7; H, 4·0. $C_{18}H_{14}O_8$ requires C, 60·3; H, 3·9%), sparingly soluble in 5% aqueous sodium hydroxide; the alkaline solution, when heated, afforded an orange salt. The acetate (prepared by acetic anhydride–perchloric acid) crystallised from ethyl acetate–light petroleum as colourless needles, m. p. 226—227°.

Melisimplin (II; R = Me, R′ = OH).—The preceding dihydroxyflavone (100 mg.) was refluxed in acetone (100 c.c.) with methyl sulphate (0·03 c.c.) and potassium carbonate (1 g.) for 8 hr. The solvent was distilled off and the residue was treated with water. The insoluble melisimplin (70 mg.) crystallised from ethyl acetate as yellow needles, m. p. 234—235°. Briggs and Locker (*loc. cit.*) reported m. p. 235—236°. It gave a pink colour with magnesium and hydrochloric acid and a green colour with alcoholic ferric chloride. The acetate (prepared by anhydride–perchloric acid) crystallised from alcohol in colourless needles, m. p. 201—202°.

Melisimplexin (II; R = Me, R′ = OMe).—The 5 : 6-dihydroxyflavone (100 mg.) was methylated with excess of methyl sulphate (0·5 c.c.) by the potassium carbonate–acetone method until the product gave a negative ferric reaction (60 hr.). Melisimplexin crystallised from ethyl acetate as colourless flattened needles, m. p. 184—185°. Briggs and Locker (*loc. cit.*) reported m. p. 185·5°.

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