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Periodate Oxidation of Phenols. XVII.* Oxidation of 2-Methylphenols with Aqueous and Methanolic Periodic and Iodic Acids

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Treatment of 2,6-dimethylphenol (*1a*) and mesitol (*1b*) in H_2O-EtOH (4:1) with H_5IO_6 results in *ortho* and *para* oxidation similar to that effected by $NaIO_4$, although *para* oxidation is more pronounced with the former oxidant. Phenols *1a* and *1b* are almost stable towards $NaIO_3$, but are oxidized by HIO_3, mainly *para* oxidation products being obtained from *1b*.

Oxidation of *1a* and *1b*, as well as of 2,4- and 2,5-dimethylphenol, with HIO_4 in methanol produces the corresponding *o*-quinol methyl ethers which slowly dimerize by Diels-Alder reaction. With respect to stereospecificity and regiospecificity, these dimerizations are similar to those of *o*-quinols and their acetates.

From the reaction mixtures obtained with 2,4- and 2,6-dimethylphenol, minor amounts of products derived from iodinated *o*-quinols were isolated.

Methylation of the dimeric *o*-quinol *3* obtained from *1a* gave the expected dimethyl ether (*18a*) and, in addition, a compound (*27*) formed by deconjugation of the α,β-enone system initially present, as well as the C-7 methylation product (*28*) of the latter compound.

As reported earlier, oxidation of 2,4-, 2,5-, 2,6-, and 2,4,6-methyl-substituted phenols with aqueous sodium periodate gives the corresponding 6-hydroxy-6-methyl-2,4-cyclohexadienones ("*o*-quinols") as major products, which undergo rapid Diels-Alder dimerization.[1–3] Depending on the substitution pattern of the starting phenol, *o*- and *p*-quinones, as well as *p*-quinols, are also formed. If 2,4,6-trimethylphenol is treated with periodate or bismuthate in 80 % aqueous acetic acid, the *o* -and *p*-quinol acetates are obtained, in addition to the *o*-quinol dimer and the *p*-quinol.[4]

These results indicate that the solvent used (H_2O or HOAc) participates in the reactions, as earlier shown for the periodate oxidation of guaiacol and hydroquinone monomethyl ether in $H_2{}^{18}O$ which gave labelled *o*- and *p*-benzoquinone and unlabelled methanol.[5]

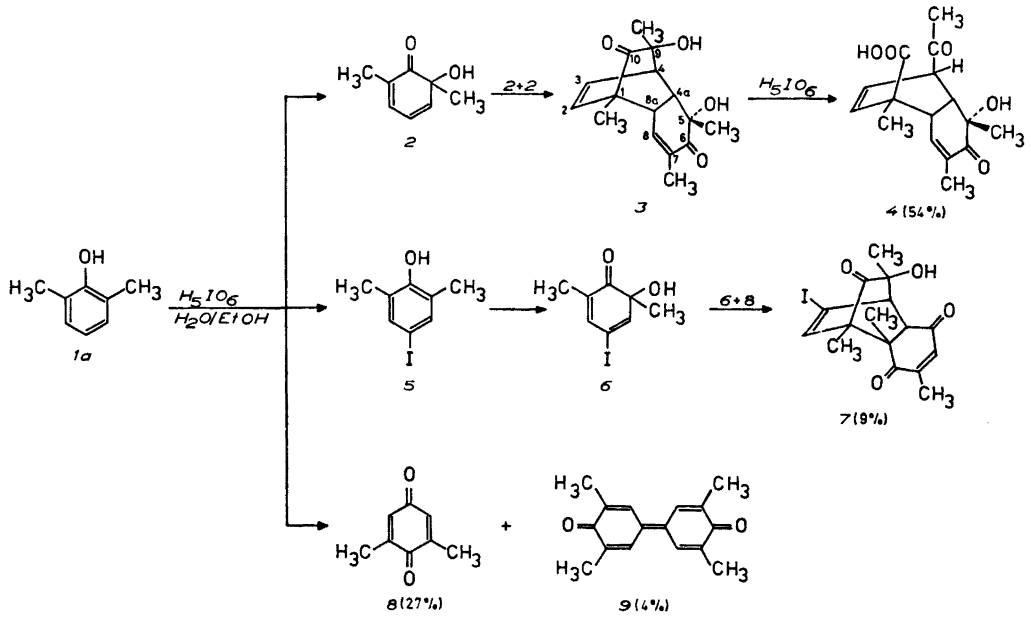
It then seemed of interest to examine the oxidation of the above-mentioned 2-methyl-substituted phenols in alcoholic solutions, which could be expected to afford *o*- and *p*-quinol alkyl ethers. Whereas several reports on the formation of *p*-quinol alkyl ethers have been published,[6–8] only three *o*-quinol analogues seem to have been described earlier.[7,8]

The present paper deals with the oxidation of the methyl-substituted *o*-cresols *1a–d* (see Scheme 4) in methanol. Since sodium periodate, which has been used as oxidant in our earlier studies, is only sparingly soluble in methanol, it was replaced by periodic acid. For comparison, the behaviour of two phenols (*1a*, *1b*) on treatment with the latter oxidant in an aqueous medium was also investigated; see following section.

Oxidation of 2,6-dimethylphenol and mesitol in aqueous solutions. The solvent used was a 4:1 mixture of water and ethanol, similar to that used in earlier experiments with sodium periodate as oxidant.[2]

Treatment of 2,6-dimethylphenol (*1a*) with periodic acid (H_5IO_6) in this solvent mixture

* Part XVI, see Ref. 10.



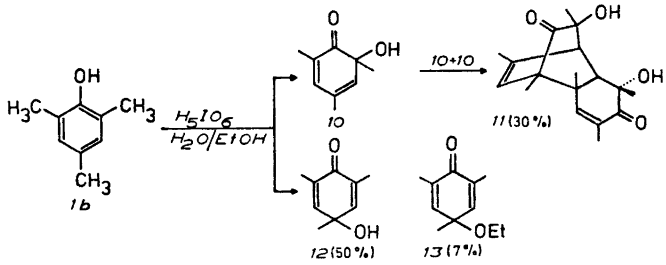
Scheme 1.

(Scheme 1) for 2 h gave the diketocarboxylic acid *4* as the major product. Its formation is due to cleavage, by excess H_5IO_6, of the 9,10-ketol bridge of dimer *3* arising by dimerization of the initially formed *o*-quinol *2*. Acid *4* has earlier been obtained either by treatment of *1a*, dissolved in water, with periodic acid for 2 h or by treatment of dimer *3* in aqueous acetic acid with sodium periodate.[9]

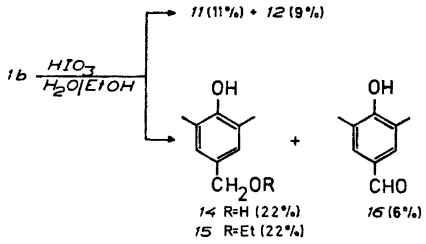
In addition, *para* oxidation of *1a* produced 2,6-dimethyl-*p*-benzoquinone (*8*), as well as a small amount of diphenoquinone *9*.

Finally, the Diels-Alder adduct *7* between the iodinated *o*-quinol *6* and *p*-quinone *8* has been isolated. The structural assignment of *7* is based on analytical and spectroscopic data. The UV spectrum of the compound was very similar to that of the corresponding iodine-free adduct,[10] and its NMR spectrum indicated the lack of a hydrogen atom in position 3. The oxidation of phenol *1a* with H_5IO_6 is accompanied by the formation of free iodine. This obviously causes iodination of some unconsumed *1a* to give *5*, the system iodine-periodic acid being an efficient iodinating agent.[11] The formation of adduct *7* then is readily understood as being due to oxidation of the iodinated phenol *5* to give *o*-quinol *6*, which adds to the dienophile *8*.

The liberation of iodine suggested that the starting phenol is attacked not only by the periodic acid, but also by iodic acid which is formed in the course of the reaction. It has been reported earlier that iodine is produced



Scheme 2.



Scheme 3. Yields are based on consumed *1b*.

when iodic acid is allowed to react with reducing substances such as reductones.[12]

In fact, iodic acid was found to oxidize phenol *1a*, although at a low rate. The *o*-quinol dimer *3* was obtained in a yield of 33 %, in addition to unchanged *1a* (55 %), after a reaction time of 24 h.

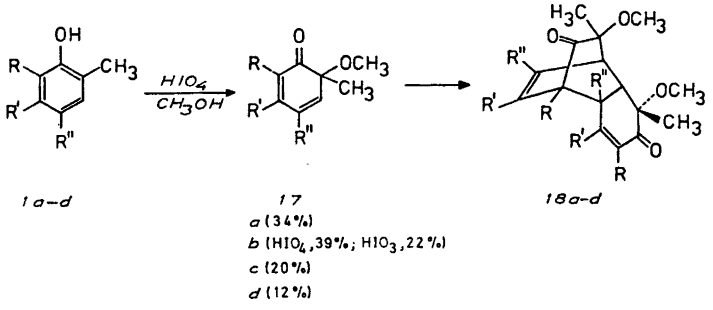
Mesitol (*1b*) reacted with H_5IO_6 as rapidly as with $NaIO_4$,[2] all phenol being consumed within 5 min. The *p*-quinol *12* was obtained as the major product (50 %); its ethyl ether *13* (7 %) and the *o*-quinol dimer *11*[2] (30 %) were also isolated (Scheme 2).

The reaction of mesitol with iodic acid was much faster than that of 2,6-dimethylphenol, which probably can be ascribed to the +I-effect of the additional methyl group present in mesitol. Only 11 % of unconsumed mesitol was recovered after 5 min reaction time. In addition to dimer *11* and *p*-quinol *12*, comparatively large amounts of the benzyl alcohol *14* and its ethyl ether *15*, as well as a small amount of benzaldehyde *16*, were isolated as reaction products (Scheme 3).

Compared with the oxidizing action of iodic acid, that of sodium iodate was much weaker. When $NaIO_3$ was allowed to act upon *1b* in the water-ethanol solvent, 80 % of the phenol could be recovered after four days and products *11* and *14* were obtained in yields of 7 and 2 %, respectively. It is known, however, that the oxidation of hydroquinone and its monomethyl ether,[13] as well as of its monoesters,[14,15] is faster with periodic acid than with periodate, and the behaviour of iodic acid and iodate, respectively, seems to be in analogy herewith.

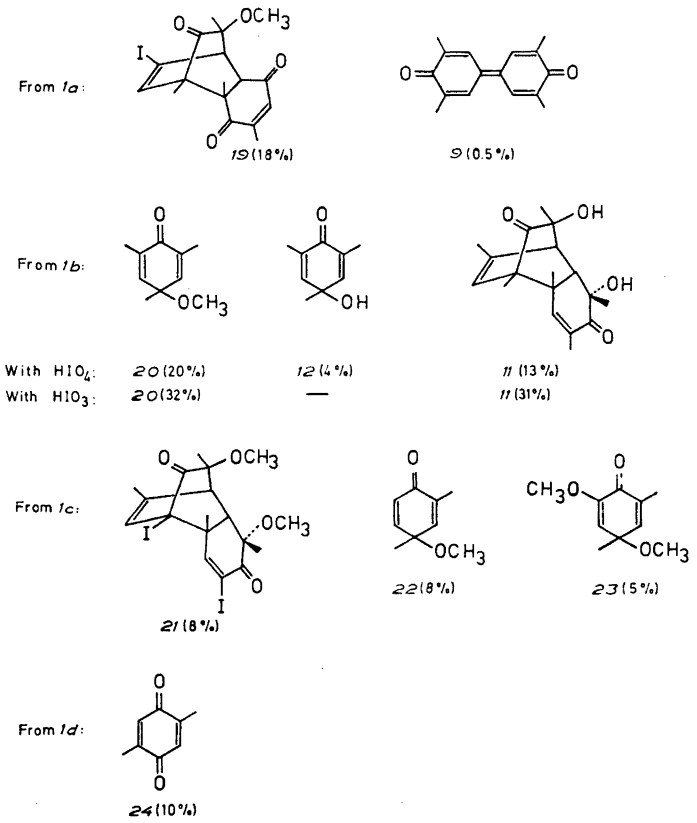
Qualitatively, the oxidation results obtained with periodic acid in H_2O/EtOH are similar to those previously obtained with sodium periodate. However, in the case of mesitol, periodic acid effects predominantly *para* oxidation, whereas *ortho* oxidation is dominant when periodate is used as oxidant.[2,3] Although less pronounced, a tendency towards increased *para* oxidation by periodic acid is also found in the case of 2,6-dimethylphenol.

Oxidation in methanol. As expected, oxidation of phenols *1a–d* (Scheme 4) with anhydrous periodic acid (HIO_4)[16] in methanolic solution produced the *o*-quinol methyl ethers *17a–d* as major products. They constituted yellow oils or solids exhibiting UV and IR characteristics closely similar to those of previously known 2,4-cyclohexadienones.[17–19] The monomers underwent Diels-Alder dimerization, conversion to *18a–d* at room temperature being complete within a few days. The freshly isolated monomers therefore already contained small amounts of the corresponding dimers. Monomer *17b*, derived from mesitol, dimerized comparatively slowly and was obtained essentially free from dimer from the oxidation mixture, as well as by retro-Diels-Alder reaction of dimer *18b* at 180 °C. The yields of the *o*-quinol



a R=CH_3, R'=R"=H; *b* R=R"=CH_3, R'=H; *c* R"=CH_3, R=R'=H; *d* R'=CH_3, R=R"=H

Scheme 4.



Scheme 5. Products formed in addition to *o*-quinol methyl ethers *17a–d* and their dimers *18a–d* on oxidation of phenols *1a–d* with HIO_4 and of *1b* with HIO_3 in methanol.

methyl ethers, determined as dimers, are given in Scheme 4.

As in the system H_5IO_6/H_2O-EtOH, iodine was liberated in the HIO_4/CH_3OH system, indicating that HIO_3 participated in the oxidation of the phenols. A separate experiment showed that mesitol on treatment with HIO_3 in methanol also gave *o*-quinol methyl ether *17b*.

In addition to the *o*-quinol methyl ethers (*17a–d*) and their dimers (*18a–d*), the compounds shown in Scheme 5 were isolated from the oxidation mixtures. They constitute by-products in the experiments using HIO_4, whereas in the oxidation of *1b* with HIO_3, the yields of both *20* and *11* exceeded the yield of *17b*.

The formation of the adduct *19* – the methyl ether of *7* (Scheme 1) – as well as of dimer *21*, derives from iodination of unconsumed phenol (*cf.* p. 910). As in the aqueous reaction systems, *para* oxidation is found to compete with *ortho* oxidation. Furthermore, the formation of products which must have involved the participation of water (*11*, *12*, *19*, *24*) is observed. Whereas *24* and the *p*-quinone incorporated in *19* may have been formed by hydrolysis of the corresponding 4,4-dimethoxy-2,5-cyclohexadienones, the occurrence of *11* and *12* indicates the direct participation of water in the oxidation sequence. (Concerning the availability of water in the systems used, see p. 915 and Scheme 7).

The comparatively low yields of products obtained from *1c* and *1d* (see Schemes *4* and *5*) may be partly due to the formation of the corresponding *o*-quinones and their conversion products. These were lost during the treatment of the crude product mixtures with alumina, which was carried out in order to remove free

iodine (see Experimental). The formation of 3,5-dimethyl-*o*-quinone on oxidation of *1c* with aqueous periodate has been reported earlier.[3]

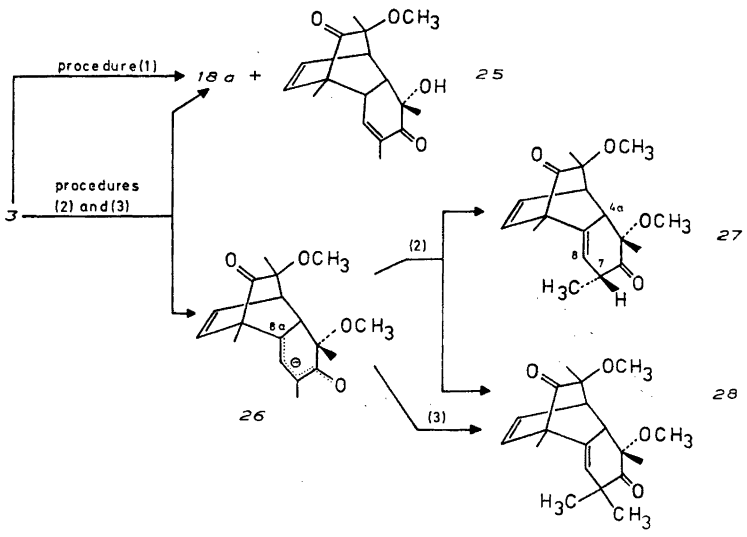
The formation of the dimethoxylated compound *23* from phenol *1c* is interpreted on p. 915.

Structures of dimeric *o*-quinol methyl ethers *18a – d*

The Diels-Alder dimerization of *o*-quinols has been shown to proceed in a stereospecific and regiospecific manner resulting in dimers with the steric orientation at C-5 and C-9, as well as the structural orientation of the addends, as represented for instance by formula *3*.[1,9,20,21] Analogous structures have been found for the dimers of spiro(oxirane-2,4-cyclohexadienones) which can be regarded as cyclic *o*-quinol ethers[1,22] and, therefore, the dimerization of *o*-quinol ethers *17a–d* could be expected to follow the same pattern. In fact, methylation of the *o*-quinol dimers *3*,[2] *11*[2] and *18c* (OH instead of OCH_3)[3] was found to give dimethyl ethers identical with those formed by spontaneous dimerization of *o*-quinol methyl ethers *17a–c*. This proves the correctness of formulae *18a–c* for the latter dimerization products. By analogy, the dimer of *17d* has been assigned structure *18d*.

The methylation of the tertiary hydroxyl groups of *o*-quinol dimers *11* and *18c* (OH instead of OCH_3) to give *18b* and *18c* was readily performed by means of a procedure described by B. Sjöberg and K. Sjöberg[23] using methyl iodide and sodium methylsulfinyl carbanion in DMSO. Methylation of *11* with methyl sulfate/BaO-$Ba(OH)_2$ in DMF[24] also gave *18b* in high yield, whereas *3* under the same conditions reacted more slowly and, in addition to 17 % of the desired dimethyl ether *18a*, gave the monomethyl ether *25* (62 %) (Scheme 6). The location of the methoxyl group in *25* at C-9 rather than C-5 became clear from a comparison of the stretching frequencies of both CO groups in dimeric *o*-quinols and their dimethyl ethers, respectively, which revealed that these frequencies are generally higher by 10 – 25 cm^{-1} for the methylated than for the nonmethylated dimers.

Methylation of dimer *3* by the procedure of Sjöberg and Sjöberg[23] produced the C-7 methyl derivative *28* (*90* % yield), whereas treatment of *3* with CH_3I/Ag_2O[25] afforded 31 % of *18a* and its isomer *27* (19 %), in addition to *28* (29 %).



Scheme 6. Procedure (1) $(CH_3O)_2SO_2$ / BaO-$Ba(OH)_2$ / DMF[24]

(2) CH_3I/Ag_2O/ DMF[25]

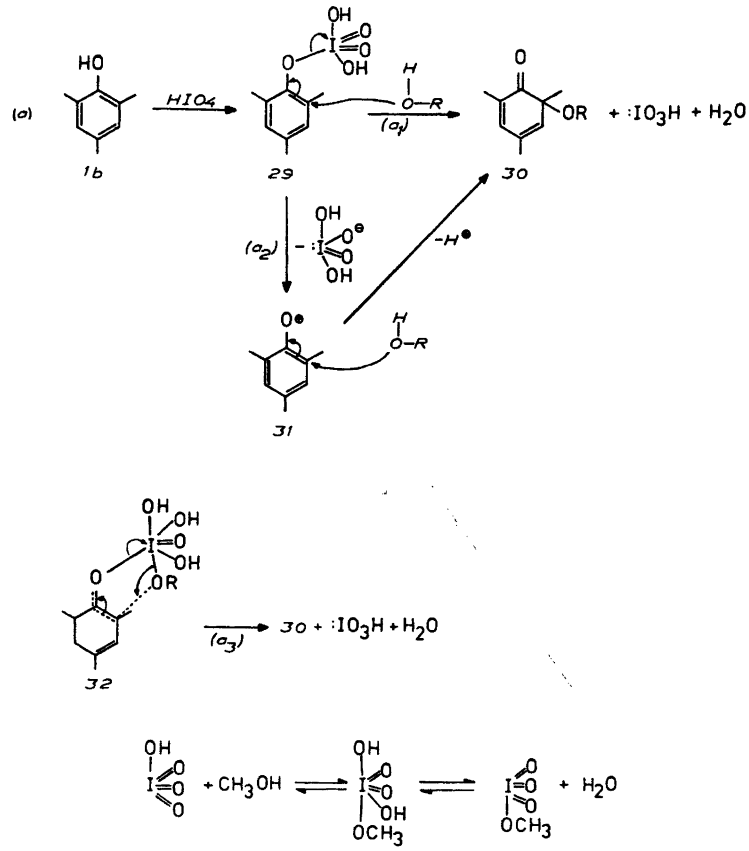
(3) $CH_3I/CH_3SOCH_2:^{\ominus}Na^{\oplus}$/ DMSO[23]

The formation of *27* and its *C*-methylation product *28* is analogous to earlier reported deconjugation reactions of α,β-conjugated ketone systems[26] and can be rationalized by assuming initial abstraction of a proton from C-8a to give anion *26* (Scheme 6; the sequence of *O*-methylation and C-7 methylation is unknown). In the NMR spectrum of *27*, the hydrogen atom at C-8 gives rise to a doublet due to coupling with the hydrogen at C-4a, the coupling constant being 2.5 Hz, which is the same value as found for $J_{4a,8}$ in compound *28*. The coupling constant $J_{7,8}$ however, is almost zero. This indicates that the hydrogen atom at C-7 in *27* is quasi-axial, the C-H bonds in positions 7 and 8 forming a dihedral angle of about 100° as shown by inspection of a Dreiding model.

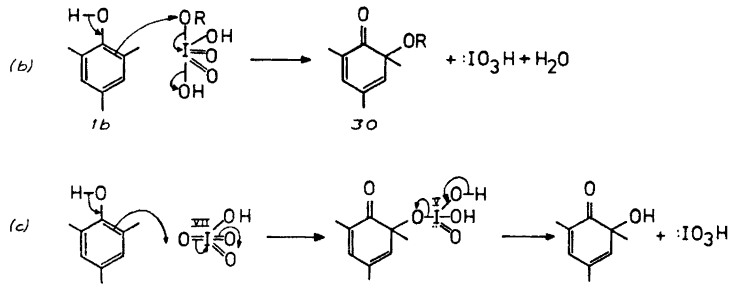
The NMR spectra of the compounds reported in this paper were in agreement with the assigned structures; in a few selected cases, NMR data are given in the experimental part.

Mechanism of phenol oxidation with periodic acid and similar oxidants

It has been suggested that the oxidation of phenols by periodate,[2] periodic acid[14] or bismuthate[27] is initiated by coordination of the phenolic hydroxyl group to the iodine or bismuthate atom. In the *ortho* oxidation of mesitol (*1b*), for instance, periodic acid is assumed to give the ester *29* (Scheme 7, route *a*), which may react further in three different ways ($a_1 - a_3$). In way a_1, two-electron transfer to iodine is concerted with nucleophilic attack of the solvent ROH (R=H, Ac or CH_3) upon one of the *o*-positions, yielding an *o*-quinol, *o*-quinol acetate,[4] or *o*-quinol ether (*30*). The alternative route a_2 involves two steps, *viz.*, formation of the phenoxonium ion (*31*) and subsequent attack of ROH. Reaction in *o*-posi-



Scheme 7.



Scheme 8.

tion may further be visualized to pass *via* a cyclic transition state (*32*). By this route (a_3), not only the formation of the *o*-quinol (*30*, R = H) in aqueous solution, but also that of the *o*-quinol ether (*30*, R = CH_3) in methanol may be possible, since, in methanol solution, coordination of solvent with HIO_4 may give periodic acid methyl esters. As shown in Scheme 7, these reversible coordination reactions involve the release of water, which may explain the formation of *o*-quinol dimer *11* (Scheme 5), in addition to the *o*-quinol methyl ether *17b*, when mesitol is treated with HIO_4 in dry methanol.

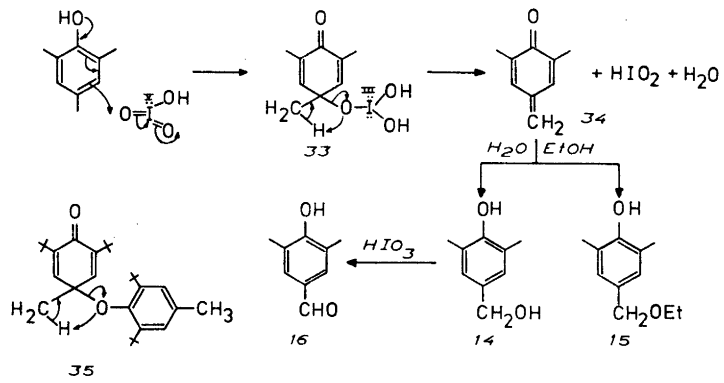
Two further two-electron mechanisms have been discussed (see the recent review article by Fatiadi[11]). In their adaptation to the phenol/periodic acid system they may be represented as shown in Scheme 8. Route *b* is analogous to a pathway proposed by Bubb and Sternhell[28] for the Wessely acetoxylation effected by lead tetraacetate and might explain the formation of *o*-(and *p*-)quinols (R = H), as well as that of their methyl ethers (R = CH_3). It seems doubtful, however, whether electrophilic attack by the group OR as depicted in this reaction scheme is acceptable, when R = CH_3. Route *c* is an adaptation of the mechanism suggested by Fatiadi[29] for the oxidation of polycyclic aromatic hydrocarbons, such as naphthalene, by periodic acid. It is not readily applicable, however, to the formation of quinol methyl ethers.

Routes a_1 and a_2, as well as *b* and *c*, naturally are applicable also to *para* oxidation, such as the formation of *p*-quinol *12* from mesitol (Scheme 2) and, at least the two first-mentioned routes, also to the analogous formation of p-quinol ether *20* (Scheme 5). Furthermore, attack upon a free *o*- or *p*-position according to *a* – *c* (R = H) will give *o*- or *p*-quinones, the primarily formed catechol or hydroquinone being readily oxidized by periodic acid.[5]

The formation of compound *23* (Scheme 5) from 2,4-dimethylphenol (*1c*) is certainly due to two consecutive oxidation steps, the first one involving the introduction of methoxyl into the free *o*-position of *1c* according to one of the reactions $a_1 - a_3$ (R = CH_3) and the second one being a *para* methoxylation of the 2-methoxy-4,6-dimethylphenol thus generated.

Fatiadi[11,30] recently reported the preparation of diphenoquinones of type *9* in yields of 60 – 94 % by treating highly concentrated solutions of 2,6-disubstituted phenols such as *1a* in dimethylformamide-water with H_5IO_6. He suggests a radical mechanism (cf. also Ref. 36) but does not exclude involvement of the phenoxonium ion. Waters[31] regards C – C-coupling in phenol oxidation to be the result of a phenoxonium ion attacking a phenol molecule. In our experiment with a dilute aqueous-ethanolic solution of *1a* and H_5IO_6 (Scheme 1) only a 4 % yield of *9* was obtained.

It seems reasonable to assume that the mechanism of phenol oxidation by iodic acid is analogous to that of the corresponding periodic acid reactions, at least in cases where the products generated by the two oxidants are similar. This is true for the oxidation of mesitol (*1b*) by the two acids in methanolic solution (see Schemes 4 and *5*). However, in the H_2O/EtOH solvent, periodic acid (Scheme 2) produced, from the same phenol, *p*-quinol *12* (50 %) and its ethyl ether *13* (7 %), in addition to the *o*-quinol dimer *11* (30 %), whereas in the iodic acid system (Scheme 3) benzyl alcohol *14* (22 %), its ethyl ether *15*



Scheme 9.

(22 %) and benzaldehyde *16* (6 %) together constituted the major type of products, quinols *11* and *12* being obtained in yields of *11* and *9* % only. This striking difference seems to indicate different mechanisms for the H_5IO_6 and the HIO_3 oxidations in the aqueous-ethanolic solvent. The formation of the aromatic compounds *14*–*16* suggests that the quinonemethide *34* (Scheme *9*) is an intermediate in the aqueous-ethanolic HIO_3 system, nucleophilic addition of H_2O or EtOH to *34* giving *14* and *15*, whereas *16* arises by slow oxidation of *14* as earlier found with $NaIO_4$ as oxidant.[4]

Initial electrophilic attack of HIO_3 to give ester *33*, similar to the first step of route (*c*)[29] in Scheme 8, seems to provide one of several possibilities for making the preferential formation of quinonemethide *34* understandable, see Scheme *9*. The formation of *33* already involves an oxidoreduction, the iodine atom changing its valence number from V to III. The structure of 33 is reminiscent of that of *p*-quinol aryl ether *35* which has been shown to decompose spontaneously into equimolar amounts of 2,6-di-*t*-butyl-4-methylphenol and the corresponding quinonemethide.[35] Similar heterolytic decomposition of *33* would give quinonemethide *34*.

Finally, it cannot be excluded that a one-electron transfer reaction between phenol *1b* and iodic acid produces a phenoxy radical which disproportionates, presumably *via* an intermediate of type *35*,[35] to give quinonemethide *34* in addition to starting phenol.

EXPERIMENTAL

UV, IR, and NMR spectra were recorded on a Cary Model 14, a Beckman 9A and a Varian A-60 instrument, respectively. Chemical shifts are given in δ units downfield from TMS (internal standard).

Oxidation in aqueous solution

General procedure. A solution of the phenol (2 g) in water-ethanol 4:1 (800 ml) was mixed at room temperature with a solution (200 ml) of H_5IO_6, HIO_3, or $NaIO_3$ in water; the molar ratio (R) of oxidant to phenol is given in the individual descriptions below. After the desired period of time (t), the mixture was extracted with five 100 ml-portions of dichloromethane. (In the experiments with H_5IO_6, uncomsumed oxidant was destroyed by addition of 2 g of ethylene glycol prior to the extraction.) The extracts obtained in the experiments with H_5IO_6 and HIO_3 were freed from iodine by washing with saturated aqueous sodium thiosulfate, then dried over anhydrous $CaSO_4$ and evaporated to dryness to give product mixture A.

Unless otherwise stated, separation of the reaction products present in A was performed by chromatography on a column (3 × 40 cm) of silica gel (Silicic Acid, Mallinckrodt, 100 mesh) using benzene-ethyl acetate 4:1 (solvent 1) or petroleum ether (b.p. 40–60 °C)-ethyl acetate 5:2 (solvent 2) as eluents. The location of the different compounds in the 15 ml fractions collected was determined by TLC on "Kieselgel 60 F 254" (E. Merck, Darmstadt), solvents 1 and 2, respectively, being used as mobile phases. In the following descriptions, the individual products are given in the order of their elution from the column.

Oxidation of 2,6-dimethylphenol (1a) *with aqueous* H_5IO_6. $R = 1.8$, $t = 2$ h. Prior to the extraction with dichloromethane, red crystals

of 3,3',5,5'-tetramethyldiphenoquinone (*9*)[10] were filtered off from the reaction mixture; yield 4 %. Product mixture A, a partially crystalline yellow oil, when treated with a small volume of ethyl ether, gave colourless crystals (1.27 g, 54 %) of *carboxylic acid 4*,[10] m.p. 183–184 °C after recrystallization from ethanol.

The ether solution was brought to dryness and the oily residue chromatographed on a column of neutral Al_2O_3 (Woelm) with ethyl acetate as solvent. The eluate fractions gave 27 % of *2,6-dimethyl-p-quinone (8)* and 9 % of *1,4,4a,8a-tetrahydro-9-hydroxy-3-iodo-1,7,8a,9-tetramethyl-1,4-ethanonaphthalene-5,8,10-trione (7)*, yellow crystals of m.p. 141–142 °C after recrystallization from isopropyl ether. (Found: C 48.22; H 4.31; I 31.48. Calc. for $C_{16}H_{17}O_4I$: C 48.02; H 4.28; I 31.71). UV (ethanol): λ_{max}, nm (log ε) 234 (4.09), 300 (2.67), 360 (1.93). IR (KBr): ν_{max}, cm^{-1} 1595 and 1625 (C=C), 1658 (conj. CO), 1718 (CO), 3400 (OH). NMR (acetone-d_6): δ 1.16, 1.23, 1.42 (s, 3 H each, 3 CH_3), 1.98 (d, 3 H, CH_3-7), 3.37 (t, 1 H, H-4), 3.54 (d, 1 H, H-4a), 5.12 (s, 1 H, OH), 6.41 (d, 1 H, H-2), 6.73 (m, 1 H, H-6). $J_{2,4} = J_{4,4a} = 2.5$ Hz $J_{6,CH_3-7} = 2$ Hz.

Oxidation of 2,6-dimethylphenol (1a) *with aqueous HIO_3*. (*a*) $R = 1.75$, $t = 5$ min. Chromatography of A (solvent 1) gave unreacted *1a* (87 %) in addition to *o-quinol dimer 3* (3 %). (*b*) $R = 1.75$, $t = 24$ h. Chromatography as under (*a*) gave unchanged *phenol 1a* (55 %), *2,6-dimethyl-p-benzoquinone (8)* (7 %) and *dimer 3* (33 %).

Oxidation of mesitol (1 b) *with aqueous H_5IO_6*. $R = 2$, $t = 5$ min. The partly crystalline product mixture A on treatment with cold hexane gave hexane-insoluble *o-quinol dimer 11*[2] in 30 % yield. The hexane-soluble fraction on column chromatography (solvent 1) provided *4-ethoxy-2,4,6-trimethyl-2,5-cyclohexadienone* (*13*) (7 %) and *4-hydroxy-2,4,6-trimethyl-2,5-cyclohexadienone* (*12*)[2,32] (50 %). Compound *13* was characterized as follows. M.p. *52–53* °C after sublimation (20 mmHg, 25 °C bath temp.) and recrystallization from isopropyl ether. Accurate mass determination, found 180.1170, calc. for $C_{11}H_{16}O_2$ 180.1150. UV (ethanol): λ_{max}, nm (log ε) 235 (4.06), sh 275 (3.01), sh 335 (1.76). IR (KBr): ν_{max}, cm^{-1} 1640, 1675. NMR ($CDCl_3$) δ1.12 (t, 3H, CH_2CH_3, $J = 7$ Hz), 1.35 (s, 3 H, CH_3-4), 1.88 (s, 6 H, CH_3-2 and CH_3-6), 3.33 (q, 2 H, CH_2CH_3, $J = 7$ Hz), 6.65 (broadened s, 2 H, H-3 and H-5).

Oxidation of mesitol (1b) *with aqueous HIO_3*. $R = 1.5$, $t = 5$ min. The oily product mixture A on chromatography (solvent 1) gave:

(*a*) Unchanged phenol *1b* (11 %).

(*b*) *4-Hydroxy-3,5-dimethylbenzyl ethyl ether* (*15*) (20 %), m.p. 36–37 °C (hexane). (Found: C 73.44; H 8.90. Calc. for $C_{11}H_{16}O_2$: C 73.30, H 8.95). In the NMR spectrum, the ethyl group gives rise to a triplet (3 H) at δ1.13 and a quartet (2 H) at δ3.43; $J = 7$ Hz. The compound was identical with a product obtained in 80 % yield by 4 h treatment of benzyl alcohol *14*[33] with ethanolic hydrochloric acid at room temperature.

(*c*) *4-Hydroxy-3,5-dimethylbenzaldehyde* (*16*) (5 %), m.p. 113–114 °C (lit.[34] 114–115 °C),

(*d*) p-*quinol 12*[2] (*8* %),

(*e*) o-*quinol dimer 11*[2] (10 %), and

(*f*) *4-hydroxy-3,5-dimethylbenzyl alcohol* (*14*) (20 %), m.p. 104–105 °C (lit.[33] 104–105 °C).

Oxidation of mesitol (1b) *with aqueous $NaIO_3$*. $R = 2.2$, $t = 96$ h. Chromatography of product A (solvent 2) gave unchanged *mesitol* (80 %), o-*quinol dimer 11*[2] (7 %) and *benzyl alcohol 14* (2 %).

Oxidation in methanolic solution

General procedure. A solution of the phenol (2 g) in anhydrous methanol (50 ml) was mixed with a solution of anhydrous periodic acid (HIO_4)[12] or HIO_3 in the same solvent (250 ml); molar ratio (R) of oxidant to phenol, see below. After the reaction time (t) water (300 ml) was added and the mixture extracted with five 100 ml-portions of dichloromethane. In the HIO_4 experiments, the combined extracts after drying over anhydrous $CaSO_4$ were evaporated and, in order to remove free iodine, the residual oil, dissolved in ethyl acetate, was passed through a column (4 × 15 cm) of neutral alumina (Woelm). The column was washed with the same solvent and the combined filtrates were evaporated to give product mixture A. For separation of the products present in A by silica gel chromatography, see preceding section. In the HIO_3 experiment, the alumina treatment was excluded.

Oxidation of 2,6-dimethylphenol (1a) *with methanolic HIO_4*. $R = 1.2$, $t = 4$ h. Chromatography of A (solvent 1) gave:

(*a*) *1,4,4a,8a-Tetrahydro-3-iodo-9-methoxy-1,7,8a,9-tetramethyl-1,4-ethanonaphthalene-5,8,10-trione* (*19*), yellow needles of m.p. 144–145 °C (isopropyl ether), in 18 % yield. (Found: C 49.14; H 4.70; OCH_3 8.08; I 31.21. Calc. for $C_{17}H_{19}O_4I$: C 49.29; H 4.62; OCH_3 7.49; I 30.64). The UV spectrum of the compound was very similar to that of *7*. IR (KBr): ν_{max}, cm^{-1} 1598 and 1632 (C=C), 1760 (conj. CO), 1728 (CO).

(b) A yellow oil, which according to its IR spectrum was *6-methoxy-2,6-dimethyl-2,4-cyclohexadienone* (*17a*) containing some dimer (*18a*). The oil crystallized within a few days at room temperature, the resulting product being identical with

(*c*) *1,4a,5,8a-tetrahydro-5,9-dimethoxy-1,5,7,9-tetramethyl-1,4-ethanonaphthalene-6,10(4H)-dione* (*18a*), colourless crystals of m.p. 134–135 °C (isopropyl ether). (Found: C 70.93; H 7.99; OCH_3 19.92. Calc. for $C_{18}H_{24}O_4$: C 71.02; H 7.95; OCH_3 20.39). UV (ethanol): λ_{max}, nm

(log ε) 207 (3.77), 238 (3.79), 310 (2.26). IR (KBr): ν_{max}, cm^{-1} 1697, 1725. NMR ($CDCl_3$): δ1.23, 1.32, 1.42 (s, 3 H each, 3 CH_3), 1.78 (d, 3 H, CH_3-7), 2.8–3.3 (m, 3 H, H-4, 4a, 8a), 3.35, 3.45 (s, 3 H each, 2 OCH_3), 5.50 (dd, 1 H, H-2), 6.05–6.4 (m, 2 H, H-3, H-8). $J_{2,3}$ = 8 Hz, $J_{2,4}$ = 1.5 Hz, $J_{CH_3-7,H-8}$ = 1.5 Hz. The yield of *18a* was 34 %.

Oxidation of mesitol (1b) *with methanolic* HIO_4. R = 1.1, t = 1 h. Product mixture A, a partly crystalline oil, was treated with cold hexane. The nonsoluble, colourless crystals were o-*quinol dimer 11*. Chromatography of the hexane-soluble material (solvent 2) gave:

(*a*) *4-Methoxy-2,4,6-trimethyl-2,5-cyclohexadienone* (*20*), m.p. 43–44 °C; yield, 19 %. (Found: C 72.45; H 8.47; OCH_3 18.66. Calc. for $C_{10}H_{14}O_2$: C 72.26; H 8.49; OCH_3 18.67). UV (ethanol): λ_{max}, nm (log ε) 234 (4.05), sh 270 (2.95), 345 (1.43). IR (KBr): ν_{max}, cm^{-1} 1648, 1680. NMR (benzene-d_6): δ 1.20 (s, 3 H, CH_3-4) 1.85 (d, 6 H, CH_3-2 and CH_3-6), 2.93 (s, 3 H, OCH_3), 6.19 (broadened s, 2 H, H-3 and H-5).

(*b*) *6-Methoxy-2,4,6-trimethyl-2,4-cyclohexadienone* (*17b*), yellow oil, containing a small amount of dimer *18b*, as revealed by IR and NMR spectra. B.p. 29 °C/0.1 mmHg, m.p. 13–16 °C. Yield, 39 %. UV (ethanol): λ_{max} 317 nm (log ε = 3.42). IR (KBr): ν_{max}, cm^{-1} sh 1650, 1666. NMR ($CDCl_3$): δ1.38 (s, 3 H, CH_3-6), 1.93 (s, 6 H, CH_3-2 CH_3-4), 3.15 (s, 3 H, OCH_3), 6.50 (broadened s, 2 H, H-3 and H-5). (Small peaks due to dimer *18b* have not been included in these IR and NMR data).

After one week, at room temperature, the oily *17b* had solidified. Recrystallization from benzene-hexane afforded *1,4a,5,8a-tetrahydro-5,9-dimethoxy-1,3,5,7,8a,9-hexamethyl-1,4-ethanonaphthalene-6,10*(4H)*-dione* (*18b*), colourless prisms, m.p. 118–119 °C (Found: C 72.45; H 8.36; OCH_3 18.72. Calc. for $C_{20}H_{28}O_4$: C 72.26; H 8.49; OCH_3 18.67). UV (ethanol): λ_{max}, nm (log ε) 212 (3.90), 228 (3.89), 313 (2.36). The IR spectrum of *18b* in KBr unexpectedly showed three strong peaks in the CO stretching region, ν = 1698, 1715, and 1730 cm^{-1}. In methanol solution, however, only two peaks appeared, ν = 1690 cm^{-1} (conj. CO) and 1720 cm^{-1} (CO).

(*c*) *4-Hydroxy-2,4,6-trimethyl-2,5-cyclohexadienone* (*12*)[2,32] (3 %).

(*d*) o-*Quinol dimer 11*.[2] Yield 13 %, including the portion which had crystallized out from A, see above.

Oxidation of mesitol (1b) *with methanolic* HIO_3. R = 1.5, t = 3 h. Product mixture A, a partly crystalline oil, on treatment with cold hexane, gave *dimer 11*[2] (31 %) as hexane-insoluble residue. From the hexane solution p-*quinol methyl ether 20* and o-*quinol methyl ether 17b* (see preceding experiment) were obtained in yields of 32 and 22 %, respectively, by chromatography using solvent 2.

Oxidation of 2,4-dimethylphenol (1c) *with methanolic* HIO_4. R = 1.15, t = 2 h. The yellow, oily product A was separated into four fractions by chromatography (solvent 2):

(*a*) Light-yellow needles of *1,4a,5,8a-tetrahydro-1,7-diiodo-5,9-dimethoxy-3,5,8a,9-tetramethyl-1,4-ethanonaphthalene-6,10*(4H)*-dione* (*21*), m.p. 155–157 °C (isopropyl ether); yield, 8 %. (Found: C 39.17; H 3.98; I 45.97; OCH_3 11.71. Calc. for $C_{18}H_{22}O_4I_2$: C 38.87; H 3.99; I 45.63; OCH_3 11.16). UV (ethanol): λ_{max}, nm (log ε) sh 205 (4.12), 257 (3.70), sh 300 (3.31). IR (KBr): ν_{max}, cm^{-1} 1710, 1730.

(*b*) Colourless crystals of *4-methoxy-2,4-dimethyl-2,5-cyclohexadienone* (*22*), after sublimation (25 °C/10 mmHg) and recrystallization from isopropyl ether m.p. 38–39 °C (lit.[6a] 40–40.5 °C). Yield, 8 %. M/e = 152 for parent peak, as expected for $C_9H_{12}O_2$. UV (ethanol): λ_{max}, nm (log ε) 227 (4.11), sh 265 (3.21). IR (KBr): ν_{max}, cm^{-1} sh 1620, 1645, 1672.

(*c*) Yellow oil, *6-methoxy-4,6-dimethyl-2,4-cyclohexadienone* (*17c*) containing a small amount of dimer *18c*; yield, 20 %. IR (KBr): ν_{max}, cm^{-1} 1556 (w), 1655 (s), 1676 (s) and an additional peak at 1720 (w) which can be ascribed to *18c*.

The oily monomer *17c* changed into a colourless solid on a few hours' heating on the steam bath or within some days at room temperature. Recrystallization from isopropyl ether gave *1,4a,5,8a-tetrahydro-5,9-dimethoxy-3,5,8a,9-tetramethyl-1,4-ethanonaphthalene-6,10*(4H)*-dione* (*18c*), m.p. 129–130 °C. (Found: C 71.03; H 7.94; OCH_3 20.73. Calc. for $C_{18}H_{24}O_4$: C 71.02; H 7.95; OCH_3 20.39). UV (ethanol): λ_{max}, nm (log ε) sh 205 (3.99), sh 227 (3.91), 310 (2.25). IR (KBr) ν_{max}, cm^{-1} 1700 (conj. CO), 1720 (CO).

(*d*) *2,4-Dimethoxy-4,6-dimethyl-2,5-cyclohexadienone* (*23*), m.p. 80–81 °C after recrystallization from isopropyl ether followed by sublimation (40 °C/5 mmHg); yield, 5 %. (Found: C 65.53; H 7.34; OCH_3 33.44. Calc. for $C_{10}H_{14}O_3$: C 65.91; H 7.74; OCH_3 34.06). UV (ethanol): λ_{max}, nm (log ε) 242 (4.03), 297 (3.05). IR (KBr): ν_{max}, cm^{-1} 1630, 1657, 1675. NMR(CCl_4): δ1.45 (s, 3 H, CH_3-4), 1.93 (d, 3 H, CH_3-6), 3.18 (s, 3 H, OCH_3-4), 3.71 (s, 3 H, OCH_3-2), 5.63 (d, 1 H, H-3), 6.55 (m, 1 H, H-5). $J_{3,5}$ = 3 Hz, $J_{5,6}$ *ca.* 1 Hz.

Oxidation of 2,5-dimethylphenol (1d) *with methanolic* HIO_4. R = 1.1, t = 4.5 h. Chromatography of the yellow oil A (solvent 1) gave:

(*a*) *2,5-Dimethyl*-p-*benzoquinone* (*24*). Yield, 10 %.

(*b*) *6-Methoxy-3,6-dimethyl-2,4-cyclohexadienone* (*17d*), a yellow oil, containing a small amount of dimer *18d*. IR (KBr): ν_{max}, cm^{-1} 1578 (w), 1649 (m) 1669 (s) and peaks due to *18d* at 1690 (w) and 1722 (w).

After a few days at room temperature, *17d* had dimerized to *1,4a,5,8a-tetrahydro-5,9-dimethoxy-2,5,8,9-tetramethyl-1,4-ethanonaphthalene-6,10*(4H)*-dione* (*18d*), m.p. 139–140 °C (isopropyl ether); yield, 12 %. Found: C 70.81; H 8.23; OCH_3 20.27. Calc. for $C_{18}H_{24}O_4$: C

71.02; H 7.95; OCH_3 20.39). UV (ethanol): λ_{max}, nm (log ε) sh 207 (3.90), 231 (3.99), 314 (2.31). IR (KBr): ν_{max}, cm^{-1} 1642 (w), 1692 (s), 1723 (s).

Methylation of o-quinol dimers

Methylation with $CH_3I/CH_3SOCH_2^-Na^+$/DMSO. The procedure of Sjöberg and Sjöberg [23] was followed. Dimer *11* [2] gave the *dimethyl ether 20b* in 85 % yield. Similarly, *dimethyl ether 20c* was obtained in 57 % yield from the corresponding *o*-quinol dimer.[3]

By the same method *o*-quinol dimer *3* gave a 90 % yield of *1,4a,5,7-tetrahydro-5,9-dimethoxy-1,5,7,7,9-pentamethyl-1,4-ethanonaphthalene-6,10(4H)-dione* (*28*), m.p. 100–101 °C (isopropyl ether). (Found: C 71.79; H 8.28; OCH_3 20.51. Calc. for $C_{19}H_{26}O_4$: C 71.67; H 8.23; OCH_3 19.49). UV (ethanol): Strong end absorption (log $\varepsilon = 4.02$ at λ 200 nm, probably due to intramolecular charge transfer in β,γ-enone systems), minimum at 270 nm (log $\varepsilon = 1.78$), max. at 315 nm (log $\varepsilon = 2.28$). IR (KBr): ν_{max}, cm^{-1} 1709 (s), 1722 (s). NMR ($CDCl_3$) δ1.14, 1.16, 1.32 (s, 3 H each, 3 CH_3), 1.35 (s, 6 H, 2 CH_3), 3.00 (s, 3 H, OCH_3), 3.03 –3.22 (m, 2 H, H-4, 4a), 3.30 (s, 3 H, OCH_3), 5.31 (d, 1 H, H-8), 5.71 (dd, 1 H, H-2), 6.31 (t, 1 H, H-3). $J_{2,3} = J_{3,4} = 7$ Hz, $J_{2,4} = 1.5$ Hz.

Methylation of o-quinol dimer 3 with CH_3I/Ag_2O/DMF.[25] Methyl iodide (6.1 g) and silver oxide (6.75 g) were added to a solution of dimer *3* (2.0 g) in DMF (25 ml) and the mixture was stirred for 18 h. After addition of chloroform (150 ml) the mixture was filtered and the filtrate, after being dried over anhydrous $CaSO_4$, was brought to dryness under vacuum. Chromatography of the resulting oil on a silica gel column (benzene-ethyl acetate 4:1) provided compounds *28* ($R_F = 0.5$), *27* ($R_F = 0.4$) and *18a* ($R_F = 0.3$) in yields of 29, 19, and 31 %, respectively.

Compound *27*, *1,4a,5,7-tetrahydro-5,9-dimethoxy-1,5,7,9-tetramethyl-1,4-ethanonaphthalene-6,10(4H)-dione*, had m.p. 179–180 °C (isopropyl ether). (Found: C 70.93; H 7.69; OCH_3 20.69. Calc. for $C_{18}H_{24}O_4$: C 71.02; H 7.95; $OCH_3$20.39). UV (ethanol): Strong end absorption (log $\varepsilon = 3.97$ at λ 200 nm), minimum at 280 nm (log ε = 2.12), maximum at 313 nm (log ε = 2.38). IR (KBr): ν_{max}, cm^{-1} 1706 (s), 1735 (s). NMR ($CDCl_3$): δ1.20–1.42 (m, 12 H, 4 CH_3), 2.96 (s, 3 H, OCH_3), 2.98–3.25 (m, 3H, H-4, 4a, 7), 3.36 (s, 3 H, OCH_3), 5.31 (d, 1 H, H-8), 5.64 (dd, 1 H, H-2), 6.31 (t, 1 H, H-3). $J_{2,3} = J_{3,4} = 7.5$ Hz, $J_{2,4} = 1.5$ Hz, $J_{4a,8} = 2.5$ Hz.

Methylation with $(CH_3O)_2SO_2/BaO-Ba(OH)_2$/DMF.[24] A suspension of BaO (4.4 g) and $Ba(OH)_2.8H_2O$(4.4 g) in a solution of *o*-quinol dimer *3* (2.0 g) in *N,N*-dimethylformamide (25 ml) was cooled to 0 °C, and dimethylsulfate (9 ml) was added dropwise without further cooling. The mixture was then stirred for 16 h at room temperature, conc. ammonia (6 ml) was added and stirring continued for one further hour. Extraction with chloroform gave a crystalline solid (1.73 g) consisting of two components according to TLC. Separation on a silica gel column (light petroleum b.p. 40–60 °C–ethyl acetate 5:2) gave *dimethyl ether 18a* (17 %) and *monomethyl ether 25* [*1,4a,5,8a-tetrahydro-5-hydroxy-9-methoxy-1,5,7,9-tetramethyl-1,4-ethanonaphthalene-6,10(4H)-dione*] (62 %). M.p. 157–158 °C (isopropyl ether). (Found: C 70.54; H 7.70. Calc. for $C_{17}H_{22}O_4$: C 70.32; H 7.64). UV (ethanol): λ_{max}, nm (log ε) 208 (3.79), 240 (3.79), 310 (2.27). IR (KBr): ν_{max}, cm^{-1} 1670 (conj. CO), 1730 (CO), 3480 (OH). The NMR spectrum ($CDCl_3$) shows one OCH_3 singlet at δ 3.38 and one OH singlet at δ 4.04 (exchangeable with D_2O).

o-Quinol dimer *11* was similarly methylated to give a 96 % yield of *dimethyl ether 18b*.

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REFERENCES

1. Adler, E. and Holmberg, K. *Acta Chem. Scand. B 28* (1974) 465.
2. Adler, E., Dahlén, J. and Westin, G. *Acta Chem. Scand. 14* (1960) 1580.
3. Adler, E., Junghahn, L., Lindberg, U., Berggren, B. and Westin, G. *Acta Chem. Scand. 14* (1960) 1261.
4. Adler, E., Holmberg, K. and Ryrfors, L.-O. *Acta Chem. Scand. B 28* (1974) 888.
5. Adler, E., Falkehag, I. and Smith, B. *Acta Chem. Scand. 16* (1962) 529.
6. a. Bamberger, E. *Ber. Deut. Chem. Ges. 40* (1907) 1930;
b. Bamberger, E. and Brun, J. *Helv. Chim. Acta 7* (1924) 115; Müller, E. and Ley, K. *Chem. Ber. 88* (1955) 60; Hecker, E. and Lattrell, R. *Angew. Chem. 74* (1962) 652; *Chem. Ber. 96* (1963) 639; Vermillion, Jr., F. J. and Pearl, I. A. *J. Electrochem. Soc. 111* (1964) 1392; Ronlán, A. and Parker, V. D. *J. Chem. Soc. C* (1971), 3214; Dietl, H. and Young, H. S. *J. Org. Chem. 37* (1967) 2967.
7. Dimroth, K., Umbach, W. and Thomas, H. *Chem. Ber. 100* (1967) 132.
8. Harrison, M. J. and Norman, R. O. C. *J. Chem. Soc. C* (1970) 728; Hewitt, D. G. *Ibid.* (1971) 2967.
9. Adler, E. and Holmberg, K. *Acta Chem. Scand. B 28* (1974) 549.
10. Holmberg, K., Kirudd, H. and Westin, G. *Acta Chem. Scand. B 28* (1974) 913.
11. Fatiadi, A. J. *Synthesis* (1974) 229.
12. Hesse, G. and Mix, K. *Chem. Ber. 92* (1959) 2427.

13. Kaiser, E. T. and Weidman, S. W. *J. Amer. Chem. Soc. 86* (1964) 4354.
14. Bunton, C. A. and Hellyer, J. *J. Amer. Chem. Soc. 89* (1967) 6252.
15. Bunton, C. A. and Hellyer, J. *Tetrahedron Lett.* (1969) 187.
16. Partington, J. and Bahl, R. *J. Chem. Soc.* (1934) 1088.
17. Waring, A. J. *Advan. Alicycl. Chem. 1* (1966) 129.
18. Derkosch, J. and Kaltenegger, W. *Monatsh. Chem. 88* (1957) 778.
19. Rieker, A., Rundel, W. and Kessler, H. *Z. Naturforsch. 24b* (1969) 547.
20. Becker, H.-D. *Justus Liebigs Ann. Chem. (1973)* 1675.
21. Karlsson, B., Pilotti, A.-M. and Wiehager, A.-C. *Acta Chem. Scand. 27* (1973) 2945, 2955.
22. Adler, E., Brasen, S. and Miyake, H. *Acta Chem. Scand. 25* (1971) 2055; Vannerberg, N. G. and Brasen, S. *Ibid. 24* (1970) 1894.
23. Sjöberg, B. and Sjöberg, K. *Acta Chem. Scand. 26* (1972) 275.
24. Kuhn, R. and Trischmann, H. *Chem. Ber. 96* (1963) 284.
25. Kuhn, R., Trischmann, H. and Löw, T. *Angew. Chem. 67* (1955) 32.
26. Carruthers, W. *Some Modern Methods of Organic Synthesis*, Cambridge Univ. Press, London 1971, p. 25; Ringold, H. J. and Malhotra, S. K. *Tetrahedron Lett.* (1962) 669; *J. Amer. Chem. Soc. 84* (1962) 3402; Conia, J. M. *Rec. Chem. Progr. 24* (1963) *43.*
27 Adler, E., Holmberg, K. and Ryrfors, L.-O. *Acta Chem. Scand. B 28* (1974) 883.
28. Bubb, W. A. and Sternhell, S. *Tetrahedron Lett.* (1970) 4499.
29. Fatiadi, A. J. *J. Res. Bur. Stand. A 72* (1968) 341.
30. Fatiadi, A. J. *Synthesis* (1973) 357.
31. Waters, W. A. *J. Chem. Soc. B* (1971) 2026; Ronlán, A. *Chem. Commun.* (1971) 1643.
32. Bamberger, E. and Rising, A. *Ber. Deut. Chem. Ges. 33* (1900) 3636.
33. Adler, E., von Euler, H. and Cedwall, J. *Ark. Kemi, Mineral. Geol. 15A* (1941) *No. 7.*
34. Hultzsch, K. *Ber. Deut. Chem. Ges. 74* (1941) 1533.
35. Becker, H.-D. *J. Org. Chem. 30* (1965) 982; *34* (1969) 1203.
36. Haynes, R. K. and Musso, H. *Chem. Ber. 107* (1974) 3723; Haynes, R. K., Hess, H. and Musso, H. *Ibid. 3733.*

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