

inate<sup>5</sup> buffer (0.064 *M*), at pH 6.0, yielded optically active benzyl methyl sulfoxide (**4**; R = Me, R' = PhCH<sub>2</sub>),  $[\alpha]_D +3.5^\circ$  in chloroform and  $-6.1^\circ$  in 95% ethanol. The optical purity of the product, with respect to the isomer with the (*R*) configuration, was 6.36% from measurements in chloroform and 6.35% from measurements in 95% ethanol. These percentages were based on the reported<sup>6</sup> specific rotation of the pure isomer with the (*S*) configuration ( $[\alpha]_D -55^\circ$  in chloroform and  $+96^\circ$  in ethanol).

Although the above oxidation reaction was more than 97% complete after 7 hr, a similar optical yield of the isomer with the (*R*) configuration was obtained whether the reaction mixture was left for 6 hr or for 60 hr before the sulfoxide was extracted. Thus, racemization of the optical isomers of the sulfoxide did not occur to an appreciable extent under the experimental conditions.

When phthalate buffer (0.064 *M*) was used as the oxidation catalyst instead of the *d*-2-methyl-2-phenylsuccinate buffer, the reaction yielded optically inactive benzyl methyl sulfoxide.

From a consideration of other dissymmetric tricoordinate sulfur compounds,<sup>7</sup> the iodosulfonium ion **2** (R = Me, R' = PhCH<sub>2</sub>) is expected to be a racemic mixture of two optically active enantiomeric forms. These would be expected to react at different rates with the optically active reagent, *d*-2-methyl-2-phenylsuccinate ion.

While the absolute configuration of *d*-2-methyl-2-phenylsuccinate has not been proved, comparison of ORD curves suggests it has the same configuration as (+)-(*S*)-phenylsuccinic acid.<sup>8</sup>

Because the yield of benzyl methyl sulfoxide (**4**; R = Me, R' = PhCH<sub>2</sub>) from the over-all reaction is

(5) The sample of *d*-2-methyl-2-phenylsuccinic acid ( $[\alpha]_D +22.6^\circ$  in 95% ethanol) used in this study was kindly donated by Parke, Davis and Co. of Detroit, Mich. This sample is estimated to have an optical purity of 80% based on the specific rotation of pure *d*-2-methyl-2-phenylsuccinic acid ( $[\alpha]_D +28.3^\circ$  in 95% ethanol, mp 150.5°) and pure *l*-2-methyl-2-phenylsuccinic acid ( $[\alpha]_D -28.5^\circ$  in 95% ethanol, mp 150.5°). An equimolar mixture of the pure enantiomers melts at 163° compared to the true racemate, mp 157–158° (P. A. S. Smith, *J. Am. Chem. Soc.*, **71**, 3418 (1949)), 163–164° (H. Le Moal, A. Foucaud, R. Carrié, J. Hamelin, and C. Sévellec, *Bull. Soc. Chim. France*, 579 (1964)), and 167° (G. Poulain, *ibid.*, 913 (1964)).

(6) K. Mislav, M. M. Green, and M. Raban, *J. Am. Chem. Soc.*, **87**, 2761 (1965).

(7) J. Grundy, "Stereochemistry," Butterworth Inc., Washington, D. C., 1964, p 36.

(8) K. Pettersson, *Arkiv Kemi*, **7**, 347 (1954).

greater than 97%, and the product was only 6.4% richer in one optical isomer than the other, either the rates of the attack of the nucleophilic asymmetric catalyst on the two enantiomeric forms of the iodosulfonium species are quite similar, or the indicated equilibrium leading to formation of the acylsulfonium species coupled with the relative rates of cyclic anhydride formation from the two optically active intermediates provide only a limited degree of specificity. Iodide dependence of the over-all reaction kinetics appears to favor the first alternative. However, this optically specific synthesis provides strong evidence that the role of the catalyst in the postulated reaction scheme is correct. An analogy between the above synthesis and a stereospecific enzymic reaction appears particularly apt, especially since, in the former, the energy of oxidation appears to be transferred to the catalyst.<sup>4</sup> Details of these experiments, including ultraviolet spectra, ORD curves, and description of other sulfide systems, will be presented separately.

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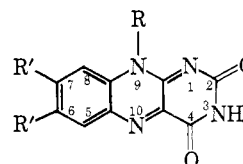
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### The Participation of the Hydroxyl Group in the Photobleaching of 9-(2'-Hydroxy-2'-methylpropyl)isoalloxazine<sup>1</sup>

Sir:

As part of a photochemical study on model flavin compounds, we have studied the photobleaching of 9-(2'-hydroxy-2'-methylpropyl)isoalloxazine (Ic). Experimental results are presented which demonstrate the participation of the hydroxyl group in this photoreaction.

Halwer<sup>2</sup> studied the photobleaching of 9-(2'-hydroxyethyl)isoalloxazine (Ib) and Ic and concluded on the basis of general acid catalysis that the 2'-hydroxyl group was active in the photoreaction. However, since Halwer's work was published it has been well established that alcohols donate hydrogens from the  $\alpha$  carbon during intermolecular photoreduction reactions if they are available.<sup>3,4</sup> Kinetic isotope effects<sup>5</sup> of 2.8 and 2.7 were found for the photoreduction of benzophenone with 2-propanol-2-*d* and benzhydrol- $\alpha$ -*d*, respectively. Photochemical studies on riboflavin (Ia) and Ib have again confirmed this concept.<sup>6,7</sup> A



Ia, R' = CH<sub>3</sub>; R = ribityl  
b, R' = H; R = CH<sub>2</sub>CH<sub>2</sub>OH  
c, R' = H; R = CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH

(1) The Photochemistry of Riboflavin. III. Part II: M. M. McBride and W. M. Moore, *Photochem. Photobiol.*, in press.

(2) M. Halwer, *J. Am. Chem. Soc.*, **73**, 4870 (1951).

(3) W. M. Moore, G. S. Hammond, and R. P. Foss, *ibid.*, **83**, 2789 (1961).

(4) W. M. Moore and M. D. Ketchum, *J. Phys. Chem.*, **68**, 214 (1964).

(5) Kinetic isotope effect ratios in this article are given as the rate or rate constant of the hydrogenated analog divided by the corresponding data for the deuterated system.

(6) W. M. Moore, J. T. Spence, F. A. Raymond, and S. D. Colson, *J. Am. Chem. Soc.*, **85**, 3367 (1963).

(7) E. C. Smith and D. E. Metzler, *ibid.*, **85**, 3285 (1963).

kinetic isotope effect of 2.7 was found for the photobleaching of 9-(2'-hydroxyethyl-2',2'-*d*<sub>2</sub>)isoalloxazine, the  $\alpha$ -deuterio analog of Ib. In addition, it was found that the rate of photobleaching of riboflavin was unaffected by deuterium oxide.<sup>6</sup> Also, 6,7-dimethyl-9-(formylmethyl)isoalloxazine has been isolated from photobleached riboflavin solutions; this confirmed that attack occurred at the 2' position in polyhydroxy flavins.<sup>7</sup> Although several other products resulted from the riboflavin photobleaching, Ib photobleached by a simple pathway which produced only one heterocyclic product, alloxazine (III), and acetaldehyde. This resulted from the collapse of the diradical produced by the hydrogen abstraction reaction.

Kendall and Leermakers<sup>8</sup> have reported that pyruvic acid was photoreduced with *t*-butyl alcohol although this alcohol has been shown to be a poor hydrogen donor<sup>3</sup> due to the absence of hydrogen on the  $\alpha$  carbon. They speculated that the aliphatic hydrogens on the methyl groups were donated, as had Cohen and Aktipis<sup>9</sup> for another system.

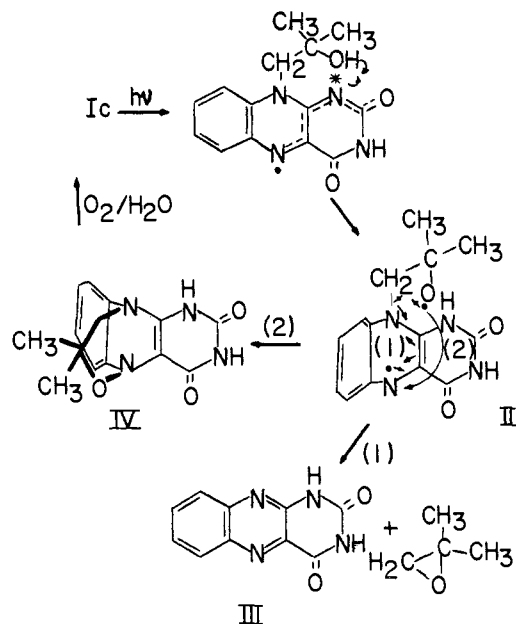
The synthesis of 9-(2'-hydroxy-2'-methylpropyl)isoalloxazine was accomplished by the method of Karrer and Meerwein.<sup>10</sup> Irradiation of  $1.5 \times 10^{-4}$  M Ic in neutral aqueous solution *in vacuo* produced alloxazine (III) and a reduced flavin in a 55:45 ratio. Air oxidation converted the reduced flavin to starting material Ic. Nmr analysis and thin-layer chromatography were used for identification. The rate of photobleaching was followed spectrophotometrically at 430 m $\mu$ , which is the long wavelength absorption maximum for Ic. The photochemical apparatus and procedure were the same as described previously<sup>6</sup> and the light intensity was  $1.2 \times 10^{16}$  quanta sec<sup>-1</sup> cc<sup>-1</sup>. The rate followed pseudo-first-order kinetics in the absorbance range 2 to 1. Simultaneous irradiation of Ic in water and deuterium oxide gave first-order rate constants of  $2.7 \times 10^{-2}$  and  $5.5 \times 10^{-3}$  min<sup>-1</sup>, respectively. This represents a kinetic isotope effect of 4.9.

Polarographic studies on the photobleaching of Ic in 0.1 M potassium chloride confirmed the other results. As measured *vs.* a silver-silver chloride electrode, half-wave potentials of -0.58, -0.42, and -0.22 v were obtained for alloxazine, Ic, and the reduced flavin, respectively. These data show that the reduced flavin is not the 1,10-dihydro form of Ic, but possibly a cyclic reduced flavin since the potential is shifted. Photoreduction of Ic with EDTA confirmed that the 1,10-dihydro form of Ic did indeed have the same half-wave potential as the oxidized flavin Ic.

These experimental results can be explained by the mechanism shown in Scheme I. The isoalloxazine nucleus abstracts the hydroxyl hydrogen atom and produces the diradical II. Although the electron density of semiquinone radical is somewhat delocalized, it is conveniently shown localized at N-10. The diradical can collapse by two pathways which have almost equal potentials. Pathway 1 permits an electronic reorganization to form an epoxide and alloxazine (III). A direct cyclization to form a reduced flavin (IV) can be visualized for pathway 2. Although reduced cyclic

flavins have previously been illustrated as coupling at N-1, the almost equal distribution of products does not permit tautomerization of II with another form containing a free radical site at N-1. However, the exact structure of IV cannot be experimentally verified at present.

Scheme I



The product distribution and the cyclic reduced flavin could be explained in terms of hydrogen abstraction of aliphatic hydrogens, but no *kinetic isotope effect would be expected*. No exchange of deuterium at the aliphatic positions was observed during nmr analysis which was performed in trifluoroacetic acid-deuterium oxide solutions. Also we have found that 9-(2'-keto propyl)isoalloxazine is stable to light,<sup>11</sup> which indicates that methyl groups are resistant to attack in this type of system. Thermochemical calculations on *t*-butyl alcohol indicate that homolytic abstraction of the hydroxyl hydrogen is comparable to abstraction of an aliphatic hydrogen. The sum of the evidence indicates that it is the hydroxyl hydrogen which participates in the anaerobic photoreaction of 9-(2'-hydroxy-2'-methylpropyl)isoalloxazine. Although the mechanism involving the participation of the hydroxyl group may only be applicable to diradical systems, other atypical hydrogen abstraction reactions should be examined more closely.

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(11) W. M. Moore and C. Baylor, Jr., unpublished results.

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### Dihedral Angle and Bond Angle Dependence of Vicinal Proton-Fluorine Spin-Spin Coupling

Sir:

**Dihedral Angle Dependence.** The assumption has been widely made that  $J_{\text{HF}}(\text{etc})$  depends on the dihedral angle between the coupling nuclei in the same way

(8) D. S. Kendall and P. A. Leermakers, *J. Am. Chem. Soc.*, **88**, 2766 (1966).

(9) S. G. Cohen and S. Aktipis, *Tetrahedron Letters*, 579 (1965).

(10) P. Karrer and H. F. Meerwein, *Helv. Chim. Acta*, **18**, 480, 1126 (1935).