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AUTORECYCLING OXIDATION OF AMINES TO CARBONYL COMPOUNDS CATALYZED BY 3,4-DISUBSTITUTED 4-DEAZATOXOFLAVIN DERIVATIVES

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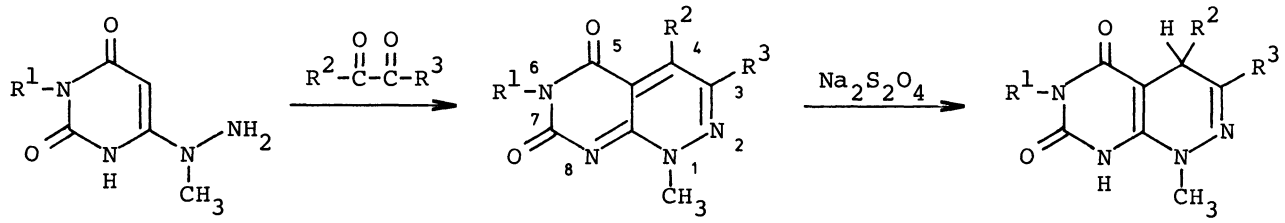
3,4-Disubstituted 4-deazatoxoflavin derivatives (II) were prepared by the condensation of 6-(1-methylhydrazino)uracils (I) with appropriate α-diketones. The compounds II oxidized long-chain alkylamines such as n-octylamine and n-dodecylamine besides benzylamine and cyclohexylamine to yield the corresponding carbonyl compounds via imines, catalytically with a markedly high turnover number.

The oxidation of various biological amines to imines, followed by hydrolysis to carbonyl compounds, is catalyzed by a group of enzymes that contain either $NAD(P)^+$, flavin, or copper as a cofactor.[1] However, no biomimetic oxidation of amines catalyzed by an $NAD(P)^+$ model or a flavin model was found in literatures, before we reported the 5-deazaflavin-dependent oxidation of amines to carbonyl compounds.[2] After that, Shinkai et al.[3] reported that 3-hydroxy-N-methylacridinium ion was also able to oxidize amines.

Recently, we demonstrated that the 1,6-dimethylpyrimido[4,5-c]pyridazine-5,7-(1H,6H)-diones (4-deazatoxoflavins), which have a conjugated system similar to that of 5-deazaflavins, effected the oxidation of benzylamine to yield benzaldehyde with a high recycling number.[4] The reaction of the 4-deazatoxoflavins with long-chain alkylamines, however, gave the corresponding 4-amino-4-deazatoxoflavins,[5] the formation of which might be considered due to the initial nucleophilic addition of amines on the 4-position of 4-deazatoxoflavins and subsequent dehydrogenation. In these cases, the oxidation of amines was extremely suppressed to give a trace of the corresponding aldehydes. Therefore, the oxidation of the amines by 4-deazatoxoflavins and the nucleophilic attack of the amines on the 4-position of the 4-deazatoxoflavins were competitive with each other. Thus it occurred to us that the substituent on the 4-position of 4-deazatoxoflavins may interfere the nucleophilic addition and favor the oxidation of amines. Here, we wish to report the autorecycling oxidation of several amines to the corresponding carbonyl compounds catalyzed by 3,4-disubstituted 4-deazatoxoflavin derivatives.

The 3,4-disubstituted 1,6-dimethylpyrimido[4,5-c]pyridazine-5,7(1H,6H)-diones (4-deazatoxoflavins) and their analogues (IIa-i) were prepared by the condensation of 6-(1-methylhydrazino)uracils (Ia-c) with appropriate α-diketones according to the known procedure.[6] Generally describing, refluxing of 6-(1-methylhydrazino)-

uracils (I) (6 mmol) and appropriate α-diketones (12 mmol) in solvents (20 ml) with or without triethylamine as indicated in Table 1 at 90 - 160 °C for 6 - 8 hr afforded the desired compounds II. In case of the preparation of IIb and IIi, the products were contaminated with the corresponding 4,8-dihydro-4-deazatoxoflavins, which were oxidized to the 4-deazatoxoflavins (II) by treatment with diethyl azodicarboxylate (DAD) at 90 °C. The 6-(1-methylhydrazino)uracils (I) which are precursors of II were prepared by the condensation of 6-chlorouracils with methylhydrazine in ethanol[7-9] (Scheme 1). Table 1 shows the reaction conditions for the preparation of 3,4-disubstituted 4-deazatoxoflavin derivatives (II), and the yields and melting points of these compounds.



I II III

Ia; R^1= H[7)]
Ib; R^1= CH_3[8)]
Ic; R^1= C_6H_5[9)]

IIa; R^1= CH_3, R^2= R^3= C_6H_5
IIb; R^1= CH_3, R^2= R^3= 4-Cl-C_6H_4
IIc; R^1= R^3= CH_3, R^2= C_6H_5
IId; R^1= R^2= R^3= CH_3
IIe; R^1= H, R^2= R^3= C_6H_5
IIf; R^1= H, R^2= R^3= 4-Cl-C_6H_4
IIg; R^1= H, R^2= C_6H_5, R^3= CH_3
IIh; R^1= H, R^2= R^3= CH_3
IIi; R^1= R^2= R^3= C_6H_5

IIIa; R^1= R^3= CH_3, R^2= C_6H_5
IIIb; R^1= R^2= R^3= CH_3
IIIc; R^1= H, R^2= C_6H_5, R^3= CH_3
IIId; R^1= H, R^2= R^3= CH_3

Scheme 1

The 4-deazatoxoflavin derivatives (II) thus obtained catalyzed the oxidation of several amines such as benzylamine, n-octylamine, n-dodecylamine, and cyclohexylamine to the corresponding imines, which readily condensed with the excess amines with evolution of ammonia to give the corresponding N-alkylidenealkylamines. The N-alkylidenealkylamines were readily hydrolyzed under acidic conditions to carbonyl compounds which were identified as the 2,4-dinitrophenylhydrazones. Namely, a mixture of II (0.0436 mmol) with appropriate amines (3 ml or 3 g) was heated at 120 °C[10)] with stirring for 10 hr. The combined reaction mixture and the ether washing solution were treated with a 2N HCl solution of 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazones of the corresponding carbonyl compounds. Under these conditions, 4,8-dihydro-4-deazatoxoflavin derivatives (III) reductively formed were reoxidized to the original II by adventitious air, and thus II acted as a turnover catalyst (Scheme 2).

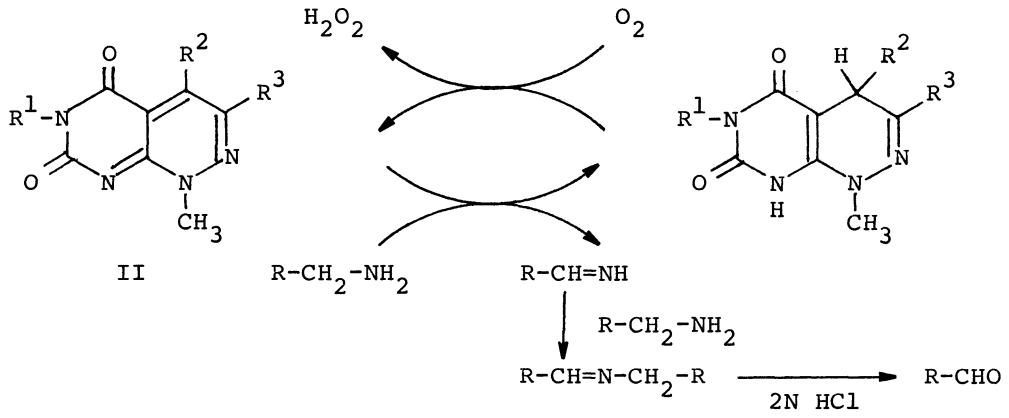
Table 2 shows the oxidation yields of several amines by II. As shown in this Table, 3,4-disubstituted 4-deazatoxoflavins (II) exhibited strong oxidizing abilities toward long-chain alkylamines. Furthermore, it was found that compounds II produced enhanced oxidizing activities toward amines in comparison to the 3-monosubstituted 4-deazatoxoflavins.[4)] For instance, the oxidation yields of benzyl-

Table 1. Formation of 3,4-Disubstituted 4-Deazatoxoflavin Derivatives (II)

Starting material	α-Diketone[a]	Reaction solvent	Product	Yield (%)	Mp (°C)[b]	Recrystn. solvent
Ib	A	AcOH	IIa[6]	53	>305 (sublim.)	DMF
Ib	B	DMF[c]	IIb	66	>266 (sublim.)	AcOH
Ib	C	EtOH	IIc	48	>278 (sublim.)	DMF+EtOH
Ib	D	DMF	IId[6]	74	243	EtOH
Ia	A	DMF	IIe	71	347	EtOH
Ia	B	DMF[c]	IIf	86	337	EtOH
Ia	C	DMF	IIg	100	>268 (sublim.)	EtOH
Ia	D	DMF	IIh	88	>295 (sublim.)	EtOH
Ic	A	DMF[c]	IIi	62	>272 (sublim.)	EtOH

a) A: $R^2 = R^3 = C_6H_5$; B: $R^2 = R^3 = 4\text{-Cl-}C_6H_4$;[11] C: $R^2 = C_6H_5$, $R^3 = CH_3$; D: $R^2 = R^3 = CH_3$ b) All compounds were obtained as yellow needles.

c) Triethylamine was used as a catalyst for the condensation.



Scheme 2

amine by 3,4-diphenyl-4-deazatoxoflavin (IIa) and 3-phenyl-4-deazatoxoflavin at 90 °C for 10 hr were 6495% and 2013%,[4] respectively. These results clearly show that the substituent on the 4-position of 4-deazatoxoflavins interferes the nucleophilic attack of amines on the 4-position and accordingly the oxidation of substrates takes place predominantly. However, a significant substituent effect in the 4-deazatoxoflavins (II) was not observed from the standpoint of the oxidation yield. Exceptionally, compounds II showed somewhat less oxidizing ability toward cyclohexylamine than that toward other amines. It would be attributable to the steric hindrance by the bulky cyclohexyl group to the interaction between the 4-deazatoxoflavins and cyclohexylamine.

In order to confirm the autorecycling of the catalysts and also the structures of IIc and IIg, we have isolated the 4,8-dihydro-4-deazatoxoflavin derivatives (III) by the sodium dithionite reduction of II in usual way (Table 3). The structures of IIc and IIg were established by the presence of the characteristic singlet signal of 4-C proton on the reduced compounds IIIa and IIIc at 4.92 ppm (CF_3COOH) in pmr. The 4,8-dihydro-4-deazatoxoflavins (III) obtained as above were also almost equally effective for the oxidation of amines (see Table 2).

Table 2. Autorecycling Oxidation of Amines to Carbonyl Compounds Catalyzed by II

Compd. No.	Yield (%) of Products[a-c]			
	Benzaldehyde	n-Octylaldehyde	n-Dodecylaldehyde	Cyclohexanone
IIa	6495 (20.6)	3413 (16.4)	2019 (10.9)	1980 (6.6)
IIb	7507 (23.8)	4540 (21.8)	2694 (14.5)	1125 (3.7)
IIc	6168 (19.5)	4558 (21.9)	2444 (13.2)	1436 (4.8)
IId	6444 (20.4)	4956 (23.8)	2355 (12.7)	295 (1.0)
IIe	7732 (24.5)	1783 (8.6)	2459 (13.2)	524 (1.7)
IIf	6179 (19.6)	3572 (17.2)	2587 (13.9)	1144 (3.8)
IIg	5172 (16.4)	1145 (5.5)	4320 (23.2)	665 (2.2)
IIh	5404 (17.1)	1866 (9.0)	4668 (25.1)	300 (1.0)
IIi	4088 (12.9)	4715 (22.7)	3083 (16.6)	111 (0.4)
IIIa	6062 (19.2)	4331 (20.8)	2547 (13.8)	1411 (4.7)

a) Yields have not been optimized. Based on the 4-deazatoxoflavins.

b) Isolated as the corresponding 2,4-dinitrophenylhydrazones.

c) Yields based on the starting amines are given in parentheses.

Table 3. 4,8-Dihydro-4-deazatoxoflavins (III)

Compd. No.	Yield (%)	Mp (°C)	Recrystn. solvent	Appearance
IIIa	72	262	EtOH	colorless plates
IIIb	79	239	EtOH	pale yellow needles
IIIc	70	290 (dec.)	AcOH	colorless powder
IIId	81	270 (dec.)	AcOH	pale brown needles

References

1) G. A. Hamilton, in " Application of Biochemical Systems in Organic Chemistry " Part II, Eds, J. B. Jones, C. J. Shi, and D. Perlman, Wiley, New York, 1976, p. 882. 2) F. Yoneda, Y. Sakuma, Y. Kadokawa, and A. Koshiro, Chem. Lett., 1979, 1467. 3) S. Shinkai, H. Hamada, H. Kuroda, and O. Manabe, Chem. Lett., 1980, 1235. 4) a) F. Yoneda and K. Nakagawa, J. Chem. Soc., Chem. Commum., 1980, 878. b) F. Yoneda, K. Nakagawa, M. Noguchi, and M. Higuchi, Chem. Pharm. Bull., 29, 379 (1981). 5) For example, 3-(p-chlorophenyl)-4-octylamino-4-deazatoxoflavin, mp 227 °C, was isolated in 60% yield, in case of the oxidation of n-octylamine by 3-(p-chlorophenyl)-4-deazatoxoflavin. 6) B. K. Billings, J. A. Wagner, P. D. Cook, and R. N. Castle, J. Heterocyclic Chem., 12, 1221 (1975). 7) F. Yoneda, K. Nakagawa, A. Koshiro, T. Fujita, and Y. Harima, Chem. Pharm. Bull., 30, 172 (1982). 8) G. D. Daves, R. K. Robins, and C. C. Cheng, J. Am. Chem. Soc., 84, 1724 (1961). 9) 6-(1-methylhydrazino)-3-phenyluracil (Ic) was prepared by stirring 6-chloro-3-phenyluracil (5 g, 22 mmol) with methylhydrazine (4.88 ml, 44 mmol) in ethanol (20 ml) at room temperature for 1 hr. Compound Ic gave mp 212 °C (82% from ethanol). 10) The oxidation of benzylamine was carried out at 90 °C. 11) H. T. Clark and E. E. Dreger, Org. Syn., Coll. Vol. 1, 87.

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