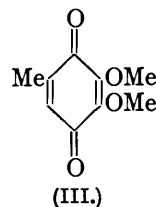
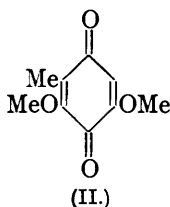
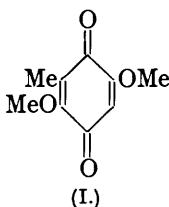


86. The Isomeric Dimethoxy-2 : 5-toluquinones and Certain Related Compounds.

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Methods are given for the synthesis of the three isomeric dimethoxy-2 : 5-toluquinones, *i.e.*, 3 : 6-dimethoxytoluquinone, 4 : 6-dimethoxytoluquinone, and 3 : 4-dimethoxytoluquinone, and also for 4-hydroxy-6-methoxytoluquinone and 6-hydroxy-4-methoxytoluquinone and their corresponding quinols.

FUMIGATIN, a hitherto undescribed mould metabolic product, has recently been isolated in these laboratories from cultures of the mould *Aspergillus fumigatus* Fresenius (Anslow and Raistrick, *Biochem. J.*, 1938, **32**, 687). It has the empirical formula $C_8H_8O_4$, and has been shown by analytical methods to be a monohydroxymonomethoxy-2 : 5-toluquinone. During the course of the investigation of its molecular constitution it became necessary to synthesise each of the three isomeric *dimethoxy-2 : 5-toluquinones* (I, II, and III), since none of these had been described previously.



(I) melts at 104—105°, (II) at 125°, and (III) at 59°. Fumigatin methyl ether, m. p. 59°, must have structure (III), since its melting point is not depressed by (III). (I) and (II) are orange-yellow to golden in colour, and (III) is bright red.

(I) was prepared by the methylation of 3 : 6-dihydroxytoluquinone (Fichter and Glaser, *Annalen*, 1908, **361**, 400). The method of preparation of Fichter's quinone—treatment of toluquinone with methylamine and hydrolysis of the resulting bismethylaminotoluquinone with sulphuric acid—leaves its orientation somewhat uncertain, but since the orientation of (II) and (III) is indisputable, the orientation of (I) follows and hence also, that of Fichter's dihydroxytoluquinone.

(II) was prepared from 6-methoxytoluquinone (Majima and Okazaki, *Ber.*, 1916, **49**, 1490) and from 4-methoxytoluquinone (Luff, Perkin, and Robinson, *J.*, 1910, **97**, 1137; Ashley, *J.*, 1937, 1471). In each case a hydroxy-group was introduced into the molecule by means of the Thiele-Winter reaction (*Annalen*, 1900, **311**, 341) and hydrolysis of the resulting triacetate. The phenol so formed was oxidised to the corresponding quinone with ferric chloride, and the above-introduced hydroxy-group was methylated with methyl sulphate. Since the resulting dimethoxytoluquinone was the same in each case, it follows that the two methoxy-groups in this quinone must be in the *o*- and *p*-positions to the methyl group, *i.e.*, that the dimethoxytoluquinone must have structure (II).

(III) was prepared by the reduction of 5-nitrohomoveratrole (5-nitro-3 : 4-dimethoxytoluene) (Oberlin, *Arch. Pharm.*, 1925, **263**, 662) to 5-aminohomoveratrole and oxidation of the amino-compound with sodium dichromate and sulphuric acid.

EXPERIMENTAL.

3 : 6-Dimethoxy-2 : 5-toluquinone (I).—3 : 6-Dihydroxytoluquinone (Fichter and Glaser, *loc. cit.*) (0.4 g.) was heated for 3 hours with a mixture of anhydrous potassium carbonate (1.5 g.), methyl sulphate (1 ml.), and acetone (20 ml.). A further 1.5 g. of potassium carbonate and 1 ml. of methyl sulphate were then added, and the heating continued for a further 4½ hours. The mixture was cooled, filtered, the solvent removed, and the product extracted with boiling light petroleum (b. p. 40—50°). It was purified by sublimation in a high vacuum, followed by crystallisation from light petroleum (b.p. 40—50°), containing a little methanol, and was finally obtained by vacuum sublimation as orange-yellow clusters of needles, m. p. 104—105°. The

yield was small (Found : C, 59.1; H, 5.3; O-CH₃, 32.4. C₉H₁₀O₄ requires C, 59.3; H, 5.5; 2O-CH₃, 34.1%). It gives a purple colour with concentrated sulphuric acid and a reddish-purple with 2*N*-sodium hydroxide.

4 : 6-Dimethoxy-2 : 5-toluquinone (II).—(a) From 6-methoxytoluquinone. 3-Nitro-2-hydroxytoluene, prepared from *o*-cresol by nitration in glacial acetic acid, was methylated by heating with a mixture of methyl sulphate, potassium carbonate, and toluene. The resulting 3-nitro-2-methoxytoluene was reduced to 3-amino-2-methoxytoluene with tin and hydrochloric acid (Hofmann and v. Miller, *Ber.*, 1881, 14, 570). 3-Amino-2-methoxytoluene (14 g.) was dissolved in a cold mixture of concentrated sulphuric acid (98 ml.) and water (280 ml.) and to it was added a suspension of potassium dichromate (14 g.) in water (80 ml.). The mixture was kept cold and well stirred. On the following day a further quantity of potassium dichromate (28 g.) in water (160 ml.) was added under the same conditions. After 4 hours the mixture was extracted with ether, the extract dried over magnesium sulphate, and the ether removed. The dark residue was distilled in a vacuum to give a yellow oil (b. p. about 130°/15 mm.), which solidified later, m. p. 19—20°. Yield from 34 g. of crude amine, 5.5 g. This quinone is the same as that prepared by Majima and Okazaki (*Ber.*, 1916, 49, 1490), but the Japanese workers did not record any m. p.

The above quinone (5.5 g.) was dissolved in a mixture of acetic anhydride (55 ml.) and concentrated sulphuric acid (2.5 ml.). After 2—3 days it was poured into ice and water; the oil obtained quickly solidified (7.6 g.). 3 : 4 : 6-Triacetoxo-2-methoxytoluene crystallised from methanol in clusters of colourless plates, m. p. 98—99° (Found : C, 56.8; H, 5.5; O-CH₃, 10.3. C₁₄H₁₆O₇ requires C, 56.7; H, 5.5; O-CH₃, 10.5%).

The triacetate (6 g.) was refluxed for $\frac{3}{4}$ hour with methanol (30 ml.) and concentrated sulphuric acid (1 ml.) in an atmosphere of nitrogen. Water was added, and the methanol removed by distillation in a vacuum. The 3 : 4 : 6-trihydroxy-2-methoxytoluene was extracted with ether, and purified by sublimation in a high vacuum. Yield of crude phenol, 3.8 g. The pure phenol is a colourless product, m. p. 146—147°. It gives a lemon-yellow colour with concentrated sulphuric acid and an apple-green colour with 2*N*-sodium hydroxide, which changes first to brown and then to cherry-red on standing (Found : C, 56.5; H, 5.9; O-CH₃, 17.8. C₈H₁₀O₄ requires C, 56.5; H, 5.9; O-CH₃, 18.2%).

The above crude phenol (2 g.) was dissolved in water (3 ml.) and to this solution were added 10 ml. of a solution of ferric chloride (50 g.) in water (110 ml.). The 4-hydroxy-6-methoxy-2 : 5-toluquinone, which quickly separated, was filtered off immediately, washed with saturated sodium chloride solution, dried in a vacuum, and sublimed in a high vacuum to give microscopic bunches of orange needles (0.94 g.), m. p. 116° (Found : C, 57.2; H, 5.0; O-CH₃, 18.4. C₈H₈O₄ requires C, 57.1; H, 4.8; O-CH₃, 18.5%). It gives a pure blue colour with concentrated sulphuric acid and a deep cherry-red with 2*N*-sodium hydroxide [indistinguishable from that given by (II)]. A mixture with fumigatin (m. p. 116°) melted at 97°.

The above quinone (0.2 g.) was methylated by heating for 3 hours with acetone (5 ml.), methyl sulphate (1 ml.), and anhydrous potassium carbonate (1 g.). The mixture was diluted with ether (50 ml.) and filtered. On evaporation the crude 4 : 6-dimethoxy-2 : 5-toluquinone (II) crystallised. It was extracted with light petroleum (b. p. 40—50°) and sublimed in a high vacuum to give 0.12 g. of orange-coloured material, m. p. 118°. This was recrystallised from light petroleum (b. p. 40—50°) to give golden needles with a constant m. p. of 125° (Found : C, 59.2; H, 5.6; O-CH₃, 34.1. C₉H₁₀O₄ requires C, 59.3; H, 5.5; 2O-CH₃, 34.1%). It gives a deep violet-blue colour with concentrated sulphuric acid and a deep cherry-red with 2*N*-sodium hydroxide.

(b) From 4-methoxytoluquinone. 4-Methoxytoluquinone (10 g.), prepared from toluquinone by the method of Ashley (*loc. cit.*), was suspended in a mixture of acetic anhydride (100 ml.) and concentrated sulphuric acid (5 ml.) and kept at room temperature for 2 days with occasional shaking. The mixture was then poured into water and worked up in the usual way. 2 : 3 : 6-Triacetoxo-4-methoxytoluene (18.5 g.) formed colourless needles, m. p. 89—90°, from 50% aqueous acetic acid (Erdtman, *Proc. Roy. Soc.*, 1933, A, 143, 188, gives 91—92°). This triacetate was described by Erdtman as 2 : 3 : 5-triacetoxo-4-methoxytoluene, but in a private communication to us of work which he has not yet published he agrees that it is 2 : 3 : 6-triacetoxo-4-methoxytoluene.

The triacetate (6 g.) was refluxed for $\frac{1}{2}$ hour in an atmosphere of nitrogen with a mixture of methanol (30 ml.) and concentrated sulphuric acid (1 ml.). Water was added, and the methanol removed by distillation in a vacuum. The 2 : 3 : 6-trihydroxy-4-methoxytoluene was extracted with ether and purified by sublimation in a high vacuum (yield of crude phenol, almost

theoretical). The pure phenol is a pale cream solid, m. p. 150° (some decomp.). It gives a lemon-yellow colour with concentrated sulphuric acid. With 2*N*-sodium hydroxide it gives at first a green colour, which quickly becomes brownish-green, then brownish-purple, and finally violet (Found: C, 56.6; H, 5.9; O·CH₃, 18.4. Calc. for C₈H₁₀O₄: C, 56.5; H, 5.9; O·CH₃, 18.2%).

The crude phenol (0.5 g.), dissolved in water (20 ml.), was treated with 2.5 ml. of a solution of ferric chloride (50 g.) in water (110 ml.). 6-Hydroxy-4-methoxytoluquinone separated as a golden-brown solid (yield, almost theoretical), which was sublimed in a high vacuum, forming brownish-orange prisms, m. p. 203—204° (decomp. with partial sublimation). It gives an intense violet colour with 2*N*-sodium hydroxide and an intense violet-blue colour with concentrated sulphuric acid (Found: C, 57.3; H, 4.9; O·CH₃, 18.4. Calc. for C₈H₈O₄: C, 57.1; H, 4.8; O·CH₃, 18.5%). 6-Hydroxy-4-methoxytoluquinone has been prepared previously by Konya (*Monatsh.*, 1900, 21, 422) by oxidising 3-amino-2 : 6-dihydroxy-4-methoxytoluene with ferric chloride and by Pollak and Solomonica (*Monatsh.*, 1901, 22, 1008) by oxidising 3-amino-2-hydroxy-4 : 6-dimethoxytoluene with ferric chloride. Konya records the m. p. as 186° and Pollak and Solomonica as 183—185°. We have repeated Konya's work, starting as he did with methyl phloroglucinol, and have succeeded in raising the m. p. to 204° by subliming the resulting 6-hydroxy-4-methoxytoluquinone in a high vacuum. This m. p. was not depressed by 6-hydroxy-4-methoxytoluquinone prepared from 4-methoxytoluquinone as described above. Further, the quinol 2 : 3 : 6-trihydroxy-4-methoxytoluene, prepared by the reduction of either of our specimens of 6-hydroxy-4-methoxytoluquinone and sublimed in a high vacuum, melted at 150°, either alone or as a mixture. Konya gives the m. p. as 134°.

4 : 6-Dimethoxytoluquinone.—6-Hydroxy-4-methoxytoluquinone (0.5 g.) was methylated by heating for 3 hours with a mixture of acetone (12.5 ml.), methyl sulphate (2.5 ml.), and anhydrous potassium carbonate (2.5 g.). The reaction mixture was diluted with ether (50 ml.) and filtered. The ether was removed, leaving an oil, which was extracted with boiling light petroleum (300 ml., b. p. 40—50°). On cooling, long golden needles (0.15 g.) were deposited, m. p. 123°. A portion was sublimed in golden needles, m. p. 125°. This m. p. was not depressed by 4 : 6-dimethoxytoluquinone (m. p. 125°) prepared from 4-hydroxy-6-methoxytoluquinone.

6-Acetoxy-4-methoxytoluquinone.—6-Hydroxy-4-methoxytoluquinone does not undergo the usual Thiele-Winter reaction. Instead, the hydroxy-group is acetylated and 6-acetoxy-4-methoxytoluquinone is formed. 6-Hydroxy-4-methoxytoluquinone (0.1 g.) was dissolved in 1.5 ml. of a mixture of acetic anhydride (30 ml.) and concentrated sulphuric acid (1 ml.), kept for 3 days, and poured into ice-water. There was an immediate separation of lemon-yellow needles (0.09 g.), which were purified by sublimation in a high vacuum, giving lemon-yellow prisms, m. p. 139° (Found: C, 57.3; H, 4.9; O·CH₃, 14.9. C₁₀H₁₀O₅ requires C, 57.1; H, 4.8; O·CH₃, 14.8%).

3 : 4-Dimethoxy-2 : 5-toluquinone (*Fumigatin Methyl Ether*) (III).—Vanillin was reduced to creosol, which was nitrated to give 5-nitrocreosol by the method of Oberlin (*Arch. Pharm.*, 1925, 263, 662). A mixture of 5-nitrocreosol (23 g.), potassium carbonate (45 g.), methyl sulphate (22 ml.), and toluene (160 ml.) was refluxed for 3 hours. A further 22 ml. of methyl sulphate were added during the next 1½ hours and the heating was continued for a total period of 6 hours. The reaction mixture was diluted with toluene, washed with 2% sodium hydroxide solution, and dried. The toluene was removed, and the residue purified by distillation in a vacuum to give 22 g. of 5-nitrohomoveratrole.

5-Nitrohomoveratrole (12.5 g.) was reduced to 5-aminohomoveratrole by refluxing for 1 hour with a mixture of concentrated hydrochloric acid (37.5 ml.), water (12.5 ml.), ethanol (25 ml.), and granulated tin (17.5 g.). The alcohol was removed in a vacuum, a solution of sodium hydroxide (31 g.) in water (125 ml.) added, and the whole extracted with ether. On removal of the ether, a pale brown oil (8 g.) remained and this was converted into the quinone without further purification. It was dissolved in a cold mixture of concentrated sulphuric acid (32 ml.) and water (100 ml.), placed in a freezing mixture, and a solution of sodium dichromate (5 g.) in water (30 ml.) was slowly added with constant stirring. The following day a further 10 g. of sodium dichromate in 60 ml. of water were added under the same conditions. After 3 hours, the mixture was extracted with ether. On removal of the solvent a reddish-black oil (2.6 g.) remained and quickly crystallised. It was sublimed in a high vacuum (bath temperature 46—48°), 3 : 4-dimethoxytoluquinone being obtained in beautiful red needles, m. p. 59°, alone or mixed with fumigatin methyl ether (Found: C, 59.4; H, 5.6; O·CH₃, 34.0. C₉H₁₀O₄ requires C, 59.3; H, 5.5; 2O·CH₃, 34.1%). With concentrated sulphuric acid it gives at once a dark brown colour, changing to cherry-red in a few minutes, and becoming an intense purple on

standing. The same sequence of colour changes is given by fumigatin. With 2N-sodium hydroxide it gives a brown colour which slowly fades on standing.

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