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A NEW SYNTHESIS OF 8-HYDROXYISOALLOXAZINES (8-HYDROXYFLAVINS)

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Treatment of isoalloxazine 5-oxides with acetic anhydride yielded the corresponding 8-acetoxyisoalloxazines exclusively, which are labile to hydrolysis to give 8-hydroxyisoalloxazines (8-hydroxyflavins).

Recently the FAD analogue of 8-hydroxy-7-methylisoalloxazine has been isolated as a novel prosthetic group which is associated with NADH dehydrogenase from Peptostreptococcus elsdenii.[1] The proposed structure was confirmed by a chemical synthesis of 8-hydroxy-7-methylisoalloxazine models, which consists of the condensation of 5-alkylamino-o-cresol and violuric acid in the presence of sodium borate (Piloty-type synthesis).[2]

Bruice and coworkers have reported a two-step synthesis of an 8-hydroxyisoalloxazine by the sulfonation of the corresponding isoalloxazine followed by oxidation with hydrogen peroxide.[3]

We now report a new convenient synthesis of 8-hydroxyisoalloxazines (8-hydroxyflavins) starting from the corresponding isoalloxazine 5-oxides.[4]

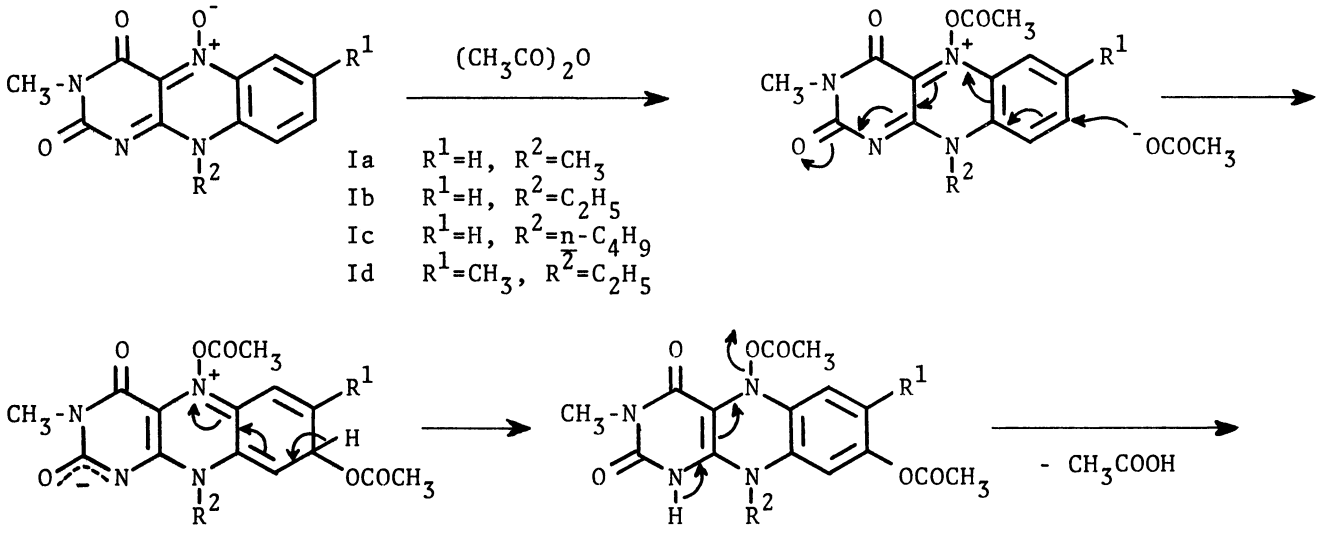
Refluxing of 3,10-dimethylisoalloxazine 5-oxide (Ia)[4] (0.5 g, 0.0019 mol) in a mixture of acetic anhydride and acetic acid (2:1) (5 ml) for 5 hr followed by evaporation of solvent in vacuo and the treatment of the residue with ethanol led to the exclusive formation of 8-acetoxy-3,10-dimethylisoalloxazine (IIa) (0.48 g, 80%). Similarly, heating other flavin 5-oxides (Ib-d) in acetic anhydride-acetic acid yielded the respective 8-acetoxyisoalloxazines (IIb-d). The structures of compounds II were derived on the basis of elemental analyses, molecular weights as determined by mass spectrometry and the presence of a typical ester absorption (1750 cm^{-1} region) in their infrared spectra.

The acetoxyisoalloxazines (II) thus obtained were treated with aqueous ammonia (10 %) at room temperature for 30 min followed by neutralization with acetic acid to afford the corresponding 8-hydroxyisoalloxazines (8-hydroxyflavins) (IIIa-d) in quantitative yields.

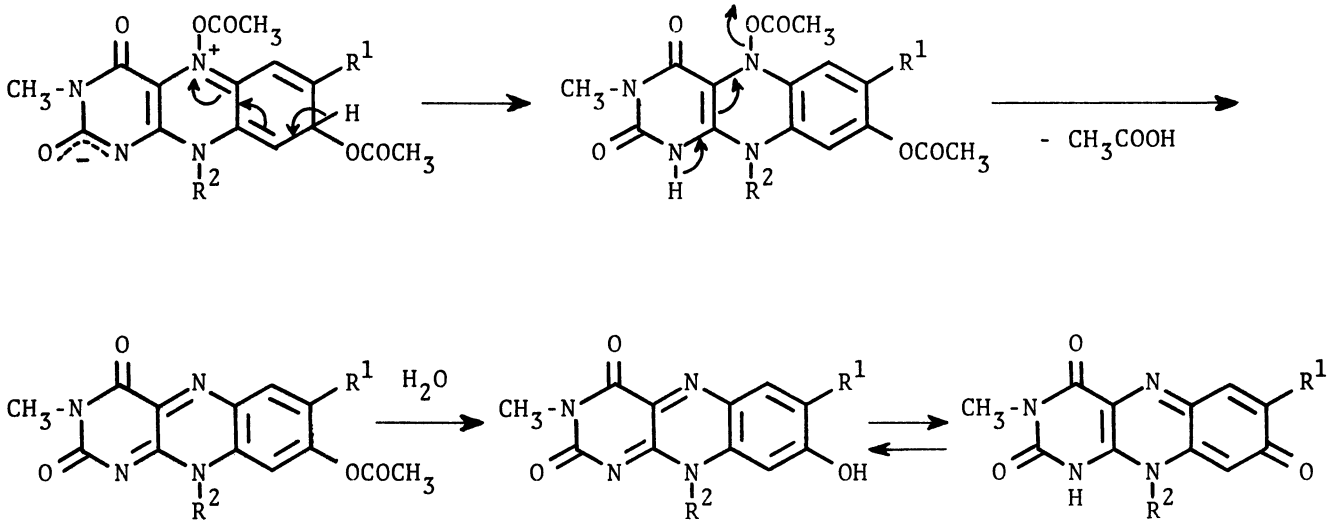
The 8-hydroxyflavins (III) showed spectral characteristics typical of paraquinoid-type flavins (IV)[2,5] in ethanolic solution (absorption maxima at 470- and 310-nm regions and two bands in the uv region), although the structure of compounds III can be represented in several different tautomeric forms.

The conversion of I into II involves the initial addition of acetyl group to the N-oxide group, followed by subsequent acetoxylation by acetoxy anion on the 8-position and loss of the N-acetoxy group. Nucleophilic hydroxylation of aromatic

N-oxides with acetic anhydride with the loss of the N-oxide group have been reviewed.[6] However it should be noted that the hydroxylation in this report was regiospecific to the 8-position of flavins and 6-acetoxyisoalloxazines were not obtained because of a presumable steric hindrance of N-acetoxy group at the 5-position.



Ia R^1=H, R^2=CH_3
Ib R^1=H, R^2=C_2H_5
Ic R^1=H, R^2=n-C_4H_9
Id R^1=CH_3, R^2=C_2H_5



- CH_3COOH

	Mp(°C)	Yield(%)
IIa	260	80
IIb	229	84
IIc	247	82
IId	251	79

	Mp(°C)	Yield(%)
IIIa-d	>360	100

IV

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