670. *The Synthesis of γ-Resorcylic Acid (2 : 6-Dihydroxybenzoic Acid).*

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With the object of providing a suitable quantity of sodium γ-resorcylate for clinical tests in cases of rheumatic fever (Reid, Watson, Cochran, and Sproull, *Brit. Med. J.*, 1951, 321), known methods of preparing γ-resorcylic acid have been re-investigated and a new synthesis evolved. Mauthner's synthesis from *m*-dinitrobenzene leads to an overall yield of 12%. A convenient synthesis from 2 : 6-dihydroxyacetophenone is described, involving methylation, hypochlorite oxidation, and demethylation with aluminium chloride. Parham and Anderson's method is suitable for small-scale operation and adaptable for the preparation of γ-resorcylic acid isotopically labelled in the carboxyl group. The ultra-violet absorption spectra of γ-resorcylic acid and some related compounds are recorded.

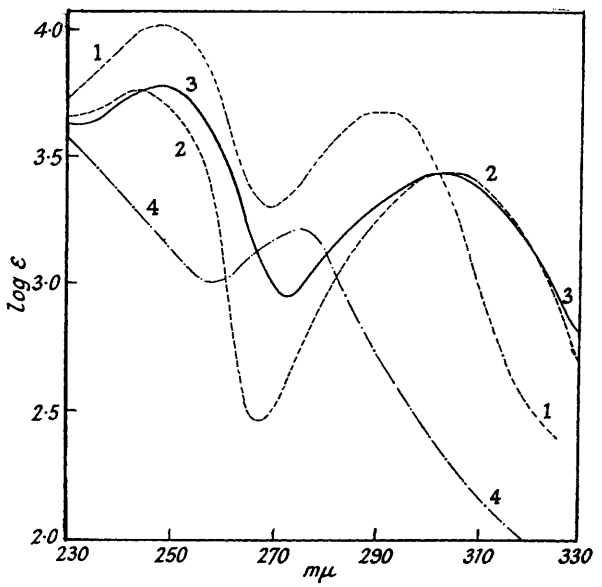
γ-Resorcylic acid was first prepared in low yield by Senhofer and Brunner (*Sitzungsber. Akad. Wiss. Wien*, 1879, **80**, II, 504, 514; *Jahresber. Fortschr. Chem.*, 1880, 835) by carboxylation of resorcinol, a re-investigation of which is described in the following paper. Mauthner's synthesis (*J. pr. Chem.*, 1929, **121**, 259; 1930, **124**, 319), in our hands, afforded at best only a 12% yield of γ-resorcylic acid. Limaye and Kelkar (*J. Indian Chem. Soc.*, 1935, **12**, 788; *Rasayanam*, 1936, **1**, 24) have reported a synthesis of γ-resorcylic acid from 3-acetyl-5-hydroxy-2-methylchromone derived from 2 : 6-dihydroxyacetophenone. The last compound affords a convenient starting point for the synthesis of the acid. We have found that methylation of the ketone followed by hypochlorite oxidation and demethylation with aluminium chloride furnishes γ-resorcylic acid in 91% yield. In the oxidation stage, failure to remove completely the excess of sodium hypochlorite before acidification results in the formation of some 3-chloro-2 : 6-dimethoxybenzoic acid. The orientation of this chloro-derivative was established by demethylation and then decarboxylation to 4-chlororesorcinol. 2-Hydroxy-6-methoxyacetophenone, obtained as a by-product of the methylation of 2 : 6-dihydroxyacetophenone, was converted by Limaye and Kelkar's method (*loc. cit.*, 1936) into 2-hydroxy-6-methoxybenzoic acid for comparison of its ultra-violet absorption spectrum with that of γ-resorcylic acid.

2-Methylresorcinol exists in the aqueous liquors from the low-temperature carbonisation of coal and is commercially available (Baker, Bondy, McOmie, and Tunnicliff, *J.*, 1949, 2835). Alkaline permanganate oxidation of its dimethyl ether furnished 2 : 6-dimethoxybenzoic acid and thence γ-resorcylic acid. An elegant synthesis of the γ-acid by Parham and Anderson (*J. Amer. Chem. Soc.*, 1948, **70**, 4187) involves metalation, with *n*-butyl-lithium, of the acetal formed from resorcinol and dihydropyran, followed by carboxylation and acid hydrolysis. This method is eminently suitable for small-scale preparations and offers a satisfactory route to the acid isotopically labelled in the carboxyl group. With this in mind, the synthesis was carried through on a *ca.* 5-millimole scale under conditions that would obtain in an isotopic synthesis and gave a 51% yield.

The ultra-violet absorption spectra of 2 : 6-dihydroxy-, 2-hydroxy-6-methoxy-, 2 : 6-dimethoxy-, and 2 : 4-dihydroxy-benzoic acid in water in the region 2300—3300 Å are recorded in Fig. 1. Since this work was done, Moser and Kohlenberg (*J.*, 1951, 804) have recorded and discussed the ultra-violet absorption spectra of a series of substituted benzoic acids, including 2 : 6-dihydroxy- and 2 : 6-dimethoxy-benzoic acid, in 95% ethyl alcohol. Our data for 2 : 6-dimethoxybenzoic acid in water are essentially the same as those given by these authors. However, for γ-resorcylic acid the spectra are significantly different in the range 2650—3000 Å. Moser and Kohlenberg record a weakly-defined peak near 2770 Å (log ε 3·29), of which we find no evidence. We believe that their sample of γ-resorcylic acid, prepared by Limaye and Kelkar's method (*loc. cit.*), was probably impure, resorcinol being the likely impurity (this could arise from decarboxylation during the hydrolysis or during purification by crystallisation). At ~2770 Å, where Moser and Kohlenberg observed

the ill-defined maximum, resorcinol has a strong absorption band ($\lambda_{max.}$ 2760, log ε 3·30) (Morton and Stubbs, *J.*, 1940, 1347; Hodgson, *J.*, 1943, 380; Adams, Cain, and Wolff, *J. Amer. Chem. Soc.*, 1940, **62**, 732). The absence of marked absorption by resorcinol in the region of the two maxima for γ-resorcylic acid accounts for the close correspondence found for the values of log ε at these wave-lengths.

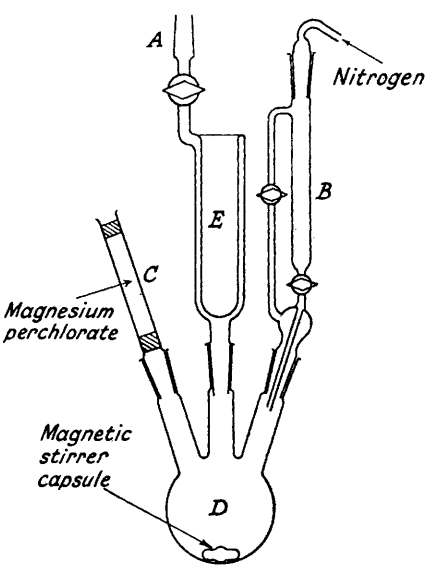
FIG. 1.



Ultra-violet absorption spectra, in water, of:

1, 2 : 4-*Dihydroxybenzoic acid*; 2, 2 : 6-*dihydroxybenzoic acid*; 3, 2-*hydroxy*-6-*methoxybenzoic acid*; 4, 2 : 6-*di-methoxybenzoic acid.*

FIG. 2.



EXPERIMENTAL

Microanalyses are by Miss M. Corner.

Mauthner's Synthesis.—For the preparation of 2 : 6-dimethoxybenzonitrile Russell and Tebbens's procedure (*Org. Synth.*, **22**, 35) was slightly modified. Potassium cyanide (690 g.) in water (1200 c.c.) was added to technical-grade *m*-dinitrobenzene (1500 g.) in methyl alcohol (22·5 l.). The mixture was stirred at 40° for 2 hours, and then set aside for at least 2 days. Cold water (200 l.) was added and the precipitate allowed to resettle overnight, filtered off, pressed, dried in air 2—3 days, and extracted exhaustively with chloroform (Soxhlet). The extract was concentrated to 1500 c.c. by distillation and light petroleum (3 l.; b. p. 60—80°) was added. The precipitated red 6-methoxy-2-nitrobenzonitrile was collected and air-dried (yield from 3 runs, 1390 g., 25%).

The crude nitrile (250 g.) with potassium hydroxide (160 g.) in methyl alcohol (3·8 l.) gave 2 : 6-dimethoxybenzonitrile (17·6%, based on the *m*-dinitrobenzene). This (100 g.) was hydrolysed for 48 hours with potassium hydroxide (2500 g.) in boiling water (5 l.). On cooling, potassium 2 : 6-dimethoxybenzoate crystallised and was removed by filtration and dissolved in the minimum amount of water, and the solution acidified with concentrated hydrochloric acid. The crude acid was filtered off and dried and, since it was advantageous to purify it before demethylation, was extracted (Soxhlet) with benzene. The average yield of purified 2 : 6-dimethoxybenzoic acid, m. p. 186—187°, was 14·8% based on *m*-dinitrobenzene.

For demethylation (cf. Mauthner, *loc. cit.*) free-flowing, sublimed, anhydrous aluminium chloride (Grant and Hardy, B.P. Appl. 19,247/49) was advantageous. The following experiment was typical. To 2 : 6-dimethoxybenzoic acid (125 g.) in benzene (3·5 l.), aluminium chloride (400 g.) was added, and the mixture heated for 2 hours under reflux, with constant stirring. The solution was cooled, poured on ice (2 kg., not more) and later filtered. The aqueous layer was made strongly acid with concentrated hydrochloric acid. γ-Resorcylic acid

separated as needles; a further small quantity was obtained by washing the filtered benzene-insoluble solids with sodium carbonate solution and acidification. In this way, γ-resorcylic acid, m.p. 160—163° (decomp.) after crystallisation from benzene, was obtained in 95—98% yield. Although the acid may be crystallised safely from benzene, some decarboxylation occurs in boiling toluene and, to a smaller extent, in boiling water. Use of the above grade of aluminium chloride led to less amorphous material which, in appreciable quantity, leads to thick emulsions from which separation of the aqueous phase containing the γ-resorcylic acid is difficult.

Synthesis of γ-Resorcylic Acid from 2 : 6-*Dihydroxyacetophenone.*—2 : 6-Dihydroxyacetophenone (Russell and Frye, *Org. Synth.*, **21**, 22; finally crystallised from toluene) and free-flowing sublimed anhydrous aluminium chloride (cf. above) gave 7-acetoxy-4-methylcoumarin in 76—79% yield. The precautions given by Russell and Frye (*loc. cit.*) for decomposing the aluminium chloride complex appear to be unnecessary and in general water was added and the decomposition allowed to take place rapidly, with external cooling if necessary. In addition, completion of the decomposition was effected by adding dilute hydrochloric acid in one stage instead of gradually.

Two routes were investigated for the methylation of 2 : 6-dihydroxyacetophenone.

(*a*) To the ketone (133 g.), suspended in water (100 c.c.) under nitrogen, sodium hydroxide (140 g.) in water (150 c.c.) was added and then methyl sulphate (320 g.) at a rate sufficient to maintain gentle ebullition, and the mixture was then heated on a steam-bath for 30 minutes. A further quantity of methyl sulphate (50 g.) was added, followed by 2N-sodium hydroxide to alkalinity. The mixture was cooled and the product filtered off and washed with water. Pure 2 : 6-dimethoxyacetophenone (127 g.), b.p. 118—120°/1·5 mm., m. p. 65—66°, was obtained by distillation of the product.

(*b*) 2 : 6-Dihydroxyacetophenone (100 g.), anhydrous potassium carbonate (220 g.), and methyl iodide (200 g.) in acetone (600 c.c.) were heated under reflux for 12 hours. After filtration and washing with acetone, the combined filtrates were evaporated and the oily residue was taken up in ether and washed with N-sodium hydroxide. The ethereal solution was dried and the residue after removal of the solvent was purified by crystallisation from light petroleum (b.p. 60—80°), giving pure 2 : 6-dimethoxyacetophenone (95 g.). Distillation is preferred for purification, affording a cleaner product in higher yield (93—97%).

It was advisable to use purified dimethoxy-ketone for the oxidation. Sodium hydroxide (110 g.) in water (100 c.c.) was added to ice (1 kg.) and chlorine passed through until the solution was neutral to litmus (or 89 g. of chlorine). Further sodium hydroxide (50 g.) in water (200 c.c.) was then added. To the resulting solution at 65°, the ketone (60 g.) was added portion-wise during ½ hour : the temperature rose to 85° and was kept thereat for a further 1½ hours. After cooling, excess of sodium hydrogen sulphite (100 g.) was added to destroy unchanged hypochlorite, and the solution was acidified (Congo-red) with hydrochloric acid. When cold the precipitated acid was washed with cold water, then benzene, and dried, giving 2 : 6-dimethoxybenzoic acid, m. p. 185—187° (58 g., 97%), pure enough for demethylation (see above).

For the preparation of the sodium salt, γ-resorcylic acid (100 g.) was washed with saturated sodium chloride solution to remove traces of aluminium salts and then dissolved in N-sodium hydrogen carbonate (300 c.c.) at 70°. Solid sodium hydrogen carbonate (~25—30 g.) was then added gradually until no further reaction ensued. The solution was filtered hot and cooled to 0°. The sodium salt was filtered off and recrystallised from 0·5N-sodium hydrogen carbonate (minimum volume) at 70—80° and the whole cooled to 0°. If necessary, the salt was finally washed with saturated sodium chloride solution to remove colour.

2-*Hydroxy*-6-*methoxybenzoic Acid.*—2-Hydroxy-6-methoxyacetophenone, m. p. 58°, was obtained as a by-product from the methylation of 2 : 6-dihydroxyacetophenone by washing the methylated product with sodium hydroxide solution and acidification. It was also prepared in 60% yield by methylating 2 : 6-dihydroxyacetophenone with one equivalent of methyl iodide, as described by Nakazawa (*J. Pharm. Soc. Japan*, 1939, **59**, 495). It was converted by Limaye and Kelkar's procedure (*loc. cit.*) into 2-hydroxy-6-methoxybenzoic acid, m. p. 134° (Found : C, 57·3; H, 4·9. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%), in low yield.

3-*Chloro*-2 : 6-*dimethoxybenzoic Acid.*—In the above oxidation of 2 : 6-dimethoxyacetophenone incomplete removal of the excess of hypochlorite before acidification results in the formation of some 3-*chloro*-2 : 6-*dimethoxybenzoic acid*, shining plates (from benzene), m. p. 132° (Found : C, 49·8; H, 4·3. $C_9H_9O_4Cl$ requires C, 49·8; H, 4·2%).

The acid (2 g.) was heated for 4 hours with aluminium chloride (6 g.) in benzene (100 c.c.). After cooling, the mixture was poured on ice (40 g.) and set aside. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Treatment of the

ethereal extract with bicarbonate solution and acidification thereof furnished *3-chloro-2 : 6-dihydroxybenzoic acid* (1·65 g.), m. p. 193° after two crystallisations from benzene (Found : C, 44·7, H, 2·8; Cl, 18·3. $C_7H_5O_4Cl$ requires C, 44·5; H, 2·7; Cl, 18·8%). With ferric chloride solution the acid gave a blue colour. On distillation the acid (1 g.) boiled with decarboxylation at about 260° and was converted into 4-chlororesorcinol (0·65 g.), m. p. 89° undepressed on admixture with an authentic specimen.

Oxidation of 2-Methylresorcinol.—To 2-methylresorcinol (50 g.) in a solution of sodium hydroxide (65 g.) in water (250 c.c.) was added methyl sulphate (100 g.) during 15 minutes. The mixture was then heated for 2 hours on a steam-bath, cooled, and extracted with ether. The dried ethereal extract, on removal of the solvent and crystallisation of the residue from benzene, furnished 2 : 6-dimethoxytoluene (57 g.).

2 : 6-Dimethoxytoluene (10 g.) in water (200 c.c.) was treated with potassium permanganate (20·7 g.) during 1 hour at 80°. After being kept overnight the precipitate was filtered off and washed. Acidification of the filtrate furnished 2 : 6-dimethoxybenzoic acid (8·74 g., 73%), m. p. 189°, and ether-extraction of the precipitate afforded unchanged 2 : 6-dimethoxytoluene (1·4 g.).

Parham and Anderson's Synthesis.—Resorcinol bistetrahydro-2-pyranyl ether, prepared as described by Parham and Anderson (*loc. cit.*) and fractionally distilled, was a colourless syrup, b. p. 199°/~2 mm., which crystallised.

n-Butyl-lithium was prepared by Reid's method (quoted in Calvin, Heidelberger, Reid, Tolbert, and Yankwich, "Isotopic Carbon," Chapman and Hall, London, 1949, p. 184), the resulting pentane solution being analysed by Gilman and Haubein's method (*J. Amer. Chem. Soc.*, 1944, **66**, 1515).

A pentane solution (12 ml.) of *n*-butyl-lithium (6 millimoles) was run into flask *D* (Fig. 2) in a current of dry nitrogen from the calibrated dropping-funnel *B*. The flask was connected at *A*, through the condenser *E*, to the vacuum-manifold described by Cox, Turner, and Warne (*J.*, 1950, 3167). Drying-tube *C* was replaced by a stopper, and pentane was distilled from the flask at *ca.* 0·5 atm. until only 1 ml. remained. Pure ether (15 ml.; stored over sodium) was then distilled into *D*, and the stirrer-capsule was agitated. Dry resorcinol bistetrahydro-2-pyranyl ether (1·58 g., 5·7 millimoles) in dry ether (10 ml.) was added quickly through the dropping-funnel. The mixture was warmed under reflux, with solid carbon dioxide in the condenser, for 6 hours and then set aside at room temperature for 16 hours. After the flask had been cooled in liquid nitrogen and evacuated, the contents were warmed to −60° and subjected to vigorous magnetic stirring. Carbon dioxide (15·25 millimoles) was then admitted to the lithium solution; absorption was rapid, the pressure falling from 60 to 10 cm. after 30 seconds and to 8 cm. after a further 2½ minutes. Nitrogen was admitted and the lithium complex decomposed by 15% hydrochloric acid (15 ml.). 2·45 Millimoles of carbon dioxide remained in the vacuum system, *i.e.*, 12·8 millimoles had been absorbed. The reaction mixture was stirred until all solid had dissolved, then the two layers were separated. The aqueous layer was extracted with six portions of ether; the combined extracts were treated with saturated sodium hydrogen carbonate solution (15 ml.), and the aqueous phase separated and acidified. The acid solution was exhaustively extracted with ether. Evaporation of the ether left a residue which on crystallisation from benzene afforded 2 : 6-dihydroxybenzoic acid (0·45 g., 51%), m. p. 168° (microscope and block).

Ultra-violet Absorption Spectra.—The spectra of β- and γ-resorcylic and 2 : 6-dimethoxy- and 2-hydroxy-6-methoxy-benzoic acid in water were measured with a Unicam Model S.P. 500 Quartz Spectrophotometer.

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