Antioxidant Activity of the Fused Heterocyclic Compounds, 2,3,7,8-Thianthrenetetrols

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Synopsis. The antioxidant activities of thianthrene-2,3,7,8-tetrols were evaluated with an oxygen-absorption method at 60 °C for tetralin. Its antioxidant activities were 4.2—6.6 times the activity of α-tocopherol.

The oxidation of unsaturated compounds by molecular oxygen causes deterioration of petroleum hydrocarbons, lubricating oils, rubbers, polymers, and foodstuffs.[1] Oxidation during storage at room temperature or during processing of various kinds at high temperature arises because of radical chain reactions. Various kinds of natural and synthetic antioxidants have been used as chain-breaking inhibitors of the peroxyl radical. For example, α-tocopherol (α-Toc) and 2,6-di-*t*-butyl-4-methylphenol (BHT) are much used as natural and synthetic phenolic antioxidants, respectively.

In our earlier studies of the antioxidant activity of phenol derivatives, we suggested that the heteroatom substituent at the position para to the hydroxyl group may be important in increasing antioxidant activity. Antioxidant activity in the induction period (IP, min) is summarized in Chart 1. 4,4′-Thiodiphenol and 4,4′-oxydiphenol, both with a heteroatom in the para position, had stronger potency than 4,4′-methylenediphenol.[2] Similarly, 9*H*-xanthene-2,7-diols, with a fused heterocyclic ring system, had stronger antioxidant activity than methylenediphenols.[3,4] The structural characteristics of 9*H*-xanthene-2,7-diol include having two phenolic moieties and an ether-type oxygen at the position para to the hydroxyl groups. On the other hand, Burton et al.[5] reported that stabilization of the phenoxyl radical of α-Toc and related compounds depends on the extent of orbital overlap between the 2p lone pair on the para oxygen atom and the aromatic π electron system. We therefore expected that 2,3,7,8-thianthrenetetrols would act as better antioxidants than α-Toc or 9*H*-xanthene-2,7-diols, since they have catechol moieties and two thioether-type sulfurs at the position para to the hydroxyl groups.

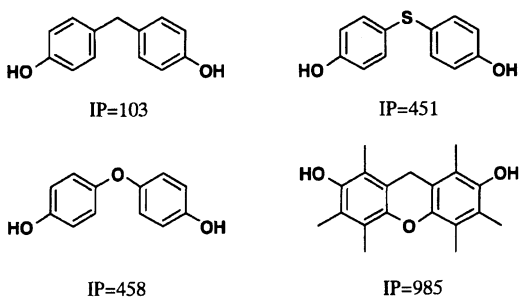

Chart 1.

In this work, we studied the antioxidant activities of compounds **1a**—**c** (Chart 2). We also compared the effects of two other compounds, catechol (**2**) and thianthrene (**3**), which are structurally related to **1** in view of their structure-activity relationships.

Results and Discussion

Figure 1 shows the results of the oxidation of tetralin in *t*-butyl alcohol initiated by 2,2′-azobisisobutyronitrile (AIBN) in the presence of thianthrenetetrol **1a**—**c** and of a control test done in the absence of an antioxidant. The control and **3** had no induction period. When antioxidant **1** was added to the reaction mixture, the oxidation was suppressed and there was an induction period. Under the same conditions, catechol **2** suppressed the oxidation but the induction period was smaller than that with **1**. Table 1 lists the length of the IP of compounds **1**—**3**, BHT, and α-Toc, the most ac-

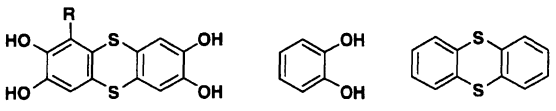

Chart 2.

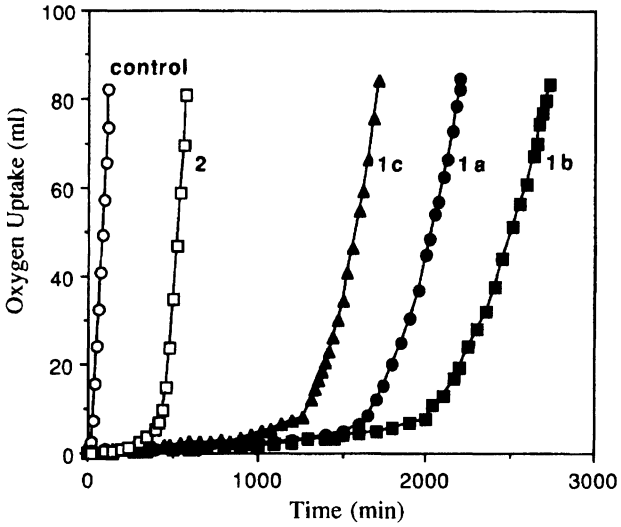

Fig. 1. Inhibition of oxidation of tetralin by thianthrenes and catechol.

Table 1. Antioxidant Activities of Compounds **1**—**3**, α-Toc and BHT

Compound	IP	Rate of oxygen consumption	n
	min	ml min^{-1}	
1a	1873	0.22	8.01
1b	2261	0.16	8.91
1c	1438	0.29	6.94
2	421	0.50	2.96
3	30	0.80	—
BHT	376	0.48	2.67
α-Toc	345	0.46	2.24
Control	13	0.56	—

tive natural antioxidant. The IP decreased in the order **1b**>**1a**>**1c**>**2**>BHT, α−Toc>**3**. In particular, compound **1b** is the most active antioxidant, being 5.4 times more active than **2** and 6.6 times more active than α-Toc.

The stoichiometric factors (n) for all of the antioxidants examined are listed in Table 1. Compounds **1** have higher stoichiometric factors, 6.9—8.9, than those of other compounds. This finding means that these three compounds **1a**—**c** react with 7—8 peroxyl radicals.

Table 1 shows also the rates of oxygen consumption after the IP. The rates of oxygen consumption with compounds **1** were lower than the rate with BHT or α-Toc. When all ArO· radicals are consumed, the rate of autoxidation should be equal to that in the control test. In fact, the rates of oxygen consumption after IP of BHT and α-Toc are close to the control value. The rates of compounds **1a**—**c** are lower than the control value. This result means that the ability to retard oxidation persists after IP is over due to transformation products of the antioxidant.

In summary, the heteroatom substituents at the para position, in combination with hydroxyl groups, may be important for antioxidant activity. There is no evidence that these factors increase peroxyl radical trapping ability of **1**, but we make the assumption that the phenoxyl radical will be stabilized by delocalization of the unpaired electrons to the lone pairs of the sulfur atoms.

Experimental

General. Melting points were measured on a Yanaco MP-J3 micromelting apparatus and are uncorrected. Infrared spectra were produced with a grating infrared spectrophotometer (Perkin–Elmer, model 1600) with a potassium bromide pellet. Nuclear magnetic resonance spectra were recorded with a JEOL GSX-400 spectrometer operating at 400 MHz for ^{1}H and 100.6 MHz ^{13}C in $(CD_3)_2CO$, and chemical shifts are in reference to TMS.

Assay of Antioxidant Activity. The volume of oxygen consumption was measured as a function of time under 760 Torrs (1 Torr=133.322 Pa) of O_2 with 50 g of tetralin/*t*-butyl alcohol (10:1) containing an antioxidant (5×10^{-5} mol) and AIBN as the initiator (5×10^{-4} mol).[4] The oxidation temperature was kept at 60±0.1°C. The IP was found graphically[6,7] on 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 found at 60 °C by the IP method.[8,9]

Materials. Tetralin used for the test was washed with concentrated sulfuric acid, aqueous sodium hydrogencarbonate, and water, and was dried over anhydrous sodium sulfate and distilled under nitrogen before use. AIBN was recrystallized from methanol.

2,3,7,8-Tetramethoxythianthrene was synthesized by the method of Weiß and Klar.[10] 2,3,7,8-Tetramethoxythianthrene was demethylated with HBr in acetic acid and then worked up in the usual way. The residue was purified by silica-gel column chromatography to give **1a** as a colorless solid. 1-Methyl-2,3,7,8-thianthrenetetrol (**1b**) was synthesized by the direct Friedel–Crafts reaction of 3-methylcatechol and catechol **2** with sulfur dichloride in ether. Short-column (silica-gel) chromatography followed by recrystallization from methanol gave a pure product. For the synthesis of **1c**, 2,3,7,8-tetramethoxythianthrene was lithiated with BuLi and then alkylated with bromoethane. Demethylation of the resulting 1-ethyl-2,3,7,8-tetramethoxythianthrene with HBr in acetic acid gave **1c**.

The 2,3,7,8-thianthrenetetrols **1** were identified from the following data.

2,3,7,8-Thianthrenetetrol (1a): Mp 288.0—289.1 °C; ^{13}C NMR δ=116.2, 127.3 and 146.0; ^{1}H NMR δ=6.95 (s, 4H), 8.26 (s, 4H); IR 3345 (br, s), 1587 (m), 1479 (s), 1415 (s), 1332 (m), 1266 (s), 1211 (m), and 1173 (m) cm^{-1}. Found: C, 51.42; H, 2.88%. Calcd for $C_{12}H_8O_4S_2$: C, 51.42; H, 2.88%.

1-Methyl-2,3,7,8-thianthrenetetrol (1b): Mp 258.5—259.5 °C; ^{13}C NMR δ=14.1, 113.7, 116.1, 116.7, 124.9, 126.5, 127.5, 128.2, 128.5, 144.5, 144.9, 146.1, and 146.3; ^{1}H NMR δ=1.91 (s, 3H), 6.79 (s, 1H), 6.85 (s, 1H), 6.91 (s, 1H), 7.44 (s, 1H), 8.18 (s, 2H), and 8.60 (s, 1H); IR 3317 (br, s), 1592 (m), 1475 (m), 1411 (s), 1333 (m), 1267 (s), and 1170 (s) cm^{-1}. Found: C, 52.89; H, 3.44%. Calcd for $C_{13}H_{10}O_4S_2$: C, 53.04; H, 3.42%.

1-Ethyl-2,3,7,8-thianthrenetetrol (1c): Mp 206.2—207.0 °C; ^{13}C NMR δ=14.3, 22.1, 113.8, 115.9, 116.0, 126.2, 126.8, 127.5, 127.8, 128.4, 143.9, 144.8, 145.9, and 146.1; ^{1}H NMR δ=1.02 (t, J=7.3 Hz, 3H), 2.79 (q, J=7.3 Hz, 2H), 6.80 (s, 1H), 6.83 (s, 1H), 6.92 (s, 1H), and 8.16 (br, s, 1H); IR 3408 (br, s), 1594 (m), 1485 (m), 1410 (s), 1322 (m), and 1271 (s) cm^{-1}. Found: C, 54.32; H, 4.01%. Calcd for $C_{14}H_{12}O_4S_2$: C, 54.53; H, 3.92%.

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