30. *The Oxidation Products of Phenols. Part I. The Structure of Purpurogallin.*

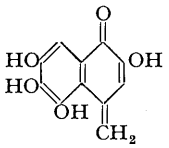
By J. A. Barltrop and J. S. Nicholson.

The evidence bearing on the structure of purpurogallin, an oxidation product of pyrogallol, is summarised, and a new structure (III), containing a seven-membered tropolone ring, is advanced. The isolation of trimethoxyphthalic anhydride as a degradation product of tetramethyl purpurogallin completely refutes Willstätter's structure (II). The relation between (III) and colchicine is emphasised.

The fact that a number of complex naturally occurring substances can be theoretically derived from relatively simple phenolic residues by oxidative coupling, *i.e.*, by a union of the phenolic

nuclei involving loss of hydrogen atoms, has led us to institute a series of researches into the oxidation products of phenols. Previous work in this field has been carried out mainly by Dianin (*Ber.*, 1873, **6**, 1252), Tiemann (*Ber.*, 1885, **18**, 3493), Cousin and Herissey (*Bull. Soc. chim.*, 1908, **3**, 1066, 1070), Pummerer *et al.* (*Ber.*, 1914, **47**, 1472, 2957; 1919, **52**, 1403, 1414; 1922, **55**, 3116; 1925, **58**, 1808; 1926, **59**, 2161), Erdtmann (*Svensk Kem. Tids.*, 1934, **46**, 226), Perkin *et al.* (*J.*, 1905, **87**, 1412; 1903, **83**, 192; 1908, **93**, 1186), and Haworth and Cartwright (*J.*, 1944, 535).

This paper is concerned with the structure of purpurogallin, a substance $C_{11}H_8O_5$, obtained from pyrogallol on oxidation, electrolytically, or with a variety of reagents, *e.g.*, sodium iodate, nitrous acid, silver ions, potassium permanganate and benzoquinone. Glucosides of purpurogallin occur naturally as the colouring matters of many galls (Nierenstein and Swanton, *Biochem. J.*, 1944, **38**, 373).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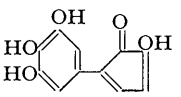
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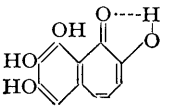
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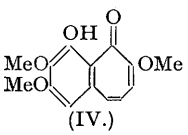
Two structures have hitherto been advanced, a methylene-quinone structure (I) due to Dean and Nierenstein (*Ber.*, 1913, **46**, 3868), and a trihydroxyphenyl*cyclo*pentadienolone (II) due to Willstätter and Heiss (*Annalen*, 1923, **433**, 17). It is the purpose of this communication to advance a third structure (III) containing a seven-membered ring.

The properties of purpurogallin are recorded in papers by Perkin *et al.* (*locc. cit.*; *J.*, 1904, **85**, 243; 1906, **89**, 802; 1912, **101**, 803), Nierenstein and his co-workers (*Ber.*, 1913, **46**, 3151, 3868), and Herzig (*Annalen*, 1923, **432**, 99). It is a brick-red solid very sparingly soluble in most solvents, which on shaking with air in alkaline solution gives an intensely blue substance. It contains four hydroxyl groups, giving a tetra-acetyl derivative. With diazomethane an orange-yellow trimethyl purpurogallin is obtained, which on treatment with hot methyl sulphate and alkali affords a colourless tetramethyl purpurogallin. On the basis of structure (III) for purpurogallin the trimethyl ether would be (IV).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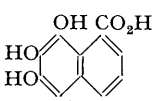
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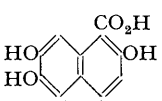
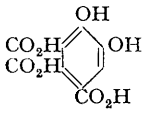

(VI.)

Other facts having a bearing on the structure are: (i) Bromine is not added to purpurogallin, but is substituted in it to form a dibromo-derivative. (ii) Purpurogallin is stable to Clemmensen reduction (Herzig, *loc. cit.*): this is very difficult to explain on either structure (I) or (II). (iii) Purpurogallin is stable to alcoholic hydrogen chloride in a sealed tube at 150°. One would expect the αβ-unsaturated ketone linkage of (II) to add hydrogen chloride under these conditions. Also methylene-quinones are extremely reactive systems (see Lindemann, *Annalen*, 1923, **431**, 270; Bistrzycki and Herbst, *Ber.*, 1903, **36**, 2333), with very strongly developed tendencies to add reagents of the type HX to afford the more stable aromatic *p*-hydroxybenzyl derivatives. The stability of purpurogallin to alcoholic hydrogen chloride is not explicable on the formulation (I). In addition, it possesses none of the properties of methylene-quinones, such as very facile hydration. (iv) Purpurogallin shows no ketonic properties. Nierenstein and Spiers's claim (*Ber.*, 1930, **46**, 3151) that tetra-acetyl purpurogallin forms a phenylhydrazone is incorrect (Herzig, *loc. cit.*), and we were unable to form a 2 : 4-dinitrophenylhydrazone from the parent substance. (v) Purpurogallin, on being heated to 170° with concentrated potassium hydroxide solution, is transformed into an isomer, purpurogallone, $C_{11}H_8O_5$, and *iso*purpurogallone, $C_{22}H_{14}O_{10}$, an oxidation product of purpurogallone. Purpurogallone has been suggested by Perkin (*J.*, 1912, **101**, 803) to be (V)—the alternative structure (VI) proposed by him is very improbable.

It should be emphasised that very little reliance can be placed in the degradations of purpurogallin reported by Dean and Nierenstein (*loc. cit.*). Although 34 years have elapsed since these authors claimed the isolation of trimethoxyphthalonic acid from trimethyl purpurogallin by hydrogen peroxide oxidation, and promised further details of its properties, no

further communication has appeared. Further, their degradation of purpurogallin by nitric acid to dihydroxyhemimellitic acid (VII) could not be repeated either by Herzig or by us. Indeed, as Herzig points out, the properties of the substance are so remarkable and so similar to those of oxalic acid, which was the only substance isolated by us, that there is considerable doubt whether they ever obtained it. The experimental support for structure (I) is thus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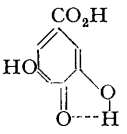
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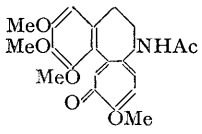
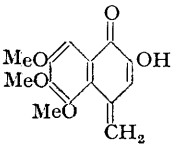

(IX.)

extremely scanty, if not non-existent, and the structure (II) not only does not adequately account for all the properties of purpurogallin, but is quite impossible in view of the oxidation of tetramethyl purpurogallin to trimethoxyphthalic anhydride described below.

It is our belief that the structure (III) is more consistent with the properties of the substance. Although it has not been definitely proved, there is evidence that *cyclo*heptatrienolone or tropolone rings occur in other natural products, *e.g.*, stipitatic acid (VIII) (Dewar, *Nature*, **1945**, **155**, 50) and colchicine (IX) (*idem*, *ibid.*, p. 141). There is a close parallel between stipitatic acid and purpurogallin. Neither shows ketonic properties, both are substituted by bromine, and both on heating with concentrated alkali are rearranged to an isomeric substance containing an extra carboxyl group.

If Dewar's suggestion (*loc. cit.*) is correct, then the tropolone ring is a new type of resonating *aromatic* system. Further, if purpurogallin contains a tropolone ring, then the facts (i)—(iv) find a ready explanation. As a resonance-stabilised aromatic molecule, the double bond and ketonic function would be masked, and thus substitutive attack by bromine, resistance to reduction by the Clemmensen method, stability to alcoholic hydrogen chloride, and lack of ketonic properties would be expected. The purpurogallone rearrangement would arise from the latent α-diketone grouping, under the drastic conditions involved, undergoing a benzilic acid rearrangement followed by dehydration; an α-naphthoic acid being thereby produced.

Having been led by the above theoretical considerations to the structure (III) for purpurogallin, we endeavoured to establish it by degradative experiments. Nierenstein and Swanton (*loc. cit.*, p. 374) baldly state that trimethyl purpurogallin is the 2 : 3 : 4-trimethyl derivative (X), although as far as is known no evidence has ever been published showing that the three methoxyl groups are all in the benzene ring. If they were, then trimethyl purpurogallin on hydrogenation should give a hexahydro-compound of structure (XI), the alicyclic ring of which could be degraded to establish its size and nature.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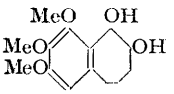
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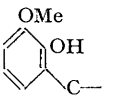

(XII.)

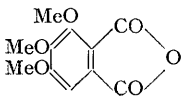
For this purpose, purpurogallin was prepared by oxidising pyrogallol with sodium nitrite and acetic acid, and by the much more convenient method of Evans and Dehn (*J. Amer. Chem. Soc.*, 1930, **52**, 3647) involving sodium iodate. This was methylated with sodium hydroxide and methyl sulphate. Perkin and Stevens (*J.*, 1903, **83**, 192) by using this procedure obtained trimethyl purpurogallin in only 10% yield, but in our hands this method has been improved to give 66% yields.

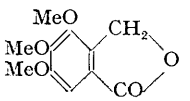
Hydrogenation of a suspension of the trimethyl ether in ethanol over Raney nickel or platinum oxide gave a *trimethyl hexahydropurpurogallin*, m. p. 147—148°. On one occasion, when only a small amount of platinum oxide catalyst was used, the hydrogenation proceeded very slowly, and only a yellow *trimethyl tetrahydropurpurogallin* could be isolated. The colour could not be removed by any crystallisation procedure, but it was subsequently found that if the compound was extensively hydrogenated over platinum oxide, a colourless specimen could be recovered. Attempts to relate the tetrahydro-derivative to the above hexahydro-trimethyl ether by hydrogenation were unsuccessful—even when 4 atoms of hydrogen had been absorbed, much unchanged tetrahydro-compound was recovered, and no other compound was isolable

from the reaction mixture, except on one occasion when a very small quantity of colourless solid, m. p. 148°, was obtained, but this depressed the m. p. of the hexahydro-compound. Both trimethyl tetra- and hexa-hydropurpurogallin are soluble in aqueous alkali and couple with *p*-nitrobenzenediazonium chloride. They are thus phenolic and this completely excludes (XI) for the hexa-hydro-compound. Confirmation of this was obtained by periodate oxidation, from which only a negligible amount of a non-homogeneous ketonic material was obtained. Further, sodium hypobromite, which has been used in the sterol series (Petrow and Starling, *J.*, 1946, 749) for conversion of α-glycols into carboxylic acids, gave no useful result—no positive evidence for the formation of a carboxylic acid could be obtained.

These results having cast some doubt on the hypothesis that the three methoxyl groups of trimethyl purpurogallin are all in the benzene ring, we felt that (IV) was a more plausible structure. Bearing in mind the marked steric hindrance associated with the phenolic grouping in systems of the type (XII), it became probable that the three methoxyl groups are distributed as shown, and, indeed, subsequent experiments showed that there was at least one phenolic grouping in the benzenoid ring.

Tetramethyl purpurogallin, obtained from the trimethyl compound with methyl sulphate and concentrated alkali, must necessarily possess three methoxyl groups in the benzene ring, and this was subjected to an oxidative degradation with potassium permanganate in aqueous acetone at room temperature. From the reaction mixture trimethoxyphthalic anhydride (XIII) was isolated by distillation, and found to be identical with a specimen prepared by the following

(XIII.) 

 (XIV.)

route. Trimethyl gallic acid was condensed with formaldehyde and hydrochloric acid to give a product containing chlorine—probably a crude chloromethyl derivative—which on treatment with potassium hydroxide yielded trimethoxyphthalide (XIV) previously prepared by Feist and Dschu (*Zentr.*, 1927, II, 58). This on oxidation with alkaline potassium permanganate gave (XIII). The isolation of this material as a degradation product at once disposes of Willstätter's structure (II) and lends support to the formulation (III). The Nierenstein structure (I) is also consistent with this piece of evidence but must be considered very improbable for the reasons previously advanced.

Trimethyl purpurogallin, when oxidised with potassium permanganate under conditions identical with those used for the tetramethyl ether, gave no trimethoxyphthalic anhydride. Much more permanganate was required to reach an end-point, and from the reaction mixture nothing could be isolated except oxalic acid and a trace of a high-melting yellow substance. There is therefore an unprotected phenolic group in the benzene ring of trimethyl purpurogallin, contrary to the statement of Nierenstein and Swanton, and their conclusions regarding the structure of eriophyesin are incorrect: the disaccharide residue must be located in the benzene ring.

There is a close structural relationship between (III) and colchicine (IX), and it may be significant that whereas colchicine is a mitosis poison, glucosides of purpurogallin are found in galls, *i.e.*, points of abnormal cell proliferation. Certain derivatives of purpurogallin have been synthesised and are being tested for their effect on cell division. This will be reported elsewhere.

Experimental.

Purpurogallin.—This was prepared according to Evans and Dehn (*loc. cit.*) in 72% yield. After crystallisation from glacial acetic acid it had m. p. 271—272° (Willstätter and Heiss give m. p. 272—273·5°, and Perkin m. p. 274—275°). Carrying out the reaction in an inert atmosphere effected no improvement in either the quality or the quantity of the product. Excess of iodate is to be avoided.

Trimethyl Purpurogallin.—A solution of sodium hydroxide (1·4 g.) in water (10 c.c.) was added to a mixture of purpurogallin (2·2 g.), methyl sulphate (3 c.c.), and ice (5 g.), and the whole shaken overnight in a stoppered bottle. The trimethyl ether (1·75 g.; 66%) was collected, washed with water, and crystallised from a large volume of ethanol (charcoal). The trimethyl purpurogallin had m. p. 170° (Perkin gives m. p. 174—177°) and was pure enough for subsequent operations.

Hydrogenation of Trimethyl Purpurogallin.—(A) Trimethyl purpurogallin (2 g.), suspended in ethanol (10 c.c.), was hydrogenated over Raney nickel catalyst at 60° (initial pressure 80 atm.) until 6 atoms of hydrogen had been absorbed. The catalyst was filtered off, and the solution concentrated to small bulk. *Trimethylhexahydropurpurogallin* (1 g.) crystallised. It recrystallised from xylene in colourless crystals, m. p. 147—148° (Found: C, 62·3; H, 7·3. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%). On occasion, only a gum was obtained on concentrating the ethanol solution, but trituration under ether induced crystallisation. An identical product could be obtained by hydrogenation over platinum oxide catalyst

at room temperature and pressure. The hexahydro-compound gives no ferric chloride coloration, but is soluble in aqueous alkali and couples with diazotised *p*-nitroaniline to give a red dye.

(B) Trimethyl purpurogallin (14 g.), suspended in ethanol (400 c.c.), was hydrogenated over platinum oxide catalyst (*ca.* 0·1 g.) at 60° and 1 atm. Hydrogen uptake was very slow. After 3 days, when the trimethyl ether had nearly all dissolved and the rate of hydrogenation was infinitesimal, the catalyst and unchanged trimethyl ether were filtered off, and the alcoholic solution evaporated under reduced pressure. The residual gum was dissolved in a small quantity of ethanol, and on standing deposited a little impure trimethyl ether, which was filtered off. On concentration to small bulk and standing, yellow needles, m. p. 78°, were slowly deposited. These were collected and washed with a little cold ethanol. After recrystallisation from water, *trimethyl tetrahydropurpurogallin* formed pale yellow needles, m. p. 80° (Found: C, 63·2, 63·1; H, 6·7, 6·7; active H, 0·4; *M*, 278. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8; 1 active H, 0·38%; *M*, 266). Light absorption in MeOH: Maxima, <2200 and 2880 A.; ε> 16,350 and 16,350. The tetrahydro-compound gave a reddish-purple ferric chloride reaction, dissolved in aqueous alkali, and coupled with *p*-nitrobenzenediazonium chloride to give a red dye.

Tetramethyl Purpurogallin.—The trimethyl ether (1·0 g.) on methylation with methyl sulphate and potassium hydroxide according to Willstätter and Heiss (*loc. cit.*) gave the tetramethyl ether (0·5 g.), m. p. 91—92°. This was recrystallised twice from methanol, once from aqueous methanol, and finally from ligroin (b. p. 80—100°), from which it separated in long, colourless rhomboids, m. p. 92° (Found: C, 65·1; H, 5·9. Calc. for $C_{15}H_{16}O_5$: C, 65·2; H, 5·8%).

Oxidation of the tetramethyl ether. To a solution of the above highly purified ether (0·15 g.) in purified acetone (5 c.c.) was slowly added, with intermittent shaking, a 2% aqueous solution of potassium permanganate (35 c.c.). The manganese dioxide was dissolved by use of sulphur dioxide, and the solution made alkaline, and concentrated to small bulk under reduced pressure. After being strongly acidified with concentrated hydrochloric acid, and exhaustively extracted with ether, the reaction products were isolated by distillation in bulbs. Trimethoxyphthalic anhydride (25 mg.), collected at 156—160° (bath)/0·03 mm., had m. p. 137°, undepressed by an authentic specimen (m. p. 140°) (Found: C, 55·5; H, 4·35. Calc. for $C_{11}H_{10}O_6$: C, 55·5, H, 4·2%). After recrystallisation from absolute ether, the anhydride was obtained with excellent recovery as colourless needles, m. p. 144°, undepressed on admixture with an authentic specimen.

Repetition of the experiment with tetramethyl purpurogallin (0·8 g.) gave the crude anhydride (0·2 g.), m. p. 134—137°.

Trimethoxyphthalide.—Trimethyl gallic acid (5 g.) was heated on the steam-bath for 30 mins. with aqueous formaldehyde (12 c.c. of 33%) and concentrated hydrochloric acid (20 c.c.). A dark oil separated and after being poured into water slowly solidified. This, after crystallisation from methanol, gave a colourless solid melting over a wide range, and which on boiling under reflux for 15 mins. with an excess of 65% potassium hydroxide solution and acidification with concentrated hydrochloric acid gave trimethoxyphthalide, m. p. 128°, raised by two crystallisations from methanol to 133° (Found: C, 58·5; H, 5·5. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Feist and Dschu (*loc. cit.*) give m. p. 134°.

Trimethoxyphthalic Anhydride.—The above phthalide was oxidised with alkaline permanganate according to Feist and Dschu (*loc. cit.*). The anhydride formed fine needles, m. p. 140°.

Oxidation of Trimethyl Purpurogallin.—The ether (0·3 g.), dissolved in acetone (60 c.c.) which had been distilled over potassium permanganate, was oxidised during several days with portions of 2% aqueous potassium permanganate until a permanent pink colour developed (100 c.c. required). The oxidation products were isolated as in the oxidation of tetramethyl purpurogallin and distilled in bulbs at 0·1 mm. Fraction 1, collected at 60° (bath), was a colourless liquid crystallising on cooling. Fraction 2, a colourless crystalline solid was collected at 80—100° (bath), and fraction 3, a yellow solid, at 180°. Fractions 1 and 2 had properties consistent with their being methyl oxalate and oxalic acid respectively. Fraction 3 was a yellow solid, m. p. 202° (decomp.), which will be investigated further. No evidence for the formation of trimethoxyphthalic anhydride could be found.

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