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A NEW SYNTHESIS OF 5-ARYL-5-DEAZAFLAVINS (5-ARYLPYRIMIDO[4,5-b]-QUINOLINE-2,4(3H,10H)-DIONES)

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The condensation of 6-(N-alkylanilino)-3-methyluracils with aryl aldehydes in the presence of polyphosphoric acid afforded the corresponding 5-aryl-3-methylpyrimido[4,5-b]quinoline-2,4(3H,10H)-diones (5-aryl-3-methyl-5-deazaflavins) in a single step and in high yields. These compounds were reduced to the corresponding 5-aryl-1,5-dihydro-5-deazaflavins by ethanolic potassium hydroxide.

5-Deazaflavin (pyrimido[4,5-b]quinoline-2,4(3H,10H)-dione),[1-3] in which the 5-nitrogen atom of the flavin is replaced by a methine group, would be considered structurally as a model not only of flavin nucleotide but also of nicotinamide nucleotide protected by annelation.[4] For example, 5-deazaflavin oxidizes alcohols under alkaline conditions to yield the corresponding carbonyl compounds, while 5-deazaflavin itself is hydrogenated to 1,5-dihydro-5-deazaflavin.[4] On the contrary, 1,5-dihydro-5-deazaflavin reduced carbonyl compounds under acidic conditions to yield the corresponding alcohols and 1,5-dihydro-5-deazaflavin was reoxidized to 5-deazaflavin.[5] Furthermore, 5-deazaflavin has shown interesting oxidation-reduction (disproportionation) at the 5-position in its hydrolysis,[6] which is in contrast with that of flavin reported previously.[7]

In order to gain more information about this ring system, we have attempted the synthesis of 5-aryl-5-deazaflavins which are sterically hindered at the 5-position. This paper describes a new synthetic approach to these compounds and their reduction to the corresponding 1,5-dihydro derivatives by ethanolic potassium hydroxide.

A mixture of 6-(N-methylanilino)-3-methyluracil (Ia) (3 mmol) and benzaldehyde (3 mmol) in polyphosphoric acid (3 ml) was heated at 110 °C for 2 hr under stirring, followed by dilution with water, to separate 3,10-dimethyl-5-phenyl-5-deazaflavin (IIa) in high yield. In completely analogy with above result, the reaction of Ia or 6-(N-ethylanilino)-3-methyluracil (Ib) with other aryl aldehydes provided the corresponding 5-aryl-5-deazaflavins (IIb-g) (Table I).

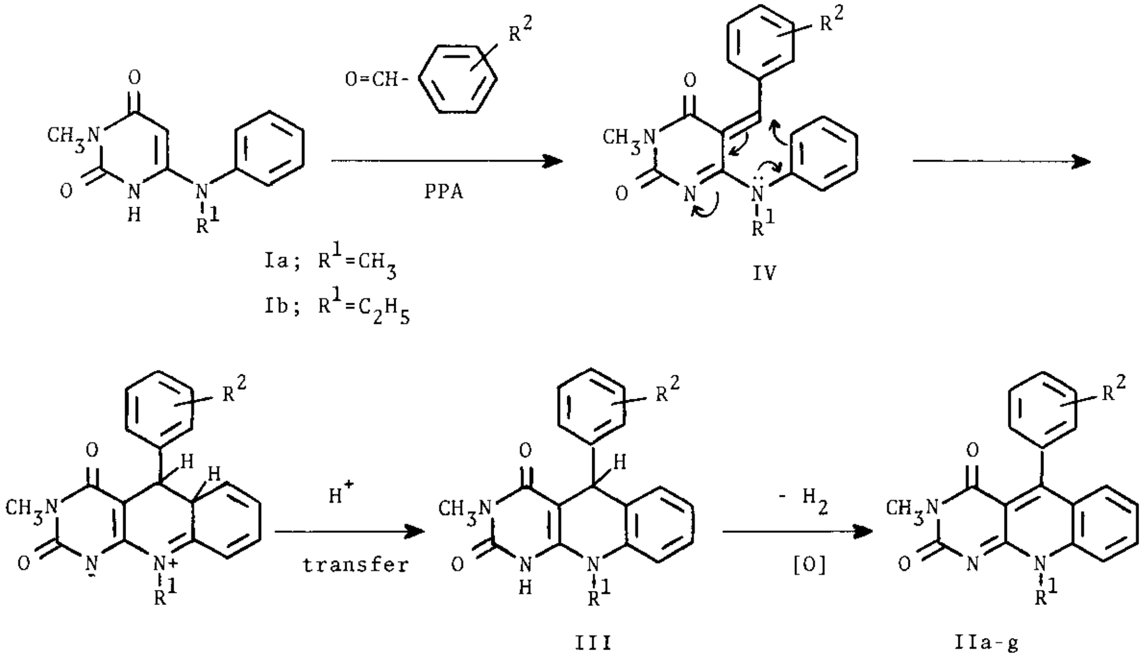


TABLE I 5-Aryl-5-deazaflavins

Compd. No.	R^1	R^2	Recrystn. solvent	M.p.(°C)	Yield(%)
IIa	CH_3	H	AcOH[a]	271	98
IIb	CH_3	4-Cl	EtOH[a]	222	88
IIc	C_2H_5	H	AcOH[a]	327	98
IId	C_2H_5	4-Cl	EtOH[a]	279	97
IIe	C_2H_5	4-CH_3O	EtOH[a]	286	96
IIf	C_2H_5	2-NO_2	AcOH-H_2O[b]	180(decomp.)	99
IIg	C_2H_5	3-NO_2	AcOH[b]	345(decomp.)	90

a) Yellow crystals b) Pale green crystals

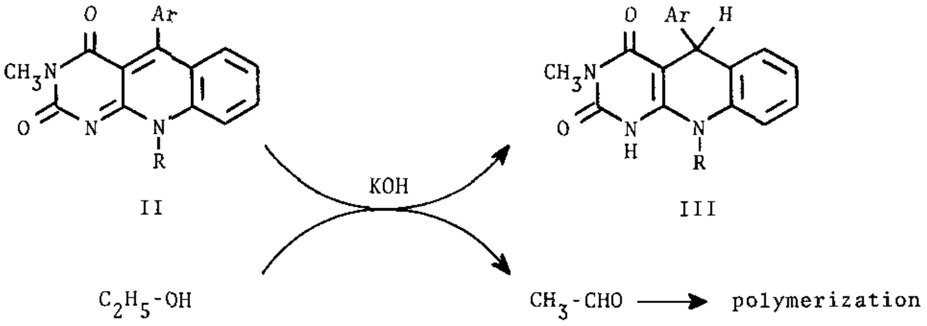
As depicted in the Scheme, the new 5-aryl-5-deazaflavin synthesis is presumably initiated by the formation of 5-benzylidene intermediate (IV). This could undergo intramolecular cyclization followed by prototropic rearrangement to give 1,5-dihydro-5-deazaflavin (III). Subsequent dehydrogenation by air would lead to the final product (II).[8]

The structures of 5-aryl-5-deazaflavins were confirmed by the satisfactory spectral data and elemental analyses. The light absorption spectra (Table 2) show one band in the 400 nm region, another in the 320 nm region, and two in the ultraviolet region in ethanolic solution; these are quite similar to those of 5-deazaflavins themselves.[2]

TABLE II U.v. and Visible Maxima of 5-Aryl-5-deazaflavins

Compound No.	λ_{max} (EtOH)/ nm (log ε)			
IIa	402.5 (3.94),	323.0 (3.98),	264.0 (4.61),	221.8 (4.59)
IIb	408.4 (3.73),	322.4 (3.85),	265.8 (4.44),	223.0 (4.50)
IIc	402.4 (3.82),	324.2 (3.81),	264.8 (4.49),	222.0 (4.50)
IId	406.0 (3.82),	324.0 (3.83),	265.0 (4.50),	244.4 (4.54)
IIe	400.0 (4.05),	324.0 (3.97),	264.0 (4.63),	224.0 (4.61)
IIf	404.8 (3.85),	327.0 (3.88),	265.0 (4.49),	223.5 (4.48)
IIg	406.8 (-),	320.8 (-),	266.0 (-),	222.5 (-)

10-Ethyl-3-methyl-5-phenyl-5-deazaflavin (IIc) (0.1 g) was added to a mixture of ethanol and water (7:3) (2 ml) including potassium hydroxide (0.1 g) and the mixture was heated at 80 °C for 1 hr under stirring. After reaction, the mixture was diluted with water and neutralized with acetic acid to separate 1,5-dihydro-10-



ethyl-3-methyl-5-phenyl-5-deazaflavin (IIIc), m.p. >350 °C, in quantitative yield, which was identical with the product prepared by the reduction of IIc with aqueous sodium dithionite in the presence of ammonia. Ethanol was oxidized to acetaldehyde, which however was not isolated because of its polymerization under alkaline conditions. Other 5-aryl-5-deazaflavins (II) are likewise reduced by ethanolic potassium hydroxide to the corresponding 1,5-dihydro derivatives.

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8. In connection with this reaction, Pfleiderer et al. reported that the condensation of 6-amino-1,3-disubstituted uracils with aldehydes afforded the corresponding bis(6-aminouracil-5-yl)methane derivatives; W. Pfleiderer, F. Sági, and L. Grüzinger, *Chem. Ber.*, **99**, 3530 (1966).

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