Synthesis of Some 10-Alkyl-5-deazaflavins and Their Use in the Oxidation of Benzyl Alcohol and Benzylamine

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A series of 3-methyl- and 3-phenyl-10-alkyl-5-deazaflavins were synthesized in order to examine whether the length of 10-alkyl-substituents influences the oxidizing power.

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Recently we reported that 5-deazaflavins (1) were considered to be NAD(P)$^+$ models which oxidized alcohols under weakly basic conditions and thereupon exhibited some recycling in the oxidation giving carbonyl compounds in more than 100% yield. Furthermore, the effect of the substituents on the benzene moiety of 5-deazaflavins was discussed in terms of the oxidizing ability toward benzyl alcohol (1). The present paper describes the synthesis of a series of 10-alkyl-5-deazaflavins and the influence of the length of their 10-alkyl-substituents upon the oxidizing power.

Synthesis of 10-Alkyl-5-deazaflavins.

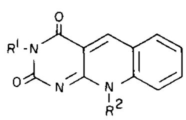
Preparation of 10-alkyl-3-methyl-5-deazaflavins (Ia-d) (2) and 10-alkyl-3-phenyl-5-deazaflavins (IIa-d) (3) was described previously. Other 5-deazaflavins (Ie-h and IIe-h) were similarly synthesized by the condensation of 6-chloro-5-formyl-3-methyluracil (2) (for I) and 6-chloro-5-formyl-3-phenyluracil (3) (for II) with the corresponding *N*-alkylanilines in dimethylformamide. *N*-*n*-Hexylaniline, *N*-*n*-octylaniline, *N*-*n*-dodecylaniline and *N*-*n*-octadecylaniline were prepared by the known procedures (4,5). The structures of Ie-h and IIe-h were derived on the basis of elemental analyses (Table I) and nuclear magnetic resonance data (Table II).

Oxidation of Benzyl Alcohol and Benzylamine by the 10-Alkyl-5-deazaflavins.

Table III shows the yields of benzaldehyde in the oxidation of benzyl alcohol by the 10-alkyl-5-deazaflavins (Ie-h and IIe-h) obtained above and also by the 5-deazaflavins (Ia-d and IIa-d) prepared previously for comparison. No strong substituent effect at the 10-position was observed, but the 5-deazaflavins possessing higher alkyl groups showed slightly stronger power than the 5-deazaflavins possessing lower alkyl groups in the oxidation of benzyl alcohol.

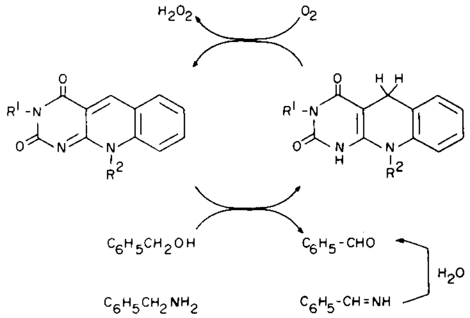
Table I

10-Alkyl-5-deazaflavins



Compound No.	R¹	R²	Yield (%)	Mp (°C) (a)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ie	CH_3	n-C_6H_{13}	50	201	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.50	69.32	6.70	13.67
If	CH_3	n-C_8H_{17}	62	196	$C_{20}H_{25}N_3O_2$	70.77	7.43	12.38	70.69	7.41	12.22
Ig	CH_3	n-$C_{12}H_{25}$	53	177	$C_{24}H_{33}N_3O_2$	72.87	8.41	10.62	72.92	8.41	10.74
Ih	CH_3	n-$C_{18}H_{37}$	51	161	$C_{30}H_{45}N_3O_2$	75.11	9.46	8.76	75.10	9.45	8.70
IIe	C_6H_5	n-C_6H_{13}	42	234	$C_{23}H_{23}N_3O_2$	73.97	6.21	11.25	73.78	6.15	11.22
IIf	C_6H_5	n-C_8H_{17}	45	175	$C_{25}H_{27}N_3O_2$	74.78	6.78	10.47	74.48	6.72	10.55
IIg	C_6H_5	n-$C_{12}H_{25}$	49	173	$C_{29}H_{35}N_3O_2$	76.11	7.71	9.18	76.08	7.64	9.10
IIh	C_6H_5	n-$C_{18}H_{37}$	47	157	$C_{35}H_{47}N_3O_2$	77.59	8.75	7.76	77.54	8.86	7.81

(a) All compounds were recrystallized from ethanol and were obtained as pale yellow needles.



Next, the oxidation of benzylamine by I and II was carried out under aqueous conditions. Compounds I and II showed strong oxidizing ability toward benzylamine to give benzaldehyde even in the presence of water. In general, compounds I showed stronger ability than compounds II in the oxidation of benzylamine. However, no significant influence of the length of 10-alkyl-substitutents upon the oxidizing power was observed.

Table II

NMR Data for the 10-Alkyl-5-deazaflavins

Compound No.	δ (CH_3COOH) ppm
Ie	0.98 (t, J = 7, N_{10}-$(CH_2)_5$-CH_3), 1.53 (m, N_{10}-CH_2-$(CH_2)_4$-CH_3), 3.65 (s, N_3-CH_3), 4.90 (m, N_{10}-CH_2-$(CH_2)_4$-CH_3), 7.80-8.63 (m, ArH), 9.75 (s, C_5-H)
If	0.93 (t, J = 7, N_{10}-$(CH_2)_7$-CH_3), 1.42 (m, N_{10}-CH_2-$(CH_2)_6$-CH_3), 3.63 (s, N_3-CH_3), 4.90 (m, N_{10}-CH_2-$(CH_2)_6$-CH_3), 7.77-8.57 (m, ArH), 9.70 (s, C_5-H)
Ig	0.92 (t, J = 7, N_{10}-$(CH_2)_{11}$-CH_3), 1.37 (m, N_{10}-CH_2-$(CH_2)_{10}$-CH_3), 3.67 (s, N_3-CH_3), 4.98 (m, N_{10}-CH_2-$(CH_2)_{10}$-CH_3), 7.85-8.68 (m, ArH), 9.83 (s, C_5-H)
Ih	0.90 (t, J = 7, N_{10}-$(CH_2)_{17}$-CH_3), 1.33 (m, N_{10}-CH_2-$(CH_2)_{16}$-CH_3), 3.63 (s, N_3-CH_3), 4.92 (m, N_{10}-CH_2-$(CH_2)_{16}$-CH_3), 7.78-8.57 (m, ArH), 9.72 (s, C_5-H)
IIe	0.95 (t, J = 7, N_{10}-$(CH_2)_5$-CH_3), 1.52 (m, N_{10}-CH_2-$(CH_2)_4$-CH_3), 5.00 (m, N_{10}-CH_2-$(CH_2)_4$-CH_3), 7.81-8.65 (m, ArH), 9.80 (s, C_5-H)
IIf	0.90 (t, J = 7, N_{10}-$(CH_2)_7$-CH_3), 1.37 (m, N_{10}-CH_2-$(CH_2)_6$-CH_3), 5.02 (m, N_{10}-CH_2-$(CH_2)_6$-CH_3), 7.20-8.63 (m, ArH), 9.80 (s, C_5-H)
IIg	0.90 (t, J = 7, N_{10}-$(CH_2)_{11}$-CH_3), 1.35 (m, N_{10}-CH_2-$(CH_2)_{10}$-CH_3), 4.98 (m, N_{10}-CH_2-$(CH_2)_{10}$-CH_3), 7.13-8.63 (m, ArH), 9.77 (s, C_5-H)
IIh	0.93 (t, J = 7, N_{10}-$(CH_2)_{17}$-CH_3), 1.38 (m, N_{10}-CH_2-$(CH_2)_{16}$-CH_3), 5.03 (m, N_{10}-$CH_2$$(CH_2)_{16}$-$CH_3$), 7.20-8.70 (m, ArH), 9.83 (s, C_5-H)

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-Al spectrometer. The nmr spectra were determine with a Hitachi R-24B spectrometer (with tetramethylsilane as an internal standard).

10-Alkyl-5-deazaflavins (Ie-h and IIe-h). General Procedure.

A mixture of a 6-chloro-5-formyluracil (0.008 mole) and an *N*-alkylaniline (0.008 mole) in dry dimethylformamide (10 ml) was heated at 90° for 3 hours with stirring. After cooling, the reaction mixture was diluted with a small amount of ethanol. The crystals which separated were collected by filtration and recrystallized from ethanol to give pale yellow needles.

Table III

Oxidation of Benzyl Alcohol by 10-Alkyl-5-deazaflavins

Compound No.	R¹	R²	Yield of Benzaldehyde (%)			
			1h	3h	5h	10h
Ia	CH_3	CH_3	39	108	139	224
Ib	CH_3	C_2H_5	55	149	220	318
Ic	CH_3	n-C_3H_7	62	141	177	262
Id	CH_3	n-C_4H_9	57	138	169	254
Ie	CH_3	n-C_6H_{13}	119	301	378	400
If	CH_3	n-C_8H_{17}	166	294	297	314
Ig	CH_3	n-$C_{12}H_{25}$	164	190	278	315
Ih	CH_3	n-$C_{18}H_{37}$	154	184	207	301
IIa	C_6H_5	CH_3	55	92	101	128
IIb	C_6H_5	C_2H_5	78	112	149	153
IIc	C_6H_5	n-C_3H_7	125	145	146	144
IId	C_6H_5	n-C_4H_9	86	116	125	136
IIe	C_6H_5	n-C_6H_{13}	125	280	305	323
IIf	C_6H_5	n-C_8H_{17}	206	230	264	299
IIg	C_6H_5	n-$C_{12}H_{25}$	230	236	284	308
IIh	C_6H_5	n-$C_{18}H_{37}$	184	284	302	318

Table IV

Oxidation of Benzylamine by 10-Alkyl-5-deazaflavins

Compound No.	R^1	R^2	Yield (%) (a)	Compound No.	R^1	R^2	Yield (%) (a)
Ib	CH_3	C_2H_5	318	IIa	C_6H_5	C_2H_5	143
Id	CH_3	n-C_4H_9	396	IId	C_6H_5	n-C_4H_9	131
Ie	CH_3	n-C_6H_{13}	571	IIe	C_6H_5	n-C_6H_{13}	162
If	CH_3	n-C_8H_{17}	488	IIg	C_6H_5	n-$C_{12}H_{25}$	226
Ig	CH_3	n-$C_{12}H_{25}$	467	IIh	C_6H_5	n-$C_{18}H_{37}$	144
Ih	CH_3	n-$C_{18}H_{37}$	656				

(a) Yield of benzaldehyde after 5 hours under aqueous conditions.

Autorecycling Oxidation of Benzyl Alcohol to Benzaldehyde by 10-Alkyl-5-deazaflavins.

A suspension of a 10-alkyl-5-deazaflavin (0.0004 mole), benzyl alcohol (1 g, 0.0093 mole) and potassium carbonate (0.001 mole) was stirred at 90° under aerobic conditions. After 1, 3, 5, 10 hours, aliquots of the reaction mixture (10 $\mu\ell$) were collected, diluted five-fold with ethanol, and analyzed by gas chromatography. The gas chromatography specifications are as follows: sample volume, 1 $\mu\ell$; column, silicone SE-30 2% Chromosorb WAW (60-80 mesh) in a metal column (3 mm × 1 m); internal standard, cycloheptanol.

Oxidation of Benzylamine by 10-Alkyl-5-deazaflavins. General Procedure.

A mixture of 10-alkyl-5-deazaflavin (0.00033 mole), benzylamine (1 g, 0.01 mole) and water (1 ml) was heated at 100° for 5 hours under stirring. The reaction mixture was diluted with ether (3 ml), and the separated 10-alkyl-5-deazaflavin was recovered by filtration. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid to cause the separation of benzaldehyde 2,4-dinitrophenylhydrazone, mp 237°.

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