Base-catalysed Oxygenolysis of 3-Hydroxyflavones [1]

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3-Hydroxyflavones, except those containing a 7-hydroxy-group, undergo base-catalysed oxygenolysis under mild conditions leading to oxidative cleavage of the heterocyclic ring to give the corresponding depsides and carbon monoxide in excellent yields. The same result is obtained in the reaction of quercetinase, a dioxygenase. The oxygenation of 3,4',7-trihydroxyflavone in aqueous solution gave *p*-hydroxyphenylglyoxylic acid and 2,4-dihydroxybenzoic acid; in absolute methanol containing sodium methoxide methyl 4-hydroxyphenylglyoxylate and methyl 2,4-dihydroxybenzoate as well as 4-hydroxyphenylglyoxylic acid were obtained. The formation of these products is rationalized by assuming that 2-hydroperoxy-4',7-dihydroxyflavan-3,4-dione is formed first and is reduced with the intervention of the 7-hydroxy-group to give 2,4',7-trihydroxyflavan-3,4-dione, which is solvated and oxidized under the reaction conditions. 2'-Substituted-3-hydroxyflavones were not susceptible to oxygenolysis.

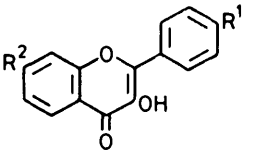
BIOLOGICAL oxygenation catalysed by oxygenase plays an important role in the metabolism of natural substances. Many model reactions have been investigated so as to give clues to the mechanism of biological oxygenation.[2] The oxygenolysis of 3-hydroxyflavones (1) catalysed by quercetinase is an interesting example of this reaction.[3] It leads to oxidative cleavage of the heterocyclic ring to give the corresponding depsides (3) and carbon monoxide.[3-5] In this paper, we report that the base-catalysed oxygenation of 3-hydroxyflavones, where there is no hydroxy-group in the 7-position, gives the same products obtained in the quercetinase reaction,[6] providing basic information for understanding the enzyme reaction from the standpoint of the reactivity of the substrate towards molecular oxygen. On the other hand, the oxygenolysis of 3-hydroxyflavones with a 7-hydroxy-group gives oxidation products different from those in the enzyme reaction. It is considered that this oxygenolysis involves decomposition of a 2-hydroperoxyflavan-3,4-dione intermediate, which is affected by the presence or absence of the 7-hydroxy-group.

RESULTS AND DISCUSSION

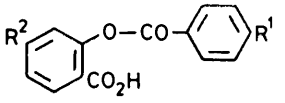
The starting 3-hydroxyflavones (1a—g) and (2a and b) were synthesized according to the Alger–Flynn–Oyamada reaction [7] with minor modifications.

When 3,4'-dihydroxyflavone (1c) was dissolved in a solution of potassium t-butoxide in *NN*-dimethylformamide (DMF) under nitrogen, a deep red colour was obtained. Oxygen was then bubbled through the solution at room temperature. The red colour turned yellow upon completion of the reaction after 30 min. A t.l.c. analysis of the reaction mixture showed the formation of a single product, 2-(4-hydroxybenzoyloxy)benzoic acid (3c), isolated as prisms in 97% yield. The elemental analysis and i.r. spectrum are in good agreement with this structure. The structure of (3c) was confirmed by its chemical reactions. Alkaline hydrolysis gave 4-hydroxybenzoic acid and salicylic acid in quantitative yields. Methylation with diazomethane gave methyl 2-(4-methoxybenzoyloxy)benzoate (4), identical with an authentic sample synthesized from methyl salicylate and 4-methoxybenzoyl chloride. I.r. spectroscopic and gas volumetric determinations of a gas collected from the reaction mixture showed that carbon monoxide was formed in 98% yield. The formation of (3c) from (1c) requires oxygen but no apparent oxygen uptake was observed, because the absorption of oxygen and the liberation of carbon monoxide compensate each other.

The reaction rate and the product in the base-catalysed oxygenolysis of (1c) are much influenced by the nature of the solvent and the amount of the base used. Oxygenolysis is fast in non-aqueous aprotic solvents with an excess of Bu^{t}OK and slows down in protic solvents. In

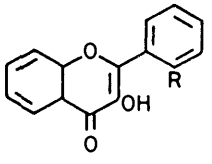


(1)



(3)

a; $R^1 = R^2 = H$
b; $R^1 = OCH_2OCH_3$, $R^2 = H$
c; $R^1 = OH$, $R^2 = H$
d; $R^1 = OCH_3$, $R^2 = H$
e; $R^1 = H$, $R^2 = OCH_3$
f; $R^1 = R^2 = OCH_2OCH_3$
g; $R^1 = R^2 = OH$



(2)

a; $R = OCH_2OCH_3$
b; $R = OH$

protic solvents the hydrolysates of (3c), 4-hydroxybenzoic acid and salicylic acid, were always formed together. With an excess of alkali in aqueous solution only the hydrolysates were obtained (Table 1).

Other 3-hydroxyflavones (1) without a 7-hydroxy-group undergo similar oxygenolysis in DMF containing Bu^{t}OK to give the corresponding depsides in nearly quantitative yield. However, the reaction rate is much affected by the nature of the substituent and was found

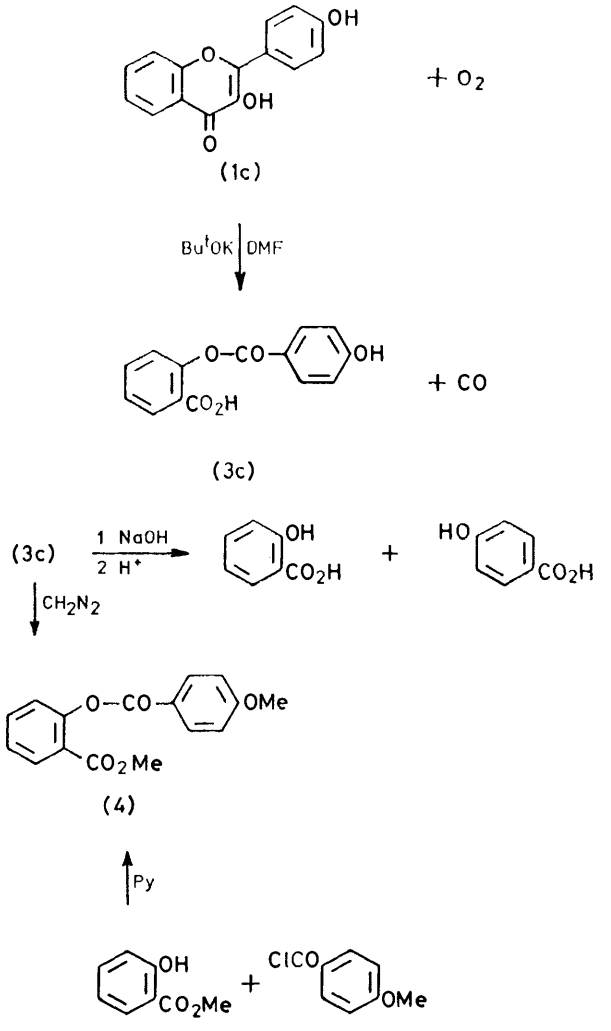
TABLE 1

Base-catalysed oxygenolysis of (1c)

Base	Base/(1c) (mol/mol)	Solvent	Reaction time (h)	Conversion (%)	Product (%) (3c) [a]	Product (%) Hydrolysate [b]
Bu^tOK	5	DMF	0.5	100	91	0
Bu^tOK	1	DMSO	1	60	88	
NaOH	1	DMF–H_2O	20	50	28	72
MeONa	10	MeOH	20	80	0	100 [c]
NaOH	1	MeOH–H_2O	20	77	70	30
NaOH	10	H_2O	20	80	0	100

[a] Yields were determined by isolation. [b] Yields were determined by g.l.c. after silylation of the reaction mixture with bis-(trimethylsilyl)acetamide. [c] Estimated during work-up.

to be in the order 4′-OH > 4′-OCH_2OCH_3 > 4′-OMe > 7-OMe > 4′,7-H (Table 2). Acceleration of the reaction by the 4′-hydroxy-group has also been reported for the oxygenation of 3-hydroxyflavones in aqueous alkaline solution.[8] Interestingly, 2′,3-dihydroxyflavone (2b) and its methoxymethyl ether (2a) were not susceptible to oxygenolysis; no reaction took place in DMF containing Bu^tOK at room temperature over ⩾68 h. Where oxygenolysis gives depsides (3) as well as their hydrolysates, the stoicheiometric formation of carbon monoxide is observed.



The oxygenolysis of (1) to give (3) and carbon monoxide is rationalized as in Scheme 1. Molecular oxygen is incorporated into the carbonion at the 2-position resulting from the enolate through resonance. The slower reaction in protic than in aprotic solvents may be due to solvation of the enolate anion. A similar solvent effect has been observed for the base-catalysed oxygenation of phenols.[9]

It is not yet clear whether oxygen incorporation into the 2-position involves a radical intermediate as suggested for the oxygenation of carbanions.[10] A direct ionic process [11] may be possible. Nucleophilic attack on the 4-carbonyl group by the peroxy-anion in intermediate (5) leads to the formation of (3) and carbon monoxide.[6,12] Another route involving nucleophilic attack on the 3-carbonyl group by the peroxy-anion giving a dioxetan intermediate can be ruled out, because

TABLE 2

Conversion rate of (1) for Bu^tOK-catalysed oxygenolysis in DMF at 25 °C

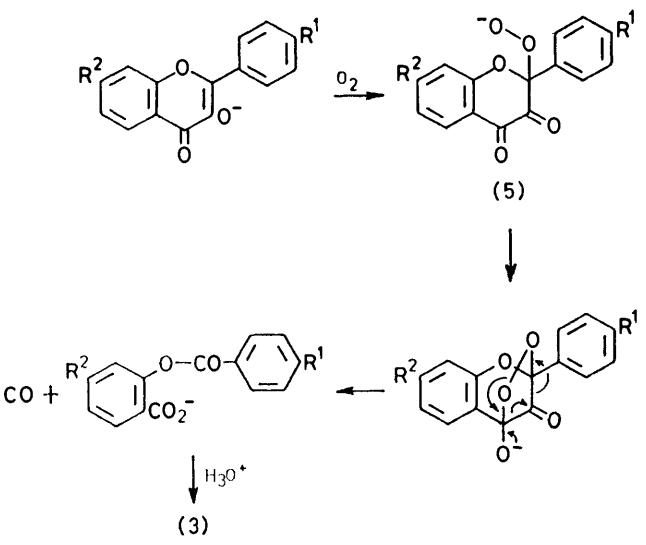
Compound	Bu^tOK/(1) (mol/mol)	Reaction time (h)	Conversion [a] (%)
(1c)	5	0.5	100
(1b)	5	3	85
(1d)	5	3	84
(1e)	5	3	77
(1a)	5	3	58

[a] Determined by isolation of (1).

the glyoxylic acid system resulting from the decomposition of such a dioxetan cannot give carbon monoxide under the reaction conditions.

The lack of susceptibility of (2) towards oxygenolysis may be attributed to restriction of the generation of the active enolate form by formation of a hydrogen bond between 3-OH and 2′-oxygen or to hindered rotation of the C(2)–C(1′) bond by a hydrogen bond producing a non-planar steric relationship between the heterocyclic system and the phenyl ring. Acceleration of the reaction by an electron-releasing group at the 4′-position may imply the rotation of C(2)–C(1′) bond requisite for the π-overlap interaction between the two rings to be significant.

The oxygenation of 3,7-dihydroxyflavones in DMF containing Bu^tOK gave a complex reaction mixture with apparent oxygen uptake, where the liberation of carbon monoxide decreased and depended on the amount of Bu^tOK used. With (1g) *ca.* 1.4 mol oxygen was

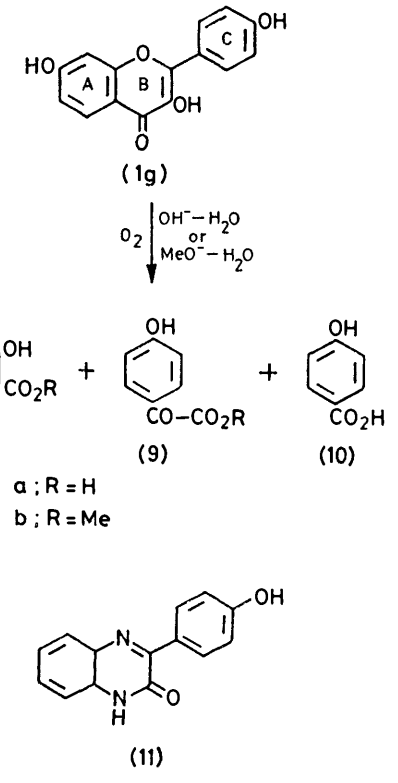


SCHEME 1

taken up with the liberation of 0.02—0.3 mol carbon monoxide. The oxygenation of quercetin (6) in aqueous alkaline solution has been reported by Nordstrom *et al.*[13,14] to give 2,4,6-trihydroxyphenylglyoxylic acid, protocatechuic acid, phloroglucinol, and 2,4,6-trihydroxybenzoic acid. In order to explain the oxygen uptake mentioned above and the results obtained by Nordstrom *et al.* for the oxygenation of quercetin, a dioxetan intermediate (7) has been suggested [1] by analogy with the results obtained in the photosensitized oxygenation of 3-hydroxyflavones.[6,12] This suggestion, however, seems unsuitable in view of the following experimental results.

As the base-catalysed oxygenation of quercetin gives a complex reaction mixture, we have investigated the oxygenation of (1g) in order to find out the effect of a 7-OH group on oxygenolysis. It was expected that the products would be easily characterized. Thus, the oxygenation of (1g) in aqueous alkaline solution at room temperature gave 2,4-dihydroxybenzoic acid (8a), 4-hydroxyphenylglyoxylic acid (9a), and 4-hydroxybenzoic acid (10) in 62, 74, and 26% yield, respectively. On the other hand, oxygenation in absolute methanol containing sodium methoxide gave (8a), methyl 2,4-dihydroxybenzoate (8b), (9a), methyl 4-hydroxyphenylglyoxylate (9b), and (10) in 33, 28, 31, 40, and 20% yield, respectively. The structure of (9a) was confirmed by oxidation with alkaline hydrogen peroxide to give (10) in quantitative yield and by the formation of the quinoxaline derivative (11). The ^{1}H n.m.r. and i.r. spectra of (9b) are in good agreement with the structure. The low yield of (8) is due to further oxidation under the reaction conditions.* These results can be rationalized by assuming the competition reactions (a) and (b) in Scheme 2.

From the material balance for oxygenation in aqueous alkaline solution the formation of (10) obviously results from path (a), which is consistent with the amount of carbon monoxide liberated [0.03—0.1 mol per mol of (1g)]. The formation of (8) and (9) is reasonably explained by path (b) involving the reduction of intermediate (5g) to (12), which is subsequently solvated and oxidized. The 7-hydroxy-group of (5g) decreases the carbonyl character at the 4-position through tautomerism (actually resonance in basic solution) resulting in suppression of nucleophilic attack on the 4-carbonyl group by the hydroperoxy-group. Thus, the



hydroperoxy-group in (5g) is somewhat stabilized and undergoes a redox process leading to (12), although the mechanism of reduction has not been clarified. Reduction of hydroperoxides to the corresponding alcohols has been known for systems where hydroperoxides have a long life time.†[16] The solvation of flavan-3,4-dione derivatives similar to the reaction (12) ⟶ (13) has been reported.[17]

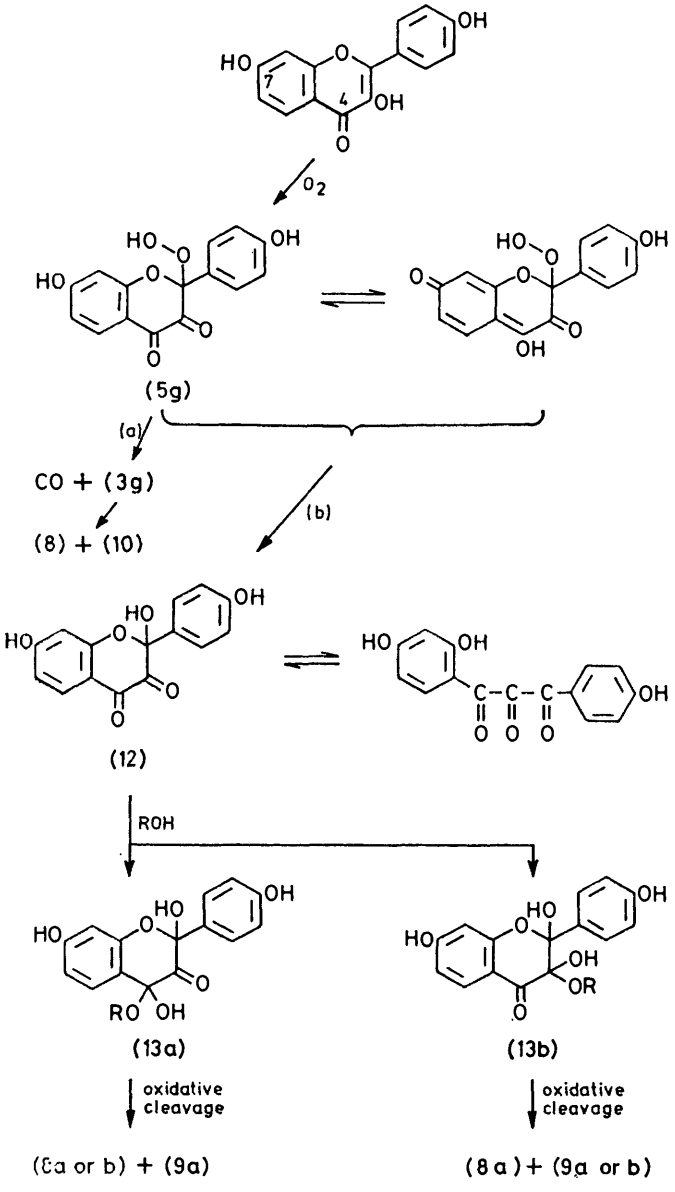
2,4,6-Trihydroxyphenylglyoxylic acid, obtained by Nordstrom *et al.*[13,14] in the oxygenation of quercetin, derives from ring A. On the other hand, the glyoxylic acid (9) obviously derives from ring C of (1g). If their

* In fact, (8a and b) underwent oxidation by O_2 under alkaline conditions to give a mixture of unidentified products.

† Peroxyquinols obtained in the base-catalysed oxygenation of 2,6-di-t-butylphenols are easily reduced to the corresponding quinols in excellent yields under alkaline conditions where the peroxyquinols are stabilized.[15]

report is correct, it is not clear how the difference arises.

Our present finding, that 3-hydroxyflavones, when 3-OH is deprotonated and the carbonyl character at 4-position is retained, undergo oxygenolysis leading to the same products obtained in the quercetinase reaction, is suggestive for the mechanism of enzyme reactions. Quercetinase contains Cu^{2+} ion in the active centre,[3]



SCHEME 2

which may function as a base specifically reacting with the 3-OH group of the substrates rather than as a one-electron oxidizing agent. The reactions of oxygenases are generally considered to involve molecular oxygen activation, but Cu^{2+} ion complexes do not normally activate molecular oxygen. It has been found that although the oxidation of 3-hydroxyflavones with one-electron oxidizing agents such as MnO_2 in oxygen does not give the corresponding depsides but their radical coupling dimers, some cobalt–oxygen complexes catalyse the oxygenolysis of 3-hydroxyflavones, including 7-hydroxy derivatives, giving rise to the depsides, providing a good model for the quercetinase reaction.[18] The cobalt–oxygen complex active in catalysis is considered to act as a base rather than an oxidizing agent.[19] Details of this catalysis will be published elsewhere.

EXPERIMENTAL

General.—M.p.s are uncorrected. Elemental analyses were performed by the Analytical Centre of Kyoto University. I.r. spectra were recorded with a Jasco IRA-1 spectrometer. ^1H N.m.r. spectra were recorded with a Varian T-60 spectrometer using Me_4Si as internal reference. Carbon monoxide was determined with a Horiba Mexa 200 analyser and by gas volumetry using a gas burette connected to an O_2 absorber containing an alkaline solution of 2,5-di-t-butylhydroquinone and to a CO absorber containing Cu_2Cl_2 dissolved in an NH_4OH–NH_4Cl buffer solution.

3-Hydroxyflavones.—3-Hydroxyflavones (1a, b, and 1d—f) were synthesized by the Alger-Flynn-Oyamada reaction[7] with minor modifications including H_2O_2 oxidation of the chalcones. Methoxymethylation of the starting phenols was accomplished by reaction with a small excess of methoxymethyl chloride in dry acetone in the presence of a large excess of K_2CO_3 at room temperature.

H_2O_2 *Oxidation Conditions.*—Solutions of 2'-hydroxychalcones, NaOH, and H_2O_2 in the molar ratio 1 : 2 : 2.2 in MeOH were left at room temperature for 3—4 h. The mixture was worked up as usual. Compounds (1c and g) were obtained nearly quantitatively from (1b and f), respectively, by acid hydrolysis; heating in AcOH with 1 mol. equiv. HCl at 80 °C for 30 min resulted in crystallization of (1c and g). All 3-hydroxyflavones were purified by repeated recrystallization from ethanol and gave a positive colour reaction (Mg + HCl in EtOH; red) confirming the 3-hydroxyflavone structure. Spectral and analytical data are as follows: (1b), pale yellow needles, m.p. 138—139 °C, $\nu_{max.}$(Nujol) 3 280 and 1 610 cm^{-1} (Found: C, 68.6; H, 4.95. Calc. for $C_{17}H_{14}O_5$: C, 68.43; H, 4.75%); (1c), yellow needles, m.p. 278 °C, $\nu_{max.}$(Nujol) 3 380 and 1 615 cm^{-1} (Found: C, 70.55; H, 4.25. Calc. for $C_{15}H_{10}O_4$: C, 70.85; H, 3.95%); (1d), yellow needles, m.p. 245—246 °C (Found: C, 71.35; H, 4.55. Calc. for $C_{16}H_{12}O_4$: C, 71.65; H, 4.5%); (1e), pale yellow needles, m.p. 181—182 °C, $\nu_{max.}$(Nujol) 3 310 and 1 620 cm^{-1} (Found: C, 71.7; H, 4.75. Calc. for $C_{16}H_{12}O_4$: C, 71.65; H, 4.5%); (1f), pale yellow needles, m.p. 151—152 °C, $\nu_{max.}$(Nujol) 3 340 and 1 615 cm^{-1} (Found: C, 63.4; H, 5.25. Calc. for $C_{19}H_{18}O_7$: C, 63.7; H, 5.05%); (1g), yellow needles, m.p. 290 °C, $\nu_{max.}$(Nujol) 3 520, 3 420, and 1 580 cm^{-1} (Found: C, 66.4; H, 4.05. Calc. for $C_{15}H_{10}O_5$: C, 66.65; H, 3.75%); (2a), yellow needles, m.p. 140—141 °C (Found: C, 68.4; H, 4.9. Calc. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.75%); (2b), pale yellow needles, m.p. 199—200 °C (Found: C, 70.6; H, 4.25. Calc. for $C_{15}H_{10}O_4$: C, 70.85; H, 3.95%).

Oxygenation of (1d) *in DMF containing* Bu^tOK.—Oxygen was bubbled through a solution of (1d) (0.54 g, 2 mmol) and Bu^tOK (0.24 g, 2.2 mmol) in DMF (10 ml) at room temperature for 1.5 h. The mixture was poured into ice-cooled dilute hydrochloric acid and extracted with ether. Unchanged (1d) was precipitated (0.05 g, 10%). After removal of (1d) the extract was dried (Na_2SO_4) and evaporated to give (3d) as crystals (0.46 g, 94%). Recrystall-

ization from a mixture of ethanol and light petroleum gave prisms, m.p. 141—142 °C, $\nu_{max.}$(Nujol) 1 740 and 1 695 cm^{-1} (Found: C, 65.95; H, 4.55. Calc. for $C_{15}H_{12}O_5$: C, 66.15; H, 4.45%). The methyl ester of (3d), prepared by methylation with diazomethane in ether, was identical with an authentic sample of methyl 2-(4-methoxybenzoyloxy)-benzoate (4) separately synthesized. Alkaline hydrolysis of (3d) gave a 1 : 1 mixture of *p*-anisic acid and salicylic acid.

Methyl 2-(4-Methoxybenzoyloxy)benzoate (4).—To a solution of methyl salicylate (3 g) in pyridine (5 ml) was added *p*-methoxybenzoyl chloride (3.7 g) prepared by reflux of *p*-methoxybenzoic acid with thionyl chloride in benzene. The reaction took place exothermically with precipitation of prisms. After 30 min the mixture was poured into ice-water to give a crystalline mass, which was collected by filtration. Recrystallization from methylene chloride–light petroleum gave (4) as prisms (5 g, 88%), m.p. 82—84 °C, $\nu_{max.}$(Nujol) 1 735 and 1 720 cm^{-1} (Found: C, 67.0; H, 5.05. Calc. for $C_{16}H_{14}O_5$: C, 67.1; H, 4.95%).

Oxygenation of (1c)—(a) *With* Bu^{t}OK *in DMF*. Oxygen was bubbled through a solution of (1c) (0.25 g, 1 mmol) and Bu^{t}OK (0.5 g, 4.6 mmol) in DMF (15 ml) put in a test tube (20 ml) equipped with a syringe (100 ml) at room temperature for 30 min. The gas which came out through the solution was collected in the syringe and was analysed as CO, obtained in 98% yield. The mixture, which showed only one spot on t.l.c. was acidified with acetic acid (1 ml), diluted with excess of aqueous NH_4Cl solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give (3c) as a crystalline residue (0.25 g, 97%), which was recrystallized from methanol–CH_2Cl_2 to give prisms, m.p. 183—184 °C, $\nu_{max.}$(Nujol) 3 300 and 1 700 cm^{-1} (Found: C, 64.85; H, 3.65. Calc. for $C_{14}H_{10}O_5$: C, 65.1; H, 3.9%). Methylation of (3c) with CH_2N_2 in ether gave (4) in quantitative yield.

(b) *In aqueous* NaOH *solution*. Oxygen was bubbled through a solution of (1c) (0.25 g, 1 mmol) in a mixture of water (10 ml) and methanol (40 ml) containing NaOH (1.5 mmol) at room temperature for 20 h. The mixture was acidified with dilute hydrochloric acid to pH 4.0 and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give a crystalline mass, which was recrystallized from aqueous methanol to give (3c) (0.17 g, 70%), identical with that obtained above.

Alkaline Hydrolysis of Compound (3c).—A solution of (3c) (0.1 g) in 1N-NaOH solution (2 ml) was warmed at 50 °C for 30 min. The mixture was acidified with 1N-HCl (2 ml) and evaporated *in vacuo* to dryness to give a residue (0.22 g) containing NaCl. The g.l.c. analysis of the residue after silylation with bis(trimethylsily)acetamide (BSA) showed that it consists of the 1 : 1 mixture of salicylic acid and *p*-hydroxybenzoic acid. Separation of the mixture by preparative t.l.c. developing with EtOAc gave salicylic acid (40 mg) and *p*-hydroxybenzoic acid (35 mg), which were identical with authentic samples.

Oxygenation of Compound (1e) *in DMF containing* Bu^{t}OK.—Oxygen was bubbled through a solution of (1e) (0.54 g, 2 mmol) and Bu^{t}OK (0.45 g, 4 mmol) in DMF (20 ml) at room temperature for 1.5 h. The mixture was acidified with AcOH, diluted with excess of aqueous NH_4Cl solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give (3e) as a crystalline solid (0.35 g), which was recrystallized from chloroform–light petroleum to give prisms, m.p. 122—123 °C, $\nu_{max.}$(Nujol) 1 730 and 1 690 cm^{-1} (Found: C, 65.65; H, 4.5. Calc. for $C_{15}H_{12}O_5$: C, 66.15; H, 4.45%). Methylation of products obtained in the alkaline hydrolysis of (3e) gave equimolar amounts of methyl 2,4-dimethoxybenzoate and methyl benzoate in quantitative yields, respectively (identical with authentic samples).

Oxygenation of Compound (1g) *in Aqueous Alkaline Solution*.—Oxygen was bubbled through a solution of (1g) (3.8 g, 14 mmol) in aqueous NaOH (42 mmol) solution (600 ml) at room temperature for 22 h. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract contained (1g) (0.14 g) as crystals which were separated by filtration. The aqueous layer after the ether extraction was evaporated under a reduced pressure to dryness to leave a solid residue containing NaCl and *p*-hydroxyphenylglyoxylic acid (9a) (yield 39%). The yield of (9a) was determined by g.l.c. analysis of its silylated product obtained by treating the residue with BSA, and by treating the residue with alkaline hydrogen peroxide at room temperature for a few minutes followed by the usual work-up to give (10) (identical with an authentic sample) in quantitative yield based on (9a) in the residue. The ethereal filtrate was dried (Na_2SO_4) and evaporated to leave a solid residue (2.6 g), which was shown to be a mixture of (8a) (62%), (9a) (35%), and (10) (26%) by g.l.c. analysis of the silylated products obtained by treating the residue from the filtrate with BSA.

Formation of Compound (11).—The residue obtained from the aqueous mother layer (see above) was heated with *o*-phenylenediamine (0.5 g) in ethanol (7 ml) at 80 °C for 30 min. 3-(p-*Hydroxyphenyl*)*quinoxalin*-2(1H)-*one* (11) crystallized when cooling the mixture, yellow crystals in 70% yield based on (9a) in the residue, m.p. 300 °C (decomp.), $\nu_{max.}$(Nujol) 3 400 and 1 680 cm^{-1} (Found: C, 70.25; H, 4.3; N, 11.4. $C_{14}H_{10}N_2O_2$ requires C, 70.6; H, 4.25; N, 11.75%).

Oxygenation of Compound (1g) *in Absolute Methanol containing* MeONa.—Oxygen was bubbled through a solution of (1g) (0.54 g, 2 mmol) in absolute methanol containing MeONa (6 mmol) at room temperature for 27 h. The mixture was acidified with 6 ml of 1N-HCl with ice-cooling, diluted with an excess of ice–water, and extracted with ether. From the aqueous layer after evaporation (9a) was obtained in 31% yield as determined by the same procedure described above. The ether layer was extracted with 5% $NaHCO_3$ solution. The organic solution was dried (Na_2SO_4) and evaporated to give an oily residue (0.26 g), which was chromatographed on t.l.c. (silica gel), eluting with ethyl acetate–chloroform (1 : 5) to give methyl 4-hydroxyphenylglyoxylate (9b) (40%) and methyl 2,4-dihydroxybenzoate (8b) (28%), identical with an authentic sample. Compound (9b) has $\nu_{max.}$(Nujol) 3 300, 1 730, and 1 700 cm^{-1}; δ ($CDCl_3$) 4.0 (3 H, s), 6.9 (2 H, d), and 7.9 (2 H, d). Alkaline H_2O_2 oxidation of the product gave (10) in quantitative yield.

The $NaHCO_3$ extract was acidified and evaporated to dryness to give a solid residue, which was shown to contain (8a) (33%) and (10) (20%) by the method described above.

[8/1942 *Received*, 7*th November*, 1978]

REFERENCES

[1] A. Nishinaga and T. Matsuura, *J.C.S. Chem. Comm.*, 1973, 9.

[2] O. Hayaishi, 'Molecular Mechanism of Oxygen Activation,' Academic Press, New York–London, 1974, pp. 405—451; T. Matsuura, *Tetrahedron*, 1977, **33**, 2869.

[3] T. Oka. E. J. Simpson, and H. G. Krishnamurty, *Canad. J. Microbiol.*, 1972, **18**, 493 and references cited therein.

[4] H. Sakamoto, *J. Japan Biochem. Soc.*, 1963, **35**, 633.

[5] S. Hattori and I. Noguchi, *Nature*, 1959, **184**, 1145.

[6] Similar results were also obtained in the photosensitized oxygenation of 3-hydroxyflavones; T. Matsuura, H. Matsushima, and R. Nakashima, *Tetrahedron*, 1970, **26**, 435.
[7] J. Alger and J. P. Flynn, *Proc. Roy. Irish. Acad.*, 1934. **42B**, 1; T. Oyamada, *J. Chem. Soc. Japan*, 1934, **55**, 1256.
[8] C. G. Nordstrom and C. Majani, *Suomen Kem.*, 1965, **B38**, 239.
[9] A. Nishinaga, T. Itahara, T. Shimizu, and T. Matsuura, *J. Amer. Chem. Soc.*, 1978, **100**, 1820.
[10] G. A. Russell, 'Peroxide Reaction Mechanism,' ed. J. O. Edwards, Interscience, New York, 1962, p. 107.
[11] A. Nishinaga, T. Shimizu, and T. Matsuura, *Chem. Letters*, 1977, 547.
[12] T. Matsuura, H. Matsushima, and H. Sakamoto, *J. Amer. Chem. Soc.*, 1967, **89**, 6370.
[13] C. G. Nordstrom, *Suomen Kem.*, 1968, **B41**, 351.
[14] C. G. Nordstrom, R. Hakalax, and L. J. Karumaa, *Suomen Kem.*, 1963, **B36**, 102.
[15] A. Nishinaga, T. Shimizu, and T. Matsuura, unpublished data.
[16] R. Hiatt, 'Organic Peroxides.' ed. D. Swern, Wiley–Interscience, New York–London–Sydney–Toronto, 1971, vol. II. pp. 1—151.
[17] M. A. Smith, R. L. Levine, and K. G. Henzel, *J. Org. Chem.*, 1972, **39**, 261.
[18] A. Nishinaga, T. Tojo, and T. Matsuura, *J.C.S. Chem. Comm.*, 1974, 896.
[19] A. Nishinaga, 'Biochemical and Medical Sspects of Active Oxygen,' eds. O. Hayaishi and K. Asada, The University of Tokyo Press, 1977, pp. 13—27.