

## Dye-sensitized Photo-oxygenation of Chalcones<sup>1</sup>

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The dye-sensitized photo-oxygenation of several chalcones has been examined. Some of the chalcones give rise to degradation products while others lead to flavonol formation. A rational explanation for the observations has been proposed. The study may have a significance in the biogenesis of naturally occurring plant polyphenolics.

The identification of the products from biological oxidations by dioxygenases and from the reactions of singlet molecular oxygen has led to a variety of reactions being proposed as non-enzymatic models for several bio-processes and the subject has received much attention both from chemists and biologists.<sup>2-7</sup> As part of our experiments on biomimetic oxidations we have carried out dye-sensitized photo-oxygenations of several chalcones and the results are presented here.

Chalcones which are considered to be the biogenetic precursors of flavonoids<sup>8</sup> were chosen as the model compounds because they are easily accessible by simple synthetic routes and also because some of the naturally occurring chalcones were available from previous studies.<sup>9</sup> They were also suitable for comparing *in vivo* and *in vitro* oxidations in plant processes.

The chalcones (1)–(9) were synthesized by condensation in the presence of aqueous alkali of the hydroxy or methoxy acetophenones which constitute ring A with the aldehydes which give ring B of the chalcones; for example, 2',4',4-trihydroxychalcone was synthesized by the condensation of 2,4-dihydroxyacetophenone with *p*-hydroxybenzaldehyde in the presence of concentrated alkali solution at ambient temperature. The chalcones were purified on a silica gel column and were recrystallized twice from an appropriate solvent before being subjected to photo-oxygenation. The substrate (1)–(9) was dissolved in methanol or benzene-methanol (1:1) and was photo-oxygenated with Methylene Blue as the sensitizer and irradiation from four 100-W tungsten filament lamps. Air was continuously passed through the solution and the progress of the reaction was followed by t.l.c. When the reaction was about 80% complete the solvent was removed under reduced pressure and the residue extracted with diethyl ether and ethyl acetate. The organic extracts, on column chromatography, gave the products given in the Table.

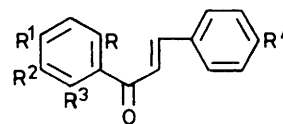
The products obtained can be explained by the presence of singlet oxygen in the dye-sensitized photo-oxygenations, and this was confirmed by carrying out the reactions in the absence of light or of sensitizer in the presence of well known singlet oxygen quenchers such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and  $\beta$ -carotene;<sup>10</sup> under these conditions no reaction took place in the case of compounds (1)–(5), and only a negligible reaction took place with the chalcones (6)–(9). The rate of photo-oxygenation for the first *ca.* 10% of the reaction was enhanced when non-polar solvents, such as carbon tetrachloride, were used and the sensitizer dye was dispersed on silica gel. The reaction was hardly affected by the presence of radical quenchers such as 2,6-di-*t*-butylphenol. These findings are in agreement with the proposed mechanism involving singlet oxygen.<sup>11,12</sup>

It is clear from the Table that the chalcones (6), (8), and (9) on photo-oxygenation give the flavonols (10), (11), and (12); the 2'-hydroxy group of the chalcones, is probably involved as previously suggested<sup>1</sup> (Scheme). Although we were unable to isolate any hydroperoxides, the flavonols being formed directly

Table. Products of photo-oxygenation of chalcones

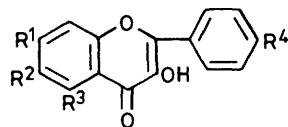
Chalcone	Yield (%) <sup>a</sup>	Time (h)	Products <sup>b</sup>
(1) <sup>c</sup>	40	113	Benzaldehyde (5%), benzoic acid (25%), methyl benzoate (10%)
(2) <sup>c</sup>	42	105	Benzaldehyde, benzoic acid (10%), <i>o</i> -hydroxybenzoylformic acid, methyl benzoate (10%)
(3) <sup>c</sup>	51	93	Benzoic acid (20%), 2,4-dihydroxybenzoic acid, methyl benzoate (15%)
(4) <sup>c</sup>	46	88	Benzaldehyde, benzoic acid (24%), methyl benzoate, 2-hydroxy-4-methoxybenzoic acid (15%)
(5)	42	70	2,4-Dimethoxybenzaldehyde, 2,4-dimethoxybenzoic acid (10%), benzoic acid (28%)
(6)	74	81	5,7-Dihydroxyflavonol (10) (54%)
(7)	56	86	2-Hydroxy-4,6-dimethoxybenzoic acid (10%), benzaldehyde, benzoic acid (15%), methyl benzoate
(8)	64	79	5,4'-Dihydroxyflavonol (11) (26%), <i>p</i> -hydroxymethylbenzoate, <i>p</i> -hydroxybenzoic acid (20%)
(9)	67	78	5-Hydroxy-7,8-dimethoxyflavonol (12) (24%), <sup>d</sup> benzaldehyde, methyl benzoate

<sup>a</sup> The yields are not optimized and are based upon the quantity of uncharged chalcone. <sup>b</sup> Some uncharged chalcone always remained in the case of (1)–(5) and (7). <sup>c</sup> Reaction was only observed after 16 h of irradiation. <sup>d</sup> R. Hansel and D. Ohlendorf, *Tetrahedron Lett.*, 1969, 431.

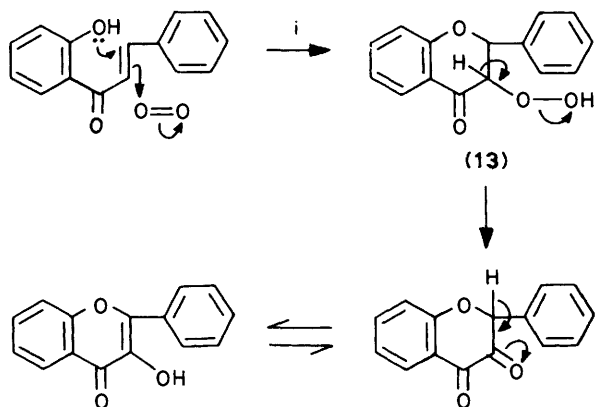


- (1) R = R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
 (2) R = OH, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
 (3) R = R<sup>1</sup> = OH, R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
 (4) R = OH, R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
 (5) R = R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
 (6) R = R<sup>1</sup> = R<sup>3</sup> = OH, R<sup>2</sup> = R<sup>4</sup> = H  
 (7) R = OH, R<sup>1</sup> = R<sup>3</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = H  
 (8) R = R<sup>3</sup> = OH, R<sup>1</sup> = R<sup>2</sup> = H, R<sup>4</sup> = OH  
 (9) R = R<sup>3</sup> = OH, R<sup>1</sup> = R<sup>2</sup> = OMe, R<sup>4</sup> = H

under the experimental conditions, the involvement of a hydroperoxide intermediate could be inferred from the positive KI-AcOH test carried out during the course of the reactions. However, the fact that the chalcones (2)–(5) gave degradation products (given in Table) instead of the expected flavonols



- (10)  $R^1 = R^3 = \text{OH}$ ,  $R^2 = R^4 = \text{H}$   
 (11)  $R^1 = R^2 = \text{H}$ ,  $R^3 = R^4 = \text{OH}$   
 (12)  $R^3 = \text{OH}$ ,  $R^1 = R^2 = \text{OMe}$ ,  $R^4 = \text{H}$

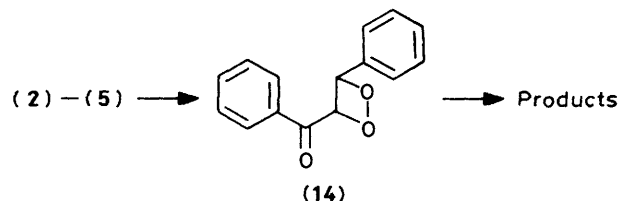


Scheme. Reagents: i, MeOH,  $^1\text{O}_2$

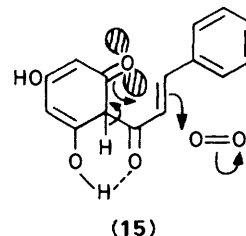
shows that this involvement of the 2'-hydroxy group is not the only factor to be considered. In addition, the AcOH-KI test, which was positive in the cases of (6), (8), and (9), was negative for (2)–(5). The products from (2)–(5) could be explained by the presence of the dioxetane intermediate (14); this would be expected to cleave to give  $\alpha$ -oxoaldehydes as well as aldehydes which may be further oxidized to the corresponding acids and esters (Table). Although the exact mechanism by which these products are obtained from dioxetanes is not clear at the moment, it is probably similar to the cleavage of  $\alpha$ -diketones in methanol solutions in the presence of singlet oxygen, observed previously.

The possibility that the high electron density in ring A controls the course of the reaction was ruled out because compound (7) also gave the degradation products, 2-hydroxy-4,6-dimethoxybenzoic acid, benzoic acid, and methyl benzoate, instead of the expected flavonols. The presence of a 4'-oxygen function also seems to be of little significance since the dimethoxy and dihydroxy chalcones (3)–(5) gave the cleavage products rather than the expected phenolics.

Thus, although the mechanism is still uncertain, we may infer from the results that the dye-sensitized photo-oxygenations of chalcones involve singlet oxygen, that the reaction takes place *via* the keto form of the hydroxychalcone, and that the presence of 2'- and 6'-hydroxy groups is essential for the formation of the flavonols. This last assumption is based on the fact that flavonol formation occurs only with the chalcones (6), (8), and (9). Compound (6) can be considered to be a phloroglucinol derivative which can exist in both the keto and enol forms, as evidenced by deuteration experiments and other reactions. Chalcones (3), (8), and (9) can be treated as resorcinol derivatives which, for energetic reasons, are less like flavonoids in their reactions towards ketonic reagents than the phloroglucinol derivatives; this has been shown by recording their n.m.r. spectra in the presence of  $\text{D}_2\text{O}$  when isotopic exchange was comparatively very slow. Thus, the reaction of the chalcone (6) takes place *via* the triketo form (15), in which the proximity of the 2'-oxo group to the electron density of the



chalcone double bond enhances the reaction of the latter with electrophilic singlet oxygen to yield the hydroperoxide which subsequently produces the flavonol as shown. When the keto



tautomer is not energetically favoured, as in the case of compounds (1)–(5), the usual [2 + 2] reaction with singlet oxygen takes place leading to dioxetane formation and hence to the cleavage products. This conclusion is supported by the fact that (8) and (9) also give flavonols, although accompanied by degradation products because the keto tautomers in this case are energetically less favoured than that of (6) which resembles phloroglucinol.<sup>13</sup> Since most naturally occurring flavonols have an oxygen function at C-5 and C-7, singlet oxygen may participate in some of the enzymatic reactions in the biogenesis of plant polyphenolics. This new aspect of dye-sensitized photo-oxygenations is being investigated in more depth.

## Experimental

**Synthesis of Chalcones.**—A typical synthetic procedure used for the preparation of chalcones is exemplified as follows.

**Synthesis of 2',6',4-trihydroxychalcone.** To a solution of 2,6-dihydroxyacetophenone (6.2 g) and *p*-hydroxybenzaldehyde (5 g) in ethanol (15 ml) was added dropwise an aqueous solution of KOH (20%; 25 ml) while the solution was stirred vigorously and the flask cooled under the cold water tap so as to keep the temperature below 15 °C. The reaction mixture was left at room temperature for 48 h and then diluted with water (20 ml) and extracted with diethyl ether to remove unchanged benzaldehyde. The aqueous portion was acidified with dilute HCl and the orange-yellow solid obtained was flash chromatographed and recrystallized from methanol as orange needles, m.p. 202–204 °C (81%, 8.5 g);  $\nu_{\text{max}}$ . 3 400 (OH) and 1 650 (C=O)  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$ , 12.90 (bs, OH), 7.54 and 6.77 (d, *J* 17 Hz,  $\alpha$ - and  $\beta$ -H), 7.50 and 6.8 (d, *J* 9 Hz, each 2 H, 2-, 6-*H* and 3-, 5-*H*), 7.52 (q, 1 H, 4'-H), 6.40 and 6.20 (q, *J* 9 Hz, 2 H, 3'-, 5'-H) (Found: C, 70.3; H, 4.7.  $\text{C}_{15}\text{H}_{12}\text{O}_4$  requires C, 70.3; H, 4.7%).

**General Procedure for Photo-oxygenation.**—Chalcone (100 mg) was dissolved in methanol or benzene-methanol (1:1) (150 ml) and Methylene Blue ( $10^{-5}\text{M}$ ) was added to it. The solution was irradiated with four 100-W tungsten lamps while air was continuously passed through the solution. When the reaction was about 80% complete (as revealed by t.l.c.), it was stopped and the mixture was distilled under reduced pressure; the residue was extracted with diethyl ether (2  $\times$  100 ml) and ethyl

acetate (3 × 50 ml) and the organic extracts were concentrated on a rotavapour. The residue was subjected to column chromatography over silica gel and the products were thus isolated. Solid compounds were identified by comparison of their m.p.; i.r. spectra, and t.l.c. with authentic samples, while liquid compounds were identified by t.l.c. in various solvent systems on neutral alumina and silica gel plates, and analysed by i.r. and n.m.r. Some of them were also purified by g.c. and the spectra of the pure compounds recorded for complete identification.

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