

## Periodate Oxidation of Phenols

### IV. Structure of the Periodate Oxidation Product of a Dimeric 3-Methoxy-*o*-quinone

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The red product, m. p. 198–199°, formed by the action of periodate on pyrogallol-1,3-dimethyl ether, pyrogallol-1-methyl ether, 3-methoxy-*o*-quinone, and dimeric 3-methoxy-*o*-quinone (m. p. 139–140°), was shown to be 3,8-dimethoxy-1,2-naphthoquinone (IIIa).

In the initial step of a series of degradation reactions, IIIa was treated with periodate at pH 6.5. Although unbuffered solutions of NaIO<sub>4</sub> (pH about 4) attack the β-naphthoquinone IIIa extremely slowly, oxidative cleavage proceeded at a satisfactory rate in the buffered medium and gave 2-carboxy-3-methoxy-*α*-methoxycinnamic acid (VIII) in good yield. A similar periodate cleavage was carried out with 3-methoxy-1,2-naphthoquinone (XVII) and with unsubstituted β-naphthoquinone.

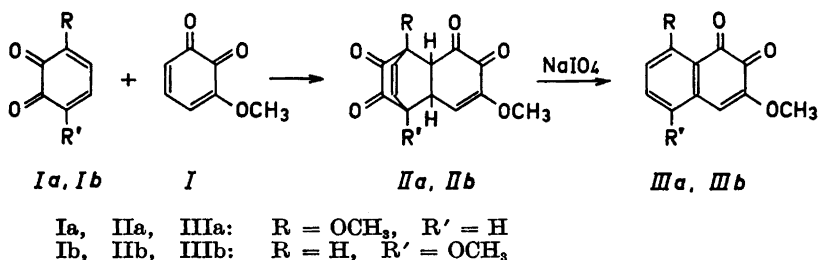
The cinnamic acid VIII was converted, via 7-methoxyphthalide-3-methoxyacetic acid (IX), into 8-methoxy-*isocoumarin*-3-carboxylic acid (X), which was demethylated to give the corresponding 8-hydroxy compound (XI). X was degraded by alkali to 2-methyl-6-methoxybenzoic acid (XII), which gave *m*-cresol on boiling with aqueous hydriodic acid.

2-Carboxy-*α*-methoxycinnamic acid (XVIII), obtained by periodate oxidation of XVII, was converted to *isocoumarin*-3-carboxylic acid (XIX) on heating.

As reported in preceding papers<sup>1,2</sup>, the action of sodium periodate on pyrogallol-1,3-dimethyl ether, pyrogallol-1-methyl ether, and 3-methoxy-1,2-benzoquinone (I) in aqueous solutions gives, among other products, a red compound, C<sub>10</sub>H<sub>4</sub>O<sub>2</sub>(OCH<sub>3</sub>)<sub>2</sub>, m. p. 198–199°. Its formation has been shown to be due to a dimerisation of I (which is either used as starting material or formed as an intermediate in the periodate oxidation of the pyrogallol ethers) followed by degradation of the dimer by the periodate present. A dimeric 3-methoxy-*o*-quinone, m. p. 139–140°, could be obtained from solutions of I in organic solvents, and a monohydrate of the dimer, m. p. 114–115°, was obtained from aqueous solutions of I. Both products were readily converted into the red substance, m. p. 198–199°, when treated with periodate. The present paper deals with the structure of the red oxidation product.

The isolation of a further dimer of 3-methoxy-*o*-quinone, m. p. 110°, which is formed in benzene solutions of the monomer, and the periodate degradation of this lower-melting dimer to a violet compound, m. p. 205–206°, isomeric with the red product, m. p. 198–199°, have been mentioned in a previous paper<sup>1</sup>. The structures of this second dimer and its oxidation product are still under investigation.

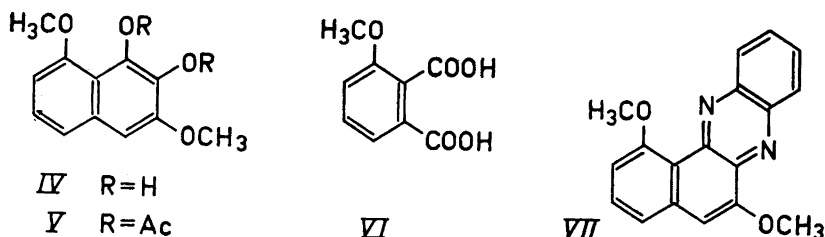
The properties of the first-mentioned dimer, m.p. 139–140°, indicated<sup>1</sup> that it was formed by Diels-Alder reaction between two molecules of monomer I, and probably had structure II, analogous to the structure of the dimeric *o*-quinone<sup>3</sup>. Due to the unsymmetrical substitution of I, its dimerisation could give rise to two isomers, IIa and IIb. The analytical composition of the red periodate oxidation product of II showed that it might be a dimethoxy-naphthoquinone, and structures IIIa or IIIb therefore seemed very probable. This paper describes experimental evidence showing that this was correct and enabling a decision to be made between IIIa and IIIb.



The absorption spectra of the red compound were in harmony with the view that it was a naphthoquinone derivative. Its infra-red absorption spectrum exhibited the double carbonyl band (maxima at 5.98 and 6.03  $\mu$ ) characteristic of quinones. Comparison of the absorption spectrum in the ultraviolet and visible region (Fig. 1) with the absorption spectra of known naphthoquinones<sup>4,5</sup> revealed a close resemblance with that reported for 3-methyl-6,8-dimethoxy-1,2-naphthoquinone<sup>5</sup>. Furthermore, reduction with zinc dust in acetic acid gave a leuco compound, m.p. 141–143°, which was converted into a diacetate, m.p. 152–153°, with an ultra-violet absorption (Fig. 1) typical for a naphthalene derivative. Oxidation of the red compound with permanganate gave 3-methoxyphthalic acid (VI), and treatment with *o*-phenylenediamine gave a yellow phenazine, m.p. 164–165°, the absorption spectrum of which (Fig. 1) was similar to those reported for benzo[*a*]phenazines<sup>4</sup>. These data clearly indicate that the red substance is a dimethoxy-1,2-naphthoquinone carrying one methoxyl group in each ring (IIIa or IIIb). The structures of the derivatives mentioned above can then be represented by formulae IV, V and VII, with the methoxyl groups arranged as in IIIa, or by corresponding formulae, in which the positions of the methoxyl groups would be those shown in IIIb.

A decision between the two possibilities IIIa and IIIb could be made by the following experiments.

Although the degradation of dimer II to  $\beta$ -naphthoquinone III by periodate was fast<sup>1,2</sup>, the latter compound, although containing a 1,2-diketo grouping,



was attacked only very slowly by excess of the oxidant under the conditions used, *i.e.* in aqueous or aqueous acetic acid solution. However, on treatment with an aqueous periodate solution, buffered to pH 6.5, naphthoquinone III was comparatively rapidly oxidised to a colourless acid, m.p. 142°. Its analytical composition and equivalent weight were in harmony with structure VIII, 2-carboxy-3-methoxy- $\alpha$ -methoxycinnamic acid, or the corresponding 6-methoxy isomer. The similarity of the ultra-violet absorption spectrum of the substance with those of 2-carboxycinnamic acid (XXII)<sup>6,7</sup> and 2-carboxy- $\alpha$ -methoxycinnamic acid (XVIII) (see below) (Fig. 2) supported this structure.

It was intended to convert the 2-carboxy-3-(or 6-) methoxy- $\alpha$ -methoxy cinnamic acid VIII, by heating with hydriodic acid, into either 2-carboxy-3-hydroxy-hydrocinnamic acid (XV) or its 6-hydroxy isomer. Identification of either of the latter products would have been easy, since the methyl ethers of both isomers and, as well, the lactone of the 6-hydroxy isomer had been made available by recent work of Eastham and Larkin<sup>8</sup>. In a preparatory attempt to demethylate 2-carboxy-3-methoxy-hydrocinnamic acid (XIV)\* with hydriodic acid, the expected acid XV was decarboxylated and 3-hydroxy-hydrocinnamic acid (XVI) was formed.

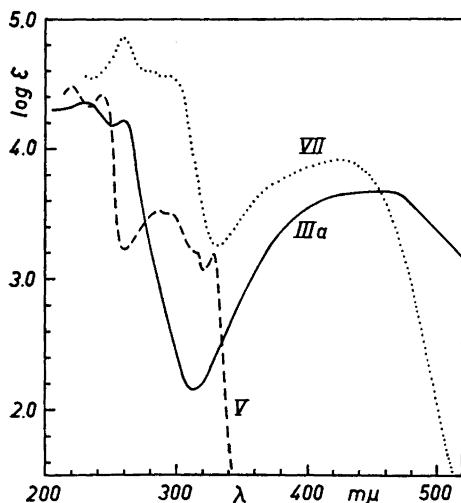


Fig. 1. Absorption spectra of 3,8-dimethoxy-1,2-naphthoquinone (IIIa), 1,2-diacetoxy-3,8-dimethoxy-naphthalene (V), and 1,6-dimethoxybenzo[*a*]phenazine (VII). Solvent: 95 % ethanol.

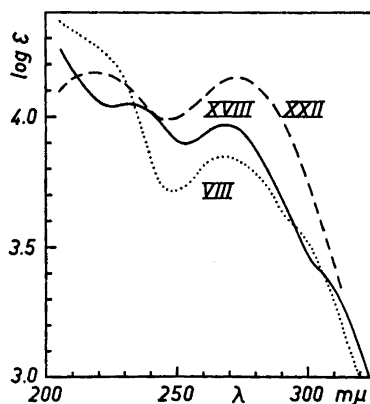
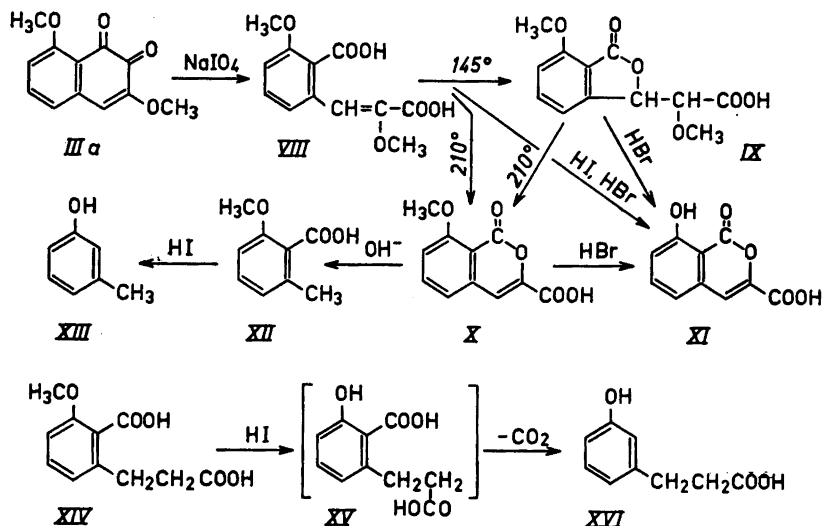


Fig. 2. Ultraviolet absorption spectra of 2-carboxycinnamic acid (XXII), 2-carboxy- $\alpha$ -methoxycinnamic acid (XVIII), and 2-carboxy-3-methoxy- $\alpha$ -methoxycinnamic acid (VIII). Solvent: 95 % ethanol.

Treatment of VIII with boiling aqueous hydriodic acid ( $d = 1.70$ ) produced neither of the possible hydrocinnamic acids, but instead, gave 8-hydroxy-*isocoumarin*-3-carboxylic acid (XI) (*cf.* below).



Like 2-carboxycinnamic acid (XXII)<sup>6,7</sup>, the dimethoxy derivative VIII (or the corresponding 6-methoxy isomer?) underwent cyclisation when heated to the melting point, giving a lactone acid, m.p.  $205^\circ$ , which must be either 7-methoxyphthalide-3-methoxyacetic acid IX or the corresponding isomer with a methoxyl group in position 4 rather than 7. These structures are supported by infra-red data (see Experimental) as well as by the general appearance of the ultra-violet absorption curve of the substance, which is similar to that of XXIII which was obtained by cyclisation of XXII, although the long-wave maximum of IX is shifted towards higher absorbance and wave-length, which can be explained by the presence of the nuclear methoxyl substituent (Fig. 3).

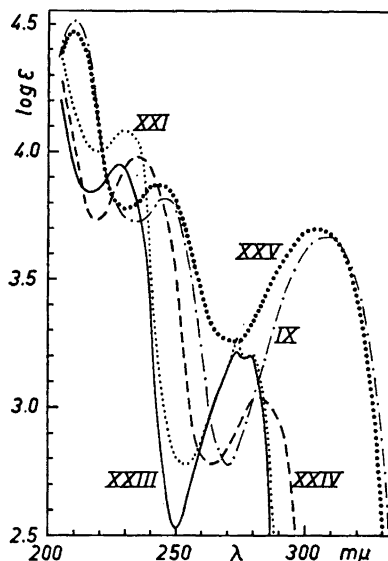
The lactone acid IX melted (at  $205^\circ$ ) with vigorous evolution of gas, and the melt solidified to yield a new compound (X), m.p.  $258^\circ$ . Analysis showed that the decomposition occurring at the melting point of IX was not due to decarboxylation but to the loss of one mol. of methanol. As expected, X was also obtained directly from the cinnamic acid VIII, by heating to  $205\text{--}210^\circ$ , the transformations VIII  $\rightarrow$  IX and IX  $\rightarrow$  X taking place consecutively at  $145^\circ$  and  $205\text{--}210^\circ$ , respectively.

The structure of compound X was elucidated in the following way.

3-Methoxy-1,2-naphthoquinone (XVII)<sup>4</sup>, when treated with periodate at pH 6.5, gave 2-carboxy-*a*-methoxycinnamic acid (XVIII), m.p.  $137^\circ$  (U.V. absorption curve see Fig. 2). On melting, this substance reacted in the same way as its 3- (or 6-)methoxy derivative (VIII). The primary cyclisation pro-

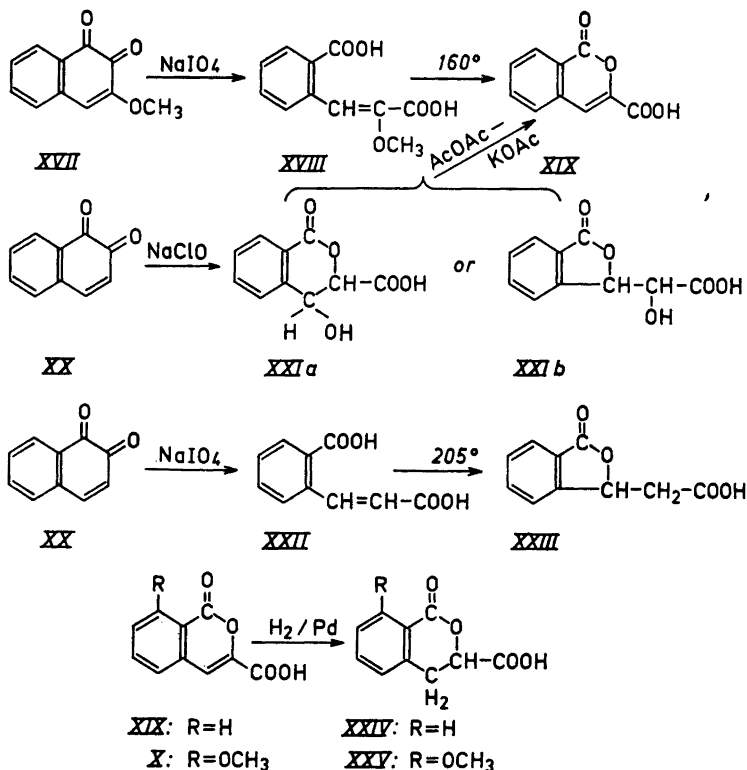
\* The authors are indebted to Prof. J. F. Eastham, University of Tennessee, Knoxville, U.S.A., for a gift of samples of the 3-methoxy and 6-methoxy derivatives of 2-carboxy-hydrocinnamic acid.

Fig. 3. Ultraviolet absorption spectra of 3-phthalide acetic acid (XXIII, —); 7-methoxyphthalide-3-methoxyacetic acid (IX, - - -);  $\gamma$ -lactone of 2-carboxyphenylglyceric acid (XXI b, .....); 3,4-dihydroisocoumarin-3-carboxylic acid (XXIV, - - -); 8-methoxy-3,4-dihydroisocoumarin-3-carboxylic acid (XXV, <sup>oooo</sup>—). Solvent: 95 % ethanol.



duct, which would correspond to structure IX (H instead of the nuclear methoxyl substituent), was not isolated in this case, as the second reaction step, *i.e.*, the loss of one mole of methanol, obviously began at a temperature only slightly above the melting point of XVIII. Thus, on heating at 142–160°, a methoxyl-free lactone acid, m.p. 244–245°, was formed. As expected, it was identical with *isocoumarin-3-carboxylic acid* (XIX) obtained by Bamberger<sup>9</sup> and Zincke<sup>10</sup> from  $\beta$ -naphthoquinone (XX) *via* the hydroxylactone acid XXI. The ultra-violet absorption spectrum of XIX is of the same type as that of product X, although the long-wave maximum of the latter is shifted to higher absorbance and wave-length due to the presence of the methoxyl group (Fig. 4). The infra-red absorption spectra of X and XIX are very similar, both exhibiting bands typical of carboxylic OH, a lactone-CO, a carboxylic CO, and a C=C bond conjugated with carboxyl, the corresponding bands for the two compounds being situated at almost the same wave-lengths (see Experimental). On the basis of these results, the analytical composition,  $C_{11}H_8O_5$ , and the neutralisation equivalent (found: 205, calc.: 220), substance X can be assigned the structure 8- (or 5-)methoxy-*isocoumarin-3-carboxylic acid*.

On treatment with boiling aqueous hydrobromic acid ( $d = 1.49$ ), X was converted into a phenol, m.p. 290°, which was also obtained from both VIII and IX by similar treatment, or by heating with aqueous hydriodic acid. The ultra-violet absorption curve of the phenolic substance (Fig. 4) was very similar to that of the ether X, and titration indicated that the carboxyl group had been retained. Ethanolic ferric chloride gave a stable, intense violet-blue colour, the absorption spectrum of which was comparable to that of the ferric complexes of salicylic acid and — at least in the position of the maximum — of methyl salicylate (Fig. 5). The phenolic product must therefore be 8-hydroxy-*isocoumarin-3-carboxylic acid* (XI). This implies that the methoxyl



groups of  $\beta$ -naphthoquinone III are in the 3,8-positions (IIIa) rather than in the 3,5-positions (IIIb). Correspondingly, the positions of the nuclear methoxyl substituent in the derivatives IV, V and VII, as well as in the degradation intermediates VIII, IX and X are those given in the formulae above.

This conclusion was confirmed by further degradation of 8-methoxy-*iso*-coumarin-3-carboxylic acid (X). Bamberger<sup>12</sup> has shown that *isocoumarin*-3-carboxylic acid (XIX), when heated with strong alkali, is broken down to *o*-toluic acid. Compound X in this way yielded 2-methyl-6-methoxybenzoic acid (XII). On heating with hydriodic acid, acid XII was demethylated, and the expected 2-methyl-6-hydroxybenzoic acid was simultaneously decarboxylated giving *m*-cresol (XIII) as the only reaction product.

These results definitely establish structure IIIa for the starting material, and, therefore, structure IIa for the dimeric 3-methoxy-*o*-quinone.

A few remarks may be added regarding the structures of some of the compounds involved in the present work, especially the structure of the hydroxylactone acid XXI mentioned above.

The five-ring lactone (phthalide) structure of the cyclisation products IX and XXIII seems to be well established, as it is highly probable that the addition of the aryl carboxylic group to the ethylenic bond of the acrylic acid substituent in VIII and XXII will follow the general mechanism of such reactions. The six-ring enol lactone (*isocoumarin*) structure of substances X, XI and XIX is also undoubtedly correct, satisfactory evidence for the structure of XIX having been provided by the work of Bamberger<sup>9</sup> and Zincke<sup>10,11</sup>.

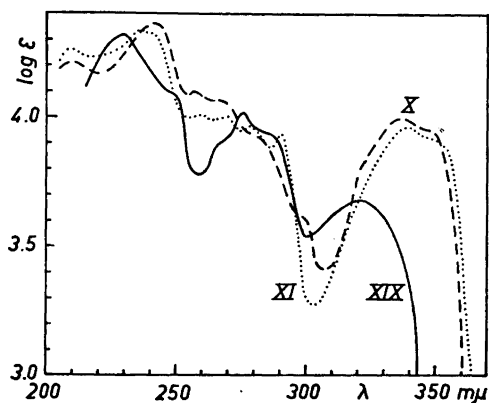


Fig. 4. Ultraviolet absorption spectra of chelates of 8-hydroxyisocoumarin-3-carboxylic acid (XIX, —); 8-methoxyisocoumarin-3-carboxylic acid (X, - - -); 8-hydroxyisocoumarin-3-carboxylic acid (XI . . . .). Solvent: 95 % ethanol.

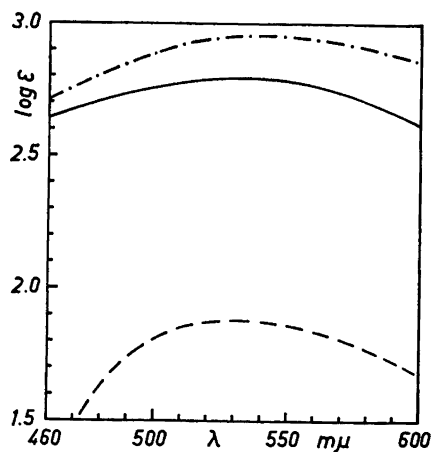


Fig. 5. Light absorption of the  $\text{Fe}^{3+}$  chelates of 8-hydroxyisocoumarin-3-carboxylic acid (XIX, —); salicylic acid, - - - -; methyl salicylate - . - . - . The ferric chelate solutions were prepared by adding 0.2 ml of a 1 % solution of  $\text{FeCl}_3$  in 96 % ethanol to 4 ml of a solution of the substance in the same solvent. The concentration of substance XIX and of salicylic acid was  $1.5 \times 10^{-3}$  M, that of methyl salicylate was  $8.5 \times 10^{-3}$  M.

However, there did not appear to be unambiguous evidence for the  $\delta$ -lactone structure XXIIa proposed by the latter authors for the hydroxylactone acid obtained by hypochlorite oxidation of  $\beta$ -naphthoquinone. The  $\delta$ -lactone structure XXIIa rather than a  $\gamma$ -lactone structure (XXIIb) had been accepted<sup>9,10</sup> as it seemed to explain the ease with which the substance was dehydrated to give the isocoumarincarboxylic acid XIX when it was heated above the m. p.<sup>10</sup>, or on heating with mineral acid<sup>9</sup>, or with acetic anhydride<sup>11</sup>. As shown above, the isocoumarin system is, however, also readily formed from a  $\gamma$ -lactone (cf. IX  $\rightarrow$  X or IX  $\rightarrow$  XI) with a methoxyacetic acid substituent at position 3 of the phthalide system. By analogy, the assumption of a  $\gamma$ -lactone structure (XXIIb) for the hydroxylactone acid of Bamberger and Zincke would also seem to be in harmony with its convertibility into the isocoumarin XIX.

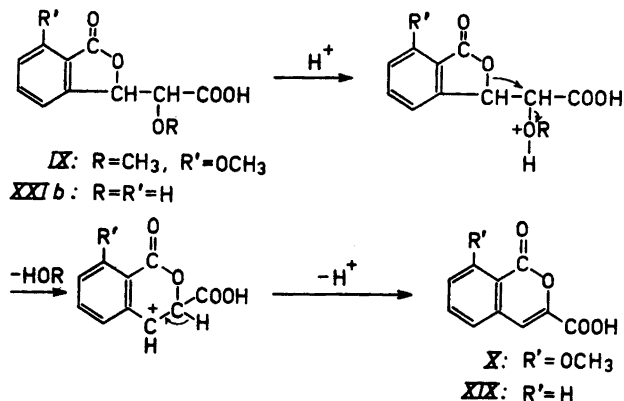
In fact, the ultra-violet spectrum of the hydroxylactone acid XXI is very similar to that of the  $\gamma$ -lactone XXIII (see Fig. 3), and differs markedly from that of 3,4-dihydroisocoumarin-3-carboxylic acid (XXIV)<sup>12</sup>, a  $\delta$ -lactone isomeric with the  $\gamma$ -lactone XXIII.

The 8-methoxyl analogue of XXIV, *i. e.*, the  $\delta$ -lactone XXV, m. p. 238°, cannot be used in this comparison, as the methoxyl group present causes a hyperchromic and bathochromic shift similar to that encountered in the case of the isomeric  $\gamma$ -lactone IX; cf. Fig. 3. XXV was obtained by catalytic hydrogenation of X.

The infra-red spectrum of the hydroxylactone acid XXI shows a lactone carbonyl band at  $5.67 \mu$ , *i. e.*, at the same position as the  $\gamma$ -lactones IX ( $5.67 \mu$ ) and XXIII ( $5.65$ – $5.70 \mu$ ). However, the corresponding bands of the  $\delta$ -lactones XXIV ( $5.63$ – $5.69 \mu$ ) and XXV ( $5.68$ – $5.73 \mu$ ) are very close to these positions, and, therefore, no conclusion on the size of the lactone ring of XXI can be drawn from the position of its lactone carbonyl band.

Consideration of the ultra-violet absorption data given above, strongly suggests however that Bamberger and Zincke's hydroxylactone acid has the  $\gamma$ -lactone structure XXIIb rather than the previously accepted  $\delta$ -lactone structure XXIIa.

The conversion of the  $\gamma$ -lactones IX and XXIb into the isocoumarin derivatives X and XIX, respectively, by loss of a molecule of methanol (or water) and simultaneous ring enlargement, could proceed by the following mechanism:



### EXPERIMENTAL

Ultra-violet spectra were measured with a Beckman DU spectrophotometer. Infra-red spectra were recorded on a Perkin-Elmer model 21 instrument, using KBr discs. Microanalyses were made by Alfred Bernhardt, Mülheim.

*3,8-Dimethoxy-1,2-naphthoquinone (IIIa)*. The isolation of this substance from reaction mixtures obtained on periodate oxidation of pyrogallol-1,3-dimethyl ether, pyrogallol-1-methyl ether, 3-methoxy-*o*-quinone (I), dimeric 3-methoxy-*o*-quinone (IIa) and the monohydrate of IIa has been described previously<sup>1,2</sup>. As a starting material in the present investigation the compound was prepared as follows.

An aqueous solution of sodium metaperiodate (20.6 g in 200 ml) was added to a stirred solution of pyrogallol-1-methyl ether (4.5 g) in water (200 ml), the temperature of the reaction mixture being kept below 20° by the addition of ice. After 10 min, ethylene glycol (6.0 g) was added. The reaction mixture was stirred a few minutes longer, diluted with water and extracted exhaustively with chloroform. The dark-red chloroform solution was dried over anhydrous calcium sulphate, and evaporated to dryness. The solid residue (2.3 g), after one recrystallisation from benzene, yielded 1.74 g (49.5 %) of nearly pure IIIa, brilliant red plates, m. p. 194–195°. Further recrystallisation increased the m. p. to 198–199°. Analyses see Ref.<sup>1</sup>. Absorption spectrum, Fig. 1.

Chromatography of the benzene mother liquors on alumina gave further amounts of IIIa and small amounts of a violet substance, m. p. 205–206° (cf. Ref.<sup>1</sup>).

*1,2-Dihydroxy-3,8-dimethoxynaphthalene (IV)*. 3,8-Dimethoxy-1,2-naphthoquinone (IIIa) (200 mg), dissolved in glacial acetic acid (5 ml), was reduced with zinc dust giving a nearly colourless solution. After dilution with water, the mixture was filtered, and the filtrate was extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and evaporated. The crystalline residue (120 mg) was found to undergo rapid autoxidation; sublimation (120° bath temperature, 0.5 mm Hg) yielded light-red crystals. This material was recrystallised from benzene, to which ascorbic acid was added, which brought about decolorisation of the boiling solution. On cooling, slightly reddish flat prisms (97 mg) were obtained, which after a further recrystallisation from benzene had m. p. 141–143°. (Found: C 66.53; H 5.75; OCH<sub>3</sub> 27.39. Calc. for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: C 65.44; H 5.49; OCH<sub>3</sub> 28.18.) Brief treatment of IV with aqueous sodium periodate regenerated the naphthoquinone.

The *diacetate* (V) was obtained by treating freshly prepared IV with a boiling mixture of acetic anhydride and pyridine for a few minutes. Colourless prisms from ethanol, m. p. 152–153°. (Found: C 63.15; H 5.27; OCH<sub>3</sub> 20.40. Calc. for C<sub>18</sub>H<sub>18</sub>O<sub>6</sub>: C 63.03; H 5.26; OCH<sub>3</sub> 20.07.)



*Permanganate oxidation of 3,8-dimethoxy-1,2-naphthoquinone (IIIa).* A 4 % aqueous solution of potassium permanganate (25 ml) was added slowly to a stirred suspension of IIIa (226 mg) in N sulphuric acid (25 ml). After 24 h sulphur dioxide was passed into the reaction mixture. The resulting solution, which was practically colourless, was continuously extracted with ether for 18 h. The ethereal solution was dried and evaporated, and the residue was recrystallised from ether, giving *3-methoxyphthalic acid (VI)*, (yield 23 %), m. p. 173–175°, undepressed on admixture of an authentic sample of VI (m. p. 174–176°), obtained by acid permanganate oxidation of 1,2-dimethyl-3-methoxybenzene<sup>13</sup>. Heating of either sample of the acid to 180°, followed by sublimation at a bath temperature of 170° (0.01 mm Hg), yielded *3-methoxyphthalic anhydride*, m. p. and mixed m. p. 164–165°. The identity of the two samples of the anhydride was confirmed by comparison of their IR absorption spectra.

*1,6-Dimethoxybenzo[a]phenazine (VII).* A solution of 3,8-dimethoxy-1,2-naphthoquinone (IIIa) (0.5 mmoles) in glacial acetic acid (40 ml) was mixed with a solution of *o*-phenylenediamine (1 mmole) in the same solvent (10 ml). After 30 min heating on a steam-bath the solvent was removed under reduced pressure and the residue was dissolved in methanol. Addition of water produced a voluminous precipitate of fine brownish-yellow needles, which softened at 80–100°, solidified again on further heating, and melted at 160°. Analysis of the substance after drying at room temperature, indicated the presence of 2 moles of water. (Found: C 66.75; H 5.47; N 8.45; OCH<sub>3</sub> 18.83. Calc. for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>·2H<sub>2</sub>O: C 66.25; H 5.56; N 8.58; OCH<sub>3</sub> 19.02.)

When dried at 60° (0.01 mm Hg), the substance lost 12.65 % of its weight (calc. for 2 H<sub>2</sub>O: 11.04 %). Recrystallisation from benzene-hexane gave golden-yellow prisms, m. p. 164–165°. (Found: C 73.94; H 4.95; N 10.07; OCH<sub>3</sub> 21.05. Calc. for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>: C 74.47; H 4.86; N 9.63; OCH<sub>3</sub> 21.38.) UV spectrum, Fig. 1.

*2-Carboxy-3-methoxy- $\alpha$ -methoxycinnamic acid (VIII).* 3,8-Dimethoxy-1,2-naphthoquinone (IIIa) (600 mg) was suspended in 0.5 M phosphate buffer solution (180 ml) of pH 6.5, sodium metaperiodate (3 g) in water (60 ml) was added and the mixture was shaken for 2.5 h. Some inorganic material (NaIO<sub>3</sub>) was removed by filtration and the pale yellow filtrate was then acidified with 2 N HCl and thoroughly extracted with ethyl acetate. After drying over anhydrous calcium sulphate the solvent was evaporated under reduced pressure. The crystalline residue (644 mg) was recrystallised from acetone-chloroform. Colourless rods (437 mg; yield 63 %), m. p. 142–143°; the melt solidified (cyclisation product IX). On slow heating substance VIII is gradually converted to IX and may not show any sharp melting point. (Found: C 57.06; H 4.86; OCH<sub>3</sub> 24.30. Calc. for C<sub>12</sub>H<sub>12</sub>O<sub>6</sub>: C 57.14; H 4.79; OCH<sub>3</sub> 24.61.) Neutralisation equivalent, found, 132, calc., 126. UV spectrum, Fig. 2. IR maxima ( $\mu$ ): 3.5 and 3.75–3.95 (carboxylic OH); 5.84–5.92 (CO of  $\alpha,\beta$ -unsaturated carboxylic and arylcarboxylic acid); 6.12 (C=C conjugated with COOH).

*7-Methoxyphthalide-3-methoxyacetic acid (IX).* A sample of substance VIII (100 mg) was heated to the melting point. The melt resolidified at the melting temperature or after some cooling. Recrystallisation from ethyl acetate-hexane gave thin colourless plates (86 mg), m. p. 204–205° (gas evolution; the melt resolidified with formation of X). (Found: C 57.08; H 4.85; OCH<sub>3</sub> 24.71. Calc. for C<sub>12</sub>H<sub>12</sub>O<sub>6</sub>: C 57.14; H 4.79; OCH<sub>3</sub> 24.61.) UV spectrum, Fig. 3. IR maxima ( $\mu$ ): 3.3 and 3.9 (broad carboxylic OH bands); 5.67 (carbonyl of  $\alpha,\beta$ -unsaturated lactone); 5.87 (CO of carboxyl group); the band at 6.12 which is present in the IR spectrum of VIII was absent.

*8-Methoxy-isocoumarin-3-carboxylic acid (X).* A sample of VIII (289 mg) was heated to 205–210°. When the evolution of gas (CH<sub>3</sub>OH) had ceased and the melt had become solid again, the product was allowed to cool. It was then treated with warm ethyl acetate; the undissolved, almost white, crystalline material (198 mg) was collected and recrystallised from methanol (charcoal) giving needles, m. p. 257–258°. Yield 75 %. The same product was obtained by heating substance IX to its melting point. The product contained about 1 mole of methanol of crystallisation, which was not completely removed unless drying was done at 100–120° (0.1 mm Hg). (Found: loss of weight, 11.75 %. Calc. for C<sub>11</sub>H<sub>8</sub>O<sub>5</sub>, CH<sub>3</sub>OH: 12.73 %. Analysis of a dried sample gave: C 60.14; H 3.65; OCH<sub>3</sub> 14.09. Calc. for C<sub>11</sub>H<sub>8</sub>O<sub>5</sub>: C 60.00; H 3.66; OCH<sub>3</sub> 14.03.) Neutralisation equivalent, found, 205, calc., 220. UV spectrum, Fig. 4. IR maxima ( $\mu$ ): 3.25–3.5 and 3.8–4.0 (carboxylic OH); 5.73 (CO of unsaturated lactone); 5.85 (CO of unsaturated carboxylic acid); 6.06 (C=C conjugated with carboxyl).

*8-Hydroxy-isocoumarin-3-carboxylic acid (XI)*. This substance was obtained by heating VIII, IX, or X with either aqueous hydriodic or hydrobromic acid. In a typical example, substance VIII (100 mg) was treated for 4 1/2 h with boiling aqueous hydriodic acid (15 ml,  $d = 1.70$ ) in the presence of red phosphorus. On cooling, the reaction product deposited as a crystalline solid; it was filtered off, together with the phosphorus, and separated from the latter by elution with ethyl acetate. The ethyl acetate solution was evaporated to dryness. The residue was washed with methylene chloride, which removed some iodine, and recrystallised from ethyl acetate-hexane; colourless prisms, m. p. 290°; yield, 36 %.

In another example, substance IX (19.5 mg) was treated for 1 h with boiling aqueous hydrobromic acid (2 ml,  $d = 1.49$ ). Crystals of XI were deposited, m. p. 287°, undepressed on admixture of a sample obtained as above. Yield, 68 %. (Found: C 58.40; H 3.10. Calc. for  $C_{15}H_8O_5$ : C 58.26; H 2.93.) Neutralisation equivalent, found, 224, calc., 206. UV spectrum, Fig. 4. Absorption spectrum of the ferric complex, Fig. 5. IR maxima ( $\mu$ ): 3.1–3.5 and 3.75–4.0 (phenolic and carboxylic OH); 5.74 (CO of unsaturated lactone); 5.90–6.02 (CO of unsaturated carboxylic acid, probably also some lactone carbonyl, chelated with phenolic OH); 6.09 (C=C conjugated with carboxyl)\*.

*Alkaline degradation of X*. A solution of substance X (190 mg) in 40 % aqueous NaOH (2 ml) was refluxed for 1 h. The mixture was diluted with water and filtered, and the filtrate was acidified with dilute sulphuric acid. On cooling, the filtrate deposited colourless needles (92 mg), m. p. 141–142°, unchanged after recrystallisation from water. For *2-methyl-6-methoxybenzoic acid (XII)* Chuit and Bolsing<sup>14</sup> reported m. p. 139°.

*m-Cresol from 2-methyl-6-methoxybenzoic acid (XII)*. A sample of XII (59 mg) was treated with boiling aqueous hydriodic acid ( $d = 1.70$ ) and some red phosphorus for 35 min. After cooling, the phosphorus was filtered off and washed with water. The filtrate was extracted with ether and the ethereal solution was shaken with aqueous sodium bisulphite, which removed iodine, and then with aqueous sodium bicarbonate. The ether phase was dried and evaporated; the IR spectrum of the oily residue was indistinguishable from the spectrum of *m-cresol*.

The bicarbonate solution contained no organic material.

*2-Carboxy- $\alpha$ -methoxycinnamic acid (XVIII) (G.B.)\*\**. 3-Methoxy-1,2-naphthoquinone (XVII)<sup>4</sup> was oxidised with periodate at pH 6.5, as described above for similar oxidation of IIIa. The quinone colour had disappeared after about 2 h. Extraction of the filtered solution with ethyl acetate gave thin plates, m. p. 137° after recrystallisation from ethyl acetate-hexane. Yield 70 %. (Found: C 59.53; H 4.58;  $OCH_3$  14.02. Calc. for  $C_{11}H_8O_5$ : C 59.46; H 4.54;  $OCH_3$  13.97.) UV spectrum, Fig. 2. IR maxima ( $\mu$ ): 3.3–3.5 and 3.75–3.95 (carboxylic OH); 5.85 and 5.90 (CO of aryl and  $\alpha,\beta$ -unsaturated carboxyl); 6.12 (C=C conjugated with carboxyl).

*Isocoumarin-3-carboxylic acid (XIX) (G.B.)*. Substance XVIII, when heated, melted at 137° and began to decompose at a temperature only slightly above the m. p. After heating to 160° the melt solidified. Recrystallisation from water gave plates, m. p. 237°

\* Note added in proof. In a recent paper, Gerd Bendz [Arkiv Kemi 14 (1959) 511] reports the isolation of 8-hydroxy-3-methylisocoumarin from the culture medium of *Marasmius ramealis*. The compound differs from substance XI only in carrying a methyl rather than a carboxyl group in the 3-position. As expected, the UV maxima of both substances are rather similar. There is, however, a striking difference in the positions of the lactone CO peaks of the two compounds. Whereas Bendz' 3-methyl compound has a CO band at 5.95  $\mu$ , the corresponding band of the 3-carboxy compound (XI) is found at 5.73  $\mu$ . As was pointed out by Bendz, the wave-length value of 5.95  $\mu$  is within the region expected for an unsaturated six-membered ring lactone carbonyl, a similar value (5.98  $m\mu$ ) being found for the 3,4-dihydro derivative of Bendz' compound. Then the value found for substance XI is unexpectedly low. Similar relationships are found for the methyl ether of Bendz' compound and its 3,4-dihydro derivative on the one hand (cf. also Ref.<sup>18</sup>) and the carboxylic compounds X, XXIV and XXV on the other hand. This seems to indicate that the 3-carboxyl substituent of the unsaturated six-membered ring lactone causes the lactone CO stretching band to be shifted to the low wave-length values observed. It may be of interest to note that a similarly low value, 5.70  $\mu$ , has been reported<sup>15</sup> for 5,6,7-trimethoxy-isocoumarin-3-aldehyde.

\*\* Experiments marked "G.B." were carried out by Mr. Gunnar Bergström.

(yield 70 %), identical by mixed m. p. and IR absorption spectrum with XIX, prepared from XXI according to Zincke and Schmidt<sup>11</sup>. The UV absorption (Fig. 4) is rather similar to that reported for isocoumarin<sup>15</sup>.

*Periodate oxidation of  $\beta$ -naphthoquinone (XX) (G.B.).* On oxidation, in the same way as for the  $\beta$ -naphthoquinones IIIa and XVII, XX yielded 2-carboxycinnamic acid (XXII), m. p. 205° (lit.<sup>6,7</sup>, 203–205°). Yield 70 %. UV absorption, Fig. 2 (see also Ref.<sup>16</sup>).

*3,4-Dihydro-isocoumarin-3-carboxylic acid (XXIV) (G.B.).* A PdCl<sub>2</sub>-BaSO<sub>4</sub> catalyst (0.5 g, with 5 % PdCl<sub>2</sub>) was hydrogenated in 93 % acetic acid (10 ml), a solution of substance XIX (95 mg) in the same solvent (5 ml) was added, and the mixture was stirred in a hydrogen atmosphere. The hydrogen uptake ceased when 1 mole of H<sub>2</sub>/mole of XIX had been consumed. Evaporation of the filtered solution, and recrystallisation of the residue from benzene gave XXIV, m. p. 154–155°. For the same substance obtained by sodium amalgam reduction of XIX, Bamberger<sup>12</sup> reported m. p. 153.5°. UV spectrum, Fig. 3. IR maxima ( $\mu$ ): 3.15 and 3.85–4.05 (carboxylic OH); 5.63–5.69 (lactone CO); 5.83 (carboxylic CO).

*3-Hydroxyhydrocinnamic acid (XVI).* A mixture of 2-carboxy-3-methoxyhydrocinnamic acid (XIV)<sup>8</sup> (see Note, p. 542) (100 mg), aqueous hydriodic acid ( $d = 1.70$ ) (7 ml) and a little red phosphorus was boiled under reflux for 45 min. After filtration, the solution was diluted with water, and extracted six times with ether. The ethereal solution was washed with aqueous sodium bisulphite and water, dried and evaporated. Recrystallisation of the residue from ethyl acetate-hexane gave colourless needles (34 mg), m. p. 110°. (Lit.<sup>17</sup>, 111°.) Neutralisation equivalent, found, 170; calc. for XVI, 166.

*3,4-Dihydro-8-methoxyisocoumarin-3-carboxylic acid (XXV).* This substance was prepared by catalytic hydrogenation of X, as described for the preparation of XXIV from XIX. It was recrystallised from ethyl acetate-hexane, prisms, m. p. 238°. (Found: C 59.47; H 4.43; OCH<sub>3</sub> 14.26. Calc. for C<sub>11</sub>H<sub>10</sub>O<sub>5</sub>: C 59.46; H 4.54; OCH<sub>3</sub> 14.97.) The UV maxima (Fig. 3) are similar to those reported for (–)-3,4-dihydro-8-hydroxy-3-methylisocoumarin (= mellein)<sup>18</sup>. IR maxima ( $\mu$ ): 3.24 and 3.7–4.0 (COOH); 5.68–5.73 (lactone carbonyl); 5.84 (COOH).

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