Base-catalysed Autoxidation of 3,4′-Dihydroxyflavone

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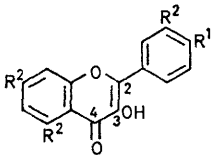
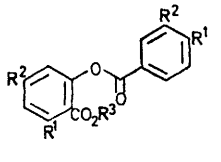
Summary Autoxidation of 3,4′-dihydroxyflavone in dimethylformamide in the presence of potassium t-butoxide results in oxidative cleavage of the heterocyclic ring to give 2-(4-hydroxybenzoyloxy)benzoic acid and carbon monoxide in excellent yield; this provides a nonenzymic model for the reaction of quercetinase.

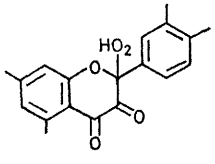
QUERCETINASE, the dioxygenase produced by *Aspergillus flavus*, catalyses oxidative cleavage of the heterocyclic ring of quercetin (Ib) and other 3-hydroxyflavones with molecular oxygen to give corresponding depsides of type (II) and carbon monoxide. Oxygen is incorporated at C-2 and C-4, and C-3 is liberated as carbon monoxide.[1] Photosensitized oxygenation of 3-hydroxyflavones causes a similar type of degradation suggesting that singlet excited oxygen may participate in the reaction.[2]



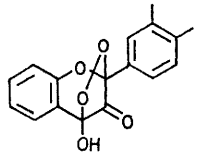
(I) a; R^1=OH, R^2=H
b; R^1=R^2=OH



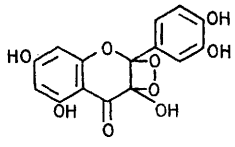
(II) a; R^1=OH, R^2=R^3=H
b; R^1=OMe, R^2=H, R^3=Me
c; R^1=R^2=OH, R^3=H
d; R^1=R^2=OMe, R^3=Me



(V)



(VI)



(VII)

We now find that autoxidation of 3,4′-dihydroxyflavone (Ia) in dimethylformamide (DMF) in the presence of Bu^{t}OK results in oxidative cleavage of the heterocyclic ring to give the depside (IIa) and carbon monoxide in excellent yield. The present result provides a nonenzymic model for the reaction of quercetinase.

When oxygen was bubbled through a solution of (Ia) (1 mmol) in DMF (20 ml) containing Bu^{t}OK (5 mmol) at room temperature, the initial red colour changed to yellow within 30 min. The mixture was then acidified and diluted with water; ether extraction gave (IIa) (91%), m.p. 183—183·5°, whose structure was confirmed by the fact that alkaline hydrolysis quantitatively gave salicylic acid (III) and 4-hydroxybenzoic acid (IV). Further, the methylated compound (IIb), m.p. 82—84°, was identical with authentic synthesized from methyl salicylate and 4-methoxybenzoyl chloride. No O_2 uptake was observed but the CO liberated (98%) was determined by i.r. analysis.

The autoxidative degradation of (Ia) is rationalized by assuming a hydroperoxide intermediate (V) probably formed by the radical-chain mechanism generally considered to operate in the base-catalysed autoxidation of organic compounds,[3] which can undergo rearrangement to the five membered cyclic peroxide (VI), C-3 being lost as CO. Such a decarbonylation has been noted previously.[2,4]

Autoxidation of (Ia) also proceeds rapidly in Me_2SO containing Bu^{t}OK to give the depside (IIa) but slowly in MeOH–MeONa or H_2O–NaOH to give a mixture of (IIa) and its hydrolysed products (III) and (IV), the ratio of (IIa) to (III) or (IV) depending on the amount of base used. Neither (III) nor (IV) is detected in anhydrous DMF or Me_2SO containing Bu^{t}OK.

3-Hydroxyflavone was not susceptible to autoxidation in DMF or Me_2SO containing Bu^{t}OK, indicating that the OH group at the 4′-position plays an important role in the autoxidation. The influence of hydroxy-substitution upon the susceptibility of 3-hydroxyflavones to autoxidation in aqueous solution has been studied; it has been shown that a 4′-OH group is necessary for a high rate of oxidation.[5] Autoxidation of (Ib) in DMF containing Bu^{t}OK is complicated and the amount of O_2 taken up and of CO liberated depend on the amount of Bu^{t}OK used. Methylation of the mixture with CH_2N_2 in MeOH gave, among other products, the methyl derivative (IId) of the depside (IIc) (5—20%). Autoxidation of quercetin in aqueous alkaline solution has been reported to give 2,4,6-trihydroxyphenylgloxylic acid besides protocatechuic acid, phloroglucinol, and 2,4,6-trihydroxybenzoic acid,[6] indicating that the decomposition of the hydroperoxide (V) from (Ib) can proceed *via* the dioxetan intermediate (VII) as well as a peroxide of type (VI).

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