New Synthesis of 5-Deazaflavins

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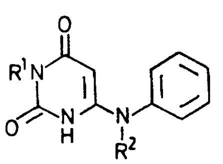
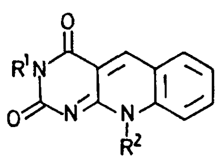
Summary Treatment of 6-(*N*-alkylanilino)uracils with a mixture of phosphorus oxychloride and dimethylformamide (or a mixture of ethyl chloroformate and dimethylformamide) gave the corresponding 5-deazaflavins; reaction of 6-chloro-5-formyl-3-methyluracil with *N*-alkylanilines also gave the corresponding 5-deazaflavins.

The 5-deazaflavin ring system has become of considerable interest recently because of the discovery that the oxidation–reduction system is similar to that of flavins.[1] The 5-deazaflavins have previously been synthesized by the condensation of anthranilaldehydes with barbituric acid.[2] We now report two new synthetic approaches to 5-deazaflavins.

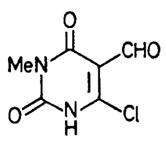


(I)

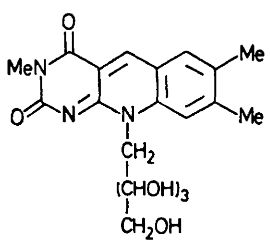


(II)

(a) R^1 = Me, R^2 = Me
(b) R^1 = Me, R^2 = Et
(c) R^1 = Me, R^2 = Pr^n
(d) R^1 = Me, R^2 = Bu^n
(e) R^1 = H, R^2 = Me
(f) R^1 = H, R^2 = Et
(g) R^1 = H, R^2 = Pr^n
(h) R^1 = H, R^2 = Bu^n



(III)



(IV)

Table 1

5-Deazaflavin formation by the reaction of 6-(*N*-alkylanilino) uracils with a mixture of phosphorus oxychloride and dimethylformamide

Starting material	Product	Recrystallisation solvent	M.p./°C	Yield/%
(Ia)	(IIa)	EtOH	327	96
(Ib)	(IIb)	EtOH	283	88
(Ic)	(IIc)	EtOH	267	86
(Id)	(IId)	EtOH	245	89
(Ie)	(IIe)	AcOH	359	95
(If)	(IIf)	AcOH	353	87
(Ig)	(IIg)	AcOH	318	90
(Ih)	(IIh)	EtOH–AcOH	302	92

Method A. The treatment of 3-methyl-6-(*N*-methylanilino)uracil (Ia)[3] with a mixture of phosphorus oxychloride and dimethylformamide ($POCl_3$+DMF) at 90 °C for 2 h, followed by dilution with water and neutralization

Table 2

5-Deazaflavin formation by the reaction of 6-chloro-5-formyl-3-methyluracil with *N*-alkylanilines

Product	Reaction conditions Temp/°C	Time/min	Yield/%
(IIa)	Room temp.	30	62
(IIb)	50	60	58
(IIc)	80	60	42
(IId)	80	60	48

with sodium bicarbonate caused the separation of 3,10-dimethylpyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)dione (IIa).† Similarly, the treatment of other 6-(*N*-alkylanilino)uracils

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

(Ib–h) with $POCl_3$+DMF under the same conditions gave the corresponding 5-deazaflavins (Table 1).

Refluxing (I) with ethyl chloroformate in dimethylformamide[4] for 2 h also gave (II) in almost the same yields.

Method B. Treatment of 1-methylbarbituric acid with $POCl_3$+DMF under reflux for 3 h, followed by evaporation of the solvent and dilution with ice–water, precipitated 6-chloro-5-formyl-3-methyluracil (III), m.p. 188 °C (decomp.), in 68% yield. Compound (III) was very unstable and used without purification. Stirring of (III) in dimethylformamide with 2 equivalents of *N*-methylaniline at room temperature for 2 h, followed by dilution with ether gave (IIa). Similarly, the treatment of (III) with other *N*-alkylanilines under the conditions described in Table 2 gave the corresponding 5-deazaflavins.

Stirring of (III) with an equimolar amount of *N*-D-ribitylxylidine in dimethylformamide in the presence of triethylamine at room temperature for 3 h, followed by dilution with ether, caused the separation of 3-methyl-5-deazaflavin (IV), m.p. 284 °C (decomp.) (from EtOH), in 43% yield.

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