A SYNTHESIS OF FLAVINS BY NITROSATIVE CYCLIZATION OF 6-(N-ALKYLANILINO)URACILS WITH N-NITROSODIMETHYLAMINE–PHOSPHORUS OXYCHLORIDE MIXTURE

Fumio Yoneda,* Kazuo Shinozuka, Yoshiharu Sakuma, and Keitaro Senga+

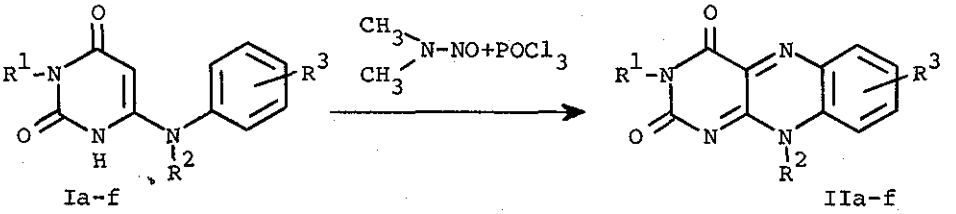
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto, Japan and +Pharmaceutical Institute, Keio University, Shinjuku-ku, Tokyo, Japan

Treatment of 6-(N-alkylanilino)uracils with a mixture of N-nitrosodimethylamine (NDA) and phosphorus oxychloride gave directly the corresponding isoalloxazines (flavins).

A mixture of N-nitrosodimethylamine (NDA) and phosphorus oxychloride (referred to hereafter as NDA+$POCl_3$) is a new type of nitrosating agent which has first been introduced by us.[1,2] For example, the nitrosation of 6-alkylamino-1,3-dimethyluracils,[1] 6-anilino-1,3-dimethyluracil,[1] 1,3-dimethyl-6-(α-methylalkylidenehydrazino)uracils[3] and 6-benzylidenehydrazino-1,3-dimethyluracil[3] with NDA+$POCl_3$ gave directly the corresponding theophyllines, alloxazine, 2-vinyl-V-triazolo[4,5-d]pyrimidines and fervenulin. In this communication we describe the nitrosative cyclization of 6-(N-alkylanilino)uracils (I) to respective isoalloxazines (flavins) with this reagent.

Heating of a mixture of 6-(N-ethylanilino)-3-methyluracil (Ib) (1.23 g, 0.005 mole), NDA (0.74 g, 0.01 mole) and $POCl_3$ (1.54 g, 0.01 mole) in dioxane (30 ml) under reflux for 3 hr, followed by evaporation in vacuo to dryness and dilution with water, caused the separation of 10-ethyl-3-methylisoalloxazine

(IIb).[4] Similarly, several other 6-(N-alkylanilino)uracils (I) yielded the corresponding isoalloxazines (II) under the same conditions (see Table).



Ia-f IIa-f

TABLE Isoalloxazines (Flavins)

Starting material	R^1	R^2	R^3	Product	M.p./°C	Yield/%
Ia	CH_3	CH_3	H	IIa	334[4]	68
Ib	CH_3	C_2H_5	H	IIb	299[4]	65
Ic	CH_3	C_2H_5	7-CH_3	IIc	276[5]	70
Id	CH_3	CH_3	7-Br	IId	293	60
Ie	CH_3	C_2H_5	7-Br	IIe	275	67
If	H	C_2H_5	H	IIf	347[4]	70

The usual nitrosation of (I) with sodium nitrite and acetic acid gives the corresponding isoalloxazine 5-oxides.[4] It should be noted that the nitrosative cyclization of (I) with NDA+$POCl_3$ gives directly isoalloxazines (flavins).

REFERENCES

1 F. Yoneda, K. Senga, and S. Nishigaki, Chem. Pharm. Bull. (Tokyo), 1973, 21, 260.

2 L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 5, John Wiley & Sons, Inc., New York, N. Y., 1976, pp 479.

3 K. Senga, Y. Kanamori, S. Nishigaki, and F. Yoneda, Chem. Pharm. Bull. (Tokyo), 1976, 24, 1917.

4 F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, J. Am. Chem. Soc., 1976, 98, 830.

5 F. Yoneda and Y. Sakuma, Heterocycles, 1977, 6, 25.

Received, 16th May, 1977