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Syntheses of 2-Deoxo-2-phenyl-5-deazaflavins and 3-Phenyl-5-deazaflavins and Their Use in the Oxidation of Benzyl Alcohol and Benzylamine

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Treatment of 6-(N-alkylanilino)-2-phenylpyrimidin-4(3*H*)-ones, which were prepared by the condensation of 6-chloro-2-phenylpyrimidin-4(3*H*)-one with N-alkylanilines, with the Vilsmeier reagent (dimethylformamide–phosphoryl chloride) gave the corresponding 10-alkyl-2-deoxo-2-phenyl-5-deazaflavins (III) in excellent yields. Heating of 6-chloro-5-formyl-3-phenyluracil with N-alkylanilines in dimethylformamide gave the corresponding 10-alkyl-3-phenyl-5-deazaflavins (VI) in a single step.

The abilities of the 5-deazaflavins (III) and (VI) thus obtained to oxidize benzyl alcohol and benzylamine were compared, and some automatic recycling of the oxidation reactions was observed. The reaction of compounds III with benzylamine exceptionally gave the adducts, 5-benzylamino-2-deoxo-2-phenyl-5-deazaflavins.

Keywords——6-(N-alkylanilino)-2-phenylpyrimidin-4(3*H*)-one; 2-deoxo-2-phenyl-5-deazaflavin; 3-phenyl-5-deazaflavin; pyrimido[4,5-*b*]quinolin-4(10*H*)-one; pyrimido-[4,5-*b*]quinolin-2,4(3*H*,10*H*)-dione; 5-phenyl-5-deazaflavin; biomimetic alcohol oxidation; biomimetic amine oxidation

Recently we have found that the 5-deazaflavin-dependent oxidation of alcohols to give the corresponding 1,5-dihydro-5-deazaflavins and carbonyl compounds is automatically recycled under weakly basic conditions.[2] For example, in the presence of potassium carbonate the 1,5-dihydro-5-deazaflavins initially formed were reoxidized to the original 5-deazaflavins by air and thus the 5-deazaflavins acted as a turn-over catalyst.

We have previously reported the synthesis of some 5-aryl-5-deazaflavin derivatives (VIII) (*vide infra*) and their oxidizing ability towards alcohols under basic conditions.[3] The present paper describes syntheses of 5-deazaflavin derivatives possessing a phenyl group at the 2- and 3-positions, and their use as an oxido-reductive catalyst in the oxidation of benzyl alcohol and benzylamine.

Synthesis of 2-Deoxo-2-phenyl-5-deazaflavins (2-Phenylpyrimido[4,5-*b*]quinolin-4(10*H*)-ones)

The 3-benzoylpyridinium ion (A) is regarded as a model of NAD^+, because the former has a nucleophilic localization energy at the 4-position (1.87β) similar to that of the 3-carbamoyl-pyridinium ion (B) (1.88β).[4] 2-Deoxo-2-phenyl-5-deazaflavins (III) can be considered structurally as azavinylogous compounds of A, which are protected by annelation, as depicted in Chart 1.

The requisite starting materials for III, 6-(N-alkylanilino)-2-phenylpyrimidin-4(3*H*)-ones (IIa—d) were readily obtained by heating 6-chloro-2-phenylpyrimidin-4(3*H*)-one (I)[5] with

1) Location: *a) Oe-honmachi, Kumamoto 862, Japan*; *b) Kurokami, Kumamoto 860, Japan.*
2) *a)* F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama, and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980); e) F. Yoneda, in "Lectures in Heterocyclic Chemistry," Vol. 5, ed. by R.N. Castle and S.W. Schneller, HeteroCorporation, Orem, Utah, 1980, p. 73.
3) F. Yoneda, T. Asano, K. Tsukuda, and A. Koshiro, *Heterocycles*, **12**, 691 (1979).
4) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, New York, 1963, p. 530.
5) *a)* H.C. Carrington, F.H.S. Curd, and D.N. Richardson, *J. Chem. Soc.*, **1955**, 1858; *b)* F. Yoneda and T. Nagamatsu, *J. Chem. Soc. Perkin I*, **1976**, 1547.

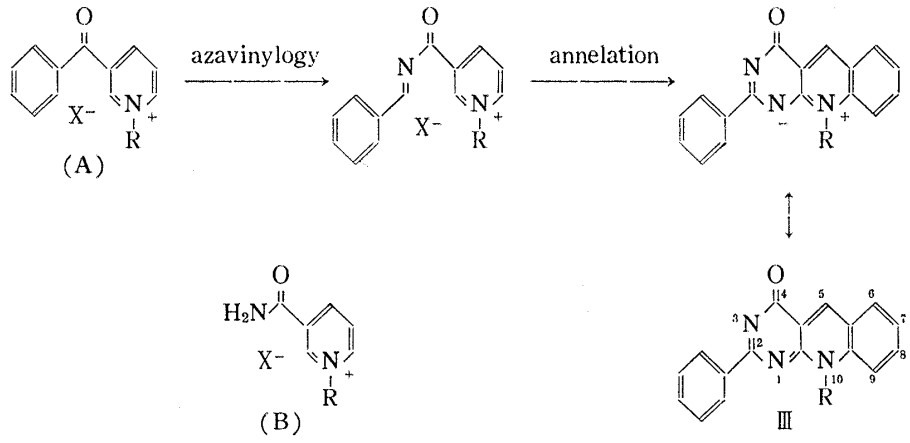
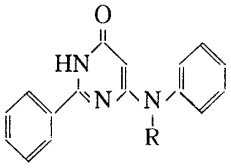


Chart 1

the appropriate N-alkylanilines (Table I). Heating of these compounds (II) with the Vilsmeier reagent (dimethylformamide–phosphoryl chloride) gave the corresponding 2-deoxo-2-phenyl-5-deazaflavins (2-phenylpyrimido[4,5-*b*]quinolin-4(10*H*)-ones) (IIIa—d) in excellent yields (Table II). This process is a successful application of the known 5-deazaflavin synthesis from 6-(N-alkylanilino)uracil derivatives.[6] The structures III were assigned on the basis of elemental analyses and satisfactory spectral data, especially the presence of the characteristic C-5 proton signal in the nuclear magnetic resonance (NMR) spectra (Table IV). Furthermore, the ultraviolet (UV) spectra of III showed a pattern similar to those of typical 5-deazaflavins,[2,6] except for their bathochromic shift (Table V).

TABLE I. 6-(N-Alkylanilino)-2-phenylpyrimidine-4(3*H*)ones



Compd. No.	R	Yield (%)	mp[a] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
IIa	CH_3	84	248	C_2H_5OH	$C_{17}H_{15}N_3O$	73.63	5.45	15.15	73.70	5.64	14.96
IIb	C_2H_5	86	265	C_2H_5OH	$C_{18}H_{17}N_3O$	74.20	5.88	14.42	73.93	5.91	14.60
IIc	n-C_3H_7	81	280	C_2H_5OH	$C_{19}H_{19}N_3O$	74.73	6.27	13.76	75.01	6.27	13.47
IId	n-C_4H_9	85	249	C_2H_5OH	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	75.19	6.58	13.08

a) All compounds were obtained as colorless needles.

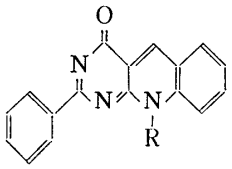
This reaction presumably involves the 5-dimethylaminomethylene intermediates (IV), which cyclize with elimination of dimethylamine (Chart 2).

Synthesis of 3-Phenyl-5-deazaflavins (3-Phenylpyrimido[4,5-*b*]quinolin-2,4(3*H*, 10*H*)-diones)

In connection with the 5-phenyl-5-deazaflavins (VIII)[3] as well as the 2-deoxo-2-phenyl-5-deazaflavins (III), we have synthesized 3-phenyl-5-deazaflavin derivatives in order to examine their oxidizing ability. The starting material, 6-chloro-5-formyl-3-phenyluracil (V)

6) F. Yoneda, Y. Sakuma, S. Mizumoto, and R. Ito, *J. Chem. Soc. Perkin I*, **1976**, 1805.

TABLE II. 10-Alkyl-2-deoxo-2-phenyl-5-deazaflavins



Compd. No.	R	Yield (%)	mp[a] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIIa	CH_3	96	290	DMF	$C_{18}H_{13}N_3O$	75.24	4.56	14.63	75.31	4.51	14.52
IIIb	C_2H_5	98	303	DMF	$C_{19}H_{15}N_3O$	75.73	5.02	13.95	75.69	4.99	13.79
IIIc	n-C_3H_7	93	232	DMF–H_2O (4:1)	$C_{20}H_{17}N_3O$	76.17	5.43	13.33	76.21	5.45	13.15
IIId	n-C_4H_9	99	257	DMF–H_2O (4:1)	$C_{21}H_{19}N_3O$	76.57	5.81	12.76	76.61	5.92	12.58

a) All compounds were obtained as yellow needles.

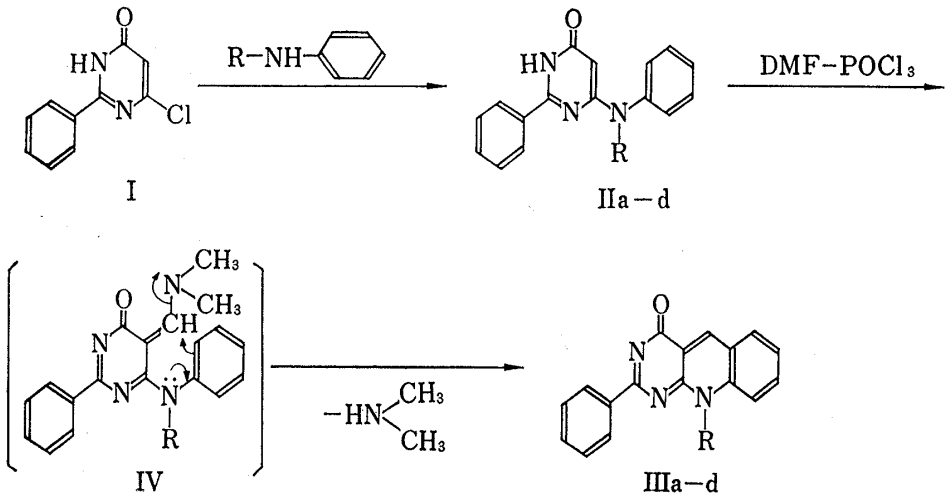


Chart 2

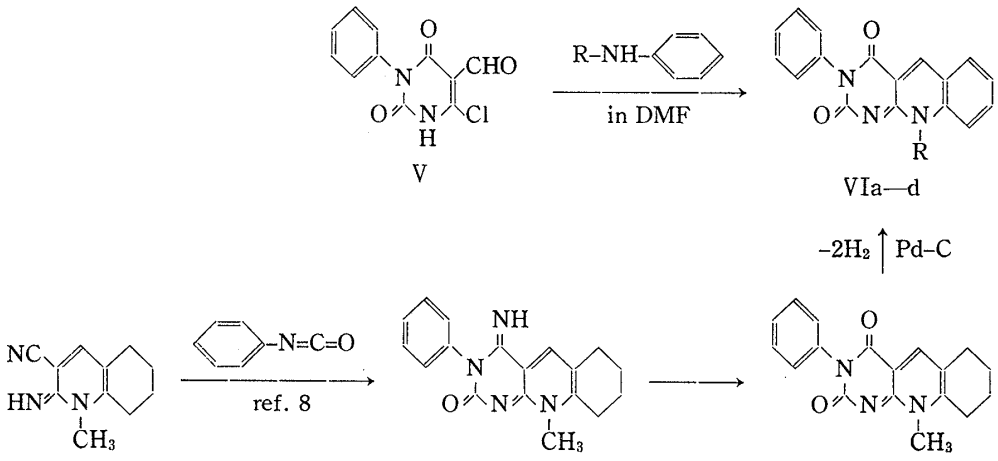


Chart 3

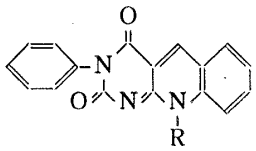
was prepared by the treatment of 3-phenylbarbituric acid with the Vilsmeier reagent according to the procedure reported by Senda and co-workers.[7]

Stirring compound V with N-alkylanilines in dimethylformamide with warming, followed by dilution with ether, caused the separation of the corresponding 3-phenyl-5-deazaflavins (3-phenylpyrimido[4,5-*b*]pyrimidin-2,4(3*H*, 10*H*)-diones) (VIa—d) in a single step (Table III). The structures of these 5-deazaflavins (VI) were supported by their analytical and NMR spectral data (Table IV) as well as typical bands of the 5-deazaflavin ring system in their UV spectra (Table V). Furthermore, compound VIa was identical with an authentic sample which was synthesized by Lacroix and Fleury[8] from 1-methyl-3-cyano-5,6,7,8-tetrahydro-2-quinoline-imine by multiple steps.

Oxidation of Benzyl Alcohol and Benzylamine by the 5-Deazaflavins

The 5-deazaflavins (III) and (VI) thus obtained could oxidize benzyl alcohol. For example, 2-deoxo-10-ethyl-2-phenyl-5-deazaflavin (IIIb) oxidized benzyl alcohol in the presence

Table III. 10-Alkyl-3-phenyl-5-deazaflavins



Compd. No.	R	Yield (%)	mp[a] (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
VIa	CH_3	72	>360	DMF	$C_{18}H_{13}N_3O_2$	71.27	4.32	13.86	71.33	4.31	14.01
VIb	C_2H_5	69	347	DMF	$C_{19}H_{15}N_3O_2$	71.91	4.76	13.24	72.15	4.77	13.06
VIc	n-C_3H_7	73	342	C_2H_5OH	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.49	5.22	12.40
VId	n-C_4H_9	71	297	C_2H_5OH	$C_{21}H_{19}N_3O_2$	73.02	5.55	12.17	73.17	5.43	11.95

a) All compounds were obtained as yellow needles.

Table IV. NMR Data for the 5-Deazaflavins

Compd. No.	δ (CF_3COOH) ppm
IIIa	4.95 (s, N_{10}-CH_3), 7.65—8.65 (m, ArH), 9.95 (s, C_5-H)
IIIb	1.89 (t, J=7, N_{10}-$CH_2\underline{CH_3}$), 5.66 (q, J=7, N_{10}-$\underline{CH_2}CH_3$), 7.70—8.70 (m, ArH), 9.97 (s, C_5-H)
IIIc	1.33 (t, J=7, N_{10}-$CH_2CH_2\underline{CH_3}$), 2.22 (m, N_{10}-$CH_2\underline{CH_2}CH_3$), 5.53 (m, N_{10}-$\underline{CH_2}CH_2CH_3$), 7.55—8.65 (m, ArH), 9.94 (s, C_5-H)
IIId	1.21 (t, J=6.5, N_{10}-$CH_2CH_2CH_2\underline{CH_3}$), 1.99 (m, N_{10}-$CH_2\underline{CH_2}\underline{CH_2}CH_3$), 5.55 (m, N_{10}-$\underline{CH_2}CH_2CH_2CH_3$), 7.50—8.65 (m, ArH), 9.93 (s, C_5-H)
VIa	4.61 (s, N_{10}-CH_3), 7.30—8.60 (m, ArH), 9.81 (s, C_5-H)
VIb	1.85 (t, J=7, N_{10}-$CH_2\underline{CH_3}$), 5.16 (q, J=7, N_{10}-$\underline{CH_2}CH_3$), 7.30—8.60 (m, ArH), 9.82 (s, C_5-H)
VIc	1.35 (t, J=7, N_{10}-$CH_2CH_2\underline{CH_3}$), 2.23 (m, N_{10}-$CH_2\underline{CH_2}CH_3$), 4.98 (m, N_{10}-$\underline{CH_2}CH_2CH_3$), 7.25—8.65 (m, ArH), 9.81 (s, C_5-H)
VId	1.16 (t, J=6.5, N_{10}-$CH_2CH_2CH_2\underline{CH_3}$), 1.95 (m, N_{10}-$CH_2\underline{CH_2}\underline{CH_2}CH_3$), 5.03 (m, N_{10}-$\underline{CH_2}CH_2CH_2CH_3$), 7.30—8.60 (m, ArH), 9.83 (s, C_5-H)

7) S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).
8) A. Lacroix and J.-P. Fleury, *Tetrahedron Lett.*, **1978**, 3469.

Table V. UV Maxima for the 5-Deazaflavins

Compd. No.	λ_{max}^{EtOH} (log ε)
IIIa	451.5 (4.05), 432 (4.01), 405 sh (3.72), 341 (4.08), 299 (4.41), 271 (4.20), 259 (4.16), 233 (4.50)
IIIb	451 (4.00), 430.5 (3.96), 404 sh (3.67), 341 (4.02), 298 (4.39), 270.5 (4.21), 259.5 (4.15), 233 (4.42)
IIIc	451 (3.87), 430 (3.83), 404 sh (3.59), 341 (3.92), 299 (4.26), 270.5 (4.22), 260 (4.19), 233 (4.27)
IIId	451 (3.44), 430 (3.41), 404 sh (3.18), 340 (3.50), 300 sh (4.03), 288 sh (4.20), 271 (4.26), 260.5 (4.27), 233 (4.11)
VIa	420 sh (4.05), 401 (4.15), 380 sh (4.00), 323 (4.07), 313 sh (4.01), 268 (4.70), 224 (4.68)
VIb	419 sh (3.99), 400 (4.08), 379 sh (3.92), 323 (3.99), 313 sh (3.93), 268 (4.62), 224.5 (4.53)
VIc	418 sh (3.74), 400 (3.82), 378 sh (3.65), 323 (3.74), 313 sh (3.68), 268 (4.38), 224.5 (4.34)
VId	418 sh (3.70), 401 (3.78), 378 sh (3.59), 323 (3.70), 313 sh (3.64), 269 (4.33), 225 (4.28)

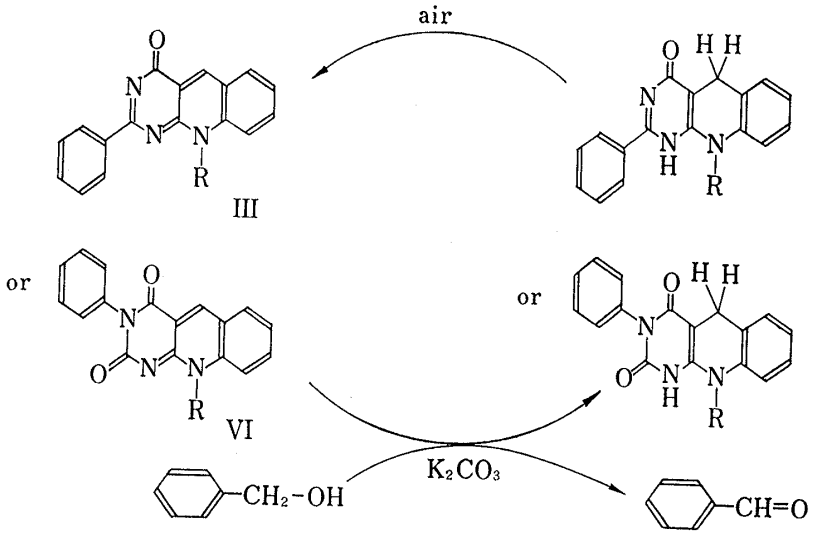


Chart 4

Table VI. Oxidation of Benzyl Alcohol to Benzaldehyde by the 5-Deazaflavins[a]

Compd. No.	Yield of benzaldehyde (%)[b]				
	1 hr	2 hr	3 hr	5 hr	10 hr
IIIa	122	138	157	162	171
IIIb	144	168	182	204	240
IIIc	93	108	110	114	137
IIId	88	106	110	113	122
VIa	55	71	92	101	128
VIb	78	104	112	149	153
VIc	125	141	145	146	144
VId	86	110	116	125	136

a) 90° in the presence of potassium carbonate.
b) Based on the 5-deazaflavins.

of potassium carbonate to afford benzaldehyde in 240% yield based on the 5-deazaflavin. Under these conditions, the 1,5-dihydro-5-deazaflavins initially formed are reoxidized to the original 5-deazaflavins (III) by adventitious air, and thus the 5-deazaflavins acted as a turnover catalyst (Chart 4). The results obtained are summarized in Table VI.

Next, the oxidation of benzylamine by compounds III and VI were carried out under aqueous conditions. Compounds VI showed strong oxidizing ability toward benzylamine to give benzaldehyde in several hundred per cent yield based on the 5-deazaflavins (Table VII). In the case of compounds III, however, the addition of benzylamine to the 5-position followed by dehydrogenation occurred predominantly to give the corresponding 5-benzylamino-5-deazaflavins (VII). Therefore compounds VI appeared to be unsuitable as oxidizing agents for amines.

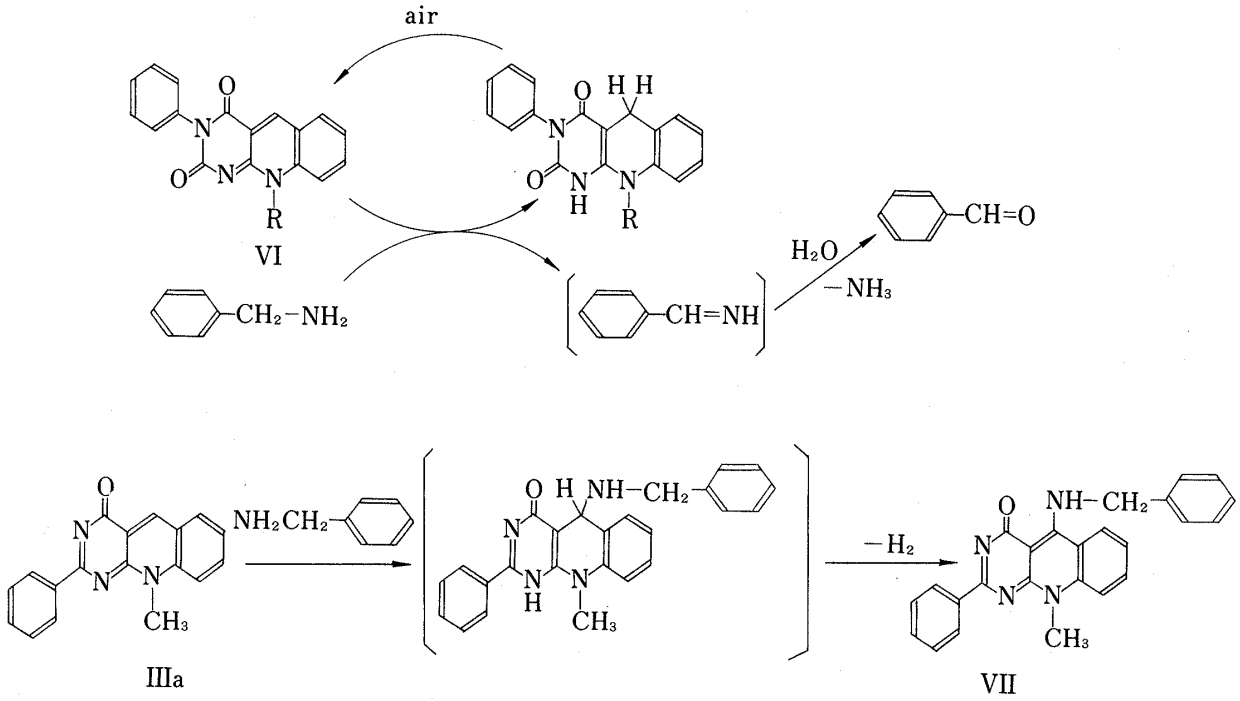


Chart 5

Table VII. Oxidation of Benzylamine to Benzaldehyde by 3-Phenyl-5-deazaflavins[a]

Compd. No.	Yield of benzaldehyde[b]
VIa	101
VIb	444
VIc	738
VId	892

a) At 100° for 5 hr under aqueous conditions.
b) Based on the 5-deazaflavins.

For comparison with the above 5-deazaflavins, the oxidation of benzyl alcohol and benzylamine by 3-methyl-5-phenyl-5-deazaflavin (VIII)[3] was performed under similar conditions. Compound VIII did not oxidize benzyl alcohol in the presence of potassium carbonate. In the case of this compound, basicity equal to or stronger than that of sodium hydroxide seems to be required for benzyl alcohol oxidation. However, compound VIII did oxidize benzylamine efficiently under aqueous conditions to yield benzaldehyde in 260% yield after 10 hr at 100° (Chart 6).

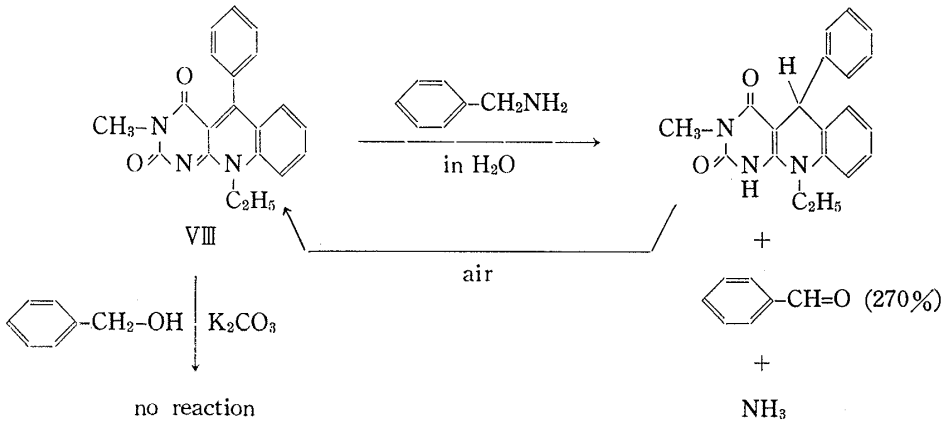


Chart 6

Experimental[9]

6-(N-Alkylanilino)-2-phenylpyrimidin-4(3*H*)-ones (IIa—d). General Procedure——A mixture of 6-chloro-2-phenylpyrimidin-4(3*H*)-one (I)[5] (0.01 mol) and an N-alkylaniline (0.05 mol) was fused at 180° for 5 hr. After cooling, the reaction mixture was diluted with ether to precipitate crystals which were filtered off, washed with water, and dried. Recrystallization from ethanol gave colorless needles in the yields indicated in Table I.

10-Alkyl-2-deoxo-2-phenyl-5-deazaflavins (IIIa—d). General Procedure——A suspension of a 6-(N-alkylanilino)-2-phenylpyrimidin-4(3*H*)-ones (II) (0.01 mol) in dimethylformamide (10 ml) was treated with phosphoryl chloride (0.05 mol) drop by drop, and the mixture was heated at 90° for 2 hr. After cooling, the reaction mixture was neutralized with aqueous ammonia to provide yellow crystals, which were collected by filtration, washed with water, dried and recrystallized from dimethylformamide or a mixture of dimethylformamide and water (4: 1) to give yellow needles (Table II).

10-Alkyl-3-phenyl-5-deazaflavins (VIa—d). General Procedure——A mixture of 6-chloro-5-formyl-3-phenyluracil (V)[7] (0.006 mol) and an N-alkylaniline (0.009 mol) in dimethylformamide (8 ml) was refluxed for 2 hr and the reaction mixture was concentrated *in vacuo*. The residue was collected by filtration, washed with water, dried and recrystallized from an appropriate solvent to give yellow needles (Table III).

Oxidation of Benzyl Alcohol by the 5-Deazaflavins (III and VI)——A suspension of a 5-deazaflavin (III or VI) (0.001 mol) and potassium carbonate (0.003 mol) in benzyl alcohol (3 ml) was stirred at 90° under aerobic conditions. After 1, 2, 3, 5, and 10 hr, aliquots of the reaction mixture (10 μl) were collected, diluted fivefold with ethanol, and analyzed by gas chromatography (Shimadzu GC 3B). The gas chromatographic specifications are as follows: sample volume, 1 μl; column, silicone SE-30 2% Chromosorb WAW (60—80 mesh) in a glass column (3 mm $\times$ 1.7 m); carrier gas, N_2 (60 ml/min); injection temp., 160°; column temp., 90°; FID detector temp., 160°; internal standard, dinonyl phthalate.

Oxidation of Benzylamine by 3-Phenyl-5-deazaflavins (VI)——A mixture of a 3-phenyl-5-deazaflavin (VI) (0.001 mol), benzylamine (3 g, 0.031 mol) and water (3 ml) was heated at 100° for 5 hr under stirring. The reaction mixture was diluted with ether (10 ml), and the separated 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°.

5-Benzylamino-2-deoxo-10-methyl-2-phenyl-5-deazaflavin (VII)——A mixture of compound IIIa (0.29 g, 0.001 mol) and benzylamine (3 g, 0.031 mol) was heated at 90° for 2 hr under stirring. After cooling the reaction mixture was diluted with ether to precipitate crystals, which were filtered off, washed with ether and dried. Recrystallization from ethanol gave pale yellow needles, mp 228°, (0.26 g, 60%). MS: *m/e* 392 (M^+). NMR: δ (CF_3COOH) ppm 4.51 (N_{10}–CH_3), 5.40 (d, J=4 Hz, $\underline{CH_2}$–C_6H_5) and 7.50—8.80 (aromatic H). *Anal.* Calcd for $C_{25}H_{20}N_4O \cdot C_2H_5OH$: C, 73.95; H, 5.98; N, 12.78. Found: C, 73.87; H, 6.28; N, 13.03.

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9) All melting points are uncorrected. NMR spectra were determined with a JEOL PMX 60 spectrometer (with tetramethylsilane as an internal standard). UV spectra were obtained with a JASCO UVIDEC-1 spectrophotometer. The identity of the compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IR-A1 spectrometer.