A SYNTHESIS OF FLAVINS BY THE REACTION OF 6-(N-ALKYL-ANILINO)-5-NITROURACILS WITH DIETHYL AZODICARBOXYLATE IN THE PRESENCE OF BASE

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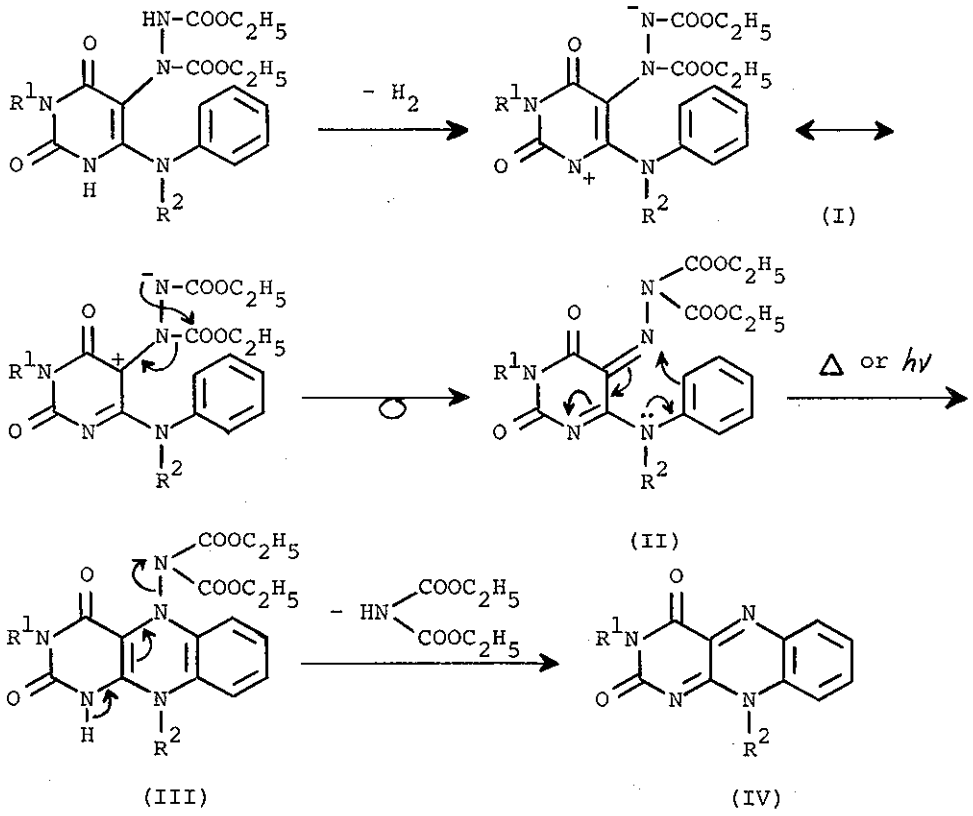
The treatment of 6-(N-alkylanilino)-5-nitrouracils with diethyl azodicarboxylate (DAD) in the presence of bases gave the corresponding isoalloxazines (flavins).

Recently we described a new route to isoalloxazines (flavins) which involves the oxidative cyclization of the Michael-type adducts from 6-(N-alkylanilino)uracils and diethyl azodicarboxylate (DAD).[1] A reasonable intermediate in this reaction is the 1,5- or 1,3-dipolar compound (I), which undergoes intramolecular rearrangement to N,N-bisethoxycarbonylhydrazone (II). Compound II could then cyclize thermally or photochemically to the dihydroisoalloxazine (III) followed by the loss of diethyl iminodiformate to give the corresponding flavin (IV) as depicted in the following scheme.

We have found that the elimination of nitrous acid from the adducts formed by a reaction of 6-(N-alkylanilino)-5-nitrouracils (V) with DAD formed directly the 1,3-dipolar intermediates (I) which



give rise to the flavins. For example, 6-(N-methylanilino)-3-methyl-5-nitrouracil (Va)[2] (1.38 g, 0.005 mol) was heated with an excess of DAD (1.74 g, 0.01 mol) at 140° for 4 hr in the presence of triphenylphosphine (0.65 g, 0.0025 mol). The reaction mixture was diluted with ether and set aside overnight to separate 3,10-dimethyl-isoalloxazine (IVa)[3] (0.90 g, 74%). The reaction of Va (1.38 g, 0.005 mol) with DAD (1.74 g, 0.01 mol) in the presence of pyridine (0.32 g, 0.004 mol) under the same conditions gave also IVa in 59%

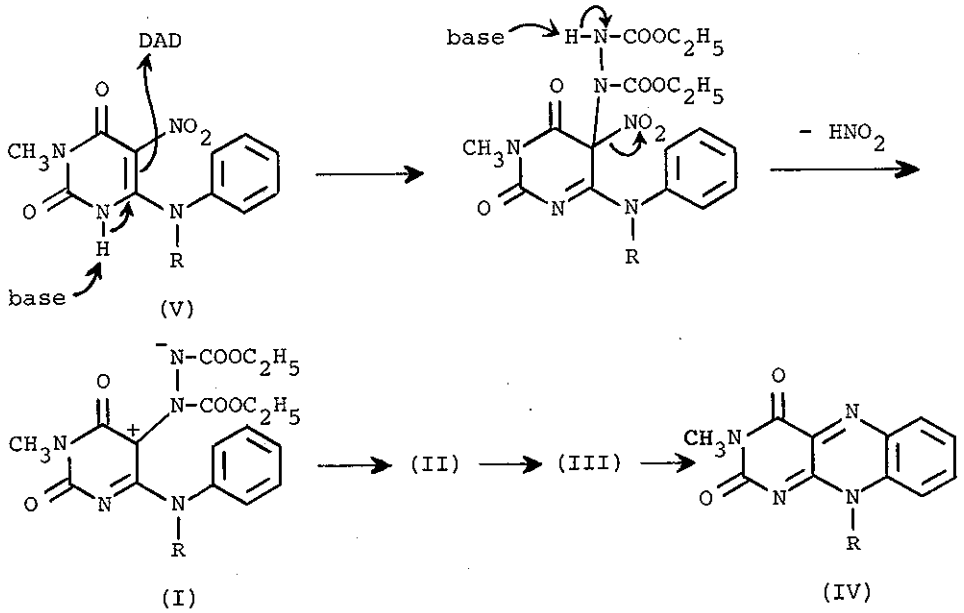
yield. Both heating Va with triphenylphosphine or pyridine alone, and heating Va with DAD in the absence of the base, did not yield the flavin, but the starting material was recovered.

Similarly, the treatment of Vb-d[2] with DAD in the presence of triphenylphosphine or pyridine gave the corresponding flavins (IVb-d)[3] (see Table).

TABLE Flavin Formation of the Reaction of 6-(N-Alkylanilino)-5-nitrouracils with DAD in the Presence of Bases

Compound No.	R	M.p. (°C)	Base	Yield (%)
IVa	CH_3	>360[3]	triphenylphosphine	74
			pyridine	59
IVb	C_2H_5	347[3]	triphenylphosphine	75
IVc	n-C_3H_7	349[3]	triphenylphosphine	70
IVd	n-C_4H_9	335[3]	triphenylphosphine	68
			pyridine	48

This reaction can be explained by initial addition of DAD on the 5-position of the pyrimidine which may be catalyzed by a base to give the Michael-type adduct. Elimination of nitrous acid by means of the base gives a 1,3-dipolar intermediate (I) directly without going through the oxidation process. Subsequent rearrangement and cyclization giving the flavin would be the same as described in the introduction.



Another possible mechanism which could involve a flavin 5-oxide formed by the dehydrative cyclization of the starting material was precluded. Because 3,10-dimethylisoalloxazine 5-oxide[3] remained unchanged when treated with a mixture of DAD and triphenylphosphine under the same conditions.

REFERENCES

1 F. Yoneda, Y. Sakuma, T. Nagamatsu, and S. Mizumoto, J. C. S. Perkin I, 1976, 2398.

2 Y. Sakuma, T. Nagamatsu, and F. Yoneda, J. C. S. Chem. Comm., 1975, 977.

3 F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, J. Amer. Chem. Soc., 98, 830 (1976).

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