Regiocontrolled Photooxygenation of Ibuprofen by Pyrimido[5,4-*g*]pteridinetetrone– and Anthraquinone–Oxygen Systems

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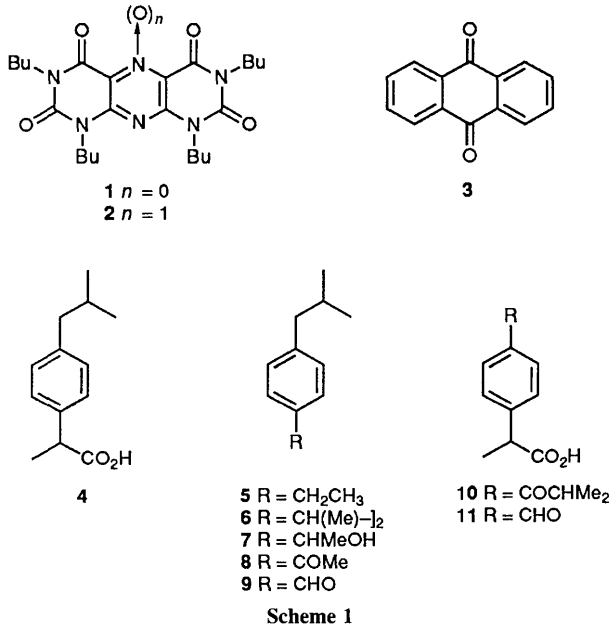
Ibuprofen [2-(4-isobutylphenyl)propionic acid] **4** underwent regiocontrolled photooxygenation on the propionic acid and isobutyl moieties in the presence of pyrimido[5,4-*g*]pteridinetetrone **1**– and anthraquinone **3**– oxygen systems.

Our previous work has shown that pyrimido[5,4-*g*]pteridinetetrone *N*-oxide **2** [$E_{\frac{1}{2}}^{red}$ = −0.97 V *vs.* standard calomel electrode (SCE) in MeCN] functions efficiently as an electron acceptor and oxygen-atom transfer agent under photochemical conditions.[1] For example, phenylacetic acids undergo photooxidative decarboxylation in the presence of **2** to give the corresponding benzaldehydes as ultimate products *via* an initial single-electron transfer (SET) from the phenylacetic acids to a singlet excited **2**. Use of pyrimido[5,4-*g*]pteridinetetrone **1** ($E_{\frac{1}{2}}^{red}$ = −1.21 V *vs.* SCE, in MeCN) as an electron acceptor under argon causes photochemical decarboxylation of the phenylacetic acids.[2]

Photolysis of Ibuprofen [2-(4-isobutylphenyl)propionic acid] **4**, a widely used nonsteroidal antiinflammatory drug, has been studied in view of its phototoxicity; the products identified arise from the initial decarboxylation of the propionic acid moiety.[3] On the other hand, biotransformations of **4** are known to give products oxygenated on the isobutyl moiety.[4] In the above context, our attention has been directed to the preferential photooxygenation on the isobutyl moiety of **4**, which chemically mimics its biotransformation.

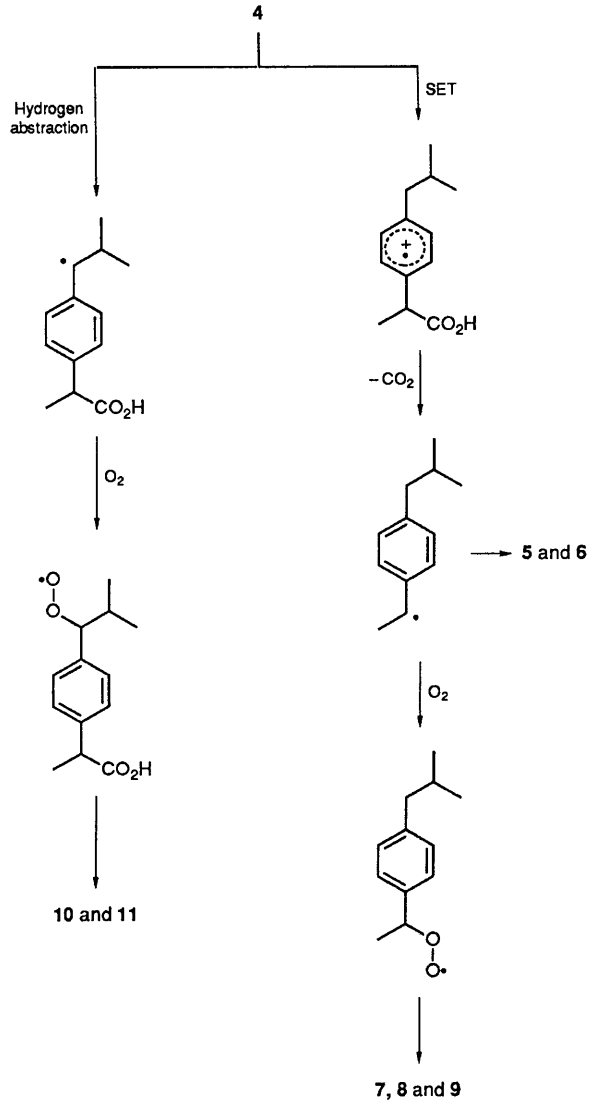
The present paper describes the regiocontrolled photooxygenation of the side chains of **4** by using **1**– and anthraquinone **3** ($E_{\frac{1}{2}}^{red}$ = −0.93 V *vs.* SCE)–oxygen systems. The present results provide an interesting example of a mechanism-based photooxygenation the regiochemistry of which is well controlled by selection of appropriate additives.

A mixture of **4** (1.0 mmol) and **1** (0.1 mmol) in dry MeCN (20 ml) was irradiated with a 400 W high-pressure mercury arc lamp through a $BiCl_3$ solution filter (>355 nm) at ambient temperature under oxygen for 3 h.† TLC–densitometric analysis of the reaction mixture showed the presence of seven



Scheme 1

† Compound **4** is very stable under the photochemical conditions used in the absence of the electron acceptors.



Scheme 2

Table 1 Photochemical degradation of **4** by using the **1**– or **3**–O_2 system

	Yield of products (%)[a]						
	5	**6**	**7**	**8**	**9**	**10**	**11**
1–O_2	trace	trace	37.1	18.0	2.2	1.1	1.7
3–O_2	trace	trace	1.9	11.0	2.2	19.5	14.0

[a] Isolated yields based on **4**.

benzenoid products, **5**–**11**,‡ along with unchanged **4** (30.3%) and **1** (85%). After repeated column chromatographic separation, the structures of the photoproducts were confirmed by NMR, UV and mass spectroscopy or by spectral comparison with authentic samples.[3,5]

In a similar manner a mixture of **4** and **3** in MeCN was irradiated under oxygen for 3 h and the formation of the products **5**–**11** was confirmed. Use of other electron acceptors such as 3,10-dibutylisoalloxazine and 9,10-dicyanoanthracene in place of **1** or **3** gave unsatisfactory results because they were inefficient (<5% conversion of **4**). Yields of the photoproducts in the reactions of **4** with **1** and **3** are summarised in Table 1.

Trace amounts of decarboxylated, **5**, and dimeric, **6**, products were obtained in both reactions.§ The most interesting observation is a significant difference in total yields of products oxygenated on the propionic acid and isobutyl moieties between **1** and **3**, *i.e.*, in the case of **1** the ratio (**10** + **11**)/(**7** + **8** + **9**) was 0.05, which changed drastically (2.22) upon use of **3** in place of **1**.

There are ample precedents for the photochemical decarboxylation of arylacetic acids in the presence of various electron acceptors involving photoinduced SET followed by decarboxylation.[2]§ Thus, the formation of the decarboxylated products **7**, **8** and **9** is reasonably interpreted by an initial SET and decarboxylation pathway. This pathway is predominant for the photooxygenation of **4** by the **1**–oxygen system (see Scheme 2). The photochemistry of quinoid compounds is well established.[6] The photooxidation by anthraquinones has been demonstrated to be initiated by a hydrogen abstraction rather than a SET.[7]

Taking these facts into consideration, the preferential formation of the products **10** and **11** in the photooxygenation of **4** by the **3**–oxygen system can be rationalised in terms of an initial hydrogen abstraction on the α-position of the isobutyl moiety by an excited **3**. The biological oxygenation of **4** has been proved to occur in the α-, β- and γ-positions of the isobutyl moiety. The formation of **10** in the present photooxygenation is analogous to one of these biological oxygenations.

In agreement with the present observation, recent studies have demonstrated that the mechanism for enzymatic α-hydroxylation of arylalkanes probably involves an initial hydrogen abstraction by an active oxygen species.[8]

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‡ When the *N*-oxide **2** was used as an oxidant under degassed photochemical conditions in place of the **1**–oxygen system, the preferential formation of the oxidative decarboxylation products **7** and **8** was observed in agreement with the example of phenylacetic acids which was previously reported (*cf.* ref. 2).

§ Photolysis of **4** in the presence of **1** under argon gave **5** and **6** as major products, indicating that **1** functions as an electron acceptor under the photochemical conditions.