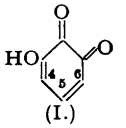
292. *Purpurogallin. Part VI. Mechanism of the Oxidation of Pyrogallol.*

By Alan Critchlow, Robert D. Haworth, and Peter L. Pauson.

As none of the three hexahydroxydiphenyls theoretically derivable from pyrogallol is converted into purpurogallin by oxidation, the mechanism advanced by Willstätter and Heiss in 1923 for the oxidation of pyrogallol must be modified. Their suggestion that 3-hydroxy-1 : 2-benzoquinone is the first product of the oxidation sequence is accepted but, in view of the dual anionoid and cationoid reactivities of hydroxy-*o*-quinones, this primary product would be expected to yield the hypothetical *o*-diphenoquinone (III), without the intermediate formation of a hexhydroxydiphenyl. The subsequent changes may follow the benzilic acid transformation, postulated by Willstätter and Heiss and modified in Part I of this series to accommodate the purpurogallin formula (VI; R = R′ = R″ = R‴ = H), but an alternative and more attractive explanation is discussed in this communication.

The modified mechanism is consistent with the formation of a monoethyl ether (VI; R = R″ = R‴ = H, R′ = Et) of purpurogallin, by oxidation of a mixture of pyrogallol and 3-ethoxycatechol, and the structure (VI; R = R″ = R‴ = H, R′ = Et) was established by methylation and oxidation to 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), which has been synthesised by an independent method.

Pyrogallol is converted with remarkable ease into purpurogallin by a variety of oxidising agents in neutral or weakly acidic solutions, and Willstätter and Heiss (*Annalen*, 1923, **433**, 17) put forward an ingenious explanation of the formation of purpurogallin which they considered to be (V; R = H). On the assumption that pyrogallol was oxidised to 3-hydroxy-1 : 2-benzoquinone (I) which in its tautomeric triketo-form reacted with excess of pyrogallol to give 2 : 3 : 4 : 3′ : 4′ : 5′-hexahydroxydiphenyl (II; R = R′ = H), it was postulated that further oxidation led to the tetrahydroxy-*o*-diphenoquinone (III; R = H). This *o*-quinone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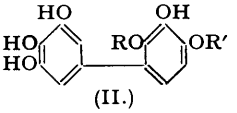
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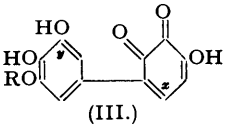
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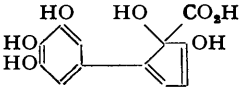
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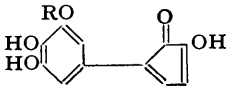
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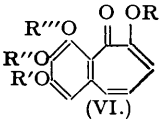

(VI.)

was believed to undergo a benzilic acid type of rearrangement to give the α-hydroxy-acid (IV) from which (V; R = H) was obtained by decarboxylation and dehydrogenation. However,

as a result of recent work, structure (V; R = H) has been disproved and the new formula (VI; R = R′ = R″ = R‴ = H) established for purpurogallin. In Part I (*J.*, 1948, 1045) it was pointed out that a modification of the Willstätter–Heiss hypothesis, in which the benzilic acid rearrangement of (III; R = H) instead of occurring at position *x*, was assumed to involve the more remotely conjugated position *y*, would be consistent with the new formula (VI; R = R′ = R″ = R‴ = H) for purpurogallin.

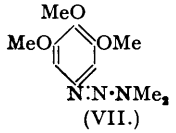
Several objections to the original, or to the modified, Willstätter–Heiss hypothesis may be raised. None of the intermediate products (II; R = R′ = H) (III; R = H), or (IV) was isolated from the reaction or proved to react as required. Of the three isomeric hexahydroxydiphenyls derivable from pyrogallol, the 2 : 3 : 4 : 2′ : 3′ : 4′-isomer was excluded because this compound, prepared by atmospheric oxidation of pyrogallol in barium hydroxide solution (Harries, *Ber.*, 1902, **35**, 2954), could not be oxidised to purpurogallin, and the 3 : 4 : 5 : 3′ : 4′ : 5-isomer (Liebermann, *Annalen*, 1873, **169**, 241) because (*a*) the oxidation of gallic acid to purpurogallin-carboxylic acid was inexplicable on this basis and (*b*) this hexahydroxydiphenyl did not yield purpurogallin on further oxidation. Consequently the 2 : 3 : 4 : 3′ : 4′ : 5′-structure (II; R = R′ = H) was the favoured intermediate diphenyl derivative, but as this compound was unknown Willstätter and Heiss were unable to verify the hypothesis experimentally. Furthermore whilst structure (II; R = R′ = H) would be expected to arise from the reaction between pyrogallol and 3-hydroxy-1 : 2-benzoquinone (I), no explanation was advanced for the preferential oxidation of (II; R = R′ = H) to the *o*-diphenoquinone (III), instead of to an isomeric *p*-diphenoquinone which could play no further part in the reaction sequence leading purpurogallin.

Attempts to condense 3 : 3-dimethyl-1-(3 : 4 : 5-trimethoxyphenyl)triazen (VII) with trimethoxybenzene by the general method of Elks and Hey (*J.*, 1943, 441) were not successful, but it has now been shown that the action of copper powder at 270° on a mixture of 4- and 5-iodotrimethoxybenzene (Erdtmann, *Proc. Roy. Soc.*, 1933, *A*, **143**, 209; Graebe and Suter, *Annalen*, 1905, **340**, 222) yields the three hexamethoxydiphenyls in approximately equal amounts. The isomers were separated by fractional crystallisation; the 2 : 3 : 4 : 2′ : 3′ : 4′- and the 3 : 4 : 5 : 3′ : 4′ : 5′-derivative were obtained from the "head" and "middle" fractions respectively, and the "tail" fraction yielded the new 2 : 3 : 4 : 3′ : 4′ : 5′-hexamethoxydiphenyl, m. p. 89°. Demethylation was effected in all three cases by boiling hydrobromic acid, but attempts to oxidise the two known hexahydroxydiphenyls or the new 2 : 3 : 4 : 3′ : 4′ : 5′-hexahydroxydiphenyl (m. p. >300°; hexa-acetate, m. p. 167°) with potassium iodate, ferricyanide, or nitrite to purpurogallin were unsuccessful. Consequently the Willstätter–Heiss theory or any alternative based on the intermediate formation of a hexahydroxydiphenyl from pyrogallol is untenable.

It will be observed that 3-hydroxy-1 : 2-benzoquinone (I) exhibits cationoid activity at position 5 (and to a less a degree at 4), and anionoid reactivity (possibly in the tautomeric triketo-form) at position 6, and consequently two molecules of this quinone would be expected to react to give the *o*-diphenoquinone (III; R = H) directly, without intermediate production of the hexahydroxydiphenyl. As the *o*-diphenoquinone (III; R = H) is unknown it is impossible to obtain direct experimental proof of its participation in the oxidation sequence, but the intermediate formation of the *o*-diphenoquinone is consistent with other evidence relating to the mechanism of formation of purpurogallin.

Willstätter and Heiss (*loc. cit.*) showed that neither 1 : 2-dihydroxy-3-methoxybenzene nor 3-methoxy-1 : 2-benzoquinone could be oxidised to a dimethyl ether of purpurogallin, but oxidation of either in the presence of pyrogallol gave a monomethyl ether of purpurogallin. The inactivity of 1 : 2-dihydroxy-3-methoxybenzene was associated with its inability to react in a triketo-form and consequently the reaction was assumed to occur between 3-hydroxy-1 : 2-benzoquinone and 1 : 2-dihydroxy-3-methoxybenzene to give either (II; R = H, R′ = Me) or (II; R = Me, R′ = H). It is difficult to appreciate the mechanism by which the latter structure could be converted into a purpurogallin methyl ether, and formula (V; R = Me) which Willstätter and Heiss suggest for the monomethyl ether is clearly impossible on the basis of the intermediate formation of either (II; R = H, R′ = Me) or (II; R = Me, R′ = H). In order to obtain experimental evidence bearing on the structure of the purpurogallin monomethyl ether we proposed to ethylate, oxidise, and locate the methyl ether group by identification of the resultant diethoxymethoxyphthalic acid. Unfortunately satisfactory ethylation of purpurogallin monomethyl ether was not realised, but an alternative solution of the problem was found. 3-Ethoxy-1 : 2-dihydroxybenzene, prepared in 61% yield by the action of alkaline hydrogen peroxide on 3-ethoxy-2-hydroxybenzaldehyde, like the corresponding

3-methoxy-derivative, could not be oxidised to a purpurogallin derivative but, in the presence of excess of pyrogallol, oxidation to purpurogallin 2′-ethyl ether, m. p. 157°, was effected in 48% yield by means of potassium iodate. This structure (VI; R = R″ = R‴ = H, R′ = Et) was established by methylation to 2′-ethoxy-3′ : 4′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one (VI; R = R″ = R‴ = Me; R′ = Et), m. p. 91—92°, which was oxidised by permanganate to 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), giving an anhydride, m. p. 127°, and a *N*-methylimide, m. p. 122°. The acid (VIII) differed from the known 3-ethoxy-4 : 5-dimethoxyphthalic acid (Späth, *Ber.*, 1932, **65**, 1778; Späth and Becke, *ibid.*, 1934, **67**, 2100; Manske and Holmes, *J. Amer. Chem. Soc.*, 1945, **67**, 95; Manske, Ledingham, and Holmes, *Canad. J. Res.*, 1945, **23**, B, 100) and 4-ethoxy-3 : 5-dimethoxyphthalic acid (Manske, Ledingham, and Holmes, *loc. cit.*), but was identified by comparison with a synthetic sample of 5-ethoxy-3 : 4-dimethoxyphthalic acid. The most attractive route to this acid (VIII) seemed to be from 5-ethoxy-6-methoxyphthalide (IX), prepared in an analogous manner to *m*-meconine (Rây and Robinson, *J.*, 1925, **127**, 1618), by nitration, reduction to (X), diazotisation, replacement of the amino-group by hydroxyl, methylation, and oxidation to (VIII). Rây and Robinson (*loc. cit.*)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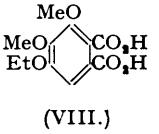
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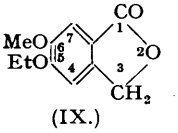
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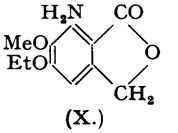
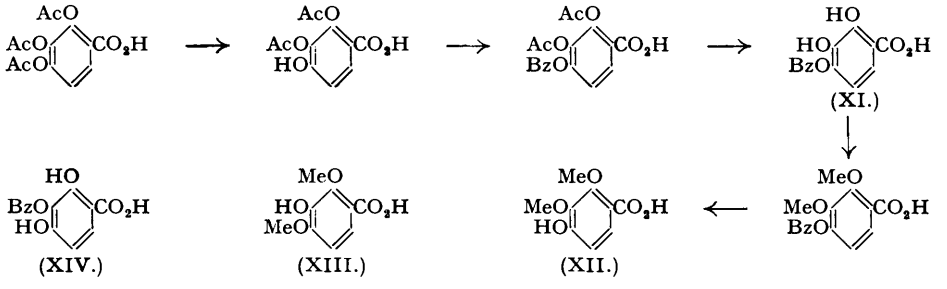
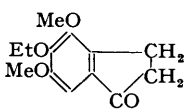

(X.)

showed that *m*-meconine was nitrated in position 7, and 5-ethoxy-6-methoxyphthalide gave, under the same conditions, a mononitro-compound assumed by analogy to be the 7-nitrophthalide. This was reduced to the weakly basic 7-amino-compound (X); this was diazotised in glacial acetic acid but the diazo-group was not replaced by hydroxyl under the conditions employed and the route was abandoned.

Pacsu (*Ber.*, 1923, **56**, 407) described the preparation of 4-hydroxy-2 : 3-dimethoxybenzoic acid, m. p. 154—155°, by the following reactions :


(XI.) (XIV.) (XIII.) (XII.)

Although Pacsu emphasised the absence of migration of the *p*-benzoyl group during this synthesis, the subsequent reaction of the final product, m. p. 150°, obtained by us, indicated that it was 3-hydroxy-2 : 4-dimethoxybenzoic acid (XIII) instead of (XII). It is suggested that, in our hands, the acid hydrolysis of the 2 : 3-diacetoxy-4-benzoyloxybenzoic acid yielded 3-benzoyloxy-2 : 4-dihydroxybenzoic acid, m. p. 227° (decomp.) (XIV), instead of (XI) for which Pacsu gives m. p. 210° (decomp.), and we failed to reacetylate our product to 2 : 3-diacetoxy-4-benzoyloxybenzoic acid. The acid (XIII), which gave a blue colour with 2 : 6-dichloroquinone chloroimide, was ethylated to 3-ethoxy-2 : 4-dimethoxybenzoic acid, m. p. 89°, but attempts to convert this into a phthalide derivative either by formaldehyde and hydrochloric acid or by chloral and sulphuric acid were unsuccessful; Manske, Ledingham, and Holmes (*loc. cit.*) encountered a similar failure with 2 : 3 : 4-trimethoxybenzoic acid. The acid, m. p. 89°,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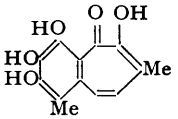
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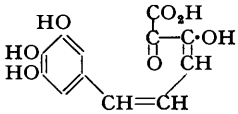
(XVII.)

was therefore reduced with lithium aluminium hydride to 3-ethoxy-2 : 4-dimethoxybenzyl alcohol which was oxidised with chromic acid to 3-ethoxy-2 : 4-dimethoxybenzaldehyde. This

aldehyde was condensed with malonic acid in pyridine in the presence of piperidine to yield 3-ethoxy-2 : 4-dimethoxycinnamic acid, which was reduced and converted into 5-ethoxy-4 : 6-dimethoxyindanone (XV). Permanganate oxidation of (XV) gave 4-ethoxy-3 : 5-dimethoxyphthalic acid which yielded an anhydride, m. p. 116°, and a *N*-methylimide, m. p. 124°, identical with authentic specimens prepared as described by Manske, Ledingham, and Holmes (*loc. cit.*).

The successful synthesis of 5-ethoxy-3 : 4-dimethoxyphthalic acid was based upon the claim of Mauthner (*J. pr. Chem.*, 1938, **150**, 257) to have prepared 2 : 3-dihydroxy-4-methoxybenzaldehyde from 1 : 2-dihydroxy-3-methoxybenzene. In a similar way 4-ethoxy-2 : 3-dihydroxybenzaldehyde is obtained by the action of zinc cyanide and hydrogen chloride on 3-ethoxy-1 : 2-dihydroxybenzene, and the constitution of this *o*-hydroxy-aldehyde was established by its conversion into 7-ethoxy-8-hydroxycoumarin. Methylation of the *o*-hydroxy-aldehyde gave 4-ethoxy-2 : 3-dimethoxybenzaldehyde which was converted *via* 4-ethoxy-2 : 3-dimethoxycinnamic acid, the corresponding phenylpropionic acid, and 6-ethoxy-4 : 5-dimethoxyindanone into 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), which was shown by comparison of the anhydride and *N*-methylimide to be identical with the product obtained from 2′-ethoxy-3′ : 4′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one (VI; R = R″ = R‴ = Me, R′ = Et).

The formation of purpurogallin 2′-ethyl ether (VI; R = R″ = R‴ = Me, R′ = Et) from pyrogallol and 3-ethoxy-1 : 2-dihydroxybenzene is entirely consistent with the mechanism suggested on p. 1319. Oxidation would lead to 3-ethoxy- and 3-hydroxy-1 : 2-benzoquinone, and in view of the reduced anionoid reactivity (or the inability to tautomerise to a triketo-form), the former will function as the cationoid component and favour the production of the ethoxy-*o*-diphenoquinone (III; R = Et); the isomer is unlikely to be found as the ethoxy-group will reduce the cationoid properties at position 4 more than at position 5. Observation on the formation of purpurogallin-carboxylic acid reported in Part VII of this series (see following paper) also confirms the mechanism now proposed. Further support is obtained from some preliminary experiments with 2 : 3 : 4-trihydroxytoluene which yields a dimethylpurpurogallin, probably 4 : 2′ : 3′ : 4′-tetrahydroxy-5 : 1′-dimethylbenzo*cyclo*heptatrien-3-one (XVI), on oxidation with potassium iodate. These and other experiments suggested by the new mechanism will be described in later communications.

At the moment we are unable to bring forward any experimental evidence bearing on the mechanism of the conversion of the *o*-diphenoquinone (III; R = H) into purpurogallin, but theoretical objections to the postulated benzilic acid rearrangement may be mentioned. Although some benzilic acid rearrangements are known to occur under weakly alkaline conditions (for example, see Malkin and Robinson, *J.*, 1925, **127**, 369), purpurogallin is produced in a neutral or faintly acidic medium, and the usual hydroxyl-ion-catalysed mechanism is unlikely to operate under these conditions. Secondly, steric conditions would appear unfavourable for the production of the appropriate transition complex between the quinonoid group and position *y* in the *o*-diphenoquinone (III; R = H). In view of these objections to the benzilic acid mechanism propounded by Willstätter and Heiss (*loc. cit.*), the following alternative explanation of the conversion of (III; R = H) into purpurogallin is more attractive. The *o*-diphenoquinone (III; R = H), in the form of its tautomeric triketonic structure, represents the vinyl analogue of a β-diketone, and consequently acid hydrolysis to (XVII), followed by cyclisation and loss of the elements of formic acid to yield purpurogallin (VI; R = R′ = R″ = R‴ = H), are not unreasonable propositions.

Experimental.

3 : 4 : 5-Trimethoxyaniline, required for the preparation of 5-iodo-1 : 2 : 3-trimethoxybenzene, was obtained by a modification of Graebe and Suter's method (*loc. cit.*) employing sodium hypochlorite instead of hypobromite, which in our hands yielded a brominated product. A solution of sodium hypochlorite was prepared by passing chlorine [from potassium permanganate (12·36 g.) and concentrated hydrochloric acid (78 c.c.)] into an ice-cold solution of sodium hydroxide (48 g.) in water (300 c.c.) and ice (200 g.). 3 : 4 : 5-Trimethoxybenzamide (Harding, *J.*, 1911, **99**, 1593) (39 g.) was added and the mixture shaken for 2 hours. The temperature of the mixture was raised with stirring to 70° during 1 hour and kept at this temperature for a further hour. Sodium hydroxide solution (72 g. in 72 c.c. of water) was then slowly added to the red-brown solution, the temperature was raised to 80°, and after 1 hour the amine which separated was collected and dried *in vacuo* (yield, 20 g.).

3 : 3-*Dimethyl*-1-(3 : 4 : 5-*trimethoxyphenyl*)*triazen* (VII).—3 : 4 : 5-Trimethoxyaniline (0·35 g.) was diazotised by dissolving it in dilute hydrochloric acid (8·5 c.c.), cooling to 0°, and adding a solution of sodium nitrite (0·135 g.) in water (5 c.c.). The resultant solution was added to a cold mixture of 33% aqueous dimethylamine (1·4 c.c.) and 10% aqueous sodium carbonate (13 c.c.). After half an hour at room temperature the *triazen* was collected; it crystallised from light petroleum (b. p. 60—80°) (charcoal) in colourless stout needles, m. p. 97—98° (Found: N, 17·5. $C_{11}H_{17}O_3N_3$ requires N, 17·6%).

2 : 3 : 4 : 3′ : 4′ : 5′-*Hexamethoxydiphenyl.*—Freshly precipitated copper powder (14 g.) was added to a mixture of 4- and 5-iodo-1 : 2 : 3-trimethoxybenzene (7 g. of each) heated at 250°, and the temperature slowly raised to 270°. After 15 minutes the molten mass was cooled, the sticky product was extracted with ethyl alcohol and filtered off, and the filtrate concentrated to 10 c.c. and cooled. The solid (A) which separated was collected and washed with alcohol, the filtrate and washings were concentrated to 4 c.c., and the process was repeated. Alcohol was removed completely from the combined concentrate, leaving a brown gum (2·3 g.) which was distilled under reduced pressure. 2 : 3 : 4 : 3′ : 4′ : 5′-Hexamethoxydiphenyl was obtained as a yellow oil (b. p. 215—220°/0·05 mm.) which crystallised from alcohol in colourless irregular prisms (1·7 g.), m. p. 89° (Found : C, 64·9; H, 6·5. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%). The solid material (A) which separated from the crude product was resolved by fractional crystallisation from ethyl alcohol into 2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxydiphenyl (1·5 g.), m. p. 122°, and 3 : 4 : 5 : 3′ : 4′ : 5′-hexamethoxydiphenyl (1·5 g.), m. p. 128°, the former being the less soluble.

2 : 3 : 4 : 3′ : 4′ : 5′-*Hexahydroxydiphenyl* (II; R = R′ = H).—2 : 3 : 4 : 3′ : 4′ : 5′-Hexamethoxydiphenyl (1·4 g.) was heated under reflux with 48% hydrobromic acid (25 c.c.) for 30 minutes. Concentration to half bulk and cooling yielded 2 : 3 : 4 : 3′ : 4′ : 5′-*hexahydroxydiphenyl* (0·45 g.) which crystallised from water containing a little sulphur dioxide in white needles, m. p. >300° (Found : C, 57·4; H, 4·2. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). Warming with excess of acetic anhydride and fused sodium acetate for 15 minutes, followed by dilution with water, gave 2 : 3 : 4 : 3′ : 4′ : 5′-*hexa-acetoxydiphenyl* which crystallised from alcohol in irregular prisms, m. p. 167° (Found : C, 57·2; H, 4·6; CH_3·CO, 51·4. $C_{24}H_{22}O_{12}$ requires C, 57·4; H, 4·4; CH_3·CO, 50·8%).

Purpurogallin 2′-Methyl Ether (VI; R = R″ = R‴ = H; R′ = Me) was prepared from 1 : 2-dihydroxy-3-methoxybenzene and pyrogallol by Willstätter and Heiss's method (*loc. cit.*) or preferably by the action of potassium iodate on the mixture. After sublimation of the crude product at 200°/0·05 mm., crystallisation from chloroform yielded deep red needles, m. p. 193° (Found : C, 61·8; H, 4·2. Calc. for $C_{12}H_{10}O_5$: C, 61·6; H, 4·3%). Willstätter and Heiss give m. p. 182—183°.

3-*Ethoxy*-1 : 2-*dihydroxybenzene.*—3-Ethoxy-2-hydroxybenzaldehyde (8·3 g.) was stirred in an atmosphere of nitrogen with N-sodium hydroxide (50 c.c.) at 40° until dissolution was complete. Hydrogen peroxide (35·5 c.c. of 20-vol.) was added in 5-c.c. portions; the addition of the last few drops caused precipitation of a fawn-coloured solid which was collected, dried, and crystallised from light petroleum (b. p. 60—80°). The product (4·7 g.; 61%) had m. p. 91—93° and showed no depression when mixed with a sample of 3-ethoxy-1 : 2-dihydroxybenzene prepared as described by Haworth and Lamberton (*J.*, 1946, 1003).

Purpurogallin 2′-Ethyl Ether (VI; R = R″ = R‴ = H, R′ = Et).—Pyrogallol (0·8 g.) and potassium iodate solution (24 c.c. of 5·77%) were added successively to a solution of 3-ethoxy-1 : 2-dihydroxybenzene (4·0 g.) in water (200 c.c.). After 15 minutes the brown precipitate was collected and further pyrogallol (0·6 g.) and potassium iodate solution (18 c.c. of 5·77%) were added to the filtrate. The process was repeated four times, pyrogallol (0·5, 0·4, 0·3, 0·3 g.) and potassium iodate solution (15, 12, 9, and 9 c.c. of 5·77%) being added alternately. The total yield of dry brown solid was 5·9 g., having m. p. 120—130°. Sublimation at 170—180°/0·05 mm. yielded a bright red solid (3·1 g.) which crystallised from damp acetone with water of crystallisation and had m. p. 157° (Found : C, 58·8; H, 5·3. $C_{13}H_{12}O_5,H_2O$ requires C, 58·8; H, 5·8%).

Purpurogallin 2′-Ethyl 3′ : 4-Dimethyl Ether (VI; R‴ = H, R′ = Et, R = R″ = Me).—Purpurogallin 2′-ethyl ether (3·0 g.) was dissolved in pure dioxan (20 c.c.), and a solution of diazomethane (1·3 g.) in ether (85 c.c.) added. After 12 hours the yellow *product* which separated was collected and crystallised from alcohol; it formed fibrous yellow needles (1·9 g.), m. p. 161° (Found : C, 65·5; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%), which dissolved readily in sodium hydroxide solution and gave an olive-brown ferric colour. Concentration of the mother-liquors yielded *purpurogallin 2′-ethyl 3′(or 4)-methyl ether* (0·5 g.) which crystallised from alcohol in deep yellow needles, m. p. 128° (Found : C, 64·2; H, 5·2. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%), dissolved in sodium hydroxide solution, and gave a wine-red ferric test.

Purpurogallin 2′-Ethyl 3′ : 4′ : 4-Trimethyl Ether (VI; R′ = Et, R = R″ = R‴ = Me).—Methyl sulphate (3·6 c.c.) was added to a finely powdered suspension of purpurogallin 2′-ethyl 3′ : 4-dimethyl ether (1·26 g.) in 65% potassium hydroxide solution (8 c.c.), and the mixture heated gently with constant shaking until a vigorous reaction set in which was allowed to become complete without further heating. After cooling and dilution with water, the brown oil which separated and quickly solidified was collected, dried, and crystallised from *cyclo*hexane; colourless plates (1·1 g.), m. p. 91—92° (Found : C, 65·9; H, 6·0. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%), were obtained.

Oxidation of Purpurogallin 2′-Ethyl 3′ : 4′ : 4-Trimethyl Ether (VI; R′ = Et, R = R″ = R‴ = Me).—Purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether (0·8 g.) was dissolved in pure acetone (20 c.c.), and 2% aqueous potassium permanganate (120 c.c.) added portionwise. After 3 hours' shaking the mixture was filtered, and the filtrate made strongly alkaline with sodium hydroxide (10 g.) and concentrated to 15 c.c. Cooling and acidification with concentrated hydrochloric acid gave a precipitate of sodium chloride, which was collected, and the filtrate was extracted six times with ether. The dried ethereal extract was concentrated and the brown oily residue on distillation at 180°/0·05 mm. yielded a yellow oil (0·2 g.) which after crystallisation first from chloroform–ether and then from ether gave 5-*ethoxy*-3 : 4-*dimethoxyphthalic anhydride* (0·08 g.) as white needles, m. p. 127° (Found : C, 57·6; H, 4·7. $C_{12}H_{12}O_6$ requires C, 57·2; H, 4·8%) undepressed on mixture with a synthetic specimen (p. 1325) This anhydride (0·03 g.) on treatment with excess of 30% methylamine solution, evaporation to dryness, heating at 180°/12 mm. and sublimation at 160°/0·05 mm. gave 5-*ethoxy*-3 : 4-*dimethoxy*-N-*methylphthalimide* (0·025 g.) which crystallised from aqueous methanol in long shining needles, m. p. 122° (Found : C, 58·9; H, 5·8; N, 5·3. $C_{13}H_{15}O_5N$ requires C, 58·9; H, 5·7; N, 5·3%) undepressed on admixture with a synthetic specimen.

4-Ethoxy-3-methoxybenzoic Acid.—A stream of carbon dioxide was passed through a stirred suspension of 4-ethoxy-3-methoxybenzaldehyde (40 g.) [prepared from vanillin as described by Tiemann (*Ber.*, 1875, **8**, 1128)] in water (300 c.c.) at 70°. Potassium permanganate (25·1 g.) in water (500 c.c.) was slowly added and the stirring continued for half an hour after the addition was complete. The reaction mixture was filtered and rendered alkaline and the neutral impurities were removed in ether. Acidification of the alkaline layer precipitated 4-ethoxy-3-methoxybenzoic acid (28 g.) which crystallsed from alcohol in colourless plates, m. p. 192°. Tiemann (*loc. cit.*) gives m. p. 193—194°

5-Ethoxy-6-methoxyphthalide (IX).—Concentrated hydrochloric acid (40 c.c.) and 40% formaldehyde solution (12 c.c.) were added to a solution of 4-ethoxy-3-methoxybenzoic acid (10·84 g.) in acetic acid (85 c.c.) and heated on the water-bath for 12 hours. After addition of charcoal, the mixture was filtered, concentrated to 40 c.c., made alkaline with potassium hydroxide, and filtered again. The alkaline solution was acidified with concentrated hydrochloric acid, boiled for 10 minutes, and cooled and the mixture of acid and lactone collected and washed with sodium hydrogen carbonate solution. The residual *lactone* (5 g.), after being dried and sublimed at 170°/0·1 mm., crystallised from alcohol in small colourless prisms, m. p. 187·5—188·5° (Found : C, 63·7; H, 6·0. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

5-Ethoxy-6-methoxy-7-nitrophthalide.—Finely powdered 5-ethoxy-6-methoxyphthalide (IX) (7·55 g.) was added in small portions, with shaking, during 20 minutes to concentrated nitric acid (16 c.c.) cooled to 5°. The mixture was kept at 3—5° for a further 2 hours and then allowed to reach room temperature during 1 hour. Water (100 c.c.) was added and the precipitate was collected, dried, and extracted with boiling alcohol (25 c.c.). The residue crystallised from glacial acetic acid in small colourless needles (5·6 g.), m. p. 169° (Found : C, 52·15; H, 4·3; N, 5·0. $C_{11}H_{11}O_6N$ requires C, 52·15; H, 4·3; N, 5·5%).

7-Amino-5-ethoxy-6-methoxyphthalide (X).—To a hot solution of crystalline stannous chloride (3·07 g.) in concentrated hydrochloric acid (5·7 c.c.) was added portionwise 5-ethoxy-6-methoxy-7-nitrophthalide (1·02 g.). After 10 minutes' heating on a water-bath a further addition of stannous chloride (0·3 g.) and concentrated hydrochloric acid (1 c.c.) effected complete dissolution of the nitro-compound. The solution was heated for half an hour, then added to cold water (25 c.c.), and the precipitated solid was collected, washed with sodium hydrogen carbonate solution, and dried. Crystallisation from absolute alcohol gave the amine (X) as long hair-like colourless needles (0·71 g.), m. p. 151° (Found : C, 59·4; H, 5·6; N, 6·6. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8; N, 6·3%).

2 : 3 : 4-Trihydroxybenzoic Acid.—The method of Baker and Smith (*J.*, 1931, 2544) gave poor yields of inferior material in our hands, but the following modification raised the yield to 70—90% of pure acid. A paste of finely powdered pyrogallol (100 g.), potassium hydrogen carbonate (200 g.), and water (50 c.c.) was heated under a stream of carbon dioxide in an oil-bath at 90°. The bath-temperature was raised to 135° during 2 hours, and kept thereat until water was no longer evolved or until the violet-coloured mixture began to char at the edges. After cooling, the product was dissolved in water (1 l.) and acidified with hydrochloric acid, and the 2 : 3 : 4-trihydroxybenzoic acid (90—110 g.), m. p. 210° (decomp.), was collected. Schiff (*Annalen*, 1888, **245**, 37) gives m. p. 206—208°.

3-Benzoyloxy-2 : 4-dihydroxybenzoic Acid (XIV).—2 : 3-Diacetoxy-4-benzoyloxybenzoic acid (30 g.), prepared by Pacsu's method (*loc. cit.*), was dissolved in acetic acid (75 c.c.) and heated on the water-bath for 3 hours with 5N-hydrochloric acid (75 c.c.). Cooling and filtration yielded a fawn-coloured solid (8 g.), m. p. 227° (decomp.), and a further crop (6 g.) was obtained by cooling the mother-liquors at 0° for 12 hours. Crystallisation from methanol gave *3-benzoyloxy-2 : 4-dihydroxybenzoic acid* as white plates, m. p. 227° (decomp.) (Found : C, 61·3; H, 3·8. $C_{14}H_{10}O_6$ requires C, 61·4; H, 3·7%).

3-Hydroxy-2 : 4-dimethoxybenzoic Acid (XIII).—3-Benzoyloxy-2 : 4-dihydroxybenzoic acid (12·8 g.) in acetone (50 c.c.) was treated with diazomethane (6·45 g.) in ether (300 c.c.) for 48 hours at room temperature. Removal of excess of diazomethane and solvents yielded crude methyl 3-benzoyloxy-2 : 4-dimethoxybenzoate (16·3 g.). The ester was dissolved in methanol (140 c.c.) and, after displacement of air in the reaction vessel with hydrogen, 5N-sodium hydroxide (56 c.c.) was added and the mixture kept at 45° for 6 hours. It was then cooled, acidified with hydrochloric acid, and evaporated to dryness; extraction with acetone gave a brown oil from which benzoic acid was removed by exhaustive extraction with light petroleum (b. p. 40—60°). The residue on crystallisation from hot water gave *3-hydroxy-2 : 4-dimethoxybenzoic acid* as white rhombs, m. p. 150° with previous softening (Found : C, 54·2; H, 4·8. $C_9H_{10}O_5$ requires C, 54·6; H, 5·0%).

3-Ethoxy-2 : 4-dimethoxybenzoic Acid.—3-Hydroxy-2 : 4-dimethoxybenzoic acid (3·45 g.) in 10% sodium hydroxide solution (15·3 c.c.) was refluxed for 30 minutes during the dropwise addition of ethyl sulphate (7·65 c.c.) and 10% sodium hydroxide solution (25·3 c.c.). Further quantities of ethyl sulphate (5·0 c.c.) and 20% sodium hydroxide solution (7·65 c.c.) were added after 1 hour and, after boiling for another 20 minutes, the mixture was concentrated to half volume, treated with charcoal, and filtered. The cooled filtrate on acidification with hydrochloric acid yielded *3-ethoxy-2 : 4-dimethoxybenzoic acid* (3·4 g.) which crystallised from hot water, containing a little alcohol, in long colourless needles, m. p. 89—90° (Found : C, 58·5; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

3-Ethoxy-2 : 4-dimethoxybenzyl Alcohol.—To a cooled solution of lithium aluminium hydride (1·5 g.) in ether (50 c.c.), 3-ethoxy-2 : 4-dimethoxybenzoic acid (1·3 g.) in ether (10 c.c.) was added dropwise, and after 3 hours at room temperature the mixture was refluxed for half an hour. After decomposition with 2N-sulphuric acid, the ethereal layer was washed with sodium hydrogen carbonate solution and dried, and the solvent removed. The residual *3-ethoxy-2 : 4-dimethoxybenzyl alcohol* (1·0 g.) had b. p. 120°/0·05 mm. (Found : C, 62·5; H, 7·4. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·5%). The *3 : 5-dinitrobenzoate* crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 116° (Found : C, 53·4; H, 4·4; N, 7·2. $C_{18}H_{18}O_9N_2$ requires C, 53·2; H, 4·4; N, 6·9%).

3-*Ethoxy*-2 : 4-*dimethoxybenzaldehyde*.—3-Ethoxy-2 : 4-dimethoxybenzyl alcohol (1·0 g.) in glacial acetic acid (13·2 c.c.) and water (1·05 c.c.) was oxidised with chromium trioxide (0·33 g.) in glacial acetic acid (8 c.c.) and water (1·05 c.c.) at 15°. After 1 hour the mixture was poured on ice (20 g.), neutralised with concentrated aqueous ammonia, and extracted with ether; the extract, after being washed with sodium hydrogen carbonate solution, dried, and freed from solvent, yielded a brown oily *aldehyde*. Distillation gave a yellow oil (0·67 g.), b. p. 140°/0·05 mm. (Found : C, 63·1; H, 6·3. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–ethyl alcohol in deep scarlet rhombs, m. p. 170° (Found : C, 52·1; H, 4·4; N, 14·4. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

3-*Ethoxy*-2 : 4-*dimethoxycinnamic Acid*.—3-Ethoxy-2 : 4-dimethoxybenzaldehyde (0·58 g.) was dissolved in pyridine (1·3 c.c.) and piperidine (0·05 c.c.). Malonic acid (0·6 g.) was added and the mixture was heated under reflux for 2 hours on the water-bath, the reaction being completed by boiling the solution for 2 minutes. The mixture was poured on ice (20 g.) and 2N-hydrochloric acid (20 c.c.); the precipitate was collected and crystallised from 10% alcohol; 3-*ethoxy*-2 : 4-*dimethoxycinnamic acid* (0·40 g.) was obtained in clusters of long needles, m. p. 159° (Found : C, 61·8; H, 6·0. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%).

β-(3-*Ethoxy*-2 : 4-*dimethoxyphenyl*)*propionic Acid*.—3-Ethoxy-2 : 4-dimethoxycinnamic acid (0·35 g.), dissolved in pure methanol (6 c.c.), was shaken under hydrogen with 10% palladium–charcoal (0·035 g.). Hydrogen uptake was complete in 1 hour, and after removal of catalyst and solvent the residual *acid* crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 51° (Found : C, 61·8; H, 6·9. $C_{13}H_{18}O_5$ requires C, 61·6; H, 7·1%).

4-*Ethoxy*-3 : 5-*dimethoxyphthalic Anhydride*.—β-(3-Ethoxy-2 : 4-dimethoxyphenyl)propionic acid (0·29 g.) in benzene (6 c.c.) was heated on the water-bath for 2 hours with phosphoric oxide (1·2 g.). The purple complex was decomposed with ice (40 g.) and after 12 hours the mixture was extracted with ether, the ethereal extract was washed successively with N-sodium hydroxide solution and water and dried, and the solvent removed. 5-Ethoxy-4 : 6-dimethoxyindanone (XV) (0·19 g.) was obtained as a yellow oil which was oxidised without further purification. 2% Potassium permanganate solution (40 c.c.) was added gradually to a warm suspension of the indanone (0·19 g.) in water (10 c.c.). When oxidation was complete, manganese dioxide was removed, the filtrate rendered alkaline with sodium hydroxide (4 g.), and neutral material removed with ether. The aqueous layer was concentrated to 10 c.c., cooled, acidified with concentrated hydrochloric acid, and extracted 6 times with ether; the dried extract yielded a brown oil (0·14 g.) which distilled at 200°/0·05 mm. and crystallised from chloroform–ether in needles, m. p. 116°, undepressed on admixture with an authentic specimen of 4-ethoxy-3 : 5-dimethoxyphthalic anhydride, prepared by the method of Manske, Ledingham, and Holmes (*loc. cit.*). The *N*-methylimide, prepared in the usual way, had m. p. 124°, undepressed on admixture with an authentic sample.

4-*Ethoxy*-2 : 3-*dihydroxybenzaldehyde*.—This was prepared by a slight modification of Mauthner's method (*loc. cit.*). 3-Ethoxy-1 : 2-dihydroxybenzene (15 g.) in ether (150 c.c.) was stirred with powdered zinc cyanide (36·3 g.) during passage of a steady stream of hydrogen chloride. The ether was decanted from the pink paste of aldimine hydrochloride which was shaken with ice-cold water (150 c.c.), and the resultant solution was extracted immediately with several 50-c.c. portions of ether. These extracts yielded unchanged 3-ethoxy-1 : 2-dihydroxybenzene (10·5 g.). The aqueous solution was boiled for 2 minutes and the *aldehyde* isolated with ether as a dark brown oil (4 g.), which solidified on addition of a little water and crystallised from hot water (150 c.c.) (charcoal) in pale yellow needles, m. p. 98° (Found : C, 58·5; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The *anil* crystallised from ethanol in groups of irregular scarlet needles, m. p. 142° (Found : C, 70·0; H, 6·0; N, 5·6. $C_{15}H_{15}O_3N$ requires C, 70·1; H, 5·8; N, 5·45%).

7-*Ethoxy*-8-*hydroxycoumarin*.—4-Ethoxy-2 : 3-dihydroxybenzaldehyde (0·42 g.), fused sodium acetate (0·8 g.), and acetic anhydride (2·5 c.c.) were heated at 120° for 2 hours and then at 180° for 6 hours. The cooled product was diluted with water (10 c.c.) and extracted with ether; the dried extract on evaporation yielded a brown oil (0·58 g.) which was refluxed for 10 minutes with methanol (12 c.c.) and concentrated hydrochloric acid (6 c.c.). The solution was diluted with water and the product, isolated with ether, was sublimed at 160°/0·05 mm. 7-Ethoxy-8-hydroxycoumarin (0·1 g.) crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 144°. Wessely and Sturm (*Ber.*, 1929, **62**, 115) give m. p. 145°.

4-*Ethoxy*-2 : 3-*dimethoxybenzaldehyde*.—A solution of 4-ethoxy-2 : 3-dihydroxybenzaldehyde (2 g.) in acetone (30 c.c.) was refluxed with potassium carbonate (8 g.) and methyl iodide (10 c.c.) for 8 hours; after 2 hours more methyl iodide (5 c.c.) was added and after 4 hours potassium carbonate (8 g.) and methyl iodide (5 c.c.) were added. The mixture was filtered and the filtrate concentrated and shaken with ether (50 c.c.) and water (50 c.c.). The ethereal extract was washed with N-sodium hydroxide, dried and concentrated; 4-*ethoxy*-2 : 3-*dimethoxybenzaldehyde* was obtained as a yellow oil (2·1 g.), b. p. 140°/0·5 mm. (Found : C, 62·7; H, 6·5. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from a mixture of ethyl acetate and methyl alcohol in irregular orange plates with a golden lustre, m. p. 158·5° (Found : C, 52·5; H, 4·7; N, 14·4. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

4-*Ethoxy*-2 : 3-*dimethoxybenzoic Acid*.—A solution of 4-ethoxy-2 : 3-dimethoxybenzaldehyde (0·06 g.) in acetone (2 c.c.) was oxidised with potassium permanganate (1·5 c.c. of 5% solution) on the water-bath for 1 hour. The mixture was filtered, the filtrate rendered alkaline, concentrated, and acidified with hydrochloric acid, and the acid collected. Crystallisation from hot water gave 4-*ethoxy*-2 : 3-*dimethoxybenzoic acid* in colourless prisms, m. p. 89° (Found : C, 58·5; H, 6·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). The m. p. was depressed 20° on admixture with 3-ethoxy-2 : 4-dimethoxybenzoic acid (m. p. 89°) or with 2-ethoxy-3 : 4-dimethoxybenzoic acid (m. p. 79°).

4-Ethoxy-2 : 3-dimethoxycinnamic acid, prepared from 4-ethoxy-2 : 3-dimethoxybenzaldehyde (2 g.), malonic acid (2 g.), pyridine (4 c.c.), and piperidine (3 drops) in the manner described for 3-ethoxy-2 : 4-dimethoxycinnamic acid, crystallised from 10% alcohol in fibrous white needles, m. p. 183° (Found : C, 62·0; H, 6·8. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

β-(4-Ethoxy-2 : 3-dimethoxyphenyl)propionic acid, prepared by catalytic reduction of 4-ethoxy-2 : 3-dimethoxycinnamic acid (1·9 g.) in methanol (40 c.c.) in presence of 10% palladium–charcoal (0·2 g.) in the manner described previously, crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 68° (Found : C, 61·3; H, 7·0. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

5-Ethoxy-3 : 4-dimethoxyphthalic Anhydride.—β-(4-Ethoxy-2 : 3-dimethoxyphenyl)propionic acid (1·9 g.), dissolved in benzene (40 c.c.), was heated with phosphoric oxide (8 g.) for 2 hours and the product isolated as described above. 6-Ethoxy-4 : 5-dimethoxyindanone (1·1 g.), isolated as described previously for an analogous case, was an oil, which was oxidised with 2% potassium permanganate solution (400 c.c.). The mixture was filtered, and the filtrate rendered alkaline, concentrated, acidified, and extracted with ether. The dried concentrated extract yielded on distillation 5-ethoxy-3 : 4-dimethoxyphthalic anhydride (0·2 g.), b. p. 200°/0·05 mm., which crystallised first from chloroform–hexane, then from ether, in pale yellow needles, m. p. 127°, undepressed on admixture with the anhydride obtained from purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether. The *N*-methylimide, m. p. 122°, was not depressed on admixture with the *N*-methylimide prepared from purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether.

Oxidation of 2 : 3 : 4-Trihydroxytoluene.—2 : 3 : 4-Trihydroxytoluene (0·74 g.), prepared by the method of Majima and Okazaki (*Ber.*, 1916, **49**, 1482), was dissolved in ice-cold water (15 c.c.), and ice-cold potassium iodate solution (10 c.c. of 5·77%) was added dropwise. After 15 minutes at room temperature, the orange *2 : 3 : 4 : 4′-tetrahydroxy-1′ : 5-dimethylbenzocycloheptatrien-3-one* (XVI) (0·42 g.) was collected, dried *in vacuo*, and sublimed at 170°/0·1 mm. as a yellow micro-crystalline powder, m. p. 185° (Found : C, 62·8; H, 4·9. $C_{13}H_{12}O_5$ requires C, 63·0; H, 4·8%).

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