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SYNTHESIS OF 2H-PYRIDO[1',2':1,6]PYRIDO[2,3-d]PYRIMIDINE-2,4(3H)DIONES ("BENT 5-DEAZAFLAVINS") AND THEIR USE IN OXIDATION OF ALCOHOL AND AMINE

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Treatment of 6-chloro-5-formyluracils with 2-benzylpyridines in dimethylformamide gave the corresponding 2H-pyrido[1',2':1,6]pyrido[2,3-d]pyrimidine-2,4(3H)diones which are a bent type of 5-deazaflavin. Similarly, treatment of 6-chloro-5-formyl-3-methyluracil with 2-aminopyridine gave a 6-azalog of the above bent 5-deazaflavin, 2H-pyrido[2',1':2,3]pyrimido[4,5-d]pyrimidine-2,4(3H)dione. These "bent 5-deazaflavins" showed oxidizing ability toward benzyl alcohol, cyclohexanol and benzylamine giving the corresponding carbonyl compounds.

Although both classes of the N-substituted 1,4-dihydronicotinamides and the Hantzsch esters have been widely used as models of NAD(P)H,[1] only one model of $NAD(P)^+$ has been shown to oxidize alcohol, because thermodynamically the redox equilibrium favors 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.[2] This unusual NAD^+ model has very high electron affinity by virtue of the three cyano groups. Neverthless the yield of fluorenone was only 8%.

Recently we reported that 5-deazaflavins are considered as "flavin shaped nicotinamide analogs" and 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.[3] It can be said that this is the first example of the practical oxidation of alcohols to carbonyl compounds by an NAD^+. In connection with this reaction, polystyrene-bound 5-deazaflavins[4] and 5-aryl-5-deazaflavins[5] also oxidized alcohols to carbonyl compounds. Furthermore, 5-deazaflavins were effective reagents for the oxidation of amines to the corresponding carbonyl compounds.[6]

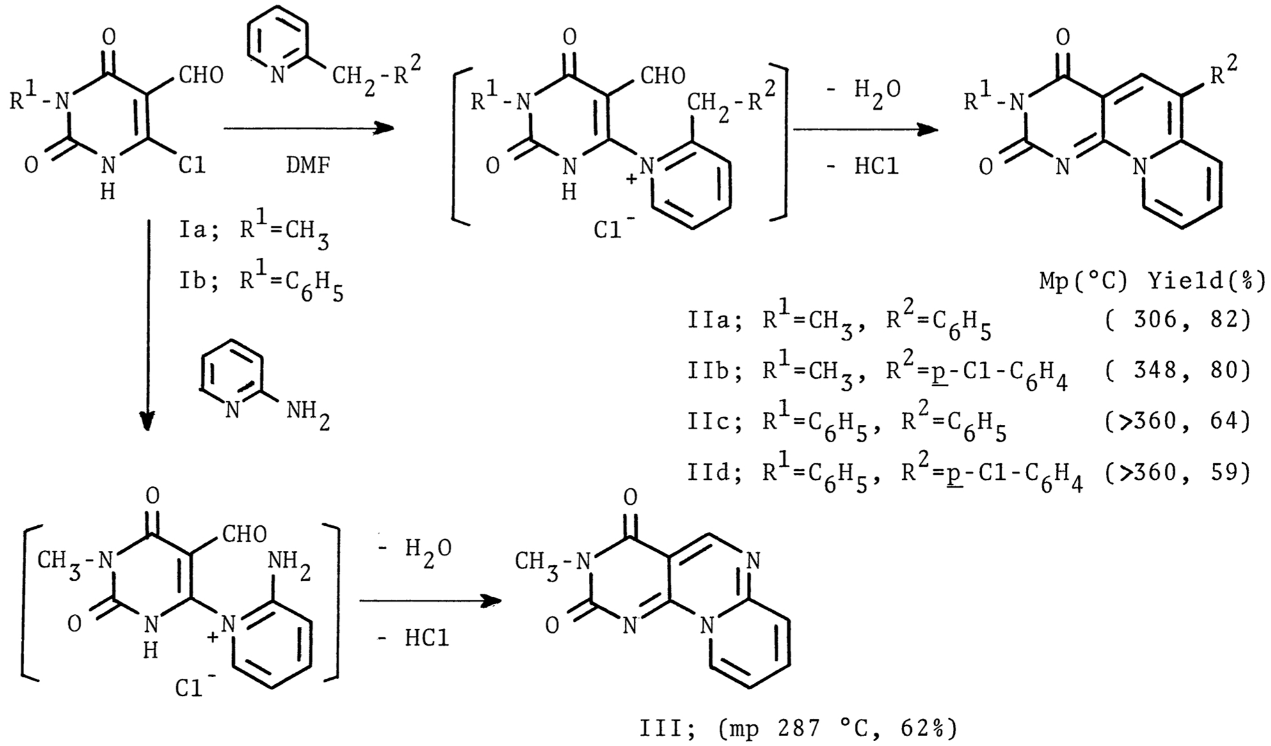
This type of biomimetic oxidation of alcohols has been successively observed on using several 5-deazaflavin-like compounds possessing similar conjugated system such as 5-deaza-10-thiaflavins[7] and 4-deazatoxoflavins.[8]

We now wish to report a synthesis of the new ring system, 2*H*-pyrido[1',2':1,6]pyrido[2,3-*d*]pyrimidine-2,4(3*H*)diones which are a bent type of 5-deazaflavin and their use in the oxidation of alcohol and amine. Additionally, we describes a synthesis of the 6-azalog of the above bent 5-deazaflavin, 2*H*-pyrido[2',1':2,3]-pyrimido[4,5-*d*]pyrimidine-2,4(3*H*)dione.

Synthesis of "Bent 5-Deazaflavins"

Heating of 6-chloro-5-formyl-3-methyluracil (Ia)[9] (1.88 g, 0.01 mol) with 2-benzylpyridine (1.70 g, 0.01 mol) in dimethylformamide (4 ml) for 4 h under reflux, followed by dilution with water, afforded 3-methyl-6-phenyl-2*H*-pyrido[1',2':1,6]-pyrido[2,3-*d*]pyrimidine-2,4(3*H*)dione (IIa) in a single step. Similarly, the treatment of compound Ia with 2-(*p*-chlorobenzyl)pyridine and of 6-chloro-5-formyl-3-phenyluracil (Ib)[10] with these 2-benzylpyridines gave the desired "bent 5-deazaflavins" (IIb-d).

The treatment of Ia (1.88 g, 0.01 mol) with 2-aminopyridine (0.94 g, 0.01 mol) in dimethylformamide (5 ml) under reflux for 3 h gave the expected 6-azalog of the



Ia; R^1=CH_3

Ib; R^1=C_6H_5

	Mp(°C)	Yield(%)
IIa; R^1=CH_3, R^2=C_6H_5	306	82
IIb; R^1=CH_3, R^2=*p*-Cl-C_6H_4	348	80
IIc; R^1=C_6H_5, R^2=C_6H_5	>360	64
IId; R^1=C_6H_5, R^2=*p*-Cl-C_6H_4	>360	59

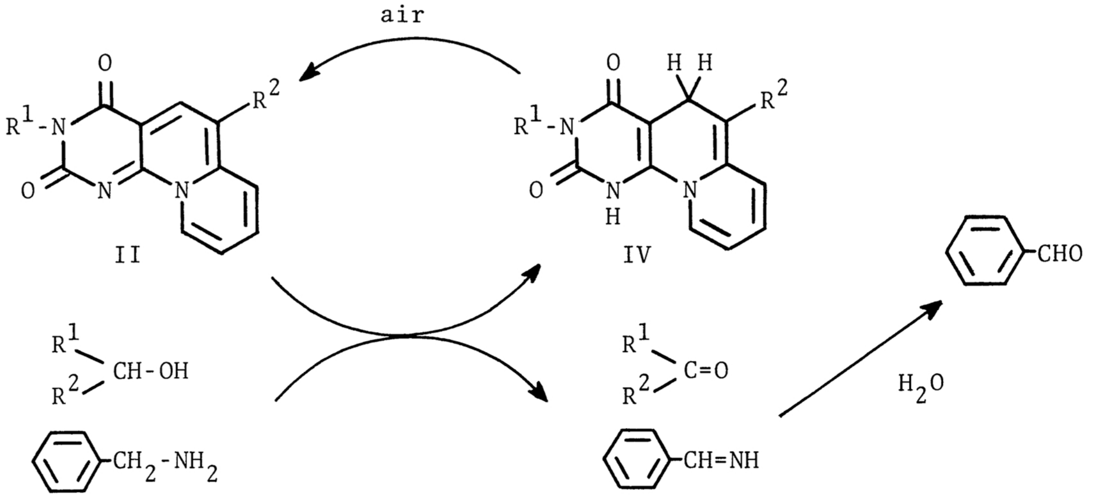
III; (mp 287 °C, 62%)

above bent 5-deazaflavin, 3-methyl-2*H*-pyrido[2',1':2,3]pyrimido[4,5-*d*]pyrimidine-2,4(3*H*)dione (III).

The structures of these compounds thus obtained were confirmed by the satisfactory spectral data and elemental analyses.

Oxidation of Alcohol and Amine by "Bent 5-Deazaflavins"

These bent 5-deazaflavins showed moderate oxidizing ability toward alcohol as follows. A mixture of IIa (0.3 g, 0.001 mol), potassium carbonate (0.3 g, 0.002 mol) and benzyl alcohol (3 g, 0.028 mol) was stirred at 90 °C for 10 h under aerobic conditions. After the reaction mixture was diluted with ether and allowed to stand overnight, the separated crystals (including IIa, 1,5-dihydro-IIa and potassium carbonate) were filtered off. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2N hydrochloric acid to cause the separation of benzaldehyde 2,4-dinitrophenylhydrazone, mp 237 °C, in 51% yield based on the bent 5-deazaflavin. Similarly, IIa oxidized cyclohexanol to cyclohexanone (2,4-dinitrophenylhydrazone, mp 161 °C) under these conditions, albeit in low yield. Other bent 5-deazaflavins (IIb-d) and the analog (III) also oxidized alcohols to give the corresponding carbonyl compounds in the yields indicated in Table. As can be seen from Table, a significant substituent effect was observed in *p*-chlorophenyl derivatives (IIb and d).



Next, the oxidation of benzylamine by compounds II and III was carried out under aqueous conditions. A mixture of II or III (0.001 mol), benzylamine (2 g, 0.019 mol) and water (2 g) was heated at 90 °C for 10 h under stirring and then treated by the same procedure as described above to give benzaldehyde 2,4-dinitrophenylhydrazone in the yields indicated in Table.

It is interesting to note that the bent 5-deazaflavin catalyzed oxidation of benzylamine is considerably recycled; under those conditions the bent 1,5-dihydro-5-deazaflavins (IV) initially formed are reoxidized to the original bent 5-deazaflavins (II) by adventitious air.

TABLE Oxidation of Benzyl Alcohol, Cyclohexanol and Benzylamine by "Bent 5-Deazaflavins"

Substrate / Product / Compound No	Benzyl alcohol	Cyclohexanol	Benzylamine
	Yield (%)[a]		
	Benzaldehyde[b]	Cyclohexanone[b]	Benzaldehyde[b]
IIa	51	18	161
IIb	114	68	515
IIc	25	13	479
IId	67	39	603
III	65	23	191

a) Based on the bent 5-deazaflavins.

b) Determined as their 2,4-dinitrophenylhydrazones.

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REFERENCES

1) R. J. Kill and D. A. Widdowson, in "Bioorganic Chemistry" Vol. 4, ed. by E. E. van Tamelen, Academic Press, 1978, p. 239.
2) K. Wallenfels and W. Hanstein, Angew. Chem. Int. Ed. Engl., 4, 869 (1965).
3) F. Yoneda, Y. Sakuma, and P. Hemmerich, J. Chem. Soc., Chem. Commun., 1977, 825.
4) F. Yoneda, Y. Sakuma, Y. Matsushita, and Y. Nitta, Heterocycles, 9, 1763 (1978).
5) F. Yoneda, T. Asano, T. Tsukuda, and A. Koshiro, Heterocycles, 12, 691 (1979).
6) F. Yoneda, Y. Sakuma, Y. Kadokawa, and A. Koshiro, Chem. Lett., 1979, 1467.
7) F. Yoneda, M. Kawazoe, and Y. Sakuma, Tetrahedron Lett., 1978, 2803.
8) F. Yoneda, M. Higuchi, M. Kawamura, and Y. Nitta, Heterocycles, 9, 1571 (1978).
9) F. Yoneda, Y. Sakuma, S. Mizumoto, and R. Ito, J. Chem. Soc., Perkin Tran. I, 1976, 1805.
10) S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, Yakugaku Zasshi, 91. 1372 (1971).

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