

2,3-Dihydro-2,3-dihydroxybenzoquinone Dimer

By H. A. Anderson and R. H. Thomson, Department of Chemistry, University of Aberdeen, Scotland

The product obtained by oxidation of benzoquinone with sodium chlorate in the presence of osmium tetroxide is a tricyclic dimer of 2,3-dihydro-2,3-dihydroxybenzoquinone. It reacts with acetic anhydride-sulphuric acid to give 1,2,6,7-tetra-acetoxydibenzo-*p*-dioxin.

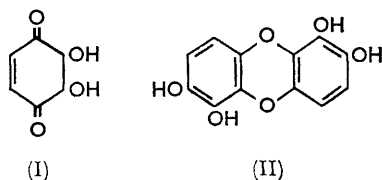
OXIDATION of quinol or benzoquinone with sodium chlorate in aqueous hydrochloric acid containing osmium tetroxide gives a colourless product for which Terry and Milas¹ tentatively suggested structure (I). This appeared to be consistent with its elementary analysis, molecular weight (ebullioscopic in water), and the formation of an acetate (regarded as 1,2,3,4-tetra-acetoxybenzene) on prolonged heating with acetic anhydride, but it did not account for the remarkable

insolubility of this compound in organic solvents. Subsequently the substance was examined by Baker and Munk² who obtained it, under modified conditions, in much lower yield than that claimed by the original workers. They were unable to recover the compound from its solution in hot water (which, as they pointed

¹ E. M. Terry and N. A. Milas, *J. Amer. Chem. Soc.*, 1962, **48**, 2647.

² W. Baker and I. Munk, *J. Chem. Soc.*, 1940, 1092.

out, invalidates the molecular weight determination) and showed that the acetate gave 1,2,3,4-tetramethoxybenzene after hydrolysis and methylation. It was concluded that Terry and Milas's compound was probably a dimer of 2,3-dihydro-2,3-dihydroxybenzoquinone (I).

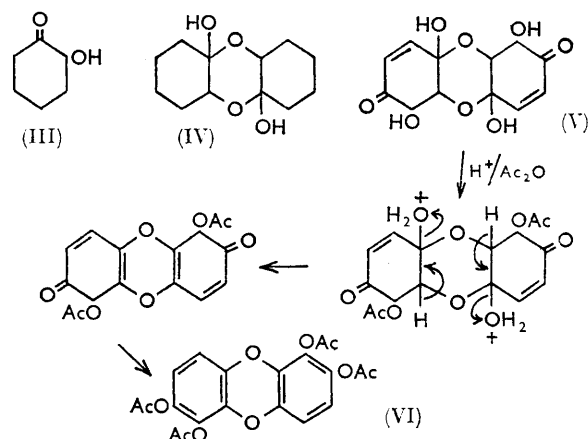


We have now re-examined this material which we obtained from benzoquinone in 20% yield. Its mass spectrum shows a minute molecular ion peak at m/e 284 indicating a dimeric structure. We confirm that the compound is completely insoluble in all organic solvents. It dissolves in boiling water, concentrated sulphuric acid, and organic and inorganic bases (with rapid darkening in air) but it cannot be recovered from solution. Only a very small amount of 1,2,3,4-tetramethoxybenzene was obtained by methylation in aqueous sodium hydroxide but acetylation with acetic anhydride-sodium acetate² gave 1,2,3,4-tetra-acetoxybenzene in 34% yield. This constitutes a practicable two-step route to derivatives of 1,2,3,4-tetrahydroxybenzene.

Chemical evidence for the dimeric nature of the oxidation product was gained by examination of a second acetyl derivative which Terry and Milas obtained by reaction with acetic anhydride in the presence of sulphuric acid. This compound ($M, 416$) gave a blue-green colour in sulphuric acid containing a trace of sodium chlorate indicative of a dibenzo-*p*-dioxin structure³ and showed ultraviolet absorption very similar to that of dibenzo-*p*-dioxin itself. It contained four *O*-acetyl groups and yielded a tetrahydric phenol on hydrolysis which was very sensitive to oxidation in alkaline solution, and formed a tetramethyl ether. The latter readily afforded a dinitro- and a tetrabromo-derivative. A symmetrical arrangement of the four hydroxy-groups is apparent from the n.m.r. spectrum of the tetra-acetate which shows only a single sharp peak in the aromatic region at τ 3.22 which may be compared with the two-proton singlet at τ 3.14 shown by 3,4-diacetoxyveratrole. However a well defined quartet ($J = 9$ c./sec.) in the aromatic region of the spectrum of the tetramethyl ether is compatible only with the AB system of the tetrahydroxydibenzo-*p*-dioxin (II). In agreement the latter forms insoluble lead and calcium salts but we were unable to prepare cyclic ether or ester derivatives. Zinc-dust distillation of the tetrahydric phenol gave pyrogallol and traces of catechol and 1,2,3,4-tetrahydroxybenzene, and a similar degradation of the tetramethyl ether yielded detectable amounts of pyrogallol

1,2-dimethyl ether, 3,4-dimethoxycatechol, and veratrole. These degradations are consistent with structure (II) but attempts to confirm this by synthesis of the tetramethyl ether were disappointing. Tomita *et al.*⁴ have shown that symmetrical dibenzo-*p*-dioxins can be obtained by fusion of potassium *o*-bromophenoxides with copper. Using this method, the potassium salt of 2-bromo-3,4-dimethoxyphenol gave a violent reaction with copper, and in the absence of the metal we obtained, at best, only a trace of material which had the same R_F value as the tetramethyl ether described above and gave a positive colour test for a dibenzo-*p*-dioxin.

On the basis of structure (II), and by analogy with the dimer (IV) of 2-hydroxycyclohexanone (III),⁵ we suggest the dimeric structure (V) for Terry and Milas's oxidation product. The infrared spectrum of the latter shows two hydroxy-absorptions at 3260 and 3475 cm^{-1} , with a carbonyl peak at 1690 cm^{-1} . In the region 1000–1200 cm^{-1} the spectrum shows a close similarity to that of the dimer (IV), and on the assumption of the analogous structure (V) the two hydroxy-absorptions can be assigned to the strongly intermolecularly hydrogen-bonded hydroxy-groups (ν_{OH} 3260 cm^{-1}) at the hemiacetal bridgeheads and to the weakly intramolecularly hydrogen-bonded α -ketol hydroxy-functions (ν_{OH} 3475 cm^{-1}),⁵



respectively. The carbonyl absorption is at somewhat shorter wavelength than is normal in $\alpha\beta$ -unsaturated ketones but this appears to be a feature of the infrared spectra of α' -oxygenated $\alpha\beta$ -unsaturated ketones due to vicinal interactions within the ketol moiety;⁶ any 'skewing' of the carbonyl-alkene bond would also lower the wavelength of the carbonyl absorption.

The structure (V) would aromatise to the tetra-acetate (VI), as indicated, in the presence of acetic anhydride and sulphuric acid. The reaction would take precedence over the normal acid cleavage of hemiacetals (*e.g.*, the conversion of the dimer into 1,2,3,4-tetra-acetoxybenzene) if the bridgehead hydroxy-groups were in a *trans*-diaxial relationship with the hydrogen atoms on the

³ M. Tomita and S. Ueda, *J. Pharm. Soc. Japan*, 1958, **78**, 674 (*Chem. Abs.*, 1958, **52**, 18,421).

⁴ M. Tomita, T. Nakano, and K. Hirai, *J. Pharm. Soc. Japan*, 1954, **74**, 934 (*Chem. Abs.*, 1955, **49**, 10,964).

⁵ J. C. Sheehan, R. C. O'Neill, and M. A. White, *J. Amer. Chem. Soc.*, 1950, **72**, 3376.

⁶ L. L. Smith, H. Mendelsohn, T. Foell, and J. Goodman, *J. Org. Chem.*, 1961, **26**, 2859.

adjacent bridgehead carbon atoms and could then undergo easy dehydration in the presence of strong acid. The aromatisation of the rings would provide a considerable 'driving force' for the reaction with concomitant suppression of acetal cleavage. Models of the structure (V) can be packed into a hydrogen-bonded helical structure which could be responsible for the insolubility of the compound. An alternative explanation of the insolubility, *i.e.*, a high-polymeric structure, is excluded by the relative intensities of the carbonyl and hydroxyl absorptions in the infrared spectrum, and by the absence of peaks above m/e 284 in the mass spectrum of the product.

EXPERIMENTAL

Oxidation of Benzoquinone.—Freshly recrystallised and powdered benzoquinone (20 g.) and sodium chlorate (30 g.) were stirred into a mixture of 2N-hydrochloric acid (20 ml.), 1% aqueous osmium tetroxide (5 ml.), and water (20 ml.). The suspension was shaken for 60 hr., and the nearly colourless dimer (V) (5.3 g.) was collected, washed with water, acetone, and ether. A sample dried in high vacuum was an off-white microcrystalline powder, decomp. 180–185° [Found: C, 50.7; H, 4.4%; M (mass spectrum), 284. Calc. for $C_{12}H_{12}O_8$: C, 50.7; H, 4.3%; M , 284]. To a suspension of the dimer (100 mg.) in water, under nitrogen, was added sodium hydroxide (150 mg.) dissolved in oxygen-free water (5 ml.), and then dimethyl sulphate (500 mg.). The dark mixture was stirred and heated on a steam-bath for 30 min., then 5N-sodium hydroxide (10 ml.) was added, and the mixture was cooled. Benzene extraction yielded a gum which was chromatographed in benzene on alumina yielding 1,2,3,4-tetramethoxybenzene, m. p. 88–89° (5 mg.), identical (i.r. and u.v. spectra, mixed m. p.) with an authentic sample.

1,2,3,4-Tetra-acetoxybenzene.—(a) The dimer (200 mg.) was suspended in acetic anhydride (10 ml.) with anhydrous sodium acetate (200 mg.), refluxed for 1 hr., and poured on ice. Crystallisation of the precipitate from ethanol ($\times 4$) (charcoal) yielded the tetra-acetate in needles, m. p. 137–139° (150 mg.), identical (i.r., mixed m. p.) with the product obtained in (b) (Found: C, 54.1; H, 4.7; Ac, 56.5. Calc. for $C_{14}H_{14}O_8$: C, 54.2; H, 4.5; Ac, 55.6%).

(b) 2,3-Dimethoxyquinol (785 mg.)⁷ was heated with pyridine hydrochloride (1.2 g.) under nitrogen at 170–190° for 30 min. After the addition of ice and hydrochloric acid, ether extraction afforded a brown oily solid (588 mg.) which crystallised from ethyl acetate–light petroleum (b. p. 80–100°) (charcoal) in pink needles (200 mg.) of 1,2,3,4-tetrahydroxybenzene, m. p. 159–161° (lit.,⁸ m. p. 160°) (Found: C, 50.4; H, 4.5. Calc. for $C_6H_6O_4$: C, 50.7; H, 4.2%). The tetra-acetate was obtained from the crude reaction product (581 mg.) by leaving for 18 hr. in acetic anhydride (10 ml.) containing concentrated sulphuric acid (2 drops) and then pouring on ice. The product crystallised from ethanol in needles, m. p. 139–141° (lit.,^{1,2} m. p. 142°).

1,2,6,7-Tetra-acetoxydibenzo-*p*-dioxin.—The dimer (V) (1.5 g.), suspended in acetic anhydride (30 ml.), was treated with concentrated sulphuric acid (2 ml.), whereupon the solid rapidly dissolved with the evolution of heat. The pale yellow solution was heated on a steam-bath for 30 min.

⁷ F. Weygand, H. Weber, and E. Mackawa, *Chem. Ber.*, 1957, **90**, 1879.

⁸ W. Mayer and R. Fikentscher, *Chem. Ber.*, 1956, **89**, 511.

and added to ice to precipitate the *tetra-acetate* which crystallised from alcohol in needles, m. p. 226–227° (lit.,¹ 217–218°) (1.6 g.) [Found: C, 57.8; H, 4.1; Ac, 36.6%; M (vapour-phase osmometry), 416. $C_{20}H_{16}O_{10}$ requires C, 57.8; H, 3.9; Ac, 38.5%; M , 416]. The 60 Mc./sec. n.m.r. spectrum, in $CDCl_3$, showed a singlet at τ 3.24 (aromatic protons) and singlets at τ 7.69 and 7.75 (acetate protons) (ratio 1:3). The dibenzo-*p*-dioxin derivative gave a blue-green colour in concentrated sulphuric acid containing a trace of sodium chlorate or nitrate,³ and showed λ_{max} (EtOH) 290 μ ($\log \epsilon$ 3.35) [dibenzo-*p*-dioxin itself shows λ_{max} (EtOH) 289 μ ($\log \epsilon$ 3.45)].

1,2,6,7-Tetrahydroxydibenzo-*p*-dioxin (II).—The above tetra-acetate (1 g.) suspended in methanol (20 ml.) under nitrogen, was heated on a steam-bath for 30 min. with an oxygen-free solution of sodium hydroxide (400 mg.) in water (10 ml.). After addition of 2N-hydrochloric acid (30 ml.) the *tetrahydroxydibenzo-*p*-dioxin* crystallised on cooling. It formed needles, m. p. > 300° (from water) (697 mg.) [Found: C, 57.9; H, 3.3%; M (vapour-phase osmometry), 250. $C_{12}H_8O_6$ requires C, 58.1; H, 3.2%; M , 248]. Re-acetylation with acetic anhydride–sodium acetate gave the original tetra-acetate. The phenol gave insoluble calcium and lead salts, and alkaline solutions rapidly darkened on exposure to air. It reduced Fehling's solution on warming, gave a red-brown ferric colour, a blue colour with phosphomolybdic acid,⁹ and an orange-red precipitate with titanous chloride.¹⁰ Methylation with dimethyl sulphate in ethanolic aqueous sodium hydroxide gave the *tetramethyl ether* as needles, m. p. 183–184° (from ethanol) which gave a green-blue colour in concentrated sulphuric acid containing a trace of sodium chlorate [Found: C, 62.9; H, 5.5; MeO, 39.0%; M (mass spectrum), 304. $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.3; MeO, 40.8%; M , 304]. The n.m.r. spectrum, in $CDCl_3$, showed an AB system centred at τ 3.21 and 3.49 ($J = 9$ c./sec.) (*o*-coupled protons) and methoxyl proton singlets at τ 6.05 and 6.14 (proton ratio 1:3). The tetramethyl ether (550 mg.) in hot acetic acid (20 ml.) was treated, dropwise, with bromine (1.2 g.) in the same solvent (5 ml.). After 30 min., the solution was allowed to cool, whereupon 3,4,8,9-tetrabromo-1,2,6,7-tetramethoxydibenzo-*p*-dioxin separated. It formed needles, m. p. 280–281°, from acetic acid (800 mg.) (Found: C, 30.8; H, 1.9; Br, 51.6; OMe, 20.6. $C_{16}H_{12}Br_4O_6$ requires C, 30.9; H, 1.9; Br, 51.6; MeO, 20.0%). The tetramethoxydibenzo-*p*-dioxin (82 mg.) in acetic acid (10 ml.) was heated on a steam-bath with gradual addition of concentrated nitric acid (0.1 ml.) in the same solvent (5 ml.). After 15 min. the yellow solution was poured into water. The *dinitro-derivative* was collected and crystallised from acetic acid in fine yellow needles, m. p. 260–262° (90 mg.) (Found: C, 48.7; H, 3.9; N, 7.2; MeO, 31.0. $C_{16}H_{14}N_2O_{10}$ requires C, 48.8; H, 3.6; N, 7.1; MeO, 31.5%).

Zinc-dust Distillations.—(a) 1,2,6,7-Tetrahydroxydibenzo-*p*-dioxin (50 mg.) and zinc dust (150 mg.) were intimately mixed in a 3 mm. soda-glass tube which was placed inside a 5 mm. 'Pyrex' tube. The sample was degraded in the usual way and the products sublimed up the tube under vacuum. Examination of the sublimate by thin-layer chromatography on kieselgel G in benzene–methanol–acetic acid (45:8:4)

⁹ K. Brauer, *Chem. Z.*, 1926, **50**, 553 (*Chem. Abs.*, 1926, **20**, 3665); I. Imada, Y. Sanno, and H. Mirimato, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 1056; I. Imada and H. Mirimato, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 130.

¹⁰ F. Weygand and E. Csendes, *Chem. Ber.*, 1952, **85**, 47.

(spray reagent, tetrazotised benzidine) revealed the presence of pyrogallol and traces of catechol and apionol. Crystallisation of the sublimate from ether-light petroleum (b. p. 40–60°) gave pale pink needles of pyrogallol, m. p. 129–132° (mixed m. p. 130–132°, identical i.r.) (10 mg.). It gave an acetate identical (mixed m. p., i.r.) with pyrogallol triacetate. A further phenolic product (5 mg.) of the zinc dust distillation did not sublime and could not be crystallised.

(b) 1,2,6,7-Tetramethoxydibenzo-*p*-dioxin (50 mg.) was degraded as above and the oily product was chromatographed on kieselgel G in benzene-methanol-acetic acid (45:8:4) and in benzene-dioxan-acetic acid (90:25:4). Of the four phenolic components two were identified as pyrogallol 1,2-dimethyl ether and 3,4-dimethoxycatechol; a non-phenolic component was identified as veratrole.

2-Bromo-3,4-dimethoxyaniline.—Bromine (45.5 g.) in acetic acid (400 ml.) was added gradually during 45 min. to a stirred solution of 5-nitroguaiacol (48 g.)¹¹ in the same solvent. The mixture was poured into ice-water and the mixed isomers (67 g.) were collected, dried at 80°, and methylated for 16 hr. in refluxing acetone containing dimethyl sulphate (50 g.) and anhydrous potassium carbonate (100 g.). The precipitate, obtained on dilution with water, was crystallised ($\times 6$) from 30% aqueous ethanol to give 3-bromo-4-nitroveratrole as needles, m. p. 79–81° (52 g.), identical (mixed m. p., i.r., R_F) with a sample prepared from guaiacol carbonate.¹² The nitro-compound (50 g.) in warm ethanol (100 ml.) was reduced with granulated tin (40 g.) and concentrated hydrochloric acid (6 \times 50 ml. portions), the violent reaction being moderated with ice-cooling. After being warmed on a steam-bath for 1 hr., the product was worked up in the usual way to give 2-bromo-3,4-dimethoxyaniline as plates, m. p. 65° [from light petroleum (b. p. 40–60°)] (34 g.) (Found: C, 41.7; H, 4.1; Br, 34.6;

N, 5.9. $C_8H_{10}BrNO_2$ requires C, 41.4; H, 4.3; Br, 34.5, N, 6.0%). The *hydrogen sulphate* formed long needles, 154–155° (from water) (Found: C, 29.3; H, 3.6; MeO, 18.8. $C_8H_{12}BrNO_4S$ requires C, 29.1; H, 3.6; MeO, 18.8%), the *acetyl derivative*, plates, m. p. 113–115° (from aqueous ethanol) (Found: N, 5.2. $C_{10}H_{12}BrNO_3$ requires N, 5.1%), and the *azo- β -naphthol derivative*, red needles, m. p. 155° (and again at 175°) (from acetic acid) (Found: N, 7.1%. $C_{18}H_{15}BrN_2O_3$ requires N, 7.2%).

2-Bromo-3,4-dimethoxyphenol.—The diazonium chloride from the above amine (36 g.) was added slowly to concentrated sulphuric acid (80 ml.) and water (80 ml.) with simultaneous steam-distillation. Ether extraction of the distillate gave the *phenol* which crystallised from ether-light petroleum (b. p. 40–60°) in plates, m. p. 113–115° (1.76 g.) (Found: C, 41.2; H, 3.9. $C_8H_9BrO_3$ requires C, 41.2; H, 3.9%). It gave a green colour with ferric chloride in chloroform containing a trace of pyridine.

The above phenol (259 mg.) was added to a solution of potassium (59 mg.) in methanol (5 ml.) and taken to dryness. The dry salt was heated at 250°(bath)/0.05 mm. for 2 hr. and the sublimate examined by t.l.c. on kieselgel G. One of the four components had the same R_F values as 1,2,6,7-tetramethoxydibenzo-*p*-dioxin in both chloroform and benzene, and on extraction from the silica gel it gave a trace of solid giving a green-blue colour in sulphuric acid containing a trace of sodium chlorate.

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¹¹ N. L. Drake, H. C. Harris, and C. B. Jaeger, *J. Amer. Chem. Soc.*, **1948**, **70**, 168.

¹² R. Robinson, *J. Chem. Soc.*, **1916**, **111**, 917.