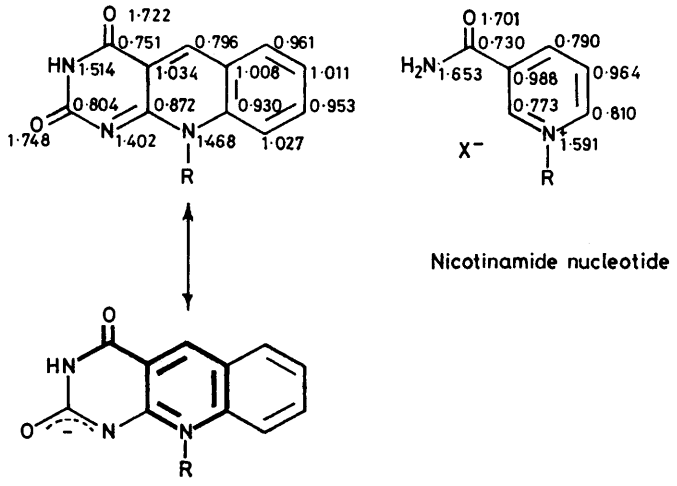
Dehydrogenation of Alcohols by Pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-Deazaflavins) as Autorecycling Oxidizing Agents

By **Fumio Yoneda,* Kenya Mori, Sawako Matsuo, Yoko Kadokawa,** and **Yoshiharu Sakuma,** Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

Pyrimido[4,5-*b*]quinoline-2(3*H*),4(10*H*)-diones (5-deazaflavins) and related compounds oxidize alcohols under alkaline conditions in the dark to yield the corresponding carbonyl compounds, while they themselves are hydrogenated to the 1,5-dihydro-derivatives. The substituent effect in the 5-deazaflavin series was examined in terms of the oxidizing ability toward benzyl alcohol. In some cases, the benzyl alcohol oxidation by the 5-deazaflavins have been shown to recycle automatically, and a >100% yield of benzaldehyde (based on the 5-deazaflavin) was obtained.

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 aroused considerable interest, because of the discovery that they serve as co-factors for several flavin-catalysed reactions,[1] and furthermore because of the recent discovery that co-enzyme F_{420} from methane-producing bacteria possesses a 5-deazaflavin nucleus.[2]

As can be seen from one of the canonical forms, 5-deazaflavins can be considered structurally as a model of the nicotinamide nucleotide protected by annulation ('flavin-shaped nicotinamide analogue') as well as a model of the flavin nucleotide. Hückel MO calculations indicate that the 5-position of the 5-deazaflavin ring



π-Electron densities of 5-deazaflavin and NAD^+ were calculated by the Hückel LCAO–MO method. The parameters of the coulomb and resonance integrals for substituent groups are as follows: for =N–, $a_x = 0.6$, $a_r = 0.1$, $l = 1$; for –N<, $a_x = 1$, $a_r = 0.1$, $l = 1$; for =O, $a_x = 2$, $a_r = 0.2$, $l = 1.41$; a_x is the coulomb integral of the substituent X: $\alpha_x = \alpha + a_x\beta$; a_r is the coulomb integral of the carbon atom adjacent to X: $\alpha_{adj.} = \alpha + a_r\beta$; l is the resonance integral between the carbon atom and X: $\beta_{C-X} = l\beta$.

system is very π-electron deficient (net charge +0.204) in the same way as the 4-position of nicotinamide nucleotide (net charge +0.210). Therefore, it would be expected that the 5-deazaflavins might abstract hydrogen equivalents from hydrogen donors under certain conditions.

Although both classes of the N-substituted 1,4-dihydronicotinamides and the Hantzsch ester have been widely used as models of NAD(P)H, only one model of NAD^+ has been shown to oxidize alcohol, because thermodynamically the redox equilibrium favours the formation of the pyridinium ion. In 1965, Wallenfels and Hanstein reported the oxidation of fluorenol to fluorenone by *N*-methyl-3,4,5-tricyanopyridinium perchlorate.[3] This unusual NAD^+ model has very high electron affinity by virtue of the three cyano-groups. Nevertheless the yield of fluorenone was only 8%.

RESULTS AND DISCUSSION

We have found that 5-deazaflavins do in fact oxidize alcohols under alkaline conditions, even in the dark, to yield the corresponding carbonyl compounds, while they themselves are hydrogenated to 1,5-dihydro-5-deazaflavins.[4] It may be said that this is the first synthetic example of the non-enzymic oxidation of alcohols to carbonyl compounds by an NAD^+ model. We now present the experimental details of alcohol oxidations by 5-deazaflavins.

For example, heating 10-ethyl-3-methyl-5-deazaflavin (1j) [5] with benzyl alcohol in aqueous dimethylformamide in the presence of potassium hydroxide in the dark (in the light also), followed by dilution with water and neutralization with hydrochloric acid, gave 10-ethyl-3-methyl-1,5-dihydro-5-deazaflavin (2j) in quantitative yield. From the filtrate, benzaldehyde was obtained in good yield (identified as the 4-phenylsemicarbazone). Other alcohols were similarly oxidized by (1j) to give the corresponding carbonyl compounds (see Table 1). In the case of ethanol, acetaldehyde was not isolated because of its polymerization under strongly alkaline conditions; however (2j) was obtained in high yield. Methanol also reacted with (1j) a little more slowly than ethanol in the presence of potassium hydroxide to give (2j). The results obtained from the experiments with (1j) under strongly basic conditions are summarized in Table 1. Prolonged heating (20 h) of the mixture of (1j) and benzyl alcohol in the presence of strong alkali gave benzoic acid and (2j) in 146 and 89% yields, respectively, along with a 45% yield of benzaldehyde. In this way, some recycling of the reaction was observed, but un-

TABLE 1

Dehydrogenation of alcohols by (1j) under strongly alkaline conditions

Substrate (Alcohol)	Catalyst	Reaction conditions: Temp. (°C)	Reaction conditions: Time/min	Yields of products (%): Carbonyl compound		(2j)
MeOH	KOH	90	120	*c*		85
EtOH	EtONa	Room temperature	60	*d*		88
EtOH	KOH	80	60	*d*		83
EtOH	KOH (H_2O) [a]	80	20	*d*		95
$PhCH_2OH$	KOH	90	20	PhCHO [e]	70	87
$PhCH_2OH$	KOH (H_2O + DMF) [b]	90	120	PhCHO [e]	82	99
Ph_2CHOH	KOH	90	60	Ph_2CO [f]	81	88
Cyclohexanol	KOH	90	60	Cyclohexanone [g]	70	82

[a] In the presence of water. [b] In the presence of water and DMF. [c] Formaldehyde was polymerized. [d] Acetaldehyde was polymerized. [e] Isolated as benzaldehyde 4-phenylsemicarbazone, m.p. 181 °C. [f] Isolated as benzophenone oxime, m.p. 140 °C. [g] Isolated as cyclohexanone 4-phenylsemicarbazone, m.p. 193 °C.

desired benzoic acid was the major product. The formation of benzoic acid is attributable to the air oxidation of the benzaldehyde initially formed, because under nitrogen benzoic acid was not obtained.

More interestingly, it was found that the 5-deazaflavin-dependent oxidation of alcohols to carbonyl compounds is automatically recycled under less basic conditions. For example, (1j) oxidized benzyl alcohol in the presence of potassium carbonate to give benzaldehyde in >100% yield. Under those conditions, the 1,5-dihydro-5-deazaflavins (2) initially formed were re-oxidized to the original 5-deazaflavins (1) by adventitious air, so that the 5-deazaflavins acted as a turn-over catalyst.

The reactions with potassium hydrogencarbonate, sodium acetate, and triethylamine instead of potassium carbonate led to the complete recovery of starting materials. Therefore, basicities equal to or stronger than that of potassium carbonate seem to be required for the above oxidation.

Next, in order to examine the substituent effect in the 5-deazaflavin-dependent oxidation, several substituted

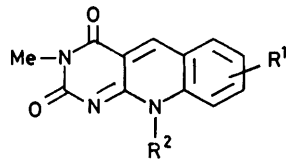
TABLE 2

Autorecycling oxidation of benzyl alcohol to benzaldehyde by 5-deazaflavins (1) [a]

5-Deazaflavin	Yield (%) of benzaldehyde [b]: 1 h	3 h	5 h	10 h
(1a)	39	108	139	224
(1b)	25	46	71	114
(1c)	61	153	223	342
(1d)	32	51	88	134
(1e)	106	105	103	100
(1f)	21	32	44	53
(1g)	10	17	25	35
(1h)	67	62	59	57
(1i)	15	31	48	67
(1j)	55	149	220	318
(1k)	57	138	169	254
(1l)	59	120	146	175
(3)	97	126	131	139
(4)	99	139	141	157
(5)	0	14	28	37

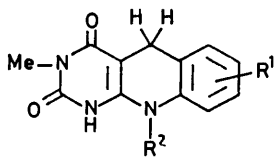
[a] At 90 °C in the presence of potassium carbonate. [b] Based on the 5-deazaflavins.

5-deazaflavins (1) [6] were used. Table 2 shows some benzyl alcohol oxidations by the 5-deazaflavins in the presence of potassium carbonate. In this series, the presence of an 8-chloro-group considerably enhanced the oxidizing power, while the presence of a 7-chloro-group

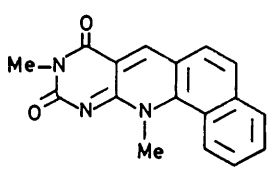


(1)

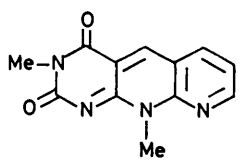
a; $R^1 = H$, $R^2 = Me$
b; $R^1 = 7\text{-}Cl$, $R^2 = Me$
c; $R^1 = 8\text{-}Cl$, $R^2 = Me$
d; $R^1 = 7,8\text{-}Cl_2$, $R^2 = Me$
e; $R^1 = 8\text{-}F$, $R^2 = Me$
f; $R^1 = 8\text{-}CN$, $R^2 = Me$
g; $R^1 = 8\text{-}OMe$, $R^2 = Me$
h; $R^1 = 8\text{-}OH$, $R^2 = Me$
i; $R^1 = 8\text{-}NHCH_2Ph$, $R^2 = Me$
j; $R^1 = H$, $R^2 = Et$
k; $R^1 = H$, $R^2 = Bu^n$
l; $R^1 = H$, $R^2 = CH_2Ph$
m; $R^1 = 8\text{-}OCH_2Ph$, $R^2 = Me$



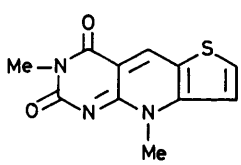
(2)



(3)



(4)



(5)

rather decreased it. It is interesting to note that the presence of a cyano-group at position 8 causes enhanced reactivity with nucleophiles at the 5-position of 5-deazaflavin,[7] but suppressed almost entirely its oxidizing ability.

3,10-Dimethyl-8-fluoro-5-deazaflavin (1e) oxidized benzyl alcohol very rapidly in the initial stage, but the reaction stopped after 1 h. This phenomenon could be ascribed to a change in the structure of (1e). In fact, from the reaction mixture, 8-benzyloxy-3,10-dimethyl-5-deazaflavin (1m) was isolated in almost quantitative yield.

In general, 5-deazaflavins carrying an electron-releasing substituent at the 8-position did not show any appreciable oxidizing ability. The exchange of substituents at the 10-position in 5-deazaflavin also influenced the oxidizing power, as shown in Table 2.

The 5-deazaflavin-like compounds such as 9,12-dimethylbenzo[*h*]pyrimido[4,5-*b*]quinoline-2(9*H*),4(12*H*)-dione (3) and 3,10-dimethylpyrimido[4,5-*b*]-1,8-naphthyridine-2(3*H*),4(10*H*)-dione (4) showed also strong oxidizing abilities in the initial stage, although auto-recycling of the reaction was not very efficient. However, 3,9-dimethylthieno[2′,3′:5,6]pyrido[2,3-*d*]pyrimidine-2(3*H*),4(9*H*)-dione (5) showed little oxidizing ability.

In conclusion, it is interesting that some 5-deazaflavin derivatives acted as a turn-over catalyst under basic conditions, even under non-enzymatic conditions, to recycle automatically the oxidation of benzyl alcohol and a >100% yield of benzaldehyde (based on the 5-deazaflavin) was obtained.

EXPERIMENTAL

M.p.s were obtained with Yanagimoto micro apparatus and are uncorrected. Identity of the compounds was confirmed by comparison of the i.r. spectra determined in Nujol with JASCO IR-A1 spectrometer.

5-Deazaflavins (1) and related compounds [(3), (4), and (5)] were prepared according to the methods described earlier.[5,6]

3,10-*Dimethyl*-8-*fluoro*-5-*deazaflavin* (1e).—A mixture of 3-methyl-6-methylaminouracil (1.55 g, 0.01 mol) and *p*-fluorobenzaldehyde (1.24 g, 0.01 mol) in acetic acid (30 ml) was refluxed for 1 h. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from acetic acid to give 5,5′-(*p*-fluorophenylmethylene)bis-(3-methyl-6-methylaminouracil), as a colourless powder, m.p. 259 °C (1.85 g, 89%) (Found: C, 55.1; H, 5.1; N, 20.0. $C_{19}H_{21}FN_6O_4$ requires C, 54.80; H, 5.08; N, 20.18).

The 5,5′-methylenebisuracil (0.42 g, 0.001 mol) was mixed with diethyl azodiformate (DAD) (0.87 g, 0.005 mol) and the mixture was heated at 160 °C for 30 min with stirring. After cooling, the mixture was diluted with ethanol and allowed to stand at room temperature overnight to precipitate yellow crystals. Recrystallization from ethanol gave 3,10-dimethyl-8-fluoro-5-deazaflavin (1e), m.p. 325 °C (0.15 g, 59%), *m/e* 259 (M^+); δ (CF_3CO_2H), 3.68 (3 H, s, 3-Me), 4.53 (3 H, s, 10-Me), 7.65—8.70 (3 H, aromatic H), and 9.78 (1 H, s, 5-H) (Found: C, 60.4; H, 4.0; N, 16.0. $C_{13}H_{10}FN_3O_2$ requires C, 60.23; H, 3.89; N, 16.21).

8-*Benzyloxy*-3,10-*dimethyl*-5-*deazaflavin* (1m).—A mixture of (1e) (0.26 g, 0.001 mol) and potassium carbonate (0.28 g, 0.002 mol) in benzyl alcohol (3 ml) was heated at 90 °C for 10 h with stirring. The reaction mixture was evaporated *in vacuo* and the residue was treated with water, filtered off, and recrystallized from acetic acid to give pale yellow needles of (1m), m.p. 298 °C (0.32 g, 96%), *m/e* 331 (M^+); δ (CF_3CO_2H), 3.65 (3 H, s, 3-Me), 4.36 (3 H, s, 10-Me), 5.52 (2 H, s, benzylic H), 7.30—8.45 (8 H, aromatic H), and 9.56 (1 H, s, 5-H) (Found: C, 72.6; H, 5.15; N, 12.55. $C_{20}H_{17}N_3O_2$ requires C, 72.49; H, 5.17; N, 12.68).

Reduction of (1j) *with Sodium Ethoxide*.—Sodium (0.3 g, 0.013 g atom) was dissolved in ethanol (30 ml). To this solution was added compound (1j) (1.02 g, 0.004 mol) and the mixture was stirred at room temperature for 1 h. After the reaction mixture was neutralized with acetic acid, the crystals which separated were filtered off, washed with water, dried, and recrystallized from acetic acid to give 10-ethyl-3-methyl-1,5-dihydro-5-deazaflavin (2j) (0.91 g, 88%), m.p. 285 °C, *m/e* 257 (M^+); δ (CF_3CO_2H) 3.56 (3 H, s, 10-Me), 3.72 (3 H, s, 3-Me), 3.90 (2 H, s, 5-H_2), and 7.24 (4 H, s, aromatic H) (Found: C, 65.2; H, 5.9; N, 16.1. $C_{14}H_{15}N_3O_2$ requires C, 65.35; H, 5.88; N, 16.33).

Reduction of (1j) *with Ethanolic Potassium Hydroxide*.—A mixture of (1j) (0.51 g, 0.002 mol) and potassium hydroxide (0.5 g, 0.009 mol) in ethanol (20 ml) was heated at 80 °C for 1 h. After cooling, the reaction mixture was diluted with water and neutralized with acetic acid. The crystals which separated were filtered off, washed with water, dried, and recrystallized from acetic acid to give (2j) (0.43 g, 83%).

Reduction of (1j) *with Aqueous Ethanolic Potassium Hydroxide*.—To a mixture of ethanol (6 ml) and water (4 ml) were added (1j) (0.51 g, 0.002 mol) and potassium hydroxide (0.5 g, 0.009 ml). The mixture was heated at 80 °C for 20 min, and then treated as above to give (2j) (0.49 g, 95%).

Oxidation of Benzyl Alcohol with (1j).—*Method A*. Compound (1j) (0.51 g, 0.002 mol) and potassium hydroxide (0.5 g, 0.009 mol) were added to benzyl alcohol (5 ml). The mixture was heated at 90 °C for 20 min, cooled, and diluted with ether (10 ml). The crystals thus separated were filtered off, washed with water, and dried to give (2j) (0.45 g, 87%). The filtrate was treated with 4-phenylsemicarbazide to give benzaldehyde 4-phenylsemicarbazone (0.33 g, 70%), m.p. 181 °C.

Method B. Compound (1j) (0.51 g, 0.002 mol) and potassium hydroxide (0.05 g, 0.009 mol) were added to a mixture of benzyl alcohol (3 ml), dimethylformamide (3 ml) and water (2 ml), and the mixture was heated at 90 °C for 1 h. The reaction mixture was diluted with water and neutralized with hydrochloric acid. The crystals which separated were collected by filtration, washed with water, and dried to give (2j) (0.51 g, 99%). The filtrate was extracted with ether and the ether extracts were treated with 4-phenylsemicarbazide to precipitate benzaldehyde 4-phenylsemicarbazone (0.39 g, 82%), m.p. 181 °C.

Oxidation of Benzhydrol with (1j).—A mixture of compound (1j) (1.02 g, 0.004 mol), potassium hydroxide (1.0 g, 0.018 mol) and benzhydrol (3.0 g, 0.016 mol) was heated at 90 °C for 1 h under stirring. After cooling, the reaction mixture was diluted with water and neutralized with hydrochloric acid. The crystals thus separated were filtered off, washed with water, and dried to give (2j) (0.91 g, 88%). The filtrate was extracted with ether and the ether extracts were evaporated. The residue was refluxed in a mixture of ethanol (5 ml) and water (1 ml) with

hydroxylamine hydrochloride (0.6 g) and potassium hydroxide (1.0 g) for 2 h. Neutralization with hydrochloric acid separated crystals, which were filtered off and recrystallized from ethanol to give benzophenone oxime (0.64 g, 81%), m.p. 140 °C.

Oxidation of Cyclohexanol with (1j).—A mixture of (1j) (1.02 g, 0.004 mol) and potassium hydroxide (1.0 g, 0.018 mol) in cyclohexanol (5 ml) was heated at 90 °C for 1 h under stirring. After cooling, the reaction mixture was diluted with water and neutralized with hydrochloric acid. The crystals of (2j) (0.84 g, 82%) were filtered off and the filtrate was extracted with ether. The ether extracts were treated with 4-phenylsemicarbazide to precipitate the cyclohexanone 4-phenylsemicarbazone (0.65 g, 70%), m.p. 193 °C.

Autorecycling Oxidation of Benzyl Alcohol by (1j) *under Strongly Basic Conditions.*—A mixture of (1j) (0.2 g, 0.0008 mol), benzyl alcohol (2 g, 0.0185 mol), and sodium hydroxide (0.3 g, 0.0075 mol) was heated at 90 °C for 20 h in the dark (in the light also) under aerobic conditions. The reaction mixture was extracted with ether, the ether solution was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2N hydrochloric acid to cause the separation of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 237 °C (0.1 g, 45%). The residue was diluted with water (10 ml) and acidified with hydrochloric acid to separate a mixture of (2j) (0.18 g, 89%) and benzoic acid (0.14 g, 146%), which were easily separated with ether. Therefore the total yield of the oxidation was 191%.

Autorecycling Oxidation of Benzyl Alcohol to Benzaldehyde by 5-Deazaflavins (1) *in the Presence of Potassium Carbonate.*—A suspension of a 5-deazaflavin (0.001 mol) and potassium carbonate (0.002 mol) in benzyl alcohol (3 ml) was stirred at 90 °C under aerobic conditions. After 1, 3, 5, and 10 h, respectively, the reaction mixture (10 μl) was collected, diluted five-fold with ethanol, and analysed by gas chromatography using Shimadzu GC 3B. The gas chromatographic specifications are as follows: sample volume, 1 μl; column, silicone E-30 2% Chromosorb WAW (60—80 mesh) in a glass column (3 mm × 1.7 m); carrier gas, N_2 (60 ml min^{-1}); injection temperature, 160 °C; column temperature, 90 °C; FID detector temperature, 160 °C.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan. F. Y. thanks Dr. Desmond J. Brown of the Australian National University in Canberra for helpful discussions.

[0/1304 *Received*, 19*th August*, 1980]

REFERENCES

[1] P. Hemmerich, V. Massey, and H. Fenner, *FEBS Lett.*, 1977, **84**, 5.

[2] (*a*) D. Eirich, G. Vogels, and R. Wolfe, *Biochemistry*, 1978, **17**, 4583; (*b*) W. Ashton, R. Brown, F. Jacobson, and C. Walsh, *J. Am. Chem. Soc.*, 1979, **101**, 4419.

[3] K. Wallenfels and W. Hanstein, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 869.

[4] Preliminary report; F. Yoneda, Y. Sakuma, and P. Hemmerich, *J. Chem. Soc., Chem. Commun.*, 1977, 825.

[5] F. Yoneda, Y. Sakuma, S. Mizumoto, and T. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1805.

[6] F. Yoneda, K. Mori, Y. Sakuma, and Y. Yamaguchi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 978.

[7] R. L. Chan and T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **90**, 6721.