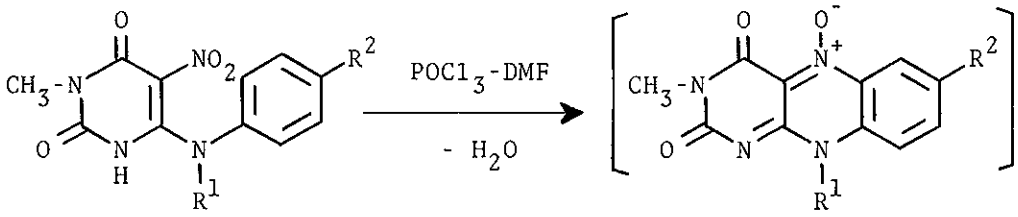
A DICHOTOMY IN THE REACTION OF 6-(N-ALKYLANILINO)-3-METHYL-5-NITROURACILS WITH A MIXTURE OF PHOSPHORUS OXYBROMIDE AND DIMETHYLFORMAMIDE. FORMATION OF FLAVINS OR 5-DEAZAFLAVINS

Yoshiharu Sakuma, Yoshiko Matsushita, and Fumio Yoneda*
Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-honmachi, Kumamoto 862, Japan
Yoshihiro Nitta
Shizuoka College of Pharmacy, Oshika, Shizuoka 422, Japan

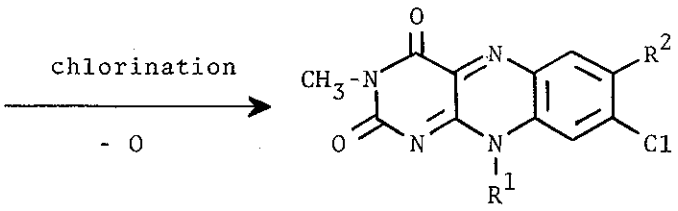
Treatment of 6-(N-alkylanilino)-3-methyl-5-nitrouracils (I) with a mixture of phosphorus oxybromide and dimethylformamide ($POBr_3$-DMF) at 80° gave the corresponding isoalloxazines (flavins). On the other hand, treatment of I with $POBr_3$-DMF at 150° led to the exclusive formation of pyrimido[4,5-b]quinoline-2,4(3H,10H)-diones (5-deazaflavins).

In the previous paper,[1] 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 ($POBr_3$-DMF) in the above reaction would lead to a synthesis of 8-bromoflavins.

We have found, however, that the reaction of I with $POBr_3$-DMF gave no desired 8-bromoflavins and led to a dichotomy of the products according to the reaction temperature as described below.



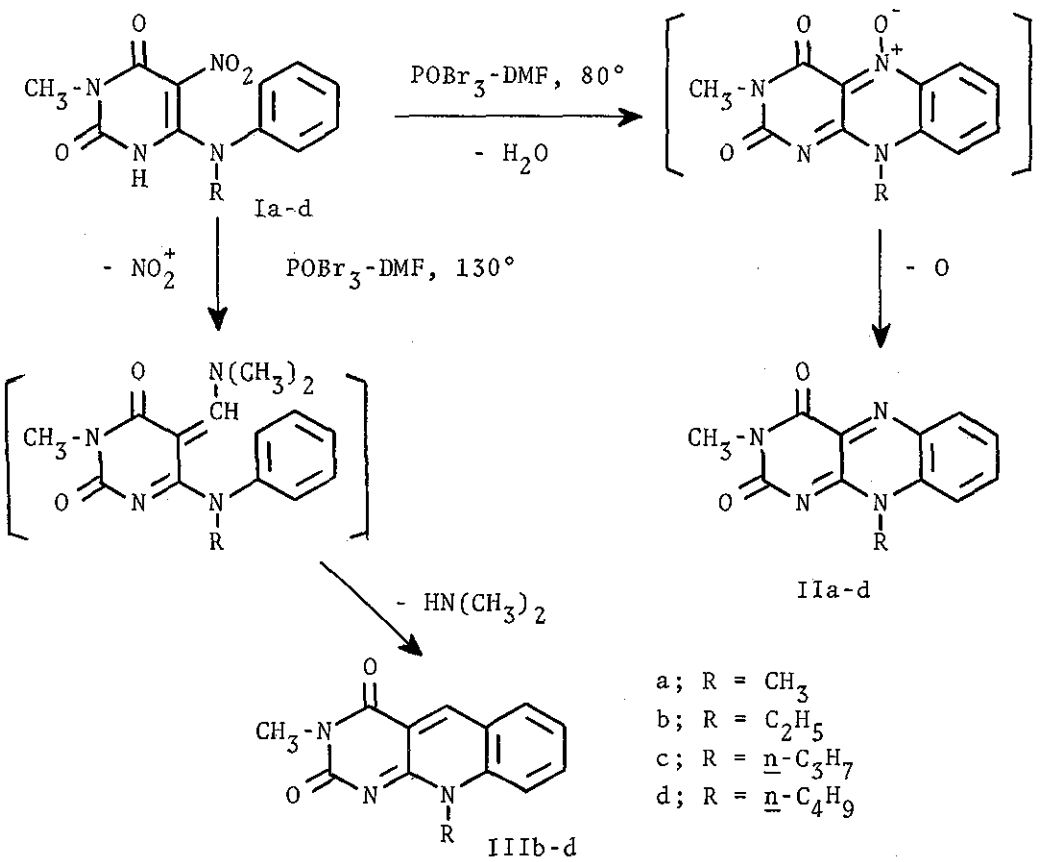
I IV



Stirring of 6-(N-alkylanilino)-3-methyl-5-nitrouracils (Ia-d)[2] in $POBr_3$-DMF at 80° for 2 hr caused intramolecular dehydrative cyclization and subsequent deoxygenation[3] to afford the corresponding isoalloxazines (flavins) (II)[4] 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)[5] was exclusively formed, probably by the introduction of N,N-dimethylaminomethylene group at the 5-position of I with $POBr_3$-DMF and simultaneous denitration, followed by intramolecular cyclization with loss of dimethylamine (see Table and Experimental). Such unusual instablity of a nitro group has other precidents in pyrimidine chemistry.[6,7]

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

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



Experimental

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

To a mixture of $POBr_3$ (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 $POBr_3$ (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.[1]

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