Novel Synthesis of Pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-Deazaflavins)

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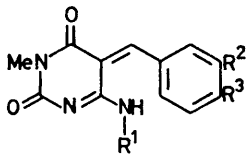
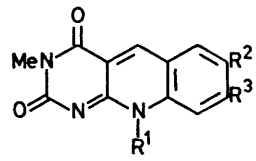
Summary Treatment of 5-benzylidene-6-(*N*-substituted amino)uracils with diethyl azodiformate led to the formation of the corresponding pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-deazaflavins).

PYRIMIDO[4,5-*b*]QUINOLINE-2(3*H*),4(10*H*)-DIONES (5-deazaflavins), where N-5 of the flavin is replaced by CH, have become of recent interest, because of the discovery that they serve as cofactors for several flavin-dependent enzymic reactions.[1] Also, the 5-deazaflavins can be considered as 'flavin shaped nicotinamide analogues,' since they oxidize simple alcohols under alkaline conditions to the corresponding carbonyl compounds and they are themselves hydrogenated to 1,5-dihydro-5-deazaflavins.[2] 5-Deazaflavins have previously been synthesized by the condensation of anthranilaldehydes with barbituric acid,[3] by the cyclization of 6-(*N*-alkylanilino)uracils with one-carbon reagents including the Vilsmeier reagent,[4] and by the condensation of 6-chloro-5-formyluracils with *N*-substituted anilines.[4] This paper describes a novel and general synthesis of 5-deazaflavins which consists of the oxidative coupling of 5-benzylidene-6-(*N*-substituted amino)uracils with diethyl azodiformate (DAD).



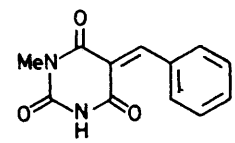
(I)



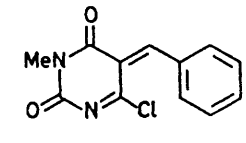
(II)

	R^1	R^2	R^3		R^1	R^2	R^3
a	Me	H	H	g	Pr^n	H	H
b	Me	H	Cl	h	Bu^n	H	H
c	Me	Cl	Cl	i	$PhCH_2$	H	H
d	Me	H	OMe	j	Ph	H	H
e	Me	H	Me	k	*p*-ClC_6H_4	H	H
f	Me	$-OCH_2O-$					

The starting materials, the 5-benzylidene-3-methyl-6-(*N*-substituted amino)uracils (Ia—k)† were synthesized by heating 6-alkylamino-[5,6] and 6-anilino-3-methyluracils[7] with the respective aryl aldehydes in refluxing acetic acid for 2 h. Compounds (Ig—k) were alternatively synthesized as follows. Refluxing of 5-benzylidene-3-methylbarbituric acid (III), m.p. 237 °C, prepared by the condensation of 3-methylbarbituric acid and benzaldehyde in ethanol, with phosphorus trichloride oxide gave 5-benzylidene-6-chloro-3-methyluracil (IV) (unstable) which, on treatment with the respective alkylamines or anilines, afforded (Ig—k).



(III)



(IV)

Fusion of compound (Ia) with excess of DAD (10 equiv.) at 150 °C for 30 min with stirring, followed by dilution with ethanol, caused the separation of the dione (IIa) (3,10-dimethyl-5-deazaflavin). The reaction is equally applicable to compounds (Ib—i) to give the corresponding 5-deazaflavins (IIb—i) (see Table). Fusion of the 6-anilino-5-benzylidene-3-methyluracils (Ij,k) with DAD at 210 °C for 3 h with stirring gave the corresponding 10-aryl-5-deazaflavins (IIj,k), whereas treatment of 6-diphenylamino-3-methyluracil with the Vilsmeier reagent according to the known procedure[4] led to complete recovery of starting material under all conditions.

TABLE. Formation of the 5-deazaflavins (II) by reaction of the 5-benzylidene-6-(*N*-substituted amino)uracils (I) with DAD.

5-Deaza-flavin	M.p./°C	Recryst. solvent	% Yield
(IIa)[a]	327	EtOH	50
(IIb)	328	$HCONMe_2$	63
(IIc)	>360	$HCONMe_2$	65
(IId)	345	EtOH	45
(IIe)	309	EtOH	55
(IIf)	>360	EtOH	52
(IIg)[a]	267	EtOH	65
(IIh)[a]	245	EtOH	58
(IIi)	249	EtOH	70
(IIj)	>360	AcOH	53
(IIk)	>360	AcOH	69

[a] *Cf.* ref. 4.

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

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