J. Chem. Soc. 2542-2549 (1931)

CCCLIII.—*Derivatives of* 1 : 2 : 3 : 4-*Tetrahydroxybenzene. Part I.*

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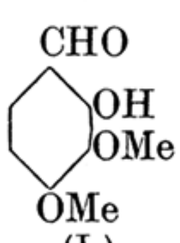
Compounds derived from tetrahydroxybenzenes are not of frequent occurrence in nature, and of these substances derivatives of 1 : 2 : 3 : 5-tetrahydroxybenzene occur most frequently. Many examples of this type are met with in compounds of the 2- and 3-phenylchromone groups, *e.g.*, the flavonols gossypetin and quercetagetin, the flavones baicalein, scutellarein and wogonin, the flavanone carthamidin, the *iso*flavones irigenin and tectorigenin, and carajurin, the anhydro-base derived from a flavylium salt. Derivatives of 1 : 2 : 4 : 5-tetrahydroxybenzene have recently been shown by Kögl to occur in certain lichen colouring matters, *e.g.*, polyporic acid and atromentin, and embelic acid is now shown by Hasan and Stedman (this vol., p. 2112) to be also derived from this parent hydroxy-compound.

Derivatives of 1 : 2 : 3 : 4-tetrahydroxybenzene are represented in nature by parsley apiole (1 : 4-dimethoxy-2 : 3-methylenedioxyallylbenzene), the isomeric dill apiole (3 : 4-dimethoxy-1 : 2-methylenedioxy-5-allylbenzene), 1 : 2 : 3 : 4-tetramethoxyallylbenzene which has been isolated from parsley oil (Thoms, *Ber.*, 1908, **41**, 2760), and the coumarin fraxetin (7 : 8-dihydroxy-6-methoxycoumarin).

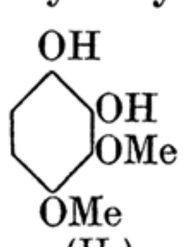
The present work describes a preliminary investigation into the possible methods of synthesising substances derived from 1 : 2 : 3 : 4-tetrahydroxybenzene, which could be used as intermediates in the synthesis of the four naturally occurring compounds of this type.

It appears that derivatives of 1 : 2 : 3 : 4-tetrahydroxybenzene have only been synthesised twice: Einhorn, Cobliner, and Pfeiffer (*Ber.*, 1904, **37**, 119) prepared 4-nitropyrogallol from pyrogallol carbonate, and hydrolysed the related base to 1 : 2 : 3 : 4-tetrahydroxybenzene; and Bargellini (*Gazzetta*, 1916, **46**, 249) oxidised 7 : 8-dimethoxycoumarin (daphnetin dimethyl ether) by means of aqueous potassium persulphate to a hydroxy-derivative which was subsequently shown by Wessely and Demmer (*Ber.*, 1929, **62**, 120) to be 6-hydroxy-7 : 8-dimethoxycoumarin.

Two new methods for the synthesis of 1 : 2 : 3 : 4-tetrahydroxybenzenes have now been devised, both starting from pyrogallol 1 : 2-dimethyl ether. This substance was prepared from pyrogallolcarboxylic acid, itself obtained by heating pyrogallol with potassium hydrogen carbonate, a process which gives more than twice the yield previously obtained by heating the reactants in aqueous solution. Under the conditions of the Gattermann reaction pyrogallol 1 : 2-dimethyl ether gave 2-*hydroxy*-3 : 4-*dimethoxybenzaldehyde* (I), whose constitution follows from its methylation to 2 : 3 : 4-trimethoxybenzaldehyde, and from the fact that it exhibits the properties of an *o*- rather than a *p*-hydroxy-aldehyde.



(I.)



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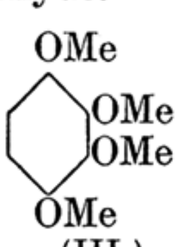

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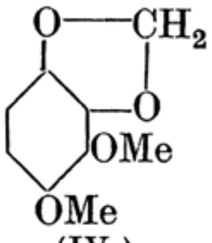
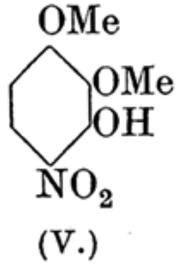


(IV.)

Oxidation of the aldehyde (I) by hydrogen peroxide in *N*-alkali solution (Dakin, *Amer. Chem. J.*, 1909, **42**, 477; Barger, J., 1918, **113**, 218) yielded 1 : 2-dihydroxy-3 : 4-dimethoxybenzene (II), which gave a *dibenzoyl* derivative, and a diacetate which was identical with the substance obtained by Ciamician and Silber (*Ber.*, 1896, **29**, 1807) from dill apiole. Methylation of (II) gave 1 : 2 : 3 : 4-tetramethoxybenzene (III), and methylenation with methylene sulphate and alkali (Baker, this vol., p. 1765) yielded 1 : 2-methylenedioxy-3 : 4-dimethoxybenzene (IV), a substance which has been obtained by the degradation of dill apiole (Ciamician and Silber, *loc. cit.*). Compound (IV), whose formation confirms the structure assigned to the aldehyde (I), was characterised by the formation of its dibromo-derivative.

Nitration of pyrogallol 1 : 2-dimethyl ether in a mixture of acetic acid and acetic anhydride gave 4-*nitropyrogallol* 1 : 2-*dimethyl ether* (V), whose constitution was established by methylation to the known 4-nitropyrogallol trimethyl ether, and from the fact that it shows the properties characteristic of an *o*-nitrophenol. Under slightly different conditions 4 : 6-*dinitropyrogallol* 1 : 2-*dimethyl ether* (VI) is obtained as well as (V).



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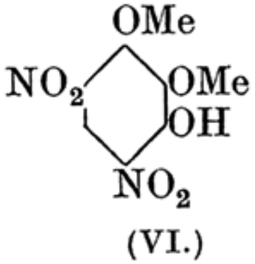
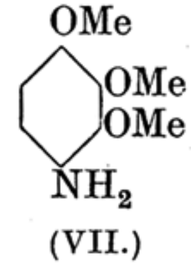
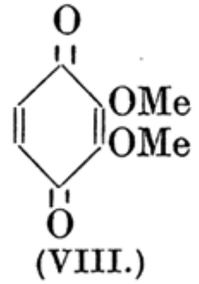


(VI.)



(VII.)

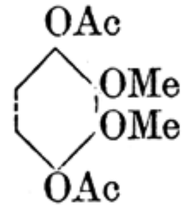


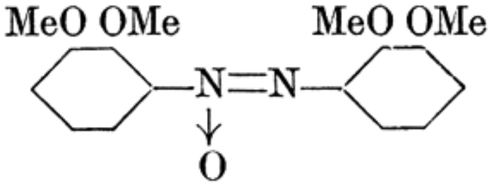
(VIII.)

Reduction of the methyl ether of (V) gave 4-aminopyrogallol trimethyl ether (VII), whose hydrochloride when oxidised in aqueous

solution with chromic acid gave 2 : 3-*dimethoxy*-p-*benzoquinone* (VIII) in over 50% yield. By reducing the quinone (VIII) with zinc and acetic acid in benzene, the corresponding quinol was obtained as an oil which gave the crystalline 2 : 3-*dimethoxyquinol diacetate* (IX), and on methylation 1 : 2 : 3 : 4-tetramethoxybenzene (III). The quinone (VIII), which can be converted into a derivative of pentahydroxybenzene by Thiele's method (*Ber.*, 1898, **31**, 1247; *Annalen*, 1900, **311**, 341), is being subjected to further investigation.

(IX.)





(X.)

The amino-group of the base (VII) could not be successfully replaced by hydroxyl through the diazonium compound, and attempts to prepare 2 : 3-dinitro-β-phenylhydroxylamine, which might rearrange to give a suitable intermediate, by reduction of 3-nitroveratrole with zinc dust and ammonium chloride gave as the chief product o-*azoxyveratrole* (X). The 3-nitroveratrole was prepared by the thermal decomposition of 2-nitroveratric acid, for a supply of which the authors are indebted to Dr. J. M. Gulland.

Other methods of synthesising 1 : 2 : 3 : 4-tetrahydroxybenzenes are being investigated, and will be described in a later communication.

Experimental.

Pyrogallolcarboxylic Acid.—Finely powdered pyrogallol (80 g.) and potassium hydrogen carbonate (400 g.) were intimately mixed in a loosely corked 2-litre flask in an atmosphere of coal gas. The flask was heated at 160—170° for 2 hours, water (1600 c.c.) added, and the product dissolved by heating on the water-bath. The hot dark solution was acidified with concentrated hydrochloric acid (400 c.c.), and after a few hours the pyrogallolcarboxylic acid was collected, washed with much cold water, and dried on the water-bath (average yield, 80 g.).

Pyrogallol 1 : 2-*Dimethyl Ether.*—Pyrogallolcarboxylic acid was converted into its 3 : 4-dimethyl ether by methylation with methyl sulphate and alkali (Mauthner, *J. pr. Chem.*, 1914, **89**, 304); elimination of carbon dioxide from this acid (100 g.) by heating and distillation in a vacuum and subsequent redistillation under ordinary pressure gave pyrogallol 1 : 2-dimethyl ether (60 g.), b. p. 230—240° (Herzig and Pollak, *Ber.*, 1903, **36**, 661).

2-*Hydroxy*-3 : 4-*dimethoxybenzaldehyde* (I).—A solution of pyrogallol 1 : 2-dimethyl ether (50 g.) and anhydrous hydrogen cyanide

(20 g.) in dry ether (200 c.c.) was slowly saturated with dry hydrogen chloride at 0° in presence of a few grams of powdered anhydrous zinc chloride. After 12 hours, fresh ether was added, and then crushed ice till all the solid had dissolved, the temperature being kept at 0°. The ethereal layer was at once separated, and the aqueous solution containing the aldimine hydrochloride was hydrolysed by refluxing it for 1 hour under a layer of ether, which was then separated. The aqueous layer was again hydrolysed as before, the ethereal layers were united, shaken with an excess of aqueous sodium bicarbonate, dried over sodium sulphate, and distilled, leaving the crude aldehyde (20 g.) as a yellowish oil which partly crystallised. The solid was collected by filtration; it crystallised from water in colourless needles or better from light petroleum (b. p. 40—60°) in compact prisms, m. p. 74° (Found: C, 59·5; H, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The non-crystalline material gave a solid bisulphite compound, from which the aldehyde was regenerated in the crystalline condition. 2-*Hydroxy*-3 : 4-*dimethoxybenzaldehyde* dissolves in sodium hydroxide solution with a yellow colour; it is slightly volatile in steam and gives a dull brownish-red colour with ferric chloride in aqueous or alcoholic solution. The *phenylhydrazone* separates from methyl alcohol in pale yellow prisms, m. p. 156° (Found: N, 10·1. $C_{15}H_{16}O_3N_2$ requires N, 10·3%).

Methylation with methyl sulphate and alkali gave a non-phenolic aldehyde crystallising from light petroleum in highly refracting prisms, whose melting point, 31·5°, was not depressed when they were mixed with 2 : 3 : 4-trimethoxybenzaldehyde (Schaaf and Labouchère, *Helv. Chim. Acta*, 1924, **7**, 357, record m. p. 37°; Barger and Ewins, J., 1910, **97**, 2258, give m. p. 30°). 2 : 3 : 4-*Trimethoxybenzaldehydephenylhydrazone* separates from methyl alcohol in very pale yellow prisms, m. p. 155—156° (Found: N, 9·6. $C_{16}H_{18}O_3N_2$ requires N, 9·8%).

The aldehyde (I) was also prepared from pyrogallol 1 : 2-dimethyl ether by the Tiemann–Reimer reaction, but the yield was very poor.

1 : 2-*Dihydroxy*-3 : 4-*dimethoxybenzene* (II).—Pure 2-hydroxy-3 : 4-dimethoxybenzaldehyde (7·5 g.; 1 mol.) was dissolved in *N*-sodium hydroxide solution (1 equiv.), and an approximately 3% solution of hydrogen peroxide (1·25 mols.) added. The yellow solution turned dark brown and the temperature rose to about 40°. After ¼ hour sodium bicarbonate was added, the solution extracted several times with ether, the extracts shaken with dilute aqueous sodium bisulphite to remove any unchanged aldehyde, dried over sodium sulphate, and distilled, leaving a pale brown oily residue (6 g.), which could not be obtained crystalline (compare Ciamician and Silber, *loc. cit.*). The substance gives a purple colour with ferric

chloride in aqueous solution, and a deep green in alcoholic solution. Prolonged treatment with boiling acetic anhydride and sodium acetate gave a diacetate, which after crystallisation from chloroform and then light petroleum formed colourless crystals, m. p. 83—84° (Found : C, 56·8; H, 5·7. Calc. for $C_{12}H_{14}O_6$: C, 56·7; H, 5·6%) (Ciamician and Silber, *loc. cit.*, record m. p. 85°). The *dibenzoyl* derivative, prepared by the Schotten–Baumann method, was crystallised from dilute alcohol and then light petroleum (b. p. 40—60°) and obtained in small colourless prisms, m. p. 96° (Found : C, 69·8; H, 5·0. $C_{22}H_{18}O_6$ requires C, 69·8; H, 4·8%).

1 : 2 : 3 : 4-*Tetramethoxybenzene* (III).—Methylation of 1 : 2-dihydroxy-3 : 4-dimethoxybenzene with methyl sulphate in aqueous alkaline solution gave a solid which crystallised from light petroleum (b. p. 40—60°) in small colourless prisms, m. p. 88·5° (Found : C, 60·6; H, 7·0. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%). Ciamician and Silber (*loc. cit.*) and Bignami and Testoni (*Gazzetta*, 1900, **30**, 240) record the melting point of 1 : 2 : 3 : 4-tetramethoxybenzene as 89°, and Einhorn, Cobliner, and Pfeiffer (*loc. cit.*) give m. p. 83°.

1 : 2-*Methylenedioxy*-3 : 4-*dimethoxybenzene* (IV).—The methylenation of the *o*-dihydroxy-derivative (II) by means of methylene sulphate and alkali in aqueous-acetone solution (compare methylenation of catechol; Baker, *loc. cit.*) yielded an oil, which was heated with excess of alkali for ½ hour, extracted with ether, and twice distilled under 2 mm. pressure, giving a colourless, fairly mobile oil (Found : C, 59·8; H, 5·8. Calc. for $C_9H_{10}O_4$: C, 59·4; H, 5·5%). 1 : 2-Methylenedioxy-3 : 4-dimethoxybenzene is volatile in steam and has an odour recalling that of veratrole; it could not be obtained in the crystalline condition, and, owing to the small amount available, its boiling point could not be accurately determined. The free positions of the nucleus are very reactive, and by the action of bromine in acetic acid at the ordinary temperature the dibromo-derivative was readily produced, which was precipitated with water; it crystallised from alcohol, and then from light petroleum in colourless needles, m. p. 91° (Found : Br, 47·4. Calc. for $C_9H_8O_4Br_2$: Br, 47·1%). Ciamician and Silber (*loc. cit.*) were also unable to obtain the substance (IV) (isolated from dill apiole) in the solid condition; they obtained the dibromo-compound (colourless needles from alcohol, m. p. 92°) by the bromination of dill-apiolic acid.

4-*Nitropyrogallol* 1 : 2-*Dimethyl Ether* (V).—The following conditions gave the maximum yield of the mononitro-compound. Pyrogallol 1 : 2-dimethyl ether (5 g.) in glacial acetic acid (20 c.c.) and acetic anhydride (5 c.c.) was cooled to about 3° and a solution of nitric acid (3·2 g.; *d* 1·42) in acetic acid (20 c.c.) added during 10 minutes, the temperature being kept below 5°. After remaining for 1 hour at room temperature, the mixture was poured into ice and water (100 g.), and the solid product was collected, washed, and crystallised from a small amount of methyl alcohol, from which yellow compact prisms (2·4 g.), m. p. 102—103°, separated (Found : N, 6·8. $C_8H_9O_5N$ requires N, 7·0%). 4-*Nitropyrogallol* 1 : 2-*dimethyl ether* is slightly volatile in steam and dissolves in aqueous alkaline solutions with a light orange colour.

4-*Nitropyrogallol Trimethyl Ether*.—A mixture of 4-nitropyrogallol 1 : 2-dimethyl ether (8 g.), methyl sulphate (25 g.), potassium carbonate (12 g.), and xylene (16 c.c.) was stirred and heated at 130° for 10 minutes. Water was then added, the xylene removed in steam, and, when cold, the solid (8 g.) was collected, washed, and dried; it crystallised from light petroleum (b. p. 60—80°) in long colourless needles, m. p. 44° (Einhorn, Cobliner, and Pfeiffer, *loc. cit.*, and Thoms and Siebling, *Ber.*, 1911, **44**, 2123, give m. p. 44°; the isomeric 5-nitropyrogallol trimethyl ether has m. p. 99°).

4 : 6-*Dinitropyrogallol* 1 : 2-*Dimethyl Ether* (VI).—The nitration of pyrogallol 1 : 2-dimethyl ether (5 g.) in acetic acid (20 c.c.) with nitric acid (5 g.; *d* 1·42) in acetic acid (20 c.c.) without cooling, gave 4-nitropyrogallol 1 : 2-dimethyl ether and also 4 : 6-*dinitropyrogallol* 1 : 2-*dimethyl ether*; the latter separated from the methyl-alcoholic mother-liquors in yellow needles, m. p. 76°, which were recrystallised from light petroleum (b. p. 60—80°) (Found : N, 11·3. $C_8H_8O_7N_2$ requires N, 11·5%). The substance is easily soluble in the usual organic solvents and dissolves in alkaline solutions with a yellow colour. Its constitution follows from its methylation by means of methyl sulphate and potassium carbonate in xylene to 4 : 6-dinitropyrogallol trimethyl ether, m. p. 85° (Thoms and Siebling, *loc. cit.*, and Pollecoff and Robinson, J., 1918, **113**, 656, record m. p. 85°; the isomeric 4 : 5-dinitropyrogallol trimethyl ether has m. p. 118·4°).

4-*Aminopyrogallol Trimethyl Ether* (VII).—4-Nitropyrogallol trimethyl ether (6 g.) was reduced by heating with tin (18 g.), concentrated hydrochloric acid (30 c.c.), and water (12 c.c.); the tin was removed as sulphide, and the filtered solution evaporated to dryness under diminished pressure in an atmosphere of carbon dioxide, leaving the hydrochloride of the base. The pure hydrochloride, obtained from the free base and hydrogen chloride in ether, had the properties described by Graebe and Suter (*Annalen*, 1905, **340**, 222).

2 : 3-*Dimethoxy*-p-*benzoquinone* (VIII).—4-Aminopyrogallol trimethyl ether hydrochloride (2 g.) in water (100 c.c.) was slowly stirred into a solution of chromic acid (4·5 g.) in water (150 c.c.), the temperature being kept between 6° and 9°. The solution was then slowly warmed to 60°, kept at room temperature for 4 hours, and

extracted several times with ether. After drying, the extracts yielded the almost pure quinone as a brownish-orange crystalline residue (1·1 g.). It separated from warm light petroleum (b. p. 60—80°) in bright orange-red needles, m. p. 66—67° (Found : C, 57·0; H, 4·8. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). 2 : 3-*Dimethoxy*-p-*benzoquinone* is easily soluble in ethyl and methyl alcohols, acetone, acetic acid, ether, and benzene. It dissolves in concentrated sulphuric acid with a bright olive-green colour, and in dilute sodium hydroxide solution with a pinkish-violet colour which rapidly becomes brown and then slowly acquires a greenish tint.

This quinone was also prepared by the oxidation of 4-aminopyrogallol trimethyl ether with ferric chloride in aqueous solution, and by the oxidation of 3-aminoveratrole with chromic acid under the conditions usually employed for oxidising aniline to *p*-benzoquinone, but both reactions gave very poor yields.

2 : 3-*Dimethoxyquinol Diacetate* (IX).—2 : 3-Dimethoxy-*p*-benzoquinone (2 g.) in benzene (50 c.c.) was shaken with water (50 c.c.), acetic acid (5 c.c.), and zinc dust until the colour of the quinone had disappeared. The benzene layer was dried over sodium sulphate, and yielded 2 : 3-dimethoxyquinol as a light-brown oily residue. This substance could not be obtained in the pure state. On distillation in a vacuum it underwent considerable decomposition, and was very readily oxidised to the parent quinone. Methylation with methyl sulphate and alkali readily yielded 1 : 2 : 3 : 4-tetramethoxybenzene, m. p. 88·5°, whose melting point was not depressed on admixture with a specimen of 1 : 2 : 3 : 4-tetramethoxybenzene prepared as previously described. 2 : 3-*Dimethoxyquinol diacetate* was obtained by boiling the dimethoxyquinol with acetic anhydride and sodium acetate for 4—6 hours, treating the solution with water, and extracting the diacetate with ether. The extracts yielded a residue which was crystallised twice from dilute alcohol (charcoal) and obtained in colourless irregular prisms, m. p. 54—56° (Found : C, 56·6; H, 5·7. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%).

3-*Nitroveratrole*.—A mixture of crude 2-nitroveratric acid (20 g.), copper powder (4 g.), and sand (20 g.) in a distilling flask attached to a receiver was cautiously heated and agitated over a naked flame. Carbon dioxide was evolved and a little 3-nitroveratrole distilled, completion of the reaction being indicated by the sudden appearance of white fumes. The substance was now distilled under diminished pressure and then redistilled, 3-nitroveratrole (9 g.) being collected as a light yellow solid, m. p. 65—66°, b. p. 168—169°/20 mm.

o-*Azoxyveratrole* (X).—3-Nitroveratrole was reduced in 50% alcohol by the addition of zinc dust in presence of ammonium chloride. After the addition of zinc the warm solution was filtered, diluted, and extracted with ether. The extracts yielded a semi-solid product which contained traces of a β-phenylhydroxylamine derivative and a primary base, but consisted almost entirely of o-*azoxyveratrole* ; this crystallised from benzene, and then from alcohol in pale yellow prisms, m. p. 125—126° (Found : C, 60·5; H, 5·7. $C_{16}H_{18}O_5N_2$ requires C, 60·4; H, 5·6%).

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[*Received, August 10th*, 1931.]