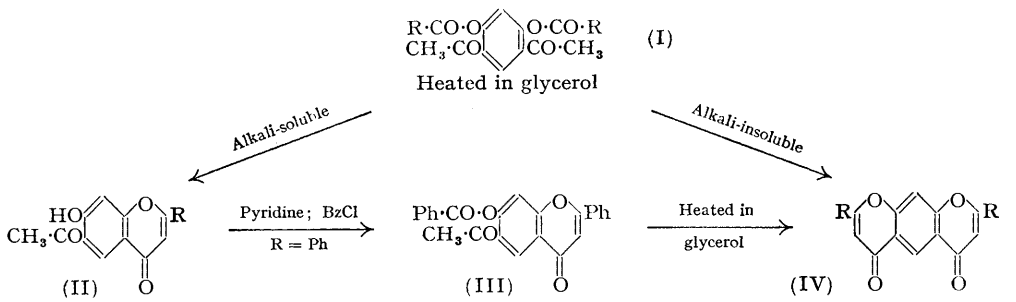
383. *Thermal Cyclization of* o-*Aroyloxyacetoarones. Part II.* Further Syntheses in the Flavone Series (Diflavones and Flavonols).*

By (Miss) H. M. Lynch, T. M. O'Toole, and T. S. Wheeler.

The method for the preparation of flavones involving thermal cyclization of aroyl esters of *o*-hydroxyacetoarones which was described in Part I (*J.*, 1950, 1252) has been applied to the production of " diflavones " and flavonol 3-methyl ethers, by using, respectively, esters of 4 : 6-diacetylresorcinol and of ω-methoxyphloroacetophenone.

Dunne, Gowan, Keane, O'Kelly, O'Sullivan, Roche, Ryan, and Wheeler (Part I *) have shown that *o*-aroyloxyacetoarones yield flavones when heated in glycerol. The reaction has now been applied to esters of diacetylresorcinols (I and V), and a synthesis of " diflavone " (IV; R = Ph) realized. Thus, the dibenzoate of 4 : 6-diacetylresorcinol (I; R = Ph) gave a mixture of (IV; R = Ph), insoluble in alkali, and 6-acetyl-7-hydroxyflavone (II; R = Ph), which is alkali-soluble. Benzoylation of (II; R = Ph) yielded 6-acetyl-7-benzoyloxyflavone (III), which was converted into (IV; R = Ph) by dehydration in glycerol. As with previous syntheses (Ryan and O'Neill, *Proc. Roy. Irish Acad.*, 1915, **32**, *B*, 48; Algar, McCarthy, and Dick, *ibid.*, 1933, **41**, *B*, 155; Algar and Hanway, *ibid.*, 1934, **42**, *B*, 9) the yield of diflavone was poor. Attempts to apply the Baker–Venkataraman transformation (Baker, *J.*, 1933, 1381; Mahal and Venkataraman, *Current Sci.*, 1933, **2**, 214; Doyle *et al.*, *Sci. Proc. Roy. Dublin Soc.*, 1948, **24**, 291) to (I; R = Ph) were unsuccessful. The di-*p*-anisoate of 4 : 6-diacetylresorcinol (I; R = *p*-C_6H_4·OMe) on dehydration in glycerol behaved similarly to the dibenzoate; monocyclization being the main reaction. The products were 6-acetyl-7-hydroxy-4′-methoxyflavone (II; R = *p*-C_6H_4·OMe) and a trace of an alkali-insoluble substance, which was probably " 4′ : 4″-dimethoxydiflavone " (IV; R = *p*-C_6H_4·OMe) first synthesized by Algar, McCarthy, and Dick (*loc. cit.*).

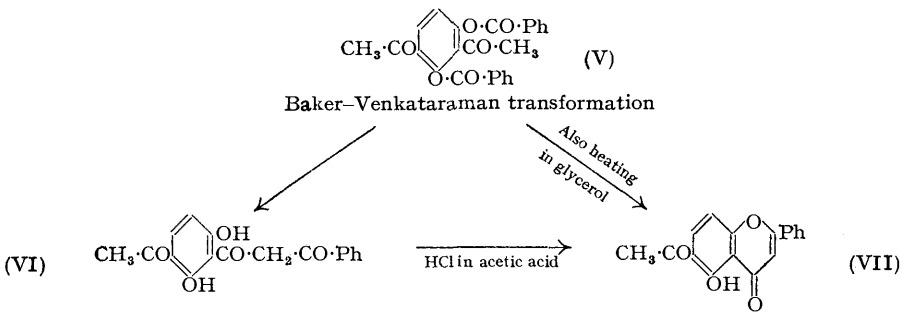


Gulati and Venkataraman (*J.*, 1931, 2378) obtained by Allan–Robinson benzoylation and *p*-anisoylation of 4 : 6-diacetylresorcinol, products to which they assigned the structures (II and IV; R = Ph and *p*-C_6H_4·OMe). Later work (Algar, McCarthy, and Dick, *Proc. Roy. Irish Acad.*, *loc. cit.*; Algar and Hanway, *ibid.*, 1934, **42**, *B*, 12; Baker, *J.*, 1934, 72) failed to confirm these results. Baker (*loc. cit.*) pointed out that the melting point (123°) recorded by Gulati and Venkataraman for (II; R = Ph) was improbably low for the structure assigned. This compound as now obtained melts at 204—207°, and its structure is confirmed by its conversion through (III) into (IV; R = Ph). Jhaveri, Khorana, and Motiwala (*Indian J. Pharm.*, 1950, **12**, 42) state, without details, that they prepared (II; R = Ph) by the method of Gulati and Venkataraman (*loc. cit.*). Again the melting point (160—161°) given by the latter authors for (II; R = *p*-C_6H_4·OMe) seems low for the structure assigned; a value of 238—241° for crystals with $\frac{1}{2}H_2O$ has now been obtained.

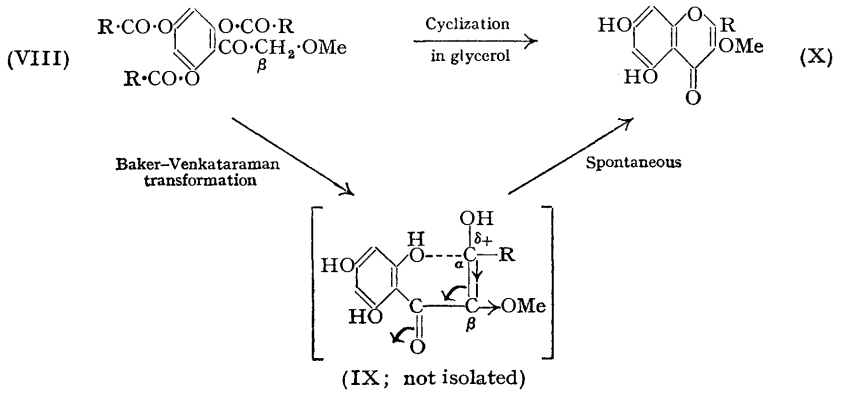
The dibenzoate (V) of 2 : 4-diacetylresorcinol when subjected to cyclization in glycerol gave 6-acetyl-5-hydroxyflavone (VII). Application of the Baker–Venkataraman transformation reaction to (V) gave a mixture of 3-acetyl-2 : 6-dihydroxydibenzoylmethane

* The following paper is to be regarded as Part I: *J.*, 1950, 1252.

(VI) and (VII); the latter compound was also obtained by cyclization of (VI) in glacial acetic acid containing a trace of hydrochloric acid (see Nowlan, Slavin, and Wheeler, *J.*, 1950, 340).



Synthesis of Flavonol 3-Methyl Ethers.—In the earlier work (Part I) it was found that ω-methoxyresacetophenone dibenzoate yielded 7-hydroxy-3-methoxyflavone on cyclization in glycerol, the method thus providing a new synthesis of a flavonol through its 3-methyl ether. Methoxyflavones, as is well known, are readily demethylated by hydriodic acid. Application of the Baker–Venkataraman reaction to the dibenzoate gave the same product as the cyclization reaction. These results have now been extended, and 5 : 7-dihydroxy-3-methoxyflavone (galangin 3-methyl ether) (X; R = Ph), 5 : 7-dihydroxy-3 : 4′-dimethoxyflavone (kaempferol 3 : 4′-dimethyl ether) (X; R = *p*-C_6H_4·OMe) and 5 : 7-dihydroxy-3 : 3′ : 4′-trimethoxyflavone (quercetin 3 : 3′ : 4-trimethyl ether) (X; R = 3 : 4-dimethoxyphenyl) have been prepared both by cyclization in glycerol and by the Baker–Venkataraman method from ω-methoxyphloroacetophenone tribenzoate (VIII; R = Ph), tri-*p*-anisoate (VIII; R = *p*-C_6H_4·OMe), and triveratroate (VIII; R = 3 : 4-dimethoxyphenyl) respectively. These flavonol ethers had previously been synthesized by Allan–



Robinson aroylation of ω-methoxyphloroacetophenone, and demethylated by hydriodic acid to the corresponding naturally occurring flavonols (Kalff and Robinson, *J.*, 1925, **127**, 182; Robinson and Shinoda, *J.*, 1925, **127**, 1980; Allan and Robinson, *J.*, 1926, 2336). An attempt to cyclize in glycerol ω : 2 : 4 : 6-tetrabenzoyloxyacetophenone (Chavan and Robinson, *J.*, 1933, 368) with a view to the production of the flavonol rather than its 3-methyl ether gave no useful result.

Contrary to the experience of Dunne *et al.* (Part I) with the tribenzoate of phloroacetophenone and the monobenzoate of its 4 : 6-dimethyl ether, cyclization in glycerol of the esters of ω-methoxyphloroacetophenone proceeded smoothly. This result is in accordance with the suggestion made in Part I that the reaction involves a thermally produced Baker–Venkataraman transformation, and so requires the removal of a proton from $C_{(\beta)}$ of (VIII; =III in *J.*, 1950, 1253). The separation of the proton is facilitated by the inductive (−*I*) effect of the methoxyl group.

Yields of flavonol ethers (X; R = Ph, *p*-C_6H_4·OMe, or 3 : 4-dimethoxyphenyl) of the same order were obtained by the glycerol cyclization, Allan–Robinson, and Baker–Venkataraman methods, but the products of the last reaction were easiest to purify. As with ω-methoxyresacetophenone dibenzoate (Part I), the intermediate diketone (IX) formed in the base-catalysed Baker–Venkataraman transformation cyclized on formation. This cyclization of a diketone to a flavone is, as indicated in (IX) (see Nowlan *et al.*, *loc. cit.*), probably equivalent to the esterification of an acid by a phenol and is therefore facilitated by the increase in the cationoid activity of $C_{(\alpha)}$ effected by the methoxyl group attached to $C_{(\beta)}$ of (IX).

The reaction mechanism for glycerol cyclization suggested in Part I (*loc. cit.*) also receives support from an observation by Mahal and Venkataraman (Venkataraman, personal communication; Mahal, Thesis, Punjab Univ., 1936; Venkataraman, *Proc. Nat. Inst. Sci. India*, 1939, **5**, 255) that the dibenzoate of ω-methoxyresacetophenone when distilled under reduced pressure gave a crude product, probably the corresponding dibenzoylmethoxymethane, which on treatment with concentrated sulphuric acid (cf. Baker, *J.*, 1933, 1382) yielded 7-hydroxy-3-methoxyflavone. It has now been found that ω-methoxyphloroacetophenone dibenzoate (VIII; R = Ph) gives, when similarly treated, 5 : 7-dihydroxy-3-methoxyflavone (X; R = Ph).*

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

Preparation of 6-Acetyl-7-hydroxyflavone (II; R = Ph) *and Diflavone* [*6′ : 6″-Diphenyldipyrono*(*2′ : 3′-1 : 2*)(*3″ : 2″-4 : 5*)*benzene*] (IV; R = Ph).—A solution of 4 : 6-diacetylresorcinol dibenzoate (I; R = Ph) (Baker, *J.*, 1934, 72) (1 g.) in glycerol (10 ml.; twice distilled at 1 mm.) was heated in an atmosphere of dry nitrogen for 3 hours at 230°, and while still warm was poured into water (30 ml.). The mixture was extracted with chloroform, and the aqueous layer discarded. The chloroform solution was extracted four times with aqueous sodium hydroxide (2%), and the combined alkaline extracts were acidified with dilute hydrochloric acid. *6-Acetyl-7-hydroxyflavone* which separated had m. p. 204—207° on crystallisation from ethanol (0·15 g.) (Found: C, 72·4; H, 4·4. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%).

The chloroform solution which had been extracted with aqueous alkali was washed with dilute acid and with water and dried (Na_2SO_4). The residue obtained on removal of the solvent separated from toluene in pale-yellow crystals, m. p. 278° (0·05 g.). This m. p. was not depressed by mixture with an authentic sample of diflavone kindly supplied by Professor Algar (see Algar, McCarthy, and Dick, *Proc. Roy. Irish Acad.*, 1933, **41**, *B*, 155) (Found: C, 78·2; H, 4·0. Calc. for $C_{24}H_{14}O_4$: C, 78·7; H, 3·8%). The product showed in sulphuric acid solution the characteristic bright blue fluorescence first described for diflavone by Ryan and O'Neill (*Proc. Roy. Irish Acad.*, 1915, **32**, *B*, 55).

Cyclization of 6-Acetyl-7-benzoyloxyflavone (III) *to Diflavone.*—6-Acetyl-7-hydroxyflavone was converted by the pyridine–acid chloride method (Doyle *et al.*, *Sci. Proc. Roy. Dublin Soc.*, 1948, **24**, 299) into *6-acetyl-7-benzoyloxyflavone* (Found: C, 74·8; H. 4·5. $C_{24}H_{16}O_5$ requires C, 75·0; H, 4·2%), which separated from ethanol in crystals, m. p. 177—178°. A solution of the ester (0·2 g.) in distilled glycerol (4 ml.) was heated in a current of nitrogen for 3 hours at 230° and poured into water. The mixture was kept at 0° for 2 hours and extracted with chloroform. The extract was dried (Na_2SO_4) and the solvent evaporated. The trace of residue had m. p. 278°, not depressed by admixture with an authentic sample of diflavone.

Preparation of 6-Acetyl-7-hydroxy-4′-methoxyflavone (II; R = *p*-C_6H_4·OMe).—4 : 6-*Diacetylresorcinol di*-p-*anisoate* (I; R = *p*-C_6H_4·OMe), prepared by the pyridine–acid chloride method, had m. p. 138—140° when crystallized from ethanol (Found: C, 67·4; H, 4·8. $C_{26}H_{22}O_8$ requires C, 67·5; H, 4·8%). It was heated in distilled glycerol (10 parts) for 1 hour in a nitrogen atmosphere at 250°, and the solution poured into water (30 parts). The material soluble in chloroform was divided into alkali-soluble and alkali-insoluble fractions as described above for 6-acetyl-7-hydroxyflavone and diflavone. *6-Acetyl-7-hydroxy-4′-methoxyflavone*, which was soluble in alkali, separated from ethanol in crystals, m. p. 238—241° (0·1 g.

* The authors are indebted to Dr. K. Venkataraman, who kindly informed them on publication of Part I of the distillation experiment which was made in 1934 in his laboratory in Lahore. His review paper in *Proc. Nat. Inst. Sci. India*, cited above, which mentioned this result was not abstracted in detail in *Chem. Abs.* (see 1940, **34**, 764).

from 1 g. of ester) (Found : C, 68·2; H, 4·5. $C_{18}H_{14}O_5,\frac{1}{2}H_2O$ requires C, 67·7; H, 4·7%). Flavones frequently retain water of crystallization (see Bernfeld and Wheeler, *J.*, 1949, 1918).

A trace of material was not extracted by alkali from solution in chloroform. It separated from aqueous acetic acid in pale-yellow crystals, m. p. 318—320° (0·007 g. from 1 g. of ester), and exhibited a yellow-green fluorescence in sulphuric acid solution. 6′ : 6″-Di-*p*-methoxyphenyldipyrono-(2′ : 3′-1 : 2)(3″ : 2″-4 : 5)benzene (4′ : 4″-dimethoxydiflavone) (IV; R = *p*-C_6H_4·OMe) forms colourless crystals, m. p. 321—322°, and gives a green fluorescence in sulphuric acid solution (cf. Algar, McCarthy, and Dick, *loc. cit.*).

Preparation of 6-*Acetyl*-5-*hydroxyflavone* (VII).—A solution of 2 : 4-diacetylresorcinol dibenzoate (V) (Baker, *J.*, 1934, 1954) (1 g.) in glycerol (5 ml.) was heated at 200° for 5 hours and poured into water (15 ml.). The product was collected and recrystallized from aqueous dioxan. It separated in pale-yellow crystals, m. p. 201° (0·5 g.), not depressed by mixture with an authentic specimen of 6-acetyl-5-hydroxyflavone prepared by the action of ethanolic potassium acetate on 2 : 4-diacetylresorcinol dibenzoate (Baker, *loc. cit.*). This reaction involves, probably, a Baker–Venkataraman transformation.

Baker–Venkataraman Transformation of 2 : 4-*Diacetylresorcinol Dibenzoate.*—A solution of the ester (4 g.) in pyridine (15 ml.) was heated with ethyl sodioacetoacetate (4 g.) on the steam-bath for 2 hours and the product when cold was treated with aqueous sodium hydroxide (100 ml.; 5%). The resulting precipitate was collected and washed with water, the washings being added to the alkaline filtrate. The washed solid on crystallization (0·3 g.) from aqueous dioxan did not depress the m. p. of an authentic sample of 6-acetyl-5-hydroxyflavone (Found : C, 72·4; H, 4·2. Calc. for $C_{17}H_{12}O_4$: C, 72·9; H, 4·3%). 6-Acetyl-5-hydroxyflavone is insoluble in dilute aqueous sodium hydroxide (Baker, *loc. cit.*).

The alkaline filtrate from the transformation reaction mixture was acidified with concentrated hydrochloric acid. 3-*Acetyl*-2 : 6-*dihydroxydibenzoylmethane* (VI), which separated, formed yellow crystals (0·3 g.), m. p. 135—137°, on crystallization from ethanol (Found : C, 68·5; H, 4·6. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). A solution of the diketone (0·6 g.) in boiling glacial acetic acid was treated with a few drops of concentrated hydrochloric acid (see Nowlan *et al.*, *loc. cit.*). The yellow colour of the solution faded and, on dilution with water, 6-acetyl-5-hydroxyflavone (mixed m. p. on crystallisation from aqueous dioxan; 0·4 g.) separated.

Synthesis of Flavonol 3-*Methyl Ethers.*

5 : 7-*Dihydroxy*-3-*methoxyflavone* (*Galangin* 3-*Methyl Ether*) (X; R = Ph). *Preparation of* ω-*Methoxyphloroacetophenone Tribenzoate* (VIII; R = Ph).—A solution of ω-methoxyphloroacetophenone (10 g.) in pyridine (50 ml.) was treated (ice-water cooling) with benzoyl chloride (25 ml.), and the resulting mixture left overnight at room temperature. The mixture was acidified with hydrochloric acid (10%), and the precipitated oil extracted with ether. The ethereal solution was washed with aqueous sodium hydroxide (5%) and with water, and dried (Na_2SO_4). The oil remaining on evaporation of the solvent was distilled at 10^{-1} mm. The solid distillate, ω-*methoxyphloroacetophenone tribenzoate*, separated from methanol in crystals (10 g.), m. p. 116—118° (Found : C, 71·1; H, 4·3. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·3%).

A solution of this tribenzoate (1 g.) in distilled glycerol (10 ml.) was heated for 30 minutes in an atmosphere of nitrogen at 250°. The mixture was cooled and poured into water (100 ml.). The solid which separated was dissolved in ether, and the ethereal solution extracted with aqueous sodium hydroxide (5%). The alkaline solution was saturated with carbon dioxide, and the precipitate collected, washed with water, and dried (yield, 0·5 g.). The sublimate obtained at 1 mm. separated from ethanol in yellow plates, m. p. 298°, which did not depress the m. p. (298°) of an authentic sample of 5 : 7-dihydroxy-3-methoxyflavone, prepared by Allan–Robinson benzoylation of ω-methoxyphloroacetophenone (Kalff and Robinson, *J.*, 1925, **127**, 182) (Found : C, 67·0; H, 4·2. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%). The identity of the diacetates prepared from the two samples of the flavonol as described by Kalff and Robinson (*loc. cit.*) was also confirmed (m. p. and mixed m. p. 175—176°).

Baker–Venkataraman Transformation of ω-*Methoxyphloroacetophenone Tribenzoate.*—A solution of the ester (1 g.) in pyridine (10 ml.) was heated with anhydrous potassium carbonate (1·2 g.) under reflux for 1 hour, and the mixture poured into excess of hydrochloric acid (10%). The precipitate formed (0·35 g.) separated from ethanol in yellow crystals which did not depress the m. p. of the authentic (Allan–Robinson) sample of 5 : 7-dihydroxy-3-methoxyflavone. The Baker–Venkataraman product was the most readily purified; intermediate preparation of the diacetyl derivative was necessary with the Allan–Robinson product, while the glycerol dehydration product required vacuum-sublimation.

Action of Heat on ω-Methoxyphloroacetophenone Tribenzoate.—The ester (1 g.) was heated for 30 minutes in a distillation apparatus at 3 mm. and 280°. No distillate was obtained. The solid which remained on evaporation of the solvent from an ethereal extract of the oily residue melted at 130° on crystallization (0·23 g.) from methanol, and gave a reddish-brown colour in ethanolic solution with ferric chloride. A solution of this substance in concentrated sulphuric acid was poured, after 15 minutes, on crushed ice. The precipitate so obtained separated from ethanol in crystals (0·08 g.), m. p. 297°, which did not depress the m. p. of galangin 3-methyl ether.

5 : 7-*Dihydroxy*-3 : 4′-*dimethoxyflavone* (*Kaempferol* 3 : 4′-*Dimethyl Ether*) (X; R = *p*-C_6H_4·OMe). *Preparation of ω-Methoxyphloroacetophenone Tri*-p-*anisoate* (VIII; R = *p*-C_6H_4·OMe).—A solution of ω-methoxyphloroacetophenone (2 g.) in pyridine (10 ml.) was treated in the cold with *p*-anisoyl chloride (5 g.). The mixture was left overnight and then acidified with hydrochloric acid (10%). ω-*Methoxyphloroacetophenone tri*-p-*anisoate*, which was precipitated, separated from glacial acetic acid in crystals, m. p. 169—171° (3·5 g.) (Found : C, 65·7; H, 4·6. $C_{33}H_{28}O_{11}$ requires C, 66·0; H, 4·7%).

The tri-*p*-anisoate (1 g.) was cyclized by heating it in glycerol as described above for the tribenzoate. The precipitate obtained by the action of carbon dioxide on the solution of the product in alkali separated from aqueous acetic acid in yellow crystals (0·21 g.), m. p. 233—234°, which did not depress the m. p. (234°) of an authentic (Allan–Robinson) specimen of 5 : 7-dihydroxy-3 : 4′-dimethoxyflavone (Robinson and Shinoda, *J.*, 1925, 1980) (Found : C, 64·8; H, 4·6. Calc. for $C_{17}H_{14}O_6$: C, 65·0; H, 4·5%).

Baker–Venkataraman Transformation of ω-Phloroacetophenone Tri-p-*anisoate.*—The reaction was carried out as described for the tribenzoate. The product separated from aqueous acetic acid in pale-yellow crystals (0·26 g.), m. p. 232—233°, not depressed by admixture with the authentic (Allan–Robinson) sample of 5 : 7-dihydroxy-3 : 4′-dimethoxyflavone. The yields of pure material obtained by the three methods were : glycerol dehydration, 40%; Baker–Venkataraman, 50%; Allan–Robinson, 60%.

5 : 7-*Dihydroxy*-3 : 3′ : 4′-*trimethoxyflavone* (*Quercetin* 3 : 3′ : 4′-*Trimethyl Ether*) (X; R = 3 : 4-*Dimethoxyphenyl*). *Preparation of ω-Methoxyphloroacetophenone Triveratroate* (VIII; R = 3 : 4-*Dimethoxyphenyl*).—ω-*Methoxyphloroacetophenone triveratroate* was prepared by the pyridine–acid chloride method as described above for the tri-*p*-anisoate. It separated from aqueous methanol in crystals, m. p. *ca.* 78°; the m. p. remained ill-defined even after several crystallizations (Found : C, 63·1; H, 5·1. $C_{36}H_{34}O_{14}$ requires C, 62·6; H, 4·9%).

Cyclization in glycerol of the triveratroate (1 g.) was carried out as described above for the tri-*p*-anisoate. The crude product (0·35 g.) when crystallised from ethanol and ethyl acetate formed a yellow powder, m. p. 238—242°, which did not depress the m. p. (240—245°) of an authentic (Allan–Robinson) specimen of 5 : 7-dihydroxy-3 : 3′ : 4′-trimethoxyflavone (Allan and Robinson, *J.*, 1926, 2336) (Found : C, 62·4; H, 4·6. Calc. for $C_{18}H_{16}O_7$: C, 62·8; H, 4·7%). The quercetin triether (mixed m. p.) was also obtained by application of the Baker–Venkataraman reaction to the triveratroate as described for the tribenzoate. The yield of crude product was 0·3 g. from 1 g. of ester.

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