Tetrahedron. Vol. 26, pp. 435 to 443. Pergamon Press 1970. Printed in Great Britain

PHOTOINDUCED REACTIONS—XXXVI

PHOTOSENSITIZED OXYGENATION OF 3-HYDROXYFLAVONES AS A NONENZYMATIC MODEL FOR QUERCETINASE[1,2]

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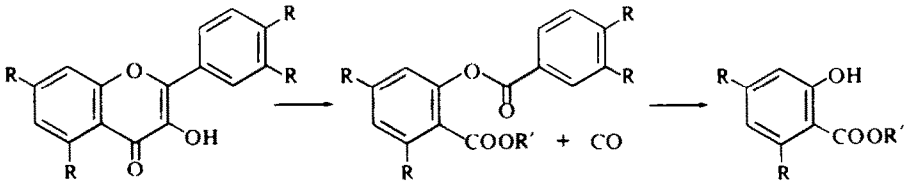
(*Received in Japan* 13 *June* 1969; *Received in the UK for publication* 15 *September* 1969)

Abstract—In connection with resemblance between photosensitized oxygenation and dioxygenase-catalysed enzymatic oxygenation, photosensitized oxygenation of 3-hydroxyflavones **1a**, **1b**, and **1c** was investigated. These compounds, on photooxygenation in the presence of rose bengal, gave corresponding depsides **2a**, **2b**, and **2c**, carbon monoxide, and carbon dioxide. The formation of the depsides and carbon monoxide represents a chemical model for the enzymatic degradation of quercetin (**1a**) by quercetinase leading to the depside **2a**. Possible mechanisms involving a hydroperoxide intermediate **5**, which may be formed by the attack of singlet oxygen to **2a**, are proposed. Photooxygenation of *p*-anisylglyoxylic acid to *p*-anisic acid and carbon dioxide and oxidative dimerization 3-hydroxyflavone (**1c**) to a dimer **10** are also described.

DIOXYGENASES are known to catalyse the activation of molecular O_2 and the subsequent fixation of two atoms of O_2 into various substrates.[3] The activation of oxygen is undoubtedly an interesting problem both from the biochemical and chemical points of view. Several authors have pointed out that some of dioxygenase-catalysed reactions resemble at least formally photosensitized oxygenation which is considered in all probability to involve singlet oxygen.[4–6] For example, photosensitized oxygenation of tryptophan results in the same type of cleavage as tryptophan pyrrolase.[7] Baldwin *et al.* recently reported a cleavage of the photoperoxide of 1,4-dimethoxy-9,10-diphenylanthracene as a model for the enzymatic cleavage of the aromatic ring.[5] Matsuura *et al.* also reported that a ring cleavage of certain dihydric phenols by photosensitized oxygenation provides a model for dioxygenases.[8]

Our attention was directed to the biological oxygenation of quercetin (**1a**) which is oxidatively decarbonylated by the action of quercetinase. It has been reported that rutin is aerobically degraded to carbon monoxide and water-soluble products by extracellular enzymes from *Asperigillus* and *Pullularia* species.[9–12] Rutin is first hydrolysed to quercetin (**1a**) and rutinose, then **1a** is oxidatively decarbonylated by the action of quercetinase to give a depside **2a** and carbon monoxide. In the last step, **2a** is hydrolysed to 2,4,6-trihydroxybenzoic acid (**3a**) and protocatechuic acid (**4a**). Among these steps, conversion of **1a** into **2a** was examined by tracer experiments, and it was shown that C-3 is liberated as carbon monoxide,[10] and that an oxygen molecule is incorporated into **2a** and its hydrolysed products, **3a** and **4a**, but not into carbon monoxide.[13,14] The results clearly indicate that quercetinase is a dioxygenase.

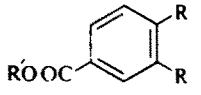
The enzymatic formation of **2a** from **1a** may rationalized by hypothetical mechanisms shown in Scheme 1. A ketohydroperoxide (**5**), which would be initially formed from **1a**, can undergo rearrangement to a 5-membered cyclic peroxide (**6**) followed by decarbonylation leading to the depside **2a** (path a). Such a decarbonylation process



1a: R = OH
1b: R = OMe
1c: R = H

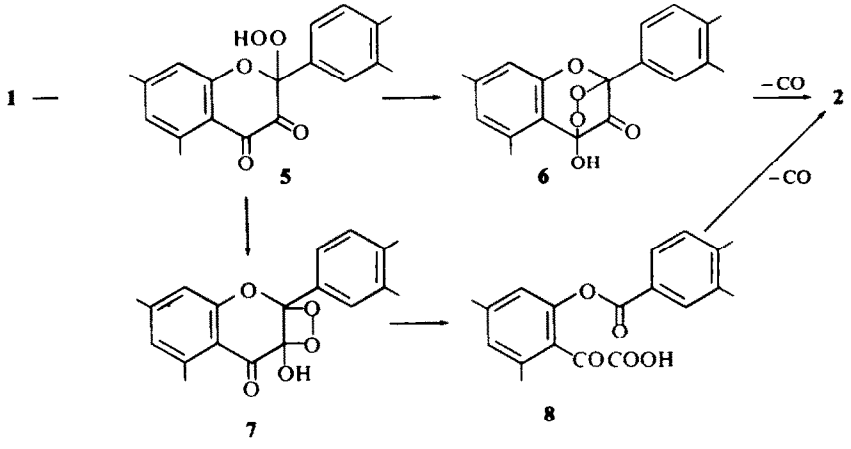
2a: R = OH, R′ = H
2b: R = OMe, R′ = Me
2c: R = H, R′ = Me

3a: R = OH, R′ = H
3b: R = OMe, R′ = Me
3c: R = H, R′ = Me



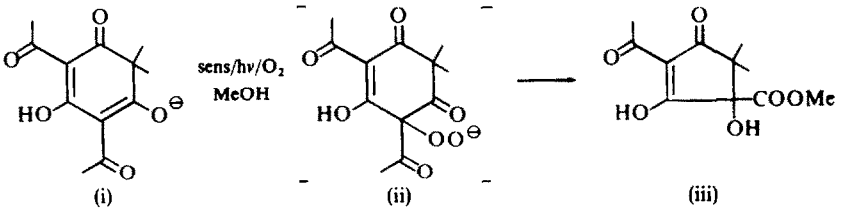
4a: R = OH, R′ = H
4b: R = OMe, R′ = Me
4c: R = H, R′ = Me

SCHEME 1



has an analogy.[15] The formation of ketohydroperoxide **5** from **1**, which is an enol of a sort, formally resembles the formation of hydroperoxides from olefins having an allylic H atom[4,16] and from enamines[17–21] by photosensitized oxygenation: $-\overset{|}{C}=\overset{|}{C}-X-H \rightarrow -\overset{|}{C}(OOH)-\overset{|}{C}=X$ ($X = \diagdown C$ or $-N$). Furthermore, it was reported that photosensitized oxygenation of the enolate anion (i) of diacetylfilicinic acid gave an ester (iii) which is considered to be formed *via* a ketohydroperoxy anion (ii).[22] An alternative pathway, which involves rearrangement of the ketohydroperoxide **5** to a 4-membered cyclic peroxide **7** followed by cleavage to a keto-acid **8** (path b), cannot account for the above tracer experiments.

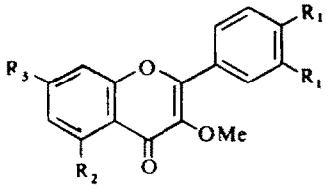
As was expected, not only quercetin (**1a**) but also other 3-hydroxyflavones, **1b** and **1c**, were found to give the corresponding depsides **2** on photosensitized oxygenation. When a solution of a 3-hydroxyflavone and a catalytic amount of rose bengal in pyridine (or methanol) was irradiated with a high-pressure mercury lamp through Pyrex or with a tungsten lamp through window glass under bubbling oxygen, the



slow absorption of oxygen was observed and carbon monoxide and carbon dioxide liberated. The non-volatile products were isolated by silica gel column chromatography after the methylation of the crude products with diazomethane. The results are summarized in Table 1.

In the case of quercetin (**1a**), the depside **2a** was detected in the original reaction mixture. Treatment of the mixture with diazomethane followed by TLC analysis of the products revealed the presence of the pentamethyl depside **2b** which could not be isolated because of complex side reactions. Photosensitized oxygenation of quercetin 5,7,3',4'-tetramethyl ether (**1b**) and 3-hydroxyflavone (**1c**) followed by methylation resulted in the formation of the expected depsides, **2b** and **2c**, respectively, in good yield, and their hydrolysed products, **3b** and **4b** and **3c** and **4c**, respectively were obtained as byproducts. The simultaneous formation of carbon monoxide in these reactions is very significant in view of the resemblance between the action of dioxygenase and photosensitized oxygenation. However, the liberation of carbon dioxide during photooxygenation indicates some discrepancy between them. It should be noted that carbon dioxide was produced in much higher yield from both **1b** and **1c**, when a high-pressure mercury lamp was used as the light source. This will be discussed later.

On the other hand, photosensitized oxygenation of 3-methoxyflavones, **9a** and **9b**, proceeded very slowly and most of the starting material was recovered unchanged.* The results clearly indicate that the presence of the 3-hydroxyl group is prerequisite for the formation of the depsides **2**.

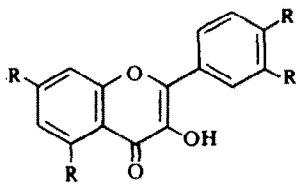
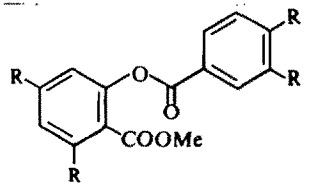
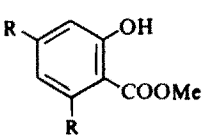
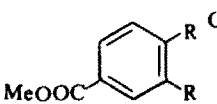


9a: $R_1 = R_2 = H, R_3 = OMe$
9b: $R_1 = R_3 = OMe, R_2 = OH$

The photochemical formation of the depsides **2** and carbon monoxide can be well rationalized by the mechanism (path a) shown in Scheme 1. One can assume that singlet oxygen, which was formed by energy transfer from the triplet excited sensitizer to the ground state triplet oxygen,[6] might react with hydroxyflavones **1** to give ketohydroperoxide **5**. In order to see whether singlet oxygen is involved in the photooxygenation, reaction of **1b** with chemically generated singlet oxygen[6,24] was examined. When a solution of **1b** in methanol was treated with hydrogen peroxide

* The photooxygenation of 3-methoxyflavones for a long period of time gave a different type of oxidation product.[23]

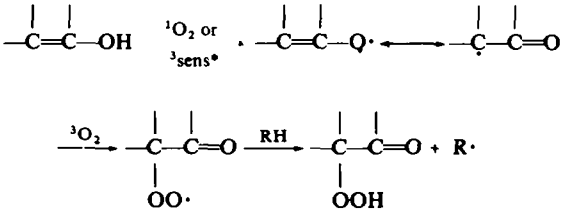
TABLE 1. PHOTOSENSITIZED OXYGENATION OF 3-HYDROXYFLAVONES

Exp. no.		Light source[a]	Product[b] (% yield) 			CO	CO_2
1	**1a** (R = OH)	A	**2b**[c]	ND[d]	ND	ND	ND
2	**1b** (R = OMe)	A	**2b**, 51	3	13	ND	107
3	**1b** (R = OMe)	B	**2b**, 77	2	11	31	17
4	**1c** (R = H)	A	**2c**, 48	17[e]	24	[f]	43
5	**1c** (R = H)	B	**2c**, 44	9	11	88	19

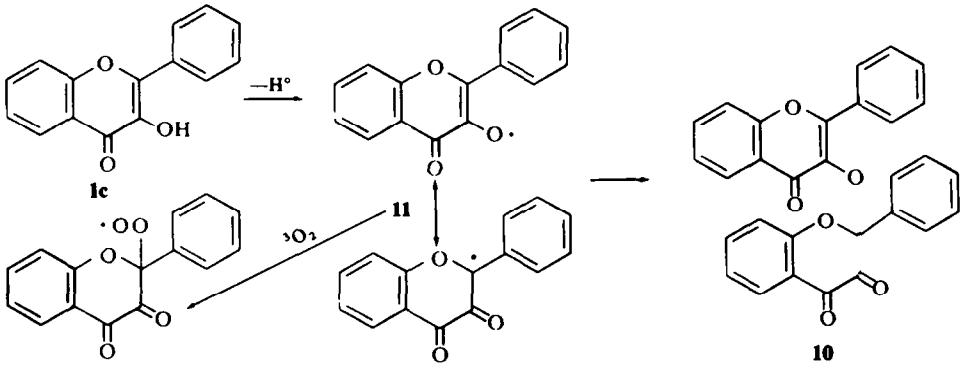
[a] A: high-pressure mercury arc lamp through Pyrex. B: tungsten lamp through window glass.
[b] Products were isolated after methylation of the reaction mixture with diazomethane.
[c] Identified by TLC.
[d] Not determined.
[e] Methyl *o*-methoxybenzoate (5% yield) was also isolated.
[f] Determined qualitatively.

and sodium hypochlorite, 2-hydroxy-4,6-dimethoxybenzoic acid (**3b**) and veratric acid (**4b**) were detected in the reaction mixture, although the corresponding depside **2b** could not be isolated because of its hydrolysable property under conditions employed. The experiment supports that the reaction species in the photooxygenation may be singlet oxygen. The most probable mechanism for the formation of the ketohydroperoxide **5** is, therefore, the concerted addition of singlet oxygen to the enol system of 3-hydroxyflavones (**1**), as generally accepted for the reaction of singlet oxygen with olefins.[6,25,26]

Nevertheless, one cannot exclude possibilities that singlet oxygen and/or the triplet excited sensitizer, abstract an H atom from the 3-OH of **1** as verified in the photosensitized oxygenation of certain phenols.[8,27] In order to see whether such a



radical intermediate is involved in the present photosensitized oxygenation, we carried out oxidation of 3-hydroxyflavone (**1c**) with manganese dioxide which is known to oxidize phenols into phenoxy radicals. Treatment of **1c** with manganese dioxide in chloroform under bubbling nitrogen gave a dimeric product in 44% yield. Under bubbling oxygen the dimeric product was obtained in 46% yield. The product was found to be identical with **10** which had been obtained by dehydrogenation of **1c** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[28] The results indicate that the radical **11**, even under oxygen, easily dimerizes rather than reacting with the ground state oxygen. Accordingly, the mechanism involving hydrogen abstraction by singlet oxygen and/or the triplet excited sensitizer is excluded.



The remaining question is how carbon dioxide is produced in the photosensitized oxygenation of 3-hydroxyflavones **1**. Three possible mechanisms involving photochemical decomposition of the keto-acid intermediate **8** (Scheme 1) were considered;

(i) decarbonylation of **8** giving the depside **2** and carbon monoxide which is photo-oxidized to carbon dioxide, (ii) decarboxylation of **8** to carbon dioxide and the corresponding aldehyde which is further photooxidized to **2**, and (iii) oxidative decarboxylation of **8** leading directly to **2** and carbon dioxide. Since carbon monoxide was not oxidized to carbon dioxide but recovered unchanged under conditions employed for the photosensitized oxygenation of 3-hydroxyflavones **1**, the first mechanism (i) is eliminated.

In order to verify the mechanism, photooxidation of *p*-methoxyphenylglyoxylic acid (**12**), a model compound for the keto-acid **8**, was investigated under various conditions. The results are shown in Table 2. Whereas **12** was easily oxidized to

TABLE 2. PHOTOOXYGENATION OF *p*-METHOXYPHENYLGLYOXYLIC ACID[a]

Light source[b]	Rose bengal (mg)	Solvent (ml)	Irrd. time (min)	Yield of products (%)	
				p-anisic acid	CO_2
A	25	pyridine (160)	40	68	40
A	0	pyridine (160)	40	75	110
A	0	methanol (160)	40	100	79
A[c]	0	pyridine (130)	60	trace	—
B	50	pyridine (130)	600	19[d]	30
B	0	methanol (130)	600		—

[a] The acid (1·2 g) was used in each run.

[b] See footnote *a* in Table 1.

[c] The irradiation was carried out under bubbling nitrogen instead of oxygen. A complex mixture was obtained.

[d] The starting material (54%) was recovered and no carbon monoxide was detected by VPC.

[e] The starting material was quantitatively recovered.

p-anisic acid and carbon dioxide either in the presence or the absence of sensitizer when irradiated with UV light filtered through Pyrex, it was slowly photooxidized only in the presence of sensitizer when irradiated with visible light.

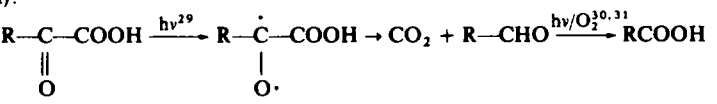
The results suggest that direct excitation of **12** rather than sensitized reaction may be advantageous for the oxidative decarboxylation. Two possible mechanisms, corresponding to the mechanisms (ii) and (iii), can be written for the oxidative decarboxylation of **12**, as shown in Scheme 2.

Although two mechanisms (ii) and (iii) cannot be distinguished from the available data, it may be concluded that, in the photosensitized oxygenation of the 3-hydroxyflavones **1**, carbon dioxide is formed by photo-oxidative decarboxylation of the keto-acid intermediate **8**. Similar decarboxylation of pyruvic acid by vanadium(V)-sensitized oxygenation has been reported.[33]

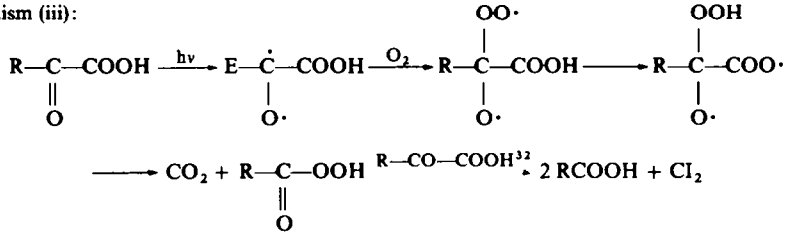
In conclusion, it seems reasonable to assume that the enzymatic cleavage of quercetin **1a** leading to the depside **2a** and carbon monoxide may proceed by a mechanism similar to path a in Scheme 1.

SCHEME 2

Mechanism (ii):



Mechanism (iii):



EXPERIMENTAL

M.ps are uncorrected. The UV spectra were determined in 99·5% EtOH, unless otherwise specified, and the IR spectra in Nujol mulls. The NMR spectra were taken in $CDCl_3$ with TMS as internal references

Materials. Compounds **1b**,[34] **1c**,[35] **9a**,[36] **9b**,[37] and **12*** were prepared according to the lit.

General procedure for photosensitized oxygenation

A 3-hydroxyflavone and a catalytic amount of rose bengal were dissolved in pyridine. The soln was irradiated with a 100 w high-pressure Hg lamp (internal) through a Pyrex water-cooled jacket or with a 300 w tungsten lamp through window glass under bubbling oxygen which was circulated during irradiation with a circulating pump. The circulating gas was bubbled through a $Ba(OH)_2$ aq and $BaCO_3$ precipitated was collected by filtration, dried, and weighed. After oxygen absorption ceased, the CO content of the gas in the reaction vessel was analyzed by VPC (molecular sieve and silica gel; carrier gas, helium; 30°). The reaction mixture was evaporated *in vacuo* and the residue was dissolved in methanol and treated with an ether soln of diazomethane. After evaporation the products were separated by column chromatography on silica gel. The results are summarized in Table 1.

Isolation of the products

Quercetin (**1a**) (Exp. 1). A soln of quercetin dihydrate (2·0 g) and rose bengal (50 mg) in MeOH (170 ml) was photooxidized for 29 hr. Paper chromatography (n-BuOH–AcOH (4:1) satd with H_2O) of the aliquot showed a spot identical to that of **2a** and two unidentified spots. After methylation, TLC of the product showed a spot identical to that of **2b**, but **2b** could not be isolated in a pure form.

Quercetin 5,7,3',4'-tetramethyl ether (**1b**) (Exp. 3). A soln of **1b** (2·0 g) and rose bengal (50 mg) in pyridine was photooxidized (visible light) for 14 hr. The methylated products were chromatographed. Elution with C_6H_6 (300 ml) yielded methyl 2-hydroxy-4,6-dimethoxybenzoate (21 mg; 2%), m.p. 105–106°, which was identical with an authentic sample (IR and TLC; silica gel, toluene–ethyl formate–formic acid, 5:4:1). Elution with C_6H_6–$CHCl_3$ (9:1, 100 ml; 7:3, 200 ml; 5:5, 400 ml) yielded **2b** (1·54 g; 77%), m.p. 143–144° (from C_6H_6), which was identical with **2b** synthesized below (IR and TLC). The photooxidation of **1b** with UV light (Exp. 2) was carried out under similar conditions. The results are given in Table 1.

3-Hydroxyflavone (**1c**) (Exp. 5). A soln of **1c** (1·0 g) and rose bengal (30 mg) in pyridine (130 ml) was photooxidized (visible light) for 14 hr. The methylated products were chromatographed. Elution with C_6H_6 (100 ml) gave an oil (118 mg), b.p. 45–57°/5 mm, which was shown by VPC (silicone DC 550; 160°; Helium) to consist of methyl benzoate (62 mg; 11%) and methyl salicylate (56 mg: 9%). Further elution with C_6H_6 (100 ml) gave **2c** (450 mg; 44%), m.p. 83–84°, which was identical with **2c** synthesized below by TLC and IR. The photooxidation of **1c** with UV light (Exp. 4) gave similar results as shown in Table 1. A solution of **1c** (1·0 g) in pyridine (130 ml) without rose bengal was photooxidized (visible light) for 12·5 hr. After evaporation of the solvent, a crystalline residue was found to be pure **1c** by IR and TLC.

3,7-Dimethoxyflavone (**9a**). A soln of **9a** (0·8 g) and rose bengal (20 mg) in pyridine (80 ml) was photooxidized (visible light) for 12·5 hr. After evaporation followed by column chromatography of the residue gave recovered **9a** (0·63 g; 77%), m.p. 118° (IR, UV, and TLC).

* The authors are indebted to Dr. Akira Nishinaga for a supply of this compound.

Quercetin 3,7,3',4'-tetramethyl ether (**9b**). A soln of **9b** (716 mg) and rose bengal (20 mg) in pyridine (150 ml) was photooxidized (UV light) for 16·5 hr. TLC of the reaction mixture showed that the product was mainly **9b** with a trace of an unidentified compound. Column chromatography (elution with C_6H_6-$CHCl_3$, 5:5; 400 ml) of the product gave recovered **9b** (633 mg; 88%), m.p. 156° (IR and TLC).

Methyl 2-veratryloxy-4,6-dimethoxybenzoate (**2b**)

A mixture of 3,4-dimethoxybenzoic acid (0·38 g) and $SOCl_2$ (5 ml) was heated at 60–70° for 5 hr. After evaporation under reduced press, the residual oil was distilled at 4 mm to give the acid chloride (0·31 g), which was added into a soln of methyl 2-hydroxy-4,6-dimethoxybenzoate (0·26 g) in pyridine (3 ml). The mixture was heated at 70–80° for several hr, then kept on standing at room temp overnight. The mixture was poured onto ice-water (150 ml) and ppts separated were collected, dried, and crystallized from C_6H_6 to give **2b** (0·19 g), m.p. 143° (lit.[11] m.p. 144°). τ_{CDCl_3} 2·06–3·13 m (3H), 3·58 s (2H), 6·05 s (6H), 6·16 s (3H), 6·18 s (3H), 6·33 s (3H). (Found: C, 60·50; H, 5·50. Clac. for $C_{19}H_{20}O_8$: C, 60·63; H, 5·36%). This compound was identical (IR) with the pentamethyl derivative obtained by methylation with diazomethane from **2a***.

Oxidation of **1b** *with singlet oxygen*

To a soln of **1b** (200 mg) and 30% H_2O_2 aq (0·9 ml) in MeOH (30 ml) was added dropwise 10% NaOCl aq (4·1 ml) over 10 min under ice-cooling. After standing for 25 min, the mixture was diluted with water, acidified with dil HCl, and extracted with $CHCl_3$. TLC of the extract showed three spots identified as **1b**, **3b**, and **4b** in addition to two unidentified spots. When a soln of **1b** and H_2O_2 in MeOH was kept on standing for 70 min and the mixture was worked up as described above, only recovered **1b** was detected on TLC.

MnO_2-*oxydation of* 3-*hydroxyflavone* (**1c**)

To a soln of **1c** (1·0 g) in dry $CHCl_3$ (100 ml) was added freshly prepared MnO_2[38] (3·5 g) under N^2. The mixture was refluxed for $1\frac{3}{4}$ hr. MnO_2 was filtered off and washed with $CHCl_3$. The filtrate and washings were combined and evaporated to dryness. The residue, which showed 2 spots on TLC, was chromatographed on a silica gel column. Elution with C_6H_6–$CHCl_3$ (95:5–20:80, 750 ml) gave recovered **1c** (109 mg). Further elution gave **1c** (15 mg) and yellow crystals (436 mg; 44%), m.p. 216–218° (capillary tube) and 239–244° (hot plate) (lit.[28] m.p. 225–227°); λ_{max}^{EtOH} 250 mμ (log ε 4·41) and 316 mμ (4·15). The IR spectrum (KBr) was identical with that of **10** prepared according to the known method.[28]

The reaction was carried out under oxygen in a similar manner to give **10** in 46% yield. In another experiment under oxygen, to a soln of **1c** (0·9 g) in boiling $CHCl_3$ (200 ml) was added MnO_2 (3·5 g) in small portions over 3 hr. The mixture was refluxed for 30 min, then treated as described above to give recovered **1c** (86 mg) and the dimer **10** (654 mg; 73%). In both cases, no other product was detected on TLC.

Photooxygenation of p-*methoxyphenylglyoxylic acid* (**12**)

A soln of **12** was photooxidized in a similar manner to that described in the photooxygenation of 3-hydroxyflavones. The sole products were found to be CO_2 and *p*-anisic acid which was separated by silica gel chromatography or by preparative TLC and identified by IR and mixed m.p. The results are shown in Table 2.

Irradiation of p-*methoxyphenylglyoxylic acid* (**12**)

A soln of **12** (1·20 g) in pyridine (130 ml) was internally irradiated with a 100 w high-pressure Hg lamp through Pyrex for 1 hr. The reaction mixture was analyzed by VPC (silicone DC 550; 170°; helium) but no *p*-anisaldehyde was detected. The mixture was found by TLC to contain at least ten products, which could not be separated.

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* The authors are indebted to Dr. Harushige Sakamoto for a generous supply of a sample of **2a** obtained by enzymatic oxygenation of **1a**.

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