9*H*-Xanthene-2,7-diols as Antioxidant for Autoxidation of Tetralin

Tomihiro NISHIYAMA,* Takafumi ISHIDA, Satoshi MIYAZAKI, Ryuhei TSUJI, and Fukiko YAMADA
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564
(Received February 16, 1993)

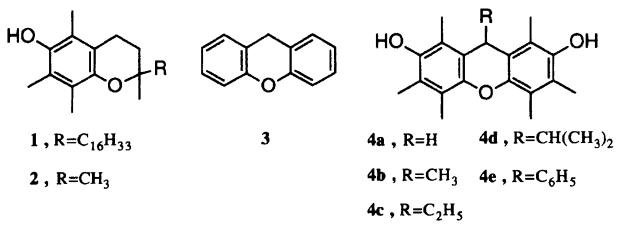
Synopsis. The antioxidant activities of 9*H*-xanthene-2,7-diols were evaluated by means of an oxygen-absorption method at 60 °C for tetralin. Very good activities were observed for 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diol and 1,3,4,5,6,8,9-heptamethyl-9*H*-xanthene-2,7-diol.

α-Tocopherol (**1**), the major component of vitamin E, is an important natural phenolic antioxidant, and is believed to play an essential role in minimizing the autoxidation of lipids in biological membranes.[1—3] The structural characteristics of α-tocopherol is that it has a long phytyl side chain, a chroman ring and a phenolic hydroxyl group. The phytyl side chain has long been of particular interest due to both its effect and role; it is known that the phytyl side chain is required for the incorporation and retainment of α-tocopherol within membranes.[4] That is, 2,2,5,7,8-pentamethyl-6-chromanol (**2**), which is structurally related with **1**, showed similar antioxidant activities for the peroxyl radical.[5]

On this basis, we expected that 9*H*-xanthene-2,7-diols would be a better antioxidant compared with **1**, since it has two active phenolic moieties to the para-positions on the xanthene skeleton. One universal approach regarding the synthesis of hydroxylated xanthenes involves an acid-catalyzed reaction of the dihydric phenols with salicylaldehyde, followed by reduction of the precipitated xanthenium salt with triethylsilane[6] or palladium-catalyzed hydrogenation.[7] Herein, we wish to report on a conceptually similar one-step synthesis and the antioxidant activities of xanthenes **4a**—**e** (Chart 1).

Results and Discussion

The xanthenes **4a**—**e** listed in Table 1 were prepared by the acid-catalyzed reaction of 2,3,5-trimethylhydroquinone with aldehydes. Although this reaction was carried out in a mixture of benzene and nitromethane or benzene, higher yields were obtained in a mixed solvent. The increased effectiveness of the mixed solvent over benzene as the solvent can be attributed to the solubility of the product. In general, reactions of phenols with aldehydes in the presence of acid give bisphenol derivatives. Since the bisphenols are not intermediate in this reaction, the reaction probably proceeds through the quinone intermediate.[8]



1, R=$C_{16}H_{33}$ **3** **4a**, R=H **4d**, R=$CH(CH_3)_2$
2, R=CH_3 **4b**, R=CH_3 **4e**, R=C_6H_5
4c, R=C_2H_5

Chart 1.

Table 1. Preparations of 9*H*-Xanthene-2,7-diols and IP Values

Compd No.	Yield %	Reaction time/h	Mp θ_m/°C	Method of purification	IP min
4a	79	0.2	230(decomp)	a	985
4b	51	16	209—211	a	957
4c	36	20	190—192	b+a	741
4d	23	20	193—195	b	738
4e	60	16	203—205	a	788
1					345
3					12
Control					13

a) recrystallization, b) column chromatography on silica gel.

Figure 1 shows the results of the oxidation of tetralin initiated with azobis(isobutyronitrile) (AIBN) in the presence of xanthenes **4a**—**e** along with commercially available α-tocopherol and xanthene (**3**). The control line shows the oxygen uptake in the absence of an antioxidant. The presence of xanthene (**3**) did not delay oxidation, and a constant rate of oxygen uptake was observed without any appreciable induction period (IP). On the other hand, when xanthenes **4a**—**e** were added to tetralin, the rate of oxidation was markedly suppressed and showed a clear IP. The last column of Table 1 shows the IP values of **1**, **3**, and **4**. The IP values decreased in the order **4a**, **4b**>**4e**, **4c**, **4d**>**1**>**3**. In par-

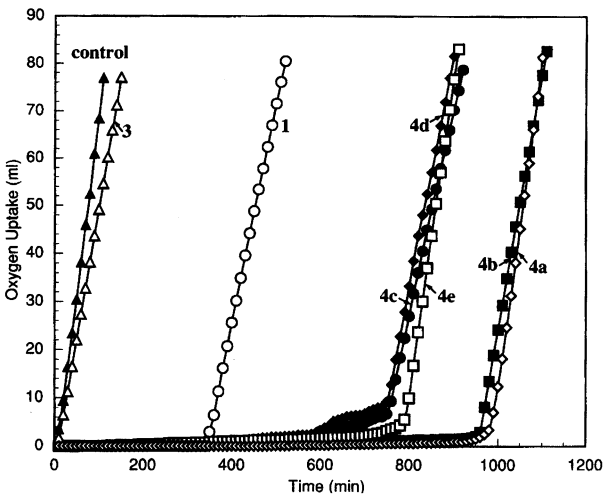


Fig. 1. Inhibitation of oxidation of tetralin by xanthenes and tocopherol.

ticular, xanthenes **4a** and **4b** exhibited a much longer IP compared with those of other xanthenes, and oxygen absorption was entirely suppressed during the IP. Although an antioxidant of catechol or amine derivatives during and after the IP turn to a yellow or deep-red solution, it is noteworthy that the color of xanthenes **4** after the IP was a slightly yellow solution.

Further studies concerning the toxicity of **4** are in progress, together with the antioxidant activities for other substrates.

Experimental

Determination of Antioxidant Activities. Measurements of the oxygen-absorption rates were performed with an isobaric gas-absorption apparatus under a closed-flow system (2.0±0.1 L oxygen/h) provided with an antioxidant (0.001 mol dm^{-3}) and AIBN as the initiator (0.01 mol dm^{-3}). The oxidation temperature was kept at 60±0.1°C and oxygen absorption was periodically measured in a constant-pressure closed system.

The IP and the oxidation rates were determined both during and after the induction period in the usual way.[9,10]

General Methods. All of the melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GSX-400 spectrometer, using $(CH_3)_4Si$ as an internal standard. Gas chromatography was performed on a Hewlet–Packard (5890A) instrument fitted with an OV-73 capillary column. The mass spectra were recorded with a Perkin–Elmer Model 910 gas-chromatographic mass spectrometer at 70 eV.

Conversion of 2,3,5-Trimethylhydroquinone into 1, 3, 4, 5, 6, 8- Hexamethyl- 9*H*- xanthene- 2, 7- diols (General Procedure). A suspension of 2,3,5-trimethylhydroquinone (66 mmol) in 50 ml of benzene/nitromethane mixture (1 : 1) in the presence of concentrated HCl (6 ml) was heated under reflux. To the resulting yellow solution was added aldehyde (34 mmol). The yellow solution changed to purple and then turned dark brown. After being stirred for 0.2—20 h at 70 °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 or column chromatography gave 1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diols **4a**—**e**. The reaction time, product yield, melting point, and purification methods, along with the IP values, are given in Table 1. The ^{1}H NMR, ^{13}C NMR, MS, and analytical data are as follows.

1,3,4,5,6,8-Hexamethyl-9*H*-xanthene-2,7-diol (4a): ^{1}H NMR (DMSO-d_6) δ=2.11 (s, 6H), 2.13 (s, 6H), 2.19 (s, 6H), 3.69 (s, 2H), and 7.72 (s, 2H); ^{13}C NMR δ=11.7, 11.8, 12.6, 24.6, 115.3, 120.2, 122.8, 142.6, and 147.1; MS *m/z* (rel intensity) 299 (15), 298 (M^+; 85), 297 (100), 284 (9), 283 (56), and 253 (5). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%. Found: C, 76.12; H, 7.54%.

1,3,4,5,6,8,9-Heptamethyl-9*H*-xanthene-2,7-diol (4b): ^{1}H NMR (CD_3OD) δ=1.16 (d, *J*=6.6 Hz, 3H), 2.18 (s, 6H), 2.27 (s, 6H), 2.30 (s, 6H), and 4.23 (q, *J*=6.6 Hz); ^{13}C NMR δ=11.4, 12.4, 12.8, 22.9, 30.6, 120.6, 122.5, 124.2, 125.2, 146.3, and 148.8; MS *m/z* (rel intensity) 312 (M^+; 20), 298 (17), 297 (100), 267 (5), 253 (6), 149 (5), and 148 (5). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%. Found: C, 76.62; H, 7.70%.

9-Ethyl-1,3,4,5,6,8-hexamethyl-9*H*-xanthene-2,7-diol (4c): ^{1}H NMR ($CDCl_3$) δ=0.71 (t, *J*=7.5 Hz, 3H), 1.62 (m, 1H), 2.20 (s, 6H), 2.28 (s, 6H), 2.19 (s, 6H), 4.24 (t, *J*=6.1 Hz, 2H), and 4.39 (s, 2H); ^{13}C NMR δ=10.3, 11.4, 12.2, 29.7, 35.3, 117.3, 120.7, 121.9, 123.1, 146.0, and 147.1; MS *m/z* (rel intensity) 326 (M^+; 10), 298 (24), 297 (100), 267 (5), and 253 (6). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%. Found: C, 76.88; H, 7.97%.

1,3,4,5,6,8-Hexamethyl-9-isopropyl-9*H*-xanthene-2,7-diol (4d): ^{1}H NMR (CD_3OD) δ=0.75 (d, *J*=7.0 Hz, 6H), 1.74 (m, 1H), 2.19 (s, 6H), 2.26 (s, 6H), 2.32 (s, 6H), and 4.07 (d, *J*=7.0 Hz); ^{13}C NMR δ=12.4, 12.8, 12.9, 20.5, 37.2, 41.9, 121.5, 122.4, 125.0, 147.9, and 148.9; MS *m/z* (rel intensity) 340 (M^+; 2), 298 (23), 297 (100), and 253 (5). Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29%. Found: C, 77.55; H, 8.26%.

1,3,4,5,6,8-Hexamethyl-7-phenyl-9*H*-xanthene-2,7-diol (4e): ^{1}H NMR ($CDCl_3$) δ=2.18 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 4.36 (s, 2H), 5.29 (s, 1H), and 7.04—7.26 (m, 5H); ^{13}C NMR δ=11.6, 12.3, 12.4, 40.9, 117.9, 121.6, 122.5, 123.0, 126.1, 127.9, 128.5, 144.6, 144.9, and 147.1; MS *m/z* (rel intensity) 375 (5), 374 (M^+; 24), 373 (5), 298 (25), 297 (100), 267 (4), 253 (6), and 77 (12). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00%. Found: C, 79.93; H, 6.95%.

References

1) L. J. Machlin, "Vitamin E," Marcel Dekker, New York (1980).
2) O. Hayashi and M. Mino, "Clinical and Nutritional Aspects of Vitamin E," Elseivier, Amsterdam (1987).
3) G. W. Burton and K. U. Ingold, *Acc. Chem. Res.*, **1986**, 19, 194.
4) E. Niki, A. Kawasaki, M. Saito, Y. Yamamoto, J. Tsuchiya, and Y. Kamiya, *J. Biol. Chem.*, **260**, 2191 (1985).
5) G. W. Burton, L. Hughes, and K. U. Ingold, *J. Am. Chem. Soc.*, **105**, 5950 (1983).
6) R. K. M. Pillai, P. Naiksatam, F. Johnson, R. Rajagopalan, P. C. Watts, R. Cricchio, and S. Borras, *J. Org. Chem.*, **52**, 717 (1986).
7) Y. Tanase, *J. Pharm. Soc. Jpn.*, **61**, 341 (1941).
8) J. W. Scott, F. T. Bigarro, D. R. Parrish, and G. Saucy, *Helv. Chem. Acta*, **59**, 290 (1976).
9) C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen., *J. Am. Chem. Soc.*, **77**, 3233 (1955).
10) F. Yamada, T. Nishiyama, Y. Suzuura, and T. Yamamura, *Bull. Chem. Soc. Jpn.*, **58**, 115 (1985).