

Periodate Oxidation of Phenols

II*. Oxidation of 2,6-Dimethoxyphenol and 3-Methoxycatechol. Formation of a 1,2-Naphthoquinone**

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The action of sodium periodate on an aqueous solution of 2,6-dimethoxyphenol (I) rapidly produces coerulignone (II), 2,6-dimethoxy-*p*-quinone (III), 3-methoxy-*o*-quinone (IV), 3,8-dimethoxy-1,2-naphthoquinone (V), m. p. 198–199°, and a violet substance (VI), m. p. 205–206°, of unknown structure. Compounds IV, V, and VI were also obtained by periodate oxidation of 3-methoxycatechol (VII). A similar treatment of IV yielded V and VI.

A dimeric 3-methoxy-*o*-quinone (VIII), m. p. 139–140°, is formed in solutions of the monomer (IV) in certain organic solvents; in aqueous solutions of IV, or of VIII, a monohydrate of dimer VIII (XIII, m. p. 114–115°) is formed. Both dimer VIII and its monohydrate XIII, when treated with periodate, are degraded to the β -naphthoquinone V. Thus, V arises from phenols I or VII in aqueous periodate solution by dimerisation of the 3-methoxy-*o*-quinone (IV) first formed and degradation of the dimer.

A second dimeric 3-methoxy-*o*-quinone (m. p. 110°) was obtained from benzene solutions of the monomer. On periodate oxidation it is converted to the violet compound VI.

In Part I¹ of this series it was shown that the action of sodium periodate on monoethers of catechol results in rapid oxidative cleavage of the ether group. Guaiacol, for instance, yielded about 90 % of the calculated amount of methanol, in addition to *o*-benzoquinone. Sodium bismuthate was found² to act in a similar way.

Lead tetraacetate however, although largely equivalent to periodate and bismuthate as a glycol-splitting agent, differs from them in its action on guaiacol. As reported by Wessely and Kotlan³, lead tetraacetate attacks mainly the free 4-position, yielding methoxy-*p*-benzoquinone as the major reaction product. Similarly, the pyrogallol derivative 2,6-dimethoxyphenol

* Part I, see Ref. ¹.

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(I) is oxidised by lead tetraacetate at the position *para* to the phenolic hydroxyl group, with the formation of 2,6-dimethoxy-*p*-quinone (II) (78 %) and coerulignone (III) (10 %) ³. The action of Fremy's salt (potassium nitrosodisulphate, ON(SO₃K)₂) on guaiacol and 2,6-dimethoxyphenol resembles that of lead tetraacetate and gives methoxy-*p*-quinone and 2,6-dimethoxy-*p*-quinone, respectively, in high yields ⁴.

PERIODATE OXIDATION OF 2,6-DIMETHOXYPHENOL (I)

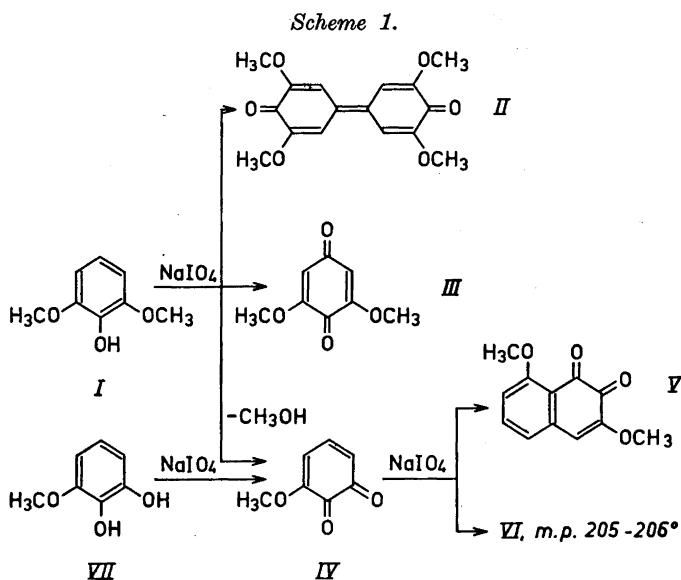
As in the case of guaiacol, periodate treatment of 2,6-dimethoxyphenol (I) in dilute aqueous solution resulted in rapid consumption of the oxidant and the liberation of nearly 1 mole of methanol per mole of phenol after a reaction time of only 1–2 min. In addition to this *ortho* oxidative demethylation, some *para* oxidation also occurred, the ratio between *ortho* and *para* oxidation being dependent on the experimental conditions used and especially on the initial concentration of the phenol.

When a reaction mixture containing 8 mmole of I and 24 mmole of NaIO₄ per litre was used, and the oxidation was allowed to proceed at 4° for only 2 min, the expected product of the *o*-oxidative demethylation, *i.e.*, 3-methoxy-*o*-quinone (IV), was formed in 58 % yield (Table 1, Expt. 1). In addition to this compound there were also obtained small amounts of a brilliant red compound, C₁₀H₄O₂(OCH₃)₂, m.p. 198–199°, and traces of a dark-violet substance (VI), m.p. 205–206°, with the same composition. As will be described in a following communication ⁵, the red substance has been shown to be the hitherto unknown β -naphthoquinone V (3,8-dimethoxy-1,2-naphthoquinone). The dark-violet product (VI), which, on treatment with *o*-phenylenediamine, yielded an orange phenazine, m.p. 229–230°, is believed to be the isomeric 3,5-dimethoxy-1,2-naphthoquinone. Further investigation of the structure of substance VI is in progress. As shown below, both products, V and VI, originate from the 3-methoxy-1,2-benzoquinone (IV) that is formed first.

The *para* oxidation of I also gave small amounts of coerulignone (II) and 2,6-dimethoxy-1,4-benzoquinone (III) (Scheme 1).

Increasing the reaction temperature to 20° and the time of oxidation to 10 min (Table 1, Expt. 2) reduced the yield of the *o*-benzoquinone IV, but increased the yields of the β -naphthoquinone V and of coerulignone (II). This change in the ratio of the yields of products II, IV, and V was still more pronounced when the initial concentration of the starting phenol was increased ten-fold (Expt. 3). *Para* oxidation, mainly with the formation of coerulignone (II), then occurred to a greater extent and the yield of the β -naphthoquinone V was also further increased, but the yield of the *o*-benzoquinone IV was insignificant.

The separation of the various reaction products was based on the following procedure (for details, see Experimental). Coerulignone (II), which is practically insoluble, was recovered from the reaction mixture by filtration, and the products III, IV, V, and VI were extracted from the filtrate with chloroform and separated by chromatography on alumina. Fractional elution yielded the pure products III, V, and VI, but the *o*-benzoquinone IV was irreversibly adsorbed (and destroyed) on the alumina column. The difference between



the weight of the crude residue, obtained on evaporation of the chloroform extract and the combined weights of compounds III, V, and VI, eluted from the alumina column, was taken as a measure of the amount of 3-methoxy-1,2-benzoquinone (IV) present.

The yields given for IV may thus be slightly too high, as they could include minor amounts of polymeric transformation products of IV (and their periodate oxidation products) formed in the aqueous reaction mixture. However, polymeric products of this

Table 1. Periodate oxidation of 2,6-dimethoxyphenol (I), 3-methoxycatechol (VII), and 3-methoxy-1,2-benzoquinone (IV) in water ^a.

Expt. No.	Starting material		Temp. °C	Time of oxid., min	Yields of reaction products, per cent					
	Compound	Conc. in react. mixt., mmole/l			II	III	IV	V	VI	Total II to VI
1	I	8	4	2	7	5	58	7	2	79
2	I	8	20	10	12	3	35	15	7	72
3	I	80	20	10	31	3	5	25	2	66
4	VII	80	20	10	—	—	12	48	2	62
5	IV	40	20	10	—	—	21 ^b	51	2	74

^a The ratio of starting material/NaIO₄ used was 1:3.

^b Unreacted starting material and polymers.

sort are sparingly soluble in chloroform and the error due to this source should be limited. As expected, the yield of water-soluble material not extractable with chloroform (= 100 minus total yield of products II–VI, as given in Table 1, last column) increases with increasing temperature, reaction time, and phenol concentration (*cf.* Expts. 1, 2, and 3).

On recrystallisation from ether, the crude solids remaining on evaporation of the chloroform extracts from reaction mixtures similar to those given in Expts. 1 and 2 (Table 1), gave 3-methoxy-1,2-benzoquinone (IV), m.p. 110°⁶, in yields of 30–40 % based on the amount of phenol I used.

OXIDATION OF 3-METHOXYCATECHOL (VII)

As reported in Part I¹, periodate oxidation of 3-methoxycatechol (VII) yielded 3-methoxy-1,2-benzoquinone (IV) (nearly 60 %), *i.e.*, the oxidation occurred preferentially at the "catechol grouping" of VII rather than at the "guaiacol grouping" which was also present in VII. The experimental conditions were comparable to those used in Expt. 1, Table 1, for the oxidation of 2,6-dimethoxyphenol (low phenol concentration, low temperature, short reaction time).

Increasing the phenol concentration, temperature or time (Table 1, Expt. 4) resulted in a remarkably high yield of 3,8-dimethoxy-1,2-naphthoquinone (V) (48 %) and a simultaneous decrease of the amount of 3-methoxy-1,2-benzoquinone (IV). This is in accordance with the results of the oxidation of 2,6-dimethoxyphenol reported above. In the case of 3-methoxycatechol no defined *para* oxidation products were detected, and the yield of the β -naphthoquinone derivative V was considerably higher than in the oxidation of 2,6-dimethoxyphenol (*cf.* Expts. 3 and 4).

THE FORMATION OF 3,8-DIMETHOXY-1,2-NAPHTHOQUINONE (V). DIMERIC 3-METHOXY-1,2-BENZOQUINONE (VIII) AND ITS MONOHYDRATE (XIII)]

While the formation of the *para* oxidation products, coerulignone (II) and 2,6-dimethoxy-*p*-quinone (III), from 2,6-dimethoxyphenol (I), and the formation of 3-methoxy-1,2-benzoquinone (IV) from I or from 3-methoxycatechol (VII) are easily understood, the formation of 3,8-dimethoxy-1,2-naphthoquinone (V) from the phenols I or VII was rather surprising. It obviously involved the fusion of two molecules of the starting phenol with the loss of two carbon atoms per two molecules of the phenol, and, in the case of 2,6-dimethoxyphenol (I), the oxidative removal of one methoxyl group per molecule of the starting phenol.

Such a fusion of two C₆-entities could be assumed to arise by spontaneous dimerisation of the 3-methoxy-1,2-benzoquinone (IV) first formed by periodate oxidation of both phenols, I and VII. In fact, comparatively concentrated aqueous solutions of the *o*-benzoquinone IV when treated with periodate (Table 1, Expt. 5) were found to give the dimethoxy-1,2-naphthoquinone V in yields (about 50 %) similar to those obtained from 3-methoxycatechol (*cf.* Expt. 4). As in the case of the phenols I and VII, respectively, the formation of the β -naphthoquinone V from the *o*-benzoquinone IV was practically complete within a reaction time of 10 min.

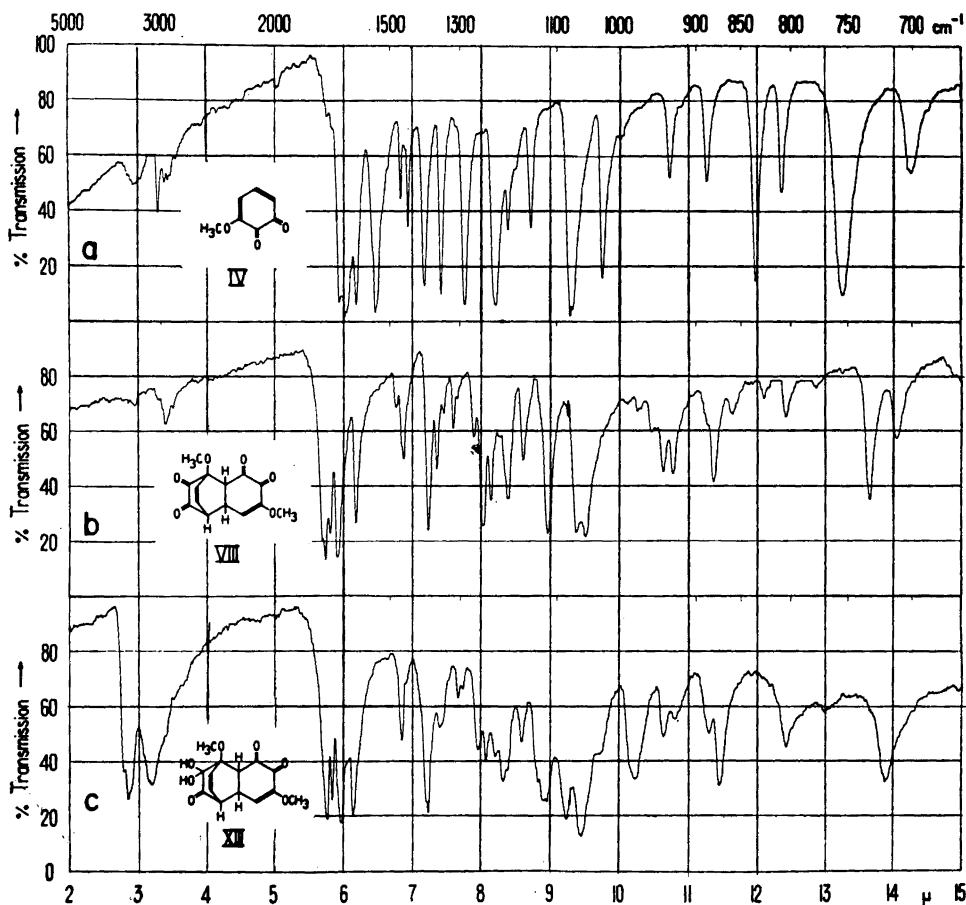


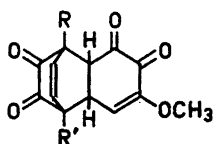
Fig. 1. Infra-red absorption spectra. a. 3-Methoxy-1,2-benzoquinone (IV). b. Dimeric 3-methoxy-1,2-benzoquinone (VIII). c. Monohydrate (XIII) of dimer VIII.

The assumption that the oxidative conversion of 3-methoxy-1,2-benzoquinone (IV) into 3,8-dimethoxy-1,2-naphthoquinone (V) involved an initial dimerisation of IV, could be examined experimentally when it was found that a dimeric 3-methoxy-1,2-benzoquinone could be easily obtained. When solutions of the monomer IV in certain solvents, such as acetone, methylene chloride, chloroform, dioxane, or ethyl acetate, were allowed to stand for a day at room temperature, a yellow product, m.p. 139–140°, was formed which had the same elemental composition as IV.

The infra-red spectrum of 3-methoxy-1,2-benzoquinone (IV) (Fig. 1a), shows very similar carbonyl absorption to that reported for the 5-ethyl homologue^{7,8}, but the infra-red spectrum of the yellow product (Fig. 1b) shows absorption bands at comparatively short wave-lengths, 5.69, 5.74, and

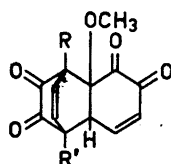
5.82 μ , indicating the presence of three isolated CO groups, and also a band at 5.93 μ , indicating an α,β -unsaturated carbonyl group. These bands, and a further band at 6.19 μ (ethylenic bond of C=C—C=O system), are practically identical with those reported by Harley-Mason and Laird⁹ (cf. also Ref.¹⁰) for the yellow dimer of unsubstituted *o*-benzoquinone described by Willstätter and Müller⁶, the structure of which was recently elucidated (VIII, H instead of CH₃O)^{10,9,11}. Its formation by diene addition of two molecules of *o*-benzoquinone is analogous to the dimerisation of alkylated *o*-quinones clarified a few years ago^{12,7,13}.

Similar diene addition of 2 molecules of 3-methoxy-1,2-benzoquinone can give rise to four isomeric adducts, VIII—VIIIc:



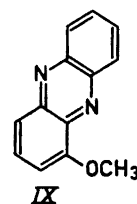
VIII: R = CH₃O; R' = H

VIIIa: R = H; R' = CH₃O



VIIIb: R = CH₃O; R' = H

VIIIc: R = H; R' = CH₃O



The light absorption of the dimeric 3-methoxy-*o*-quinone, m.p. 139—140°, (Fig. 2, curve 1) seems to be in harmony with structures VIII or VIIIa rather than VIIIb or VIIIc. The main maximum at 300 m μ can be ascribed to the methoxyl-substituted conjugated ene-dione chromophore of VIII or VIIIa, and the broad maximum at higher wave-length will be due to the 1,2-diketo groupings present.

Treatment of dimeric 3-methoxy-*o*-quinone with *o*-phenylenediamine, in pyridine solution, gave a yellow phenazine derivative, m.p. 172—173°, which was identical with 1-methoxyphenazine (IX) obtained from monomeric 3-methoxy-*o*-quinone. The yield was 90 %, indicating that both the monomer units in VIII had reacted, "retrodiene cleavage" giving rise to the phenazine derivative of the free monomer. A similar reversed diene reaction has been observed in the reaction between dimeric 4,5-dimethyl-*o*-quinone and *o*-phenylenediamine¹².

It appeared not quite impossible that 3-methoxy-*o*-quinone (IV), when treated with *o*-phenylenediamine in an organic solvent, might dimerise before condensation with the amine, and that consequently the phenazine derivative obtained from IV might be that of the dimeric rather than the monomeric *o*-quinone. However a determination of the molecular weight of the phenazine (Rast, found 224, calc. 210) confirmed that the derivative actually was that derived from the monomer.

Structures VIII—VIIIc, proposed for the dimeric 3-methoxy-*o*-quinone, clearly suggest that it should be possible to convert the substance, by periodate oxidation, into a β -naphthoquinone. In fact, treatment of the dimer with periodate gave 3,8-dimethoxy-1,2-naphthoquinone (V)⁵, m.p. 198—199°, in

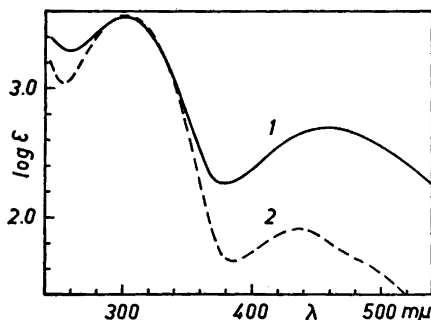


Fig. 2. Absorption spectra of dimeric 3-methoxy-1,2-benzoquinone (VIII) (curve 1), and the monohydrate XIII of dimer VIII (curve 2). Solvent: Chloroform.

87 % yield *. Together with the data reported above (analysis, IR and UV absorption), this proves structure VIII for the yellow dimer, and excludes the alternative structures VIIIa—c. The conversion VIII \rightarrow V by treatment with periodate obviously involved oxidative removal of the diketo group of the bicyclooctene system as well as of the two angular hydrogen atoms. The mechanism of this reaction will be discussed further in a subsequent communication ¹⁴.

The results just described strongly supported the view that the formation of β -naphthoquinone V from 3-methoxy-1,2-benzoquinone (IV) or its precursors, *i.e.* the phenols I or VII, in aqueous periodate solution, is due to dimerisation of IV followed by periodate degradation of the dimer. As mentioned above, this conversion of the *o*-benzoquinone IV into the β -naphthoquinone V proceeds very rapidly; under the conditions used (see, for instance, Table 1, Expt. 5) V could be detected already after a reaction time of 2 min, and the reaction was practically complete in 10 min.

Thus, it had to be assumed that the first step of the reaction, the dimerisation of the *o*-benzoquinone IV, proceeds in water at a comparatively high rate. This assumption, however, was not self-evident, since the dimerisation

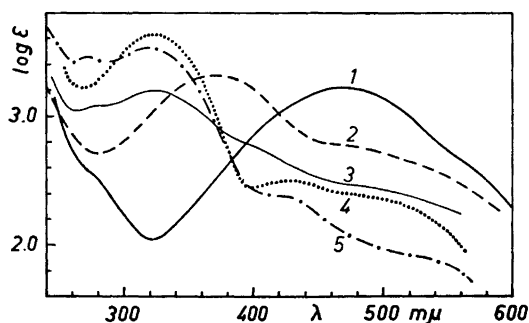
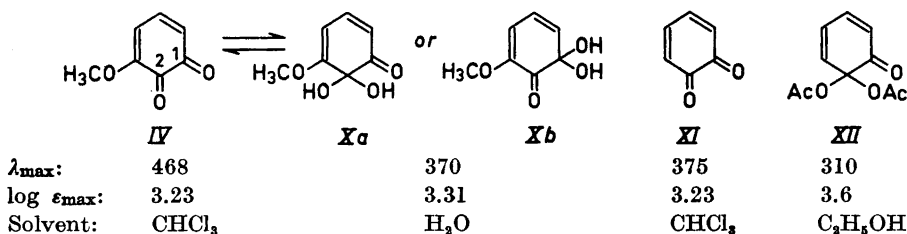


Fig. 3. Absorption spectra of 3-methoxy-1,2-benzoquinone (IV) in chloroform (curve 1), of IV dissolved in water to give a concentration of 0.6 mmole/l (curve 2), of IV dissolved in water to give a saturated solution (40 mmole/l), and then diluted to 0.6 mmole/l (curve 3) and of dimeric 3-methoxy-1,2-benzoquinone (VIII) dissolved in 25 % aqueous acetic acid (curve 4) and in water (curve 5).

* Briefly reported in Part I¹.

of IV in the organic solvents mentioned above appeared to be a comparatively slow reaction. The behaviour of 3-methoxy-1,2-benzoquinone in water — in the absence of periodate — was therefore examined in some detail.

While dilute solutions (about 1 mmole/l) of 3-methoxy-1,2-benzoquinone (IV) in chloroform show the absorption spectrum presented in Fig. 3 (curve 1, λ_{\max} 468 $m\mu$, $\log \epsilon$ 3.23, which is very similar to the curve reported ⁷ for the 5-ethyl homologue of IV), a freshly prepared aqueous solution of similar concentration showed an absorption maximum at a considerably lower wavelength (Fig. 3, curve 2; λ_{\max} 370 $m\mu$, $\log \epsilon$ 3.31). Since the absorption curve for a chloroform extract of a freshly prepared dilute aqueous solution of IV was practically identical with curve 1, the lower wavelength of the maximum in the aqueous solution could not be caused by any irreversible reaction between the methoxy-*o*-quinone and water. It might however be caused by the reversible addition of one molecule of water, forming one of the monohydrates Xa and Xb. The assumption of an equilibrium between the *o*-quinone IV and its hydrate X seems also to find support in the appearance of the long-wave branch of absorption curve 2, which has a shoulder at 460–470 $m\mu$, *i.e.*, at the maximum position of the absorption curve of the quinone in chloroform solution (curve 1). Hydration in this way would imply the conversion of the *o*-quinonoid system of IV into an *o*-quinol-like



(2,4-dienone) system (Xa or Xb), which would appear compatible with the hypsochromic shift of the absorption maximum by 98 $m\mu$.

For comparison, absorption data for *o*-benzoquinone (XI) ⁷ and 2-acetoxy-*o*-quinol acetate (XII) ³ are given above; the 2,4-dienone XII has a maximum at a wavelength 65 $m\mu$ shorter than that of the *o*-quinone XI. A comparison of the pair IV and X with the pair XI and XII also shows the strongly bathochromic effect of the methoxyl substituent in the chromophoric systems involved.

Of the two isomeric hydrates Xa and b, the first seems more probable. Due to the mesomeric effect of the methoxyl group, carbon atom 1 in IV (see formula above) will be less positive than 2, and therefore less accessible to nucleophilic attack by water; furthermore, the inductive effect of the methoxyl group will strengthen the positive character of carbon atom 2. Thus, both effects will act together, and the formation of Xa will be favoured. The comparatively strong bathochromic effect of the methoxyl group, indicated by a comparison of the maxima of XII and X, would also be in harmony with formula Xa, in which the methoxyl group is at the end of the conjugated system (δ -methoxydienone).

If a freshly prepared dilute aqueous solution of 3-methoxy-1,2-benzoquinone (IV), showing absorption curve 2 (Fig. 3), is kept at room temperature, the maximum at 370 $m\mu$ gradually decreases, and new maxima at 265 and 300 $m\mu$ form during the course of a few hours. Simultaneously, the initial deep-red colour of the solution turns to brown, the material extracted by chloroform gradually decreases in amount and develops maxima at 262 and 296 $m\mu$ rather than the broad maximum at 468 $m\mu$ characteristic of the intact *o*-quinone IV. These comparatively slow transformations of the monomer in dilute aqueous solutions have not yet been further examined.

An absorption curve quite different from curve 2 in Fig. 3 (freshly prepared 0.6 mmolar aqueous solution of *o*-quinone IV) was obtained by preparation of a saturated, *i.e.*, about 40 mmolar, solution of the quinone in water and then as soon as the substance had dissolved (after about 5 min), diluting the solution with water to a concentration suitable for absorption measurement (0.6 mmolar) (Fig. 3, curve 3). The long-wave branch with a shoulder at about 470 $m\mu$ (unchanged 3-methoxy-*o*-quinone (IV)?) was markedly lower than in curve 2, and the absorption maximum of curve 2 at 370 $m\mu$ (monohydrate X?) was now only a weak inflection. A new maximum had, however, appeared at 315 $m\mu$.

A similar maximum was also shown by aqueous and aqueous acetic acid solutions of the dimeric 3-methoxy-*o*-quinone VIII (Fig. 3, curves 5 and 4, respectively), which suggested that dimerisation of the *o*-quinone IV had taken place in the saturated aqueous solution. When the latter solution was concentrated *in vacuo*, a pale-yellow crystalline solid, m.p. 114–115° (decomp.), deposited. On treatment with periodate in aqueous acetic acid, this compound was converted, in high yield, into 3,8-dimethoxy-1,2-naphthoquinone (V). It thus behaved in the same way as dimer VIII.

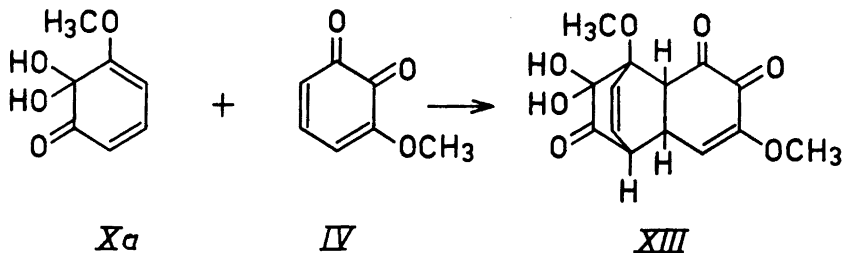
The new, pale-yellow product, in an air-dry condition analysed for a dimeric methoxy-*o*-quinone containing 3 molecules of water. Two molecules of water were removed on drying at 0.04 mm Hg over phosphorus pentoxide at room temperature and can therefore be regarded as water of crystallisation, but the third molecule could not be removed. The ultra-violet absorption of the substance in chloroform solution (Fig. 2, curve 2) exhibited a maximum at 302 $m\mu$ close to that of the anhydrous dimer VIII (Fig. 2, curve 1), which indicates that the main chromophores of both compounds are similar. However, the long-wave absorption band of the new compound was markedly weaker than that of dimer VIII, indicating the presence of only one 1,2-diketo grouping.

In contrast to dimer VIII (Fig. 1b), the new product (Fig. 1c) showed a distinct hydroxyl band (2.84 μ) in the infra-red spectrum, and only three CO stretching vibration bands (5.74, 5.81, 5.95 μ) instead of the four CO bands characteristic of dimer VIII. The presence of a strong absorption band at 6.12 μ , in addition to the CO band at 5.95 μ , indicates the presence of a C=C—C=O grouping.

These data indicate that the compound, m.p. 114–115°, is a monohydrate of dimer VIII, the molecule of water being linked to VIII by covalent bonds. Since the conjugated ene-dione chromophore appears to be unaffected, the molecule of water present must have been added to one of the keto groups of the bicyclooctene system. Structure XIII is therefore proposed for the substance.

Like the anhydrous dimer VIII, the hydrate XIII, when treated with *o*-phenylenediamine in pyridine, gave 1-methoxyphenazine (IX) in excellent

Scheme 2.



yield (93 %), indicating that both monomer halves reacted and that a "retro-diene cleavage" had occurred. This result also supports structure XIII.

As expected, a solution of the isolated dimer hydrate XIII in water or aqueous acetic acid showed the absorption maximum at 315 $m\mu$ which had been observed in a saturated solution of 3-methoxy-*o*-benzoquinone (IV) a few minutes after it had been dissolved (*cf.* p. 523). There is therefore no doubt that XIII is formed very rapidly in aqueous solutions of IV, provided that the concentration is comparatively high, and this explains the rapid conversion of phenols I and VII and of *o*-quinone IV into β -naphthoquinone V by aqueous periodate, as described above.

The remarkably high rate of the dimerisation of 3-methoxy-*o*-quinone in water could possibly be explained as follows. It has been found earlier (preliminary report, see Ref.¹⁵) that *o*-quinols undergo dimerisation by Diels-Alder addition, and also that an *o*-quinol and an *o*-quinone molecule may add in a similar way, with the *o*-quinol molecule acting as a diene and the *o*-quinone molecule as a philodiene. Both types of reactions have been found to proceed very rapidly in an aqueous medium, and, in the special case studied, the *o*-quinol-*o*-quinone addition proceeded considerably faster than the self-dimerisation of the *o*-quinone involved. Monohydrate X, assumed to be formed from 3-methoxy-*o*-quinone in water (see p. 522), would be of an *o*-quinol type, and, hence, would probably possess a strong tendency to undergo a Diels-Alder reaction. The rapid formation of XIII in saturated aqueous solutions of 3-methoxy-*o*-quinone IV might then be regarded as a dimerisation of monohydrate X with subsequent loss of one molecule of water, or, alternatively, as an addition of a molecule of the *o*-quinol-like monohydrate X (diene) to a molecule of unchanged *o*-quinone IV (philodiene), as shown in Scheme 2*.

* Note added in proof. It has been found that an aqueous solution of 3-methoxy-5-methyl-1,2-benzoquinone⁷ has its main absorption maximum at 370 $m\mu$, an additional, weak band with maximum at 480 $m\mu$ also being present, whereas a single, strong band with maximum at 480 $m\mu$ is observed in chloroform solution. Although this behaviour of the compound is similar to that shown by 3-methoxy-1,2-benzoquinone (IV), the 5-methyl homologue differs from IV in being comparatively stable in aqueous solutions and showing no marked tendency to dimerisation. Therefore the view presented above (p. 524) that hydration of IV, which is believed to be the reason for the short-wave absorption in aqueous solution, might be responsible for the rapid dimerisation of this *o*-quinone in concentrated aqueous solution, seems to be contradicted by the results obtained with the 5-methyl homologue.

Alcoholic solutions of IV and its 5-methyl homologue show short-wave absorption maxima similar to those observed in water (hemiketal formation?). This behaviour is specific for 3-

There is also of course the third possibility of a diene-addition between two molecules of the *o*-quinone, followed by hydration of the dimer, which cannot be excluded.

The absorption spectrum of the dimer hydrate XIII in 25 % acetic acid was identical with that of the anhydrous dimer VIII in the same solvent (Fig. 3, curve 4), indicating that the dimer VIII, when dissolved in aqueous solvents, is converted into XIII. In fact, crystalline XIII deposited from aqueous or aqueous acetic acid solutions of VIII on concentration under reduced pressure.

The anhydrous dimer VIII dissolves rather slowly in water at room temperature, the rate of hydration probably being the limiting factor. During the time necessary for dissolution (1–2 h), the solution acquires a slightly red colour, and the absorption spectrum (Fig. 3, curve 5) differs somewhat from that of a freshly prepared, pale yellow solution in 25 % acetic acid (Fig. 3, curve 4), in which dimer VIII dissolves much more rapidly than in water; an "aged" solution in aqueous acetic acid, however, shows similar changes to those in the aqueous solution.

Neither freshly prepared nor "aged" solutions of VIII or XIII in water or in alcohols gave distinct colour reactions with ferric chloride. Heating the solutions gave dark browned products which were not further investigated. These also gave negative ferric chloride reactions. The dimeric 3-methoxy-*o*-quinone VIII and its monohydrate XIII thus differ from the similar dimer of unsubstituted *o*-quinone⁹⁻¹¹, which, on heating for a short time in water, enolises to yield the corresponding phenolic isomer. The latter gives coloured ferric complexes typical of a catechol structure.

Only one case of oxidative conversion of a phenol into a β -naphthoquinone seems to have been reported in the literature. Zinke and Francke^{16 **} found that treatment of 6-bromoprotocatechuic acid with conc. nitric acid yields 3,6-dibromo-1,2-naphthoquinone-7-carboxylic acid. It can be assumed that the course of this reaction is similar to that described in the present paper.

Note: A second dimer of 3-methoxy-1,2-benzoquinone. After solutions of 3-methoxy-1,2-benzoquinone (IV) in benzene had been kept at room temperature for several hours, there could be isolated a yellow crystalline substance, m. p. 110° (decomp.). It is obviously a dimeric *o*-quinone different from the dimer VIII (m. p. 139–140°) which is formed in the (polar) organic solvents mentioned on p. 519. On treatment with *o*-phenylenediamine the new product behaved like dimer VIII (see p. 520), yielding the phenazine derivative IX of monomeric 3-methoxy-*o*-quinone (1-methoxyphenazine, m. p. 172–173°). This supports the view that the new product is formed by diene addition of 3-methoxy-*o*-quinone, in an analogous way to the formation of VIII, and reverts to the monomer when the phenazine is formed.

The dimer of m. p. 110° is still less stable than dimer VIII, and, although it was apparently obtained in a state of purity, elemental analysis has not yet given any clear results.

When treated with periodate, the new dimer is converted in high yield into the dark-violet compound (VI), m. p. 205–206°, which was obtained as a by-product in the periodate oxidation of phenols I and VII and the *o*-quinone IV in aqueous solutions (see p. 516). Thus, the dimer of m. p. 110°, or possibly a hydrate of it, appears to be formed,

methoxy-1,2-quinones; aqueous or alcoholic solutions of 4-methoxy-1,2-quinone and of 3-methyl- and 3-bromo-1,2-quinones, for instance, have absorption curves very similar to those found in chloroform solutions (Adler, E., Thomelius, H. and Granerus, G. *To be published*).

One of the ketonic oxygen atoms is very rapidly exchanged for ¹⁸O, if 3-methoxy-5-methyl-1,2-quinone is dissolved in water enriched of H₂¹⁸O, and reextracted with methylene chloride. This supports the view (see above) that rapid reversible hydration of one of the keto groups takes place (Adler, E. and Falkehaug, I. *To be published*).

** Prof. H. Erdtman, Stockholm, has kindly drawn the authors' attention to this paper.

in small amounts, in aqueous solutions of *o*-quinone IV, in addition to the hydrate XIII of dimer VIII. If the assumed structure for substance VI, *i. e.*, 3,5-dimethoxy-1,2-naphthoquinone (*cf.* p. 516), is correct, the structure of the new dimer, which is the precursor of VI, will probably be represented by formula VIIIa (p. 520).

Mixtures of both dimers, VIII and VIIIa (?), were repeatedly obtained when 3-methoxy-*o*-quinone (IV) was allowed to dimerise in various organic solvents. The mixtures showed melting points between those of the pure dimers. Attempts to separate the two components by fractional crystallisation were unsuccessful and, furthermore, both dimers are adsorbed and destroyed on alumina. The presence of both dimers in these mixtures is easily demonstrated, however, by periodate oxidation and chromatographic separation of the crude oxidation product; this gives both β -naphthoquinone V and the violet substance VI in a pure state.

The dimerisation of IV in nitromethane, yielding a product with m.p. 130° (mixture of VIII and VIIIa ?), was recently reported by Horner and Dürckheimer²⁰.

EXPERIMENTAL

Ultra-violet spectra were measured with a Beckman DU instrument; infra-red spectra with a Perkin-Elmer instrument, model 21. Microanalyses were done by A. Bernhardt, Mülheim (Ruhr), Germany.

Periodate consumption and methanol formation were determined as described previously^{17,18}.

Periodate oxidation of 2,6-dimethoxyphenol (I). An ice-cooled, stirred solution of I (1.004 g = 6.52 mmole) in water (400 ml), was treated with sodium metaperiodate (4.164 g = 19.45 mmole) in ice-cold water (400 ml), added all in one lot, and the temperature of the mixture was kept at about 4°. After 2 min, excess periodate was reduced by addition of ethylene glycol (1.2 g). The dark-blue needles which had settled out during the oxidation period, were filtered off and were identified with *coerulignone (II)* by comparison with an authentic sample and by reduction with warm 50 % aqueous sodium bisulphite to dihydrocoerulignone, m. p. 190°¹⁸. The yield of *coerulignone* was 70 mg (7 %).

The dark brown-red filtrate was extracted with five 100 ml portions of chloroform. The combined dark-red chloroform solutions were dried briefly over anhydrous sodium sulphate, filtered, and divided into two equal parts, which were evaporated to dryness under reduced pressure. (Both the chloroform extraction and the evaporation were carried out as rapidly as possible in order to avoid any appreciable dimerisation of the *o*-quinone.)

a) Isolation of 3-methoxy-1,2-benzoquinone (IV). One of the crude, partially-crystalline chloroform residues (328 mg, *i. e.* 65 % yield by weight, based on I) was treated with three 150 ml portions of boiling, dry ethyl ether. The ether extracts after filtration and cooling to -80° deposited dark brown-red crystals (166 mg), m. p. 98–105°; no depression with 3-methoxy-*o*-quinone, m. p. 107–110°, prepared according to Willstätter and Müller⁶. The infra-red spectra of the two samples were essentially identical. The lower m. p. of the sample obtained by periodate oxidation was due to the presence of traces of oxidation products III and V, detected by chromatography on alumina (see below), and probably also of dimer VIII, which could not be completely removed even by repeated recrystallisation from ether.

b) Isolation of 2,6-dimethoxy-1,4-benzoquinone (III), 3,8-dimethoxy-1,2-naphthoquinone (V) and substance VI. The second of the two chloroform residues (325 mg) obtained above was treated with three 100 ml portions of boiling benzene. A small amount of undissolved material (2 mg) was removed by filtration, and the solution was chromatographed on a column of neutral alumina (1 × 20 cm). Elution with benzene gave the yellow 2,6-dimethoxy-*p*-quinone (III), m. p. and mixed m. p. 255–256° (31 mg, 5 % based on I), followed by the dark-violet compound VI, m. p. 205–206° (12 mg, 2 %), needles from benzene-hexane. Analysis of VI indicated the composition C₁₀H₄O₂(OCH₃)₂. (Found: C 66.05; H 4.61; OCH₃, 27.99. Calc. for C₁₂H₁₀O₄: C 66.05; H 4.62; OCH₃, 28.44.)

Further elution of the alumina column with benzene containing 3 % ethanol eluted the red 3,8-dimethoxy-1,2-naphthoquinone (V), flat prisms or plates from benzene or acetone,

m. p. 198–199° (20 mg, 7%). (Found: C 66.25; H 4.54; OCH₃ 28.36. Calc. for C₁₁H₁₀O₄: C 66.05; H 4.62; OCH₃ 28.44.) For derivatives of V and proof of its structure see Ref.⁵.

After elution of compounds III, VI, and V, a broad black zone remained in the upper part of the column. It could not be washed out with common solvents. 3-Methoxy-1,2-benzoquinone (IV) and its dimer (VIII) both gave similar, very strongly adsorbed degradation products on alumina. The difference between the total weight of solids chromatographed (323 mg) and the combined weights of the eluted substances III, V, and VI (63 mg), *i. e.* 260 mg, was taken as a measure of the amount of 3-methoxy-1,2-benzoquinone (IV) formed in the periodate oxidation (yield 58%).

The experiment described above is listed as Expt. 1 in Table 1. The same procedure was used in the other experiments presented in Table 1, although neither coerulignone nor 2,6-dimethoxy-*p*-quinone were formed from 3-methoxycatechol (VII) and 3-methoxy-*o*-quinone (IV) on treatment with periodate.

Phenazine derivative obtained from VI. When the dark-violet solution of substance VI (80 mg) in pyridine (8 ml) was mixed with a solution of *o*-phenylenediamine (200 mg) in the same solvent (2 ml), the colour of the mixture immediately turned to orange. After 1 h at room temperature part of the solvent was removed under reduced pressure. Addition of water gave a crystalline precipitate which was recrystallised from methanol and methanol-water. Orange needles or prisms, m. p. 229–230°. (Found: C 74.31; H 4.84; N 9.89; OCH₃ 21.09; Mol. wt. (Rast) 299. Calc. for C₁₆H₁₄O₂N₂: C 74.47; H 4.86; N 9.63; OCH₃ 21.38; Mol. wt. 290.)

Dimeric 3-methoxy-1,2-benzoquinone, m. p. 139–140° (VIII). A solution of 3-methoxy-1,2-benzoquinone (IV) (1.6 g) in acetone (200 ml) was kept at room temperature for about 16 h. The solvent was evaporated under reduced pressure and the partially crystalline residue was washed with cold chloroform which removed unchanged monomer and brown, amorphous material. The yellow crystals remaining (yield 30–40%), m. p. 136–138°, were dissolved in acetone with brief heating (prolonged heating in any solvent causes discoloration). Cooling to –20° yielded the dimer VIII as deep-yellow prisms, m. p. 139–140°. (Found: C 60.74; H 4.50; OCH₃ 22.55. Calc. for C₁₄H₁₂O₆: C 60.87; H 4.31; OCH₃ 22.47.)

Dimer VIII was also obtained in the same way from solutions of IV in methylene chloride, chloroform, ethyl acetate, and dioxane. Dimerisation of IV could also be carried out in the solid state. For instance, a solution of IV in methylene chloride was taken to dryness under reduced pressure in a rotating film evaporator, giving a layer of solid IV spread over the wall of the round-bottomed flask. A few millilitres of acetone or methylene chloride were then added without dissolving the major part of the solid, and the flask was stoppered. After about 16 h the initially dark-brown layer of IV had turned yellow. The crude product was purified as described above.

The product has to be stored at –20°. At room temperature and in day-light, it gradually darkens.

IR spectrum, see Fig. 1. UV spectrum, see Figs. 2 and 3.

1-Methoxyphenazine (IX) from dimer VIII. The yellow solution of dimer VIII (100 mg) in pyridine (5 ml) was mixed with a solution of *o*-phenylenediamine (130 mg) in 1 ml of the same solvent. The mixture turned orange. After 1 h at room temperature, the solvent was removed under reduced pressure and the solid residue was dissolved in chloroform. The chloroform solution was washed with 0.5 N sulphuric acid and water, and then was dried and evaporated. The yellow crystalline residue (140 mg) had m. p. 170–171°. Yield 90%. Recrystallisation from methanol-water raised the m. p. to 172–173°, undepressed by a sample of 1-methoxyphenazine, m. p. 172–173°, (Literature¹⁹: 169°) obtained from 3-methoxy-*o*-quinone. The IR spectra of both samples also proved their identity.

Periodate oxidation of dimer VIII. A solution of dimer VIII (77 mg) in 50% aqueous acetic acid (10 ml) was mixed with an aqueous solution (20 ml) of sodium metaperiodate (245 mg). After 2.5 h at room temperature, the red solution was extracted with methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous calcium sulphate, and evaporated. Dark-red crystals of nearly pure 3,8-methoxy-1,2-naphthoquinone (V), m. p. 194–195°, remained. Yield 87%. Recrystallisation from benzene raised the m. p. to 198–199°, undepressed on admixture of V, prepared as above.

*Monohydrate of dimeric 3-methoxy-*o*-quinone (XIII). a) From 3-methoxy-*o*-quinone (IV).* A freshly-prepared, almost saturated solution of IV (100 mg) in water (20 ml)

(36 mmole/l) was concentrated under reduced pressure to a volume of about 5 ml. On cooling in the refrigerator, a greyish yellow crystalline product deposited. Recrystallisation from acetone-hexane, ethyl acetate-hexane, or acetone-water (without heating) gave pale-yellow plates or prisms, m. p. 114–115° (decomp.). Yield 25 %.

b) *From dimer VIII*. Dimer VIII (439 mg) was dissolved in 25 % aqueous acetic acid (50 ml); the time required for it to dissolve completely (with shaking) was about 20 min. The solution was concentrated under reduced pressure to a volume of a few millilitres; water was added gradually in the final stages of the evaporation in order to reduce the amount of acetic acid in the concentrate. After cooling in the refrigerator the crystalline product which deposited, was collected. Yield 40 %. The product was identified by m. p., mixed m. p., and IR spectrum with the dimer monohydrate obtained from 3-methoxy-*o*-benzoquinone.

The methoxyl content of the air-dry product indicated that the dimer contained 3 mols. of water. (Found: OCH₃ 18.52. Calc. for C₁₄H₁₂O₆, 3H₂O: 18.79.) On drying over P₂O₅ for 6 h at room temperature and 0.04 mm Hg the substance lost 2 mols. of water (loss of weight found, 10.5 %, calc., 10.9 %). The dried product analysed for a monohydrate of a dimeric methoxyquinone. (Found: C 56.80; H 5.04; OCH₃ 20.65. Calc. for C₁₄H₁₄O₇: C 57.14; H 4.80; OCH₃ 21.09.) An aqueous solution of the substance was neutral. Ferric chloride colour tests for phenolic or catechol groupings were negative. The substance darkened gradually, even at low temperature. IR spectrum, Fig. 1. UV spectrum, Figs. 2 and 3.

When allowed to react with *o*-phenylenediamine in pyridine, the hydrated dimer VIII gave 1-methoxyphenazine (IX), m. p. 171–172°, in 93 % yield.

Treatment of an aqueous acetic acid solution of the monohydrate XIII with periodate gave 3,8-dimethoxy-1,2-naphthoquinone (V) in about 80 % yield.

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