Oxidation–Reduction in Hydrolysis of Pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-Deazaflavins)

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Summary Treatment of pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-deazaflavins) with concentrated aqueous potassium hydroxide led to the exclusive formation of 1,5-dihydro-5-deazaflavins and 1,5-dihydro-5-deazaflavin-5-ones *via* intermolecular oxidation–reduction between initially formed 5-hydroxy-1,5-dihydro-5-deazaflavins and unchanged 5-deazaflavins; under dilute alkaline conditions reverse oxidation–reduction between 1,5-dihydro-5-deazaflavins and 1,5-dihydro-5-deazaflavin-5-ones occurred to form the original 5-deazaflavins and 5-hydroxy-1,5-dihydro-5-deazaflavins, which were oxidized into 1,5-dihydro-5-deazaflavin-5-ones by air.

SEVERAL chemical and biological analogies between {pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-dione} (5-deazaflavin)[1,2] and flavin have been pointed out.[3] In particular, 5-deazaflavins serve as cofactors for some flavin-dependent enzymatic reactions.[4] Also, 5-deazaflavin can be considered chemically as well as structurally as a model of nicotinamide nucleotide protected by annelation. For example 5-deazaflavin oxidizes simple alcohols under alkaline conditions to yield the corresponding carbonyl compounds, while it is itself hydrogenated to 1,5-dihydro-5-deazaflavin.[5] This paper describes the hydrolysis of 5-deazaflavins, which is in contrast with that of flavins reported previously.[6]

Stirring of the 10-ethyl-3-methyl compound (Ib)[2] (2 mmol) in 60% aqueous potassium hydroxide (5 ml) at 90 °C for 4 h, followed by neutralization with acetic acid, caused the separation of a mixture of the dihydro-compound (IIb)† and the dihydro-ketone (IIIb) in high yields. Compounds (Ia), (Ic), and (Id) similarly gave the corresponding reduced derivatives (IIa), (IIc), and (IId) and the 5-ketones (IIIa), (IIIc), and (IIId) exclusively (see Table 1). Furthermore, treatment of the 5-deuterio-compound (IV)‡ with 60% aqueous potassium hydroxide under the same conditions gave the corresponding 5,5-dideuterio-derivative (V) and (IIIb) in almost quantitative yields.

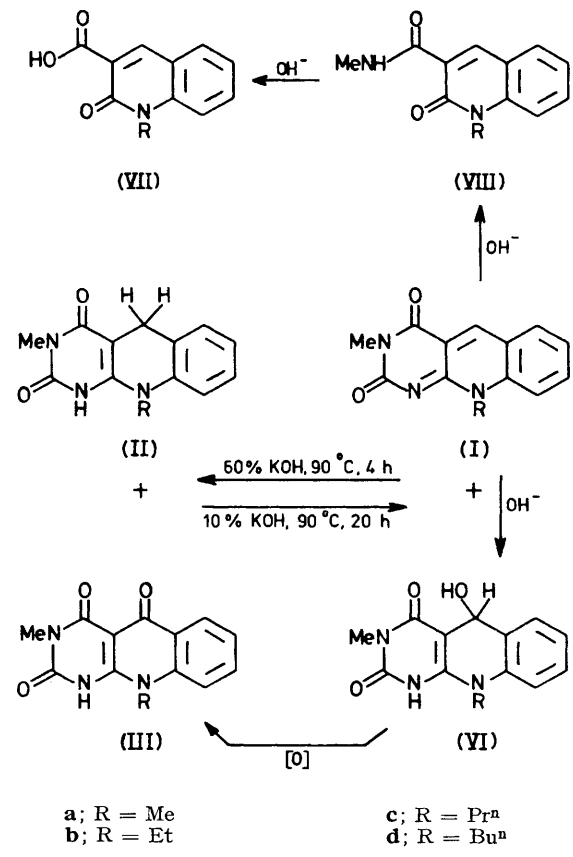


TABLE 1. Disproportionation of the 5-deazaflavins (Ia)—(Id) with 60% aqueous potassium hydroxide.

Starting deazaflavin	% Yield (II)[a]	(m.p./°C)	(III)[a]	(m.p./°C)	Total
(Ia)	44·9	(278)	46·3	(295)	92·1
(Ib)	46·8	(285)	47·4	(275)	94·2
(Ic)	46·6	(257)	48·2	(263)	95·0
(Id)	47·2	(214)	46·0	(229)	93·2

[a] Recrystallized from acetic acid.

Therefore, we rationalize the reaction in terms of initial nucleophilic attack of hydroxide ion on the 5-position of (I) giving the 5-hydroxy-compound (VI). Subsequent transfer of a hydrogen equivalent from the 5-position of (VI) to the 5-position of another molecule of (I) affords the corresponding products (II) and (III). An analogous disproportionation was reported in the reaction of pyrimido[4,5-*b*]quinolinium salts with aqueous sodium hydroxide.[7]

When the hydrolysis was carried out with 10% aqueous potassium hydroxide at 90 °C for 4 h, the corresponding quinolone-3-carboxylic acid derivatives (VIIa—d) and

† Satisfactory analytical and spectral data were obtained for products.

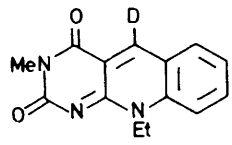
‡ Prepared by the cyclization of 6-(*N*-ethylanilino)-3-methyluracil with a mixture of [$^2H_7$]dimethylformamide and phosphorus chloride oxide according to the known procedure.[2]

TABLE 2. Hydrolysis of 5-deazaflavins with 10% aqueous potassium hydroxide

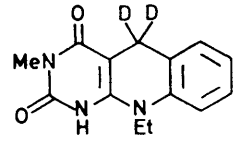
Starting deazaflavin	Conditions[a]	% Yield (VII)[b]	(VIII)[c]	(II)	(III)	Total
(Ia)	A	40·0	0	26·0	26·8	92·8
	B	50·0	0	0	37·7	87·7
(Ib)	A	37·2	0	26·5	27·1	90·8
	B	43·8	0	0	43·4	87·2
(Ic)	A	31·2	18·5	21·9	22·8	94·4
	B	44·2	13·6	0	34·0	91·8
(Id)	A	45·2	8·9	17·4	18·5	90·0
	B	51·2	4·9	9·0	24·0	89·1

[a] A: 90 °C, 4 h; B: 90 °C, 20 h. [b] M.p.s (VIIa), 228; (VIIb), 187; (VIIc), 163; (VIId), 159 °C. [c] (VIIIc), 107; (VIIId), 108 °C.

(VIIIc and d) were obtained besides the disproportionation products (II) and (III) (see Table 2). However, on prolonged hydrolysis (20 h) the yields of the ketones (III) and the acids (VII) increased significantly, with a corresponding decrease in the yields of the reduction products (II). This phenomenon suggests that reverse oxidation–reduction of (II) and (III) into (I) and (VI) occurs under these conditions.



(IV)



(V)

Compound (VI) could be converted into the ketones (III) by air oxidation and (I) could again undergo the usual disproportionation and hydrolytic scission at the 2-position into the acid derivatives.

Treatment of (IIb) (1 mmol) and (IIIb) (1 mmol) in 10% aqueous potassium hydroxide (5 ml) gave the ketone (IIIb) (1·5 mmol) and the acid (VIIb) (0·3 mmol). No other products were detected. Treatment of (IIb) alone with 10% aqueous potassium hydroxide led to complete recovery of starting material.

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