640. *Derivatives of* 4 : 5-*Dimethylresorcinol.*

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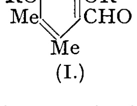
In contrast to the behaviour of the analogous resorcinol derivative (III ; R = H), 4 : 5-dimethylresorcinol has been found to give by Gattermann's method only 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde (I ; R = R′ = H), the orientation of which has been established. Application of the same reaction to the methyl ester (V ; R = H, R′ = Me) gave the formyl derivative (VI) which on hydrolysis and decarboxylation yielded 2 : 6-dihydroxy-3 : 4-dimethylbenzaldehyde (II).

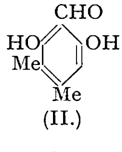
2 : 6-Dihydroxy-3 : 4 : 5-trimethylbenzaldehyde was prepared from 4 : 5 : 6-trimethylresorcinol and on reduction yielded 2 : 4 : 5 : 6-tetramethylresorcinol.

Carboxylation of 3 : 4-dimethylresorcinol has been shown to give the acid (VII ; R = R′ = H).

IN the course of experiments on the synthesis of certain degradation products of citrinin (Brown *et al.*, this vol., p. 867) it was observed that the application of the Gattermann aldehyde synthesis to the resorcinol derivative (III ; R = H) gave rise to a mixture of the two possible isomeric aldehydes in which the isomeride (III ; R = CHO) unexpectedly predominated. On the other hand, Butenandt and Stodola (*Annalen*, 1939, **539**, 40) and Karrer and Schick (*Helv. Chim. Acta*, 1943, **26**, 800) obtained from the analogous phenol, 4 : 5-dimethylresorcinol, only one product to which they allocated the structure (I ; R = R′ = H) mainly on the grounds that reduction of this aldehyde gave a trimethylresorcinol considered to be identical with the trimethylresorcinol prepared by Simons (*Annalen*, 1903, **329**, 309) who formulated the compound as 4 : 5 : 6-trimethylresorcinol but did not establish its orientation. In view of the striking contrast in the behaviour of the two closely related phenols, 4 : 5-dimethylresorcinol and (III ; R = H), in the Gattermann reaction, it seemed desirable to re-examine the product obtained from the former and to determine the orientation of the aldehyde (I ; R = R′ = H) and consequently that of the trimethylresorcinol obtained from it on reduction. Accordingly the experiments described in this communication were undertaken.



(I.)



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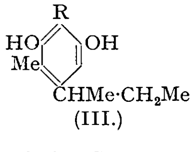

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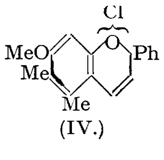
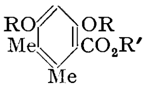


(IV.)

Under standard conditions the application of the Gattermann reaction to 4 : 5-dimethylresorcinol gave an almost theoretical yield of 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde (I ; R = R′ = H) unaccompanied by detectable amounts of the isomeric 2 : 6-dihydroxy-3 : 4-dimethylbenzaldehyde (II). Partial methylation of the compound (I ; R = R′ = H) gave rise to a *monomethyl ether* which, since it exhibited a strong ferric reaction and condensed with acetophenone to give the *flavylium chloride* (IV), must have the orientation (I ; R = Me, R = H). On the other hand, partial benzylation of (I ; R = R′ = H) furnished the corresponding *monobenzyl ether* (I ; R = CH_2Ph, R′ = H) which on methylation gave the *benzyl methyl ether* (I ; R= CH_2Ph ; R′ = Me). Debenzylation of the latter ether yielded a *monomethyl ether* which, since it did not give a ferric reaction or form a flavylium salt, must clearly have the structure (I ; R = H, R′ = Me). The formation of two monomethyl ethers having these properties can only arise if the parent aldehyde has the orientation (I; R = R′ = H) and not (II) and hence the reduction product of (I; R = R′ = H) is 4 : 5 : 6-trimethylresorcinol.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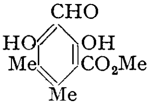
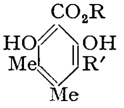

(VI.)


(VII.)

The aldehyde (II), which could not be obtained directly from 4 : 5-dimethylresorcinol, was prepared by the following route. Oxidation of the *diacetate* (I; R = R′ = Ac) and subsequent deacetylation of the product gave rise to 4 : 6-*dihydroxy*-2 : 3-*dimethylbenzoic acid* and on application of the Gattermann reaction to the *methyl* ester of this acid 2 : 6-*dihydroxy*-5-*carbomethoxy*-3 : 4-*dimethylbenzaldehyde* was obtained which with boiling aqueous potassium hydroxide underwent simultaneous hydrolysis and decarboxylation, yielding 2 : 6-*dihydroxy*-3 : 4-*dimethylbenzaldehyde* (II). The latter compound closely resembled the analogous γ-resorcylaldehydes, *viz.*, *m*-xylorcylaldehyde (Robertson and Robinson, *J.*, 1947, 2196) and 2-(3 : 5-dihydroxy-4-formyl-2-methylphenyl)butane (III; R = CHO) (*loc. cit.*), in having a bright yellow colour and in giving a dark green ferric reaction. Further, the view expressed by Brown *et al.* (this vol., p. 859) that the aldehyde obtained from 4-methyl-5-ethylresorcinol is 4 : 6-dihydroxy-3-methyl-2-ethylbenzaldehyde finds substantial support in the fact that the properties of this compound closely resemble those of the homologous β-aldehyde (I; R = H; R′ = H) and not those of the γ-aldehyde (II).

By the standard method 2 : 6-*dihydroxy*-3 : 4 : 5-*trimethylbenzaldehyde* was prepared from 4 : 5 : 6-trimethylresorcinol in satisfactory yield and on reduction according to the method of Clemmensen gave 2 : 4 : 5 : 6-*tetramethylresorcinol* characterised by the formation of the *di*-p-*nitrobenzoate*. Like *m*-xylorcin 4 : 5 : 6-trimethylresorcinol failed to undergo the Hoesch reaction with methyl cyanide.

Carboxylation of 4 : 5-dimethylresorcinol by the procedure employed for *p*-orsellinic acid (Robertson and Robinson, *loc. cit.*) gave 2 : 6-*dihydroxy*-3 : 4-*dimethylbenzoic acid* (VII; R = R′ = H), m. p. 179° (decomp.), oriented by the fact that its *methyl* ester furnished a *formyl* derivative (VII; R = CHO, R′ = Me) which on simultaneous hydrolysis and decarboxylation gave rise to 2 : 4-dihydroxy-5 : 6-dimethylbenzaldehyde (I; R = R′ = H). From its properties and method of preparation it now seems reasonably certain that the acid, m. p. 159—160°, described by Koller and Passler (*Monatsh.*, 1930, **56**, 131) is 4 : 6-dihydroxy-2 : 3-dimethylbenzoic acid and not the isomeride (VII; R = R′ = H).

EXPERIMENTAL.

Methyl Ethers of 4 : 6-*Dihydroxy*-2 : 3-*dimethylbenzaldehyde*.—Prepared in almost quantitative yield by the hydrogen chloride–hydrogen cyanide method, 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde formed pale yellow prisms, m. p. 196°, which retained its colour on being sublimed in a high vacuum and gave a 2 : 4-*dinitrophenylhydrazone* forming stout crimson prisms, m. p. 286° (decomp.), from alcohol (Found : N, 16·2. $C_{15}H_{14}O_6N_4$ requires N, 16·2%) (compare Butenandt and Stodola, *loc. cit.*, and Karrer and Schick, *loc. cit.*, who state the yield of aldehyde to be *ca.* 75%). Methylation of the aldehyde (1 g.) with potassium carbonate (4 g.) and an excess of methyl iodide in boiling acetone (75 ml.) during 10 hours gave 4 : 6-*dimethoxy*-2 : 3-*dimethylbenzaldehyde* (I; R = R′ = Me) which formed colourless prisms (1 g.), m. p. 128°, from dilute alcohol and had a negative ferric reaction (Found : C, 67·9; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in tufts of bright red needles, m. p. 267° (decomp.) (Found : N, 15·3. $C_{17}H_{18}O_6N_4$ requires N, 15·0%).

A mixture of 2 : 4-dihydroxy-5 : 6-dimethylbenzaldehyde (2 g.), methyl iodide (2 g.), potassium carbonate (4 g.), and acetone (75 ml.) was heated under reflux for 1 hour, filtered, and evaporated. A solution of the residue in ether (250 ml.) was extracted with 0·5N-sodium hydroxide (50 ml. × 3) to remove unchanged aldehyde and then with 2N-sodium hydroxide (50 ml. × 8) with the addition of water as required to dissolve the rather sparingly soluble sodium salt which separated during the extraction. Acidification of the latter combined extracts with hydrochloric acid gave a colourless crystalline precipitate of 6-*hydroxy*-4-*methoxy*-2 : 3-*dimethylbenzaldehyde* (I; R = Me, R′ = H) which, on recrystallisation from aqueous methanol, was obtained in magnificent, long, colourless prisms (1 g.), m. p. 121°, having a reddish-brown ferric reaction in alcohol (Found : C, 66·6; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright red prisms, m. p. 291° (decomp.) (Found : N, 14·9. $C_{16}H_{16}O_6N_4$ requires N, 15·6%). On being saturated at 0° with hydrogen chloride a solution of this monomethyl ether (0·5 g.) and acetophenone (0·5 g.) in ethyl acetate (5 ml.) deposited 7-*methoxy*-5 : 6-*dimethylflavylium chloride* during 48 hours, which crystallised from dilute hydrochloric acid in long, slender, orange-yellow needles, m. p. 179° (decomp.) (Found : Cl, 10·8. $C_{18}H_{17}O_4Cl$ requires Cl, 11·7%).

Monobenzylation of 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde (3 g.) was effected with benzyl bromide (3·3 g.) and potassium carbonate (6 g.) in boiling acetone (75 ml.) during 1 hour; the resulting 6-*hydroxy*-4-*benzyloxy*-2 : 3-*dimethylbenzaldehyde* (I; R = Bz, R′ = H) separated from dilute alcohol in colourless needles (3 g.), m. p. 85°, having a reddish-brown ferric reaction in alcohol (Found : C, 74·8; H, 6·4. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). The 2 : 4-*dinitrophenylhydrazone* formed tiny, bright crimson prisms, m. p. 242° (decomp.), from ethyl acetate (Found : N, 13·2. $C_{22}H_{20}O_6N_4$ requires N, 12·8%). Methylation of this monobenzyl ether (2·4 g.) with potassium carbonate (7 g.) and an excess of methyl iodide in boiling acetone (75 ml.) during 10 hours gave 4-*benzyloxy*-6-*methoxy*-2 : 3-*dimethylbenzaldehyde* (I; R = CH_2Ph, R′ = Me) which crystallised from dilute alcohol in colourless needles (2·7 g.), m. p. 118°, and had a negative ferric reaction (Found : C, 75·6; H, 6·7. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* formed tiny, bright crimson needles, m. p. 216° (decomp.), from ethyl acetate (Found : N, 12·0. $C_{23}H_{22}O_6N_4$ requires N, 12·4%).

Debenzylation of the mixed ether (1·5 g.) by means of a hot mixture of acetic acid (15 ml.) and concentrated hydrochloric acid (10 ml.) on the steam-bath for 10 minutes and subsequent dilution of the resulting dark green solution with water (35 ml.) gave a crystalline precipitate of 4-*hydroxy*-6-*methoxy*-2 : 3-*dimethylbenzaldehyde* (I; R = H, R′ = Me) (0·5 g.) which separated from benzene–methanol in colourless needles, m. p. 253°, having a negative ferric reaction (Found : C, 66·5; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in slender, bright crimson needles, m. p. 270° (decomp.) (Found : N, 15·3. $C_{16}H_{16}O_6N_4$ requires N, 15·6%).

2 : 6-*Dihydroxy*-3 : 4-*dimethylbenzaldehyde* (II).—Acetylation of 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde (5 g.) with acetic anhydride (15 ml.) and pyridine (5 g.) on the steam-bath for ½ hour gave rise to 4 : 6-*diacetoxy*-2 : 3-*dimethylbenzaldehyde* (I; R = R′ = Ac) which formed colourless prisms (5·7 g.), m. p. 111°, from aqueous alcohol (Found : C, 62·3; H, 5·7. $C_{13}H_{14}O_5$ requires C, 62·3; H, 5·6%). This diacetate (4 g.), dissolved in acetone (75 ml.), was oxidised by the gradual addition of a solution of potassium permanganate (5 g.) in water (150 ml.) during ½ hour. The reaction mixture was then kept for ½ hour, cleared with sulphur dioxide, and treated with an excess of dilute sulphuric acid. After the evaporation of the greater part of the acetone in a vacuum the precipitate was collected and purified by means of aqueous sodium hydrogen carbonate and then by crystallisation from benzene, giving a product consisting of 4 : 6-diacetoxy-2 : 3-dimethylbenzoic acid (V; R = Ac, R′ = H) in stout colourless prisms (3 g.), m. p. 144°, contaminated with traces of an impurity which appeared to be the partly deacetylated compound and could not be economically removed. A specimen of the acid was esterified with an excess of ethereal diazomethane, and on repeated crystallisation from benzene–light petroleum the product gave *methyl* 4 : 6-*diacetoxy*-2 : 3-*dimethylbenzoate* (V; R = Ac, R′ = Me) in massive colourless prisms, m. p. 76° (Found : C, 60·2; H, 5·9. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%).

The foregoing 4 : 6-diacetoxy-2 : 3-dimethylbenzoic acid (2 g.) was deacetylated with 10% aqueous potassium hydroxide (15 ml.) at room temperature during 2 hours and, on isolation with the aid of ether, the resulting 4 : 6-*dihydroxy*-2 : 3-*dimethylbenzoic acid* (V; R = R′ = H) separated from water or benzene–acetone in colourless needles (1·2 g.), m. p. 163°, exhibiting a reddish-brown ferric reaction in alcohol (Found : C, 59·3; H, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). Ethereal diazomethane was slowly added to a solution of this acid (5 g.) in ether (100 ml.) until a faint yellow colour persisted and 5 minutes later the mixture was washed with dilute aqueous sodium hydrogen carbonate, dried, and evaporated, leaving a residue which partly crystallised and appeared to retain traces of diazomethane. The product was purified by being dissolved in 2N-aqueous sodium hydroxide and re-precipitated with ice-cold dilute hydrochloric acid and then crystallised from benzene–light petroleum (b. p. 60—80°), giving *methyl* 4 : 6-*dihydroxy*-2 : 3-*dimethylbenzoate* (V; R = H; R′ = Me) in colourless needles (4 g.), m. p. 126°, which had a violet ferric reaction in alcohol (Found: C, 61·1; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

A mixture of methyl 4 : 6-dihydroxy-2 : 3-dimethylbenzoate (1 g.), zinc cyanide (1·7 g.), and ether (100 ml.) was saturated at 0° with hydrogen chloride and 48 hours later the viscous oil which had separated was isolated, washed with ether, and dissolved in water (30 ml.). This solution was almost neutralised with aqueous ammonia and then heated on the steam-bath for 15 minutes, giving a precipitate of *methyl* 2 : 4-*dihydroxy*-3-*formyl*-5 : 6-*dimethylbenzoate* (VI); unchanged ester (0·5 g.) was recovered from the combined ethereal liquors. Crystallised from dilute methanol, this aldehydo-ester was obtained in pale yellow needles (0·25 g.), having a reddish-brown ferric reaction in alcohol (Found : C, 58·8; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). The 2 : 4-*dinitrophenylhydrazone* separated from a large volume of acetic acid or chloroform in tiny bright orange-yellow needles, m. p. 276° (decomp.) (Found : N, 14·1. $C_{17}H_{16}O_8N_4$ requires N, 13·9%).

A mixture of the aldehydo-ester (0·2 g.), water (5 ml.), and potassium hydroxide (0·75 g.) was heated under reflux in an atmosphere of nitrogen for 2 hours, cooled, and acidified with concentrated hydrochloric acid, and the precipitate recrystallised from benzene–light petroleum (b. p. 60—80°), giving 2 : 6-*dihydroxy*-3 : 4-*dimethylbenzaldehyde* (II) (0·15 g.) in stout, yellow prisms, m. p. 140°, readily soluble in alcohol and sparingly soluble in light petroleum (Found : C, 65·2; H, 6·2. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). This aldehyde, which gave an intense deep-green ferric reaction in alcohol, formed a 2 : 4-*dinitrophenylhydrazone* which separated from alcohol–ethyl acetate in thick crimson prisms, m. p. 289° (decomp.) (Found : N, 15·8. $C_{15}H_{14}O_6N_4$ requires N, 16·2%). A mixture of this compound and the corresponding derivative of 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde began to melt at about 260°.

2 : 6-*Dihydroxy*-3 : 4 : 5-*trimethylbenzaldehyde*.—Reduction of 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde by the method of Clemmensen gave an almost quantitative yield of 4 : 5 : 6-trimethylresorcinol, forming colourless prisms, m. p. 165°, from benzene (cf. Butenandt and Stodola, *loc. cit.*, who give m. p. 162·5—163·5°). The *di*-p-*nitrobenzoate* of this phenol separated from much acetic acid in thick, colourless prisms, m. p. 249° (Found : C, 61·3; H, 4·1; N, 6·5. $C_{23}H_{18}O_8N_2$ requires C, 61·3; H, 4·0; N, 6·2%).

The aldimine hydrochloride formed by the interaction of 4 : 5 : 6-trimethylresorcinol (1 g.) with hydrogen cyanide (5 ml.) and an excess of hydrogen chloride in ether (75 ml.) at 0° was hydrolysed with water (50 ml.) on the steam-bath for ½ hour, and the resulting 2 : 6-*dihydroxy*-3 : 4 : 5-*trimethylbenzaldehyde* purified from aqueous alcohol, being obtained in slender, rectangular, lemon-yellow prisms, m. p. 136°, which gave an intense deep-green ferric reaction in alcohol (Found : C, 66·7; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in bright crimson needles, m. p. 288° (decomp.) (Found : N, 14·9. $C_{16}H_{16}O_6N_4$ requires N, 15·6%).

A solution of this aldehyde (1·5 g.) in alcohol (20 ml.) was added to boiling 20% hydrochloric acid (25 ml.) containing amalgamated zinc (30 g.) during 15 minutes, the mixture was then refluxed for ½ hour, the liquor was decanted, the residual amalgam was washed with a small amount of warm alcohol, and the combined liquor and washings were diluted with water (100 ml.), giving a crystalline precipitate of 2 : 4 : 5 : 6-*tetramethylresorcinol* which formed colourless feathery needles (1 g.), m. p. 140°, from benzene–light petroleum (b. p. 60—80°). Purified from solvents, this phenol had a somewhat variable m. p. owing apparently to solvation, but on being sublimed at 140°/0·01 mm. the compound was desolvated and obtained in colourless needles, m. p. 157° (Found : C, 72·0; H, 8·7. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). The *di*-p-*nitrobenzoate* separated from acetic acid in colourless prisms, m. p. 226° (Found : N, 5·9. $C_{24}H_{20}O_8N_2$ requires N, 6·0%).

Methyl 2 : 6-*Dihydroxy*-5-*formyl*-3 : 4-*dimethylbenzoate* (VII; R = Me; R′ = CHO).—A mixture of 4 : 5-dimethylresorcinol (3 g.), glycerol (25 ml.), and potassium hydrogen carbonate (20 g.) was kept at 150° for 3 hours and simultaneously a stream of carbon dioxide was bubbled through the hot melt. A solution of the cooled reaction mixture in water (250 ml.) was extracted with ether to remove unchanged phenol and then acidified with hydrochloric acid, giving a precipitate of 2 : 6-*dihydroxy*-3 : 4-*dimethylbenzoic acid* (VII; R = R′ = H) which formed colourless needles (3·2 g.), m. p. 179° (decomp.), from aqueous acetone and had a sky-blue ferric reaction in alcohol (Found : C, 59·4; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). Prepared by means of ethereal diazomethane, the *methyl* ester separated from aqueous methanol in thick colourless prisms, m. p. 108°, having a greenish-blue ferric reaction in alcohol (Found : C, 61·1; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). A solution of this ester (1·4 g.) in ether (150 ml.), containing zinc cyanide (2 g.), was saturated at 0° with hydrogen chloride, and 24 hours later the crystalline product was collected and hydrolysed with water (75 ml.) on the steam-bath during ½ hour, giving *methyl* 2 : 6-*dihydroxy*-5-*formyl*-3 : 4-*dimethylbenzoate* (VII; R = Me, R′ = CHO) which separated from the cooled hydrolysate. Recrystallised from methanol, this compound formed colourless needles (1·5 g.), m. p. 148°, having a reddish-brown ferric reaction in alcohol (Found : C, 58·7; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright red needles, m. p. 249° (decomp.) (Found : N, 14·2. $C_{17}H_{16}O_8N_4$ requires N, 13·9%).

On being heated under reflux with a solution of potassium hydroxide (1·75 g.) in water (6 ml.) in an atmosphere of nitrogen the foregoing aldehydo-ester (0·5 g.) underwent simultaneous hydrolysis and decarboxylation, giving rise to 4 : 6-dihydroxy-2 : 3-dimethylbenzaldehyde which was isolated from the cooled and acidified hydrolysate by means of ether and on purification from aqueous methanol had m. p. 196°, being identical in every way with an authentic specimen.

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