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The base-catalyzed oxygenation of quinoline derivatives

Miklós Czaun[a] and Gábor Speier[a,b,*]

[a]*Department of Organic Chemistry, University of Veszprém, Veszprém 8201, Hungary*
[b]*Research Group for Petrochemistry, Hungarian Academy of Sciences, 8200 Veszprém, Hungary*

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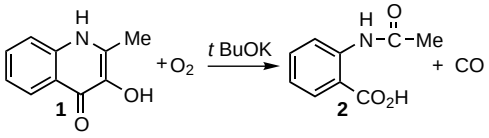
Abstract—The base-catalyzed oxygenation of 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline leads to cleavage products derived from either an endoperoxide or a 1,2-dioxetane intermediate. A persistent 1*H*-2-phenyl-3-oxy-4-oxoquinoline radical could also be detected by EPR in the reaction mixture.

Quinolines and related *N*-heterocyclic compounds are widespread in our environment and are used as raw materials in the chemical industry. They are produced naturally, mainly by higher plants and many of them are biologically more active than their homocyclic analogues.[1] Bacteria have evolved strategies for metabolizing these heteroaromatic compounds.[2] Bacterial strains utilizing quinoline or quinoline derivatives have been isolated and their metabolism has been studied. Intermediates of the catabolic pathways were isolated and characterized, and enzymes catalyzing the degradative steps have been purified, and two different pathways for the degradation of quinoline were proposed.[3,4] A novel type of ring-scission enzyme was discovered (1*H*-3-hydroxy-4-oxoquinaldine 2,4-dioxygenase) that catalyzes the cleavage of two C–C double bonds with concomitant formation of carbon monoxide.[5] With flavonol 2,3-dioxygenase[6] and aci-reductone oxidase[7] they form a unique class of CO-releasing enzymes. Base-catalyzed dioxygenolytic cleavage of 1*H*-3-hydroxy-4-oxoquinaldine **1** was claimed to proceed in the same way (Eq. (1)).[4] Due to our interest in CO-releasing enzyme models and especially on quercetin 2,4-dioxygenase models,[8] studies on the base-catalyzed oxygenation of the isoelectronic 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline were conducted in order to disclose the product composition and possible pathway(s) of the reaction.



(1)

We reacted 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline **3a** with dioxygen in various solvents such as DMF, DMSO, acetonitrile, and THF in the presence of potassium *tert*-butoxide. The reaction mixture was then hydrolyzed, methylated with diazomethane and subjected to GC-MS analysis. The composition of the reaction products is compiled in Table 1 and a possible mechanism of formation is depicted in Scheme 1. The EPR spectrum of the reaction mixture (Fig. 1) indicated the presence of the 1*H*-2-phenyl-3-oxy-4-oxoquinoline radical **5a** with hyperfine structure ($g = 2.0052$, $a_N = 1.69$, $a_H = 1.19$, $a_{H'} = 1.07$, and $a_{H''} = 0.24$ G). Its concentration was calculated as ~12% (after 10 min, conditions as in Table 1) based on quantitation of the EPR spectrum and UV–vis measurements ($\lambda_{max} = 532$ nm; $\varepsilon = 141900$). The radical does not form when either O_2 or ^{t}BuOK is absent. The intense red color of the

Table 1. Product composition of the base-catalyzed oxygenation of **3a** in various solvents[a]

Product	THF	MeCN	DMF	DMSO
7a	0.1384	0.0823	0.6210	0.3264
8a	0.1421	0.3791	0.0664	0.0419
9	0.3435	0.4305	0.1024	0.2817
12a	0.0891	0.1475	0.0276	0.1043
13	0.2011	0.0514	0.0314	0.2664

[a] The amounts are given in mmols determined by GC–MS using benzoin as internal standard. Reaction conditions: 1 mmol substrate, 1 mmol ^{t}BuOK, 15 mL solvent, atmospheric O_2, 25°C, 6 h.

Keywords: quinoline; dioxygenation; base-catalysis; endoperoxide; 1,2-dioxetane.

* Corresponding author. Tel.: +36-88-422-022/4657; fax: +36-88-427-492; e-mail: speier@almos.vein.hu

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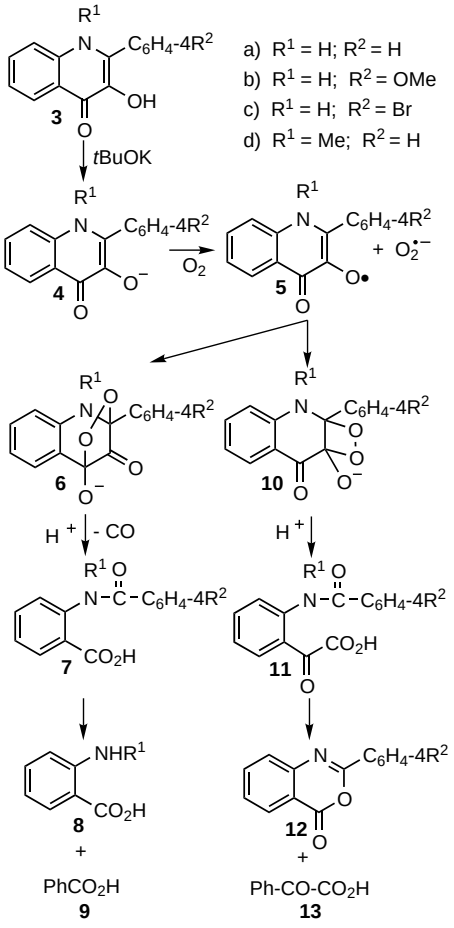

Scheme 1. The proposed mechanism for the oxygenation of 1*H*-2-phenyl-3-hydroxy-4-oxoquinolines.

solution prevails for some hours, and on heating to boiling, slow decay was observed. The radical **5a** could not be generated by the reaction of **3a** with either TEMPO or galvinoxyl. They did not catalyze the oxygenation of **3a** contrary to the O-analog flavonol.[9]

The degradation products formed, their composition, and the presence of an organic radical in the reaction mixture led us to conclude that the reaction proceeds via a SET mechanism and the products can be derived from either the endoperoxide **6a** and/or 1,2-dioxetane **10a** intermediates. The ratio of the two reaction pathways, based and calculated from the product composition, is dependent on the solvent. Estimated endoperoxide/1,2-dioxetane ratios are as follows: 50:50 (THF), 70:30 (MeCN), 92:8 (DMF), and 50:50 (DMSO). Product distributions of the oxygenation of compounds **3b–d** are shown in Table 2. In conclusion, the base-catalyzed oxygenation of 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline and its 4-substituted derivatives proceeds via a SET mechanism, where the 1*H*-2-phenyl-3-hydroxy-4-oxoquinolines **3** are deprotonated by the base to their anions **4**, which transfer one electron to dioxygen forming the radicals **5** and superoxide ion. The persistent 1*H*-2-phenyl-3-oxy-4-oxoquinoline radical **5a** could be detected by EPR, and the ratio of the two main reaction pathways—via an endoperoxide or 1,2-dioxetane—could be deduced from the product composition. Their ratio is very much dependent on the solvent. Kinetic studies on these reactions are underway in our laboratory in order to gain more insight into the mechanism of the oxidative degradation of quinoline derivatives.

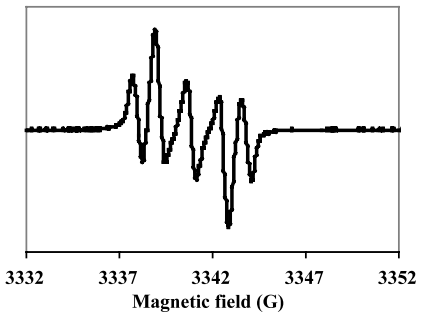

Figure 1. The EPR spectrum of the 1*H*-2-phenyl-3-oxy-4-oxoquinoline radical in DMF.

Table 2. Product composition of the base-catalyzed oxygenation of **1b–d** in DMF[a]

Products	3b	3c	3d
7	0.2707	0.0986	–
8	0.1913	0.1723	0.3147
9	0.2127	0.5240	0.4256
12	0.2245	0.0560	0.3121
13	0.0214	0.0181	0.0196

[a] Conditions as indicated in Table 1.

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