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Influence of Polar Substituents on the Antioxidant Properties of para-Vinyl Phenols and on the Stabilization of the Corresponding Phenoxy Radicals

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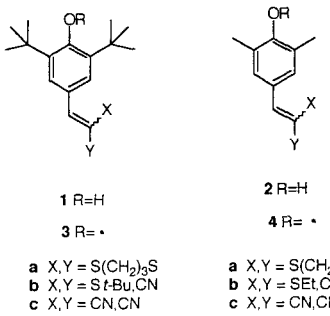
Abstract. Phenols **1** substituted in the para position by vinyl groups bearing different combinations of thioether and cyano substituents in the β positions were synthesized. The determination of their efficiency as antioxidants led to the following order of reactivity: RS,RS ≫ RS,CN > CN,CN. The analysis of the ESR spectra of analogous phenoxy radicals **4** indicates however a different order for the radical stabilization: RS,CN > RS,RS ≫ CN,CN. This behavior is explained by a charge or electron transfer in the transition state as the main factor governing the reactivity. Relative stabilizations of the phenoxy radicals are easily explained according to the captodative concept.

Introduction

Phenols are among the most efficient antioxidants due to their high rate of hydrogen transfer to peroxy radicals [1]. Donor substituents (OH, OMe, ...) in the para position are known to increase the rate of hydrogen transfer [2]. This behavior has been ascribed to a higher stabilization for phenoxy radicals para-substituted by donor groups [3] or as evidence of a polar effect or a charge transfer component in the transition state [2, 4].

In order to examine the effect of a further substituent, we studied phenols with vinylogous substitution in the para position. In this paper, we report the synthesis of phenols **1** and **2** substituted in the para position by vinylic groups bearing the three possible combinations of an electron-withdrawing (nitrile) and an electron-donating (thioether) substituent. The antioxidant properties of **1** were investigated, as well as the relative stabilizations of their corresponding phenoxy radicals **3** and **4**.



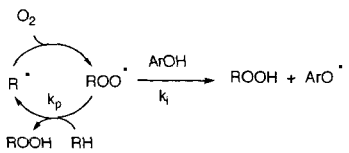


Fig. 1 General reaction scheme for the autooxidation of hydrocarbons in the presence of phenolic antioxidants.

Synthesis of the substituted Phenols

Phenols **1** and **2** were synthesized by two different strategies summarized in Figures 2 and 3.

The synthesis of the tert-butyl substituted phenols **1** is centered on the di-tert-butyl substituted quinomethane **5**. Addition of carbanions derived from dithiane or tert-butylthioacetonitrile to this quinomethane led to phenols **6a** and **6b**, respectively. Quinomethane **7a** is directly obtained by oxidation of **6a** with $K_3Fe(CN)_6$; it isomerizes efficiently into phenol **1a** in the presence of triethylamine. It was not possible to obtain **1b** by the same reactions: oxidation by $K_3Fe(CN)_6$ gave only the phenoxy radical **3b**. This dif-

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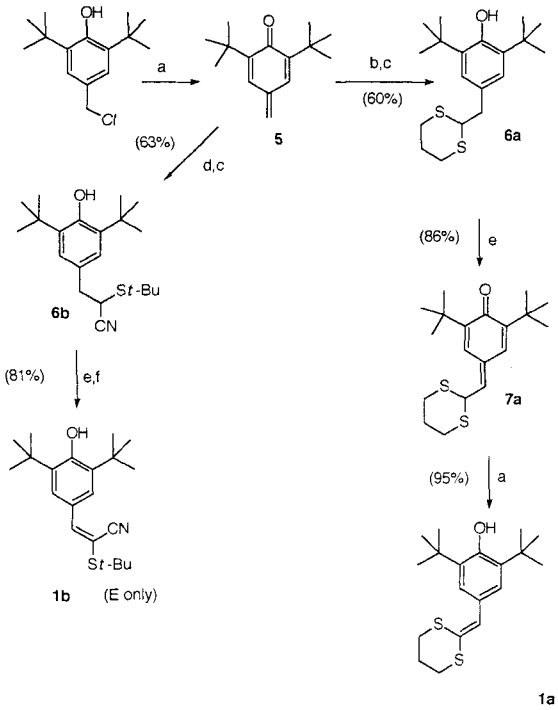


Fig. 2 a) Et_3N; b) dithiane/BuLi; c) NH_4Cl; d) t-$BuSCH_2CN$/LDA; e) $K_3Fe(CN)_6$/KOH; f) PhSH

ferent behavior is due to the higher acidity of the intermediate quinomethane. Under the experimental conditions (KOH), the quinomethane isomerizes directly to the phenolate. This phenolate then reacts with $K_3Fe(CN)_6$ to produce the radical **3b**. In order to obtain **1b**, the solution containing this phenoxy radical **3b** was treated subsequently with thiophenol.

Because of the instability of the 2,6-dimethyl-4-quinomethane, the dimethyl substituted phenols **2** cannot be synthesized by the same strategy. Direct condensation on 3,5-dimethyl 4-hydroxy-benzaldehyde or on 3,5-dimethyl 4-trimethylsilyloxy-benzaldehyde afforded the desired phenols **2a** and **2b**. Phenols **1c** and **2c** were synthesized according to a published method [5].

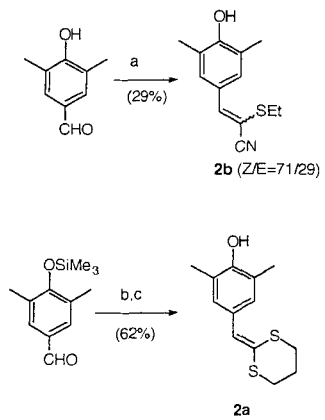


Fig. 3 a) $EtSCH_2CN$/EtONa/EtOH; b) 2-diethyl-phosphonato-1,3-dithiane/NaH; c) NH_4Cl

Antioxidant Properties of Phenols 1

Antioxidant efficiencies are classically characterized by the rate constants ratio k_i/k_p (see Figure 1). In order to obtain this value, we determined the initial rate of autoxidation for neat 1,2,3,4-tetrahydronaphthalene (Tetralin) in the presence of pure oxygen and a catalytic amount of AIBN as initiator. In the presence of a phenol, the rate of the reaction was found to be typical of kinetics involving retarders [6]. Under the above conditions, the initial rate of oxidation R_{ox} for phenols substituted by bulky substituents in the ortho positions follows the equation [6]:

$$R_{ox} = R_{in} + R_{in}\,(k_p\,[RH]_o/k_i\,[ArOH]_o) \quad \text{[eq. 1]}$$

where:

R_{in} = rate of initiation (= rate of decomposition of AIBN),

$[RH]_o$ = initial concentration of 1,2,3,4-tetrahydronaphthalene,

$[ArOH]_o$ = initial concentration of the phenol,

k_p = rate constant for the reaction:

$$RH + ROO^{\cdot} \rightarrow R^{\cdot} + ROOH$$

k_i = rate constant for the reaction:

$$ArOH + ROO^{\cdot} \rightarrow ArO^{\cdot} + ROOH$$

2,6-Di-t-butyl-4-methyl-phenol (BHT), for which the rate constants ratio k_i/k_p is known [7], was first investigated in order to check the accuracy of the experimental system.

The results obtained for the phenols **1** at 50 °C are summarized in table 1. As predicted from equation 1, BHT, **1b**, and **1c** show a linear relationship between R_{ox} and $[RH]_o/[ArOH]_o$. For **1a**, it was impossible to determine k_i/k_p at more than one $[RH]_o/[ArOH]_o$ ratio because of the sensitivity of the experimental system. This value is thus slightly less accurate than the other ones. Nevertheless, this problem has no influ-

Table 1 Kinetics data for the phenols **1** and BHT[a]

#		k_i/k_p 10^{-3}	Correlation coefficient	k_i rel.
	BHT	2.57[b]	0.9800	1[c]
1a	$S(CH_2)_3S$	5.8	no[d]	2.26
1b	StBu, CN	1.52	0.9999	0.59
1c	CN, CN	0.83	0.9959	0.32

[a] At 50 °C; AIBN (0.1M); $R_{in} = a\,k_{in}\,[AIBN]$ with $a = 1.2$ and $k_{in} = 3.7 \times 10^{15}.e^{-31300 cal/RT}\ sec^{-1}$ [8].

[b] Literature: 1.99×10^3 (see text).

[c] By definition.

[d] Only one $[RH]_o/[ArOH]_o$ (see text).

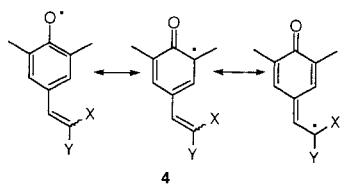
ence on the determination of the relative reactivity: **1a** ≫ BHT ≫ **1b** > **1c**.

Relative Stabilization of the Phenoxy Radicals

To estimate the relative stabilizations of radicals, the experimentator generally faces the problem of choosing between three different approaches: thermochemical, kinetic, or spectroscopic methods. Thermochemical methods are excellent when large effects are involved, but experimental errors are relatively important (for example, bond dissociation energies are rarely obtained with an accuracy better than 2 kcal/mol [9]) and limit their use to problems where the differences in stabilization energies are large compared with errors due to available methods. Kinetic approaches are often more accurate, but imply various assumptions.

Finally, spectroscopic methods can be considered [10, 11]. They are derived from known linear relationships (Mc Connell's and Fischer's relationships [12]) between spin densities and proton-electron hyperfine coupling constants observed by electron paramagnetic resonance (EPR) spectroscopy. Because coupling constants can be determined very accurately, spectroscopic methods are generally very sensitive; for example, they were used to evaluate the relative stabilization energies of parasubstituted triphenylmethyl radicals [13]. Another advantage is their independence from any assumptions on precursors: they are only related to the ground state of the observed radical. The only debatable assumption is on the existence of a direct relationship between spin density and stabilization. This was discussed some years ago in the literature [14], but since then, studies have demonstrated that such a linear relationship indeed exists [11, 15].

In our case, the stabilization afforded by a substituent in the para position of a phenoxy radical is described by the EPR coupling constant a(CH_3) between the unpaired electron and the protons of methyl groups located in the ortho positions of **4**. These coupling constants are linearly related to the spin density on the carbon adjacent to the methyl group. Because of the delocalization by resonance through the pi-system, they are also directly related to the spin density at the para position and on the oxygen:



4

Experimentally, the phenoxy radicals were generated in an ESR cell by the oxidation of their precursors **2** with PbO_2. The experimental spectra were simulated with a computer so as to reach a perfect fit. We were however unable to fully simulate the spectrum for **4c**, but the coupling constant with the six CH_3 hydrogens can be extracted directly. Figures 4 – 6 reproduce the experimental and simulated spectra. The coupling constants are summarized in Table 2.

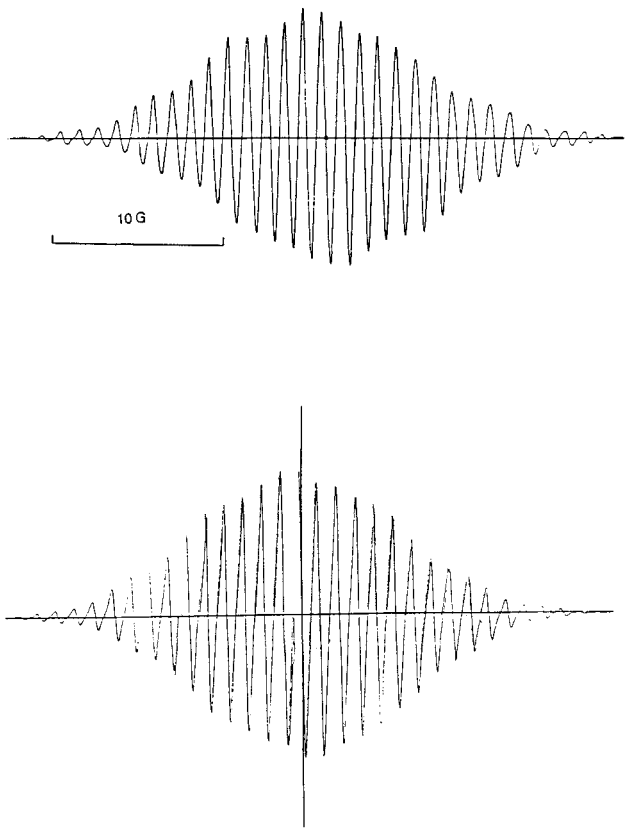


Fig. 4 Experimental (top) and simulated (bottom) ESR spectra for **4a**

Table 2 Coupling constants for the phenoxy radicals **4** (in Gauss)

#	X, Y	a(CH3)	a_H(meta)	a_H(vinyl)	others
4a	$S(CH_2)_3S$	4.32	1.01	2.10	$a_H(SCH_2) = 1.075$
4b	SEt, CN	4.15	1.70	3.50	$a_N(CN) = 0.8$ $a_H(SCH_2) = 0.9$
4c	CN, CN[a]	6.07	2.10	3.15	

[a] Determined directly from the experimental spectrum (see text).

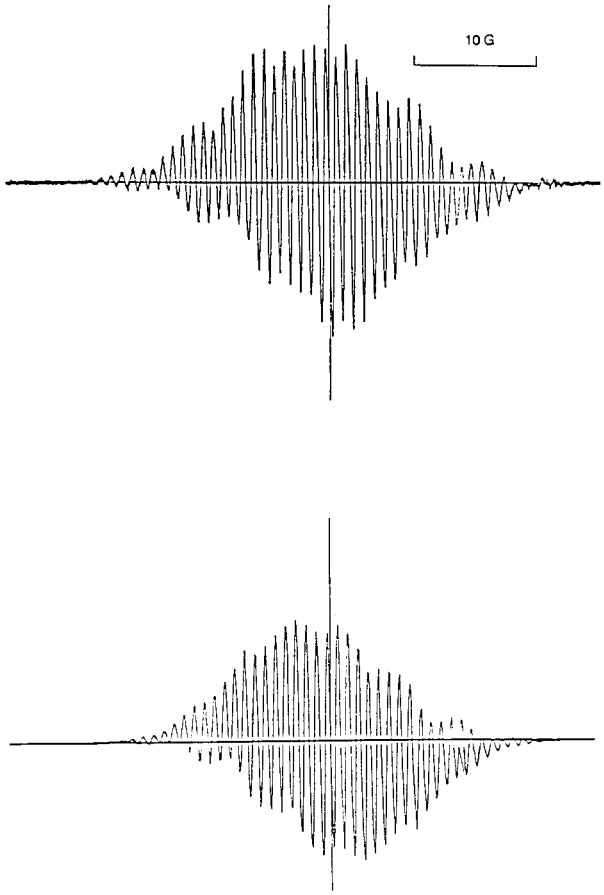


Fig 5 Experimental (top) and simulated (bottom) ESR spectra for **4b**

From these a(CH_3) values and from the reported one (6.06 G) [16] for the radical derived from BHT analog (2,4,6-trimethylphenoxy radical), the following order of stabilization can be drawn: **4b** > **4a** ≫ BHT

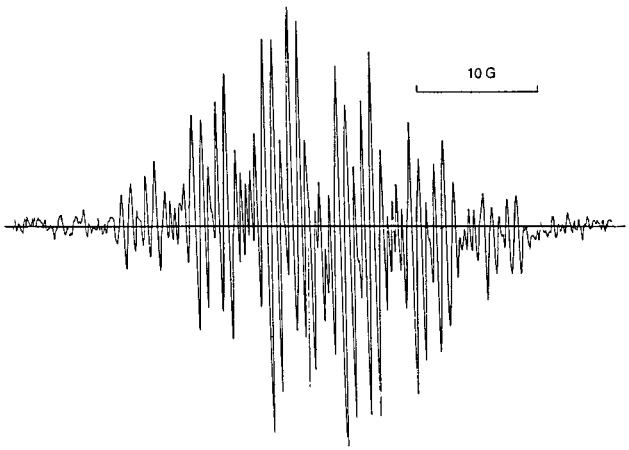


Fig 6 Experimental ESR spectrum for **4c**

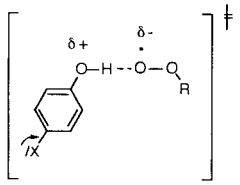
analog ≈ **4c** radical. It seems reasonable to assume that the same order also holds for the t-butyl-substituted phenoxy radicals **3**.

Discussion

Numerous data are available in the literature on the relative or absolute values for the rate constant k_i [17]:

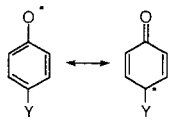
$$ROO + X\text{-}C_6H_4\text{-}OH \xrightarrow{k_i} ROOH + X\text{-}C_6H_4\text{-}O^{\cdot}$$

Substituents in the para position are known to increase the reactivity with their increasing electron donating ability [2]. As we mentioned in the introduction, this behavior has been rationalized as due either to the relative stabilizations of the produced phenoxy radical [3], or to a moderate degree of charge separation in the transition state [2, 4]:



Upon examination of recent results from the literature, it is very tempting to favor the first part of the alternative. Both k_i rate constants [2] and O-H bond dissociation energies of substituted phenols [18] (a measure of the stabilization of phenoxy radicals) correlate linearly with σ^+ substituent parameters. This means obviously that they correlate with each other.

The proposition that phenoxy radicals substituted by electron-donor substituents are more stabilized than other phenoxy radical, is in accordance with the captodative concept [19] as easily illustrated by the following resonance forms for a para-substituted phenoxy radical:



If the substituent Y is an electron-donating substituent, the captodative synergistic interaction with the carbonyl group through the double vinylic system is maximum. It allows the phenoxy radical to be more stabilized than its analogs where Y is an electron-withdrawing substituent.

From these experimental facts, we inferred that phenols able to give rise to very stabilized phenoxy radicals would also be very efficient antioxidants. Our results show that this is not the case.

Table 3 resumes a(CH_3) values for 4-substituted 2,6-dimethylphenoxy radicals, including ours. a(CH_3) for **1c** (CN,CN) is very close to the value reported for BHT, but **1c** was found to be three times less reactive than BHT. **1a** (dithianyl) generates a radical largely more stabilized than BHT, but is only two times more reactive. More interestingly, **1b** (SEt,CN) for which the phenoxy radical is largely more stabilized than BHT-derived radical (4.2 vs 6.2), is in fact *less* reactive than BHT. Finally, we found no correlation between increasing stabilization of the phenoxy radicals (SEt, CN > $S(CH_2)_3S \gg$ BHT ≈ CN,CN) and reactivity order ($S(CH_2)_3S \gg$ BHT ≫ StBu,CN > CN,CN).

It has to be noted that the difference between the coupling constants a(CH_3) for the $S(CH_2)_3S$- and SEt, CN-substituted phenoxy radicals is small and very close to the experimental error. Inversion of this pair would not however affect our conclusions on the inadequation of the radical stabilization theory to rationalize our results.

The previous explanation describing a transition state with a partial charge separation [2, 4] seems more appropriate to explain our results. A two-step reaction consisting of an electron transfer from the phenol to the peroxy radical followed by a proton transfer, could also be a valid alternative explanation: hydrogen abstractions from trialkylamines constitute a known analogy to this two-step reaction [20].

Table 3 Coupling constants with the ortho methyl groups for para-substituted 2,6-dimethylphenoxy radicals

X	a(CH_3) (Gauss)	Ref.
(C=O)Ph	7.0	[16]
COOH	6.8	[16]
CH_3	6.2	[16]
t-Bu	6.1	[16]
$CH=C(CN)_2$	6.07	this work
OMe	4.7	[16]
CH=C (dithianyl)	4.32	this work
CH=C(SEt)(CN)	4.15	this work

Conclusion

We determined the antioxidant efficiency of phenols para-substituted with vinyl groups. Unlike all previously studied examples, the kinetic efficiency does not increase with the increasing thermodynamic stabilization of the formed phenoxy radicals. This finding strongly suggests that the effects responsible for the reactivity are polar (either by a partial charge or electron transfer in the transition state). The reaction is then best described with a transition state exhibiting some partial charge or electron transfer between the reactants. Furthermore, the captodative concept was found to be a powerful heuristic model in rationalizing the relative stabilization of phenoxy radicals.

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Experimental

Melting points were determined with a heating microscope Leitz. ^1H NMR spectra were recorded on a Varian XL-200 spectrometer. ^{13}C NMR spectra were recorded on a Varian XL-200 or on a Varian CFT 20 spectrometer. $CDCl_3$ was used as a solvent. ^{13}C spectra are listed with the multiplicity relative to one-bond coupling constants. IR spectra were recorded on a Perkin-Elmer 297 and 681 spectrometers. Elemental analyses were obtained from the Microanalysis Laboratory of the University of Vienna. The mass spectra were determined on a Varian MAT 44S spectrometer using an ionization potential of 70 eV. ESR spectra were recorded with a Varian E-109 spectrometer.

2,6-Di-t-butyl-4-(2,2-dicyanoethylidene)-phenol (**1c**) and 2,6-dimethyl-4-(2,2-dicyanoethylidene)-phenol (**2c**) were synthesized according to procedures from the literature [5]. 2,6-Di-t-butyl-4-methylene-cyclohexa-2,5-diene-1-one (**5**) was prepared in situ by a described method [21].

2,6-Di-t-butyl-4-(1,3-dithian-2-yl-methyl)-phenol (**6a**)

In a flask maintained at − 78 °C and under argon, a solution of 1.44 g (12 mmol) of 1,3-dithiane in 10 ml of anhydrous THF was added dropwise to a solution containing 12 mmol of n-BuLi in approximately 50 ml of anhydrous THF (the n-BuLi solution was previously titrated). After 15 minutes, the in situ prepared solution of **5** was added dropwise under argon and at − 78 °C. After the end of the addition, the temperature was slowly raised to normal temperature. 100 ml of an NH_4Cl saturated aqueous solution were added. After decantation, the aqueous part was extracted with ether. All organic phases were dried with $MgSO_4$. After the removal of the solvent, the residual oil was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (95/5: v/v) solution as eluent. **6a** was isolated in a 60% yield (2.44 g) as white crystals: m.p. 103 °C. IR($CHCl_3$): 3640(OH), 2980 − 2940 cm^{-1}; ^1H NMR (200 MHz) δ 7.03 (s, 2H), 5.12 (s, 1H, OH), 4.1 − 4.2 (m, 3H), 3.1 − 2.9 (m, 4H), 2.2 − 1.8 (m, 2H), 1.43 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 152.4 (s), 135.0 (s, 2C), 127.8 (s), 127.0 (d, 2C), 48.9 (d), 41.8 (t), 34.2 (s, 2C), 30.4 (t, 2C), 30.3 (q, 6C), 25.7 (t); MS m/e 338 (M^+). Anal. Calcd. for $C_{19}H_{30}OS_2$: C, 67.45; H, 8.87; S, 9.46. Found: C, 67.38; H, 8.99; S, 9.43.

2,6-Di-t-butyl-4-[(1,3-dithian-2-yl)-methylene]-cyclohexa-2,5-diene-1-one (**7a**)

To a solution of 0.85 g (2.5 mmol) of **6a** in a mixture of 50 ml benzene and 50 ml water, were added under argon 1.65 g (5 mmol) of $K_3Fe(CN)_6$ and 0.28 g (5 mmol) of KOH. The solution was stirred during 30 min under argon. After decantation and extraction with benzene, the organic phase

was dried with $MgSO_4$. After the evaporation of the solvent, the recovered oil was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (95/5: v/v) solution as eluent. **7a** was isolated in 86% yield (0.72 g) as white crystals: m.p. 122 °C. IR($CHCl_3$) 2980 – 2940, 1630, 1620 cm^{-1}; ^1H NMR (200 MHz) δ 7.27 (d, 1 H, ^4J = 2.2 Hz), 6.80 (d, 1 H, ^4J = 2.2 Hz), 6.19 (d, 1 H, ^3J = 10.3 Hz), 5.21 (d, 1 H, ^3J = 10.3 Hz), 3.0 – 2.94 (m, 4 H), 2.0 (m, 2 H), 1.32 (s, 9 H), 1.27 (s, 9 H); ^{13}C NMR ($CDCl_3$) σ 190.6 (s), 153.3 (s), 152.3 (s), 141.7 (d), 138.0 (d), 136.4 (s), 129.2 (d), 46.3 (d), 39.4 (s), 38.9 (s), 33.4 (t, 2 C), 33.4 (q, 6 C), 28.5 (t); MS m/e 336 (M^+). Anal. Calcd. for $C_{19}H_{28}OS_2$: C, 67.85; H, 8.40; S, 19.05. Found: C, 67.86; H, 8.33; S, 19.05.

2-(3,5-Di-t-butyl-4-hydroxy-benzylidene)-1,3-dithiane (**1a**)

1.00 g (3 mmol) of **7a** was dissolved in a solution of 0.51 g (5 mmol) of triethylamine in 20 ml of benzene. The solution was maintained at reflux temperature during 3 h. After the evaporation of the solvent, the recovered oil was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (95/5: v/v) solution as eluent. **1a** was isolated in 95% yield (0.95 g) as white crystals: m.p. 65 °C. IR($CHCl_3$) 3640 (OH), 1440 cm^{-1}; ^1H NMR (200 MHz) σ 7.3 (s, 2 H), 6.87 (s, 1 H, vinylic), 5.26 (s, 1 H, OH), 3.0 – 2.9 (m, 4 H, CH_2S), 2.2 – 2.16 (m, 2 H, CH_2), 1.44 (s, 18 H, tBu); ^{13}C NMR ($CDCl_3$): δ 153.0 (s), 135.4 (s, 2 C), 131.0 (d, vinylic), 127.4 (s), 126.3 (d, 2 C), 125.6 (s, vinylic), 34.3 (s, 2 C), 30.2 (q, 6 C), 29.5 (t, 2 C), 24.6 (t); MS m/e 336 (M^+).

2,6-Di-t-butyl-4-(2-t-butylthio-2-cyano-ethyl)-phenol (**6b**)

In a flask maintained at – 78 °C and under argon, a solution of 1.56 g (12 mmol) of t-butylthio-acetonitrile in 10 ml of dry THF was added dropwise to a solution containing 12 mmol of lithium di-isopropyl amide prepared according to the classical procedure [22] in approximately 50 ml of dry THF. After 15 minutes, the in situ-prepared solution of **5** was added dropwise under argon and at – 78 °C. At the end of the addition, the temperature was slowly raised to normal temperature. 100 ml of an NH_4Cl saturated aqueous solution were then added. After decantation, the aqueous part was extracted with ether. The organic phases were dried with $MgSO_4$. After the removal of the solvent, the residual oil was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (98/2: v/v) solution as eluent. **6b** was isolated in 63% yield (2.87 g) as white crystals: m.p. 103 °C. IR(CCl_4) 3650 (OH) cm^{-1}; ^1H NMR (200 MHz) δ 7.08 (s, 2 H), 5.19 (s, 1 H, OH), 3.5 (m, 1 H), 3.1 – 2.9 (m, 2 H), 1.44 (s, 18 H, tBu), 1.38 (s, 9 H, StBu); ^{13}C NMR ($CDCl_3$): δ 153.3 (s), 136.0 (s, 2 C), 126.8 (s), 125.9 (d, 2 C), 121.1 (s, CN), 45.1 (s), 39.8 (t), 34.3 (s, 2 C), 31.9 (d), 30.8 (q, 3 C), 30.3 (q, 6 C); MS m/e 347 (M^+), 258 (M^+-StBu). Anal. Calcd. for $C_{21}H_{33}NOS$: C, 77.62; H, 9.51; N, 4.03. Found: C, 72.60; H, 9.50; N, 4.09.

E-2,6-Di-t-butyl-4-(2-t-butylthio-2-cyano-ethenyl)-phenol (**1b**)

To a solution of 1.59 g (4.2 mmol) of **6b** in a mixture of 50 ml benzene and 50 ml water, were added under argon 4.15 g (12.6 mmol) of $K_3Fe(CN)_6$ and 0.84 g (15 mmol) of KOH. The solution was stirred during 15 min under argon. 0.47 g (4.25 mmol) of thiophenol were added. Thereafter, the solution was stirred during 15 min. After decantation and extraction with benzene, the organic phase was dried with $MgSO_4$. After the evaporation of the solvent, the recovered oil was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (97/3: v/v) solution as eluent. **1b** was isolated in 81% yield (1.28 g) as white crystals: m.p. 118 °C. IR(CH_2Cl_2) 3625 (OH), 2205 (CN), 1590, 1570 cm^{-1}; ^1H NMR (200 MHz) δ 7.71 (s, 2 H), 7.39 (s, 1 H, OH), 5.67 (s, 1 H, vinylic), 1.41 (s, 18 H, tBu), 1.40 (s, 9 H, StBu); ^{13}C NMR ($CDCl_3$): δ 157.4 (d), 157.0 (s), 136.5 (s, 2 C), 127.2 (d, 2 C), 124.8 (s), 119.8 (CN, $^3J_{C-H}$ = 13.6 Hz), 96.4 (s, vinylic), 48.2 (s), 34.5 (s, 2 C), 30.6 (q, 3 C), 30.0 (q, 6 C); MS m/e 345 (M^+). Anal. Calcd. for $C_{21}H_{31}NOS$: C, 73.04; H, 8.98; N, 4.05; S, 9.27. Found: C, 73.05; H, 9.01; N, 4.11; S, 9.31.

2-(3,5-Dimethyl-4-hydroxy-benzylidene)-1,3-dithiane (**2a**)

2.56 g (10 mmol) of 2-(diethylphosphonato)-1,3-dithiane was added to a suspension of 0.24 g (10 mmol) of sodium hydride in 20 ml of THF. The stirring was maintained until the end of the gaseous release. 1.94 g (10 mmol) of 4-trimethylsilyloxy-benzaldehyde in 60 ml of anhydrous THF was added to the solution. The new solution was maintained at reflux temperature during 12 h. 100 ml of a NH_4Cl saturated aqueous solution were added. After extractions with ether, the organic phases were dried with $MgSO_4$. The solvent was removed with a rotatory evaporator, and the residue was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (95/5: v/v) solution as eluent. **2a** was isolated in 62% yield (1.56 g) as white crystals: m.p. 78 °C. IR(CCl_4) 3620 (OH) cm^{-1}; ^1H NMR (60 MHz) δ 7.05 (s, 2 H), 6.7 (s, 1 H, vinylic), 4.6 (s, 1 H, OH), 3.1 – 2.8 (m, 4 H, CH_2S), 3.2 (s, 6 H, Me); MS m/e 234 (M^+).

4-(2-Cyano-2-ethylthio-ethenyl)-2,6-dimethyl-phenol (**2b**)

A solution of sodium ethanolate in ethanol was prepared from 80 ml of anhydrous ethanol and 4.56 g (198 mmol) of sodium. To this solution maintained at 0 °C with an ice bath, 3.50 g (34.6 mmol) of ethylthio-acetonitrile and 4.0 g (27 mmol) of 3,5-dimethyl-4-hydroxy-benzaldehyde in 40 ml of anhydrous ethanol was added dropwise. The solution was maintained at room temperature during 15 h, then at reflux temperature during 20 h. 1.4 g (13.8 mmol) of ethylthioacetonitrile was added and the solution was heated at reflux temperature during 6 h, then maintained at room temperature during 35 h. 600 ml of a NH_4Cl saturated aqueous solution and 100 ml ethanol were added. The solvent was evaporated with a rotary evaporator and the residue was extracted with 200 ml of CH_2Cl_2. This solution was dried with $MgSO_4$. The solvent was removed with a rotatory evaporator and the residue was purified by flash chromatography on silica gel with a petroleum ether / ethyl acetate (98/2: v/v) solution as eluent. **2b** was isolated in 29% yield (1.82 g) as a mixture of two solid isomers (Z/E = 71/29). IR($CHCl_3$) 3610 (OH), 2210 (CN), 1605, 1490 cm^{-1}; Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 66.96; H, 6.52; N, 6.01; S, 13.77. MS m/e 233 (M^+). Z-isomer: ^1H NMR (200 MHz) δ 7.32 (s, 2 H), 7.16 (s, 1 H, vinylic), 5.12 (s, 1 H, OH), 3.03 (q, J = 7.4 Hz, 2 H, SCH_2), 2.26 (s, 6 H, Me), 1.36 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 154.0 (s), 143.6 (d, vinylic), 131.4 (d, 2 C), 126.4 (s), 123.3 (s, 2 C), 117.0 (CN, $^3J_{C-H}$ = 7.9 Hz), 104.7 (s, vinylic), 28.5 (t), 15.9 (q, 2 C), 14.9 (q).

E-isomer: ^1H NMR (200 MHz) δ 7.43 (s, 2 H), 7.23 (s, 1 H, vinylic), 5.16 (s, 1 H, OH), 2.91 (q, J = 7.3 Hz, 2 H,

SCH_2), 2.26 (s, 6H, Me), 1.32 (t, J = 7.3 Hz, 3H); ^{13}C NMR $CDCl_3$): δ 154.8 (s), 148.2 (d, vinylic), 129.7 d, 2C), 125.6 (s), 123.7 (s, 2C), 116.6 (CN, $^3J_{C-H}$ = 13.7 Hz), 99.9 (s, vinylic), 28.0 (t), 15.9 (q, 2C), 14.5 (q).

Determination of the antioxidant properties

We adapted an experimental procedure described in the literature [7] in order to work with little quantities: a flask containing the solution and maintained at constant temperature in a thermostatted bath, was connected to a Warburg gas burette containing the oxygen. Vigorous stirring of the solution led rapidly to thermal equilibrium. The initial rate of autoxidation R_{ox} was directly measured by reading the amount of absorbed oxygen with time.

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