

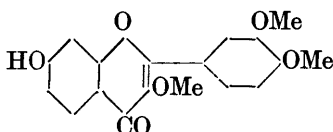
CCCIX.—*A New Synthesis of Fisetin and of Quercetin.*

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THE first examples of the "direct" synthesis of flavone and flavonol derivatives by arylation of substituted *o*-hydroxyacetophenones were reported by the present authors (J., 1924, 125, 2192), and the method has already been applied to the syntheses of myricetin (Kalf and Robinson, J., 1925, 127, 181), galangin methyl ether (*ibid.*), datiscetin (Kalf and Robinson, J., 1925, 127, 1968) and kaempferol (Robinson and Shinoda, J., 1925, 127, 1973) among naturally occurring members of the group. In the present communication the synthesis of fisetin and of quercetin along similar lines is described. These colouring matters have been previously synthesised by Kostanecki, Lampe and Tambor (*Ber.*, 1904, 37, 784, 1402).

## E X P E R I M E N T A L.

*Veratric Anhydride*,  $[C_6H_3(OMe)_2 \cdot CO]_2O$ .—(A) Pyridine (35 g.) was added to a solution of veratroyl chloride (24 g.) in ether (180 c.c.) and after 2.5 hours small pieces of ice were added. A certain amount of the anhydride crystallised from the solution and was collected. The separated ethereal layer was washed with dilute hydrochloric acid, dried, and evaporated (yield, 16 g.). The substance crystallises from benzene or from ethyl acetate in rectangular prisms, m. p. 124—125° (Found: C, 62.5; H, 5.3.  $C_{18}H_{18}O_7$  requires C, 62.4; H, 5.2%). (B) A 20% solution (50 c.c.) of carbonyl chloride in benzene was added to a stirred, ice-cooled mixture of veratric acid (33 g.), pyridine (15 g.) and benzene (50 c.c.). After 2 hours, ice and dilute hydrochloric acid were introduced and the benzene solution was separated, dried and evaporated (yield 75—80%).

7-Hydroxy-3 : 3' : 4'-trimethoxyflavone (*Fisetin Trimethyl Ether*),

—A mixture of  $\omega$ -methoxyresacetophenone (2.5 g.) (Slater and Stephen, J., 1920, 117, 314), veratric anhydride (24 g.) and potassium veratrate (10 g.) was heated for 4.5 hours in an oil-bath at 175—180°. Alcohol (150 c.c.) was added and the solution boiled for 15 minutes, then mixed with potassium hydroxide (8 g.) dissolved in water (25 c.c.) and the alcohol removed by distillation. Carbon dioxide was passed through the filtered solution of the residue in water until no further precipitation occurred. The solid (3.2 g.) crystallised from ethyl acetate (charcoal) in almost colourless needles, m. p. 220° (Found : C, 66.1; H, 4.8.  $C_{18}H_{16}O_6$  requires C, 65.9; H, 4.9%). The substance does not develop a coloration with ferric chloride in alcoholic solution and its yellow solution in sulphuric acid exhibits a weak green fluorescence. The *acetyl* derivative, obtained by treatment with boiling acetic anhydride for 2 hours, crystallised from alcohol in colourless needles, m. p. 229° (Found : C, 65.1; H, 5.0.  $C_{20}H_{18}O_7$  requires C, 64.9; H, 4.9%). On hydrolysis with aqueous-alcoholic sodium hydroxide *fisetin trimethyl ether* was easily regenerated.

3 : 7 : 3' : 4'-*Tetramethoxyflavone*.—Methyl sulphate (8 c.c.) was gradually added with shaking to a solution of *fisetin trimethyl ether* (0.7 g.) in water (25 c.c.) containing potassium hydroxide (2 g.). Finally, the solution was rendered strongly alkaline and the precipitated solid (0.7 g.) was collected and crystallised from ethyl acetate in prismatic needles, m. p. 150° (Found : C, 66.3; H, 5.3. Calc. for  $C_{19}H_{18}O_6$  : C, 66.7; H, 5.3%). This compound has the properties of *fisetin tetramethyl ether* which is stated by Schmid (*Ber.*, 1886, 19, 1746) to melt at 152°.

3 : 7 : 3' : 4'-*Tetra-acetoxyflavone* (*Tetra-acetylfisetin*).—7-Acetoxy-3 : 3' : 4'-trimethoxyflavone was converted into *fisetin* in 35 minutes, by boiling hydriodic acid ( $d$  1.7). The yellow solid obtained on the addition of sulphurous acid exhibited the reactions and properties of *fisetin*, but, as this substance has m. p. (decomp.) above 360°, it was identified by the preparation of the *tetra-acetyl* derivative in the usual manner. This crystallised from alcohol in colourless needles, m. p. 196—198° (Found : C, 60.4; H, 4.3. Calc. for  $C_{23}H_{18}O_{10}$  : C, 60.8; H, 4.0%). *Tetra-acetylfisetin* is stated by A. G. Perkin (J., 1897, 71, 1195) to melt at 196—198°.

5 : 7-Dihydroxy-3 : 3' : 4'-trimethoxyflavone (*Quercetin Trimethyl Ether*).—The veratrolylation of  $\omega$ -methoxyphloracetophenone (3 g.) (Slater and Stephen, *loc. cit.*) was carried out substantially in the manner described above for the resorcinol derivative. The yield of the crude product was 4.9 g. and the substance was crystallised from alcohol and then from ethyl acetate in very pale yellow needles, m. p. 240—245° (Found : C, 62.6; H, 4.5.  $C_{18}H_{16}O_7$  requires C, 62.8; H, 4.7%). The addition of ferric chloride to an alcoholic solution produces an intense greenish-brown coloration, and the bright yellow solution in sulphuric acid exhibits a very weak green fluorescence. The *diacetyl* derivative crystallised from alcohol in needles, m. p. 159—160° (Found : C, 61.9; H, 4.5.  $C_{22}H_{20}O_9$  requires C, 61.7; H, 4.7%).

3 : 5 : 7 : 3' : 4'-Pentamethoxyflavone (*Quercetin Pentamethyl Ether*).—The trimethyl ether was methylated by means of methyl sulphate and aqueous potassium hydroxide (compare Waliasco, *Arch. Pharm.*, 1904, **242**, 225, for the similar methylation of quercetin), and the product crystallised from ethyl acetate in needles, m. p. 148°, unaltered by admixture with an authentic specimen prepared from quercetin.

*Penta-acetylquercetin*.—The quercetin trimethyl ether yielded on demethylation in the usual manner a yellow crystalline product, m. p. 312—316° (decomp.), which exhibited the properties and reactions of quercetin and on acetylation gave a compound crystallising from alcohol in colourless needles, m. p. 191—195°. The m. p. was unaltered by admixture with an authentic specimen of penta-acetylquercetin.

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