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Oxidative Dimerization of 2,6-Di-*tert*-butyl-4-(2-hydroxyethyl)phenol

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Abstract—2,6-Di-*tert*-butyl-4-(2-hydroxyethyl)phenol undergoes oxidative self-coupling by the action of $K_3Fe(CN)_6$ in alkaline medium at room temperature to give 7,9-di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-hydroxymethyl-2-oxaspiro[4.5]deca-6,9-dien-8-one. The composition of the reaction products has been determined, and the mechanism of their formation is discussed.

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Oxidation of sterically hindered phenols in model media is used to assess their antioxidant efficiency. In other words, the antioxidant activity of phenolic compounds is reflected in their oxidation and specific features of their oxidative transformations which are disclosed by studying the behavior of initially formed radicals. Studies in this line are promising from the viewpoint of synthesis of new phenol derivatives [1]. Oxidation of 4-R-2,6-di-*tert*-butylphenols (R = CH_2CH_2COOMe, CH_2CH_2COMe [2], $CH{=}CHCO_2Me$ [3]) yields dimeric products via oxidative β,β′-coupling of initially formed quinomethanes. In the presence of bases such products rearrange into dimeric vinylphenols possessing high antioxidant and light-stabilizing activity [4]. The formation of analogous biologically active dimers may be expected in oxidative transformations of some other *para*-substituted 2,6-dialkylphenols containing a functional group in the aliphatic chain of the *para*-substituent.

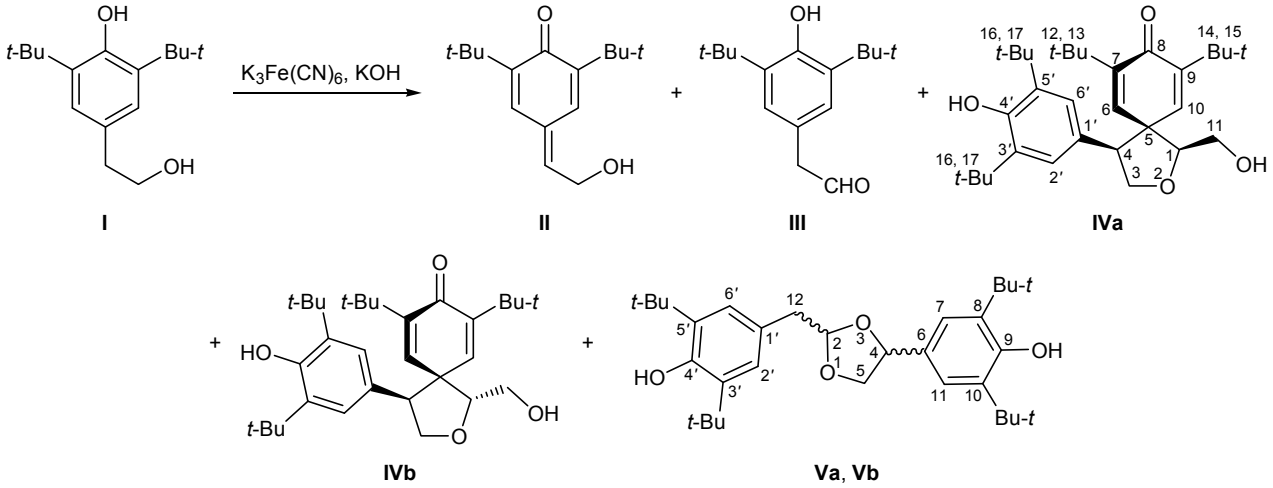
The ability to undergo oxidative dimerization was found for a new practically interesting group of phenolic polymer modifiers, and this reaction has facilitated the search for their new representatives [5]. The oxidation of the most important commercial phenolic antioxidants, fenozans (irganoxes), leads to oligomeric products [6]. However, oxidative transformations of phenolic bioantioxidants (flavonoids and catechins) have not been studied even for model compounds [1]. Such model compounds may be hydroxyalkylphenols; the first their representative, 4-(2-hydroxyethyl)phenol, constitutes a structural fragment of many natural phenolic compounds [7].

We previously studied the oxidation of a number of 2,6-di-*tert*-butyl-4-(ω-hydroxyalkyl)phenols with excess potassium hexacyanoferrate(III) in alkaline medium with a view to obtain substituted quinomethanes. It was found that the first member of this series, 2-hydroxyethyl-substituted phenol **I** is converted into quinomethane **II** in a poor yield [8, 9]. In the present work we made an attempt to elucidate whether the low yield of **II** is related to previously unknown concurrent processes involving oxidative dimerization of **I**.

Our efforts were initially directed toward optimization of the reaction conditions for the formation of quinomethane **II** and minimization of other processes. We succeeded in improving the yield of **II** to 65% by adhering to the following conditions: rapid addition of the oxidant to the reaction mixture, short reaction time (overall reaction time no longer than one hour at 50°C), dilution of the reaction mixture with a solvent, and high alkalinity of the reaction medium. However, even these conditions did not ensure complete avoidance of side processes.

When the reaction temperature was reduced to ambient with simultaneous increase of the reaction time and reactant concentration, the yield of quinomethane **II** decreased from 65 to 5%. According to the GLC and GC/MS data, the product mixture contained 50% of unreacted initial compound **I**, 5% of **II**, 3% of alde-

Scheme 1.



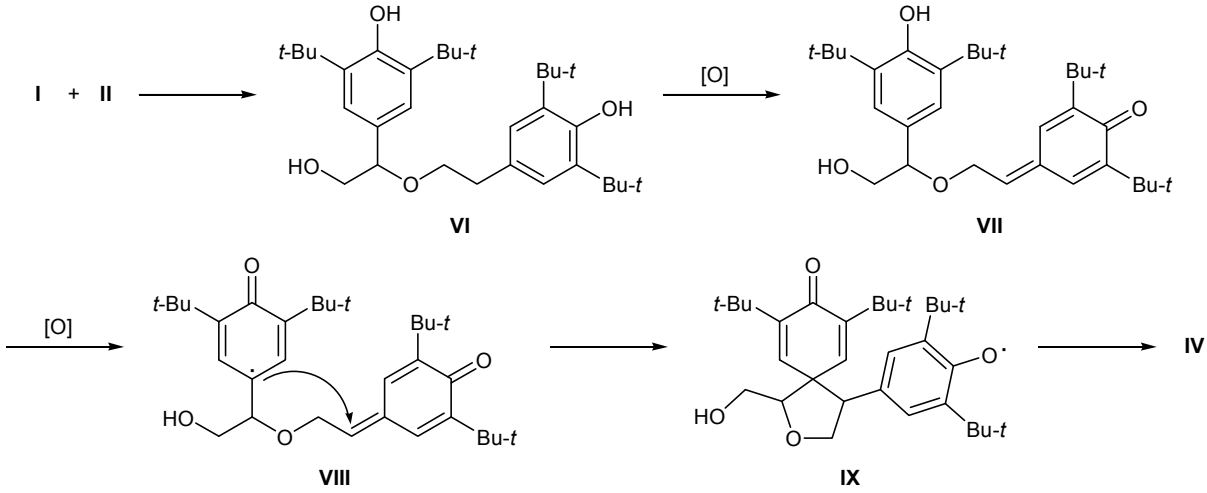
hyde **III**, and four compounds (20, 11, 5, and 3%) with a molecular weight of 496 which corresponds to products of oxidative dimerization of phenol **I**.

By column chromatography we isolated two groups of products, each containing (according to the NMR data) two diastereoisomers. One group was a mixture of stereoisomeric dienones **IVa** and **IVb**, and the other, a mixture of two bisphenols **Va** and **Vb** (structures **IV** and **V** possess two asymmetric carbon atoms; Scheme 1). The stereoisomeric products had equal molecular weights and displayed similar UV spectra, but they differed by GC/MS retention times. The major product, dienone **IVa**, was isolated as individual substance by repeated recrystallization. The steric structure of isomers **IVa** and **Vb** was determined by NMR spectroscopy with the aid of two-dimensional NOESY, COSY, COLOC, and HXCO techniques. Probable mechanisms of formation of stereoisomeric compounds **IV** and **V** are shown in Schemes 2 and 3, respectively.

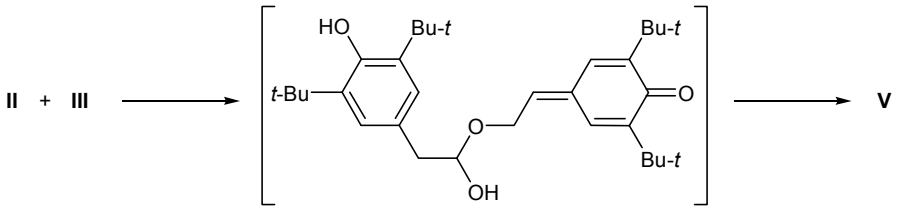
We failed to separate stereoisomers **Va** and **Vb** which were obtained at a ratio of 2:1. Their structure was assigned on the basis of differences in their mass and NMR spectra. The singlet at δ_C 105.6 ppm in the ^{13}C NMR spectrum was attributed to aliphatic carbon atom linked to two oxygen atoms. The other signals in the ^{13}C NMR spectrum were consistent with the assumed structures of **Va** and **Vb**.

Presumably, initially formed quinomethane **II** reacts with phenol **I** to produce ether **VI**. Easy formation of analogous ethers in reactions of quinomethanes with alcohols in the presence of bases was reported in [10]. As shown in Scheme 2, stereoisomeric dienones **IVa** and **IVb** are formed as a result of oxidation of both aromatic rings in ether **VI** to give radical **VIII** and intramolecular ring closure of the latter. This

Scheme 2.



Scheme 3.



transformation may be regarded as C-alkylation of phenols with compounds possessing an activated double bond. Although the mechanism of such processes in the presence of bases remains unclear [11], we believe that in our case radical path shown in Scheme 2 is operative.

Stereoisomers **Va** and **Vb** are likely to be formed via reaction of quinomethane **II** with aldehyde **III**, followed by dioxolane ring closure in intermediate adduct **X** (Scheme 3). Scheme 3 is analogous to the scheme proposed by us previously [8] for the oxidation of 2,6-di-*tert*-butyl-4-(4-hydroxybutyl)phenol to phenol derivative containing a five-membered ring.

The new path of oxidative transformations of phenol **I** disclosed in the present work should be taken into account while determining the structure of products resulting from oxidation of natural phenolic compounds at room temperature.

EXPERIMENTAL

The IR spectra were recorded on a Bruker Tensor-27 instrument. The NMR spectra were measured on Bruker AM-400 and AV-600 spectrometers. Gas chromatographic–mass spectrometric analyses were carried out on an HP 5890 Series II gas chromatograph coupled with an HP 5971 mass-selective detector. The molecular weights were determined from the high-resolution mass spectra which were obtained on a Thermo Electron Corporation DFS instrument. The melting points were determined using a Mettler Toledo FP 900 melting point apparatus.

2,6-Di-*tert*-butyl-4-(2-hydroxyethyl)phenol (**I**), mp 99–101°C, was prepared by reaction of 2,6-di-*tert*-butylphenol with ethylene oxide [12].

2,6-Di-*tert*-butyl-4-(2-hydroxyethylidene)cyclohexa-2,5-dien-1-one (II). A solution of 7.5 g (0.03 mol) of phenol **I** in 120 mL of benzene was mixed with a solution of 20 g (0.06 mol) of $K_3Fe(CN)_6$ in 80 mL of water, and 4.0 g (0.072 mol) of pelletized potassium hydroxide was added in small portions over a period of 45 min under stirring at 50°C. Immediately after addition, the mixture was washed with water until neutral reaction, the organic layer was separated and evaporated, the oily residue (7.8 g) was treated with 2 mL of petroleum ether, and the resulting solution was kept at –20°C. The precipitate was filtered off and washed with 10 mL of petroleum ether cooled to –20°C. Yield 4.5 g (60%), light yellow substance, mp 98–100°C; published data [7]: mp 100–101°C.

The filtrate was evaporated to isolate 3.0 g of a red oily material which solidified on prolonged storage. According to the GLC and GC/MS data, it contained 50% of unreacted phenol **I**, 15% of dienone **IVa**, 25% (overall yield) of five isomeric compounds with a molecular weight of 496, 2% of 2,6-di-*tert*-butyl-1,4-benzoquinone, 3% of aldehyde **III**, 5% of **II**, and a product with a molecular weight of 743.5 (assumingly, trimer of **II**).

(1*RS*,4*RS*)-7,9-Di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-hydroxymethyl-2-oxaspiro[4.5]-deca-6,9-dien-8-one (IVa). A solution of 6.58 g (0.02 mol) of $K_3Fe(CN)_6$ in 25 mL of water was added to a solution of 5.0 g (0.02 mol) of compound **I** in 25 mL of benzene, and an aqueous solution of 1.2 g (0.021 mol) of potassium hydroxide was added dropwise over a period of 60 min under vigorous stirring. The mixture was kept for 12 h at room temperature, and the organic layer was separated, washed with water, and evaporated. The residue, 5.0 g, contained (GLC) 62% of initial compound **I** and 28% of dimers **IVa** and **IVb** (*M* 496). The product mixture was dissolved in petroleum ether on heating, and 1.5 g of phenol **I** separated therefrom on cooling and was filtered off. The filtrate was evaporated, and the oily residue (3.5 g) was subjected to silica gel column chromatography using petroleum ether–chloroform (1:1) as eluent to isolate 1.4 g (28%) of a mixture of stereoisomers **IVa** and **IVb** at a ratio of 2:1 as a white solid.

Stereoisomer **IVa** was isolated by triple recrystallization from hexane. Yield 0.7 g, fine needles, mp 120.1°C. UV spectrum, λ_{max}, nm (logε): 232 (4.07),

248 (4.01), 285 (3.48). IR spectrum (CCl_4), ν, cm^{-1}: 3644 (OH), 1841 and 1658 (C=C, C=O). ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm: 1.00 s (9H, 7-*t*-Bu), 1.21 s (9H, 9-*t*-Bu), 1.34 s (18H, 3′-*t*-Bu, 5′-*t*-Bu), 1.70 br.s (1H, $CH_2O\mathbf{H}$), 3.31 d.d (1H, $C\mathbf{H}_2OH$, J = 11.8, 3.0 Hz), 3.52 d.d (1H, $C\mathbf{H}_2OH$, J = 11.8, 7.8 Hz), 3.80 t (1H, 4-H, J = 9 Hz), 4.16 d.d (1H, 1-H, J = 7.8, 3.0 Hz), 4.44 t and 4.53 t (1H each, 3-H, J = 9 Hz), 5.06 s (1H, 4′-OH), 6.51 and 6.52 (2H, 6-H, 10-H, *AB* system, J = 2.9 Hz), 6.76 s (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 29.1 (C^{13}), 29.5 (C^{15}), 30.1 (C^{17}), 34.2 (C^{16}), 34.88 (C^{12}), 34.91 (C^{14}), 53.6 (C^5), 56.2 (C^4), 62.4 (CH_2OH), 70.4 (C^3), 87.6 (C^1), 123.9 ($C^{2'}$, $C^{6'}$), 125.2 ($C^{1'}$), 135.4 ($C^{3'}$, $C^{5'}$), 136.8 (C^6), 140.2 (C^{10}), 148.0 (C^7), 150.3 (C^9), 152.9 ($C^{4'}$), 185.9 (C^8). Found: m/z 496.3563 $[M]^+$. $C_{32}H_{48}O_4$. Calculated: $[M]^+$ 496.3552.

(1*RS*,4*SR*)-7,9-Di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-hydroxymethyl-2-oxaspiro-[4.5]deca-6,9-dien-8-one (IVb). ^1H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm: 0.95 s (9H, 7-*t*-Bu), 1.24 s (9H, 9-*t*-Bu), 1.37 s (18H, 3′-*t*-Bu, 5′-*t*-Bu), 1.9 br.s (1H, $CH_2O\mathbf{H}$), 3.48 d.d (1H, $C\mathbf{H}_2OH$, J = 11.8, 3.0 Hz), 3.64 d.d (1H, $C\mathbf{H}_2OH$, J = 11.8, 7.8 Hz), 3.55 t (1H, 4-H, J = 9 Hz), 4.00 d.d (1H, 1-H, J = 7.8, 3.0 Hz), 4.35 t and 4.53 t (1H each, 3-H, J = 9 Hz), 5.11 s (1H, 4′-OH), 6.12 and 6.75 (2H, 6-H, 10-H, *AB* system, J = 2.9 Hz), 6.88 s (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 29.07, 29.52, 30.11, 34.20, 34.57, 34.90, 52.45, 55.90, 62.97, 71.62, 86.20, 124.12, 127.25, 135.84, 140.21, 140.47, 147.16, 147.60, 185.89.

Subsequent column chromatography on silica gel using petroleum ether–chloroform as eluent (gradient elution) gave 0.3 g of a mixture of stereoisomeric 2,6-di-*tert*-butyl-4-[2-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-1,3-dioxan-4-yl]phenols **Va** and **Vb** at a ratio of 2:1, mp 185–187°C. UV spectrum: λ_{max} 278 nm. Mass spectrum: m/z (I_{rel}, %): 496 (2) $[M]^+$, 290 (1), 248 (2) $[M]^{2+}$, 232 (100), 219 (12), 217 (38), 57 (30). Found: m/z 496.35 $[M]^+$. $C_{32}H_{48}O_4$. Calculated: $[M]^+$ 496.3552.

Stereoisomer **Va**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 s and 1.40 s (36H, *t*-Bu), 2.87 d (1H, 12-H, J = 3.0 Hz), 3.40–3.60 m (1H, 12-H), 3.80–4.00 (1H, 5-H), 4.12–4.19 d.d (1H, 5-H, J = 7.8, 3.0 Hz), 4.30 t (1H, 4-H, J = 7.8 Hz), 4.75 s (1H, OH), 4.80 s (1H, OH), 7.01 s and 7.07 s (2H each, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 30.1 and 30.2 $[(\mathbf{C}H_3)_3C]$; 34.2, 34.88, 34.91 $[(CH_3)_3\mathbf{C}]$; 52.3 (C^{12}), 59.5 (C^4), 73.6 (C^5), 105.5 (C^2), 124.0 and 124.1 ($C^{2'}$, $C^{6'}$, C^7, C^{11}), 130.3 and 130.5 (C^6, $C^{1'}$), 135.7 and 135.8 ($C^{3'}$, $C^{5'}$, C^8, C^{10}), 152.4 ($C^{4'}$, C^9).

Stereoisomer **Vb**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 s and 1.39 s (36H, *t*-Bu), 2.48 d (1H, 12-H, J = 3.0 Hz), 3.40–3.60 m (1H, 12-H), 3.80–4.00 (1H, 5-H), 4.12–4.19 d.d (1H, 5-H, J = 7.8, 3.0 Hz), 4.55 t (1H, 4-H, J = 7.8 Hz), 4.60 s (1H, OH), 4.80 s (1H, OH), 7.01 s and 7.10 s (2H each, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 30.1 and 30.2 $[(\mathbf{C}H_3)_3C]$, 34.2 $[3'\text{-}\mathbf{C}(CH_3)_3, 5'\text{-}\mathbf{C}(CH_3)_3]$, 34.88 and 34.91 $[8\text{-}\mathbf{C}(CH_3)_3, 10\text{-}\mathbf{C}(CH_3)_3]$, 45.7 ($C^{12}$), 56.7 ($C^4$), 74.7 ($C^5$), 99.8 ($C^2$), 125.5 and 125.8 ($C^{2'}$, $C^{5'}$, C^7, C^{11}), 129.4 and 130.3 (C^6, $C^{1'}$), 135.5 and 135.7 ($C^{3'}$, $C^{5'}$, C^8, C^{10}), 152.5 ($C^{4'}$, C^9).

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