A New Synthetic Method for the Preparation of 5-Deazaflavins and 5-Deaza-10-oxaflavins

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The condensation of 6-chlorouracils with *o*-(substituted amino)benzyl alcohols and *o*-hydroxybenzyl alcohol gave directly 5-deazaflavin and 5-deaza-10-oxaflavin derivatives, respectively.

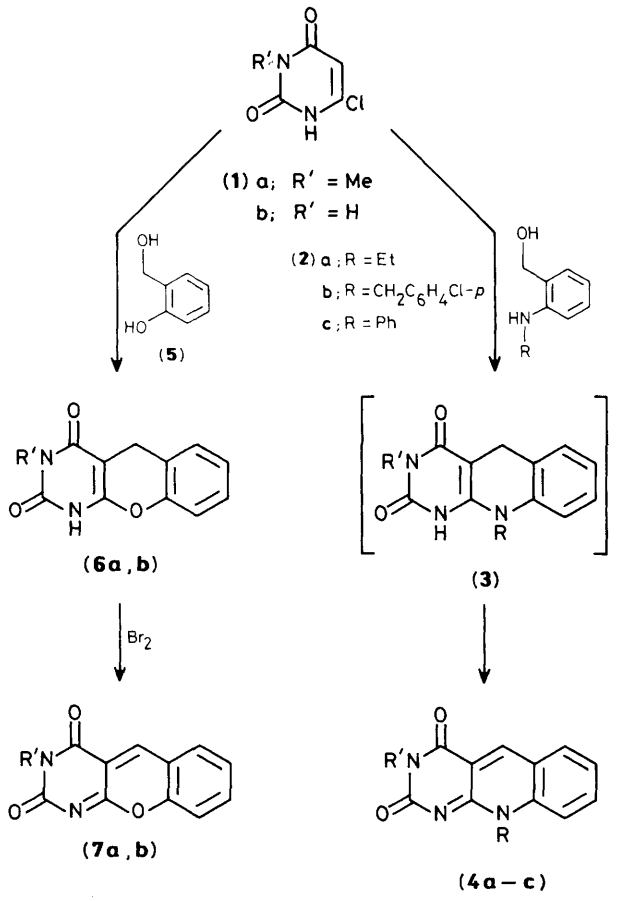
5-Deazaflavins (5-deazaisoalloxazines) have received much attention since the discovery that some naturally occurring coenzymes possess the 8-hydroxy-5-deazaflavin moiety.[1—4] Existing methodologies for the synthesis of 5-deazaflavins involve (a) the condensation of anthranilaldehydes with barbituric acid,[5] (b) the cyclization of 6-(*N*-alkylanilino)uracils with one-carbon reagents including Vilsmeier reagent,[6] (c) the condensation of 6-chloro-5-formylpyrimidine with *N*-alkylanilines,[6] (d) the oxidative cyclization of aryl bis(6-substituted aminouracil-5-yl)methanes with diethyl azodicarboxylate (DAD),[7] and (e) the condensation of 6-(substituted amino)-uracils with *o*-halogenobenzaldehydes.[8] We now report a new and simple synthetic route to 5-deazaflavins by the condensation of 6-chlorouracils (**1**) with *o*-(substituted amino)benzyl alcohols (**2**). Additionally we describe a similar synthesis of 5-deaza-10-oxaflavins which are regarded as 5-deazaflavin analogues.[9]

The requisite starting materials, *o*-(substituted amino)-benzyl alcohols (**2a—c**), were prepared by reduction of the corresponding amides of methyl anthranilate with $LiAlH_4$.[10] A mixture of 3-methyl-6-chlorouracil (**1a**) and (**2a—c**) (2

Table 1. Syntheses of 5-deazaflavins and 5-deaza-10-oxaflavins.

Compound	R	R′	Yield (%)	M.p. (°C)
(**4a**)	Et	Me	26	281
(**4b**)	$CH_2C_6H_4Cl$-*p*	Me	16	260
(**4c**)	Ph	Me	17	>360
(**6a**)		H	35	>300
(**6b**)		Me	80	288
(**7a**)		H	98[a]	>300
(**7b**)		Me	95[a]	>300

[a] Yield for dehydrogenation of (**6**) to (**7**) by bromine.



Scheme 1

equiv.) in dimethylformamide (DMF) (or in nitrobenzene) was heated under reflux (or at 200 °C) for 24 h. Concentration of the reaction solution under reduced pressure and purification of the residue by chromatography gave directly the corresponding 3-methyl-5-deazaflavins (**4a—c**) in moderate yields (Table 1).† Similarly, heating (**1a,b**) with *o*-hydroxybenzyl alcohol (**5**)[11] (3 equiv.) in nitrobenzene at 200 °C for 4 h afforded the 1,5-dihydro-5-deaza-10-oxaflavins (**6a,b**) in better yields. As compounds (**6**) were stable in air, they were treated with bromine (1 equiv.) in acetic acid under reflux for 30 min to give the corresponding 5-deaza-10-oxaflavins (**7a, b**)[9] in almost quantitative yields (Table 1).

The reaction presumably involves the initial formation of intermediate heterodiene derivatives by intramolecular dehydration of (**2**) and (**5**), followed by intermolecular 1,4-cycloaddition with 6-chlorouracils (**1**) to yield the corresponding cycloadducts. Then the dehydrochlorination would give the 1,5-dihydro-5-deazaflavins (**3**) and 1,5-dihydro-5-deaza-10-oxaflavins (**6**). In fact, there are precedents for the 1,4-cycloaddition of dienophiles with *o*-hydroxybenzyl alcohol (**5**) which is the precursor of 1,2-benzoquinone-2-methide.[12] Alternatively, the initially formed 6-(*o*-hydroxymethylanilino)uracils or 6-(*o*-hydroxymethylphenoxy)uracils may undergo dehydrative cyclization to the corresponding 1,5-dihydrodeazaflavins.

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† All compounds were fully characterized by combustion analyses and spectroscopic data, in particular, by the presence of a C-5 proton resonance at δ 8.9—9.2 ($CDCl_3$ or Me_2SO) for (**4**) and δ 9.7—9.8 [CF_3CO_2H–$CDCl_3$ (1 : 1)] for (**7**) in the ^1H n.m.r. spectra.

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