Hydrolysis of Isoalloxazines (Flavins) in the Ground and Excited States

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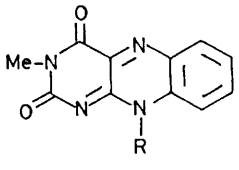
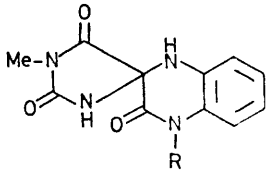
Summary The hydrolysis of 10-alkyl-3-methylisoalloxazines (flavins) and their 5-oxides with benzyltrimethylammonium hydroxide in dimethylformamide or alcoholic potassium hydroxide in the dark gave the corresponding spirohydantoins, while the same reaction under irradiation brought about the elimination of the 10-alkyl group

(in the case of lower alkyls) to give 3-methylalloxazine; treatment of the spirohydantoins with concentrated sulphuric acid caused intramolecular dehydration to give the original isoalloxazines.

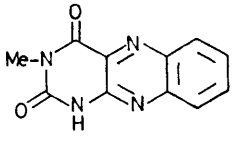
WE report the initial reaction of simple 3,10-disubstituted isoalloxazines with hydroxide ion as a representative nucleophile in the ground state, which eventually gives the corresponding spirohydantoins as the main products *via* nucleophilic addition to the 10a-position. Furthermore, we describe the hydrolysis of isoalloxazines in the excited state, which leads to the elimination of the 10-alkyl groups (in the case of lower alkyls) to give the corresponding alloxazines.



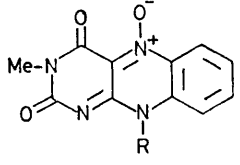
(I)



(II)



(III)



(IV)

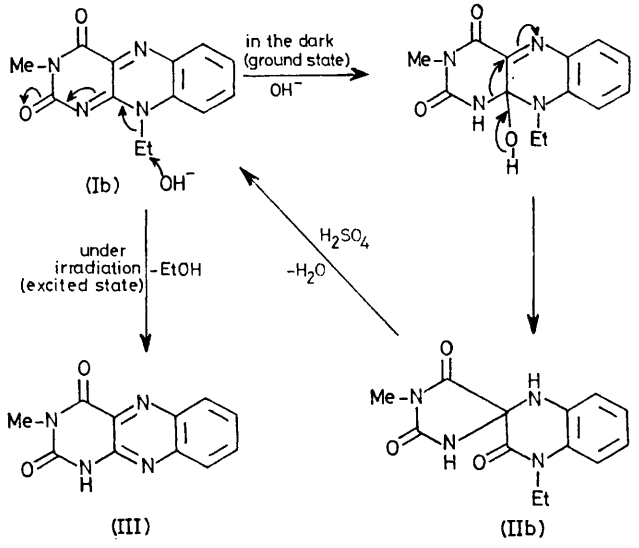
Stirring of 3,10-dimethylisoalloxazine (Ia)[1] (1·2 mmol) in dimethylformamide (3 ml) with 30% methanolic benzyltrimethylammonium hydroxide (1·8 mmol) at 70 °C for 3 min (or for 40 min at room temperature) in the dark, followed by neutralization with acetic acid, concentration *in vacuo*, and dilution with water, caused the separation of a mixture of the spirohydantoin (IIa)[2] (35%) and 3-methylalloxazine (III)[3] (30%). Treatment of other isoalloxazines (Ib—d)[1] possessing higher alkyl groups at the 10-position with benzyltrimethylammonium hydroxide under the same conditions gave the corresponding spirohydantoins (IIb—d) almost exclusively (Table).

TABLE. Formation of spirohydantoins (II).[a]

	R	M.p./°C	% Yield
a	Me	294	35
b	Et	232	59
c	Pr^n	225	67
d	Bu^n	211	72

[a] Typical i.r. data: (IIa), ν_{max} (Nujol) 3305, 3220, 1779, 1728, 1635, and 1600 cm^{-1}.

Calculations on isoalloxazine[4] show that in the first excited state the π-electron density at the 10a-position increases and that at the 10-position decreases in comparison with those in the ground state. This implies that the susceptibility of the 10a-position to nucleophilic addition would decrease and the nucleophilic dealkylation at the 10-position would be accelerated in the excited state. In fact, treatment of compounds (Ia and b) (1 mmol) with 30% methanolic benzyltrimethylammonium hydroxide (1·8 mmol) in dimethylformamide (3 ml) at 70 °C for 3 min under irradiation with a 100 W high-pressure mercury lamp at a distance of 10 cm (or in indirect sunlight) resulted in elimination of the 10-alkyl group to give 3-methylalloxazine (III) in 85 and 70% yields, respectively. From the mother liquors methanol and ethanol were detected qualitatively by g.l.c. The Scheme shows the typical hydrolysis of (Ib) with hydroxide ion. However, the reactions of (Ic and d) with hydroxide ion under irradiation did not give (III) but only the corresponding spirohydantoins (IIc and d). The alkaline hydrolysis of (I) with 10% alcoholic potassium hydroxide in the dark and with irradiation gave almost the same results as above.



SCHEME

In order to confirm that the dealkylation of (Ia and b) at the 10-position is a nucleophilic displacement in the excited state, we carried out the same experiments in the absence of hydroxide ion under irradiation; the starting materials were completely recovered.

Similar results were obtained for the hydrolysis of the isoalloxazine 5-oxides (IVa—d)[1] both in the dark and under irradiation; the 5-oxide group was first eliminated by nucleophilic attack with hydroxide ion and then the isoalloxazines thus formed gave the same products as described above. The corresponding isoalloxazines were detected at a very early stage of this reaction.

The spirohydantoins (IIa—d) could be considered as a special type of hydrated isoalloxazines. For example, treatment of (IIc) (1 mmol) with 80% aqueous sulphuric acid (3 ml) at 60 °C for 3 min, followed by dilution with water and neutralization with sodium hydrogen carbonate, yielded the original isoalloxazine (Ic) in 75% yield. The present study hints that such an interconversion between isoalloxazines and spirohydantoins might occur in a living organism.

It has been stated that addition to the 10a-position in flavins occurs only under certain circumstances and that the formation of spirohydantoins is 'absolutely irreversible'.[5] Both statements conflict with the evidence presented in this paper.

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