340. *γ-Substitution in the Resorcinol Nucleus. Part I. Synthesis of γ-Resorcylaldehyde.*

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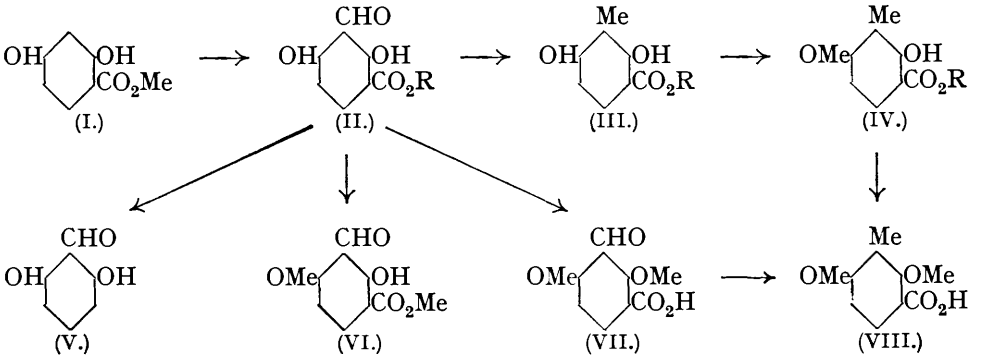
Methyl β-resorcylate, by the Gattermann reaction under modified conditions, gave *methyl* 2 : 4-*dihydroxy*-3-*formylbenzoate*, whose constitution was established by its conversion, by Clemmensen reduction, followed by partial methylation, into the known methyl 2-hydroxy-6-methoxy-*m*-toluate. The aldehydo-ester on hydrolysis by cold alkali gave 2 : 4-*dihydroxy*-3-*formylbenzoic acid*, which on decarboxylation by heating with water in a sealed tube afforded γ-resorcylaldehyde.

The introduction of the formyl group in the 3-position is noteworthy, as 3-substitution in β-resorcylic acid or its ester has not been previously observed. This appears to show that the chelation between the hydroxy- and the carbomethoxy-group in methyl β-resorcylate under the experimental conditions leads to a fixation of the double bonds in the resorcinol nucleus and a consequent stabilisation of one of the Kekulé forms.

The Gattermann reaction failed when it was applied to methyl β-resorcylate (I) under the usual conditions, *viz.*, in the presence of zinc chloride with ether as diluent, or in the presence of aluminium chloride with benzene as diluent (Gattermann, *Ber.*, 1898, **31**, 1765; 1899, **32**, 278). It proceeded readily, however, in the presence of aluminium chloride dissolved in dry ether (cf. Shah, *Current Science*, 1934, 157). The aldehydo-ester obtained was shown to be *methyl* 2 : 4-*dihydroxy*-3-*formylbenzoate* (II, R = Me) by its reduction by the Clemmensen method to *methyl* 2 : 6-*dihydroxy*-m-*toluate* (III, R = Me), which on partial methylation by sodium methoxide and methyl iodide afforded the known methyl 2-hydroxy-6-methoxy-*m*-toluate (IV, R = Me) (Perkin, J., 1895, **67**, 993; Jones and Robertson, J., 1932, 1689).

The aldehydo-ester (II, R = Me) gave the characteristic *o*-hydroxy-aldehyde reaction when condensed with ethyl malonate in the presence of piperidine (Knoevenagel, *Ber.*, **1904, 37**, 4461); the product is formulated as *ethyl 5-hydroxy-6-carbomethoxycoumarin-3-carboxylate* on account of its insolubility in aqueous alkali and its positive ferric chloride reaction. Bromination of (II, R = Me) gave *methyl 5-bromo-2 : 4-dihydroxy-3-formylbenzoate*.

Methylation of (II, R = Me) by the methyl iodide–potassium carbonate–acetone method gave *methyl 2-hydroxy-4-methoxy-3-formylbenzoate* (VI), whereas methylation by methyl sulphate and concentrated alkali solution led to 2 : 4-*dimethoxy*-3-*formylbenzoic acid* (VII). The latter compound on Clemmensen reduction gave 2 : 6-*dimethoxy*-m-*toluic acid* (VIII), which was also obtained by methylation of 2-hydroxy-6-methoxy-*m*-toluic acid (IV, R = H) (Perkin, *loc. cit.*) by methyl sulphate and concentrated alkali solution. The related 2 : 6-*dihydroxy*-m-*toluic acid* (III, R = H) resulted on hydrolysis of (III, R = Me), and also on carboxylation of 2-methylresorcinol by potassium hydrogen carbonate.



Hydrolysis of (II, R = Me) by the prolonged action of cold dilute alkali solution readily produced 2 : 4-*dihydroxy*-3-*formylbenzoic acid* (II, R = H). This acid, heated with water at about 100°, afforded γ-resorcylaldehyde (V), m. p. 155—156°, which dissolved in dilute alkali solution with a deep yellow colour, owing probably to the existence of the ordinary and the quinonoid form in tautomeric equilibrium (cf. Robertson and Robinson, J., 1927, 2196). The constitution of the aldehyde follows from the constitution (II, R = Me) for the aldehydo-ester, and from its reduction by the Clemmensen method to 2-methylresorcinol. The Knoevenagel condensation of γ-resorcylaldehyde with ethyl malonate gave *ethyl 5-hydroxycoumarin-3-carboxylate*.

When the above work (cf. Shah and Laiwalla, *Current Science*, 1936, 197) was nearly completed, a synthesis of γ-resorcylaldehyde by a different and highly involved method was reported (Limaye, *Rasayanam*, 1936, **1**, 8; *Brit. Chem. Abstr.*, 1937, *A*, ii, 258).

The modification of the Gattermann reaction mentioned above may find application in other cases. The introduction of the formyl group in the 3-position in methyl β-resorcylate is of special interest as being the first case of the kind; (II, R = Me) is formed exclusively in high yield and none of the isomeric 2 : 4-dihydroxy-5-formylbenzoate is obtained. These results seem to show that chelation between the carbomethoxy- and the *o*-hydroxy-group in methyl β-resorcylate, under the experimental conditions, requires the presence of a double bond between the carbon atoms bearing these two groups, one of the Kekulé forms being thus stabilised. As 3-substitution in β-resorcylic acid or its ester has not previously been observed, it has hitherto appeared that chelation between the carbomethoxy- or the carboxyl group and the *o*-hydroxy-group does not lead to stabilisation of one of the Kekulé forms (Baker, J., 1934, 1689; Baker and Carruthers, J., 1937, 479).

Experimental.

Formation of Methyl 2 : 4-Dihydroxy-3-formylbenzoate (II, R = Me) *from Methyl β-Resorcylate by the Gattermann Reaction.*—All the experiments were carried out with zinc cyanide instead of anhydrous hydrogen cyanide (Adams and Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373).

The specially prepared zinc cyanide of those authors was conveniently replaced by Kahlbaum's pure zinc cyanide, which was almost equally effective.

In a number of experiments under various conditions in which (*a*) zinc cyanide with ether as diluent, or (*b*) zinc cyanide and aluminium chloride with benzene as diluent, were used, methyl β-resorcylate was completely recovered.

To a solution of anhydrous methyl β-resorcylate (Robinson and Shah, J., 1934, 1496) (15 g.; 1 mol.) in dry ether in a flask fitted with a mercury seal and a mechanical stirrer and cooled by a freezing mixture, zinc cyanide (21 g.; 2 mols.) was added, followed by a solution of anhydrous aluminium chloride (24 g.; 2 mols.) in dry ether. Dry hydrogen chloride was then passed for 5 hours through the cooled stirred mixture; the zinc cyanide gradually disappeared, the solution turned red, and a pasty mass separated. Water (200 c.c.) was added, the first 50 c.c. gradually, and the mixture was heated at 100° for ½ hour. The yellow flocculent precipitate was separated while hot; the filtrate slowly deposited methyl β-resorcylate (2 g.). The precipitated aldehydo-ester was purified by distillation in steam or by crystallisation from boiling alcohol. *Methyl* 2 : 4-*dihydroxy*-3-*formylbenzoate* formed colourless needles (11 g.), m. p. 138—140° (Found: C, 55·2; H, 4·1. $C_9H_8O_5$ requires C, 55·1; H, 4·1%), insoluble in water, very sparingly soluble in cold and moderately soluble in hot alcohol, and readily soluble in cold benzene. It gave a bright yellow colour with alkali solution and a deep red coloration with alcoholic ferric chloride.

The 2 : 4-*dinitrophenylhydrazone* crystallised from glacial acetic acid in tiny yellow needles, m. p. 291—293° (decomp.) (Found: N, 14·9. $C_{15}H_{12}O_8N_4$ requires N, 14·9%). The *semicarbazone*, prepared in aqueous-alcoholic solution, crystallised from acetic acid in colourless needles, decomp. 260—265° (Found: N, 16·3. $C_{10}H_{11}O_5N_3$ requires N, 16·6%). The *oxime* crystallised from alcohol in colourless tiny needles, m. p. 164—165° (Found: N, 6·8. $C_9H_9O_5N$ requires N, 6·6%). The *anil*, prepared from the ester and excess of aniline at 100°, crystallised from alcohol in fine yellow needles, m. p. 131—132° (Found: N, 5·4. $C_{15}H_{13}O_4N$ requires N, 5·2%).

Methyl 2 : 6-*Dihydroxy*-m-*toluate* (III, R = Me).—The aldehydo-ester (3 g.), dissolved in hot alcohol, was gradually added to a mixture of zinc amalgam (prepared from 40 g. of zinc dust; Robinson and Shah, J., 1934, 1497) and dilute hydrochloric acid (1 : 1; 50 c.c.) at 100°, more alcohol being added whenever necessary to keep the substance in solution. After 1 hour, concentrated hydrochloric acid (10 c.c.) was added, and heating continued for a further ½ hour. The hot liquid after filtration deposited long colourless needles, m. p. 134—135°, on cooling. An ethereal extract of the zinc amalgam gave a further quantity of the same substance. Total yield, 2 g. (Found: C, 59·6; H, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%).

Methyl 2-*Hydroxy*-6-*methoxy*-m-*toluate* (IV, R = Me).—The foregoing compound (0·2 g.), dissolved in the minimum quantity of hot methyl alcohol, was added to sodium methoxide (from 0·5 g. of sodium) dissolved in methyl alcohol (5 c.c.). Methyl iodide (5 c.c.) was added, and the mixture refluxed for 5 hours. Most of the methyl alcohol was evaporated, water added, and the mixture acidified with dilute hydrochloric acid and extracted with ether. The extract was washed twice with N-sodium hydroxide and water, and the solvent evaporated. The residue crystallised from dilute alcohol in colourless needles, m. p. 77—79°, not depressed by authentic methyl 2-hydroxy-6-methoxy-*m*-toluate (Perkin, *loc. cit.*, gives m. p. 76—77°) (Found: C, 61·2; H, 6·3. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·1%).

Ethyl 5-*Hydroxy*-6-*carbomethoxycoumarin*-3-*carboxylate*.—Piperidine (4 drops) was added to a mixture of (II, R = Me) (2 g.) and ethyl malonate (2 g.), dissolved in pyridine, and the mixture heated at 100° for 1 hour. The solid obtained on addition of dilute hydrochloric acid was triturated with 2N-potassium hydroxide to remove the unchanged aldehydo-ester. The insoluble solid crystallised from alcohol in colourless prismatic needles (1·7 g.), m. p. 157—158° (Found: C, 57·5; H, 4·1. $C_{14}H_{12}O_7$ requires C, 57·5; H, 4·1%). It was insoluble in aqueous alkali, but dissolved to a yellow solution without fluorescence in aqueous-alcoholic alkali. It gave a deep red colour with alcoholic ferric chloride. The *compound* was obtained in inferior yield on carrying out the condensation at room temperature in absence of pyridine.

Methyl 5-*bromo*-2 : 4-*dihydroxy*-3-*formylbenzoate*, m. p. 133—134°, was prepared by bromination of (II, R = Me) (1 g.) in hot glacial acetic acid; it crystallised on cooling (Found: Br, 29·0. $C_9H_7O_5Br$ requires Br, 29·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from boiling acetic acid in needles, m. p. 294—295° (Found: N, 11·7. $C_{15}H_{11}O_8N_4Br$ requires N, 12·2%).

Methyl 2-*hydroxy*-4-*methoxy*-3-*formylbenzoate* (VI), prepared in poor yield by the potassium carbonate–methyl iodide–acetone method, crystallised from benzene–light petroleum in colour-

less plates, m. p. 121—122° (Found: C, 56·9; H, 4·6. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). It was insoluble in dilute alkali solution and gave a reddish-violet coloration with alcoholic ferric chloride.

2 : 4-*Dimethoxy*-3-*formylbenzoic Acid* (VII).—The aldehydo-ester (5 g.), dissolved in hot methyl alcohol (25 c.c.), was methylated with methyl sulphate (20 c.c.) and 20% potassium hydroxide solution (100 c.c.), added alternately in small portions during ½ hour, the mixture being cooled at intervals. The mixture was then made distinctly alkaline and heated at 100° for ¼ hour. The flocculent yellow precipitate obtained on acidification was washed, dried, and washed with cold benzene. The product, which gave an appreciable coloration with alcoholic ferric chloride, was repeatedly crystallised, first from dilute methyl alcohol, then from chloroform–light petroleum, and finally from hot water; the *dimethoxy-acid* was obtained in pale yellow needles, m. p. 185—187° (Found: C, 57·1; H, 4·7. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%), which gave no coloration with alcoholic ferric chloride.

2 : 6-*Dimethoxy*-m-*toluic Acid* (VIII).—(i) The foregoing compound (VII) (0·2 g.) in hot alcoholic solution was added in small portions to a mixture of zinc amalgam (from 5 g. of zinc) and dilute hydrochloric acid (10 c.c.; 1 : 1) at 100°, and the mixture further treated as in the reduction of (II, R = Me) (p. 1830). The *product* crystallised from hot alcohol in colourless needles, m. p. 146—147° (Found: C, 61·3; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). The ferric reaction was negative. (ii) Methyl 2-hydroxy-6-methoxy-*m*-toluate (IV, R = Me) (Perkin, *loc. cit.*) was hydrolysed by boiling alkali. The acid (IV, R = H) obtained on acidification was recrystallised from hot alcohol; m. p. 214—215° (Perkin gives m. p. 210°) (Found: C, 59·3; H, 5·6. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). It was methylated in acetone with methyl sulphate and 20% potassium hydroxide solution; the dimethoxy-acid, precipitated by hydrochloric acid, crystallised from alcohol in colourless needles, m. p. and mixed m. p. with the acid from (i), 146—147°.

2 : 6-*Dihydroxy*-m-*toluic Acid* (III, R = H).—(i) Methyl 2 : 6-dihydroxy-*m*-toluate (1 g.) was hydrolysed by 2N-sodium hydroxide (50 c.c.) at 100° and the cooled solution after acidification was extracted with ether. The solid residue obtained from the extract crystallised from boiling xylene in colourless flat needles, m. p. 198—199° (Found: C, 57·3; H, 5·1. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). (ii) A mixture of 2-methylresorcinol (Jones and Robertson, *loc. cit.*) (0·25 g.), potassium hydrogen carbonate (1·25 g.), and water (5 c.c.) was heated on the water-bath for 4 hours and subsequently refluxed for ½ hour. Acidification with concentrated hydrochloric acid afforded a brownish granular solid, which crystallised from hot dilute hydrochloric acid in flat needles, m. p. 200—201° (decomp.), identical with the compound from (i).

2 : 4-*Dihydroxy*-3-*formylbenzoic Acid* (II, R = H).—The aldehydo-ester (10 g.) was dissolved in N-sodium hydroxide (167 c.c.) and left at room temperature for 45 hours. Acidification of the brownish-red solution with concentrated hydrochloric acid precipitated the *acid*, which was extracted with ether, recovered, triturated with cold benzene to remove unchanged ester, and crystallised from dilute methyl alcohol; it formed colourless needles (7·5 g.), m. p. 193—194° (decomp.) (Found: C, 53·3; H, 3·4. $C_8H_6O_5$ requires C, 52·7; H, 3·3%), readily soluble in methyl and ethyl alcohols and sparingly in benzene.

γ-Resorcylaldehyde (V).—Attempts to decarboxylate the acid (II, R = H) by the usual methods gave unsatisfactory results. The acid (2 g.) and water (30 c.c.) were heated together in a sealed tube at 100—110° for 10 hours. The mixture was extracted with ether, in which the red resinous matter formed was sparingly soluble. The oily reddish residue obtained on evaporation of the ether was extracted with the minimum quantity of boiling water; the pale yellow solution, on cooling, deposited tiny, slightly yellowish needles of the aldehyde (0·5 g.), m. p. 155—156°. Limaye (*loc. cit.*) gives m. p. 154—155° (Found: C, 60·4; H, 4·3. Calc. for $C_7H_6O_3$: C, 60·9; H, 4·3%). It was sparingly soluble in cold water, much more soluble in hot, readily soluble in cold alcohol and in benzene, and dissolved in alkali with a deep yellow colour, which slowly changed to brown owing to oxidation. It gave a dark brown coloration with aqueous or alcoholic ferric chloride.

The 2 : 4-*dinitrophenylhydrazone* crystallised from much boiling alcohol in tiny yellow needles, m. p. 288—291° (Found: N, 16·5. $C_{13}H_{10}O_6N_4$ requires N, 17·6%). The *semicarbazone* crystallised from hot alcohol in colourless plates, m. p. 245° (Found: N, 20·9. $C_8H_9O_3N_3$ requires N, 21·5%).

Ethyl 5-Hydroxycoumarin-3-carboxylate.—Piperidine (2 drops) was added to a cooled mixture of γ-resorcylaldehyde (0·3 g.) and ethyl malonate (0·4 g.). The resulting red liquid, left at room temperature overnight, solidified. It was treated with dilute hydrochloric acid; the

resulting solid crystallised from alcohol in yellowish plates, m. p. 229—230° (Found: C, 61·5; H, 4·8. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

Clemmensen-reduction of γ-Resorcylaldehyde.—The aldehyde (0·4 g.) was reduced with a mixture of zinc amalgam (from 10 g. of zinc) and dilute hydrochloric acid (20 c.c.) similarly to (II, R = Me). The hot solution was filtered, cooled, saturated with sodium chloride, and extracted with ether. The solid residue obtained from the extract crystallised from benzene in colourless plates, m. p. 117—118°, not depressed by 2-methylresorcinol (m. p. 117—118°) prepared by the action of hydriodic acid on 2-hydroxy-6-methoxy-*m*-toluic acid (cf. Jones and Robertson, *loc. cit.*).

All the analyses are microanalyses by Dr. Schoeller.

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