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Periodate Oxidation of Phenols

III. The Conversion of Dimeric *o*-Benzoquinones into β-Naphthoquinones *

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Dimeric *o*-benzoquinone (VI) and its phenolic isomer (VIII) both react with 3 moles of periodate to give β-naphthoquinone in 70 % yield. In the same way both dimeric 3-methoxy-*o*-benzoquinone (IV) and its monohydrate (IVa) are degraded by periodate to 3,8-dimethoxy-1,2-naphthoquinone (V). The course of these reactions was investigated. Dehydrogenation of the catechol grouping present in VIII with silver oxide gave the *o*-quinone IX, which was converted, by treatment with 2 moles of periodate, into β-naphthoquinone. Periodate cleavage of the α-diketo grouping in the diacetyl derivative of VIII, followed by alkaline hydrolysis of the product (XI), yielded 1,2-dihydroxy-5,8-dihydronaphthalene-5,8-dicarboxylic acid (XII). The latter was converted into β-naphthoquinone by treatment with periodate (2 moles) or with silver oxide. IX and XII are probable intermediates in the conversions of VI and VIII, respectively, into β-naphthoquinone.

A reaction scheme is given showing the probable course of these conversions (Scheme 3).

As reported in Part II [1] of this series, the action of excess sodium periodate on pyrogallol-1,3-dimethyl ether (I) in aqueous solution results mainly in oxidative removal of one of the methoxyl groups with the liberation of methanol and the formation of 3-methoxy-1,2-benzoquinone (II). The *o*-quinone undergoes further reactions, which are rapid when relatively high initial concentrations of phenol I are used. For instance, periodate oxidation of phenol I in 80 mM solution gave 3,8-dimethoxy-1,2-naphthoquinone (V) in 25 % yield, with a reaction time of 10 min. Under similar conditions, the β-naphthoquinone V was obtained in yields of about 50 % when pyrogallol-1-methyl ether (III) or 3-methoxy-1,2-benzoquinone (II) were treated with periodate.

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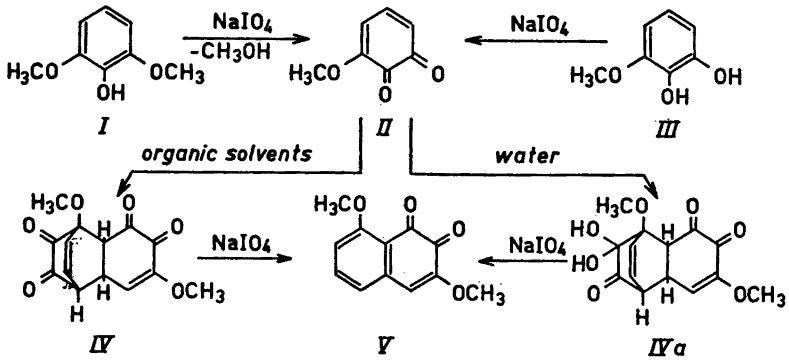
Scheme 1.



It was also found [1] that 3-methoxy-1,2-benzoquinone (II) in various organic solvents undergoes dimerisation by diene-philodiene addition, yielding the yellow dimer IV, m.p. 139—140°; in aqueous solution a monohydrate of IV, (IVa) m.p. 114—115°, is produced. Both forms of the dimeric 3-methoxy-*o*-quinone, when treated with aqueous periodate solution, were smoothly converted into the *β*-naphthoquinone V.

The formation of the 1,2-naphthoquinone V from the 1,2-benzoquinone II, in aqueous solution in the presence of periodate, is thus the result of dimerisation of II followed by periodate oxidation (*cf.* Scheme 1).

As briefly reported previously [8], the dimer of unsubstituted *o*-benzoquinone (VI) [2-5], when treated with periodate, undergoes a similar degradation, with the formation of *β*-naphthoquinone (VII). (Scheme 2).

The present communication deals with the mechanism of this oxidative conversion of dimeric 1,2-benzoquinones into 1,2-naphthoquinones. For reasons presented below, detailed studies have, as yet, only been made on the conversion of dimeric *o*-benzoquinone into *β*-naphthoquinone but probably the results obtained in these studies are also valid for the analogous reaction of the dimeric 3-methoxy-*o*-benzoquinone.

CONVERSION OF DIMERIC *o*-BENZOQUINONE (VI, VIII) INTO *β*-NAPHTHOQUINONE (VII)

Dimeric *o*-quinone (VI), dissolved in 50 % acetic acid, was found to consume nearly 3 moles of sodium periodate in about 20 min (Fig. 1, curve 1); the resulting orange solution gave *β*-naphthoquinone (VII), m.p. 145—146°, in 70 % yield.

The phenolic isomer (VIII) of dimeric *o*-quinone (VI), which is obtained by heating the quinone with ethanolic hydrochloric acid [3] or simply with water [4,5], also consumes 3 moles of periodate. In aqueous solution, the main reaction is complete after 3 min, giving *β*-naphthoquinone in 70 % yield. In 50 % acetic acid the reaction is slightly slower (Fig. 1, curves 2 and 3).

The rapid main reaction is followed by further slow periodate consumption. The similar slow oxidation of *β*-naphthoquinone itself (Fig. 1, curve 4) indicates

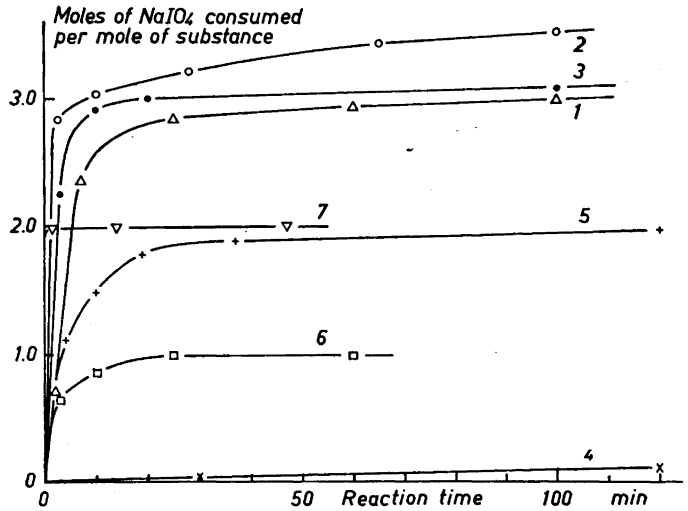


Fig. 1. Periodate consumption by dimeric *o*-quinone (VI) in 50 % aqueous acetic acid (curve 1), by the phenolic isomer VIII of dimeric *o*-quinone in water (curve 2) and in 50 % aqueous acetic acid (curve 3) and by β-naphthoquinone (VII) (curve 4), the *o*-quinone IX (curve 5), the diacetyl derivative of VIII (X) (curve 6), and 1,2-dihydroxy-5,8-dihydronaphthalene-5,8-dicarboxylic acid (XII) (curve 7), in 50 % aqueous acetic acid. The molar ratio substance/$NaIO_4$ was 1/4.

that this is due to cleavage of the 1,2-diketo grouping of the β-naphthoquinone formed in the main reaction.

When β-naphthoquinone was treated with periodate at pH 6.5 instead of the slightly acidic conditions used above (the pH value of an unbuffered aqueous solution of sodium metaperiodate is about 3.5) the oxidation proceeded at a satisfactory rate, and *o*-carboxycinnamic acid was obtained in good yield [6].

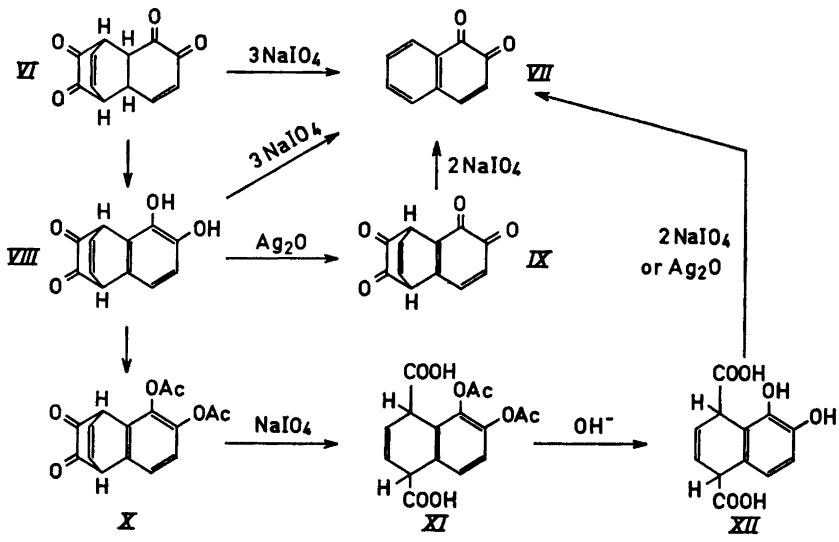
The next step in the investigation of the conversions VI → VII and VIII → VII, was the preparation of substances IX and XII, which obviously were possible intermediates.

The red *o*-quinone IX was obtained by dehydrogenating the phenolic dimer VIII with silver oxide. It has also been prepared recently by Horner and Dürckheimer [5], who used tetrachloro-*o*-quinone as dehydrogenating agent.

The dicarboxylic acid XII, m.p. 182—183°, was made by cleaving the diketo bridge of the diacetate (X) [4] of the phenolic dimer (VIII) with periodate (Fig. 1, curve 6), to give the dicarboxylic acid XI, m.p. 189—190°, and then removing the protecting acetyl groups by alkaline hydrolysis under nitrogen.

The ultra-violet and visible light absorption spectra of the ketonic dimer VI, its phenolic isomer VIII, the *o*-quinonoid substance IX, and the diacetate X are shown in Fig. 2; the spectra of the dicarboxylic acids XI and XII are shown in Fig. 3. Substances VI, VIII, IX, and X show the characteristic absorption band between 400 and 500 mμ of α-diketones. As expected, this long-wave absorption is absent from the spectra of the dicarboxylic acids XI

Scheme 2.



and XII. The infra-red absorption data for the acids XI and XII (see Experimental) are also in harmony with the proposed structures.

An examination was then made of the behaviour of compounds IX and XII on treatment with periodate. The *o*-quinone IX consumed 2 moles of the oxidant (Fig. 1, curve 5), and was converted into β-naphthoquinone. The dicarboxylic acid XII also consumed 2 moles of periodate very rapidly (Fig. 1, curve 7), and gave β-naphthoquinone. Surprisingly enough, the same transformation, (XII → VII), could be brought about merely by shaking a solution of XII in acetone with silver oxide.

The results described so far are summarised in Scheme 2. They suggest that the periodate oxidation of the two forms of dimeric *o*-benzoquinone (VI, VIII) giving β-naphthoquinone (VII) follows the reaction sequences shown in Scheme 3.

As indicated in Scheme 3, the primary step in the oxidation of the ketonic dimer (VI) with excess periodate can be assumed to be the cleavage of the diketo grouping of the bi*cyclo*octene system. However, attempts to isolate the expected cleavage product, *i.e.*, the diketodicarboxylic acid XIII, after treating VI (in aqueous acetic acid solution) with an equimolar amount of periodate, were without success. β-Naphthoquinone (VII) was formed, but the yield was only about a third of that obtained in experiments with excess periodate. Three moles of the oxidant were required for maximum conversion of the dimer VI into the end product, VII. This seems to indicate that the diketodicarboxylic acid (XIII) first formed, rapidly enolises to give the dihydroxydicarboxylic acid (XII), which is then converted into β-naphthoquinone (VII) with further consumption of periodate.

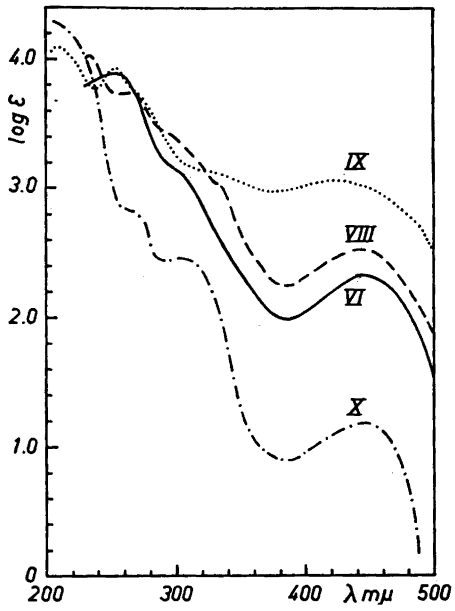


Fig. 2. Absorption spectra of dimeric *o*-quinone (VI), the phenolic isomer of dimeric *o*-quinone (VIII), the diacetyl derivative of VIII (X), and the *o*-quinone IX. Solvents: For VI and VIII, methylene chloride, for X and IX, 95 % ethanol.

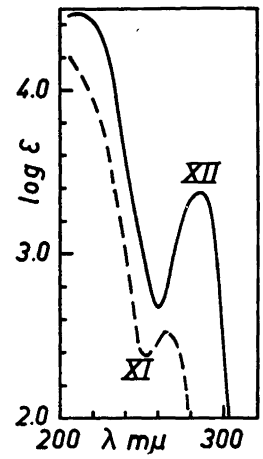


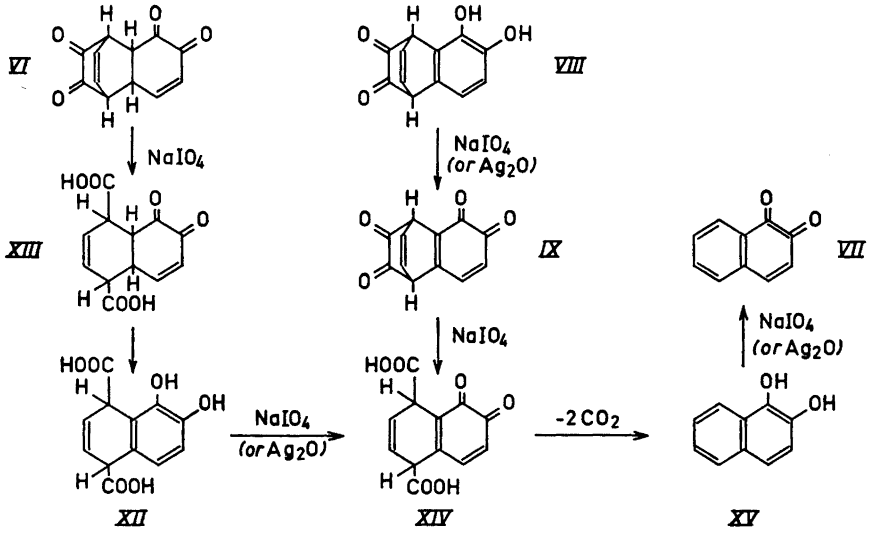
Fig. 3. Ultraviolet absorption of 1,2-dihydroxy-5,8-dihydronaphthalene-5,8-dicarboxylic acid (XII) and its diacetyl derivative (XI), in 95 % ethanol.

As described above, the dihydroxydicarboxylic acid XII is almost instantly converted into VII not only by periodate (2 moles) but also by silver oxide. This suggests that the conversion XII → VII involves dehydrogenation of the catechol grouping of XII to form an intermediate *o*-quinonoid dicarboxylic acid XIV, which immediately undergoes spontaneous decarboxylation to yield 1,2-dihydroxynaphthalene (XV), which is then dehydrogenated to give the end-product, VII. As expected, the suggested final step, XV → VII, could be shown to proceed with great ease when XV was treated either with periodate in aqueous acetic acid, in which case an equimolar amount of $NaIO_4$ was consumed almost instantly, or with silver oxide in acetone.

Starting from the phenolic form of dimeric *o*-benzoquinone (VIII), the primary step is assumed to be the dehydrogenation of the catechol grouping rather than the oxidative opening of the diketo bridge. The diketo grouping of the *o*-quinone IX thus formed would then be opened by a further mole of periodate to give the hypothetical intermediate XIV; the rapid concluding steps XIV → XV → VII are identical with those postulated above for the oxidation of the ketonic dimer VI.

The assumption of two different paths, VI → XIII → XII → XIV and VIII → IX → XIV, for the initial steps of the oxidation of the ketonic dimer

Scheme 3.



(VI) and of its phenolic isomer (VIII) might appear unnecessary. It could be supposed instead that in polar solvents the ketonic dimer VI was in equilibrium with the phenolic form VIII and that in both cases it was the phenolic form that was attacked by the periodate. However, freshly prepared solutions of the ketonic dimer VI in aqueous acetic acid or aqueous ethanol do not give the catechol colour reaction with ferric chloride, given by solutions of the phenolic dimer VIII. In these solvents the isomerisation VI → VIII proceeds so slowly at room temperature that it cannot be involved in the rapid conversion of the ketonic dimer VI into β-naphthoquinone by periodate.

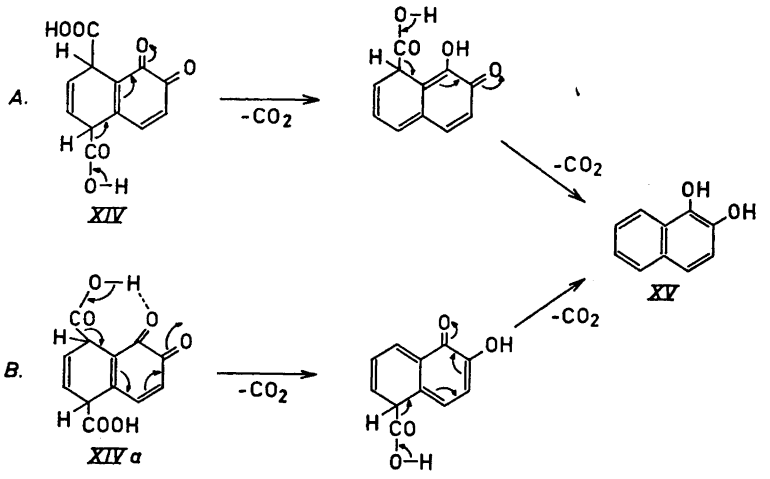
It was assumed above that the hypothetical primary intermediate XIII enolises rapidly to give the partially aromatic compound XII which readily undergoes further oxidation. This assumption may seem to be in contrast to the remarkably low tendency of VI to enolise. However, an inspection of Stuart-Briegleb models indicates that the stability of VI might be explained by the greater strain shown by the bridged ring system in the enol form (VIII) than in the keto form (VI). This would cause some resistance to enolisation in the latter compound. The dihydronaphthalene derivative XII on the other hand is not more strained than XIII and enolisation of the latter would therefore be expected to proceed easily.

In dioxane or aqueous dioxane solution the enolisation VI → VIII was found to take place comparatively rapidly even at room temperature; this was indicated by the appearance of a distinct ferric chloride colour reaction immediately after dissolving the ketonic dimer (VI). The intensity of the colour increased and after about one hour approached that given by a solution of the phenolic isomer (VIII).

According to the view presented above (cf. also Scheme 3), the keto bridge carbon atoms of dimers VI and VIII are removed as carbon dioxide from the intermediate XIV, which is assumed to be formed by oxidation of both the dihydroxydicarboxylic acid (XII) and the *o*-quinone IX. Compound XIV is thus common to both pathways, VI → VII, and VIII → VII. The finding that both VI and VIII require 3 moles of periodate for conversion into β-naphthoquinone, supports this view. If, for instance, β-naphthoquinone were formed directly from the diketodicarboxylic acid XIII, by the loss of two molecules of formic acid, then one mole of periodate would have been sufficient to convert dimer VI into β-naphthoquinone.

The spontaneous rapid decarboxylation of the postulated *o*-quinonoid intermediate XIV can be attributed to the special position of the carboxylic groups, both of which are part of vinylogous β-keto acid structures (Scheme 4 A). Furthermore, a Stuart-Briegleb model of XIV suggests the possibility

Scheme 4.



of chelation between the carboxyl group in position 8 and the keto group in position 1, as indicated in formula XIVa. This points to a mechanism for the decarboxylation of the 8-carboxyl group that is closely related to the generally accepted mechanism [7] for the decarboxylation of β-keto acids (Scheme 4 B).

CONVERSION OF DIMERIC 3-METHOXY-1,2-BENZOQUINONE (IV) AND ITS MONOHYDRATE (IVA) INTO 3,8-DIMETHOXY-1,2-NAPHTHOQUINONE(V)

As reported previously [1], treatment of dimeric 3-methoxy-1,2-benzoquinone (IV) with periodate in aqueous solution produces 3,8-dimethoxy-1,2-naphthoquinone (V) in about 85 % yield. Fig. 4, curve 1, shows the consumption of the oxidant as a function of reaction time. The comparatively rapid initial phase of the reaction seems to be completed after about 1 h. In 25 % aqueous

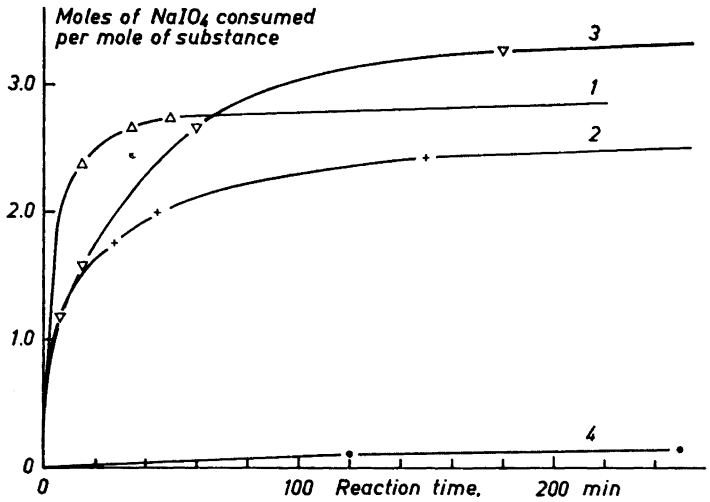


Fig. 4. Periodate consumption by dimeric 3-methoxy-1,2-benzoquinone (IV) in water (curve 1) and in 25 % aqueous acetic acid (curve 2), by the monohydrate of IV (IVa), (curve 3), and by 3,8-dimethoxy-1,2-naphthoquinone (V) in 25 % aqueous acetic acid (curve 4). Molar ratio, substance/$NaIO_4$ = 1/4.

acetic acid the reaction proceeded at a somewhat decreased rate (Fig. 4, curve 2).

The periodate consumption of the hydrated dimer IVa, in 25 % aqueous acetic acid, is shown in curve 3.

As in the degradation of dimeric *o*-quinone, further oxidation of the *β*-naphthoquinone formed was very slow; the rate of periodate consumption by isolated 3,8-dimethoxy-1,2-naphthoquinone (V) in 25 % aqueous acetic acid is shown in curve 4.

In a buffered aqueous medium (pH 6.5) the naphthoquinone V was oxidised fairly rapidly and gave 2-carboxy-3-methoxy-α-methoxycinnamic acid. This reaction was used in the elucidation of the structure of V, which will be reported in a following paper[6].

Extrapolation of curves 1 and 2 back to time zero indicates that 2,7 and 2,4 mole $NaIO_4$ per mole of dimer IV were required for the production of the naphthoquinone V, in water and dilute acetic acid, respectively. The hydrated dimer IVa however consumed about 3 mole $NaIO_4$/mole (curve 3), thus behaving in the same way as the dimeric *o*-quinone (VI, VIII, Fig. 1). The reason for the somewhat lower consumption of periodate in the case of the anhydrous dimer IV is still unknown. In spite of the differences in periodate consumption the yields of naphthoquinone V were equally high (80—85 %)[1] in the three experiments represented by curves 1, 2 and 3. Since, as reported in Part II[1], the anhydrous dimer IV, when dissolved in water, or 25 % acetic acid, is converted into the hydrate IVa, it would be expected that IV and IVa would also show the same periodate consumption. Possibly, the anhydrous

dimer to some extent undergoes some periodate-saving reaction (autoxidative cleavage of the diketo bridge?) before the hydration is complete.

Apart from the minor discrepancies just mentioned, the periodate uptake by dimeric 3-methoxy-*o*-quinone (IV, IVa) was similar to that found for dimeric *o*-quinone (VI). It therefore seems probable that the mechanism discussed above for the conversion VI → VII, will also be valid for the similar conversion IV (IVa) → V but it has not yet been possible to carry out a more detailed investigation of this reaction. The phenolic isomer of IV has not so far been obtained. Attempts to prepare its diacetate by treating IV with acetic anhydride in pyridine gave a product, which, although showing some of the properties expected, has not yet been obtained in a state of purity. For these reasons, possible intermediates corresponding to compounds IX and XII in the *o*-quinone series, have not been available for an examination of their role in the degradation of the 3-methoxy-*o*-quinone dimers (IV, IVa).

EXPERIMENTAL

Ultra-violet and visible absorption spectra were measured with a Beckman DU spectrophotometer, infra-red spectra with a Perkin-Elmer model 21 instrument (KBr). Analyses were carried out by A. Bernhardt, Mülheim (Ruhr), Germany.

Periodate consumption. In the experiments of Fig. 1 the substance (1 mmole) was dissolved (or suspended) in glacial acetic acid (50 ml) (except for curve 2, where water was used instead of HOAc), and a solution of $NaIO_4$ (4 mmole) in water (50 ml) was added. Substances VI and IX only dissolved completely about 10 min after the addition of the periodate. In the experiment of Fig. 4, curve 1, the dimeric 3-methoxy-*o*-quinone (IV) was allowed to dissolve in water, which required about 1.5 h at room temperature (hydration, *cf.* Ref.[1]), before the periodate solution was added. In the remaining experiments of Fig. 4 the samples were readily soluble in the solvents used. The concentrations were the same as given above.

Unconsumed periodate was determined on 5 ml samples of the reaction mixture as described previously [8]. The β-naphthoquinones formed were extracted before the addition of the thiosulphate-iodide mixture.

Periodate oxidation of dimeric o-*benzoquinone (VI).* A suspension of the substance (108 mg = 0.5 mmole) in glacial acetic acid (25 ml) was mixed with an aqueous solution of sodium metaperiodate (25 ml containing 440 mg = 2.0 mmole). After 30 min the clear orange-red solution was extracted with methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous sodium sulphate, and taken to dryness under reduced pressure. The red crystalline residue had m.p. 144°, after recrystallisation from ether 146°, undepressed on admixture of *1,2-naphthoquinone*, m.p. 145—147° [9]. The infra-red spectra of both samples were identical. Yield of crude product, 70 %.

In the same way, *1,2-naphthoquinone* was obtained (70 %) from the *phenolic isomer VIII* by periodate oxidation in aqueous or aqueous acetic acid solution.

o-*Quinone IX.* A solution of the phenolic isomer of the dimeric *o*-quinone (VIII) [4] (300 mg) in acetone (20 ml) was shaken, in the presence of anhydrous sodium sulphate, with silver oxide (1.0 g) for 10 min. The solution was filtered and evaporated under reduced pressure. The crystalline residue was washed with cold ethyl acetate and recrystallised, without heating, from acetone-hexane. Dark-red prisms, decomposing above 220°. (Found: C 67.23; H 3.08. Calc. for $C_{12}H_6O_4$: C 67.29; H 2.83.)

The same substance has been obtained by Horner and Dürckheimer [5], who used tetrachloro-*o*-quinone as dehydrogenating agent. UV absorption see Fig. 2; the infra-red spectrum shows CO stretching vibration bands at 5.76, 5.89 and 6.02 μ. Oxidation with periodate yielded *β-naphthoquinone.*

The diacetate (X) of the phenolic form of dimeric o-*quinone*, which was previously obtained from VIII with boiling acetic anhydride [4], was prepared by treatment with acetic anhydride-pyridine at room temperature; m.p. 144°.

1,2-Diacetoxy-5,8-dihydronaphthalene-cis-*5,8-dicarboxylic acid (XI).* A solution of the diacetate X (150 mg = 0.5 mmole) in glacial acetic acid (25 ml) was mixed with an aqueous solution of $NaIO_4$ (3 mmole). After 60 min the colourless solution was extracted with methylene chloride and the extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. Colourless prisms, m.p. 189—190° after recrystallisation from ethyl acetate. Yield 70 %. (Found: C 57.47; H 4.35. Calc. for $C_{16}H_{14}O_8$: C 57.49; H 4.22.) Potentiometric titration in ethanolic solution gave two equivalence points, corresponding to equivalent weights of 342 and 170, respectively (calc.: 334 and 167).

UV-absorption spectrum see Fig. 3. IR-absorption bands: 3.2 and 3.75—4.0 μ (COOH); 5.72—5.82 μ (CO of vinyl ester and carboxyl groups); 6.17, 6.30 (both weak) and 6.72 μ (aromatic nucleus).

1,2-Dihydroxy-5,8-dihydronaphthalene-cis-*5,8-dicarboxylic acid (XII).* Diacetate XI (500 mg) was dissolved, with careful exclusion of air, in a mixture of ethanol (25 ml) and 10 % aqueous sodium hydroxide (6 ml). After 6 h, the solution was acidified with aqueous sulphuric acid. Extraction with methylene chloride removed only traces of an oily material; the solution was then extracted with ethyl acetate and the extract was washed with water, dried over anhydrous calcium sulphate and evaporated to dryness. The crystalline residue (yield 67 %) was recrystallised from ethyl acetate-hexane; colourless prisms, m.p. 182—183° (decomp.). The product contained 1/3 mole of water of crystallisation, which was not removed on drying over P_2O_5 in a high vacuum at room temperature. (Found: C 56.46; H 4.16. Calc. for $C_{12}H_{10}O_6$,1/3 H_2O: C 56.25; H 4.20). When heated for 2 h at 90° (0.1 mm Hg), the substance lost 2.30 % of its weight (calc. for 1/3 mole H_2O: 2.48 %) and then analysed for the anhydrous product. (Found: C 57.66; H 4.20. Calc. for $C_{12}H_{10}O_6$: C 57.60; H 4.03). Neutralisation equivalent of the substance before dehydration: found 128, calc. 125.

Addition of ferric chloride to an ethanolic solution of the substance produced a rather unstable dark-green colour, which turned to blue-violet on addition of aqueous sodium bicarbonate. UV absorption of the substance see Fig. 3. IR absorption bands: 2.91 μ (phenolic OH); 3.25 and 3.65—3.90 μ (COOH); 5.79 μ (COOH) and 5.91 μ (8-COOH chelated with 1-OH?); 6.14, 6.26 and 6.67 μ (aromatic nucleus).

Oxidation of XII. a) A solution of XII in 50 % aqueous acetic acid was treated with sodium periodate (3 mole/mole of XII); 2 moles $NaIO_4$ were consumed in 1—2 min (*cf.* Fig. 1). Extraction with methylene chloride gave *β-naphthoquinone* in high yield.

b) A solution of XII in acetone was shaken for 5 min with silver oxide and anhydrous Na_2SO_4. Filtration and evaporation yielded red crystals, identified as *β-naphthoquinone* by m.p. (145—146° after sublimation *in vacuo*), mixed m.p. and infra-red absorption.

Oxidation of 1,2-dihydroxynaphthalene (XV) with periodate or with silver oxide, as in the preceding experiments, also yielded *β-naphthoquinone.*

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