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Comparison of the Efficiencies of the Fused Heterocyclic Compounds, 9*H*-Xanthene-2,7-diols, and Related Chain-Breaking Phenolic Antioxidants

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The antioxidant activities of 9*H*-xanthene-2,7-diols that are structurally related to tocopherols and 2,2′-alkylidenedi(hydroquinones) were measured by the inhibition of the thermally initiated autoxidation of tetralin at 60 °C using an oxygen-absorption method. The stoichiometric factors were calculated as $n=3.3$—5.5 for 9*H*-xanthene-2,7-diols and 0.5—0.9 for 2,2′-alkylidenedi(hydroquinones) that lack the fused six-membered heterocyclic ring. Comparison of the alkyl substituent on the bridged methylene carbon showed that 9-methyl-9*H*-xanthene-2,7-diols increased in n value compared with 9-ethyl-9*H*-xanthene-2,7-diols. For the 9-methyl-9*H*-xanthene-2,7-diols, alkyl groups *ortho* to the phenolic hydroxyl group decreased the R_{inh} value: two methyl groups by 10-fold, one methyl group by 1.9-fold, and one *t*-butyl group by 1.4-fold, compared to that for the 9-methyl-9*H*-xanthene-2,7-diol. On the other hand, 2,2′-alkylidenedi(hydroquinones) were poorer antioxidants than the structurally comparable 9*H*-xanthene-2,7-diols. The low reactivity of 2,2′-alkylidenedi(hydroquinones) compared to those of 9*H*-xanthene-2,7-diols is attributed to electronic factors. The p-type lone pair on the hydroxyl oxygen can not help stabilizing the phenoxyl formed upon abstraction of the phenolic hydrogen.

In various chemical industries, antioxidants have commonly been used to prevent deterioration due to the oxidation of organic substrates, such as rubbers, plastics, and lubricating oils.[1—3] The major pathway of the oxidation of organic materials involves a radical chain mechanism. It is well known that phenolic compounds act as inhibitors of the radical chain reactions during the autoxidation of such organic substrates. Consequently, the inhibition of these oxidations has received much attention and various natural and synthetic antioxidants have been used as chain-breaking inhibitors of the peroxyl radical. For example, tocopherols (Toc) and 2,6-di-*t*-butyl-4-methylphenol (BMP, often called BHT) are popular as natural and synthetic phenolic antioxidants, respectively.

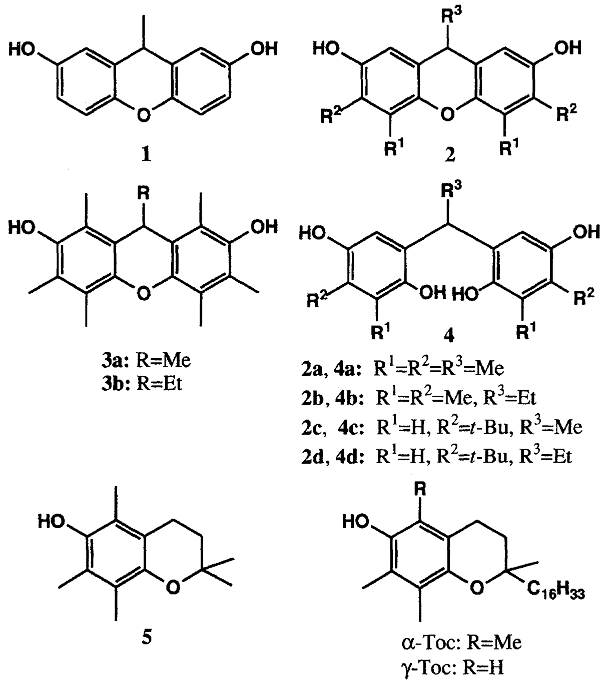
In a recent paper,[4] we described the one-step synthesis of 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols, and evaluated their antioxidant activity during the autoxidation of tetralin. In these studies, it was found that the antioxidant activities of 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols were close to that of α-Toc, the most important antioxidant in vivo.[5,6]

In this paper, we report the antioxidant activities of new synthetic tocopherol model compounds, 9*H*-xanthene-2,7-diols having alkyl groups of varying size (methyl and *t*-butyl) *ortho* to the phenolic hydroxyl group. We also compare the peroxyl radical trapping ability of the 9*H*-xanthene-2,7-diols with the corresponding 2,2′-alkylidenedi(hydroquinones) that lack the fused six-membered heterocyclic ring and with tocopherols in view of the electronic effects of the electron-donating group bonded to the ether-type oxygen atom in the position *para* to the phenolic hydroxyl groups.

Results and Discussion

The phenols examined in this work are divided for convenience into the five classes shown in Scheme 1. These classes are the following: 9-methyl-9*H*-xanthene-2,7-diol **1** (model compound); 3,4,5,6-tetramethyl-, 3,6-di-*t*-butyl-9*H*-xanthene-2,7-diols **2**; 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols **3**: 2,2′-alkylidenedi(hydroquinones) **4**; 6-hydroxy-2,2,5,7,8-pentamethylchroman **5**, and tocopherols, α- and γ-Toc. Figure 1 shows the results of the oxidation of tetralin thermally initiated using α,α'-azobisisobutyronitrile (AIBN) in the presence of selected antioxidants, and of a control test done in the absence of an antioxidant. The oxidation proceeded smoothly in the absence of antioxidant without a noticeable induction period and a constant rate of oxygen uptake was observed (control in Fig. 1). In the presence of γ-Toc, **1**, and **2**, the rate of oxygen uptake was significantly suppressed and a distinct induction period was observed. On the other hand, in the presence of **4**, the rate of oxygen uptake was less suppressed, and a very short induction period was observed.

Efficient phenolic antioxidants (ArOH) are well known to terminate free radical chain peroxidations according to Eqs. 1 and 2.



Scheme 1. Chemical structures of 9*H*-xanthene-2,7-diols **1**—**3**, 2,2′-alkylidenedi(hydroquinones) **4**, hydroxychroman **5**, *α*- and *γ*-Toc.

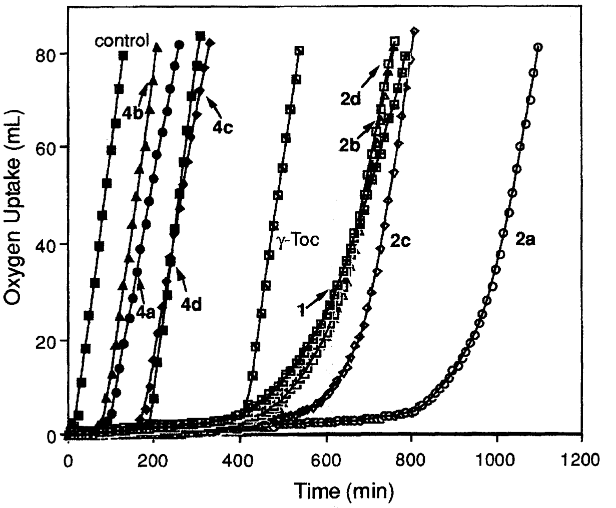


Fig. 1. Rates of oxygen uptake in the oxidation of 50 mL tetralin in the absence (control) and presence of 1 mM antioxidants initiated by 10 mM AIBN at 60 °C under oxygen.

$$\mathrm{ROO\cdot} + \mathrm{ArOH} \xrightarrow{k_{\mathrm{inh}}} \mathrm{ROOH} + \mathrm{ArO\cdot} \tag{1}$$

$$\mathrm{ROO\cdot} + \mathrm{ArO\cdot} \xrightarrow{\mathrm{fast}} \text{nonradical products} \tag{2}$$

During the induction period, the rate of oxidation can be represented by Eq. 3,[7] where k_p is the propagation rate constant of the chain reaction, k_{inh} is the rate constant of inhibition,

$$-\mathrm{d}[\mathrm{O_2}]/\mathrm{d}t = R_{\mathrm{inh}} = k_pR_i[\mathrm{RH}]/nk_{\mathrm{inh}}[\mathrm{ArOH}] \tag{3}$$

R_i is the rate of chain initiation, n is a stoichiometric factor, and RH represents the organic substrate. The t_{inh} can be represented by Eq. 4. From the above equations,

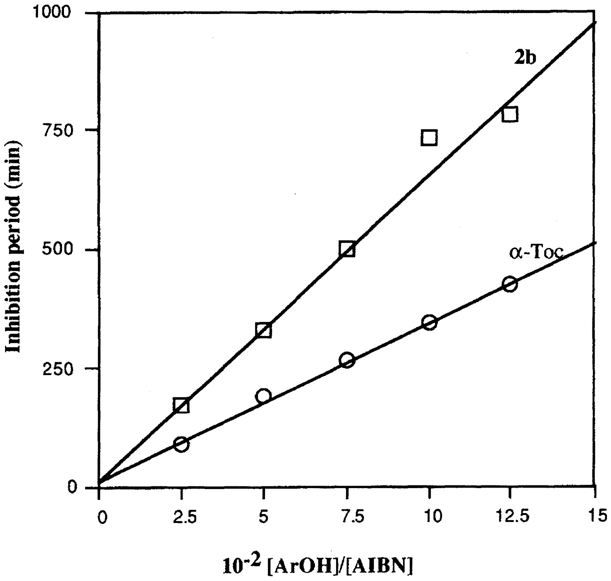


Fig. 2. Inhibition period produced by **2b** and *α*-Toc in the oxidation of tetralin induced by 10 mM AIBN at 60 °C.

$$t_{\mathrm{inh}} = n[\mathrm{ArOH}]/R_i \tag{4}$$

the peroxyl radical trapping activities by antioxidants can be expressed by three values: t_{inh}, n, and k_{inh}. However, the value of k_{inh} is difficult to obtain experimentally. Consequently, instead of this value the rate of oxygen absorption (R_{inh}) in Eq. 3 was used.

Equation 4 suggests that the induction period is proportional to the antioxidant concentration. Figure 2 shows that the induction period produced by the addition of **2b** and *α*-Toc in the oxidation of tetralin initiated with AIBN is proportional to [ArOH]/[AIBN] as expected from Eq. 4.

From the traces of oxygen uptake it is possible to measure the t_{inh} during the inhibited oxidation. Table 1 shows the t_{inh} for the oxidation of tetralin in the absence and presence of **1**,**2**,**4** and *γ*-Toc together with the results of inhibition by **3** and *α*-Toc (reported from a previous paper[4]) for comparison). The t_{inh} values of antioxidants tested are affected by the structure. That is, the t_{inh} values decrease in the order: 9*H*-xanthene-2,7-diols>Toc>2,2′-alkylidenedi(hydroquinones). 2,2′-Alkylidenedi(hydroquinones) **4** that lack the fused six-membered heterocyclic ring showed very lower t_{inh} values than did the 9*H*-xanthene-2,7-diol derivatives. From comparisons between **2a** and **4a**, **2b** and **4b**, **2c** and **4c**, **2d** and **4d**, the t_{inh} values of **2** are about 4—10 times larger than that for **4**.

At first the stoichiometric factor, n, for antioxidants tested was obtained. The stoichiometric factor n is 2 for efficient antioxidants such as the *α*-Toc.[8,9] This factor is determined relative to *α*-Toc for antioxidants **1**—**5** by determination of the rate of chain initiation R_i, employing *α*-Toc under the same conditions and measuring the t_{inh} for a known amount of antioxidant where n is to be measured. Under these conditions, Eq. 4 is used to calculate the stoichiometric factor. The stoichiometric factors obtained by measuring the length

Table 1. Inhibition of Oxidation of 50 mL Tetralin by 1 mM Antioxidants Initiated by 10 mM α,α'-Azobisisobutyronitrile (AIBN) at 60 °C

Compd No.	t_{inh} / min	n	R_{inh} / 10^8 M s^{-1}
1	564	3.3	13.7
2a	939	5.4	7.14
2b	666	3.9	9.46
2c	802	4.6	9.92
2d	605	3.5	7.93
3a[a]	957	5.5	1.33
3b[a]	741	4.3	1.72
4a	93	0.54	26.2
4b	83	0.48	33.6
4c	145	0.84	13.9
4d	152	0.88	14.9
5	377	2.7	2.77
γ-Toc	413	2.4	7.66
α-Toc	345	(2.0)	2.83
Control	22	—	—

a) The data of **3a** and **3b** were taken from Ref. 4.

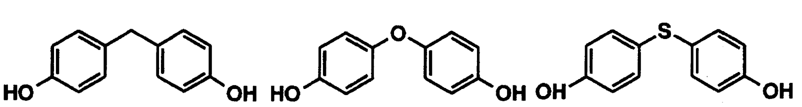
of the t_{inh} for all of the antioxidants examined are listed in Table 1, along with the results of the oxidation of tetralin for **3** and α-Toc. 9*H*-Xanthene-2,7-diols **1**—**3** have much higher stoichiometric factors of 3.3—5.5 in comparison with Toc or **5**. This means that 9*H*-xanthene-2,7-diols **1**—**3** can trap 3—5 peroxyl radicals, whereas α-, γ-Toc, and **5** can trap 2—3 peroxyl radicals. By comparison of alkyl substituents on the bridged methylene carbon between **2a** and **2b**, **2c** and **2d**, **3a** and **3b**, a methyl group increases the *n* values compared with an ethyl group. We have reported similar phenomena for the oxidation of tetralin of the 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols.[4] That is, bulky substituents such as ethyl, isopropyl or phenyl groups on the bridged methylene carbon reduced the *n* value compared with unsubstituted or 9-methyl substituted 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols. It is of interest that 2,2′-alkylidenedi(hydroquinones) **4** exhibit lower *n* values (less than 1) than their fused heterocyclic analoges. From these results, incorporation of a fused heterocyclic ring causes a remarkable increase in the stoichiometric factors. Iwatsuki et al.[10] reported that the poor antioxidant activity of ubiquinol-10 may be ascribed to the formation of hydroperoxyl radical from the interaction of oxygen and ubisemiquinone radical. Furthermore, Barclay et al.[11] reported that the polyalkylhydroquinones exhibit lower antioxidant activities than their cyclic chromanol analogs.

The rate of oxidation, R_{inh}, during the induction period was determined from the slopes of the oxygen uptake traces in the presence of antioxidant. The results summarized in Table 1 show that all antioxidants except for the 2,2′-alkylidenedi(hydroquinones) **4** are good chain-breaking antioxidants. In particular, the α-Toc, **3**, and **5** have smaller R_{inh} than the 9*H*-xanthene-2,7-diols **1**—**2**, and γ-Toc. For the 9-methyl-9*H*-xanthene-2,7-diols, alkyl groups *ortho* to the phenolic hydroxyl groups decreased the R_{inh} value: two methyl groups by 10-fold, one methyl group by 1.9-fold, and one *t*-butyl group by 1.4-fold, compared to that of the 9-methyl-9*H*-xanthene-2,7-diol **1**. For other pairs of α- and γ-Toc, the R_{inh} values increase from 2.83×10^{-8} to 7.66×10^{-8} M s^{-1} (M=mol dm^{-3}). On the other hand, the R_{inh} value for the chromanol **5** is the same as that for the α-Toc, indicating that the phytyl side chain has no effect on antioxidant activity at least in the oxidation of tetralin. An analogous observation has been observed for the oxidation of styrene.[7,11] By comparison of alkyl substituents on the 9-position, the R_{inh} of 9-methyl- and 9-ethyl-9*H*-xanthene-2,7-diols are similar, in contrast to remarkable differences observed for the *n* value. From these results, the main effect causing the reduction of the antioxidant activity of **1**, **2**, and γ-Toc compared to **3** and α-Toc is the lack of stabilizing electron-donating two methyl groups *ortho* to the OH group.

Burton et al.[7—9] have reported that the rate constant for the H-atom abstraction by peroxyl radicals for α-Toc and related compounds depends on steric and electronic effects stabilizing the phenoxyl radical formed in a rate-controlling inhibition reaction in which the phenol traps the chain-propagating peroxyl radicals. Stabilization of the phenoxyl radical depends on two factors: (i) the extent of orbital overlap between the 2p type lone pair on the *para* oxygen atom and the aromatic π-electron system, and (ii) the electron-donating ability of the group bonded to the *para* oxygen atom.

It is of interest to note that the R_{inh} of 2,2′-alkylidenedi(hydroquinones) **4** that lack the fused six-membered heterocyclic ring is higher than the value of their corresponding 9*H*-xanthene-2,7-diols **2**. From comparisons between **2a** and **4a**, **2b** and **4b**, **2c** and **4c**, **2d** and **4d**, the R_{inh} of **2** were about 1.4—3.7 times smaller than that for **4**. Similar observations have been reported by Barclay.[11] That is, the relative k_{inh} and *n* values of α-tocopherol hydroquinone were 2 and 4 times less than α-Toc during the peroxidation of styrene in chlorobenzene, respectively. This shows that the *para* ether-type oxygen should be located in a fused ring system to optimize the stereoelectronic effect on stabilization of the incipient phenoxyl radical.

Finally, the antioxidant activities as measured by t_{inh} of diphenols under the same reaction conditions employed in this study are summarized in Scheme 2.[12] 4,4′-Oxydiphenol and 4,4′-thiodiphenol, those with a heteroatom in the



t_{inh}=103 min R_{inh}=1.49×10^{-8} M/s

t_{inh}=458 min R_{inh}=2.31×10^{-8} M/s

t_{inh}=451 min R_{inh}=1.26×10^{-8} M/s

Scheme 2. Inhibition of oxidation of tetralin by 1 mM antioxidants initiated by 10 mM AIBN at 60 °C.

para position and with an electron-donating group bonded to the *para* heteroatom, showed higher t_{inh} than did the 4,4′-methylenediphenol that lack the heteroatom in the position *para*. Similarly, Burton et al.[9)] reported that 4-methoxyphenols are ca. 5 times more reactive than 4-methylphenols. The normal enhancement of antioxidant activities is due to stabilization of the phenoxyl formed during oxidation reactions by delocalization of the unpaired electron to the p-type orbital of the methoxyl oxygen.

Conclusions

The overall efficiency of an antioxidant is determined by the stoichiometric factor and the inhibition rate of oxidation. Judging from the R_{inh} and n values, it can be said that 9*H*-xanthene-2,7-diols **1**—**3** behaved as better chain breaking antioxidants for the autoxidation of tetralin than the structurally comparable 2,2′-alkylidenedi(hydroquinones) **4**. Among these 9*H*-xanthene-2,7-diols, the compound having two methyl groups *ortho* to the OH group and methyl group on the 9-position, as in **3a**, enhanced the antioxidant activity. The higher reactivities of **1**—**3** relative to **4** can be assumed to be due to the structural characteristics of the 9*H*-xanthene-2,7-diols. That is, the structural characteristics of a fused heterocyclic compounds **1**—**3** include having the fused ether-type oxygen atom in the *para* position to the hydroxyl groups and moreover, having an electron-donating group bonded to the ether-type oxygen atom. The phenoxyl radical having these ether-type oxygen atoms will be stabilized by delocalization of the unpaired electron to the lone pair of an ether-type oxygen.

Experimental

General. Melting points were measured on a Yanaco MP-J3 micro melting apparatus and are uncorrected. Infrared spectra were produced using a grating infrared spectrophotometer (Perkin–Elmer, model 1600) with a potassium bromide pellet. Nuclear magnetic resonance spectra were recorded using a JEOL GSX-400 spectrometer operating at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C in $CDCl_3$, and chemical shifts are referenced to $(CH_3)_4Si$. Mass spectra were recorded using a Perkin–Elmer Model 910 gas chromatographic mass spectrometer at 70 eV.

Assay of Antioxidant Activity. The volume of oxygen consumption was measured as a function of time at 760 Torr (1 Torr=133.322 Pa) of O_2 with 50.0 mL of tetralin containing an antioxidant (5×10^{-5} mol) and AIBN (5×10^{-4} mol) as the initiator. The oxidation temperature was maintained at $60\pm0.1\,^{\circ}$C. The measurements of antioxidant activities were replicated three times in each compound. The t_{inh} was graphically found[9,13)] from the plot of oxygen consumption versus time as the point of the intersection of the line for the rate of oxygen uptake after the inhibitor was consumed and a line tangent to the curve with a slope equal to half of the slope of the line after the inhibitor was consumed. Stoichiometric factors, n, were determined using the induction period method.[14,15)]

Materials. Tetralin used for the test was washed with concentrated sulfuric acid, aqueous sodium hydrogencarbonate, and water, then dried over anhydrous sodium sulfate, and distilled under nitrogen before use. AIBN was recrystallized from methanol. 1,3,4,5,6,8-Hexamethyl-9*H*-xanthene-2,7-diols **3** and 2,2′-alkylidenedi(hydroquinones) **4** were synthesized by the previously reported method.[4,16)] 6-Hydroxy-2,2,5,7,8-pentamethylchroman was prepared according to the method of Nilsson et al.[17)] 9*H*-Xanthene-2,7-diols **2** were synthesized by the acid catalyzed cyclization of 2,2′-alkylidenedi(hydroquinones). A suspension of **4a** (2.0 g, 6.85 mmol) in 150 mL of water in the presence of concentrated HCl (3 mL) was heated under reflux. After being stirred for 15 h at 100 °C, the mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. Purification of the residue by recrystallization gave 3,4,5,6,9-pentamethyl-9*H*-xanthene-2,7-diol **2a**.

9*H*-Methyl-9*H*-xanthene-2,7-diol **1** was prepared by de-*t*-butylation of the corresponding 3,6-di-*t*-butyl-9-methyl-9*H*-xanthene-2,7-diol **2c**. To a solution of **2c** (0.30 g, 0.88 mmol) in dry benzene (20 mL) was added anhydrous $AlCl_3$ (0.16 g, 1.2 mmol) at room temperature. The reaction mixture was warmed to 50—60 °C and stirred for 2 h after which the mixture was poured into 5% HCl and ethyl acetate. The organic layer was dried, and solvent was removed under reduced pressure to provide crude **1**. Purification by recrystallization from a mixed solvent of ethyl acetate and benzene (1 : 5) gave 70 mg of **1** as a white solid. The yield, melting point, spectral, and analytical data are as follows.

9-Methyl-9*H*-xanthene-2,7-diol (1): Yield, 35%; mp 123—124 °C. ^{1}H NMR δ=1.36 (d, J=6.9 Hz, 3H), 2.98 (bs, 2H), 3.97 (q, J=6.9 Hz, 1H), 6.67—6.87 (m, 6H); ^{13}C NMR δ=27.3, 34.5, 114.9, 115.3, 117.5, 127.8, 145.7, 153.8. MS *m/z* (rel intensity) 228 (M^+; 20), 214 (14), 213 (100), 184 (11). Found: C, 73.71; H, 5.27%. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%.

3,4,5,6,9-Pentamethyl-9*H*-xanthene-2,7-diol (2a): Yield, 75%; mp 197—198 °C. ^{1}H NMR δ=1.17 (d, J=7.0 Hz, 3H), 2.00 (s, 6H), 2.15 (s, 6H), 3.68 (q, J=7.0 Hz, 1H), 6.45 (s, 2H), 7.65 (s, 2H). ^{13}C NMR δ=12.0, 12.3, 27.2, 34.8, 111.4, 122.8, 124.7, 125.5, 144.3, 151.0. MS *m/z* (rel intensity) 284 (M^+; 35), 283 (6), 270 (16), 269 (100), 239 (5), 225 (7). IR (KBr) 3228, 2926, 1602, 1426, 1224, 1087 cm^{-1}. Found: C, 75.71; H, 7.07%. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%.

9-Ethyl-3,4,5,6-tetramethyl-9*H*-xanthene-2,7-diol (2b): Yield, 91%; mp 204—205 °C. ^{1}H NMR δ=0.72 (t, J=7.3 Hz, 3H), 1.61—1.68 (m, 2H), 2.15 (s, 6H), 2.31 (s, 6H), 3.68 (t, J=7.0 Hz, 1H), 6.57 (s, 2H), 7.79 (s, 2H). ^{13}C NMR δ=10.5, 12.0, 12.4, 33.6, 41.7, 111.9, 122.7, 123.4, 125.3, 145.3, 150.9. MS *m/z* (rel intensity) 298 (M^+; 20), 270 (41), 269 (100), 239 (6), 239 (5), 225 (5). IR (KBr) 3334, 2920, 1608, 1441, 1215, 1083 cm^{-1}. Found: C, 76.29; H, 7.40%. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.

3,6-Di-*t*-butyl-9-methyl-9*H*-xanthene-2,7-diol (2c): Yield, 63%; mp 199—201 °C. ^{1}H NMR δ=1.37 (d, J=9.9 Hz, 3H), 1.41 (s, 18H), 3.88 (q, J=9.9 Hz, 1H), 6.70 (s, 2H), 6.87 (s, 2H), 8.09 (s, 2H). ^{13}C NMR δ=27.1, 32.9, 35.0, 115.1, 115.6, 124.3, 136.2, 145.2, 151.9. MS *m/z* (rel intensity) 340 (M^+; 15), 326 (18), 325 (100), 295 (8). IR (KBr) 3412, 2959, 1501, 1417, 1305, 1174 cm^{-1}. Found: C, 77.43; H, 8.35%. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29%.

3,6-Di-*t*-butyl-9-ethyl-9*H*-xanthene-2,7-diol (2d): Yield, 30%; mp 217—218 °C. ^{1}H NMR δ=0.69 (t, J=7.7 Hz, 3H), 1.41 (s, 18H), 1.66—1.75 (m, 2H), 3.79 (t, J=5.5 Hz, 1H), 6.68 (s, 2H), 6.89 (s, 2H), 8.03 (s, 2H). ^{13}C NMR δ=10.0, 33.3, 35.0, 39.7, 114.9, 115.9, 122.9, 136.2, 146.5, 151.8. MS *m/z* (rel intensity) 354 (M^+; 7), 326 (21), 325 (100), 295 (8). IR (KBr) 3444, 2961, 1504, 1424, 1311, 1207, 1178 cm^{-1}. Found: C, 77.80; H, 8.50%. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53%.

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