Oxygenation of 3-Hydroxyflavones by Superoxide Anion

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Summary The oxidation of 3-hydroxyflavones by superoxide anion in tetrahydrofuran results in oxidative cleavage of the heterocyclic ring to give 2-benzoyloxyphenylglyoxylic acids without the loss of carbon monoxide.

QUERCETINASE, the dioxygenase produced by *Aspergillus flavus*, catalyses the oxidative cleavage of the heterocyclic ring of quercetin and other 3-hydroxyflavones (**1**) with molecular oxygen to give the corresponding depsides (**3**) and carbon monoxide.[1] Photosensitized,[2] base-catalysed,[3] and Co(salen)-catalysed[4] [salen = ethylenebis(salicylideneaminato)] oxygenation of 3-hydroxyflavones causes a similar type of degradation.

Superoxide ion is formed in several biochemical reactions involving molecular oxygen. The study of the interaction of superoxide ion with organic substances, especially with metabolic intermediates, should aid our understanding of the mechanism of biological oxidations involving molecular oxygen.[5]

We now find that the reaction of the 3-hydroxyflavones (**1**) with superoxide anion in tetrahydrofuran (THF) results in oxidative cleavage of the heterocyclic ring to give the 2-benzoyloxyphenylglyoxylic acids (**2**) in good yield without the loss of carbon monoxide. No reaction was observed, however, with (**1**; R^1 = OH, R^2 = R^3 = H). KO_2 and 18-crown-6 ether were treated with a solution of (**1**) in THF at ambient temperature. The mixture was then diluted with 10% hydrochloric acid and extracted with ether; evaporation then gave the crystalline products (**2**) (Table).

The structures of the products (**2**) were confirmed by their spectral data and elemental analyses and also by alkaline hydrolysis which yielded the known hydrolysates.

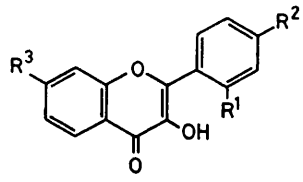
The ring-cleavage reaction rate was dramatically increased by adding $Cu(acac)_2$ (Hacac = pentane-2,4-dione) to the reaction mixture.

The sodium salt of 3-hydroxyflavone (**1a**) did not react with KO_2 and Na_2O_2 (with added 18-crown-6 ether). However, its reaction with O_2 in THF proceeded rapidly and yielded the corresponding depside (**3a**) and carbon monoxide.

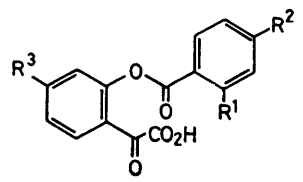
TABLE. Oxygenation of 3-hydroxyflavones (**1**) by O_2^- in THF at room temperature.[a]

	t/h[b]	% yield[c] of (**2**)	M.p./°C	ν_{CO}/cm^{-1}
(**1a**)	5	90	149	1690, 1670
(**1b**)	10	76	155	1720, 1700, 1680
(**1c**)	10	83	180—181	1693 (br.)
(**1d**)	10	52	152	1670, 1650
(**1e**)	10	73	94	1695, 1670
(**1f**)	10	75	159	1690, 1650
(**1g**)	10	84	148	1680 (br.)

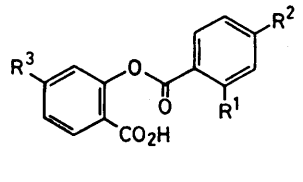
[a] 2 mmol of (**1**), 8 mmol of KO_2, and 0·8 mmol of 18-crown-6 ether in 10 ml THF were used. [b] Reaction time. [c] Isolated yield.



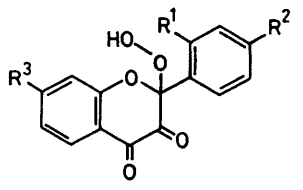
(**1**)



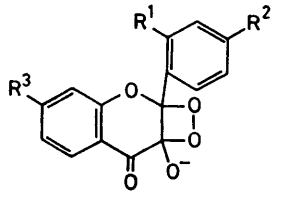
(**2**)



(**3**)



(**4**)



(**5**)

a; R^1 = R^2 = R^3 = H
b; R^1 = R^3 = H, R^2 = OH
c; R^1 = R^3 = H, R^2 = OMe
d; R^1 = H, R^2 = R^3 = OH
e; R^1 = OMe, R^2 = R^3 = H
f; R^1 = R^2 = H, R^3 = OMe
g; R^1 = H, R^2 = R^3 = OMe

The degradation reaction of the flavones (**1**) with O_2^- is rationalized by assuming a radical intermediate, formed through hydrogen abstraction by O_2^-, which reacts further with O_2^- to give a 2-hydroperoxide intermediate (**4**) from which the final products (**2**) are formed *via* the dioxetan intermediate (**5**). It seems likely that by the decomposition of the hydroperoxide the intramolecular A_N reaction proceeds exclusively at the C-3 position of (**4**).

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