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PHOTOINDUCED REACTIONS. XXXI. PHOTOOXIDATIVE RING-CLEAVAGE OF DIHYDRIC PHENOLS AS POSSIBLE MODELS FOR BIOLOGICAL OXYGENATION[1]

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Activation of oxygen in the action of dioxygenases, by which an oxygen molecule is incorporated into a substrate, is undoubtedly interesting problem in both biological and chemical points of view.[2] We have shown that a cleavage of 3-hydroxyflavones by photosensitized oxygenation, possibly involving singlet oxygen, provides a model for the enzymatic degradation of quercetin by the action of a dioxygenase.[3] We wish to report additional examples providing models for the enzymatic cleavage of aromatic ring.[4]

When a solution of 4,6-di-t-butylresorcinol (**1**) in methanol containing rose bengal was irradiated (> 280 mμ) under bubbling oxygen, about two moles of oxygen was absorbed. Chromatographic separation gave two crystalline products; a ketoester **2** (16%), $C_{15}H_{24}O_4$,[5] mp. 96.5°, and a lactone **3** (6%), $C_{12}H_{20}O_3$, mp. 97°. The ketoester [λ_{max}^{EtOH} 228 mμ (ε 8100); ν_{max}^{KBr} 3560, 1740, and 1695 cm^{-1}; n.m.r.($CDCl_3$): τ 3.05(1H), 6.25(3H), 6.50(1H), 6.68(1H), 8.80(9H), and 9.00(9H)(all appear as singlet)] was transformed by mild alkaline hydrolysis to a ketoacid **4**, $C_{14}H_{22}O_4$, mp. 99°, [ν_{max}^{KBr} 3450, 1720, and 1690 cm^{-1}; n.m.r.($CDCl_3$): τ 2.75(s,1H), 3.50-4.20 (broad s, 2H), 6.35(s,1H), 8.70(s, 9H), and 8.95(s, 9H)] which was easily decarboxylated to give a ketone **5**, $C_{13}H_{22}O_2$, mp. 78.4°, [λ_{max}^{EtOH} 224 mμ (ε 8400); ν_{max}^{CCl4} 3610 and 1710 cm^{-1}; n.m.r. ($CDCl_3$): τ 2.90(s, 1H), 7.20(d, 1H, J=18 cps), 7.72(d, 1H, J=18 cps), 8.10(s, 1H), 8.80(s, 9H), and 9.02(s, 9H)]. The spectral properties of these compounds and the sequence of reactions led us to assign structure **2** for the ketoester. Structure **3** was assigned for the lactone from its spectral properties [λ_{max}^{EtOH} 210 mμ (ε 9800); ν_{max}^{KBr} 3480 and 1740 cm^{-1}; n.m.r. ($CDCl_3$): τ 3.35(1H), 5.55(1H), 8.80(9H), and 9.00(9H)(all appear as singlet)].

When the photooxygenation of **1** was carried out without sensitizer (> 280 mμ), about 1.5 moles of oxygen was slowly consumed after a long induction period. The products were found to be a complex mixture from which **2** and **3** could not be detected. In the preceding communication,[6] we have provided evidence that singlet oxygen and the excited triplet sensitizer are capable of hydrogen abstraction from a phenol in its photosensitized oxygenation. Consequently it may be considered that the initial attack of singlet oxygen and/or the excited sensitizer are responsible for the formation of **2** and **3**. When reaction of **1** with singlet oxygen generated from 9,10-diphenylanthracene 9,10-peroxide[7] was carried out in a mixture of benzene and methanol under nitrogen, neither **2** nor **3** was obtained, whereas **2** could be detected from the reaction mixture when the reaction was carried out under oxygen. These results indicate that sufficiently high oxygen pressure is necessary for the formation of **2**.

We can now formulate possible reaction pathways as shown in Scheme 1. The first step involves hydrogen abstraction from **1** by singlet oxygen and/or the excited triplet sensitizer giving a phenoxy radical **6** to which the ground-state triplet oxygen adds to form **8** via **7**. The key intermediate **9**, which is formed from **8** by hydrogen abstraction, is converted to **2** with participation of the solvent methanol and to **3** by further oxidative cleavage. Another possible intermediate **10** can be eliminated, since the known hydroperoxide **10**,[7] when treated under similar conditions to those for the photosensitized oxygenation of **1**, did not give **2** and **3** but gave a complex mixture of products.

The present result represents a possible model for the enzymatic cleavage of homogentisic acid by a dioxygenase.[9] It should be noted that the photooxidative cleavage of **1** is initiated by hydrogen abstraction in contrast with that of 3-hydroxyflavones[3] which is initiated most probably by the addition of singlet oxygen to the substrate.

The second part of this communication deals with a model for pyrocatechase-catalyzed reactions in which pyrocatechase cleaves at 1,2-position to give cis,cis-muconic acid.[10,11] 3,5-Di-t-butylpyrocatechol (**11**) was easily oxidized by rose bengal-sensitized photooxygenation (visible light) and also by irradiation with ultraviolet light (> 280 mμ) without sensitizer. The results were virtually same in both cases. For example, when a methanol solution of **11** was irradiated with ultraviolet light under oxygen, about 1.5 moles of oxygen was absorbed. Chromatographic separation gave two products; an acid **12** (24%), $C_{14}H_{22}O_4$, mp. 133-136°, [ν_{max}^{KBr} 3400-2600, 1750, 1725, 1705, and 1640 cm^{-1}; n.m.r.($CDCl_3$): τ 0.65(s, 1H), 3.33(s, 1H), 7.10(d, 1H, J=13.5 cps), 7.37(d, 1H, J=13.5 cps), 8.84(s, 9H), and 9.06(s, 9H)] and an ester **13** (7%), $C_{15}H_{24}O_4$, mp. 70-72°, [ν_{max}^{KBr} 1748, 1733, and 1634 cm^{-1}; n.m.r.($CDCl_3$): τ 3.25(s, 1H), 6.53 (s, 3H), 7.08(d, 1H, J=13.5 cps), 7.35(d, 1H, J=13.5 cps), 8.80(s, 9H), and 9.05(s, 9H)]. Methylation of the acid with diazomethane gave the ester **13**. From the above results we assigned structure 12 and 13 for the acid and the ester, respectively.

A phenoxy radical intermediate 14 can account for the formation of 12 and 13. In the case of ultraviolet irradiation without sensitizer, 14 may be formed from the excited state of 11.[12] As shown in Scheme 2, the radical 14 reacts with the ground-state triplet oxygen to give a hydroperoxy radical 15 which is converted to a cyclic peroxide 16 either via path a or path b. Cleavage of 16 gives α,β'-di-t-butylmuconic acid (17) which cyclizes to give 12. Alternatively, the radical 14 can disproportionate to 11 and 3,5-di-t-butyl-o-benzoquinone (18) which may be also transformed into 12. However, this possiblity is less favorable, since photooxygenation of 18 under similar conditions proceeded more slowly than that of 11 itself and resulted in a complex mixture of products from which only a small amount of 13 (6%) was obtained but no 12 was detected.

We further examined photooxygenation of 2,5-di-t-butylhydroquinone (19) in the presence of rose bengal (visible light) and also in the absence of sensitizer (> 280 mμ). The results were virtually same in both cases giving two products 20 and 21.[13] It was confirmed that 2,5-di-t-butyl-p-benzoquinone (22) is the intermediate of the reaction as shown in Scheme 3. Details of the reaction will be described in a full paper.

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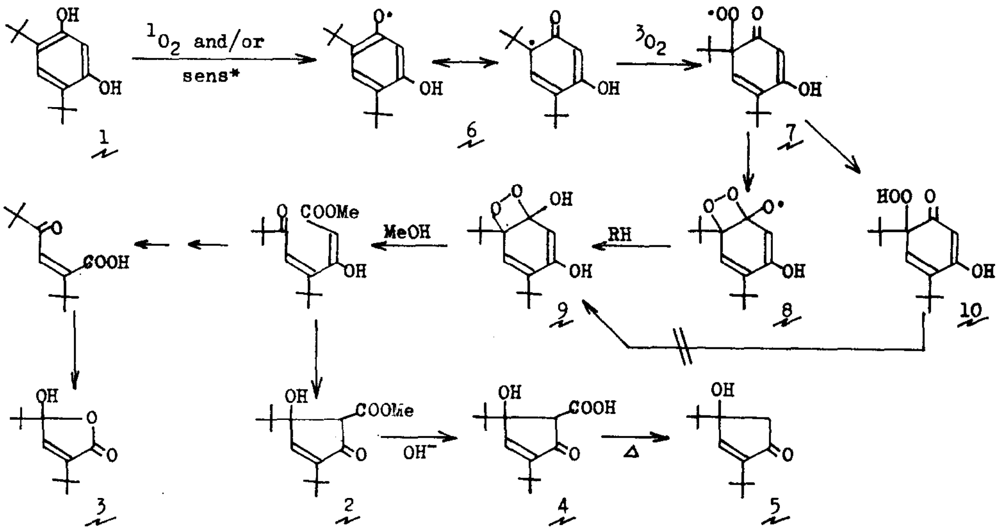
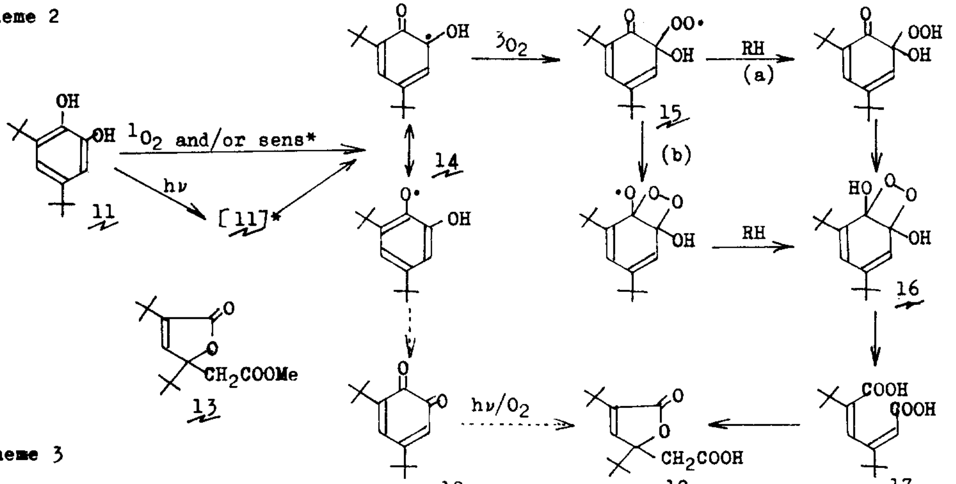
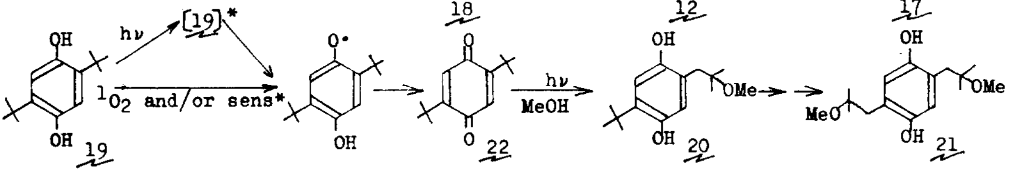
Scheme 1



Scheme 2



Scheme 3



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