Autorecycling in the Oxidation of Alcohols and Amines by 1,6-Dimethylpyrimido-[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-diones (4-Deazatoxoflavins)

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Summary Oxidation of alcohols and amines by 3-aryl-4-deazatoxoflavins (a model of NAD^+) is automatically recycled under weakly basic conditions to give the corresponding carbonyl compounds in more than 100% yields usually.

4-DEAZATOXOFLAVIN {1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione}[1] in which N-4 of the antibiotic toxoflavin[2] is replaced by CH, has a conjugated system similar to that of flavin and 5-deazaflavin. Furthermore, one of its canonical forms can be considered to be a model of the 6-aza-analogue of nicotinamide nucleotide. Therefore it was expected that 4-deazatoxoflavin derivatives might abstract hydrogen equivalents from hydrogen donors under certain conditions. In fact, 3-phenyl-4-deazatoxoflavin[3] oxidized alcohols in the presence of potassium hydroxide to yield the corresponding carbonyl compounds in stoicheiometric yield and was itself hydrogenated to 4,8-dihydro-3-phenyl-4-deazatoxoflavin.

We have now found that the 4-deazatoxoflavin-dependent oxidation of alcohols is automatically recycled under less basic conditions. This communication describes a remarkable recycling in the oxidation of alcohols and amines by 3-aryl-4-deazatoxoflavins.

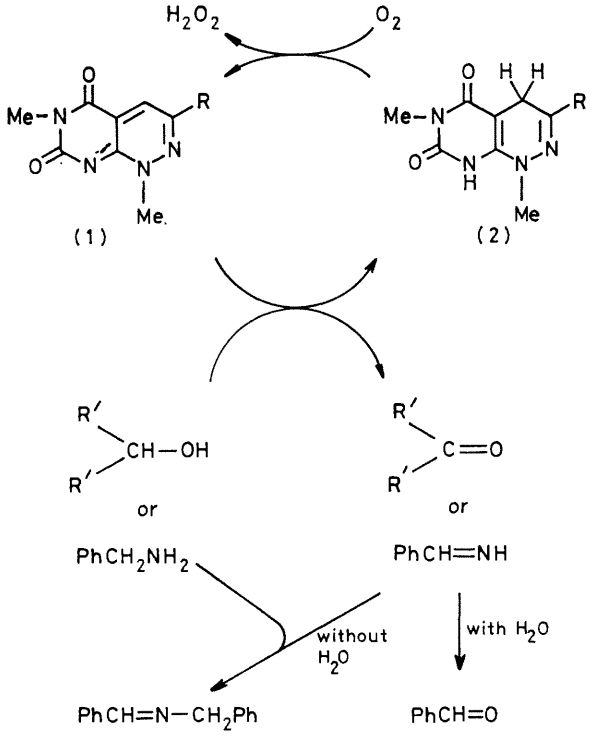
A mixture of a 3-aryl-4-deazatoxoflavin (**1**) (0·35 mmol) and potassium carbonate (1 mmol) in benzyl alcohol or cyclohexanol (1 ml) was stirred under aerobic conditions at 90 °C. The reaction mixture was diluted with ether and the crystals (including recovered 4-deazatoxoflavin and its reduced compound) thus separated were filtered off. The filtrate was treated with a 2N HCl solution of 2,4-dinitrophenylhydrazine to give the corresponding 2,4-dinitrophenylhydrazone of benzaldehyde or cyclohexanone. Under these conditions, the 4,8-dihydro-4-deazatoxoflavin (**2**) initially formed is reoxidized to the original 4-deazatoxoflavin (**1**) by air; thus (**1**) acts as a turn-over catalyst (Scheme).

Table 1 shows the experimental results of alcohol oxidations by several 4-deazatoxoflavins. In this series, a significant substituent effect was observed; in particular (**1d**) exhibited a strong oxidizing ability towards both benzyl alcohol and cyclohexanol. It should be noted that (**1f**) did not oxidize alcohols to any appreciable degree. This may be attributed to the non-planarity of this compound due to the *ortho*-chloro-group and to the hindrance to formation of a complex between the 4-deazatoxoflavin and alcohols.

TABLE 1. Oxidation of benzyl alcohol and cyclohexanol by 3-aryl-4-deazatoxoflavins at 90 °C.

Compd.	R	Yield/%[a] Benzaldehyde[b,c] (after 5 h)	Cyclohexanone[b,c] (after 10 h)
(**1a**)	Ph	191(7)	135(5)
(**1b**)	4-BrC_6H_4	325(12)	370(14)
(**1c**)	4-ClC_6H_4	365(14)	253(9)
(**1d**)	4-FC_6H_4	660(25)	618(23)
(**1e**)	3,4-$Cl_2C_6H_3$	239(9)	244(9)
(**1f**)	2,4-$Cl_2C_6H_3$	65(2)	60(2)
(**1g**)	3,4-$CH_2O_2C_6H_3$	<100(<4)	<100(<4)
(**1h**)	3,4-$(MeO)_2C_6H_3$	<100(<4)	<100(<4)

[a] Based on the 4-deazatoxoflavins. [b] Isolated as 2,4-dinitrophenylhydrazone. [c] Based on alcohols given in parentheses.



SCHEME

The oxidation of benzylamine by (**1**) was then carried out under aqueous and non-aqueous conditions. Heating a mixture of (**1**) (0·35 mmol) in 50% aqueous benzylamine (2 ml) at 90 °C with stirring, followed by the same procedure as that described above, gave benzaldehyde 2,4-dinitrophenylhydrazone (Table 2). This is a biomimetic conversion by an NAD^+ model of an amine into a carbonyl compound *via* an imine.

When the reaction between the 4-deazatoxoflavin (0·35 mmol) and benzylamine (10 ml) was carried out in the absence of water under the same conditions, a remarkable recycling of its oxidation to benzylideneamine was observed. The latter readily condensed with the excess of benzylamine with evolution of ammonia to give *N*-benzylidenebenzyl-

TABLE 2 Oxidation of benzylamine to benzaldehyde[a] by 4-deazatoxoflavins under aqueous and nonaqueous conditions at 90 °C.

Compd.	Aqueous conditions Yield/%[b,c] (after 10 h)	Nonaqueous conditions Yield/%[b,c] (after 10 h)	(after 20 h)	(after 40 h)
(**1a**)	160(6)	2013(15)	4682(35)	
(**1b**)	331(12)	3561(27)	6257(47)	
(**1c**)	355(13)	3000(22)	5352(40)	10,579(72)
(**1d**)	419(17)	7340(27)[d]	14,254(53)[d]	25,370(95)[d]
(**1g**)		1808(13)	4189(31)	
(**1h**)		470(4)	960(7)	

[a] Isolated as benzaldehyde 2,4-dinitrophenylhydrazone. [b] Based on the 4-deazatoxoflavins. [c] Based on benzylamine given in parentheses. [d] Reaction between (**1d**) (0·175 mmol) and benzylamine (10 ml).

amine which accumulated in the reaction mixture. The *N*-benzylidenebenzylamine was treated with a 2N HCl solution of 2,4-dinitrophenylhydrazine to give benzaldehyde 2,4-dinitrophenylhydrazone in the yields indicated in Table 2.

In control experiments without 4-deazatoxoflavins in the above alcohol and amine oxidations, at most only a trace of carbonyl compounds was detected.

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[2] G. D. Daves, R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, 1962, **84**, 1724.
[3] 3-Aryl-4-deazatoxoflavins were synthesized by the condensation of 3-methyl-6-(1-methylhydrazino)uracil with phenacyl bromides or by the cyclization of the aryl aldehyde *N*-methyl-*N*-(3-methyluracil-6-yl)hydrazones; see F. Yoneda, M. Higuchi, M. Kawamura, and Y. Nitta, *Heterocycles*, 1978, **9**, 1571.