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OXIDATION OF TETRA-t-BUTYL DERIVATIVES OF 4,4'-DIHYDROXYDIPHENYL ETHER

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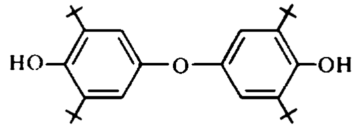
Abstract—Acid catalyzed alkylation of 4,4'-dihydroxydiphenyl ether with isobutylene gives rise to two isomeric tetraalkyl derivatives (I, II). The oxidation of the symmetrically substituted derivative (I) occurs with elimination of the ether oxygen. The unsymmetrically substituted isomer (II) yields by oxidative coupling a trinuclear phenol (VI), which is further oxidized to a stable mono- and biradical.

THE PRESENT PAPER, which is part of the study of phenolic biradicals and the mechanism of antioxidative action of polynuclear phenols, deals with the oxidation of tetratert-butyl derivatives of 4.4'-dihydroxydiphenyl ether.

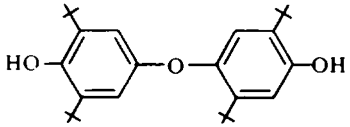
The alkylation of 4.4'-dihydroxydiphenyl ether with isobutylene, catalyzed by H_2SO_4, gives rise to two isomeric tetratert-butyl derivatives, namely, a symmetrically substituted one at positions 3.5.3'.5' (I) and an unsymmetrically substituted one at positions 2.5.3'.5' (II). The structure of both isomers was established from their spectral properties. The symmetry of substitution of compound I follows quite unambiguously from its NMR spectrum, which exhibits only three signals having the following chemical shifts (τ): 8·61 for the t-Bu groups, 5·24 corresponding to the protons of phenolic OH groups, and 3·27 for the aromatic protons. The IR spectrum also has only one band at 3634 cm^{-1} for sterically hindered OH groups. The IR spectrum of isomer II contains in this region two bands at 3630 and 3550 cm^{-1}, which suggests the presence of differently hindered phenolic OH groups in the molecule. As to the NMR spectrum, the unsymmetry of isomer II is most markedly demonstrated by the t-Bu resonances, where instead of a single line there are three (τ = 8·63, 8·67 and 8·73) with intensity ratio 2:1:1. To obtain further evidence for the structure of the above isomer, its monomethoxy derivative (III) was prepared by alkylation with dimethyl sulphate. The methylation occurs preferentially on the less sterically hindered OH group. Compound III was also prepared independently by the Ullman reaction of 4-bromo-2.6-ditert-butylphenol with potassium 2.5-ditert-butyl-4-methoxyphenoxide. The identity of both methoxy derivatives proves that isomer II contains t-Bu groups at positions adjacent to the OH group in the one ring, and in the other at positions *ortho* and *meta* to the OH group.

RESULTS AND DISCUSSION

Oxidation of the symmetrically substituted tetratert-butyl dihydroxydiphenyl ether (I) in C_6H_6 with alkaline $K_3Fe(CN)_6$ yields an orange solution whose ESR spectrum has the form of a triplet 1:2:1 with the splitting constant a_H = 1·1 G. The



I



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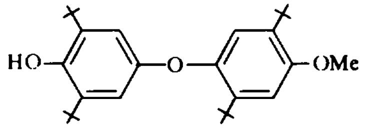
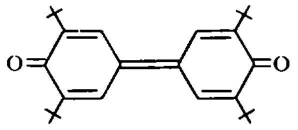


III



IV

yellow oxidation product of I. isolated after oxidation in the homogeneous medium of the Claisen solution exhibits in C_6H_6 the same ESR signal. TLC showed that the oxidation product consists of two compounds of quinod character. which after chromatography were identified as 2.6-ditert-butyl-1.4-benzoquinone and 3.5.3'.5'-*tetratert-butyl*-4.4' biphenoquinone (IV). The compound yielding the ESR spectrum could not be detected by TLC owing to the instability of radicals under chromatographic conditions.

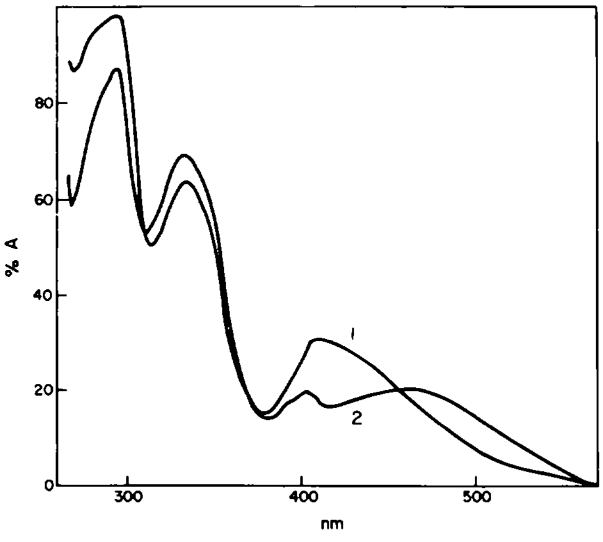
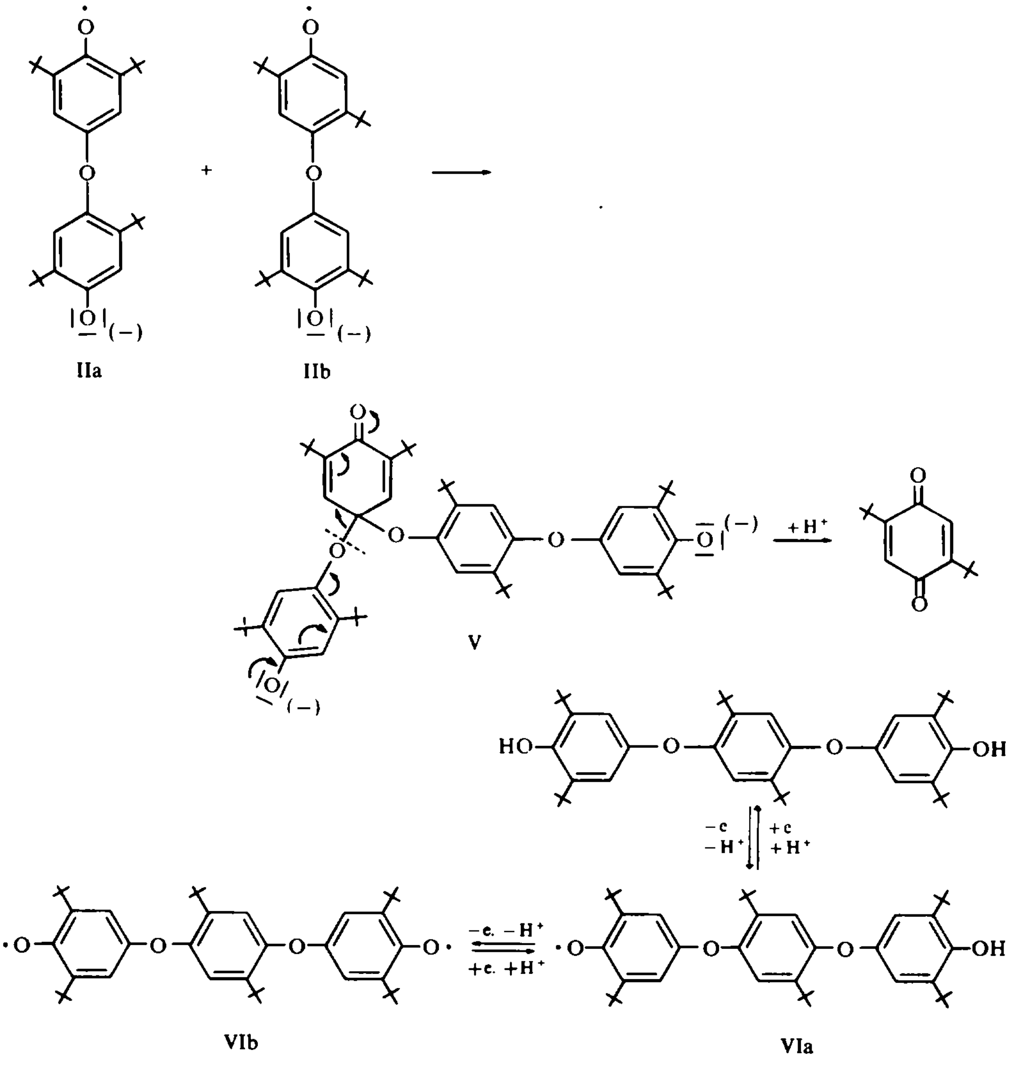


FIG. 1. Electron absorption spectra of the oxidation products of phenol VI in cyclohexane
1—4·5 × 10^{-5} M VIb (oxidation with MnO_2)
2—4·5 × 10^{-5} M VIb + thirtyfold excess of VI

In view of the symmetrical structure of isomer I it is possible to assume that both phenolic groups will be oxidized to form a biradical. The oxidation products show that this biradical is not stable. Simultaneously with the formation of the biradical. the scission of the ether bond occurs. and diphenoquinone (IV) is formed by recombination of the fragments. The recorded ESR spectrum. even if it were compatible with the possibly formed biradical on the assumption of a weak mutual interaction of unpaired electrons. originates in the secondary product. In case the above spectrum were that of the biradical. the original phenol (I) should have appeared among the reduction products of the oxidized form. However. what was found after reduction by the TLC analysis were only the reduction products of quinones. *i.e.* 2.6-ditert-butylhydroquinone and 3.5.3'.5'-tetratert-butyl-4.4'-dihydroxybiphenyl. The radical yielding the above spectrum is only a by-product of oxidation. since isolated quinones represent 86% of the transformation of the initial phenol (I).

The oxidation of tetratert-butyl dihydroxydiphenyl ether (II) with alkaline $K_3Fe(CN)_6$ leads to a product soluble in non-polar solvents to give an intensely red solution. The solutions are paramagnetic and show an intense ESR spectrum in the form of a triplet 1:2:1 with a splitting $a_H = 1{\cdot}1$ G. The spectrum may be interpreted as a result of the interaction of the unpaired electron with two aromatic *meta* protons. The stability of the radical is comparable with the common stable phenoxy radicals.

SCHEME 1



After reduction of the above radical product with NaI or Zn in glacial AcOH. two main phenolic products—2.5-ditert-butyl hydroquinone and a trinuclear phenol (VI) were found by means of TLC. The initial phenol (II) was present in small amount.

When oxidizing isomer II in a homogeneous solution by adding one equivalent of $K_3Fe(CN)_6$ it was possible to isolate phenol VI in 68% yield. In this case. another main product of oxidation was 2.5-ditert-butyl-1.4-benzoquinone. TLC also revealed the formation of a small amount of 2.6-ditert-butyl-1.4-benzoquinone. The constitution of phenol VI follows from spectral data (IR. NMR). elemental analysis and molecular weight. Under the conditions of acetylation with Ac_2O catalyzed with $HClO_4$. when even sterically hindered phenols are acetylated.[3] phenol VI yields diacetate. which indicates the presence of two phenolic OH groups in the molecule. In contrast with the original phenol II. the IR spectrum exhibits one band of sterically hindered OH groups at 3634 cm^{-1}. slightly split into a doublet. The position of the band is the same as in the spectrum of the symmetrically substituted phenol (I). The splitting may originate from the possible conformations of the longer molecule of phenol (VI). The symmetrical substitution at both end rings and the whole molecule is confirmed by NMR spectrum. whose signals correspond only to two types of the t-Bu groups and aromatic protons in the intensity ratio 2:1.

The formation of the trinuclear phenol (VI) may be explained in terms of formation of primary radicals IIa and IIb and their reaction to the dimeric quinone ketal intermediate V (Scheme I). The quinone ketal then immediately undergoes cleavage into 2.5-ditert-butyl-1.4-benzoquinone and phenol VI. The transient formation of monoradicals IIa. IIb as the first step of oxidation is indicated by the fact that in the case of oxidation of phenol II with one equivalent of oxidising agent the product contains only a small amount of unoxidized initial compound. and phenol VI is obtained in high yield. The detection of the formation of radicals IIa. IIb by means of ESR spectrometry was unsuccessful. With respect to the similar structure of radical IIa and the final oxidation product. the presence of the former cannot be deduced from the ESR spectrum. On the other hand. the ESR spectrum of radical IIb ought to be different. since in the case of the phenoxy radicals the interaction constant with the proton at the position *ortho* is approx. 6·5 G.[4] However. the spectrum of this radical could not be observed even in a flow arrangement of the oxidation. The lifetime of radical IIb is apparently shorter than 10^{-6} s. It is known. from the oxidation of 2.5-ditert-butyl-4-methoxyphenol.[5] that the primary phenoxy radicals with t-Bu groups at positions 2 and 5 have very short lifetimes. Similarly. ketal V could not be detected either, owing to its instability.

The final radical products of the oxidation of phenol II. obtained if an excess of oxidizing agent is used. are identical with the oxidation products of the trinuclear phenol VI. It was possible to distinguish the oxidation states of the latter phenol on the basis of the electronic spectra of the radicals formed (Fig 1). The spectra exhibit absorption maxima. characteristic of the phenoxy radicals.[6] Oxidation of phenol VI with alkaline $K_3Fe(CN)_6$ yields mainly monoradical VIa. whose spectrum has maxima at 296. 334. 403 and 460 nm. If MnO_2 is used as the oxidizing agent. the spectrum of the radical is different (Fig 1. curve 1): the maximum at 460 nm disappears and a pronounced absorption appears at 410 nm. The oxidation state reached in this case is higher. since if phenol VI is added to the above solution. the spectrum changes and becomes identical with that obtained by the oxidation with ferricyanide (Fig 1.

curve 2). The reduction of radicals leads in both cases to phenol VI. No other products have been detected by TLC. The above results imply. therefore. that we have here a reversible redox system phenol VI $\rightleftharpoons$ monoradical VIa $\rightleftharpoons$ biradical VIb. The ESR spectra of radicals VIa and VIb had the same form of the triplet. 1:2:1. This means that the interaction of the unpaired electron with the neighbouring ring is weaker than the resolution of the ESR spectrometer used. and also that the mutual interaction of unpaired electrons of biradicals VIb is weak.

As is shown by the results of the present paper. the biradical of the binuclear phenol (I) whose rings are both connected by an oxygen bridge is not capable of existence. The cause of its instability obviously lies in the mutual interaction of both unpaired electrons *via* the ether oxygen. On the other hand. in the case of the tri-nuclear biradical VIb the central aromatic ring with the ether bridges is already a sufficient hindrance to the mutual interaction of the unpaired electrons. which is probably the reason of the comparable stability of this biradical.

EXPERIMENTAL

4.4'-Dihydroxydiphenyl ether was prepared from 4.4'-diaminodiphenyl ether by a modified procedure.[1] The final purification of the crude product was carried out by chromatography on silicagel ($CHCl_3$-EtOAc 1:1). Yield 55%. m.p. 165–168°.

Alkylation of dihydroxydiphenyl ether with isobutylene. 4.4'-Dihydroxydiphenyl ether (3·4 g) dissolved in toluene (80 ml) was alkylated at 65° in the presence of conc H_2SO_4 (0·15 ml) by introducing isobutylene over 12 h. The reaction was neutralized with NaOMe. extracted with 5% NaOH. and toluene removed. The partly crystalline residue was chromatographed on a silicagel column. elution with hexane–C_6H_6 (3:1). giving two isomeric tetratert-butyl derivatives. I and II. 3.5.3'.5'-*Tetratert-butyl-4.4'-dihydroxydiphenyl ether* (I). 2 g. (28%). m.p. 145–147° (C_6H_6–hexane). (Found: C. 79·05; H. 10·02. $C_{28}H_{42}O_3$ requires: C. 78·86; H. 9·88%; M = 426 *m/e*); ν_{max}^{KBr} 3636 cm^{-1} (bonded OH); NMR (τ) 3·27 (s. arom H). 5·24 (s. OH). 8·61 (s. t-Bu); TCL R_f 0·47 (silicagel G. hexane–C_6H_6 3:1). 2.5.3'.5'-*Tetratert-butyl-4.4'-dihydroxydiphenyl ether* (II). 2 g. (28%). m.p. 187–8°(C_6H_6–hexane). (Found: C. 78·90. H. 9·96%; M = 426 *m/e*); ν_{max}^{KBr} 3550. 3630 cm^{-1} (bonded OH): NMR (τ) 3·25. 3·36 (arom H). 5·30 (OH). 8·63. 8·67. 8·73 (t-Bu); R_f 0·17. In some other alkylation experiments. isomer II was formed in greater amount than I.

2.5.3'.5'-*Tetratert-butyl-4-methoxy-4'-hydroxydiphenyl ether* (III). To 200 mg of compound II. dissolved in acetone (3 ml). a soln of KOH in water (2 ml) and 60 μl dimethyl sulphate was added. The mixture was heated to 50° for 30 min. diluted with water. acidified. and extracted with C_6H_6. From the partly crystalline residue after the removal of C_6H_6 the pure methoxy derivative was isolated by chromatography on silicagel (hexane–C_6H_6 5:1). 150 mg of the product. m.p. 159–161° (EtOH) was obtained. (Found: C. 78·97; H. 10·19. $C_{29}H_{44}O_3$ requires: C. 79·04; H. 10·06%); TLC R_f 0·46 (hexane–C_6H_6 5:1).

Condensation of 2.5-ditert-butyl-4-methoxyphenol with 4-bromo-2.6-ditert-butylphenol. 2.5-ditert-butyl-4-methoxyphenol (3 g) was dissolved in MeOH (20 ml) containing 0·72 g KOH. and after addition of 20 ml C_6H_6 solvents were removed. To the phenoxide thus obtained. 2·5 g of 4-bromo-2.6-ditert-butylphenol and 0·2 g of freshly prepared active Cu[2] were added. and the mixture heated to 190–210° for two hr. A compound with R_f 0·46 was isolated from the mixture by repeated chromatography. 0·3 g of product. m.p. 161–163° (EtOH) was obtained. (Found: C. 78·94; H. 10·06%). The m.m.p. with the above mentioned methoxy derivative was without depression: the IR spectra were identical.

Oxidation of isomer I with potassium ferricyanide. 200 mg I in 15 ml Claisen soln (1 part KOH. 1 part H_2O. 2 parts MeOH) was oxidized while stirring under N_2 by adding a soln of 390 mg of $K_3Fe(CN)_6$ (2·5 eq.) in 30 ml of MeOH–H_2O (2:1). After 5 min. the mixture was diluted with 100 ml H_2O. and the yellow product filtered. washed with H_2O and chromatographed on silicagel (180 mg). Elution with hexane–C_6H_6 (3:1) gave 2.5.3'.5'-*tetra-tert-butyl-4.4'-biphenoquinone* (IV) (96 mg). m.p. 247–8°. and 2.6-*di-tert-butyl-1.4-benzoquinone* (76 mg). m.p. 65–66°. identified on the basis of identical R_f values and m.m.ps with authentic compounds.

The same products were found when the oxidation was carried out in a heterogeneous medium. *i.e.* by shaking a C_6H_6 soln of phenol (I) with an alkaline soln of $K_3Fe(CN)_6$.

1.4-Ditert-butyl-2.5-bis(3.5-ditertbutyl-4-hydroxyphenoxy) benzene (VI) *by oxidation of isomer* II *with potassium ferricyanide.* To 300 mg of II. dissolved in 15 ml Claisen soln a soln of 270 mg $K_3Fe(CN)_6$ in 24 ml of $MeOH-H_2O$ (2:1) was added over 30 min while stirring under N_2. After standing for 15 min. the mixture was diluted with 100 ml H_2O. and the ppt. filtered and water washed. The pink-violet crude product was subjected to sublimation at 180°/12 Torr. 133 mg of yellow sublimate was obtained. which gave yellow needles from EtOH. m.p. 148–9°. identified by comparison with an authentic compound as *2.5-ditert-butyl-1.4-benzoquinone.* The slightly pinkish sublimation residue (152 mg) after recrystallization from DMF–. AcOH. formed colourless leaflets. m.p. 287–290°. (Found: C. 79·94; H. 9·91. $C_{42}H_{62}O_4$ requires: C. 79·96; H. 9·91%; M = 630·4 *m/e*); ν_{max}^{KBr} 3634 cm^{-1} (bonded OH); NMR (τ) 3·17. 3·22 (arom H); 8·60. 8·72 (t-Bu). *Diacetate*: m.p. 210–212° (AcOH). (Found: C. 77·18; H. 9·47. $C_{46}H_{66}O_6$ requires: C. 77·27; H. 9·30%).

Oxidation of phenol VI *and electronic spectra.* 5 ml of 6×10^{-3} M soln of VI in C_6H_6 was oxidized by shaking with either 80 mg of active MnO_2 or a soln of 80 mg $K_3Fe(CN)_6$ in 3 ml of 1 N KOH over 2 min. An aliquot of the C_6H_6 soln of the radical was diluted with cyclohexane to a concentration of $4{\cdot}5 \times 10^{-5}$ M. The electronic spectra of this soln was measured in 1 cm cells with a spectrophotometer CF 4 (Optica. Milano) in the region 270–600 nm. The spectra of the oxidation products of phenol II prepared in the same way was identical in this region.

The ESR spectra were measured on a JES-3B spectrometer (Jeol. Tokyo) with 100 kc/s modulation. The measurements were carried out under N_2 with 10^{-3} M soln of oxidation product of I and 10^{-4} M soln of oxidation products of II or VI in C_6H_6 using a measuring capillary of 3 mm diameter.

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