

A DICHOTOMY IN THE REACTION OF 6-(N-ALKYLANILINO)-3-METHYL-5-NITROURACILS WITH A MIXTURE OF PHOSPHORUS OXYBROMIDE AND DIMETHYLFORMAMIDE. FORMATION OF FLAVINS OR 5-DEAZAFLAVINS

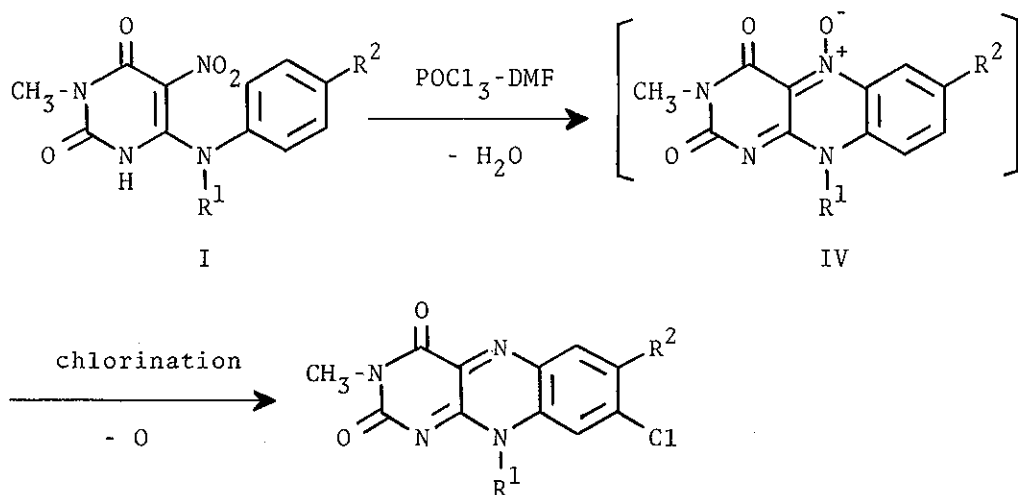
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Treatment of 6-(N-alkylanilino)-3-methyl-5-nitrouracils (I) with a mixture of phosphorus oxybromide and dimethylformamide ( $\text{POBr}_3$ -DMF) at  $80^\circ$  gave the corresponding isoalloxazines (flavins). On the other hand, treatment of I with  $\text{POBr}_3$ -DMF at  $150^\circ$  led to the exclusive formation of pyrimido[4,5-b]quinoline-2,4(3H,10H)-diones (5-deazaflavins).

In the previous paper,<sup>1</sup> it was shown that the treatment of 6-(N-alkylanilino)-5-nitrouracils (I) with a mixture of phosphorus oxychloride and dimethylformamide (the Vilsmeier reagent) caused the initial formation of the flavin 5-oxides (IV) by dehydrative cyclization of I, followed by subsequent chlorination of IV and loss of the N-oxide group to afford the corresponding 8-chloroflavins in a single step. It appeared that the use of a mixture of phosphorus oxybromide and dimethylformamide ( $\text{POBr}_3$ -DMF) in the above reaction would lead to a synthesis of 8-bromoflavins.

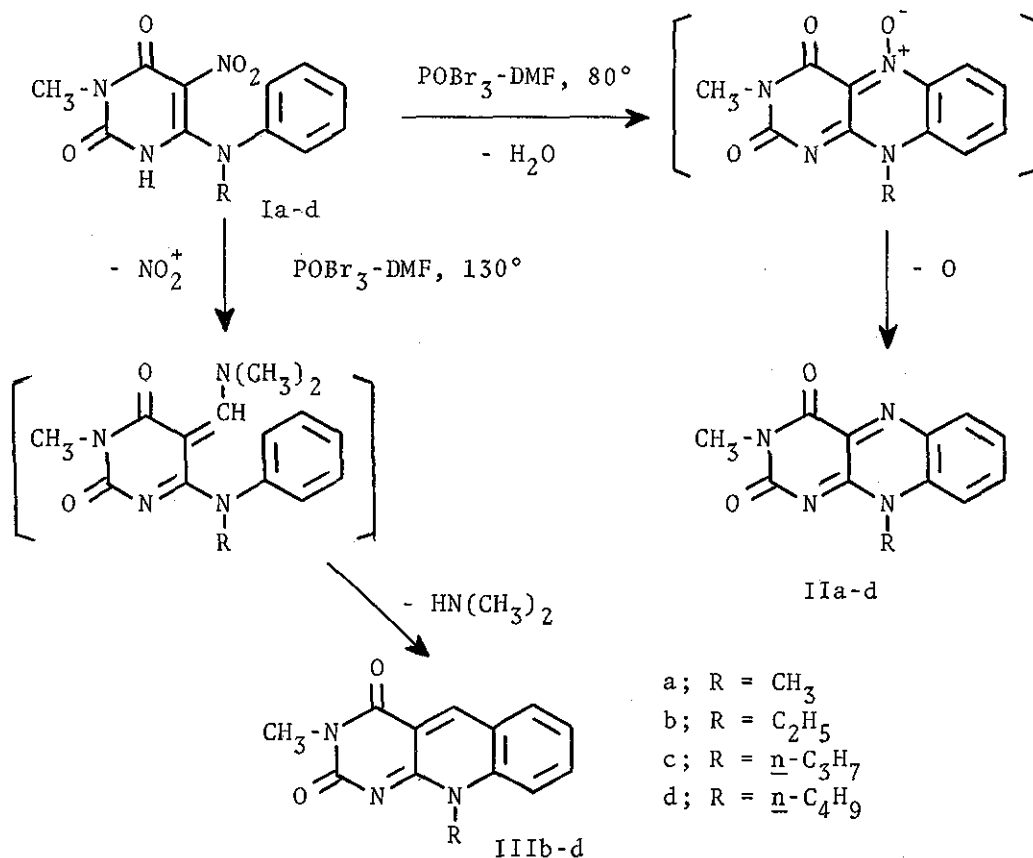
We have found, however, that the reaction of I with  $\text{POBr}_3$ -DMF gave no desired 8-bromoflavins and led to a dichotomy of the products according to the reaction temperature as described below.



Stirring of 6-(N-alkylanilino)-3-methyl-5-nitrouracils (Ia-d)<sup>2</sup> in  $\text{POBr}_3$ -DMF at 80° for 2 hr caused intramolecular dehydrative cyclization and subsequent deoxygenation<sup>3</sup> to afford the corresponding isoalloxazines (flavins) (II)<sup>4</sup> which include no bromine (see Table and Experiment). When this reaction was carried out at 130° for 1 hr, the corresponding pyrimido[4,5-b]quinoline-2,4(3H,10H)-diones (5-deazaflavins) (III)<sup>5</sup> was exclusively formed, probably by the introduction of N,N-dimethylaminomethylene group at the 5-position of I with  $\text{POBr}_3$ -DMF and simultaneous denitration, followed by intramolecular cyclization with loss of dimethylamine (see Table and Experimental). Such unusual instability of a nitro group has other precedents in pyrimidine chemistry.<sup>6,7</sup>

TABLE Formation of Flavins (II) and 5-Deazaflavins (III)

Starting material	Products	
	80° [M.p.(°C), Yield(%)]	130° [M.p.(°C), Yield(%)]
Ia	IIa <sup>4</sup> [334, 87]	
Ib	IIb <sup>4</sup> [299, 73]	IIIb <sup>5</sup> [283, 63]
Ic	IIc <sup>4</sup> [332, 55]	IIIc <sup>5</sup> [267, 81]
Id	IIId <sup>4</sup> [315, 68]	IIIId <sup>5</sup> [245, 72]



Experimental

3,10-Dimethylisoalloxazine (3,10-Dimethylflavin) (IIa) —

To a mixture of POBr<sub>3</sub> (1.04 g, 3.62 mmol) and DMF (2 ml) was added

3-methyl-6-(N-methylanilino)-5-nitrouracil (Ia) (0.5 g, 1.81 mmol) and the mixture was heated at 80° for 2 hr under stirring. The reaction mixture was poured into water (20 ml) and stirred for further 1 hr to cause the separation of yellow crystals of 3,10-dimethylisoalloxazine (0.38 g, 87%), m.p. 334° (from AcOH).

3-Methyl-10-n-propylpyrimido[4,5-b]quinoline-2,4(3H,10H)-dione (3-Methyl-10-n-propyl-5-deazaflavin) (IIIc) — A mixture of POBr<sub>3</sub> (0.94 g, 3.29 mmol) and DMF (2 ml) was heated up to 130° and to this hot solution was added 3-methyl-5-nitro-6-(N-n-propylanilino)-uracil (Ic) (0.5 g, 1.64 mmol) and the mixture was heated at this temperature for 1 hr under stirring. The reaction mixture was diluted with water (20 ml) to precipitate pale yellow crystals of the corresponding 5-deazaflavin (0.36 g, 81%), m.p. 267° (from EtOH).

#### REFERENCES AND NOTES

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- 3 It is known that the Vilsmeier reagent acts as a reducing agent; this also appears to be the case in reductive deoxygenation.<sup>1</sup>
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