Experiments concerning the Structure of a Constituent of Orcein.

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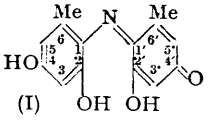
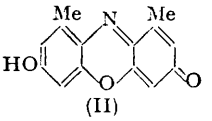
Condensation of 6-methoxy-*p*-toluquinone 4-chloroimide with orcinol in alkaline solution gives evidence for the formation of the sterically hindered indophenol (III; R = Me). The instability of the latter together with the failure of the appropriate reaction to yield the trihydric phenol (III; R = H) make it unlikely that the compound isolated by Liebermann from orcein possesses the structure (III; R = H) and even less likely that it has the more hindered structure (I) which was suggested by Henrich.

Liebermann (*Ber.*, 1875, **8**, 1649) isolated two purple compounds from the mixture obtained by the action of air and ammonia on orcinol, one of the methods used commercially for the preparation of the purple dye orcein. Henrich (*Sitzungsber. physik.-med. Soz. Erlangen*, 1939, **71**, 199; *Chem. Zentr.*, 1940, I, 858) suggested that one of the compounds ($C_{14}H_{13}O_4N$) was 2 : 2′-dihydroxy-6 : 6′-dimethylindophenol (I), but it has not been possible to consult Henrich's paper, and structure (I) appears unlikely. Scale drawings reveal a large amount of steric hindrance which would prevent the molecule from being planar and hence would lessen its stability. The steric hindrance could be relieved by loss of a molecule of water to give the known dye orcirufin (II), and indeed, the latter is actually formed by the condensation of 2-nitroso-orcinol with orcinol in concentrated sulphuric acid instead of the " expected " indophenol (I) (Nietzki and Mackler, *Ber.*, 1890, **23**, 722).

It seemed possible that 2 : 3′-dihydroxy-5′ : 6-dimethylindophenol (III; R = H), isomeric with the indophenol (I), might be formed from orcinol by amination followed by coupling with another molecule of orcinol and introduction of the fourth oxygen atom by aerial oxidation. The indophenol (III) is somewhat sterically hindered, but much less so than its isomer (I). The closely related dye, 2 : 6 : *N* : *N*-tetramethylindoaniline, was

prepared by Vittum and Brown (*J. Amer. Chem. Soc.*, 1947, **69**, 152) and, in contrast to Liebermann's compound, it was rapidly decomposed by water. Despite the expected instability of the indophenol (III; R = H), attempts were made to synthesise it together with its mono- and di-methyl ethers and some related indophenols because (*a*) if it could be made it might be identical with Liebermann's compound, and (*b*) if it could not be made by the usual methods, this would be evidence for its instability and at the same time further evidence against the existence of the much more hindered indophenol (I).


(I)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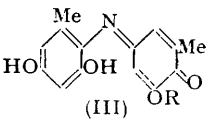
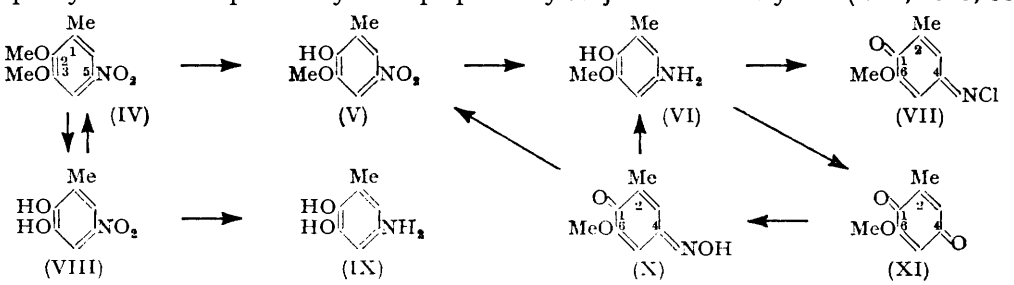

(III)

2-Hydroxy-3-methoxy-5-nitrotoluene (V) was made by the partial demethylation of 2 : 3-dimethoxy-5-nitrotoluene (IV). Its structure was proved by reduction to the amine (VI) followed by oxidation to the known 6-methoxy-*p*-toluquinone (XI). The required nitrophenol was also obtained by the oxidation of 6-methoxy-*p*-toluquinone 4-mono-oxime (X), but it could not be prepared by direct nitration of 2-hydroxy-3-methoxytoluene; instead, this reaction gave 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone (cf. below).

Reduction of the nitrophenol (V) with sodium dithionite gave the unstable 5-amino-2-hydroxy-3-methoxytoluene (VI), best isolated as its hydrochloride. The overall yield of the aminophenol (VI) by this route (IV ⟶ V ⟶ VI) was poor. A better method involved coupling 2-hydroxy-3-methoxytoluene with diazotised sulphanilic acid and reducing the azo-dye with stannous chloride. The best method, however, was the reduction of the mono-oxime (X), which is conveniently prepared by nitrosation of 2-hydroxy-3-methoxytoluene with pentyl nitrite and sodium ethoxide. The same mono-oxime (X) was obtained in poor yield by the action of hydroxylamine on 6-methoxy-*p*-toluquinone (XI). During an attempt to prepare the mono-oxime (X) by the action of hydroxylamine and hydrogen peroxide on 2-hydroxy-3-methoxytoluene (cf. Wurster, *Ber.*, 1887, **20**, 2632) a colourless compound was isolated. The same compound was also formed in the absence of hydroxylamine and was shown to be 4 : 4′-dihydroxy-3 : 3′-dimethoxy-5 : 5′-dimethyldiphenyl which had previously been prepared by Majima and Takayama (*ibid.*, 1920, **53**,


(IV) (V) (VI) (VII) (VIII) (IX) (X) (XI)

1913) by reduction of the corresponding diphenoquinone, itself prepared by oxidation of 2-hydroxy-3-methoxytoluene by ferric chloride. Similarly, we obtained the diphenoquinone by the action of nitrous acid on 2-hydroxy-3-methoxytoluene.

5-Amino-2-hydroxy-3-methoxytoluene (VI) was smoothly converted into 6-methoxy-*p*-toluquinone 4-chloroimide (VII) by the action of sodium hypochlorite. Complete demethylation of 2 : 3-dimethoxy-5-nitrotoluene (IV) was effected by boiling with hydrobromic acid in acetic acid. The resulting 2 : 3-dihydroxy-5-nitrotoluene (VIII) was reduced to the very unstable amine (IX) which could not be converted into the desired 6-hydroxy-*p*-toluquinone 4-chloroimide.

Condensation of the chloroimide (VII) with orcinol in presence of alkali gave a deep blue solution of the sodium salt of 2-hydroxy-3′-methoxy-5′ : 6-dimethylindophenol (III; R = Me), but the compound decomposed in a few hours and no pure product could be isolated. Similar results were obtained when the same chloroimide was condensed with

resorcinol and with phloroglucinol dimethyl ether. On the other hand, the following condensations under appropriate conditions failed to yield indophenols: 2-nitroso-orcinol with 3-methylcatechol to give the indophenol (III; R = H); 6-methoxy-*p*-toluquinone 4-mono-oxime (X) or the chloroimide (VII) with orcinol monomethyl ether to give the dimethyl ether of the indophenol (III; R = H).

Some preliminary experiments were carried out with the readily available 2 : 6-dichloro-*p*-benzoquinone 4-chloroimide (Apte and Panse, *J. Indian Chem. Soc.*, 1947, **24**, 375). Condensation with resorcinol gave a purple solution, but decomposition occurred before any product could be isolated. Reaction with resorcinol monomethyl ether was smooth, but analysis of the product showed that the empirical formula was $C_{13}H_8O_3NCl_2$·OMe instead of $C_{12}H_6O_2NCl_2$·OMe for the expected 3 : 5-dichloro-2'-methoxyindophenol. The compound is possibly a hydroxymethyl derivative of the expected indophenol.

The failure of the appropriate reactions to yield 2 : 3'-dihydroxy-5' : 6-dimethylindophenol (III; R = H) or its dimethyl ether, together with the instability of the monomethyl ether (III; R = Me) are strong indications that Liebermann's compound does not possess the indophenol structure (III; R = H) and renders Henrich's suggested structure (I) even less likely. We now consider that the purple colour and stability of Liebermann's compound are in better accord with an oxazine type of structure.

Experimental

2 : 3-*Dimethoxy*-5-*nitrotoluene* (IV).—2 : 3-Dimethoxytoluene (b. p. 95—96°/19 mm.) was made in 93% yield by methylation of 2 : 3-dihydroxytoluene and was nitrated in 55% yield by a modification of Majima and Okazaki's method (*Ber.*, 1916, **49**, 1482).

2-*Hydroxy*-3-*methoxy*-5-*nitrotoluene* (V).—(a) *From* 2 : 3-*dimethoxy*-5-*nitrotoluene* (IV). Potassium hydroxide (16 g.) was added cautiously to 2 : 3-dimethoxy-5-nitrotoluene (IV) (10 g.) in hot 50% aqueous ethanol (150 ml.). The mixture was boiled under reflux for 23 hr., then set aside for 2 days. After filtration, the solution was distilled through a short fractionating column until 70—80 ml. of distillate had been collected. The cooled solution was extracted with a large volume of ether to remove unchanged material, then acidified, and the brown needles were collected. Recrystallisation from aqueous ethanol (charcoal) gave 2-*hydroxy*-3-*methoxy*-5-*nitrotoluene* (1·4 g.), m. p. 104—107°. Two more recrystallisations gave almost colourless needles (1·1 g., 12%), m. p. 106—108° (Found: C, 52·8; H, 5·0; N, 7·8. $C_8H_9O_4N$ requires C, 52·5; H, 5·0; N, 7·7%). The compound is readily soluble in ethanol and benzene, less readily in light petroleum, and sparingly soluble in water. It gives a bright red colour in aqueous alkali, but no colour with ferric chloride. 2-*Acetoxy*-3-*methoxy*-5-*nitrotoluene*, thrice crystallised from aqueous ethanol, formed pale yellow needles, m. p. 98—99° (Found: C, 53·1; H, 5·1; N, 6·0. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2%).

(b) *From* 6-*methoxy*-p-*toluquinone* 4-*mono-oxime* (X). A hot solution of potassium ferricyanide (4·0 g.) in 2N-sodium hydroxide (10 ml.) was added to a boiling solution of 5-methoxy-*p*-toluquinone 4-mono-oxime (2-hydroxy-3-methoxy-5-nitrosotoluene) (0·5 g.) in 2N-sodium hydroxide (5 ml.), and the mixture heated on a steam-bath for 2½ hr. The cold solution was filtered, acidified, and extracted with ether. The ethereal solution was washed with dilute aqueous sodium hydroxide, then the aqueous solution was acidified and the nitro-phenol collected.

Recrystallisation from water (charcoal) gave silky needles, m. p. 107—108°, undepressed when mixed with the nitro-phenol (V) prepared as above.

5-*Amino*-2-*hydroxy*-3-*methoxytoluene* (VI).—(a) *From* 2-*hydroxy*-3-*methoxy*-5-*nitrotoluene* (V). Sodium dithionite (hydrosulphite) (*ca.* 5 g.) was added gradually to 2-hydroxy-3-methoxy-5-nitrotoluene (V) (1·0 g.) in 10% sodium hydroxide (40 ml.) at 70—80° until the deep red colour was discharged. The cold solution was acidified with acetic acid, and the 5-amino-2-hydroxy-3-methoxytoluene [needles, m. p. 128—130° (decomp.)] was collected. It was dissolved in dilute hydrochloric acid containing a little stannous chloride, and treated with charcoal, and the solution concentrated. The *amine hydrochloride* separated as almost colourless prisms, decomp. between 230° and 250° (Found: C, 50·4; H, 6·5; N, 7·3; Cl, 18·1. $C_8H_{12}O_2NCl$ requires C, 50·7; H, 6·4; N, 7·4; Cl, 18·7%). 5-*Acetamido*-2-*acetoxy*-3-*methoxytoluene*, recrystallised from water, then twice from benzene–light petroleum (b. p. 60—80°), formed plates, m. p. 157—158° (Found: C, 61·1; H, 6·3; N, 5·7. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·4; N, 5·9%).

(b) *By reduction of* 6-*methoxy*-p-*toluquinone* 4-*mono-oxime* (X). The powdered mono-oxime (4·9 g.) was added in small portions to a hot solution of stannous chloride (18 g.) in concentrated

hydrochloric acid (55 ml.). Heating on the steam-bath was continued for 20 min. When cool, the crystals were collected and dissolved in water (150 ml.). The tin salts were removed by precipitation with hydrogen sulphide. After filtration, concentrated hydrochloric acid (20 ml.) and a little stannous chloride were added. Concentration of the solution gave 5-amino-2-hydroxy-3-methoxytoluene hydrochloride as almost colourless prisms (4·6 g., 85%). The pure hydrochloride is comparatively stable. A sample kept for 3 years was dark, but was only slightly impure.

(c) *From 2-hydroxy-3-methoxytoluene.* 2-Hydroxy-3-methoxytoluene (4·6 g.) (Cosgrove and Waters, *J.*, 1949, 3193) was coupled with diazotised sulphanilic acid, and the resulting azo-dye reduced by stannous chloride in the usual way. The amine hydrochloride obtained (1·0 g., 16%) gave a diacetate identical (mixed m. p.) with that prepared in two steps from the nitro-compound and from the oxime in (a) and (b) above.

Oxidation of 5-Amino-2-hydroxy-3-methoxytoluene (VI).—Hydrated ferric sulphate (5·0 g.) was added carefully (frothing) to 5-amino-2-hydroxy-3-methoxytoluene hydrochloride (0·5 g.) in water (40 ml.) containing sodium hydrogen carbonate (0·25 g.). Steam was then blown through the mixture until the distillate was no longer yellow. The 6-methoxytoluquinone (XI) was collected from the distillate by extraction with ether, and recrystallised from light petroleum (b. p. 60—80°), being thereby obtained as fluffy yellow needles, m. p. 148—150°, undepressed by admixture with an authentic sample made by the oxidation of orcinol dimethyl ether (Asahina and Fuzikawa, *Ber.*, 1934, **67**, 167).

6-Methoxy-p-toluquinone 4-Chloroimide (VII).—Chlorine (40—50 g.) was absorbed in sodium hydroxide (35 g.) in water (50 ml.) and ice (500 g.). The sodium hypochlorite thus prepared was added gradually, with stirring, to the hydrochloride of the amine (VI) (5 g.) in water (200 ml.) and ice (80 g.) at 0° until the orange colour was just discharged. The canary-yellow precipitate (4·5 g.) was collected and recrystallised from ethanol, giving the *chloroimide* (VII) as orange-yellow needles or plates (3·2 g., 65%), m. p. 131—133° (decomp.), raised to 140—142° (decomp.) by recrystallisation from light petroleum (b. p. 60—80°) (charcoal) (Found: C, 52·2; H, 4·3; N, 7·4; Cl, 19·9. $C_8H_8O_2NCl$ requires C, 51·8; H, 4·3; N, 7·5; Cl, 19·1%).

6-Methoxy-p-toluquinone 4-Mono-oxime (X).—(a) *From 2-hydroxy-3-methoxytoluene.* Freshly distilled pentyl nitrite (3·8 g.) was added to a solution of 2-hydroxy-3-methoxy toluene (4·1 g.) in ethanolic sodium ethoxide (0·9 g. of sodium in 44 ml. of ethanol). After 3 days, the solution was diluted with water (150 ml.) and filtered. The filtrate was acidified rapidly at 0° with dilute sulphuric acid. After several hours the emulsion yielded orange-brown prisms (3·2 g.). If the emulsion is agitated, a less pure product is obtained. Recrystallisation from acetone–light petroleum (b. p. 60—80°) gave the *mono-oxime* (X) as pale orange prisms (2·6 g., 53%). After two more recrystallisations, this had m. p. 195—198° (decomp.; sintering from 185°) (Found: C, 57·5; H, 5·4; N, 8·5. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%).

(b) *From 6-methoxy-p-toluquinone* (XI). A solution of hydroxylamine hydrochloride (0·35 g.) in water (7 ml.), adjusted to pH 6—7, was added with shaking to a solution of 6-methoxy-*p*-toluquinone (XI) (0·5 g.) in chloroform (10 ml.) and ethanol (25 ml.). Next day the mixture was concentrated to a few ml., diluted with water, and then extracted with chloroform, yielding a dark solid. After 3 recrystallisations from chloroform–benzene (charcoal) and shaking of the solution with silica gel in the third crystallisation, the product was obtained as orange prisms. Three recrystallisations from acetone–light petroleum (b. p. 60—80°) gave the pure mono-oxime (X), m. p. *ca.* 203—205° (decomp.) (Found: C, 57·4; H, 5·4; N, 8·5%).

The products from (a) and (b) were shown to be identical by the similarity of their *X*-ray powder photographs and of their crystal form.

Oxidation of 2-Hydroxy-3-methoxytoluene.—(a) *With nitric acid.* A mixture of concentrated nitric acid (1·6 ml.) and glacial acetic acid (3·5 ml.) was added dropwise with vigorous stirring to 2-hydroxy-3-methoxytoluene (2·4 g.) in glacial acetic acid (50 ml.), the temperature rising to *ca.* 40°. After 1½ hr., 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone (0·9 g.) was filtered off. A portion thrice recrystallised from acetone had m. p. 203° (decomp.) (Found: C, 70·2; H, 5·6. Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 5·9%).

Crude diphenoquinone (0·9 g.) was reduced by sodium dithionite (hydrosulphite) and then methylated by methyl sulphate and potassium hydroxide, thereby yielding 3 : 3′-4 : 4′-tetramethoxy-5 : 5′-dimethyldiphenyl (0·6 g.) as leaflets, m. p. 110—111°, after one recrystallisation from aqueous ethanol [Found: C, 71·4; H, 7·3; OMe, 41·0. Calc. for $C_{14}H_{10}(OMe)_4$: C, 71·5; H, 7·3; OMe, 41·0%].

Majima and Takayama (*Ber.*, 1920, **53**, 1913) record m. p. 202—203° and 102—103° for the diphenoquinone and the tetramethoxydiphenyl respectively.

(b) *With hydrogen peroxide.* A mixture of 2-hydroxy-3-methoxytoluene (4 g.), ethanol (35 ml.), and hydrogen peroxide (40 ml.; 90—100-vol.) was boiled for 2½ hr. under reflux. After steam-distillation to remove ethanol and unchanged phenol, the solution was cooled and the solid collected. Recrystallisation from methanol gave 4 : 4′-dihydroxy-3 : 3′-dimethoxy-5 : 5′-dimethyldiphenyl as needles (0·4 g.), m. p. 185—186°, raised to 188° by another recrystallisation (Majima and Takayama, *loc. cit.*, record m. p. 189°). Methylation by methyl sulphate and sodium hydroxide gave 3 : 3′ : 4 : 4′-tetramethoxy-5 : 5′-dimethyldiphenyl, m. p. and mixed m. p. 109—111°.

(c) *With nitrous acid.* Dilute sulphuric acid (4·1 g. of acid of *d* 1·84 in 30 ml. of water) was added slowly to a stirred solution at 0° of 2-hydroxy-3-methoxytoluene (1·6 g.), potassium hydroxide (1·0 g.), and sodium nitrite (2·1 g.) in water (50 ml.). After 1 hr. the product was collected by filtration and recrystallised from acetone, giving 3 : 3′-dimethoxy-5 : 5′-dimethyl-4 : 4′-diphenoquinone as dark violet needles, m. p. and mixed m. p. 200—203° (decomp.).

2 : 3-*Dihydroxy-5-nitrotoluene* (VIII).—A mixture of 2 : 3-dimethoxy-5-nitrotoluene (IV) (7·5 g.), 60% aqueous hydrobromic acid (60 ml.), and acetic acid (40 ml.) was boiled under reflux for 2 hr. More hydrobromic acid (40 ml.) was added and the boiling continued for another 3 hr. The cooled mixture was diluted with water (400 ml.) and neutralised with solid sodium hydrogen carbonate, then the product was collected in ether. After removal of the solvent, the residue was dissolved in water, and lead acetate solution added until precipitation of the bright red lead salt was complete. The latter was suspended in water (250 ml.), and dilute sulphuric acid added with vigorous stirring. After filtration the solution was concentrated (charcoal), and cooled, yielding bright yellow crystals of 2 : 3-*dihydroxy-5-nitrotoluene* (3·0 g.), m. p. 134—135°, raised to 138° by three recrystallisations from water (Found: C, 47·0; H, 4·6; N, 8·2. $C_7H_7O_4N,\frac{1}{2}H_2O$ requires C, 47·2; H, 4·5; N, 7·9%). The compound is apparently a trihydrate which is converted into the hemihydrate on drying at 100° under reduced pressure (loss in wt., 18·2; theor., 20·2%). It gives a deep blood-red colour in aqueous alkali. Methylation of the nitro-compound regenerated 2 : 3-dimethoxy-5-nitrotoluene. Acetylation gave 2 : 3-*diacetoxy-5-nitrotoluene*, m. p. 114—115° (Found: C, 52·1; H, 4·2; N, 5·4. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·3; N, 5·5%).

5-*Amino*-2 : 3-*dihydroxytoluene* (IX).—Finely powdered 2 : 3-dihydroxy-5-nitrotoluene (VIII) (2·6 g.) and stannous chloride (14·4 g.) in concentrated hydrochloric acid (24 ml.) were warmed on a steam-bath for 1 hr. After dilution with water (100 ml.) and removal of tin as sulphide, the solution was concentrated. The resulting crystals were twice recrystallised from concentrated hydrochloric acid, giving 5-*amino*-2 : 3-*dihydroxytoluene hydrochloride* as needles, m. p. 212° (decomp.). The dry solid rapidly darkened and could not be analysed satisfactorily.

2 : 3-*Diacetoxy- and* 2 : 3-*Dibenzoyloxy-toluene.*—Acetylation of 2 : 3-dihydroxytoluene gave 2 : 3-*diacetoxytoluene*, m. p. 70—71° after recrystallisation from aqueous ethanol (Found: C, 63·4; H, 5·5. $C_{11}H_{12}O_4$ requires C, 63·4; H, 5·8%). Benzoylation of the same catechol gave 2 : 3-*dibenzoyloxytoluene* as plates, m. p. 121—122° after three crystallisations from methanol (Found: C, 75·8; H, 4·8. $C_{21}H_{16}O_4$ requires C, 75·9; H, 4·8%).

Reaction of 2 : 6-*Dichloro*-p-*benzoquinone* 4-*Chloroimide with Resorcinol Monomethyl Ether.*—The dichloro-chloroimide (1·0 g.) (Apte and Panse, *J. Indian Chem. Soc.*, 1947, **24**, 375) was added gradually with vigorous stirring to resorcinol monomethyl ether (0·9 g.) and sodium hydroxide (1·1 g.) in water (21 ml.) at 0°. Stirring was continued for a further 20 min., then the precipitate was collected. It was recrystallised by dissolving it in a small volume of hot water and adding a hot saturated brine solution until the sodium salt of the indophenol began to separate. After two repetitions of this process, the indophenol was dissolved in water and acidified with dilute hydrochloric acid. The precipitate of free *indophenol* was collected, well washed with water, and dried in a vacuum-desiccator. Two samples from different preparations were analysed (Found: C, 51·4, 51·5; H, 3·4, 3·3; N, 4·3, 4·2; Cl, 21·3, 21·4; OMe, 10·0, 10·3. $C_{12}H_6O_2NCl_2{\cdot}OMe$ requires C, 52·4; H, 3·0; N, 4·7; Cl, 23·8; OMe, 10·4. $C_{13}H_8O_3NCl_2{\cdot}OMe$ requires C, 51·2; H, 3·4; N, 4·3; Cl, 21·6; OMe, 9·5%). The sodium salt is stable and gives a deep blue solution in water, which becomes brown when acidified. Reductive acetylation of the compound by zinc dust, acetic anhydride, and acetic acid gave an uncrystallisable yellow oil.

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