396. *The Synthesis of 5-Hydroxy-8-methoxyflavone (Primetin Monomethyl Ether).*

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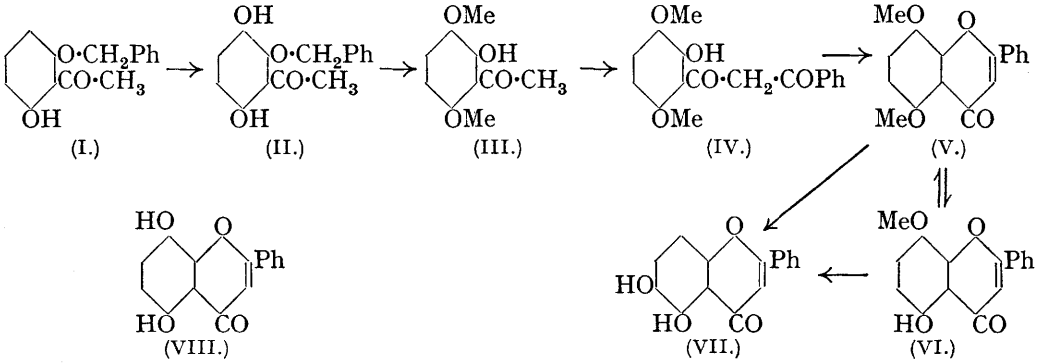
Evidence has recently been brought forward to show that primetin is 5 : 8-dihydroxyflavone (VIII), and not 5 : 6-dihydroxyflavone (VII) as previously believed. This view is now confirmed by the synthesis of 5-*hydroxy*-8-*methoxyflavone* (VI) *via* the stages (I) to (V), and this compound is identical with primetin monomethyl ether. The demethylation of (VI) to primetin has not been satisfactorily accomplished; the use of hydrobromic acid causes rearrangement to 5 : 6-dihydroxyflavone (VII). Experiments having as their object the synthesis of 6 : 8-dihydroxyflavone are described.

A RECENT paper (Baker, this vol., p. 956) described the synthesis of 5 : 6-dihydroxyflavone (VII), which was found to differ widely from primetin isolated from *Primula modesta* (Hattori and Nagai, *J. Chem. Soc. Japan*, 1930, **51**, 162; *Acta Phytochim.*, 1930, **5**, 1). A careful review of the available evidence led to the conclusion that primetin must be 5 : 8-dihydroxyflavone (VIII), and this is now confirmed by the synthesis of 5-*hydroxy*-8-*methoxyflavone* (VI), which proves to be identical with primetin monomethyl ether.

2 : 6-Dihydroxyacetophenone was converted into 2-*hydroxy*-6-*benzyloxyacetophenone* (I), and this was then oxidised in alkaline solution by potassium persulphate, giving 2 : 5-*dihydroxy*-6-*benzyloxyacetophenone* (II). The yield of (II) from (I) was 85%, which is considerably higher than any previously recorded in this reaction; the high yield appears to be largely due to the mild conditions which had to be employed in the hydrolysis of the intermediate phenyl hydrogen sulphate derivative in order to prevent hydrolysis of the benzyloxy-group. Compound (II) was now methylated, giving 2 : 5-*dimethoxy*-6-*benzyloxyacetophenone*, and removal of the benzyl group with hydrochloric in acetic acid at 60° gave 2-*hydroxy*-3 : 6-*dimethoxyacetophenone* (III). The *benzoyl* derivative of this ketone when treated with sodamide in toluene underwent a ready rearrangement to 2-*hydroxy*-3 : 6-*dimethoxydibenzoylmethane* (IV) and ring closure to 5 : 8-*dimethoxyflavone* (V) was brought about with sodium acetate in acetic acid.



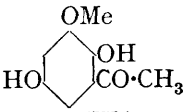
Demethylation of 5 : 8-dimethoxyflavone (V) to 5-*hydroxy*-8-*methoxyflavone* (VI), m. p. 209—210°, was readily effected by the action of aluminium chloride in ether, and that no alteration of orientation had occurred was proved by the facts that (VI) regenerated

5 : 8-dimethoxyflavone (V) on vigorous methylation, and was not identical with 5-hydroxy-6-methoxyflavone (Baker, *loc. cit.*). The properties of 5-hydroxy-8-methoxyflavone (VI) agree with those of primetin monomethyl ether, m. p. 210—211°, and complete identity was confirmed by a mixed melting-point determination. The *acetyl* derivative of (VI) was, moreover, found to have the same melting point, 175—176°, as the acetyl derivative of primetin monomethyl ether. Hattori and Nagai (*loc. cit.*) state that primetin monomethyl ether gives a violet-brown ferric chloride reaction, but we have found that both the synthetical and the natural material give a bluish-green reaction.

Attempts to bring about the further demethylation of (VI) to primetin have not been completely successful. The compound was unchanged when (1) refluxed with aluminium chloride or bromide in dry ethereal or dioxan solution for periods up to 5 days, (2) refluxed with a 50% mixture of acetyl bromide and acetic anhydride, (3) treated for 2 days at 0° with acetic anhydride saturated with hydrogen bromide (see Hess and Neumann, *Ber.*, 1935, **68**, 1371), (4) heated for varying times and at various temperatures with aluminium chloride in nitrobenzene or a mixture of nitrobenzene and ether. In some of the last experiments, however, further but incomplete demethylation occurred; a yellow product was isolated which dissolved in alkali with a reddish colour, gave an intense olive-green colour with alcoholic ferric chloride, and melted above 220° and was undoubtedly crude primetin, but the amount was too small for proper identification or analysis. The employment of more vigorous conditions led to decomposition. The resistance to demethylation with aluminium halides appears to be due to the formation of a stable aluminium complex of (VI) (see experimental section). Demethylation of (V) or (VI) with hydrobromic acid in acetic acid was accompanied by rearrangement, involving the opening and closing of the heterocyclic ring, to 5 : 6-dihydroxyflavone (VII) (Baker, *loc. cit.*).

The formation of the monobenzyl ether of 2 : 6-dihydroxyacetophenone (I) was accompanied by the production of a smaller quantity of 2 : 6-*dibenzyloxyacetophenone*. The preparation of these ethers disproves the statement by Gulati and Venkataraman (J., 1936, 267) that " hydroxyl in the *o*-position to a keto-group cannot be benzylated," the statement referring to benzylation under the conditions employed in the present paper. It has been observed that the oxidation of 2 : 6-dihydroxyacetophenone with alkaline persulphate gives 2 : 3 : 6-*trihydroxyacetophenone*, which was characterised as its *triacetyl* derivative.

As a contribution to our knowledge of the structure of primetin, experiments were begun having as their object the synthesis of 6 : 8-dihydroxyflavone, which is now the only unknown of the six dihydroxyflavones with an unsubstituted phenyl group. 2 : 3-Dimethoxyacetophenone was demethylated with aluminium chloride in ether to 2-hydroxy-3-methoxyacetophenone, which was then oxidised with alkaline potassium persulphate to 2 : 5-*dihydroxy*-3-*methoxyacetophenone* (IX). Owing to the poor yield of (IX) and the labour involved in preparing the starting material this line of approach was abandoned. 2-Hydroxy-5-methoxyacetophenone (convenient preparation from quinol dimethyl ether) was oxidised with alkaline persulphate, giving 2 : 3-*dihydroxy*-5-*methoxyacetophenone* (X) and 2 : 2′-*dihydroxy*-5 : 5′-*dimethoxy*-3 : 3′-*diacetyldiphenyl*. The usual flavone synthesis did not take place when (X) was fused with benzoic anhydride and sodium benzoate at 180—190°; only a trace of amorphous material was isolated. The monomethyl ether of (X) was converted into its benzoyl derivative, 2-*benzoyloxy*-3 : 5-*dimethoxyacetophenone*, but when treated with sodamide in toluene the benzoyl group did not undergo the usual ready migration to give a dibenzoylmethane.



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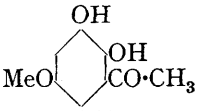

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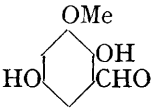
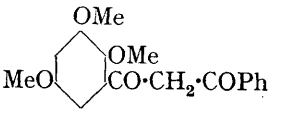


(XI.)



(XII.)

The third method started from *o*-vanillin, which was oxidised by alkaline potassium persulphate to 2 : 5-*dihydroxy*-3-*methoxybenzaldehyde* (XI), a small quantity of 4 : 4′-*dihydroxy*-3 : 3′-*dimethoxydiphenyl*-5 : 5′-*dialdehyde* being also isolated. The aldehyde

(XI) was methylated, giving 2 : 3 : 5-trimethoxybenzaldehyde, and then oxidised to 2 : 3 : 5-trimethoxybenzoic acid, whose *methyl* ester was condensed with acetophenone under the influence of sodium in toluene, yielding 2 : 3 : 5-*trimethoxydibenzoylmethane* (XII). This compound, however, underwent decomposition when heated with hydrobromic acid in acetic acid, and no recognisable product was formed when it was refluxed with aluminium chloride in ether.

Experimental.

2-*Hydroxy*-6-*benzyloxyacetophenone* (I).—A mixture of 2 : 6-dihydroxyacetophenone (60 g.) (Baker, J., 1934, 1953), acetone (300 c.c.), benzyl chloride (70 g.), and anhydrous potassium carbonate (120 g.) was refluxed for 3 hours with continual stirring, more potassium carbonate (40 g.) being then added and heating continued for 6 hours. The reaction mixture was now diluted, acidified, and the sticky solid collected, drained, washed with water, dried, and crystallised from light petroleum (b. p. 80—100°) (yield of crystallised material, 55 g.). 2-*Hydroxy*-6-*benzyloxyacetophenone* forms almost colourless, prismatic needles, m. p. 109—110° (Found: C, 74·2; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). Its alcoholic solution gives a dull violet coloration with ferric chloride.

2 : 6-*Dibenzyloxyacetophenone*, produced in small quantity as a by-product in the preceding preparation, was isolated by means of its insolubility in alkali and crystallised from dilute alcohol and then from absolute alcohol, being obtained in long, flat needles, m. p. 71·5° (Found: C, 79·2; H, 5·8. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%).

2 : 5-*Dihydroxy*-6-*benzyloxyacetophenone* (II).—To a stirred solution of 2-hydroxy-6-benzyloxyacetophenone (I) (24·2 g.; 1 mol.) in water (200 c.c.) containing sodium hydroxide (20 g.; 5 mols.) was added dropwise during 4 hours a solution of potassium persulphate (29·7 g.; 1·1 mols.) in water (600 c.c.), the temperature being kept at 15—20°. After 24 hours the solution was acidified to Congo-red, the precipitate of unchanged 2-hydroxy-6-benzyloxyacetophenone collected, washed, and dried (10 g.), and the filtrate extracted twice with ether (the ether contained 2·1 g. of a brown, non-crystalline material). To the aqueous layer was now added concentrated hydrochloric acid (100 c.c.) and a layer of ether (300 c.c.), and the whole refluxed on the water-bath for 1 hour, after which the ethereal layer was separated, dried by sodium sulphate, and evaporated, leaving the dihydroxy-compound as a light brown, crystalline solid (10·3 g.) (it is advisable to remove the last few c.c. of ether in a current of air; the quinol derivative undergoes decomposition when heated for some time on the water-bath). A second refluxing for 2 hours under ether (300 c.c.) yielded a further quantity (2·3 g.) of the slightly less pure material. 2 : 5-*Dihydroxy*-6-*benzyloxyacetophenone* separates from light petroleum (b. p. 60—80°) in thin, yellow plates, m. p. 94° (Found: C, 70·0; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%). It dissolves in aqueous sodium hydroxide with a bright yellow colour, and its alcoholic solution gives a light, transient green colour, turning to orange, on the addition of ferric chloride. Its solution in concentrated sulphuric acid is orange.

2 : 5-*Dimethoxy*-6-*benzyloxyacetophenone*.—The preceding compound (12 g.; not recrystallised) was dissolved in a solution of potassium hydroxide (30 g.) in water (120 c.c.) and acetone (20 c.c.) in an atmosphere of coal gas, and vigorously stirred during the addition of methyl sulphate (30 c.c.) (1 hour). Further similar quantities of alkali and methyl sulphate were then slowly added, and after 3 hours the solid *dimethoxy*-compound was collected, washed, dried (11 g.), and crystallised from light petroleum (b. p. 60—80°). It separated in thin, rhombic plates, m. p. 74° (Found: C, 71·4; H, 6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

2-*Hydroxy*-3 : 6-*dimethoxyacetophenone* (III).—2 : 5-Dimethoxy-6-benzyloxyacetophenone (5 g.; recrystallised from light petroleum), glacial acetic acid (20 c.c.), and concentrated hydrochloric acid (10 c.c.) were heated at 60° for 1 hour, and the yellow solution diluted with water and extracted with ether. The ethereal layer was washed with water, and then with an excess of aqueous sodium hydroxide, which, after acidification and seeding, deposited the hydroxyketone as a brownish-yellow solid, which was collected, washed, and dried (yield 3·4 g.). 2-*Hydroxy*-3 : 6-*dimethoxyacetophenone* (III) separated from light petroleum (b. p. 40—60°) in large, thin, bright yellow, " diamond-shaped " plates, m. p. 61° (Found: C, 61·0; H, 6·0. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). Its solution in aqueous sodium hydroxide is yellow, and in concentrated sulphuric acid orange; with alcoholic ferric chloride it gives an intense blue-green coloration. This ketone is only very slightly volatile in steam, whereas the isomeric 2-hydroxy-5 : 6-dimethoxyacetophenone (Baker, this vol., p. 960) is extremely easily volatile in steam.

2-*Benzoyloxy*-3 : 6-*dimethoxyacetophenone*.—2-Hydroxy-3 : 6-dimethoxyacetophenone (III) (1·5 g.), pyridine (5 c.c.), and benzoyl chloride (1·08 g.; 1 mol.) were heated on the water-bath for 20 minutes, dilute hydrochloric acid then added, and the crystalline solid collected, washed with dilute hydrochloric acid and water, and dried (yield 2·0 g.). The *substance* separated from light petroleum (b. p. 40—60°) in nacreous plates, m. p. 119° (Found: C, 67·9; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

2-*Hydroxy*-3 : 6-*dimethoxydibenzoylmethane* (IV).—2-Benzoyloxy-3 : 6-dimethoxyacetophenone (5 g.) was added to finely powdered sodamide (10 g.) under toluene (50 c.c.), and the mixture heated on the water-bath for 4 hours, a fairly vigorous evolution of ammonia occurring during the first few minutes. The solids were now collected, washed with benzene, dried, and stirred slowly into ice-water (unchanged sodamide !), and the solution saturated with carbon dioxide. The precipitated yellow diketone was collected, washed, dried (yield 3·2 g.), and crystallised from benzene. It separated in small, bright yellow, rhombic prisms, m. p. 165° (Found: C, 67·9; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). It dissolved in warm, dilute, aqueous sodium hydroxide with a very pale yellow colour and in cold concentrated sulphuric acid with a bright orange-yellow colour. Its alcoholic solution gave an intense reddish-brown colour with ferric chloride. The toluene filtrates and benzene washings from several experiments were united and shaken with aqueous sodium hydroxide, and the alkaline layer saturated with carbon dioxide, giving a further quantity of (IV).

5 : 8-*Dimethoxyflavone* (V).—2-Hydroxy-3 : 6-dimethoxydibenzoylmethane (IV) (1·0 g.) was heated on the water-bath for 2 hours with glacial acetic acid (10 c.c.) and anhydrous sodium acetate (1 g.), water added, and the colourless precipitate collected, washed, dried (yield 0·9 g.), and crystallised first from ethyl alcohol at 0°, then from benzene (needles containing solvent of crystallisation which is lost at 100°, the crystals becoming opaque) and finally from ether after heating to 100°. It formed colourless needles which, after loss of water at about 120°, had m. p. 144—145° (Found in material fused at 160°: C, 72·4; H, 4·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). Its solution in concentrated sulphuric acid was bright yellow.

5-*Hydroxy*-8-*methoxyflavone* (*Primetin Monomethyl Ether*) (VI).—5 : 8-Dimethoxyflavone (V) (0·5 g.) was added to a solution of anhydrous aluminium chloride (5 g.) in absolute ether (30 c.c.) and the mixture, which immediately became yellow, was refluxed for 18 hours. Water was now cautiously added, the ether being allowed to escape, the orange-coloured aluminium complex which separated was collected, washed, and heated on the water-bath for 5 minutes with acetic acid (10 c.c.) and concentrated hydrochloric acid (2 c.c.), and the solution poured into water. The yellow precipitate was collected, washed with dilute sodium hydroxide solution and then water, and crystallised twice from ethyl alcohol, in which it was sparingly soluble. It separated in long, thin, sulphur-yellow needles (0·15 g.), m. p. 209—210° (Found: C, 71·6; H, 4·7. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). The m. p. of a mixture with natural primetin monomethyl ether (m. p. 207—208°) was 208—209°. 5-*Hydroxy*-8-*methoxyflavone* gives an intense bluish-green coloration with alcoholic ferric chloride. It is insoluble in cold, but dissolves very slightly in boiling dilute sodium hydroxide solution with a yellow colour. In concentrated sulphuric acid it gives a yellow solution without fluorescence. Vigorous methylation with a large excess of methyl sulphate and potassium hydroxide in dilute acetone solution regenerated 5 : 8-dimethoxyflavone, which, after crystallisation from ether, had m. p. and mixed m. p. 144—145°. The *acetyl* derivative, prepared by boiling with an excess of acetic anhydride and a drop of pyridine for 2 hours and pouring into water, crystallised from alcohol in long, colourless, silky needles, m. p. 175—176° (Found: C, 70·2; H, 4·8. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Hydrolysis with boiling dilute aqueous alcoholic potassium hydroxide for 2 minutes, dilution, and acidification regenerated 5-hydroxy-8-methoxyflavone, m. p. and mixed m. p. 209—210°.

5 : 6-*Dihydroxyflavone* (VII).—5 : 8-Dimethoxyflavone (or 5-hydroxy-8-methoxyflavone) (0·15 g.) was refluxed for 18 hours with acetic acid (2 c.c.) and hydrobromic acid (2 c.c.; *d* 1·5), water added, and the precipitated greenish solid collected, and crystallised from dilute alcohol (charcoal). The slightly impure yellow needles, m. p. 185—190° with previous softening, showed all the properties of 5 : 6-dihydroxyflavone, and gave a diacetyl derivative which separated from alcohol in colourless flakes, m. p. 164°, either alone or mixed with 5 : 6-diacetoxyflavone of the same m. p.

2 : 3 : 6-*Trihydroxyacetophenone*.—2 : 6-Dihydroxyacetophenone (12·5 g.; 1 mol.) in a solution of sodium hydroxide (17 g.) in water (150 c.c.) was stirred for 4 hours at 15—20° during the dropwise addition of a solution of potassium persulphate (24·4 g.; 1·1 mols.) in water (500 c.c.). After 24 hours the solution was acidified to Congo-red, filtered, extracted with ether,

boiled for 20 minutes with the addition of concentrated hydrochloric acid (150 c.c.), filtered hot after the addition of charcoal, and cooled, and after several hours the dark greenish-yellow crystalline product was collected. A little more of the substance was obtained by ether extraction of the filtrate (total yield, 4 g.). It was recrystallised from slightly diluted alcohol (charcoal) and obtained as fine, bright yellow needles, which decomposed above 230° without melting (Found in material dried in a vacuum at 100°: C, 57·3; H, 4·9. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). 2 : 3 : 6-*Trihydroxyacetophenone* dissolves in aqueous sodium hydroxide with a yellow colour turning in several seconds to a dark greenish-blue. The addition of ferric chloride to its alcoholic solution gives a dull, yellow-brown colour, a dark precipitate subsequently separating from the solution. The *triacetyl* derivative, prepared by boiling with acetic anhydride for 2 hours and then shaking with water, separated from alcohol in small, thick rhombs, m. p. 155° (Found: C, 57·5; H, 4·6. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

2-*Hydroxy*-3-*methoxyacetophenone*.—2 : 3-Dimethoxyacetophenone (13·5 g.) (Baker and Smith, J., 1936, 347) was added to a solution of aluminium chloride (90 g.) in anhydrous ether (300 c.c.), and the solution refluxed for 12 hours, poured on ice and dilute hydrochloric acid, and steam-distilled. The distillate yielded to ether 2-hydroxy-3-methoxyacetophenone (12 g.), which separated from light petroleum (b. p. 40—60°) in pale yellow prisms, m. p. 54° (Found: C, 65·2; H, 6·2. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%) (Reichstein, *Helv. Chim. Acta*, 1927, **10**, 392, gives m. p. 53—54°). It gives an indigo-blue colour with alcoholic ferric chloride, and yields a sparingly soluble yellow sodium salt.

2 : 5-*Dihydroxy*-3-*methoxyacetophenone* (IX).—2-Hydroxy-3-methoxyacetophenone (14 g.) was oxidised with alkaline potassium persulphate in the usual manner (see oxidation of 2-hydroxy-6-benzyloxyacetophenone), unchanged material (4 g.) being recovered. The product was crystallised first from water and then benzene and obtained as light ochre-yellow prisms (0·3 g.), m. p. 172° (Found: C, 59·4; H, 5·2. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). 2 : 5-*Dihydroxy*-3-*methoxyacetophenone* gives in aqueous sodium hydroxide a yellow solution which quickly turns brown, and with alcoholic ferric chloride a bluish-green coloration which soon fades. The *diacetyl* derivative, prepared by boiling with acetic anhydride for 3 hours, separated from methyl alcohol in hexagonal tablets, m. p. 127° (Found: C, 58·8; H, 5·6. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%).

2-*Hydroxy*-5-*methoxyacetophenone*.—Powdered anhydrous aluminium chloride (56 g.) and acetyl chloride (29 g.) were added to a solution of quinol dimethyl ether (56 g.) in carbon disulphide (150 c.c.). After 24 hours the carbon disulphide was distilled from the product (which contains 2 : 5-dimethoxyacetophenone; see Kaufman and Beisswenger, *Ber.*, 1905, **38**, 792), anhydrous ether (900 c.c.) and then aluminium chloride (200 g.) added, and the solution refluxed for 12 hours and poured on ice. The ethereal layer was separated, the aqueous layer shaken with more ether, and the united ethereal solutions shaken with excess of aqueous sodium hydroxide. The 2-hydroxy-5-methoxyacetophenone liberated on acidification was collected by means of ether and distilled (yield 36 g., b. p. 138—142°/12 mm.; m. p. 47—48°) (the pure substance has m. p. 50—51°).

2 : 3-*Dihydroxy*-5-*methoxyacetophenone* (X).—The preceding compound (50 g.) was oxidised with alkaline potassium persulphate in the usual manner, and the dihydric phenol purified by distillation in steam and collected in ether. 2 : 3-*Dihydroxy*-5-*methoxyacetophenone* (0·5 g.) was obtained as yellow prisms, m. p. 120°, from light petroleum (b. p. 60—80°) (Found: C, 59·4; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). Its alcoholic solution gives a green colour with ferric chloride and a yellow precipitate with aqueous lead acetate. The solution in alkali is yellow.

2 : 2′-*Dihydroxy*-5 : 5′-*dimethoxy*-3 : 3′-*diacetyldiphenyl*.—In the preparation of 2 : 3-dihydroxy-5-methoxyacetophenone (X) a considerable brown precipitate was thrown down when the solution was acidified to Congo-red after the oxidation. This crystallised directly from benzene, but was best purified by extraction with ether from its solution in dilute aqueous sodium hydroxide and subsequent crystallisation from benzene–light petroleum. It separated in yellow needles, m. p. 202° (Found: C, 65·5; H, 5·5. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·4%). It is a weak phenol and dissolves in dilute aqueous sodium hydroxide only on heating, giving a bright yellow solution. With alcoholic ferric chloride it gives a weak green colour.

2-*Benzoyloxy*-3 : 5-*dimethoxyacetophenone*.—2 : 3-Dihydroxy-5-methoxyacetophenone (X) (1 g.) in benzene (15 c.c.) was refluxed for 10 hours with methyl sulphate (0·8 g.) and excess of anhydrous potassium carbonate; dilute sulphuric acid and ether were then added, and the phenolic material isolated from the ethereal layer by shaking with alkali, acidification and extraction. The crude oily product (0·8 g.) was heated on the water-bath for ½ hour with

pyridine (5 c.c.) and benzoyl chloride (0·7 g.), the mixture shaken with dilute hydrochloric acid and ether, and the ethereal layer shaken with aqueous sodium bicarbonate and evaporated, leaving the solid *benzoyl* compound (0·8 g.). It was crystallised from light petroleum and then from methyl alcohol and obtained in hexagonal tablets, m. p. 142° (Found : C, 68·2; H, 5·7. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

2 : 5-*Dihydroxy*-3-*methoxybenzaldehyde* (XI).—*o*-Vanillin (45 g.) was oxidised as a stirred suspension in water (300 c.c.) containing sodium hydroxide (60 g.) by the slow addition of a saturated solution of potassium persulphate (81 g.). Unchanged *o*-vanillin (12 g.) and the crude oxidation product (5 g.) were isolated in the usual way, a portion of the latter being purified by crystallisation from benzene and then from a large volume of light petroleum (b. p. 100—120°). 2 : 5-*Dihydroxy*-3-*methoxybenzaldehyde* forms small yellow prisms, m. p. 143° (Found : C, 57·3; H, 4·9. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). It gives a transient green colour with alcoholic ferric chloride and an orange solution in aqueous sodium hydroxide.

4 : 4′-*Dihydroxy*-3 : 3′-*dimethoxydiphenyl*-5 : 5′-*dialdehyde*.—In the preparation of (XI) a precipitate sparingly soluble in ether was thrown down on acidification of the persulphate oxidation mixture, and this was united with the non-steam-volatile portion of the ethereal extract containing the unchanged *o*-vanillin. The product was washed with ether (Soxhlet) and crystallised twice from toluene–light petroleum (b. p. 80—100°) (yield, *ca.* 0·5 g.). It formed short, yellow needles, m. p. 210° (Found : C, 63·8; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%), which gave an intensely yellow solution in aqueous sodium hydroxide and a greenish-blue coloration with alcoholic ferric chloride.

2 : 3 : 5-*Trimethoxybenzaldehyde*.—The preceding aldehyde was treated with a large excess of methyl sulphate and aqueous sodium hydroxide, and the product, isolated by means of ether and distilled (b. p. 168—170°/20 mm.), was crystallised twice from light petroleum (b. p. 40—60°) and then from dilute alcohol. It formed colourless silky needles, m. p. 63°. This aldehyde was prepared in a different manner by Smith and LaForge (*J. Amer. Chem. Soc.*, 1931, **53**, 3074), who gave m. p. 71° after crystallisation from 50% alcohol. This discrepancy is possibly due to dimorphism.

Methyl 2 : 3 : 5-*Trimethoxybenzoate*.—2 : 3 : 5-Trimethoxybenzaldehyde was oxidised to 2 : 3 : 5-trimethoxybenzoic acid by shaking its solution in aqueous sodium carbonate with excess of potassium permanganate at 60°, passing sulphur dioxide and extracting with ether. The acid separated from water in fine needles, m. p. 104° (Smith and LaForge give m. p. 105°). The *methyl* ester, prepared by the Fischer–Speier method, was isolated as a colourless oil (8 g. from 11·8 g. of 2 : 3 : 5-trimethoxybenzaldehyde), b. p. 178—180°/20 mm. (Found : C, 58·7; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

2 : 3 : 5-*Trimethoxydibenzoylmethane* (XII).—To finely divided sodium (0·5 g.) under toluene (25 c.c.) were added acetophenone (3 g.) and methyl 2 : 3 : 5-trimethoxybenzoate (4 g.), and the mixture heated on the water-bath for 10 hours. After the addition of a little alcohol the product was treated with dilute sulphuric acid and ether, and the ethereal layer washed with aqueous sodium bicarbonate and then aqueous sodium hydroxide; the latter solution on acidification deposited the crude oily ketone, an ethereal solution of which was shaken with saturated aqueous copper acetate. The resulting copper derivative was collected, washed with water and alcohol, and decomposed by stirring for 2 hours with dilute sulphuric acid and ether. The ethereal layer yielded the solid *diketone* (1·1 g.), which, after twice crystallising from light petroleum (b. p. 60—80°), formed aggregates of minute, faintly yellow needles, m. p. 82° (Found : C, 68·8; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). It gave a deep reddish-brown coloration with alcoholic ferric chloride.

The authors gratefully acknowledge the gift of a few milligrams of primetin and its diacetyl derivative from Professor S. Hattori of the Imperial University of Tokyo. The amount of material was just sufficient for the preparation of the primetin monomethyl ether used in this work.

(*Note added in proof.*) In a letter dated August 24th, 1939, Professor Hattori, who was informed in May of the views of one of us (W. B.) on the structure of primetin (see *Nature*, **1939, 143,** 900), reports the successful synthesis of 5 : 8-dihydroxyflavone by Dr. K. Nakazawa, the product being identical with natural primetin. The synthesis was along different lines from those employed in the present paper.—W. B.

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