

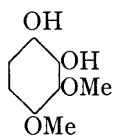
**368.** *Derivatives of 1 : 2 : 3 : 4-Tetrahydroxybenzene. Part III. The Synthesis of Dill Apiole, and the Extension of the Dakin Reaction.*

By WILSON BAKER, E. H. T. JUKES, and (in part) C. A. SUBRAHMANYAM.

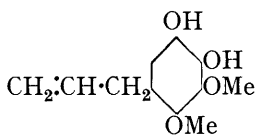
IN Part I (Baker and Smith, J., 1931, 2542) was described the synthesis of dill apione (1 : 2-methylenedioxy-3 : 4-dimethoxybenzene) by the methylenation of 1 : 2-dihydroxy-3 : 4-dimethoxybenzene (I), the latter substance being obtained by the oxidation of 2-hydroxy-3 : 4-dimethoxybenzaldehyde by means of hydrogen peroxide in aqueous alkaline solution (see Dakin, *Amer. Chem. J.*, 1909, **42**, 477). The difficulties attending the preparation of 2-hydroxy-3 : 4-dimethoxybenzaldehyde in quantity excluded the possibility of using 1 : 2-dihydroxy-3 : 4-dimethoxybenzene (I) as an intermediate in the synthesis of the naturally occurring dill apiole itself (1 : 2-methylenedioxy-3 : 4-dimethoxy-5-allylbenzene) (III).

A convenient method for the preparation of (I) in quantity has now been found in the oxidation of the accessible gallacetophenone 3 : 4-dimethyl ether with hydrogen peroxide in alkaline solution, and it has been used in the synthesis of dill apiole in the following manner. Treatment with allyl bromide in acetone in presence of potassium carbonate yielded a monoallyl ether, which underwent molecular rearrangement on heating with production of 1 : 2-dihydroxy-3 : 4-dimethoxy-5-allylbenzene (II) (uncharacterised) as the chief product. Since migration of an allyl group under these conditions always yields

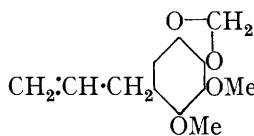
an *o*- or a *p*-hydroxyallylbenzene, the production of (II) probably means that the monoallyl ether is chiefly the 2-*O*-allyl ether. Methylenation of (II) with methylene iodide and anhydrous potassium carbonate in acetone yielded directly almost pure dill apiole (III), characterised by the formation of monobromodill apiole dibromide, which was directly compared (mixed m. p.) with a specimen prepared from natural dill apiole. The allyl



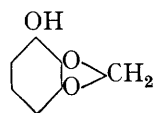
(I.)



(II.)



(III.)



(IV.)

groups in these compounds cannot occupy position 6, since the final product would then be an isomeride of dill apiole and not dill apiole itself, the constitution of which was definitely established by the researches of Ciamician and Silber (*Ber.*, 1896, **29**, 1799) and Thoms (*Arch. Pharm.*, 1904, **242**, 328). Dill apiole has been isolated from dill oil (Ciamician and Silber, *loc. cit.*), from matico oil from the leaves of *Piper augustifolium* (Thoms, *loc. cit.*), from sea-fennel oil (Delépine, *Compt. rend.*, 1909, **149**, 215), and from *Crithmum maritimum* (Francesconi and Sernagiotti, *Atti R. Accad. Lincei*, 1913, **22**, 231, 312).

Methylation of (II) with methyl sulphate and alkali readily gave 1 : 2 : 3 : 4-tetra-methoxy-5-allylbenzene, which is apparently identical with a product isolated by Thoms (*Ber.*, 1908, **41**, 2753) from parsley oil and to which this constitution was assigned. Direct comparison of the synthetic and the natural product was not possible in this case.

As possible intermediates in the synthesis of parsley apiole the following compounds have been prepared: *pyrogallol methylene ether* (2 : 3-methylenedioxyphenol) (IV), by the direct methylenation of pyrogallol with methylene bromide and potassium carbonate in acetone; gallacetophenone 4-methyl ether, by the nuclear acylation of pyrogallol 1-monomethyl ether (Baker, Montgomery, and Smith, *J.*, 1932, 1282); 7-methoxy-8-acetyl-2-methylchromone—this compound could not be hydrolysed to the monomethyl ether of 2 : 4-diacetylresorcinol. Hydrolysis of 7-hydroxy-8-acetyl-2-methylchromone (Baker, this vol., p. 73) with 4% aqueous sodium hydroxide at 100° gives resacetophenone, the nuclear acetyl group in position 8 having been replaced by hydrogen; 2 : 4-diacetylresorcinol is unaffected under these conditions, although it has been recorded that reduction of this diacetyl resorcinol by Clemmensen's method yields 4-ethylresorcinol (Rosenmund, Buchwald, and Deligiannis, *Arch. Pharm.*, 1933, **271**, 344).

*The Extension of the Dakin Reaction.*—This reaction, as applied to the oxidation of the hydroxybenzaldehydes to give polyhydroxybenzenes and formic acid, has found but few synthetical applications, probably owing to the difficulty in obtaining the appropriate aldehydes. Dakin observed that the reaction could be extended to the oxidation of hydroxyacetophenones, but he found it necessary to heat the reactants and observed that "the reaction does not take place as easily as in the case of the corresponding aldehydes and the yields, particularly in the case of the dihydroxybenzenes, are smaller." We are, however, unable to agree with this statement, and find that the hydroxyacetophenones are oxidised just as easily as the hydroxyaldehydes (see examples in this paper). Since the hydroxyacetophenones are, in general, very readily accessible in quantity, it is evident that this provides a valuable synthetical method, and also a simple method for establishing the position of a nuclear acetyl group in derivatives of *o*- or *p*-hydroxyacetophenones (see Baker, *loc. cit.*).

The higher ketones may also be oxidised in the normal manner. Dakin obtained a small yield of quinol by the oxidation of *p*-hydroxyphenyl ethyl ketone, but we have now extended the reaction to the oxidation of hydroxyphenyl benzyl ketones and hydroxyphenyl β-phenylethyl ketones, and in all cases the reaction proceeds normally (see experimental section). This extension may prove to be an important method for degrading and establishing the constitution of naturally occurring hydroxy-ketones.

#### EXPERIMENTAL.

*Gallacetophenone 3 : 4-Dimethyl Ether.*—To a boiling mixture of gallacetophenone (16.8 g.; 1 mol.), benzene (400 c.c.) and anhydrous potassium carbonate (55 g.) was added methyl sulphate

(26 g.; 2.05 mols.) in one portion, and the whole refluxed for 6 hours with occasional shaking. After the addition of water (750 c.c.) and shaking, the benzene layer was separated and shaken several times with sodium hydroxide solution, and the alkaline extracts solidified. The precipitated gallacetophenone 3 : 4-dimethyl ether after crystallisation from methyl alcohol had m. p. 75—77° (yield, 10 g.) (for previous methods of preparation from gallacetophenone, see Perkin, J., 1895, **67**, 997; Perkin and Wilson, J., 1903, **83**, 132; David and von Kostanecki, *Ber.*, 1903, **36**, 127).

**1 : 2-Dihydroxy-3 : 4-dimethoxybenzene (I).**—Gallacetophenone 3 : 4-dimethyl ether (9.8 g.) in 10% sodium hydroxide solution (40 c.c.) was oxidised by the addition of a 3% solution of hydrogen peroxide (75 c.c.) in an atmosphere of coal gas. Considerable rise of temperature occurred and the mixture darkened. After about  $\frac{1}{2}$  hour the solution was acidified, and extracted with ether, the extracts dried and distilled, and 1 : 2-dihydroxy-3 : 4-dimethoxybenzene obtained as a pale yellow oil (5 g.), b. p. 160—170°/20 mm. The diacetyl derivative (acetic anhydride and sodium acetate for 6 hours) had m. p. 85°, and the dimethyl ether (1 : 2 : 3 : 4-tetramethoxybenzene), m. p. 89°; the methylene ether (1 : 2-methylenedioxy-3 : 4-dimethoxybenzene; dill apione), b. p. 75—80°/5 mm., was characterised by its dibromide, m. p. 91° (see Baker and Smith, *loc. cit.*).

**1 : 2-Dihydroxy-3 : 4-dimethoxy-5-allylbenzene (II).**—To 1 : 2-dihydroxy-3 : 4-dimethoxybenzene (12 g.) and allyl bromide (8.5 g.) in acetone (25 c.c.) was added anhydrous potassium carbonate (12 g.), and the mixture refluxed for 18 hours with frequent shaking. After evaporation of the acetone, the mixture was acidified with dilute sulphuric acid and extracted with ether, the extracts shaken with excess of dilute aqueous sodium hydroxide, and the phenolic products reprecipitated from the alkaline layer by acid and again extracted with ether. After removal of the solvent the monoallyl ether was heated in an oil-bath to about 165°; its temperature then suddenly rose to 190°, and, after being kept at 200° for a few minutes, it was distilled under diminished pressure. The thick oily product (4 g.), b. p. 160—173°/14 mm., which partly solidified, was directly used for the subsequent experiments.

**Dill Apiole (1 : 2-Methylenedioxy-3 : 4-dimethoxy-5-allylbenzene) (III).**—Crude 1 : 2-dihydroxy-3 : 4-dimethoxy-5-allylbenzene (4 g.), methylene iodide (5.2 g.), acetone (25 c.c.), and anhydrous potassium carbonate (3 g.) were refluxed for 8 hours. After removal of the acetone and dilution, the methylenated product was extracted with ether, and the extracts were shaken with dilute aqueous sodium hydroxide and distilled twice under diminished pressure. The dill apiole (1 g.) distilled as a colourless, almost odourless oil at 172—173°/16 mm. (Found : C, 64.2; H, 6.4. Calc. for  $C_{12}H_{14}O_4$  : C, 64.9; H, 6.3%) and was converted into monobromodill apiole dibromide (excess bromine in acetic acid; the crude substance melted directly at 104—106°), needles from alcohol, m. p. 107°, which was not depressed on admixture with a specimen of the same melting point prepared from natural dill apiole (Found : C, 31.6; H, 2.6; Br, 51.9. Calc. for  $C_{12}H_{13}O_4Br_2$  : C, 31.2; H, 2.8; Br, 52.1%).

**1 : 2 : 3 : 4-Tetramethoxy-5-allylbenzene.**—1 : 2-Dihydroxy-3 : 4-dimethoxy-5-allylbenzene (3 g.) in methyl alcohol (15 c.c.) was shaken with methyl sulphate (8 g.) and a 10% solution of potassium hydroxide (60 c.c.), added in portions, and finally heated on the steam-bath. After the addition of water ether extracted the tetramethoxyallylbenzene as an oil, which after distillation under diminished pressure (b. p. 145°/12 mm.) solidified when strongly cooled, and had m. p. 25° (Found : C, 65.3; H, 7.4. Calc. for  $C_{13}H_{18}O_4$  : C, 65.5; H, 7.4%) (Thoms, *loc. cit.*, records m. p. 25°).

**Pyrogallol Methylene Ether (IV).**—Pyrogallol (50 g.), acetone (400 c.c.), methylene bromide (110 g.), and anhydrous potassium carbonate were refluxed for 30 hours, then diluted, acidified, and extracted with a large volume of ether. The ethereal extract was shaken several times with water, filtered, and shaken with aqueous sodium hydroxide. The alkaline layer was acidified, extracted several times with warm light petroleum (b. p. 40—60°), and yielded a semi-solid product which, after being pressed on porous porcelain and recrystallised from light petroleum (b. p. 40—60°), had m. p. 65° (Found : C, 60.8; H, 4.4.  $C_7H_6O_3$  requires C, 60.9; H, 4.4%) (yield, 0.06 g.). *Pyrogallol methylene ether* gives a brownish colour with a dilute alcoholic solution of ferric chloride.

**Gallacetophenone 4-Methyl Ether.**—Pyrogallol 1-monomethyl ether was prepared by the oxidation of *o*-vanillin with hydrogen peroxide in alkaline solution (Baker, Montgomery, and Smith, *loc. cit.*; the quantity of 3% hydrogen peroxide there recorded should be 146 c.c. instead of 46 c.c.). Pyrogallol 1-monomethyl ether (1 g.) in acetic acid (8 c.c.) and anhydrous zinc chloride (10 g.) was heated at 155—160° for 8 minutes and poured into water (35 c.c.). Crystallisation occurred on stirring, and the product (0.6 g.) was collected and recrystallised from methyl alcohol; m. p. 132° (compare Perkin and Wilson, *loc. cit.*).

*7-Methoxy-8-acetyl-2-methylchromone.*—7-Hydroxy-8-acetyl-2-methylchromone (Baker, *loc. cit.*) was refluxed for 2 hours in acetone with anhydrous potassium carbonate and  $1\frac{1}{2}$  mols. of methyl sulphate. The product, isolated in the usual way, separated from methyl alcohol as a colourless crystalline powder, m. p. 161—162° (Found: C, 67.1; H, 5.1.  $C_{13}H_{12}O_4$  requires C, 67.2; H, 5.2%). Yield, almost quantitative. The substance slowly turns pale yellow on exposure to light.

*1 : 2 : 4-Trimethoxybenzene.*—Resacetophenone (30.4 g.) in 12% sodium hydroxide solution (150 c.c.) in an atmosphere of coal gas was oxidised by the addition of 6% hydrogen peroxide (143 c.c.) at such a rate that the temperature remained at about 50°. Half an hour after the addition of the hydrogen peroxide the solution was cooled in ice, a solution of sodium hydroxide (50 g.) added, and the mixture mechanically stirred during and after the addition of acetic anhydride (60 c.c.). The solution was then acidified with dilute hydrochloric acid, and the mixed acetyl derivatives were extracted with ether, and, after removal of the solvent, subjected to simultaneous hydrolysis and methylation by the action of excess methyl sulphate and aqueous potassium hydroxide. Ether ultimately extracted 1 : 2 : 4-trimethoxybenzene (11 g.), which, after distillation under diminished pressure, solidified on cooling and had m. p. 19—20°; b. p. 251—252°/756 mm. with slight decomposition.

*Oxidation of Higher Ketones.*—The oxidation of 2 : 4-dihydroxyphenyl benzyl ketone may be taken as a typical case. The ketone (4.56 g.; 1 mol.) in *N*-sodium hydroxide (60 c.c.; 3 mols.) at 25° was oxidised by the addition of 3% hydrogen peroxide (34 c.c.; 1.5 mols.) in an atmosphere of coal gas. The temperature rose to 48°, and after 10 minutes the solution was heated on the steam-bath for 10 minutes, acidified with dilute sulphuric acid, and extracted several times with ether; the extracts were shaken with sodium bicarbonate solution and the alkaline layer was acidified and extracted, yielding phenylacetic acid (2.6 g.; 95% yield). The first ethereal extract, when evaporated and methylated, gave 1 : 2 : 4-trimethoxybenzene. In a similar way 2 : 4-dihydroxyphenyl *p*-methoxybenzyl ketone (ononetin) gave *p*-methoxyphenylacetic acid (60% yield) and 1 : 2 : 4-trimethoxybenzene; homopiperonylresacetophenone gave  $\beta$ -piperonylpropionic acid (90% yield) and 1 : 2 : 4-trimethoxybenzene; and 2-hydroxy-4-methoxyphenyl benzyl ketone—reaction did not start below 60°—gave phenylacetic acid (50% yield).

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