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PHOTOINDUCED REACTIONS—LVIII

ADDITION OF SINGLET OXYGEN TO 4,6-DI-t-BUTYLRESORCINOL AND ITS DERIVATIVES[1,2]

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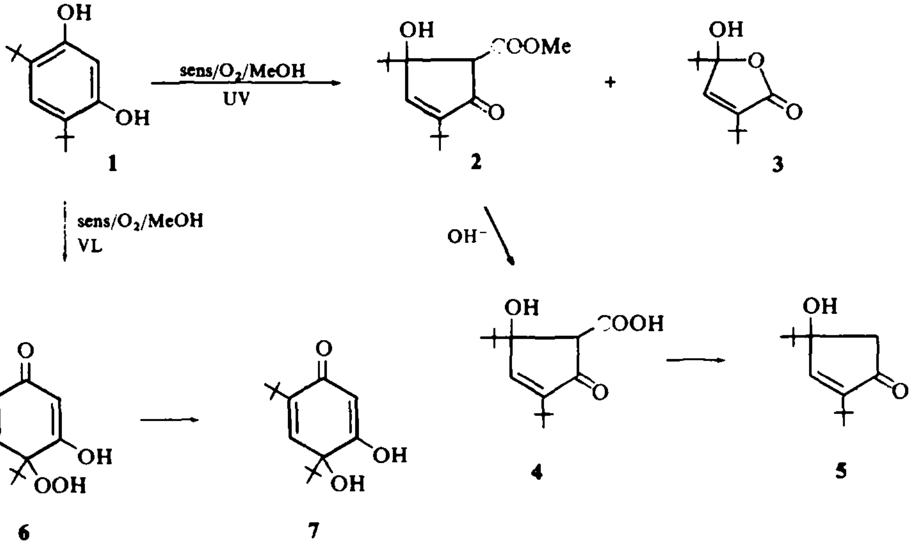
Abstract— The photosensitized oxygenation of 4,6-di-t-butylresorcinol (**1**) and its methyl ethers **8** and **10** in methanol have been examined. Resorcinol (**1**) affords ketoester **2** and lactone **3**. Photosensitized oxygenation of monoethyl ether **8** and dimethyl ether **10** gives hydroperoxide **9** and epoxy-ketone **11**, respectively; participation of singlet oxygen in these reactions is demonstrated. A mechanism involving 1,4-cycloaddition of singlet oxygen to the aromatic nucleus is proposed for the formation of **9** and **11**, but a mechanism involving a phenoxy radical intermediate **14** for the formation of **2** and **3**.

IN THE PRECEDING PAPER on biological oxygenations catalyzed by dioxygenases, we reported that photosensitized oxygenation, 3,5-di-t-butylcatechol and its monomethyl ether, caused oxidative ring cleavage.[1] The primary process in these reactions was demonstrated to be hydrogen abstraction from a phenol by the triplet excited sensitizer and singlet oxygen.[1,3] Here we report the first example of the addition of singlet oxygen to monocyclic aromatic rings. Addition of singlet oxygen to a monocyclic benzene derivative has not been reported, although the addition to polynuclear aromatic compounds has been well known in the field of singlet oxygen chemistry.[4,5]

When a solution of 4,6-di-t-butylresorcinol (**1**) in MeOH containing rose bengal as sensitizer was irradiated with a high-pressure mercury lamp through Pyrex filter (>280 nm) under bubbling oxygen, about two moles of oxygen were absorbed. Among a complex product mixture two crystalline compounds, ketoester **2** ($C_{15}H_{24}O_4$ 16%) and lactone **3** ($C_{12}H_{20}O_3$ 6%) were isolated by silica gel chromatography. Keto ester **2** exhibited the following spectral properties; λ_{max}^{EtOH} 228 nm (ε 8100); ν_{max}^{KBr} 3560, 1740, 1695 cm^{-1}; τ ($CDCl_3$; TMS) 3·05 (1H), 6·25 (3H), 6·50 (1H), 6·68 (1H), 8·80 (9H) (all singlets). Ketoester **2** was transformed by alkaline hydrolysis to crystalline ketoacid **4** ($C_{14}H_{22}O_4$), which easily decarboxylated to give ketone **5** ($C_{13}H_{22}O_2$) indicating a β-ketoacid moiety in **4**; λ_{max}^{EtOH} 224 nm (ε 8400); $\nu_{max}^{CCl_4}$ 3610, 1710 cm^{-1}; τ ($CDCl_3$; TMS) 2·90 (s, 1H), 7·20 (d, 1H, *J*18 Hz), 7·72 (d, 1H, *J*18 Hz), 8·10 (s, 1H), 8·80 (s, 9H), 9·02 (s, 9H). Structure **3** was assigned for the lactone from its spectral properties; λ_{max}^{EtOH} 210 nm (ε 9800); ν_{max}^{KBr} 1740, 3480 cm^{-1}; τ ($CDCl_3$; TMS) 3·35 (1H), 5·55 (1H), 8·80 (9H), 9·00 (9H) (all singlets).

When a methanolic solution of **1** was irradiated by visible light (tungsten-bromine lamp) under oxygen, one mole of oxygen was consumed. Hydroperoxide **6** was found to be the only product and neither **2** nor **3** could be detected in the mixture. **6** was identified by converting it to a quinol (**7**)[6] with triphenylphosphine. The result indicates that UV irradiation may play an important role in the formation of **2** and **3** from **1**.



Photosensitized oxygenation (rose bengal/visible light) of the monoethyl ether **8** of 4,6-di-t-butylresorcinol (**1**) in MeOH afforded hydroperoxide **9**[6] (48%). The dimethyl ether **10** also suffered photosensitized oxygenation to give epoxy-ketone **11** (70%). This is a contrast to the previous finding that the dimethyl ethers of 3,5-di-t-butylpyrocatechol and 2,5-di-t-butylhydroquinone resisted photosensitized oxygenation.[1] Epoxy-ketone **11** showed following spectral properties; λ_{max}^{EtOH} 262 nm (ε 9700); $\nu_{max}^{CHCl_3}$ 3400–3500, 1665, 1625 cm^{-1}, indicative of an intramolecular hydrogen bonding; τ ($CDCL_3$; TMS) 4·78 (1H), 6·25 (1H), 6·31 (3H), 7·35 (1H, OH), 8·86 (9H), 8·99 (9H) (all singlets). Zn/AcOH reduction of **11** gave **8** in 70% yield. Hydrogenation (Pd/C) of **11** gave an enone **12** (35%); λ_{max}^{EtOH} 250 nm (ε 15400); $\nu_{max}^{CHCl_3}$ 3500, 1670, 1620 cm^{-1}; τ ($CDCl_3$; TMS) 4·75 (s, 1H), 6·35 (s, 3H), 7·60 (s, 3H), 7·40 ~ 8·30 (m, 3H), 8·90 (s, 9H), 8·93 (s, 9H), which was also obtained by hydrogenation of **13**.[6] The above results led us to assign structure **11** for the epoxy-ketone.*

To ascertain the possibility of the participation of singlet oxygen in the photosensitized oxygenation of **8** and **10** we carried out the oxidation of these compounds with chemically generated oxygen. Reaction of **8** and **10** with hydrogen peroxide–hypochlorite[8] gave **9** (70%) and **11** (75%) respectively. Relative rates of **8** and **10** to tetramethylethylene for photosensitized and chemical oxygenation were determined by competitive reaction[8] (Table 1).

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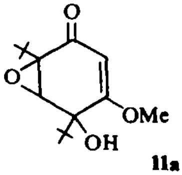
* The formation of **8** and **12** from the epoxy-ketone can also be explained by an alternative structure **11a**.[7] However, the existence of intramolecular hydrogen bonding in its IR spectrum supports **11** rather than **11a**.

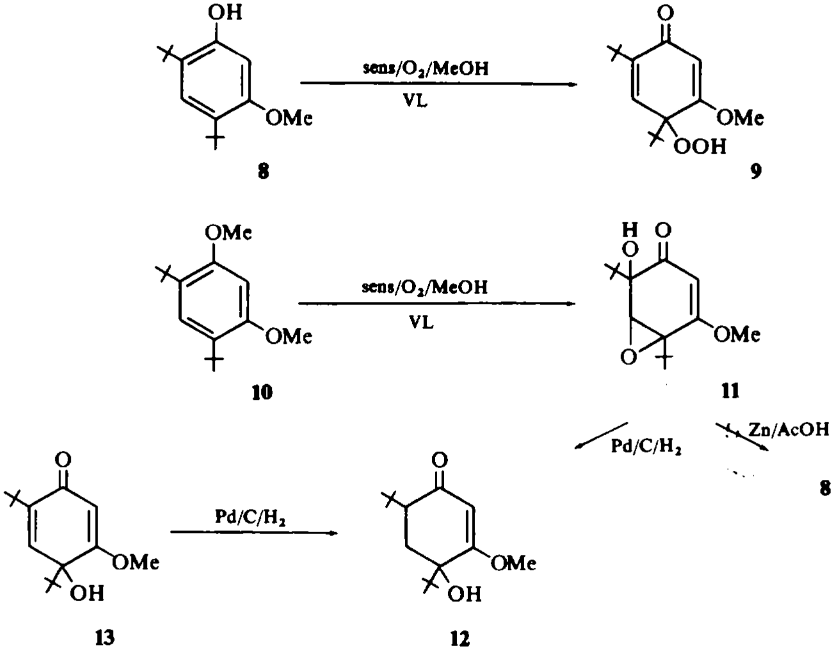


11a

TABLE 1. RELATIVE REACTIVITIES TO TETRAMETHYLETHYLENE (1·0)

Compounds	Photooxygenation	Chemical oxygenation
8	0·0070	0·0067
10	0·0023	0·0030

Reactivities of **8** and **10** for photosensitized and chemical oxygenations are virtually the same. Therefore, it can be concluded that the reactive species in the photosensitized oxygenation of **8** and **10** is singlet oxygen, presumably $^1\Delta$ g state.[8] Oxidation with hydrogen peroxide–hypochlorite could not not be applied to **1**, since **1** easily reacted with hypochlorite alone. On the other hand, when **1** was treated with singlet oxygen generated by thermolysis of 9,10-diphenylanthracene 9,10-peroxide in C_6H_6—MeOH under N_2,[9] neither **2** nor **3** was obtained. However, ketoester **2** could be detected in the reaction mixture when the reaction was carried out under oxygen-bubbling. The results indicate that not only singlet oxygen but also sufficient amounts of ground state oxygen are necessary for formation of **2**.



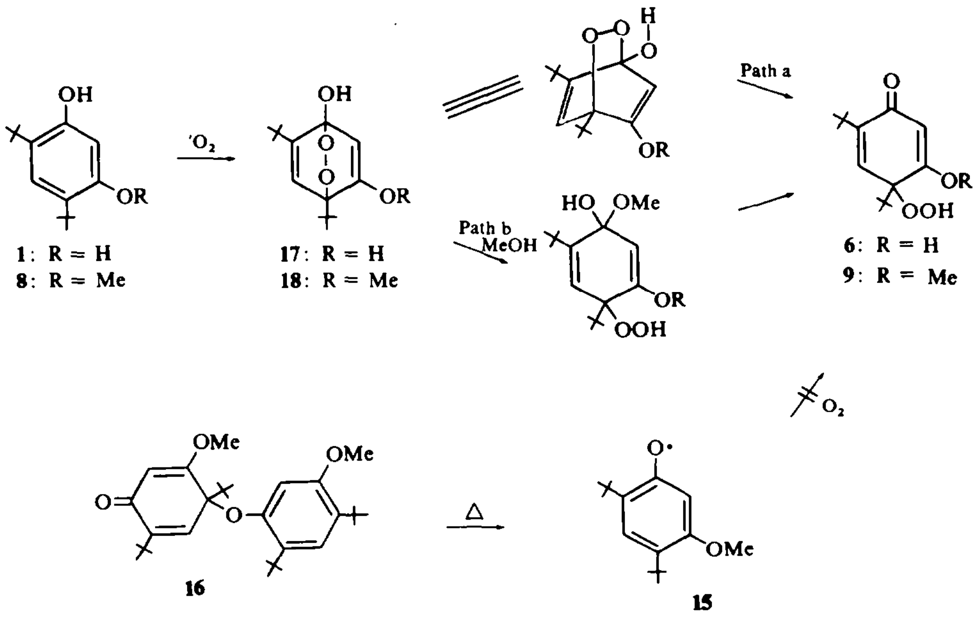
We have previously showed that in photosensitized oxygenation, either singlet oxygen or the triplet excited sensitizer is capable of hydrogen abstraction from a phenol.[1,3] Consequently, it may be possible that the initial attack of singlet oxygen and or the triplet sensitizer to **1** and **8** leads to the formation of phenoxy radicals **14** and **15**, respectively (Scheme 1 and 3). In order to ascertain this possibility, autooxidation of stable radical **15** generated by thermolysis of dimer **16**[10] in MeOH was examined. The main product was found to be **8** but no hydroperoxide **9** could be detected. This result and the finding that dimethyl ether **10** was reactive to singlet oxygen indicate that the phenoxy radical **15** may not be involved in the photosensitized oxygenation of **8**.

On the other hand, in the photooxygenation of **1** under UV irradiation a phenoxy radical **14** would be an intermediate for the formation of **2** and **3**. In this case **14** can be directly formed from the excited state of **1**[1,11] or by hydrogen abstraction from **1** with singlet oxygen and/or the triplet sensitizer.[1,3]

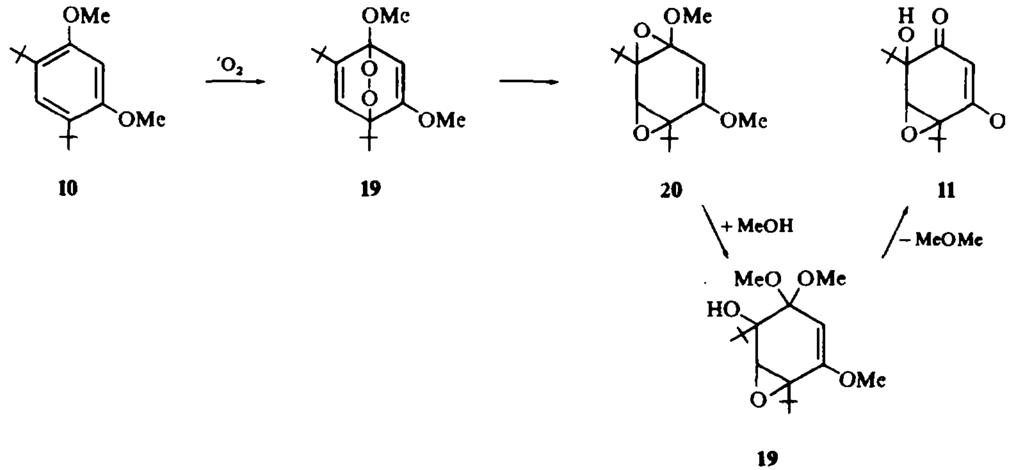
We can now formulate a possible pathway for the formation of **6** and **9** (Scheme 1). The first step may involve 1,4-cycloaddition of singlet oxygen to the aromatic ring of **1** and **8** giving endo-peroxides **17** and **18**, respectively. The peroxide-oxygen atom of **17** may abstract a hydrogen intramolecularly to give **6** and **9** (a),[12] or the peroxide **17** may be solvolyzed with MeOH followed by the loss of MeOH to give **6** and **9** (b). The formation of **11** from **10** may be explained by a similar mechanism involving 1,4-cycloaddition of singlet oxygen to form an *endo*-peroxide **19** (Scheme 2). The *endo*-peroxide[19] may rearrange thermally[4] rather than photochemically[13–15] to bis-epoxide **20** which is then solvolyzed to give **11**. Similar 1,4-cycloaddition of singlet oxygen to methoxybenzenes has been recently demonstrated.[16]

The formation of **2** and **3** from **1** may be rationalized by a mechanism involving a phenoxy radical **14** (Scheme 3). Singlet oxygen and the excited triplet sensitizer under visible light irradiation, and the excited state of **1** under UV irradiation could be responsible for the formation of radical **14**. Ground state triplet oxygen may react with **14** to give a hydroperoxy radical **21**, which then transforms to **22**. The key intermediate **23**, which can be formed from **22** by hydrogen abstraction, may be

SCHEME 1

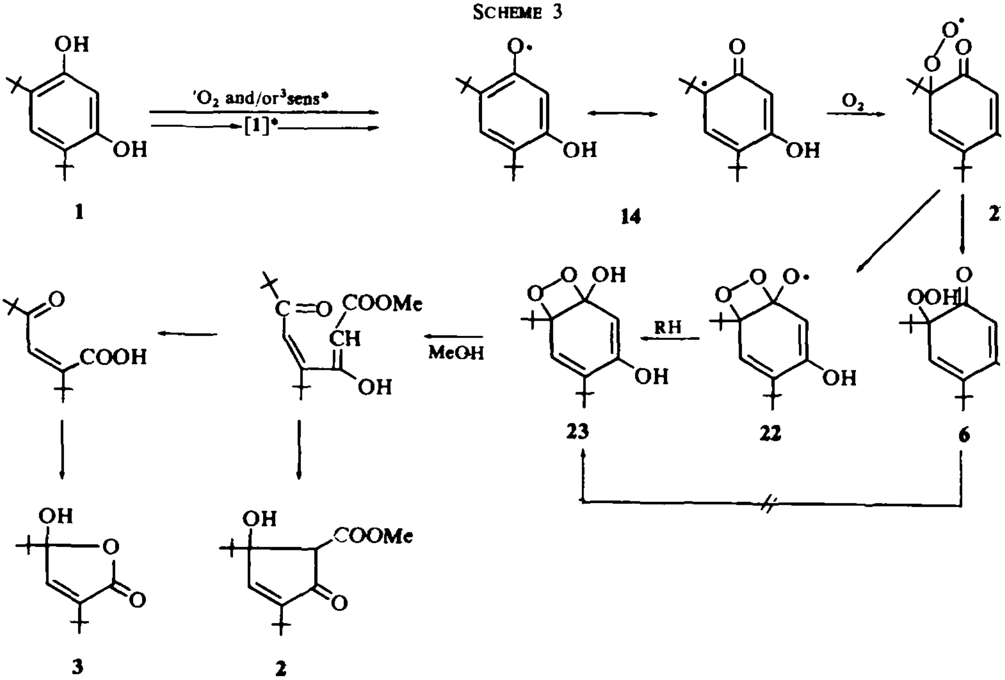


SCHEME



converted to **2** with participation of MeOH and by further oxidative cleavage to **3**. Another possible intermediate **6** was also considered. However, it is unlikely that **6** is the intermediate for the formation of **2**, since **6** gave neither **2** nor **3** but a complex mixture of products upon similar photooxygenation under UV irradiation. The present result represents a possible model for the enzymatic cleavage of homogetistic acid by an oxygenase.[17]

SCHEME 3



EXPERIMENTAL

Photosensitized oxygenation of 4,6*-di-t-butylresorcinol* **1**. *A. UV irradiation.* A solution of **1** (5·0 g) and rose bengal (150 mg) in MeOH (400 ml) was irradiated with a 450 W high-pressure mercury lamp through a Pyrex water-cooling jacket under bubbling oxygen. After 6·5 hr, 1260 ml (2·3 mol equiv.) of oxygen was consumed. The mixture was evaporated to dryness and the residue chromatographed on silica gel (210 g). Elution with $CHCl_3$ and $CHCl_3$-acetone (97:3) gave 2·73 g of a semicrystalline liquid which was further chromatographed on alumina (110 g). Elution with benzene gave 0·96 g (16%) of **2** which on recrystallization from light petroleum gave colourless crystals, m.p. 96·5°; *m/e* 269 (M + 1 peak). (Found: C, 67·33; H, 8·98. Calc. for $C_{15}H_{24}O_4$: C, 67·13; H, 9·02%). Further elution with ether gave 0·30 g (6%) of **3** which on recrystallization from light petroleum gave colourless crystals, m.p. 97°; *m/e* 212 (M peak). (Found: C, 67·98; H, 9·80. Calc. for $C_{12}H_{20}O_3$: C, 67·89: H, 9·5%).

B. By visible light irradiation. A solution of **1** (2·0 g) and rose bengal (50 mg) in MeOH (200 ml) was irradiated with a tungsten-bromine lamp through a window glass cooling jacket under bubbling oxygen. The reaction vessel was cooled in an ice-bath during irradiation. After 3 hr, 1 mole equivalent of oxygen was absorbed. TLC of the mixture showed only one spot which has the same R_f value as that of the hydroperoxide **6**.[6] Attempts to isolate **6** were unsuccessful. An aliquot of the mixture was reduced by the addition of triphenylphosphine at 0°, until a peroxide test with iodide became negative. From the reduction mixture, **7** was isolated by prep. TLC and identified by IR comparison with an authentic sample.[6]

Alkaline hydrolysis of **2**. A solution of **2** (235 mg) in EtOH (20 ml) was mixed with 1N NaOH (5 ml) and the mixture heated on a water-bath. The hydrolysate was evaporated and acidified with dil. HCl to give a precipitate which was dissolved in ether. Dilution of the ether solution with light petroleum gave **4** as colourless crystals (73 mg) m.p. 99–100°. (Found: C, 66·54; H, 9·07. Calc. for $C_{14}H_{22}O_4$: C, 66·11; H, 8·72%). The mother liquor was evaporated and the residue separated by prep. TLC (silica gel, benzene–AcOH, 5:2) to give an additional **4** (4 mg) and **5** (71 mg) which on recrystallization from light petroleum gave colourless crystals, m.p. 78°. (Found: C, 74·39; H, 10·46. Calc. for $C_{13}H_{22}O_2$: C, 74·24; H, 10·54%).

Photosensitized oxygenation of 3*-methoxy-*4,6*-di-t-butylphenol* **8**. A solution of 3-methoxy-4,6-di-t-butylphenol (**8**)[10] (2·0 g, 8·1 mmole) in MeOH (300 ml) containing rose bengal was irradiated by a tungsten-bromine lamp through a window glass cooling jacket at room temp. During irradiation oxygen was circulated through the solution and the oxygen consumption determined manometrically. After oxygen (8·9 mmole) had been consumed, the mixture was treated with charcoal and was evaporated *in vacuo* below 60°. Recrystallization of the residue from n-hexane gave hydroperoxide **9** (1·1 g, 48%) as needles, m.p. 151–153°, (lit,[6] 163° ~ 165°), identified by IR and NMR spectrum comparison with an authentic sample prepared by the method of Musso.[6] Triphenylphosphine reduction of **9** in ether solution gave 1-hydroxy-6-methoxy-1,3-di-t-butyl-cyclohexadiene-(2,5)-one-(4) (**13**)[6] (56%).

Photosensitized oxygenation of dimethyl ether **10** *of* 4,6*-di-t-butyl-resorcinol.* A solution of **10** (3·0 g, 12 mmole) in MeOH (500 ml) containing rose bengal (30 mg) was irradiated for 5 hr as described above until oxygen (270 ml, 12 mmole) was consumed. The mixture was treated with charcoal. After solvent removal, the residue was recrystallized from acetone. Recrystallization gave **11** (2·2 g, 70%); m.p. 183°; mass spectrum (*m/e*), 268 (parent peak). (Found: C, 67·11; H, 9·07. Calc. for $C_{15}H_{24}O_4$: C, 67·13; H, 9·02%).

Reduction of **11** *by zinc dust-acetic acid.* The epoxide **11** (50 mg) was heated with Zn dust in refluxing AcOH for 3 hr. The mixture was poured into cold water and ether extracted. Evaporation of the ether layer, the residue (450 mg) was chromatographed on silica gel (25 g). Elution with benzene (200 ml) gave **8** (0·28 g, 68%), identified by IR.

Catalytic hydrogenation of **11**. A solution of **11** (600 mg, 2·2 mmole) in MeOH (100 ml) was shaken with 1·0 g of 10% Pd/C at room temp under H_2 for 3 hr. After consumption of hydrogen (95 ml, 4·1 mmole), the catalyst was filtered and the filtrate evaporated to dryness. Recrystallization from n-hexane gave **12** (200 mg 35%); m.p. 136–137°. (Found: C, 70·59; H, 10·46; Calc. for $C_{15}H_{26}O_3$: C, 70·83: H, 10·30%).

Catalytic hydrogenation of **13**. A solution of **13** (200 mg, 0·8 mmole) in MeOH (50 ml) was hydrogenated as above. VPC analysis of the mixture showed it to contain at least five compounds. A main product, which was isolated by prep VPC, was identified as **12** by IR and NMR.

Autoxidation of phenoxy radical **15**. Phenoxy radical was generated by thermolysis of dimer **16**.[10] A solution of **16** (200 mg) in abs MeOH (100 ml) was bubbled with oxygen at room temp for 2 days. The mixture was found by TLC to consist of unreacted **16** (~50%), methoxyphenol **8** (~20%) and three unidentified compounds, no hydroperoxide **9** could be detected.

Oxidation of **8** *with hydrogen peroxide and hypochlorite.* The reaction was carried out according to the procedure of Foote *et al.*[8] A soln of **8** (1·0 g, 4·4 mmole) in MeOH (30 ml) was cooled in an ice-bath, and

30% H_2O_2 (2·2 ml, 20 mmole) added. To the mixture 9% NaOCl aq. (12 ml, 15 mmole) was added dropwise under stirring over 1 hr. The mixture was diluted with H_2O (200 ml) and ether extracted. VPC analysis (Apiezon, 190°, 2·5 kg/cm^2) of the extract showed it to contain unreacted **8** (0·61 g), hydroperoxide **9** (0·28 g 70%), and unidentified compounds.

Oxidation of **10** *with hydrogen peroxide and hypochlorite.* A solution of **10** (1·25 g, 5 mmole) in MeOH (500 ml) was treated with 30% H_2O_2 (5 ml, 45 mmole) and 9% NaOCl aq. (28 ml, 33 mmole) as described above. The mixture was diluted with H_2O (50 ml) and ether extracted. The extract was chromatographed on silica gel (30 g). Elution with benzene (500 ml) gave unreacted **10** (1·1 g, 88% recovery). Further elution with $CHCl_3$-acetone (10:1: 600 ml) gave **11** (110 mg, 75% on the basis of reacted **10**).

Relative reactivity to singlet oxygen. (A) Photooxygenation. Relative rate of photooxygenation was determined by competitive reactions according to the method of Foote *et al.*[8] To a solution of each substrate (0·05 M) in MeOH containing an equimolar amount of linalool was added rose bengal as a sensitizer. Under oxygen atmosphere the solution was irradiated as described above. Within 50% conversion of the substrate, the disappearance of the substrate and linalool were analyzed by VPC (Silicon DC 550) at 150°. Relative reactivity of linalool to tetramethylethylene (1·0) was independently determined by the competitive reaction.

(B) Hydrogen peroxide and hypochlorite. A solution (0·05 M) of the substrate and linalool in MeOH was oxidized with H_2O_2 and hypochlorite by the same procedure as mentioned previously. The disappearance of each substrate was analyzed by VPC.

Oxidation of **1** *with singlet oxygen generated from* 9,10-*diphenylanthracene* 9,10-*peroxide.* A solution of **1** (2·04 g, 9·2 mmole) and 9,10-diphenylanthracene 9,10-peroxide[9] (3·07 g, 8.5 mmole) in C_6H_6-MeOH (1:1, 40 ml) was refluxed for 60 hr under N_2. Neither **2** nor **3** was detected by TLC of the mixture which consisted of many products. A similar experiment was carried out under oxygen-bubbling. Chromatographic separation of the products on silica gel gave 30 mg of **2** identified by IR and m.m.p. The other products were not isolated in a pure form.

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