121. Derivatives of Pentahydroxybenzene, and a Synthesis of Pedicellin.

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Recorded syntheses of derivatives of pentahydroxybenzene are reviewed, and the naturally occurring derivatives are mentioned. The methods now described make use, in the final stage, of the oxidation of *o*-hydroxytrimethoxyacetophenones by means of alkaline hydrogen peroxide to give dihydroxytrimethoxybenzenes, (II) to (III), and (VII) and (X) to (VIII). Pentamethoxybenzene (IV) is best prepared in quantity from the very accessible 1 : 2 : 3 : 5-tetramethoxybenzene (I) *via* the compounds (II) and (III). The catechol (III) is oxidised by aqueous ferric chloride to the quinone (XI), of which various derivatives are described. Compound (II) is oxidised by alkaline potassium persulphate to the pentahydroxyacetophenone derivative (XVI), from which the naturally occurring chalkone pedicellin (XVIII) has been synthesised. Pentamethoxybenzene, treated with acetyl and aluminium chlorides in ethereal solution, yields the hydroxypentamethoxyacetophenone (XIX), which may be readily converted into hexamethoxybenzene.

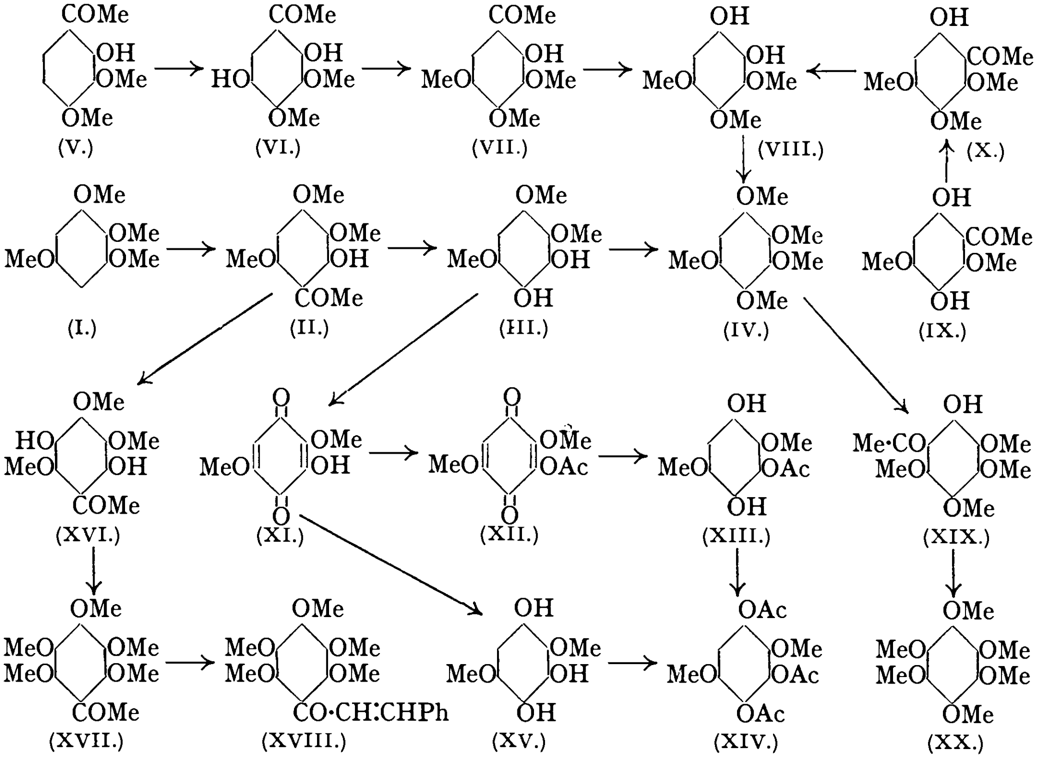
The possibility of extending the author's work on the synthesis of derivatives of 1 : 2 : 3 : 4-tetrahydroxybenzene (papers in this Journal from 1931 to 1941) to derivatives of pentahydroxybenzene has been investigated as occasion offered during the last three years. A complete investigation of the chemistry of such compounds was originally planned, but this has had to be abandoned for the time being. In view of the increasing interest in naturally occurring derivatives of pentahydroxybenzene it seems desirable that the synthetical methods which have been developed should be described, especially as, for the first time, some of these substances may now be very readily prepared.

The following derivatives of pentahydroxybenzene have been isolated from plant sources: the flavonol calycopterin (thapsin) (Ratnagiriswaran, Sehra, and Venkataraman, *Biochem. J.*, 1934, **28**, 1964; Karrer, *Helv. Chim. Acta*, 1934, **17**, 1560; Karrer and Venkataraman, *Nature*, 1935, **135**, 878; see also Bose and Bose, *J. Indian Chem. Soc.*, 1939, **16**, 184, footnote); nobiletin, 5 : 6 : 7 : 8 : 3′ : 4′-hexamethoxyflavone (Tseng and Yu, *J. Chinese Pharm. Assoc.*, 1936, **1**, 1; Tseng, J., 1938, 1003; Robinson and Tseng, *ibid.*, p. 1004); spinulosin, 3 : 6-dihydroxy-4-methoxy-2 : 5-toluquinone (Anslow and Raistrick, *Biochem. J.*, 1938, **32**, 687); erianthin, 5 : 7-dihydroxy-3 : 6 : 8 : 3′ : 4′-pentamethoxyflavone (Bose and Dutt, *J. Indian Chem. Soc.*, 1940, **17**, 45); and pedicin, 2 : 3-dihydroxy-4 : 5 : 6-trimethoxyphenyl styryl ketone, and the closely related compounds pedicellin (dimethyl ether of pedicin), *iso-* and *ψ*-pedicin, and pedicinin (Siddiqui, *J. Indian Chem. Soc.*, 1937, **14**, 703; Sharma and Siddiqui, *ibid.*, 1939, **16** 1; Warsi and Siddiqui, *ibid.*, p. 519; Bose and Dutt, *ibid.*, 1940, **17**, 499).

Four separate methods for the synthesis of pentahydroxybenzene derivatives have been recorded. (1) Wenzel and Weidel (*Verh. Vers. Deut. Naturf. Aerzte*, 1902, ii, **1**, 88; see *Chem. Centr.*, 1903, II, 829), and Wenzel (*Chemikerzeitung*, 1902, 943) hydrolysed triaminoresorcinol diethyl ether, and diaminophloroglucinol trimethyl ether, and Einhorn, Cobliner, and Pfeiffer (*Ber.*, 1904, **37**, 100) hydrolysed diaminopyrogallol, the yields being of the order of 5%. (2) Baker and Smith (J., 1931, 2544) oxidised 4-aminopyrogallol trimethyl ether to 2 : 3-dimethoxy-1 : 4-benzoquinone, the latter compound then yielding 1 : 2 : 5-triacetoxy-3 : 4-dimethoxybenzene when submitted to the action of acetic anhydride and sulphuric acid (Erdtman, *Proc. Roy. Soc.*, 1934, *A*, **143**, 177). The method is limited by the difficulty of obtaining the quinone in quantity, an alternative route to which is given by Baker and Savage (J., 1938, 1601; see also Anslow and Raistrick, J., 1939, 1454). An exactly similar reaction is involved in the conversion of fumigatin (see succeeding paper) into spinulosin (Anslow and Raistrick, *Biochem. J.*, 1938, **32**, 687). (3) Aulin and Erdtman (*Svensk Kem. Tidskr.*, 1937, **49**, 208; see also Robinson and Vasey, preceding paper) converted 2 : 6-dimethoxy-1 : 4-benzoquinone into the dibromo-derivative, hydrolysed one bromine atom and a methoxyl group with alkali, removed the remaining bromine atom by catalytic reduction, and submitted the product to reductive acetylation, giving 1 : 2 : 4 : 5-tetra-acetoxy-3-methoxybenzene. The yield is not stated. (4) Anslow and Raistrick (*Biochem. J.*, 1938, **32**, 803; J., 1939, 1446) treated dihydroxybenzoquinone derivatives with methylamine and submitted the products to acid hydrolysis; the yields were generally good.

In the present work a very simple synthesis of pentahydroxybenzene derivatives has been developed starting from pyrogallol. This was converted by known methods into 1 : 2 : 3 : 5-tetramethoxybenzene (I), and with the improvements described in the experimental section the overall yield of (I) was rather over 50%. Compound (I), when treated with acetyl chloride and anhydrous aluminium chloride in dry ethereal solution at room temperature, gave a 70% yield of 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (II), the highest yield previously claimed in this much investigated reaction being 42% (Wesseley and Kallab, *Monatsh.*, 1932, **60**, 26; for other references see experimental section); the increase is due to the use of ether as solvent, and employment of a low temperature. When (II) was oxidised by hydrogen peroxide in alkaline solution under the conditions of the Dakin reaction, it yielded 1 : 2-*dihydroxy*-3 : 4 : 6-*trimethoxybenzene* (III). Methylation of (III) with methyl sulphate and alkali readily gave pentamethoxybenzene (IV), identical with that described by Aulin and Erdtman (*loc. cit.*). By this route it is possible to prepare just over 50 g. of pentamethoxybenzene from 126 g. of pyrogallol.

An alternative route to pentamethoxybenzene started from gallacetophenone, which was converted into its dimethyl ether (V) (improved preparation), and oxidation of this with alkaline potassium persulphate gave 2 : 5-dihydroxy-3 : 4-dimethoxyacetophenone (VI) in 36% yield. Partial methylation of (VI) with methyl sulphate and potassium carbonate in benzene gave 2-*hydroxy*-3 : 4 : 5-*trimethoxyacetophenone* (VII), which was then oxidised with hydrogen peroxide in alkaline solution to give 1 : 2-*dihydroxy*-3 : 4 : 5-*trimethoxybenzene* (VIII). Methylation of (VIII) again gave pentamethoxybenzene (IV). The fact that compound (VIII), about whose structure there can be no ambiguity, differs from its isomer (III) establishes the position of the two hydroxyl groups in the latter, and hence proves the position of the free hydroxyl group in the ketone (II). A considerably less convenient way of preparing (VIII) is from 2 : 6-dimethoxyquinol diacetate, which is converted first by the action of aluminium chloride into 2 : 5-dihydroxy-4 : 6-dimethoxyacetophenone (IX) (Mauthner, *J. pr. Chem.*, **1933**, **147**, 287), and then by monomethylation with methyl sulphate and anhydrous potassium carbonate in benzene into the bright yellow 2-*hydroxy*-4 : 5 : 6-*trimethoxyacetophenone* (X). Oxidation of (X) with hydrogen peroxide then gave 1 : 2-dihydroxy-3 : 4 : 5-trimethoxybenzene (VIII) identical with that prepared by the oxidation of the isomer (VII).



Oxidation of 1 : 2-dihydroxy-3 : 4 : 6-trimethoxybenzene (III) in aqueous solution with ferric chloride readily gave an insoluble, dark red quinone, analysis of which showed that one methoxyl group had suffered demethylation during the oxidation, and this substance has been proved to be the *p*-quinone (XI), 2-*hydroxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone*. Acetylation of the free hydroxyl group gave the bright yellow 2-*acetoxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone* (XII), whose structure as a *p*-quinone was established by reduction with sodium hydrosulphite to 2-*acetoxy*-3 : 6-*dimethoxyquinol* (XIII), a compound whose aqueous solution gave no precipitate with lead acetate and which must, therefore, be a quinol and not a catechol derivative. Since the yellow quinone (XII) is merely the acetyl derivative of the red quinone (XI), it follows that this also must be a *p*-quinone, a structure consistent with its complete stability towards both acids and alkalis (see experimental section). Neither (XI) nor (XII) undergoes the Thiele acetylation (*Ber.*, 1898, **31**, 1247); indeed the most convenient way to prepare the yellow from the red quinone is to treat it with acetic anhydride and a trace of sulphuric acid. Reduction of the quinone (XI) with sodium hydrosulphite gave 2-*hydroxy*-3 : 6-*dimethoxyquinol* (XV), the *triacetyl* derivative (XIV) of which was identical with the *diacetate* of (XIII). No recognisable quinone could be obtained by the oxidation of (VIII) with ferric chloride.

Two routes leading to the preparation of pentahydroxyacetophenone derivatives have been investigated. In the first, 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (II) was oxidised by potassium persulphate in alkaline solution to give 2 : 5-*dihydroxy*-3 : 4 : 6-

trimethoxyacetophenone (XVI), and this readily yielded 2 : 3 : 4 : 5 : 6-*pentamethoxyacetophenone* (XVII) on treatment with excess of methyl sulphate and alkali. The *C*-methyl group of the ketone (XVII) shows the usual chemical reactivity, condensing with ethyl benzoate in the presence of sodium to give 2 : 3 : 4 : 5 : 6-*pentamethoxydibenzoylmethane*, and with benzaldehyde in dilute alcoholic alkaline solution to give 2 : 3 : 4 : 5 : 6-*pentamethoxyphenyl styryl ketone* (XVIII). This pentamethoxychalkone is the naturally occurring substance pedicellin, isolated from the leaves of *Didymocarpus pedicellata* (see earlier references), and, although a direct comparison of the synthetical and the natural product was not possible, the melting points, and the fact that they both dissolve in concentrated sulphuric acid with a red colour, allow little doubt of their identity. Since pedicellin may be converted into pedicinin by treatment with nitric acid in acetic acid, followed by the action of dilute alkali, the synthesis of pedicellin completes the synthesis of pedicinin. In the second route pentamethoxybenzene (IV) was treated with acetyl chloride and aluminium chloride in ethereal solution and yielded the bright yellow 2-*hydroxy*-3 : 4 : 5 : 6-*tetramethoxyacetophenone* (XIX), an important intermediate for the synthesis of flavones and related compounds; it yielded pentamethoxyacetophenone (XVII) on methylation with methyl sulphate and alkali. The partial methylation of 2 : 5-dihydroxy-3 : 4 : 6-trimethoxyacetophenone (XVI) to give (XIX), under conditions which converted (IX) into (X), gave only traces of the desired product.

A natural extension of this work to the hexahydroxybenzene series was effected by the oxidation of (XIX) by means of alkaline hydrogen peroxide to give 1 : 2-dihydroxytetramethoxybenzene, a product not isolated in the pure state, but methylated directly to hexamethoxybenzene (XX), which proved to be identical with the hexamethoxybenzene prepared by Robinson and Vasey (*loc. cit.*).

In connection with the use by the author of an ethereal solution of aluminium chloride as a method of demethylating *o*-methoxy-ketones (see J., **1939**, 961, 1925, 1926; **1940**, 1373), it may be mentioned that in order to bring about demethylation the methoxyl groups must be activated by carbonyl groups in either the *o*- or *p*-positions. Demethylation in the *p*-position takes place much less readily than in the *o*-position, but has now been observed in the case of 2 : 3 : 4-trimethoxyacetophenone, which by the prolonged action of boiling ethereal aluminium chloride yields 2 : 4-dihydroxy-3-methoxyacetophenone. The remarkably inert nucleus of 1 : 2 : 4 : 5-tetramethoxybenzene is not attacked by an ethereal solution of aluminium chloride and acetyl chloride.

EXPERIMENTAL.

1 : 2 : 3 : 5-*Tetramethoxybenzene* (I).—Considerable quantities of this substance have been made from pyrogallol *via* the stages (1) pyrogallol trimethyl ether, (2) 2 : 6-dimethoxy-1 : 4-benzoquinone, and (3) 2 : 6-dimethoxyquinol, and the yields represent a very considerable improvement over those previously described. The modifications of recorded conditions are described in the following notes, and enable over 100 g. of the tetramethoxybenzene to be obtained from 126 g. of pyrogallol. (1) *Pyrogallol trimethyl ether :* The methylation of pyrogallol (126 g.) is carried out as described by Chapman, Perkin, and Robinson (J., 1927, 3028), but it is essential that the reaction mixture should be cooled in a trough of water so that the temperature keeps between 18° and 22°, and the addition of sodium hydrosulphite (10 g.) as recommended by Kohn and Grün (*Monatsh.*, 1925, **46**, 75) ensures a water-white product. After stirring for a total of 6 hours, crushed ice (1 kg.) is added, and the product collected, washed, and dried. Yield, 155 g. (2) 2 : 6-*Dimethoxybenzoquinone* (see Graebe and Hess, *Annalen*, 1905, **340**, 237) : The above pyrogallol trimethyl ether (155 g.), alcohol (775 c.c.), and nitric acid (775 c.c.; *d* 1·2) are warmed to 35° and allowed to stand until the vigorous reaction sets in, and the temperature then kept just below 50° till the main heat evolution ceases (¼ hour). After 4 hours with occasional shaking the quinone is collected, drained, washed with alcohol (400 c.c.), then water (800 c.c.), and dried on the water-bath. Yield, 124 g. (3) 2 : 6-*Dimethoxyquinol :* To the above quinone (124 g.) and sodium hydrosulphite (250 g.) was quickly added boiling water (1250 c.c.), and the mixture vigorously shaken till a clear solution was obtained (less than 1 minute) and then cooled rapidly under the tap with shaking. After ½ hour the product was collected, drained, washed with ice-water (600 c.c.), and dried on the steam-bath (local darkening). Yield, 110 g. If the filtrate and washings from the quinol

are saturated with salt and extracted with ethyl acetate at 40—50°, a further 8 g. of the quinol are obtained, but the labour involved is hardly justified. (4) 1 : 2 : 3 : 5-*Tetramethoxybenzene* : To a continually stirred mixture of 2 : 6-dimethoxyquinol (55 g.), alcohol (130 c.c.), methyl sulphate (250 g.), and sodium hydrosulphite (4 g.) in an atmosphere of coal gas was added dropwise during 4 hours a solution of sodium hydroxide (80 g.) in water (180 c.c.), the temperature being kept at 15—20°. The mixture was then heated on the water-bath for ½ hour with frequent shaking, diluted with water (500 c.c.), cooled, and seeded, and the solid product collected, thoroughly washed, and dried. Yield 54 g., m. p. 35—40° (m. p. of the pure material 47°).

2-*Hydroxy*-3 : 4 : 6-*trimethoxyacetophenone* (II).—Anhydrous aluminium chloride (50 g.) was dissolved in absolute ether (250 c.c.) with cooling, and then 1 : 2 : 3 : 5-tetramethoxybenzene (50 g.; as obtained directly from the methylation of 2 : 6-dimethoxyquinol) added. To the mixture, which was vigorously stirred and cooled in a vessel of water, acetyl chloride (25 g.) was added during 1 hour, and stirring continued for a further 6 hours. During this time the yellow, solid, aluminium complex of 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone began to separate. After standing overnight, water (350 c.c.) and concentrated hydrochloric acid (50 c.c.) were cautiously added and the mixture was heated on the water-bath for ½ hour, the ether being allowed to distil away, and, while hot, extracted with benzene (200 c.c.). The benzene layer was washed with dilute hydrochloric acid and shaken with excess of 10% aqueous sodium hydroxide, and the aqueous layer acidified. The rather dark, solid product was collected, washed (dry weight 46·5 g.; m. p. 101—104°), and crystallised from dilute alcohol (charcoal), giving a light fawn, crystalline powder (42·5 g.; 70% yield), m. p. 103—105°. The nuclear acetylation of 1 : 2 : 3 : 5-tetramethoxybenzene has been investigated by Bargellini and Bini (*Atti R. Accad. Lincei*, 1910, [v], **19**, ii, 595), Chapman, Perkin, and Robinson (J., 1927, 3020), Kuroda (*Proc. Imp. Acad. Tokyo*, 1929, **5**, 86), Hattori (*Acta phytochimica*, 1930, **5**, 99), Wesseley and Kallab (*loc. cit.*), and Bargellini and Zoras (*Gazzetta*, 1934, **64**, 192). Nierenstein (J., 1917, **111**, 6) mentions compound (II), and also compounds (X) and (XVI), but none can be identical with the compounds described in this paper.

1 : 2-*Dihydroxy*-3 : 4 : 6-*trimethoxybenzene* (III).—2-Hydroxy-3 : 4 : 6-trimethoxyacetophenone (22·6 g.) was dissolved in a solution of sodium hydroxide (8 g.) in water (160 c.c.) with heating, and cooled to 20°, and a 3% solution of hydrogen peroxide (142 c.c.; 1·25 mols.; made by diluting perhydrol) at 20° added. The temperature rose gradually at first, then rapidly to 54°, and then fell. After 2 hours the solution was acidified with sulphuric acid, and unchanged material collected by filtration, washed, and dried (2·2 g.). The filtrate was saturated with salt and extracted six times with ether (100 c.c. each time), and the extracts shaken with an excess of a suspension of sodium bicarbonate and water to remove acetic acid, dried over sodium sulphate, and distilled, leaving 1 : 2-*dihydroxy*-3 : 4 : 6-*trimethoxybenzene* as an oil which solidified completely on scratching (yield, 12·3 g.). This product shows little tendency to undergo aerial oxidation in alkaline solution, so an inert atmosphere is unnecessary during its preparation. It was crystallised from benzene–light petroleum, and then twice from a little benzene, being obtained in flat prisms, m. p. 82° (Found : C, 54·2; H, 6·0. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%). The *diacetyl* derivative, prepared by boiling with acetic anhydride for 3 hours and shaking with water, separated from alcohol in thick tablets, m. p. 147° (Found : C, 54·9; H, 5·8. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%).

Pentamethoxybenzene (IV).—The preceding compound (III) (10 g., not crystallised), alcohol (10 c.c.), water (10 c.c.), and sodium hydrosulphite (1 g.) were vigorously shaken during the alternate portionwise addition of methyl sulphate (25 g.) and a solution of sodium hydroxide (50 c.c.; containing 10 g. of sodium hydroxide). The temperature was allowed to rise to about 50°, and the reaction was completed by heating on the water-bath for ½ hour. The alkaline solution was extracted three times with benzene, and the extracts dried and distilled, leaving a very light-brown oil (10·2 g.) which solidified on cooling (m. p. *ca.* 45—53°). This pentamethoxybenzene separated from light petroleum (b. p. 40—60°), in which it was easily soluble, in colourless, nacreous, rhombic plates, m. p. 58—59° (Found : C, 58·0; H, 7·0. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·0%). It is most easily purified by distillation under diminished pressure; b. p. 150°/14 mm., 167°/21 mm.

2-*Hydroxy*-3 : 4-*dimethoxyacetophenone* (V).—The following method, based on that described by Baker, Jukes, and Subrahmanyam (J., 1934, 1682), gives an increased yield and enables the compound to be prepared easily and in quantity.

Crude gallacetophenone (67·2 g.; 1 mol.; prepared according to Badhwar and Venkataraman, *Organic Syntheses*, 1934, **14**, 40, but not recrystallised), benzene (800 c.c.), anhydrous potassium carbonate (220 g.), and methyl sulphate (104 g.; 2·05 mols.) were refluxed for 8 hours with occasional shaking. Hot water (1 l.) was now added, the mixture acidified with concentrated hydrochloric acid (250 c.c.) (much carbon dioxide!), and whilst still hot the benzene layer was separated, washed four times with 10 c.c. of water, shaken with charcoal (10 g.), and filtered with the aid of a pump, the residue being washed with a little benzene. The benzene solution was now shaken once with 300 c.c. and four times with 50 c.c. of 10% aqueous sodium hydroxide, the united alkaline solutions acidified with hydrochloric acid and cooled, and the precipitated 2-hydroxy-3 : 4-dimethoxyacetophenone collected, washed, and dried at a gentle heat. The pale brown product (51 g.), m. p. 71—73°, is readily purified, if desired, by crystallisation from light petroleum (b. p. 80—100°) and then forms pale yellow prisms, m. p. 77°. Some 2 : 3 : 4-trimethoxyacetophenone is also produced in this reaction and may be isolated by heating the alkali-washed benzene solution with aqueous alkali to remove methyl sulphate, drying and distilling; the trimethyl ether is isolated as a colourless oil, b. p. 178°/20 mm. (yield, 10 g.).

2 : 5-*Dihydroxy*-3 : 4-*dimethoxyacetophenone* (VI).—This reaction was studied in considerable detail, and the following method gives the maximum yield. The use of the equivalent of potassium hydroxide diminishes the yield by 20%, and the addition of a little ferrous sulphate as recommended by Bargellini (*Gazzetta*, 1916, **46**, i, 249) reduces the yield by 5%. 2-Hydroxy-3 : 4-dimethoxyacetophenone (20 g.; prepared as described above but not recrystallised) was dissolved in a solution of sodium hydroxide (30 g.) in water (200 c.c.) and, with continual stirring, oxidised by the addition during 4 hours of a solution of potassium persulphate (40 g.) in water (800 c.c.), the reaction vessel being cooled in a trough of water. After standing for 48 hours, the mixture was made distinctly acid to Congo-red paper with concentrated hydrochloric acid, anhydrous sodium sulphite (5 g.) and powdered charcoal (10 g.) stirred in, and the liquid filtered and extracted with benzene (100 c.c.) (this benzene extract was heated with the charcoal, filtered, and distilled, leaving a residue of crude 2-hydroxy-3 : 4-dimethoxyacetophenone, which, after crystallisation from light petroleum, weighed 3·2 g.). To the solution were now added concentrated hydrochloric acid (200 c.c.) and benzene (400 c.c.), the mixture gently refluxed on the water-bath for 6 hours, partially cooled, and shaken, and the benzene layer separated. The aqueous solution was now extracted twice with benzene (100 c.c. each time), and the benzene extracts united, dried over sodium sulphate, and distilled under slightly diminished pressure, leaving the 2 : 5-dihydroxy-3 : 4-dimethoxyacetophenone as a pale brown, crystalline mass, m. p. 105—110° (yield, 6·6 g.). It separated from water (charcoal) in small, pale yellow prisms, m. p. 119° (Found : C, 56·5; H, 5·6. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·6%) (Bargellini, *loc. cit.*, records m. p. 119—121°).

2-*Hydroxy*-3 : 4 : 5-*trimethoxyacetophenone* (VII).—A mixture of 2 : 5-dihydroxy-3 : 4-dimethoxyacetophenone (VI) (21·2 g.; 1 mol.), anhydrous benzene (200 c.c.), freshly ignited potassium carbonate (50 g.), and anhydrous acid-free methyl sulphate (12·6 g.; 1 mol.) was refluxed with occasional shaking for 14 hours. Water (200 c.c.) was now added, the mixture shaken, the benzene layer separated, and the aqueous layer extracted twice with benzene (100 c.c. each time). The united extracts were dried over sodium sulphate and distilled, leaving an oil which solidified on scratching, and which was extracted three times with boiling light petroleum (b. p. 60—80°; 200 c.c., 50 c.c., 50 c.c.). On cooling, the extracts deposited 2-*hydroxy*-3 : 4 : 5-*trimethoxyacetophenone* as pale yellow, large, flat, rhombic, crystalline aggregates (total yield, 16·5 g.), m. p. 86°, after twice crystallising from light petroleum (Found : C, 58·6; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). With copper acetate in dilute alcoholic solution the compound gave a green co-ordinate copper derivative, soluble in chloroform. It dissolved in aqueous sodium hydroxide with a bright yellow colour, and gave a deep slate-blue colour with alcoholic ferric chloride.

1 : 2-*Dihydroxy*-3 : 4 : 5-*trimethoxybenzene* (VIII).—2-Hydroxy-3 : 4 : 5-trimethoxyacetophenone (11·3 g.) was oxidised in the same manner as the isomeric 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (II), but in an atmosphere of coal-gas, the temperature rising to 53°. Recovered starting material (0·2 g.) and the crude catechol derivative (7·8 g.) were obtained, the latter as a light brown oil which solidified on scratching. After twice crystallising from benzene containing a little light petroleum, the 1 : 2-*dihydroxy*-3 : 4 : 5-*trimethoxybenzene* was obtained in colourless, thin, elongated, hexagonal plates, m. p. 90—91° (Found : C, 54·1; H, 6·0. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%). The m. p. of a mixture with the isomeride (III) was 50—60°. The compound was easily oxidised and turned pinkish on exposure to the air. With very dilute sodium hydroxide it gave a light green solution which soon turned yellow. Its aqueous solution, when treated with a trace of ferric chloride, gave an orange colour turning to cherry-

red; with excess of ferric chloride a deep brown solution was obtained. Treatment of the alkaline solution with methyl sulphate in the usual way (see methylation of the isomeride III) gave pentamethoxybenzene, m. p. and mixed m. p. 58—59°. The *diacetyl* derivative, prepared by boiling for 4 hours with five times its weight of acetic anhydride and shaking with water, separated from alcohol in highly refracting, thick, rhombic plates, m. p. 77° (Found : C, 54·8; H, 5·7. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%).

2-*Hydroxy*-4 : 5 : 6-*trimethoxyacetophenone* (X).—2 : 5-Dihydroxy-4 : 6-dimethoxyacetophenone (IX) (8 g.) (Mauthner, *J. pr. Chem.*, 1933, **147**, 287), benzene (75 c.c.), anhydrous potassium carbonate (19 g.), and methyl sulphate (4·8 g.) were refluxed for 14 hours. After the addition of water the mixture was extracted with benzene, the extracts shaken with aqueous sodium hydroxide, and the alkaline layer acidified. The oily product (3·2 g.) was taken up in ether, filtered from some unchanged material, and distilled under diminished pressure, giving a yellow-brown oil, collected at 185—195°/25 mm. The distillate was now treated with light petroleum (b. p. 40—60°), causing a little more (IX) to separate, the two liquid layers filtered, the solvent removed, and the product again distilled. 2-*Hydroxy*-4 : 5 : 6-*trimethoxyacetophenone* (X) distilled as a bright yellow oil (1·3 g.), b. p. 184—186°/27 mm. (Found : C, 58·2; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). Its alcoholic solution gave with aqueous copper acetate a green co-ordinate copper derivative soluble in chloroform, and with ferric chloride a deep violet-grey colour. It dissolved in aqueous sodium hydroxide with a yellow colour.

1 : 2-*Dihydroxy*-3 : 4 : 5-*trimethoxybenzene* (VIII).—The preceding compound (1·2 g.) was oxidised, and the product isolated, as in the case of the isomeride (VII), the temperature in the Dakin reaction rising from 25° to 50°. The crude catechol derivative (0·8 g.; m. p. *ca.* 75—80°) separated from benzene–light petroleum in elongated hexagonal plates, m. p. 91°, not depressed on admixture with the specimen of the same m. p. prepared by the oxidation of (VII).

2-*Hydroxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone* (XI).—1 : 2-Dihydroxy-3 : 4 : 6-trimethoxybenzene (III) (1·0 g.; as isolated directly from the Dakin reaction) was dissolved in water (20 c.c.), and to the filtered solution at 10° was added dropwise a solution of anhydrous ferric chloride (2 g.; *ca.* 2·5 mols.) in water (10 c.c.). The solution, at first very dark, rapidly became red, and bright red crystals began to separate. After 4 hours the quinone (0·65 g.) was collected, washed, and dried. It separated from water in dark red, sharp bipyramids, m. p. *ca.* 208° (rapid heating) (Found : C, 52·4, 52·3; H, 4·4, 4·4. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). 2-*Hydroxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone* crystallises easily from glacial acetic acid in bright scarlet platelets which appear to contain solvent of crystallisation, since on treatment with cold water or alcohol they immediately give the usual dark red product. It dissolves in very dilute sodium hydroxide solution, giving an intensely purple-red solution, and is precipitated unchanged on acidification. It crystallises in the scarlet platelets from acetic acid containing a trace of concentrated sulphuric acid.

2-*Acetoxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone* (XII).—To 2-hydroxy-3 : 6-dimethoxy-1 : 4-benzoquinone (XI) (0·65 g.) was added acetic anhydride (13 c.c.) containing concentrated sulphuric acid (2 drops), and the mixture gently agitated. The red quinone rapidly dissolved to a yellow solution, and after 2 hours water was added, the mixture shaken till hydrolysis of the acetic anhydride had occurred and extracted several times with benzene till the aqueous layer was colourless, and the extracts shaken once with water, dried over sodium sulphate, and distilled, leaving a yellow solid (0·7 g.). 2-*Acetoxy*-3 : 6-*dimethoxy*-1 : 4-*benzoquinone* separated from slightly diluted alcohol in bright yellow needles, m. p. 147° (Found : C, 53·0; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%). It dissolved in dilute aqueous sodium hydroxide with an intense purple-red colour. This same compound (mixed m. p.'s) is also obtained from the red quinone either by boiling with acetic anhydride for several minutes till a yellow solution is obtained, or by the action of acetic anhydride and a trace of pyridine at about 40° (several minutes), or at room temperature (½ hour).

2-*Acetoxy*-3 : 6-*dimethoxyquinol* (XIII).—The preceding quinon (XII) (0·5 g.), alcohol (2·5 c.c.), and a solution of sodium hydrosulphite (1 g.) in water (5 c.c.) were warmed to 60°, cooled, and extracted three times with ethyl acetate. The extracts were shaken once with water, dried over sodium sulphate, and distilled, leaving an oil which solidified completely on scratching. It separated from benzene, in which it was very sparingly soluble, in colourless prisms, m. p. 151° (Found : C, 52·5; H, 5·3. $C_{10}H_{12}O_6$ requires C, 52·6; H, 5·3%). Vigorous methylation of this compound with methyl sulphate and alkali in an atmosphere of coal gas, final heating on the water-bath, and extraction with ether gave pentamethoxybenzene (IV), m. p. and mixed m. p. 58—59°. Boiling with excess of acetic anhydride for 2 hours, shaking with water, extracting with ethyl acetate, and crystallising the residual solid from alcohol gave 2-*acetoxy*-3 : 6-*dimethoxyquinol diacetate* (XIV) as small, opaque, white crystals, m. p. 114—115° [Found : C, 54·0; H, 5·2; OMe, 20·1. $C_{12}H_{10}O_6(OMe)_2$ requires C, 53·8; H, 5·1; OMe, 19·9%].

2-*Hydroxy*-3 : 6-*dimethoxyquinol* (XV).—The quinone (XI) (0·4 g.) was suspended in cold water (10 c.c.), and sodium hydrosulphite added with shaking until the red colour of the solution had faded to pale yellow (several minutes). The solution was now extracted with ether, and the extracts dried and distilled, leaving a solid residue which separated from benzene in colourless, branching, fern-like crystals, m. p. 144° (darkening, rapid heating) [Found : C, 51·6; H, 5·5; OMe, 33·0. $C_6H_4O_3(OMe)_2$ requires C, 51·6; H, 5·4; OMe, 33·3%]. This *hydroxyquinol* derivative slowly turns pink on keeping owing to oxidation. Its aqueous solution gives a deep purple-red colour with a trace of dilute sodium hydroxide, which becomes brownish-purple with an excess of alkali, and with ferric chloride gives a red solution which, if in sufficient concentration, deposits the red quinone (XI). The triacetyl derivative (XIV), prepared as described above, had m. p. and mixed m. p. 114—115°.

2 : 5-*Dihydroxy*-3 : 4 : 6-*trimethoxyacetophenone* (XVI).—To a stirred mixture of 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (II) (11·2 g.) and a solution of sodium hydroxide (20 g.) in water (120 c.c.) was added during 4 hours a solution of potassium persulphate (17·6 g.) in water (360 c.c.); stirring was continued for a further 2 hours. After standing overnight, the solution was acidified to Congo-red, filtered from a crystalline deposit, extracted with benzene (100 c.c.) (the benzene extract and solid yielded 1·3 g. of crude starting material), and refluxed for 4 hours after the addition of benzene (200 c.c.) and concentrated hydrochloric acid (100 c.c.). The benzene layer was separated, dried over anhydrous sodium sulphate, and distilled, leaving a yellow, crystalline mass (3·5 g.). 2 : 5-*Dihydroxy*-3 : 4 : 6-*trimethoxyacetophenone* separated from water in fine, yellow needles, m. p. 116—117° (Found : C, 54·5; H, 5·9. $C_{11}H_{14}O_6$ requires C, 54·5; H, 5·8%). It gives a bright yellow solution in aqueous sodium hydroxide, and with ferric chloride in alcoholic solution it gives an apple-green coloration which rapidly fades to yellow.

2 : 3 : 4 : 5 : 6-*Pentamethoxyacetophenone* (XVII).—2 : 5-Dihydroxy-3 : 4 : 6-trimethoxyacetophenone (5·5 g.) was shaken in dilute acetone with a large excess of methyl sulphate and aqueous potassium hydroxide, added alternately, and the alkaline mixture was finally heated on the water-bath for ½ hour. Light petroleum (b. p. 40—60°) then extracted a colourless oil which became crystalline on cooling, and the product was distilled under diminished pressure (b. p. 163°/13 mm.) (yield, 4·8 g.), and then crystallised twice from light petroleum (b. p. 35—50°) at 0°, giving fine needles, m. p. 43° [Found : C, 57·6; H, 6·7; OMe, 57·3. $C_8H_3O(OMe)_5$ requires C, 57·8; H, 6·6; OMe, 57·4%]. It was extremely easily soluble in all organic solvents.

2 : 3 : 4 : 5 : 6-*Pentamethoxydibenzoylmethane*.—A mixture of pentamethoxyacetophenone (0·7 g.), powdered sodium (0·14 g.), and ethyl benzoate (2·1 g.) was heated for 1½ hours in an oil-bath at 125°. Dilute sulphuric acid was now added, the mixture extracted with ether, and the ethereal layer shaken with water and then with excess of 2N-sodium hydroxide. The alkaline layer was saturated with carbon dioxide, and the solid collected, washed, and crystallised from warm dilute alcohol, forming very pale yellow, slender needles (0·08 g.), m. p. 91° (Found : C, 64·2; H, 5·7. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). It gave a cherry-red colour with alcoholic ferric chloride.

2 : 3 : 4 : 5 : 6-*Pentamethoxyphenyl Styryl Ketone* (*Pedicellin*) (XVIII).—To a solution of 2 : 3 : 4 : 5 : 6-pentamethoxyacetophenone (0·5 g.) and benzaldehyde (0·2 g; 1 mol.) in alcohol (2 c.c.) was added a strong solution of sodium in alcohol (10 drops) and then a little water till a clear solution was obtained. After standing overnight, the mixture was diluted, and the solid collected, washed, dried, and crystallised twice from a small volume of light petroleum (b. p. 60—80°), being obtained in colourless, prismatic needles, m. p. 93° (Found : C, 66·9; H, 6·2. Calc. for $C_{20}H_{22}O_6$: C, 67·0; H, 6·1%). Siddiqui (*loc. cit.*) records m. p. 98° for pedicellin, but in the subsequent investigation by Bose and Dutt (*loc. cit.*) the most careful purification failed to raise the m. p. above 93°. The synthetical pedicellin dissolved in concentrated sulphuric acid with a deep orange-red colour.

2-*Hydroxy*-3 : 4 : 5 : 6-*tetramethoxyacetophenone* (XIX).—To a solution of aluminium chloride (5 g.) in anhydrous ether (25 c.c.) were added pentamethoxybenzene (5 g.) and then acetyl chloride (5 g.) in portions during ½ hour. The mixture was kept at room temperature with occasional shaking for 16 hours. Water (35 c.c.) and concentrated hydrochloric acid (5 c.c.) were then cautiously added, the mixture heated on the water-bath for ½ hour, the ether being allowed to distil away, and the residual liquid extracted with benzene (20 c.c.). The benzene layer was washed with dilute hydrochloric acid and shaken with excess of 10% sodium hydroxide solution, the alkaline layer acidified and extracted with benzene, and the benzene layer finally dried and distilled, leaving a residue (1·7 g.) which distilled as a bright yellow oil (1·4 g.), b. p. 183°/14 mm. (Found: C, 56·1; H, 6·3. $C_{12}H_{16}O_6$ requires C, 56·3; H, 6·2%). 2-*Hydroxy*-3 : 4 : 5 : 6-*tetramethoxyacetophenone* is very slightly volatile in steam. With aqueous and alcoholic ferric chloride it gives intense brown and deep brownish-green colours respectively; and addition of aqueous copper acetate to its alcoholic solution gives a green co-ordinate copper derivative soluble in chloroform.

1 : 2-*Dihydroxytetramethoxybenzene, and Hexamethoxybenzene* (XX).—The preceding *o*-hydroxyacetophenone (3·2 g.) in a solution of sodium hydroxide (1 g.) in water (20 c.c.) at 20° was treated with a 3% solution of perhydrol (18 c.c.) in an atmosphere of coal gas. Rapid rise of temperature to 46° occurred and the intense yellow colour faded. After ½ hour the solution was acidified, filtered after the addition of a little charcoal, saturated with salt, and extracted four times with ether; the extracts were shaken with aqueous sodium bicarbonate to remove acetic acid, dried over sodium sulphate, and distilled, leaving a light brown oil (1·4 g.). This gave a weak brownish-purple coloration with ferric chloride in aqueous solution. Without further purification this crude 1 : 2-dihydroxytetramethoxybenzene was shaken in dilute acetone solution with a large excess of aqueous potassium hydroxide and methyl sulphate, added in portions. After the alkaline liquid had been heated on the water-bath for ½ hour, it was extracted twice with ether; the extracts yielded an oil which rapidly solidified. After pressing on a porous tile the product (0·4 g.) crystallised from light petroleum (b. p. 40—60°), in which it was very easily soluble, in clusters of fine colourless needles, m. p. 80° (Found: C, 55·7; H, 7·2. Calc. for $C_{12}H_{18}O_6$: C, 55·8; H, 7·0%). The m. p. was not depressed on admixture with a specimen of hexamethoxybenzene, m. p. 81°, prepared by the method of Robinson and Vasey (*loc. cit.*).

2 : 4-*Dihydroxy*-3-*methoxyacetophenone*.—2 : 3 : 4-Trimethoxyacetophenone (23 g.) was added to a solution of anhydrous aluminium chloride (40 g.) in absolute ether (200 c.c.), and the mixture refluxed for 12 hours with occasional shaking. Water (200 c.c.) and concentrated hydrochloric acid (50 c.c.) were now added, the mixture heated on the water-bath for ½ hour and cooled, and the sticky product collected, washed, and dissolved in ether. The ethereal solution was shaken with aqueous sodium hydroxide, and the solid obtained by acidification of the aqueous solution collected, and washed successively with water, light petroleum, and a little methyl alcohol. The pale yellow product (3 g.) was crystallised first from water (charcoal), giving an almost colourless hydrate, and then from benzene, forming pale yellow crystals, m. p. 130—131° (Found: C, 59·2; H, 5·4. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%) (see Perkin and Wilson, J., 1903, **83**, 131; Perkin and Storey, J., 1928, 243; these authors prepared the compound by methylation of monopotassium gallacetophenone, or a diacetylgallacetophenone, followed by hydrolysis, and recorded the m. p.'s 132—133° and 134—135°).

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