75. *Derivatives of* 1 : 2 : 3 : 4-*Tetrahydroxybenzene. Part IV. Attempted Syntheses.*

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The paper describes a number of compounds which were made with the ultimate object of synthesising derivatives of 1 : 2 : 3 : 4-tetrahydroxybenzene. Investigation of the properties of these compounds, however, showed that they could not be used as intermediates in the production of substances of the desired type.

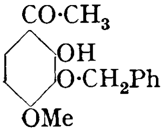
SEVERAL methods for the synthesis of naturally occurring derivatives of 1 : 2 : 3 : 4-tetrahydroxybenzene, in particular parsley apiole and fraxetin, have been explored. The compounds described in this paper were prepared as intermediates, but their properties were such as to render them useless for the object in view. We have not considered it necessary to record the proposed steps of any of the synthetical schemes.

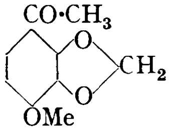
The sodium salt of 2 : 5-*dimethoxybenzenesulphonic acid* could not be converted into 2 : 5-dimethoxyphenol by fusion with caustic alkalis, the only isolable product being quinol dimethyl ether. The sulphonic acid group is extremely easily eliminated from this acid; its dihydrate undergoes rapid hydrolysis to sulphuric acid and quinol dimethyl ether at 150°.

2 : 5-Dimethoxyaniline yielded only minute traces of unrecognisable phenolic material when diazotised under a layer of light petroleum to prevent frothing (cf. Perkin and Rubenstein, J., 1926, 360), and decomposed by pouring into a boiling copper sulphate solution. Other methods of decomposing the diazonium solution were equally unsuccessful.

Pyrogallol 1-monomethyl ether was converted by the method of Gattermann into 2 : 3-*dihydroxy*-4-*methoxybenzaldehyde*. This compound was unattacked by hydrogen peroxide under the usual conditions of the Dakin reaction, and the same inertness was shown by 2 : 3-dihydroxy-4-methoxyacetophenone (Baker, Jukes, and Subrahmanyam, J., 1934, 1683). The position assigned to the aldehyde group is based on analogy with the position taken up by the acetyl group when introduced into the nucleus of pyrogallol 1-monomethyl ether. Benzylation of 2 : 3-dihydroxy-4-methoxyacetophenone yielded 2-*hydroxy*-3-*benzyloxy*-4-*methoxyacetophenone* (I); attempts to oxidise this to a catechol derivative by means of the Dakin reaction were unsuccessful, and the oxidation which occurred was accompanied by the production of benzyl alcohol.

2 : 4-Dihydroxyanisole (convenient preparation of the intermediate 5-amino-2-methoxyphenyl acetate) was converted into 7-*hydroxy*-6-*methoxy*-4-*methylcoumarin* (4-*methylscopoletin*) by the action of acetoacetic ester and sulphuric acid, and the related *acetyl* derivative yielded 7-*hydroxy*-6-*methoxy*-8-*acetyl*-4-*methylcoumarin* when heated with aluminium chloride. Hydrolysis of this compound gave, not the desired 2 : 4-dihydroxy-3-acetylanisole, but 2 : 4-dihydroxyanisole.


(I.)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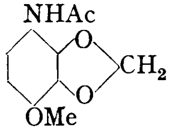
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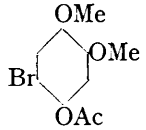
(IV.)

Treatment of 2 : 3-dihydroxy-4-methoxyacetophenone with methylene sulphate and alkali gave 4-*methoxy*-2 : 3-*methylenedioxyacetophenone* (II), the *oxime* of which was converted into 4-*methoxy*-2 : 3-*methylenedioxyacetanilide* (III) by the action of phosphorus pentachloride in ether. The corresponding free amine gave some indications of being converted into a quinone on oxidation (cf. oxidation of 2 : 3 : 4-trimethoxyaniline to 2 : 3-dimethoxy-*p*-benzoquinone; Baker and Smith, J., 1931, 2547), but the small amount of material available was insufficient for a complete investigation of the reaction.

4-Hydroxyveratrole (considerably improved preparation from 4-aminoveratrole) was converted into 5-*bromo*-4-*acetoxyveratrole* (IV) (1) by bromination, followed by acetylation, (2) by conversion into 4-*acetoxyveratrole* and subsequent bromination, the latter method being the better. Attempts to effect the migration of the acetyl group in (IV) into position 3 by treatment with aluminium chloride under various conditions, or to introduce a new acetyl group into position 3 by the action of acetic acid and zinc chloride or acetic anhydride and sulphuric acid (Schneider and Kraft, *Ber.*, 1922, **55**, 1892) were unsuccessful. Position 3 appears to be very unreactive and vigorous conditions lead to decomposition. 5-Bromo-1 : 2 : 4-trimethoxybenzene, when treated with acetyl chloride and aluminium chloride under various conditions, gave, not a nuclear acetyl derivative, but 2 : 3 : 5 : 2′ : 3′ : 5′-hexamethoxydiphenyl, which was also produced under the same conditions in the absence of acetyl chloride.

EXPERIMENTAL.

2 : 5-*Dimethoxybenzenesulphonic Acid*.—This acid has been referred to by Hantzsch and Langbein (*Z. anorg. Chem.*, 1932, **204**, 193), but no description of the acid or of its preparation occurs in the literature, apart from the statement by Hantzsch and Langbein that, after drying at 100° in air, it contains $1H_2O$. We find, however, that under these conditions the acid contains $2H_2O$.

Quinol dimethyl ether (100 g.) and concentrated sulphuric acid (200 c.c.) were warmed at 60° for 5 minutes (slight exothermic reaction), and after 10 minutes water (400 c.c.) was added, and the solution cooled. After several hours the crystals were collected, drained, and dried as far as possible over sulphuric acid (weight, 174 g.). 2 : 5-*Dimethoxybenzenesulphonic acid* crystallises from ethyl acetate in large, highly refracting bi-pyramids or elongated prisms. The crystals become slightly opaque on the surface on standing or on heating to 100° (Found in material powdered and heated at 100° : C, 37·7; H, 5·3; S, 12·5; equiv., 257. $C_8H_{10}O_5S,2H_2O$ requires C, 37·8; H, 5·5; S, 12·6%; equiv., 254). The acid dissolves in its water of crystallisation at 100—105°.

2 : 3-*Dihydroxy*-4-*methoxybenzaldehyde*.—To pyrogallol 1-methyl ether (10 g.) (Baker, Montgomery, and Smith, J., 1932, 1282; Baker, Jukes, and Subrahmanyam, *loc. cit.*) in dry ether (100 c.c.) was added anhydrous zinc cyanide (6·8 g.) and a rapid current of dry hydrogen chloride passed in with vigorous stirring until the cyanide had dissolved. After 1½ hours the ether was decanted from the crystalline solid, the latter boiled with water for 10 minutes, and the solution extracted several times with ether. After drying and distilling, the extracts yielded the *aldehyde* as a colourless solid, m. p. 69·5°, b. p. 172—178°/14 mm. (Found: C, 57·1; H, 5·0. $C_8H_8O_4$ requires C, 57·1; H, 4·8%).

2-*Hydroxy*-3-*benzyloxy*-4-*methoxyacetophenone* (I).—2 : 3-Dihydroxy-4-methoxyacetophenone (10 g.) (Baker, Jukes, and Subrahmanyam, *loc. cit.*) in dry toluene (750 c.c.) was boiled under reflux with continual stirring in presence of anhydrous potassium carbonate (110 g.), and benzyl chloride (60 g.) added at intervals during 9 hours. Water was now added, the toluene removed in steam, and the residue, which solidified, crystallised from light petroleum (b. p. 60—80°). The *benzyl* derivative separates from this solvent or methyl alcohol in colourless needles, m. p. 79—80° (Found: C, 70·8; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·7; H, 5·9%). Yield, 40%. Its alcoholic solution gives a deep purplish-brown colour on the addition of ferric chloride. The position of the benzyl group is established by the fact that hydroxyl ortho to a carbonyl group cannot be benzylated under the normal conditions (Gulati and Venkataraman, J., 1936, 267).

5-*Amino*-2-*methoxyphenyl Acetate*.—This intermediate in the preparation of 2 : 4-dihydroxyanisole was most conveniently prepared by the catalytic reduction of the corresponding nitro-compound (cf. Seka and Kallir, *Ber.*, 1931, **64**, 913). 5-Nitro-2-methoxyphenyl acetate (40 g.) in alcohol (150 c.c.) was shaken in hydrogen under 3 atms. pressure in presence of a palladium–strontium carbonate catalyst (7·5 g.; from 50 g. of strontium carbonate and 1 g. of palladium chloride) till reduction was complete (about 2 hours). The free amine was obtained by evaporation of the filtered solution and was used directly in the diazonium reaction. 5-*Acetamido*-2-*methoxyphenyl acetate* separated from hot water in glistening plates, m. p. 156—157° (Found: C, 59·1; H, 5·7; N, 6·3. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8; N, 6·3%).

2 : 4-*Dihydroxyanisole*.—This was prepared directly from 5-amino-2-methoxyphenyl acetate, simultaneous hydrolysis of the acetoxy-group occurring. Decomposition of the diazonium sulphate was effected by pouring into a boiling copper sulphate solution (cf. preparation of 4-hydroxyveratrole; p. 375), and the 2 : 4-dihydroxyanisole isolated in 52% yield, following the directions given by Seka and Kallir (*loc. cit.*), who prepared it from 5-amino-2-methoxyphenol.

7-*Hydroxy*-6-*methoxy*-4-*methylcoumarin* (4-*Methylscopoletin*).—A mixture of 2 : 4-dihydroxyanisole (7·5 g.) and acetoacetic ester (5·5 g.) was added to concentrated sulphuric acid (25 g.) at 0°. After 12 hours the solution was poured on ice, and the precipitate collected, washed, and crystallised from dilute alcohol. The *coumarin* separated in minute prisms, m. p. 213·5° (Found: C, 64·1; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·8%). Its solutions in water, alcohol, and concentrated sulphuric acid possess marked blue fluorescence. The ferric chloride reaction is green, and the solution in sodium hydroxide is yellow with a strong blue fluorescence. The *acetyl* derivative, prepared by refluxing with acetic anhydride for ½ hour, forms colourless, prismatic needles from methyl alcohol, m. p. 188—189° (Found: C, 62·7; H, 5·1. $C_{13}H_{12}O_5$ requires C, 63·0; H, 4·9%).

7-*Hydroxy*-6-*methoxy*-8-*acetyl*-4-*methylcoumarin*.—The foregoing acetyl derivative (2 g.) was mixed with powdered aluminium chloride (4 g.) and placed in an oil-bath at 120°, the temperature being raised to 170° during 1½ hours. The product was decomposed with dilute hydrochloric acid, and the resulting solid crystallised twice from alcohol (charcoal) and then from dilute alcohol. It formed very pale yellow needles, m. p. about 250° (decomp. and previous softening) (Found: C, 63·0; H, 4·6. $C_{13}H_{12}O_5$ requires C, 63·0; H, 4·9%). The compound is only sparingly soluble in cold sodium hydroxide to an intensely yellow solution with a slight blue-green fluorescence, the weakly phenolic character being consistent with the position assigned to the acetyl group. The alcoholic solution is coloured a deep olive-green by the addition of ferric chloride.

4-*Methoxy*-2 : 3-*methylenedioxyacetophenone* (II).—2 : 3-Dihydroxy-4-methoxyacetophenone (5 g.) in dry acetone (200 c.c.) was stirred (mercury seal) and boiled under reflux in an atmosphere of coal gas, a solution of potassium hydroxide (10 g.) in water (150 c.c.) and methylene sulphate (12 g.) (Baker, J., 1931, 82) being added alternately in portions so that the solution did not become very strongly alkaline. After the addition was complete (1½ hours) the solution was stirred for a further ¼ hour and made alkaline with potassium hydroxide, the acetone removed by distillation, and the methylenated *product* collected in ether and crystallised from light petroleum (b. p. 60—80°); it separated in prismatic needles, m. p. 102·5° (Found: C, 61·8; H, 5·1. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·1%). Yield, 18%.

4-*Methoxy*-2 : 3-*methylenedioxyacetophenoneoxime*.—A mixture of the preceding compound (0·5 g.), hydroxylamine hydrochloride (0·165 g.; 1 mol.) and N-sodium hydroxide (2·5 c.c.) was heated on the steam-bath, and alcohol added until a clear solution was obtained, which was then refluxed for 3 hours and poured into a little water. The solid precipitate crystallised from dilute alcohol in minute prisms, m. p. 148·5° (Found: C, 57·0; H, 5·3. $C_{10}H_{11}O_4N$ requires C, 57·3; H, 5·3%). Yield, 72%.

4-*Methoxy*-2 : 3-*methylenedioxyacetanilide* (III).—To the preceding oxime (0·8 g.) in dry ether (50 c.c.) was added phosphorus pentachloride (0·8 g.). After 24 hours the ether was removed by distillation, water (10 c.c.) added, and the *anilide* collected and crystallised from a small volume of hot water. It separated in bunches of needles, m. p. 138—139° (Found : N, 6·5. $C_{10}H_{11}O_4N$ requires N, 6·7%).

4-*Hydroxyveratrole*.—The preparation of this compound from 4-aminoveratrole (Fargher, J., 1920, **117**, 869) has been considerably improved and the yield raised from 20% (Robertson, J., 1932, 1385) to 45% by decomposing the diazonium salt in boiling copper sulphate solution. 4-Aminoveratrole (60 g.) in a mixture of concentrated sulphuric acid (55 c.c.) and water (500 c.c.) was diazotised at −10° to −5° by the addition of a solution of sodium nitrite (27 g.) in water (100 c.c.). The resulting solution was run in a thin stream into a boiling solution of copper sulphate (400 c.c.; saturated at about 30°), and, after cooling, the solution was extracted six times with ether. After the ethereal solution had been dried with sodium sulphate, the ether was distilled, and the resulting oil distilled under diminished pressure; the fraction, b. p. 160—180°/18 mm., was redistilled and yielded 4-hydroxyveratrole (27 g.) as a pale yellow oil, b. p. 173°/17 mm., m. p. about 70°. It crystallises readily from carbon tetrachloride in prisms, m. p. 80—81°; the use of a mixture of dibutyl ether and light petroleum as recommended by Clarke (*J. Amer. Chem. Soc.*, 1931, **53**, 3896) is unnecessary. The *acetyl* derivative, prepared by boiling with acetic anhydride and a drop of pyridine for 10 minutes and pouring into water, separates from very dilute alcohol in hexagonal plates, m. p. 44° (Found : C, 61·4; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

5-*Bromo*-4-*acetoxyveratrole* (IV).—4-Acetoxyveratrole (8 g.) was dissolved in acetic anhydride (20 c.c.), and a solution of bromine in acetic acid (32 c.c.; containing 20 g. of bromine in 100 c.c. of solution) added in several portions, keeping the temperature at about 10°. After a short time water was added, the solid product collected, dried (weight 6 g.), and crystallised from light petroleum (b. p. 60—80°), from which it separated in blunt-ended prisms, m. p. 67° (Found : C, 43·9; H, 4·3; Br, 29·4. $C_{10}H_{11}O_4Br$ requires C, 43·6; H, 4·0; Br, 29·1%). The same substance was also obtained by bromination of 4-hydroxyveratrole in slightly diluted acetic acid at 0° and acetylation of the product, but the yield by this method is poor. It slowly undergoes decomposition when kept in a specimen tube for several weeks. When simultaneously hydrolysed and methylated by the action of hot aqueous potassium hydroxide and methyl sulphate, it yielded 5-bromo-1 : 2 : 4-trimethoxybenzene, which separated from light petroleum (b. p. 60—80°) in rhombic prisms, m. p. 54°; the m. p. was not depressed on admixture with a specimen of 5-bromo-1 : 2 : 4-trimethoxybenzene, m. p. 54°, prepared by the direct bromination of 1 : 2 : 4-trimethoxybenzene (Fabinyi and Szeki, *Ber.*, 1910, **43**, 2679).

5-*Bromo*-1 : 2 : 4-*trimethoxybenzene*.—No details for the direct bromination of 1 : 2 : 4-trimethoxybenzene are given by Fabinyi and Szeki (*loc. cit.*) A solution of bromine in acetic acid (160 c.c., containing 20 g. of bromine per 100 c.c.) was added at 15° to 1 : 2 : 4-trimethoxybenzene; instant bromination occurred and the addition of a large volume of water threw down the bromo-derivative as a solid, which was crystallised from light petroleum as above (yield, 47 g.).

2 : 3 : 5 : 2′ : 3′ : 5′-*Hexamethoxydiphenyl*.—5-Bromo-1 : 2 : 4-trimethoxybenzene (1 g.) was added to a solution of aluminium chloride (1 g.) in either anhydrous ether (10 c.c.) or nitrobenzene (10 c.c.). After 20 hours the solvents were removed in steam, and the solid collected, boiled with dilute alkali, and recrystallised from alcohol and then acetic acid. The diphenyl derivative separated in colourless prisms, m. p. 174—175·5°, whose m. p. was not depressed on admixture with a specimen of the compound prepared by the action of copper powder on 5-bromo-1 : 2 : 4-trimethoxybenzene (Fabinyi and Szeki, *loc. cit.*). The ready formation of a diphenyl derivative is characteristic of hydroxyquinol, its trimethyl ether and derivatives (see Erdtman, *Proc. Roy. Soc.*, 1933, **143**, 198).

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[*Received, January 28th*, 1938.]