New Syntheses of Flavins

By YOSHIHARU SAKUMA, TOMOHISA NAGAMATSU, and FUMIO YONEDA*
(*Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto* 862, *Japan*)

Summary Dehydrative cyclization of 5-nitro-6-(*N*-substituted-anilino)uracils with concentrated sulphuric acid gave the corresponding flavin 5-oxides, which were converted into the respective flavins; autoxidation of 5-amino-6-(*N*-substituted-anilino)uracils also gave the flavins.

WE report here two new synthetic approaches to flavins in which readily available 5-nitro-6-(*N*-substituted-anilino)-uracils are key intermediates.

The treatment of 6-chloro-3-methyl-5-nitrouracil (Ia)[1] with *N*-methylaniline in ethanol at room temperature for 1 h gave 3-methyl-6-(*N*-methylanilino)-5-nitrouracil (IIa), m.p. 236 °C † in 85% yield. Similarly, 6-(*N*-ethylanilino)-3-methyl-5-nitrouracil (IIb), m.p. 234 °C, and 6-(*N*-n-butylanilino)-3-methyl-5-nitrouracil (IIc), m.p. 157 °C, were obtained in 75 and 82% yields, respectively. 3-Methyl-5-nitro-6-(*N*-phenylanilino)uracil (IId), m.p. 168 °C, was prepared in 70% yield by heating (Ia) with diphenylamine in ethanol at 80 °C for 1 h. 6-(*N*-methylanilino)-5-nitrouracil (IIe), m.p. > 320 °C was likewise prepared in 80% yield from 6-chloro-5-nitrouracil (Ib)[2] and *N*-methylaniline.

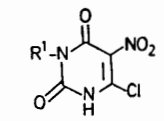
TABLE

Flavin 5-oxide formation by the reaction of 5-nitro-6-(*N*-substituted-anilino)uracils with sulphuric acid

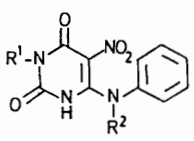
Starting material	Temp/°C	Time/min	Product	M.p. /°C	Yield /%
(IIa)	60	30	(IIIa)[3]	322	83
(IIb)	80	30	(IIIb)	267	80
(IIc)	80	60	(IIIc)	308	85
(IIe)	80	60	(IIIe)	330	75

† Satisfactory analytical and spectral data were obtained for all products.

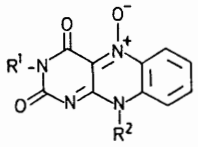
These key intermediates (IIa–e) were converted into the corresponding flavins by the following two methods;



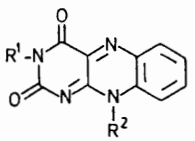
(IIa); R^1 = Me
(IIb); R^1 = H



(II)



(III)



(IV)

(a); R^1 = Me, R^2 = Me
(b); R^1 = Me, R^2 = Et
(c); R^1 = Me, R^2 = Bu^n
(d); R^1 = Me, R^2 = Ph
(e); R^1 = H, R^2 = Me

Method A. Warming (IIa) in excess concentrated sulphuric acid (*ca.* 10 mol equiv.) at 60 °C for 30 min, followed by dilution with water and neutralization with potassium carbonate, caused the separation of 3,10-dimethylisoalloxazine 5-oxide (IIIa).[3] Similarly, the treatment of (IIb,c,e) with concentrated sulphuric acid gave the corresponding flavin 5-oxides (IIIb,c,e) in good yields (Table). However, (IId) did not react with sulphuric acid to give the desired flavin 5-oxide. The deoxygenation of (III) was effected with sodium dithionite in water to yield the desired flavins, 3,10-dimethyl- (IVa),[3] m.p. 334 °C, 10-ethyl-3-methyl- (IVb), m.p. 299 °C, 3-methyl-10-n-butyl- (IVc), m.p. 332 °C, and 10-methyl-isoalloxazine (IVe),[4] m.p. > 350 °C, in almost quantitative yields.

Method B. Compounds (IIa—e) were hydrogenated in ethanol over palladium–carbon. After the consumption of hydrogen stopped, the reaction solution was filtered and the filtrate was warmed at 80 °C for 8 h while introducing air. It was then concentrated to a small volume and allowed to stand in a refrigerator when the same flavins (IVa—c,e) as described above separated; 3-methyl-10-phenylisoalloxazine (IVd),[5] m.p. > 350 °C, could also be obtained by this method.

Yields of the flavins have so far reached 30—40% but have not yet been optimised.

(*Received*, 19*th September* 1975; *Com.* 1068.)

[1] G. D. Daves, R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, 1962, **84**, 1724.
[2] K.-Y. Zee-Cheng and C. C. Cheng, *J. Medicin. Chem.*, 1968, **11**, 1107.
[3] F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *Chem. Pharm. Bull.* (*Japan*), 1972, **20**, 1832.
[4] R. Kuhn and F. Weygand, *Ber.*, 1934, **67**, 1409.
[5] R. Kuhn and F. Weygand, *Ber.*, 1935, **68**, 1282.