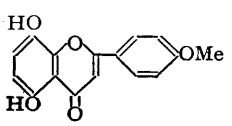
431. *The Structure of Ginkgetin. Part I. Synthesis of 5 : 8-Dihydroxy-4′-methoxyflavone.*

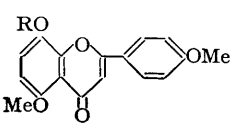
By Wilson Baker and G. F. Flemons.

5 : 8-Dihydroxy-4′-methoxyflavone (I) has been synthesised, and is not identical with ginkgetin, thus confirming the earlier suggestion that the latter is a flavone of more complex nature. The synthesis was achieved *via* 2 : 3-dihydroxy-6-methoxyacetophenone (III), new methods for the preparation of which have been developed.

The yellow phenolic colouring matter of the autumnal leaves of the maidenhair tree (*Ginkgo biloba*, L.), since termed ginkgetin, was first investigated by Furukawa (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1932, **19**, 27; 1933, **21**, 278) who suggested on somewhat inconclusive evidence that it was probably 5 : 8-dihydroxy-4′-methoxyflavone (I). The synthesis of a number of derivatives of 5 : 8 : 4′-trihydroxyflavone and comparison with the corresponding derivatives of the natural pigment showed, however, that it was most unlikely that ginkgetin could be the simple flavone (I), but was almost certainly a more complex, closely related compound of higher molecular weight (Baker and Simmonds, *J.*, 1940, 1370).

This conclusion has now been confirmed by the synthesis of 5 : 8-*dihydroxy-4′-methoxyflavone* (I) (m. p. 215°, decomp.), which is clearly not identical with ginkgetin (m. p. 238—240°, Furukawa), but nevertheless bears a very close resemblance to it. Both substances give stable, green colorations with alcoholic ferric chloride, and (I) therefore affords an example of a quinol derivative exhibiting a reaction usually regarded as characteristic of a 1 : 2-dihydroxybenzene (other cases are 3 : 6-dihydroxy-2-methoxyacetophenone and primetin, 5 : 8-dihydroxyflavone; see Baker, *J.*, 1939, 956). The investigation of ginkgetin itself is in progress.

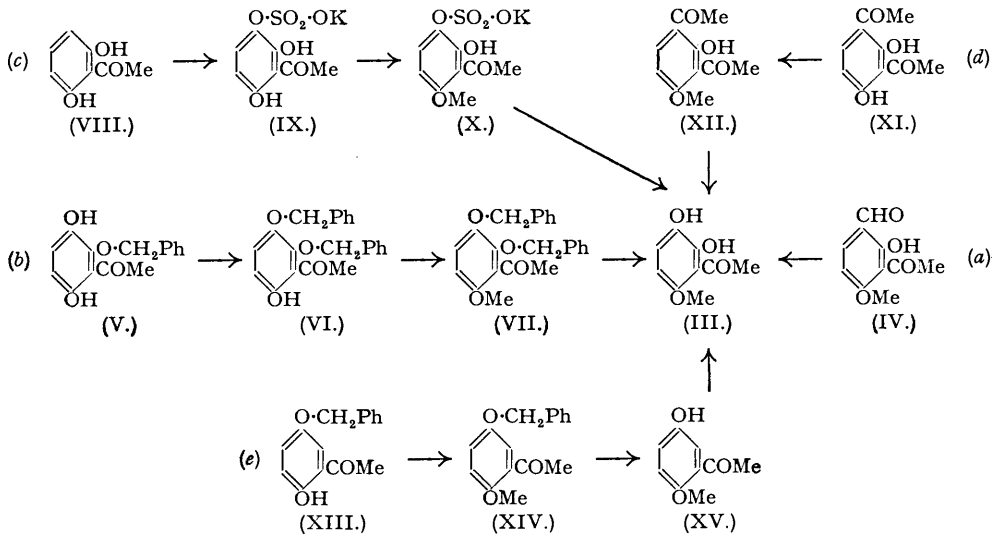
(I.) 



(II.)

The intermediate required for the synthesis of 5 : 8-dihydroxy-4′-methoxyflavone (I) is 2 : 3-dihydroxy-6-methoxyacetophenone (III) which has been prepared by Nakazawa (*J. Pharm. Soc. Japan*, 1939, **59**, 199; see *Chem. Abs.*, 1940, **34**, 1017) by formylation of 2-hydroxy-6-

methoxyacetophenone under the conditions of the Gattermann reaction to give 2-hydroxy-6-methoxy-3-formylacetophenone (IV), and oxidising this with hydrogen peroxide in presence of one equivalent of alkali (process *a*). A considerably improved formylation process is now described, but we find that the aldehyde (IV), whether prepared by Nakazawa's method (zinc cyanide) or by the improved process (hydrogen cyanide), is bright yellow, whereas Nakazawa describes it as colourless, though we agree as to its melting point. In view, however, of the fact that the aldehyde (IV) possesses a nuclear acetyl group, it was thought possible that it might have undergone intermolecular condensation to a chalkone which would undoubtedly be yellow, but this was excluded by the analysis and molecular weight, and by the ready oxidation in good yield to 2 : 3-dihydroxy-6-methoxyacetophenone (III), the structure of which has been established by four further independent synthetical methods (see below). An attempt was made to prepare the chalkone from the aldehydic acetophenone (IV), but the compound was, rather remarkably, recovered unchanged after treatment with alcoholic potassium hydroxide. It was noted, however, that the aldehyde undergoes change on keeping or prolonged drying, the carbon content slowly increases by several units %, the colour tends to deepen, the melting point falls slightly, and the material then shows signs of non-homogeneity and gives a yellow colour with boric and citric acids in acetone, a test which is supposed to be diagnostic for the grouping $-\overset{|}{C}(OH)-\overset{|}{C}-CO-C=\overset{|}{C}-$ (Wilson, *J. Amer. Chem. Soc.*, **1939**, **61**, 2303; Wolfram, Mayhan, Morgan, and Johnson, *ibid.*, **1941**, **63**, 1248). It may be noted that the position of the formyl group in (IV) is established by the facts that (1) the related dihydroxy-compound (III) prepared from it by the Dakin reaction shows the colour and expected properties of a 2 : 3-dihydroxy-carbonyl compound (see Baker, *J.*, 1934, 1688; Baker and Smith, *J.*, 1936, 346), and (2) the flavone ultimately synthesised is methylated to 5 : 8 : 4′-trimethoxyflavone (II; R = Me) and not the isomeric 5 : 6 : 4′-trimethoxyflavone. An attempt to prepare 2 : 6-dihydroxy-3-formylacetophenone by treating β-resorcylaldehyde with acetonitrile under the conditions of the Hoesch reaction led to the production of dark, intractable material



The alternative syntheses of 2 : 3-dihydroxy-6-methoxyacetophenone (III) are the following (*b*) *From* 3 : 6-*dihydroxy*-2-*benzyloxyacetophenone* (V). The ketone (V) (Baker, Brown, and Scott, *J.*, 1939, 1924) was benzylated to 6-*hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI), the free hydroxyl group in (VI) methylated with production of 2 : 3-*dibenzyloxy*-6-*methoxyacetophenone* (VII), and the benzyl groups removed by hydrolysis with hydrochloric acid giving (III). (*c*) *From* 2 : 6-*dihydroxyacetophenone* (VIII). Baker, Brown, and Scott (*loc. cit.*) oxidised the acetophenone (VIII) with alkaline potassium persulphate, and hydrolysed the resulting solution of the potassium phenyl sulphate derivative (IX) to 2 : 3 : 6-trihydroxyacetophenone. The intermediate (IX) has now been monomethylated in alkaline solution to (X), and removal of the sulphato-group by acid hydrolysis gave 2 : 3-dihydroxy-6-methoxyacetophenone (III). This method is a general one for the preparation of quinol monoalkyl ethers of known orient

ation, and is described by Baker and Brown elsewhere (*J.*, in the press). (*d*) *From* 2 : 4-*diacetylresorcinol* (XI). 2 : 4-Diacetylresorcinol (XI) was monomethylated to 2-*hydroxy*-4-*methoxy*-3-*acetylacetophenone* (XII), and (XII) was then oxidised by hydrogen peroxide under the conditions of the Dakin reaction, giving (III). (*e*) *From* 2 : 5-*dihydroxyacetophenone*. Monobenzylation of 2 : 5-dihydroxyacetophenone gave 2-*hydroxy*-5-*benzyloxyacetophenone* (XIII), methylation then yielded 5-*benzyloxy*-2-*methoxyacetophenone* (XIV), and debenzylation then gave 5-*hydroxy*-2-*methoxyacetophenone* (XV). Reactivity in (XV) was expected to be exhibited in position 6 by analogy with the behaviour of its *O*-allyl ether (Baker and Lothian, *J.*, 1936, 276), and oxidation of (XV) by alkaline potassium persulphate gave directly 2 : 3-dihydroxy-6-methoxyacetophenone (III) as the sole isolable product. As with other such persulphate oxidations involving the introduction of a new hydroxyl group into the ortho-position of a phenol, the yield was very poor (see Baker and Brown, *loc. cit.*). Of the five separate methods used for the preparation of (III), probably the most convenient is route (*a*), which has been studied in some detail and involves seven steps from resorcinol, some of which are tedious; route (*d*), requiring five steps from resorcinol, is potentially much simpler but involves the separation of pure 2 : 4-diacetylresorcinol from 4 : 6-diacetylresorcinol, which has not yet been satisfactorily achieved in a simple manner.

Fusion of (III) with anisic anhydride and sodium anisate, and alkaline hydrolysis of the product gave 8-hydroxy-5 : 4′-dimethoxyflavone (II; R = H) in poor yield; most of the material used in this investigation was prepared in this manner. A somewhat improved yield of (II; R = H) may be obtained by isolation of the intermediate 8-*anisoyloxy*-5 : 4′-*dimethoxyflavone* (II; R = anisoyl), and removal of the anisoyl group with aqueous-alcoholic hydrochloric acid. No improvement was effected in the fusion process by substituting 2 : 3-*dianisoyloxy*-6-*methoxyacetophenone* for (III), and only a minute yield of (II; R = H) was obtained by treatment of the same compound with sodamide in benzene to cause molecular rearrangement to the corresponding 1 : 3-diketone, followed by ring closure and hydrolysis (Baker, *J.*, 1933, 1381). Methylation of 8-hydroxy-5 : 4′-dimethoxyflavone (II; R = H) gave 5 : 8 : 4′-trimethoxyflavone (II; R = Me) identical with that previously prepared in another manner by Baker and Simmonds (*J.*, 1940, 1373). Partial demethylation of (II; R = H) with anhydrous aluminium chloride in nitrobenzene gave the desired 5 : 8-dihydroxy-4′-methoxyflavone (I), characterised as its *diacetyl* derivative. The preparation of the flavone (II; R = H) from (III) is unexpectedly difficult; the yields are very small, and the products difficult to obtain pure.

An attempt was made to prepare 6-hydroxy-2-anisoyloxyacetophenone, a possible intermediate in a synthesis of (I). Molecular quantities of 2 : 6-dihydroxyacetophenone and anisoyl chloride in pyridine gave a mixture of 2 : 6-*dianisoyloxyacetophenone* and the monoanisoyl derivative which could not be effectively separated; the latter compound is rapidly hydrolysed by cold N/1-sodium hydroxide solution, and could not be prepared by the Baumann–Schotten technique.

Experimental.

2-*Hydroxy*-6-*methoxy*-3-*formylacetophenone* (2-*Hydroxy*-4-*methoxy*-3-*acetylbenzaldehyde*) (IV).—The formylation in 36% yield of 2-hydroxy-6-methoxyacetophenone by the Gattermann reaction using zinc cyanide has been described by Nakazawa (*loc. cit.*), but we find that the reaction proceeds much more cleanly in 68% yield by the use of anhydrous hydrogen cyanide in presence of aluminium chloride.

To a solution of anhydrous aluminium chloride (3·5 g.) in dry ether (25 c.c.), cooled in an ice–salt bath, was added 2-hydroxy-6-methoxyacetophenone (4·15 g.; Baker, *J.*, 1939, 959), and anhydrous hydrogen cyanide (3·5 c.c.), and hydrogen chloride was passed in for 1¾ hours at 0°. After 18 hours at room temperature dry ether was added till no further precipitation occurred, the ether decanted, the residue washed twice with ether, cooled to 0°, and treated with water (25 c.c.). Hydrolysis of the aldimine was effected by heating on the water-bath for 15 minutes, the crude aldehyde extracted with chloroform, and after removal of the solvent the product was ground with silver sand and extracted continuously with light petroleum (b. p. 60—80°) at the b. p. of the solvent for many hours until the extract became colourless. The extracted material was recrystallised from ethyl alcohol, giving pure 2-hydroxy-6-methoxy-3-formylacetophenone as bright yellow needles (3·3 g.), m. p. 89° (Found: C, 62·0; H, 5·3. Calc. for $C_{10}H_{10}O_4$: C, 61·9; H, 5·2%). Nakazawa (*loc. cit.*) describes the compound as colourless prisms, m. p. 89·5°, but we have been quite unable to bring about any loss of colour. It gives a brownish-red coloration with alcoholic ferric chloride.

2 : 3-*Dihydroxy*-6-*methoxyacetophenone* (III).—(a) *From* 2-*hydroxy*-6-*methoxy*-3-*formylacetophenone* (IV). The oxidation of (IV) by the Dakin reaction was effected in 65% yield in N/1-sodium hydroxide (1 mol.) with 3% hydrogen peroxide (1·1 mols.) after the manner described by Nakazawa (*loc. cit.*). The oxidation cannot be successfully carried out if, as is usual, more than 1 equiv. of alkali is used this modification of the Dakin reaction may find other applications where the normal procedure fails 2 : 3-Dihydroxy-6-methoxyacetophenone forms bright yellow needles from aqueous acetone, m. p. 147—148° (Found: C, 59·2; H, 5·5. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). It gives a very strong

green ferric chloride reaction in alcoholic solution, but unlike other 2 : 3-dihydroxyacetophenones it gives no precipitate in dilute alcoholic solution with neutral lead acetate.

(b) *From* 2 : 3-*dibenzyloxy*-6-*methoxyacetophenone* (VII) (see below). Debenzylation of (VII) (0·1 g.) was effected by heating in glacial acetic acid (2 c.c.) and concentrated hydrochloric acid (1 c.c.) for 1 hour at 60°. The product, isolated by dilution and extraction with ether, was crystallised from ethyl acetate at a low temperature, giving a yellow, microcrystalline product, m. p. 145—146°, showing no depression of m. p. when mixed with 2 : 3-dihydroxy-6-methoxyacetophenone, m. p. 146—147°, prepared by method (a).

(c) *From* 2 : 6-*dihydroxyacetophenone* (VIII) via (IX) *and* (X). 2 : 6-Dihydroxyacetophenone (9 g.; 1 mol.) in a solution of sodium hydroxide (12 g.; 5 mols.) in water (110 c.c.) was stirred at room temperature for 4 hours during the addition of a solution of potassium persulphate (17·5 g.; 1·1 mols.) in water (400 c.c.). The green solution, after standing overnight, was acidified to Congo-red, filtered from red, flocculent material (charcoal), extracted twice with ether, made alkaline to litmus, and evaporated to a small bulk (50 c.c.) at 50—60° under diminished pressure. After addition of acetone (10 c.c.) the intermediate sulphato-compound was methylated by vigorous shaking for 1½ hours with portionwise addition of potassium hydroxide (5 g.) in water (5 c.c.) and methyl sulphate (7·5 g.). After standing overnight and addition of water to dissolve the precipitated salts, the solution was acidified to Congo-red and extracted with ether, concentrated hydrochloric acid (50 c.c.) was added, and the mixture was heated on the steam-bath for ½ hour under a layer of light petroleum (b. p. 60—80°; 250 c.c.). The hydrolysis and extraction were repeated, and the extracts united and distilled, leaving a yellow solid (0·4 g.) which was crystallised from dilute methyl alcohol (charcoal), and then from a small volume of benzene, being obtained in brownish-yellow prisms, m. p. and mixed m. p. 148—149°.

(d) *From* 2-*hydroxy*-6-*methoxy*-3-*acetylacetophenone* (XII) (see below). To (XII) (0·52 g.; 1 mol.) dissolved in N/1-sodium hydroxide (5 c.c.; 2 mols.) was added 3% hydrogen peroxide (6·6 c.c.; 1·15 mols.). The temperature rapidly rose from 22° to 47° and the solution darkened. After 2 hours standing, addition of acid precipitated 2 : 3-dihydroxy-6-methoxyacetophenone (III) (0·15 g.; 33% yield), m. p. 145—146·5°. One recrystallisation from 50% aqueous acetone gave bright yellow needles, m. p. and mixed m. p. 147—148°.

(e) *From* 5-*hydroxy*-2-*methoxyacetophenone* (XV) (see below). (With Mr. F. Glockling.) A solution of 5-hydroxy-2-methoxyacetophenone (3 g.; 1 mol.) in water (60 c.c.) containing sodium hydroxide (5 g.) was stirred for 5 hours during the addition of a solution of potassium persulphate (4·6 g.; 0·95 mol.) in water (150 c.c.). After 48 hours the mixture was made just acid to Congo-red, extracted with ether, rendered more strongly acid, and refluxed for 1 hour under a layer of ether (100 c.c.) The ether layer was separated, and the process repeated. The united extracts left a brown oil which yielded to hot benzene well-crystalline 2 : 3-dihydroxy-6-methoxyacetophenone (III) (40 mg.). From dilute acetone it formed yellow needles, m. p. and mixed m. p. 146—148°.

6-*Hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI) *and* 2 : 3 : 6-*Tribenzyloxyacetophenone*.—3 : 6-Dihydroxy-2-benzyloxyacetophenone (V) (12·9 g.; 1 mol.; Baker, Brown, and Scott, *loc. cit.*), anhydrous acetone (40 c.c.), anhydrous potassium carbonate (15 g.), and benzyl chloride (7 g.; 1·1 mols.) were stirred and refluxed for 10 hours, with the addition of more potassium carbonate (10 g.) after 3 hours. The dark product was treated with water (750 c.c.) and 5% sodium hydroxide (100 c.c.), extracted 4 times with ether, leaving some undissolved tarry material, and the ethereal extracts yielded a deep brown syrup which partially crystallised and was pressed on a porous tile. The resulting solid 2 : 3 : 6-*tribenzyloxyacetophenone*, after several crystallisations from alcohol (charcoal), formed almost colourless prisms (0·7 g.), m. p. 110° (Found : C, 79·4; H, 6·1. $C_{29}H_{26}O_4$ requires C, 79·4; H, 5·9%).

The yellow alcoholic mother-liquors from the crystallisation of the 2 : 3 : 6-tribenzyloxyacetophenone after some concentration and cooling in ice deposited crystals which, after recrystallisation from alcohol, formed short, canary-yellow prisms (1·65 g.), m. p. 57·5° (Found : C, 75·8; H, 5·7. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·7%). This 6-*hydroxy*-2 : 3-*dibenzyloxyacetophenone* (VI) is quite insoluble in cold aqueous alkalis, but gives an intense green coloration with alcoholic ferric chloride.

2 : 3-*Dibenzyloxy*-6-*methoxyacetophenone* (VII).—The hydroxy-compound (VI) was treated under vigorous conditions in acetone with a large excess of 20% aqueous potassium hydroxide and methyl sulphate. After dilution with water the precipitated oil was extracted with ether and distilled, giving the *methoxy*-compound as a yellow, very viscous oil, b. p. *ca.* 220—224° (oil-bath temp.)/0·1 mm. (Found : C, 76·2; H, 6·3. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%).

2 : 4-*Diacetylresorcinol* (XI).—Resacetophenone (Robinson and Shah, *J.*, 1934, 1494) is most conveniently monoacetylated (95% yield) by an application of the technique due to Simokoriyama (*Bull. Chem. Soc. Japan*, 1941, **46**, 284). Resacetophenone (97 g.; 1 mol.) was stirred for ½ hour with acetic anhydride (330 g.; 5 mols.) and pyridine (3 c.c.), warmed to 45°, cooled, and poured into water (1 l.), yielding 4-*O*-acetylresacetophenone (118 g.), m. p. 75—76°. From this compound (100 g.), a mixture (90 g.; m. p. 77—148°) of 2 : 4-diacetylresorcinol (XI) and 4 : 6-diacetylresorcinol was prepared according to Baker (*J.*, 1934, 1690). The 2 : 4-diacetylresorcinol was finally obtained in a purer state than previously recorded by repeated crystallisation from methyl alcohol, and then formed fine, very pale yellow needles, m. p. 92° (lit. m. p. 89°) (Found : C, 61·8; H, 5·2. Calc. for $C_{10}H_{10}O_4$: C, 61·8; H, 5·2%).

2-*Hydroxy*-6-*methoxy*-3-*acetylacetophenone* (XII).—Pure 2 : 4-diacetylresorcinol (XI) (m. p. 92°; 1·21 g.; 1 mol.) was refluxed with dry acetone (15 c.c.), anhydrous potassium carbonate (2·2 g.; 2·5 mols.) and methyl sulphate (0·65 c.c.; 1·1 mols.) for 8 hours, then diluted, boiled, and acidified. The precipitated 2-*hydroxy*-6-*methoxy*-3-*acetylacetophenone* was crystallised twice from alcohol and obtained as stout, colourless prisms (0·65 g.), m. p. 104° (Found : C, 63·7; H, 5·7. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). The compound gives a brownish-red coloration with alcoholic ferric chloride.

2-*Hydroxy*-5-*benzyloxyacetophenone* (XIII). (With Mr. F. Glockling.)—2 : 5-Dihydroxyacetophenone (120 g.; m. p. 198—200°) was stirred and refluxed for 10 hours with acetone (600 c.c.), anhydrous potassium carbonate (250 g.), and benzyl chloride (110 g.). The filtered liquor was treated with charcoal, the acetone distilled off, the residue dissolved in ether, and the ethereal solution shaken

with aqueous sodium hydroxide, dried, and distilled finally under diminished pressure to remove unchanged benzyl chloride. The residual *2-hydroxy-5-benzyloxyacetophenone*, after crystallisation from methyl alcohol, formed yellow needles (60 g.), m. p. 69—70° (Found: C, 73·9; H, 5·5. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). It is insoluble in aqueous sodium hydroxide, but gives a dull slate-blue colour with alcoholic ferric chloride.

5-Benzyloxy-2-methoxyacetophenone (XIV). (With Mr. F. GLOCKLING.)—The preceding compound (XIII) (50 g.) was vigorously shaken in acetone (200 c.c.) with methyl sulphate (80 c.c.) and a solution of potassium hydroxide (150 g.) in water (500 c.c.) for 10 minutes, refluxed for ½ hour, and the acetone layer separated. The aqueous layer was extracted with ether, the extract added to the acetone layer, distilled, and the residual solid mass crystallised from methyl alcohol, giving colourless needles (54 g.). For analysis the *5-benzyloxy-2-methoxyacetophenone* was crystallised from ethyl alcohol and then from light petroleum (b. p. 40—60°); needles, m. p. 56° (Found: C, 74·8; H, 6·1. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

5-Hydroxy-2-methoxyacetophenone (XV). (With Mr. F. GLOCKLING.)—Compound (XIV) (52 g.) was treated for 1 hour at 65—70° with acetic acid (300 c.c.) and concentrated hydrochloric acid (120 c.c.), poured into water (1 l.), and extracted with ether. The ethereal solution was extracted into aqueous sodium hydroxide, and the alkaline layer separated, acidified, and extracted with ether. The extract yielded a dark oil which was crystallised first from chloroform (charcoal) and then from water, yielding finally *5-hydroxy-2-methoxyacetophenone* (10·3 g.) as faintly yellow needles, m. p. 83° after drying in a vacuum at 65° (Found: C, 65·3; H, 6·0. $C_9H_{10}O_3$ requires C, 65·0; H, 6·0%). It gives no characteristic coloration with alcoholic ferric chloride.

8-Hydroxy-5 : 4′-dimethoxyflavone (II; R = H).—2 : 3-Dihydroxy-6-methoxyacetophenone (4 g.), anisic anhydride (28 g.), and sodium anisate (4 g.) were stirred at 180—190° for 7 hours. The product was now dissolved in a mixture of alcohol (200 c.c.) and a little water, refluxed for ¼ hour with an excess of 30% aqueous potassium hydroxide, most of the alcohol removed by distillation, and the cold diluted solution saturated with carbon dioxide. The dark brown amorphous solid was crystallised first from alcohol (600 c.c.) (charcoal), and then twice from glacial acetic acid (40 c.c.), being obtained as thin, honey-yellow prisms (0·4 g.), m. p. 267° (Found, in material heated for several hours at 145° in a vacuum over potassium hydroxide: C, 67·9; H, 4·6; MeO, 19·3. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7; MeO, 20·8%). This *8-hydroxy-5 : 4′-dimethoxyflavone* tenaciously retains a trace of acetic acid, which can only be completely expelled by fusion.

Acetylation by means of acetic anhydride at the b. p. for 5 hours, concentration and addition of water, and crystallisation from alcohol gave a mixture of pale yellow prisms (A), and clusters of fine, colourless needles (B). Product (A) (m. p. 171°) is assumed to be *8-acetoxy-5 : 4′-dimethoxyflavone*; recrystallisation from alcohol gave colourless needles, m. p. 172° (Found: C, 66·8; H, 5·0. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%). Product (B), unlike recrystallised (A), becomes yellow on drying at room temperature, but it has not been further investigated.

8-Anisoyloxy-5 : 4′-dimethoxyflavone (II; R = anisoyl).—The fusion product obtained as described in the preceding section was treated with a hot mixture of ethyl acetate (200 c.c.) and water (50 c.c.), cooled, shaken for ¼ hour with 10% aqueous sodium carbonate (150 c.c.), and the whole filtered.* The residual solid was washed successively with aqueous sodium carbonate, water, and ethyl acetate, dried (2·3 g.), and crystallised from ethyl acetate (600 c.c.), giving light brown prisms, m. p. 225° (1·48 g.), and a further crop (0·46 g.) was obtained from the mother-liquor. Recrystallisation from alcohol gave *8-anisoyloxy-5 : 4′-dimethoxyflavone* as long, lustrous, cream-coloured needles, which, after drying at 145° in a vacuum over phosphoric anhydride, had m. p. 225·5° [Found: C, 69·2; H, 4·7; OMe, 18·4; *M* (Rast), 399. $C_{25}H_{20}O_7$ requires C, 69·4; H, 4·7; OMe, 21·5%; *M*, 432]. Hydrolysis to 8-hydroxy-5 : 4′-dimethoxyflavone (II; R = H) was brought about in 72% yield by refluxing for 12 hours with a large volume of alcohol containing one-third of its volume of concentrated hydrochloric acid, the mixture being finally distilled with the addition of water till no further separation of crystals occurred. The product, after crystallisation from a very large volume of alcohol, had m. p. 267°, undepressed on admixture with the specimen previously described.

From the ethyl acetate layer above * were obtained by repeated concentration and crystallisation (*a*) 0·36 g. of 8-anisoyloxy-5 : 4′-dimethoxyflavone, m. p. 224·5°, and (*b*) a more soluble compound (0·45 g.) separating from alcohol in fine, pale cream-coloured needles, m. p. 224·5—225°, and at 197—204° when mixed with 8-anisoyloxy-5 : 4′-dimethoxyflavone (Found: C, 70·0; H, 4·9; OMe, 22·0. $C_{33}H_{26}O_9$ requires C, 69·9; H, 4·6; OMe, 21·9%). There can be little doubt that this compound is *8-anisoyloxy-5 : 4′-dimethoxy-3-anisoylflavone*.

2 : 3-Dianisoyloxy-6-methoxyacetophenone.—To a solution of 2 : 3-dihydroxy-6-methoxyacetophenone (3·64 g.; 1 mol.) in anhydrous pyridine (25 c.c.) was added anisoyl chloride (8·6 g.; 2·5 mols.) with stirring, and the mixture heated on the water-bath for ½ hour. Cautious addition of dilute hydrochloric acid yielded *2 : 3-dianisoyloxy-6-methoxyacetophenone* as a solid which separated from alcohol (400 c.c.) in very pale cream-coloured prisms (7·75 g.; 86%); after a further recrystallisation it had m. p. 164·5° (Found: C, 66·6; H, 4·9. $C_{25}H_{22}O_8$ requires C, 66·7; H, 4·9%).

5 : 8 : 4′-Trimethoxyflavone.—8-Hydroxy-5 : 4′-dimethoxyflavone was readily methylated by treatment with methyl sulphate in aqueous potassium hydroxide. The alkali-insoluble product after crystallisation from benzene (charcoal) gave almost colourless prisms, m. p. 162·5° (Found, in material dried at 80° in a vacuum: C, 69·4; H, 5·5. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·2%). A specimen of 5 : 8 : 4′-trimethoxyflavone, m. p. 161°, prepared by the method of Baker and Simmonds (*loc. cit.*), after crystallisation from alcohol (charcoal) and then benzene had m. p. 162·5°, either alone or when mixed with the flavone prepared as above.

5 : 8-Dihydroxy-4′-methoxyflavone (I).—8-Hydroxy-5 : 4′-dimethoxyflavone (II; R = H) (0·32 g.), anhydrous aluminium chloride (0·2 g.), and freshly distilled nitrobenzene (6 c.c.) were heated at 100° for 1 hour. To the dark product was added dilute hydrochloric acid, the nitrobenzene removed in steam, and the yellow-brown solid collected, washed, and dried. It was crystallised from dilute acetic acid (300 c.c.), giving bright yellow prisms, m. p. 215° (decomp.). This flavone tenaciously retained a

trace of acetic acid from which it could not be entirely freed (Found, in material dried at 145° in a vacuum over potassium hydroxide for 2 hours: C, 64·3; H, 4·1; for 4 hours: C, 65·7; H, 4·3; for 36 hours: C, 66·1; H, 4·1; OMe, 10·4. $C_{15}H_9O_4$·OMe requires C, 67·6; H, 4·2; OMe, 10·9%). 5 : 8-*Dihydroxy-4′-methoxyflavone* gives a strong green coloration with alcoholic ferric chloride, and dissolves in aqueous sodium hydroxide with an orange colour. It does not give a red colour when reduced with magnesium and hydrochloric acid, as does ginkgetin.

The *diacetyl* derivative, prepared in the usual way, was twice crystallised from alcohol (charcoal) and then from benzene, forming aggregates of minute needles, m. p. 230° [Found: C, 64·8; H, 4·4; Ac, 28·2. $C_{16}H_{10}O_3(OAc)_2$ requires C, 65·2; H, 4·3; Ac, 23·3%]. The diacetyl derivative of ginkgetin has m. p. 226—228° (Furukawa).

2 : 6-*Dianisoyloxyacetophenone*.—2 : 6-Dihydroxyacetophenone (10 g.) in anhydrous pyridine (40 c.c.) was slowly treated, whilst being shaken and cooled, with anisoyl chloride (11·2 g.; 1 mol.), and finally heated on the water-bath for 20 minutes, cooled, and dilute hydrochloric acid added. The product (19 g.) which solidified was ground, washed with water, and crystallised several times from alcohol (100 c.c.), giving a powder, melting at 99—99·5° to a turbid liquid which cleared at 105°. No effective method was found of isolating both constituents of this mixture in the pure state, but the higher-melting product, 2 : 6-*dianisoyloxyacetophenone*, was obtained by crystallisation from benzene–light petroleum and then from alcohol, in fine, colourless prisms, m. p. 141° (Found: C, 68·6; H, 4·9. $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·8%).

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