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Synthesis and Properties of 3,4-Disubstituted 1-Methylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-diones (3,4-Disubstituted 4-Deazatoxoflavins) and 3,4-Disubstituted 4-Deazatoxoflavin Bound to Polystyrene and Their Use in Autorecycling Oxidation of Amines

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3,4-Disubstituted 1-methylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-diones (3,4-disubstituted 4-deazatoxoflavins) and their analogues (II) were synthesized by the condensation of 6-(1-methylhydrazino)uracil derivatives (I) and appropriate α-diketones. Reduction of II with sodium dithionite in aqueous ammonia gave the corresponding 3,4-disubstituted 4,8-dihydro-4-deazatoxoflavins (III). Ethylation of IIf with ethyl iodide yielded the corresponding 3,4-disubstituted 6-ethyl-4-deazatoxoflavin (VI). Treatment of IIh with chloromethylated polystyrene and potassium carbonate in dimethylformamide (DMF) gave the corresponding 3,4-disubstituted 4-deazatoxoflavin resin (VII). The reaction of II with *m*-chloroperbenzoic acid in chloroform gave the corresponding 3,4-disubstituted 4,4a-epoxy-4-deazatoxoflavins (IV). Treatment of IV with 10% aqueous sodium carbonate resulted in the formation of oxazolonopyridazine derivatives (V).

The oxidizing abilities of II, VI, and VII toward amines were examined to explore the usefulness of these compounds as oxidation–reduction catalysts. These compounds (II, VI, and VII) oxidized long-chain alkylamines such as *n*-octylamine, *n*-dodecylamine besides benzylamine and cyclohexylamine to yield the corresponding carbonyl compounds (*via* imines) catalytically with a remarkably high turnover number.

Keywords——3,4-disubstituted pyrimido[4,5-*c*]pyridazine; 3,4-disubstituted 4-deazatoxoflavin; 3,4-disubstituted 4,8-dihydro-4-deazatoxoflavin; 3,4-disubstituted 4-deazatoxoflavin resin; biomimetic amine oxidation; autorecycling; turn-over catalyst

The oxidation of various biological amines to imines, followed by hydrolysis to carbonyl compounds, is catalyzed by a group of enzymes that contain either nicotinamide adenine dinucleotide (NAD(P)$^+$), flavin, or cofactor.$^{1)}$ However, no biomimetic oxidation of amines catalyzed by an NAD(P)$^+$ model or a flavin model had been described until we reported the 5-deazaflavin-dependent oxidation of amines to carbonyl compounds.$^{2)}$ After that, Shinkai *et al.*$^{3)}$ reported that the 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(1*H*, 6*H*)-diones (4-deazatoxoflavins), which have a conjugated system similar to that of 5-deazaflavins, effected the oxidation of benzylamine to 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 to be due to the initial nucleophilic addition of amines to the 4-position of 4-deazatoxoflavins, followed by dehydrogenation (Chart 1). In these cases, the oxidation of amines was greatly suppressed, giving only 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 a substituent on the 4-position of 4-deazatoxoflavins might interfere with the nucleophilic addition and favor the oxidation of amines.

On the other hand, we previously reported that 5-deazaflavin bound to polystyrene oxidized alcohols under weakly basic conditions, and showed some recycling in the oxidation.[6] We also reported the preparation of several kinds of pyridodipyrimidine resins and carried out autorecycling oxidation by using these resins.[7] We have designed resins containing 3,4-disubstituted 4-deazatoxoflavins as functional groups in order to examine their oxidative abilities from an organic synthetic point of view.

In the case of the autorecycling oxidation of amines, the 3,4-disubstituted 4,8-dihydro-4-deazatoxoflavins initially formed are reoxidized to the original 3,4-disubstituted 4-deazatoxoflavins by adventitious oxygen (air), while oxygen may be hydrogenated to hydrogenperoxide. It is possible that the hydrogenperoxide thus formed will partially be captured by the 3,4-disubstituted 4-deazatoxoflavins to give the corresponding 3,4-disubstituted 4,4a-epoxy-4-deazatoxoflavins (IV). Therefore, the reactivity of IV might be of concern in connection with the fate of 3,4-disubstituted 4-deazatoxoflavins and their analogues (II) in the oxidation procedures. We report here the autorecycling oxidation of several amines to the corresponding carbonyl compounds catalyzed by 3,4-disubstituted 4-deazatoxoflavin derivatives (II) and by a resin containing II. We also describe a synthesis of IV and some properties of IV.

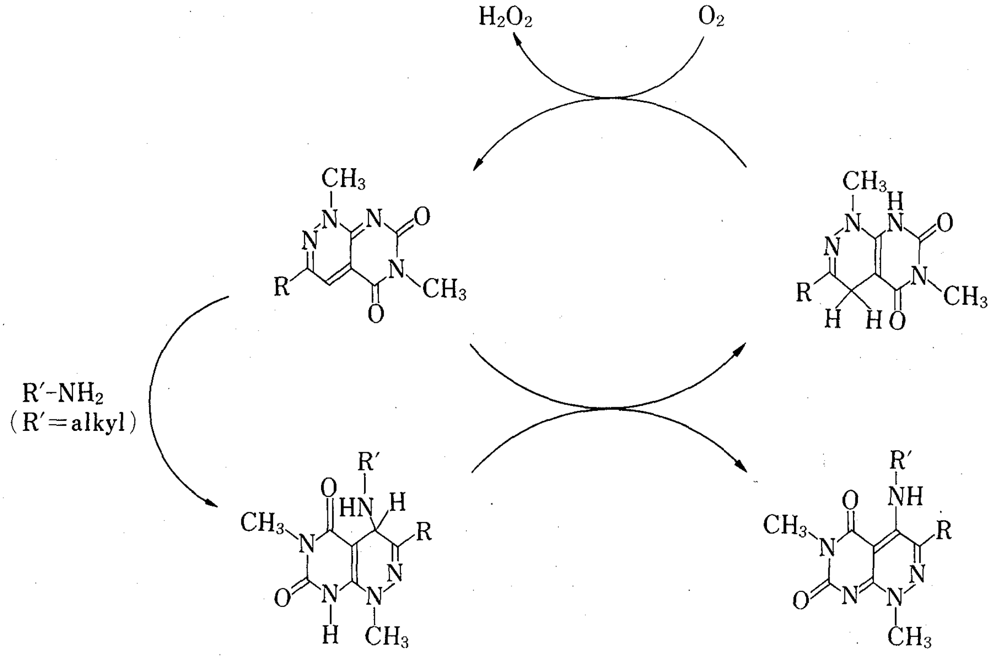


Chart 1

Syntheses of 3,4-Disubstituted 4-Deazatoxoflavin Derivatives (IIa—i and VI) and 3,4-Disubstituted 4-Deazatoxoflavin Bound to Polystyrene (VII)

The starting materials, 6-(1-methylhydrazino)uracil (Ia),[8] 3-methyl-6-(1-methylhydrazino)uracil (Ib)[9] and 6-(1-methylhydrazino)-3-phenyluracil (Ic), were prepared by the condensation of 6-chlorouracil, 6-chloro-3-methyluracil, and 6-chloro-3-phenyluracil, respectively, with methylhydrazine. The 3,4-disubstituted 1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-diones (3,4-disubstituted 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.[10] For example, refluxing of 6-(1-methylhydrazino)uracils (I) and appropriate α-diketones with or without triethylamine afforded the desired compounds (II) (Chart 2) (Tables I and II). In the case of the preparation of IIb and IIi, the products were contaminated with the corresponding 3,4-disubstituted 4,8-dihydro-4-deazatoxoflavins, which were oxidized to the 4-deazatoxoflavins (IIb, i) by treatment with diethyl azodicarboxylate (DAD) at 90 °C. The structures of II were assigned on the basis of elemental analyses, molecular weight as determined by mass spectrometry, and nuclear magnetic resonance (NMR) data (Table III). Furthermore, IIf was converted into the 3,4-bis(*p*-chlorophenyl)-6-ethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-dione (VI) with ethyl iodide in dimethylformamide (DMF) in the presence of potassium carbonate (Chart 2).

Refluxing of 3,4-dimethyl-4-deazatoxoflavin (IIh) with chloromethylated polystyrene in DMF in the presence of potassium carbonate gave polystyrene-bound 1,3,4,6-tetramethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-dione (1,3,4,6-tetramethyl-4-deazatoxoflavin) (VII). From the analytical values, the amount of the 1,3,4,6-tetramethyl-4-deazatoxoflavin groups introduced onto the resin is presumed to be 0.48 mmol/g (Chart 3).

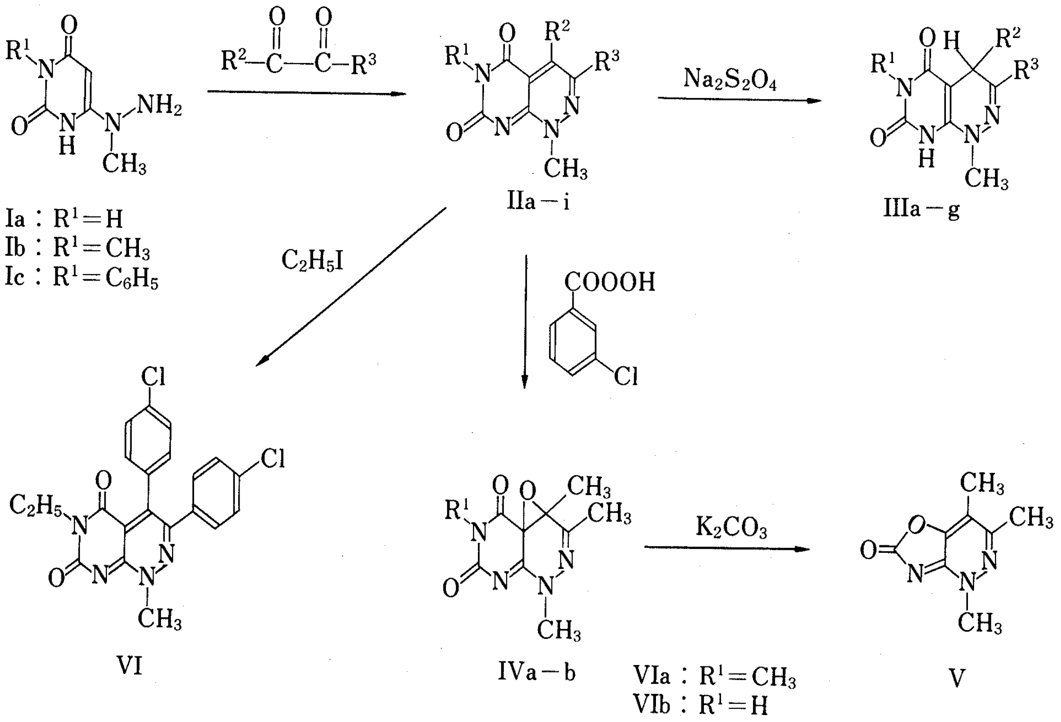


Chart 2

TABLE I. Formation of 3,4-Disubstituted 4-Deazatoxoflavin Derivatives (II)

Starting material	α-Diketone[a)]	Reaction solvent	Product	Yield (%)	mp[b)] (°C)	
Ib	A	AcOH	IIa[10)]	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[10)]	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

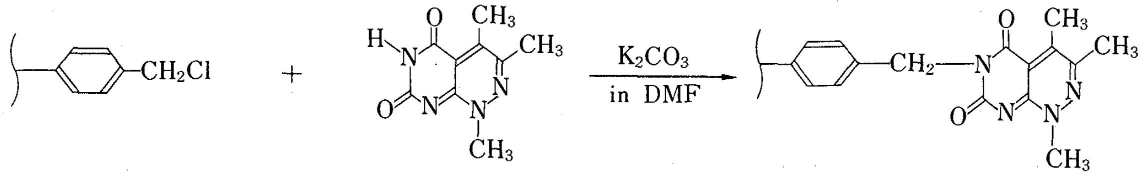
a) A, $R^2=R^3=C_6H_5$; B, $R^2=R^3=4\text{-Cl-}C_6H_4$;[13)] C, $R^2=C_6H_5$, $R^3=CH_3$; D, $R^2=R^3=CH_3$.
b) All compounds were obtained as yellow needles.
c) Triethylamine was used as a catalyst for the condensation.

TABLE II. 3,4-Disubstituted 4-Deazatoxoflavin Derivatives (II)

Compd. No.	R^1	R^2	R^3	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	CH_3	C_6H_5	C_6H_5	$C_{20}H_{16}N_4O_2$	69.75	4.68	16.27
					(69.72	4.89	16.11)
IIb	CH_3	4-Cl-C_6H_4	4-Cl-C_6H_4	$C_{20}H_{14}Cl_2N_4O_2$	58.13	3.41	13.56
					(58.27	3.51	13.41)
IIc	CH_3	C_6H_5	CH_3	$C_{15}H_{14}N_4O_2$	63.82	5.00	19.85
					(64.16	5.09	19.75)
IId	CH_3	CH_3	CH_3	$C_{10}H_{12}N_4O_2$	54.54	5.49	25.44
					(54.95	5.43	24.76)
IIe	H	C_6H_5	C_6H_5	$C_{19}H_{14}N_4O_2$	69.08	4.27	16.96
					(68.19	4.03	17.31)
IIf	H	4-Cl-C_6H_4	4-Cl-C_6H_4	$C_{19}H_{12}Cl_2N_4O_2$	57.12	3.03	14.03
					(56.78	2.95	13.92)
IIg	H	C_6H_5	CH_3	$C_{14}H_{12}N_4O_2$	62.68	4.51	20.89
					(63.03	4.51	20.74)
IIh	H	CH_3	CH_3	$C_9H_{10}N_4O_2$	52.42	4.89	27.17
					(52.78	4.91	26.56)
IIi	C_6H_5	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_2$	73.87	4.46	13.79
					(74.07	4.38	13.75)

TABLE III. NMR Data for 3,4-Disubstituted 4-Deazatoxoflavins (II)

Compd. No.	δ (CF_3COOH) ppm
IIa	3.53 (3H, s, N_6-CH_3), 4.76 (3H, s, N_1-CH_3), 6.76—7.85 (10H, m, ArH)
IIb	3.57 (3H, s, N_6-CH_3), 4.83 (3H, s, N_1-CH_3), 7.03—8.22 (8H, m, ArH)
IIc	2.51 (3H, s, C_3-CH_3), 3.44 (3H, s, N_6-CH_3), 4.63 (3H, s, N_1-CH_3), 7.04—7.89 (5H, m, ArH)
IId	2.83 (3H, s, N_1-CH_3), 3.14 (3H, s, C_3-CH_3), 3.54 (3H, s, N_6-CH_3) 4.53 (3H, s, N_1-CH_3)
IIe	4.75 (3H, s, N_1-CH_3), 6.97—7.72 (10H, m, ArH)
IIf	4.75 (3H, s, N_1-CH_3), 6.88—7.18 (8H, m, ArH)
IIg	2.53 (3H, s, C_3-CH_3), 4.62 (3H, s, N_1-CH_3), 7.00—7.80 (5H, m, ArH)
IIh	2.84 (3H, s, C_4-CH_3), 3.14 (3H, s, C_3-CH_3), 4.58 (3H, s, N_1-CH_3)
IIi	4.76 (3H, s, N_1-CH_3), 6.84—7.70 (15H, m, ArH)



IIh VII

Chart 3

Autorecycling Oxidation of Amines to Carbonyl Compounds Catalyzed by 3,4-Disubstituted 4-Deazatoxoflavin Derivatives (IIa—i, IIIa and VI) and by 3,4-Disubstituted 4-Deazatoxoflavin Resin (VII)

The 3,4-disubstituted 4-deazatoxoflavin derivatives (IIa—i) 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.[4] The alkylidenealkylamines were readily hydrolyzed under acidic conditions to carbonyl compounds which were identified as the 2,4-dinitrophenylhydrazones.

A mixture of a catalytic quantity of IIa—i with appropriate amines was heated at 120 °C (the oxidation of benzylamine was carried out at 90 °C) with stirring for 10 h. The reaction

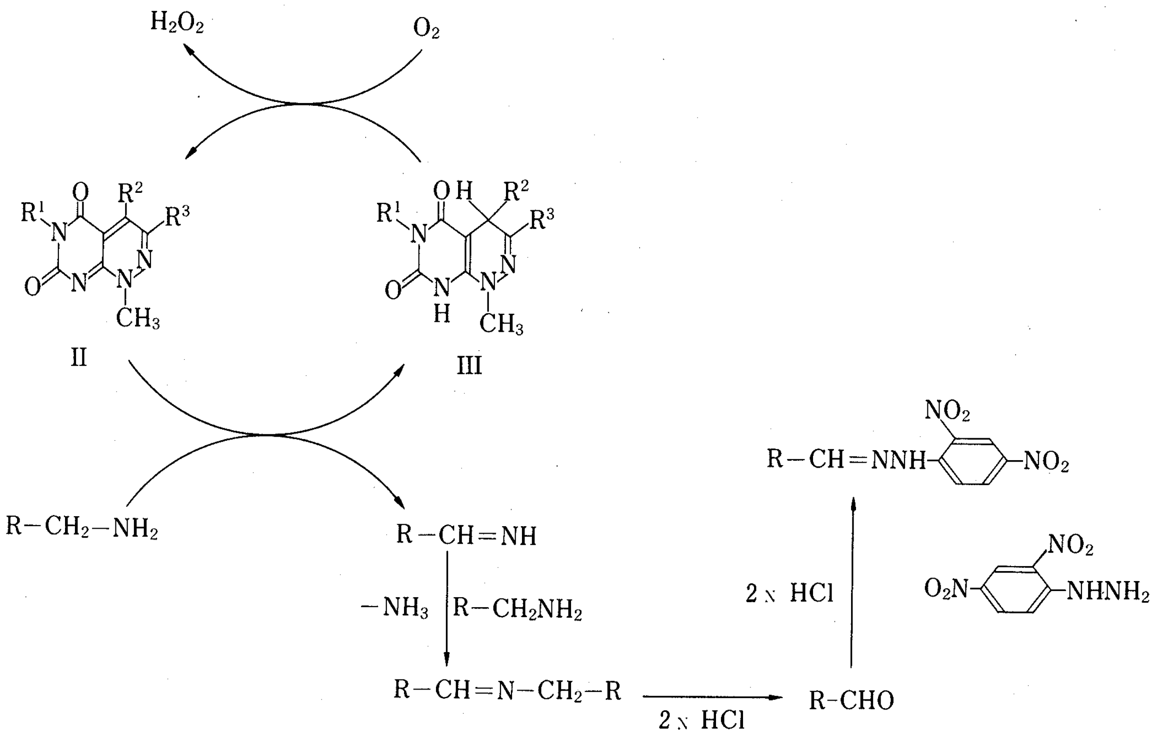


Chart 4

TABLE IV. Autorecycling Oxidation of Amines to Carbonyl Compounds Catalyzed by II, IIIa, and VI

Compd. No.	Yield (%) of products[a-d]			
	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 (17.7)	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)
VI	7334 (23.3)			
VII	1216 (3.9)	2744 (13.2)	2638 (14.2)	855 (2.9)

a) Yield was not optimized. Based on the 4-deazatoxoflavins.
b) Isolated as the corresponding 2,4-dinitrophenylhydrazone.
c) Yields based on the starting amines are given in parentheses.
d) An amount of 90.0 mg of the resin was used, containing 9.0 mg (0.0436 mmol) of IIh.

mixture was treated with a 2 N 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 (Chart 4) (Table V).

Table IV 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, II showed enhanced oxidizing activities toward amines in comparison to the 3-monosubstituted 4-deazatoxoflavins.4) For instance, the oxidation yields of benzylamine with 3,4-diphenyl-4-deazatoxoflavin (IIa) and 3-phenyl-4-deazatoxoflavin at 90 °C for 10 h were 6495 and 2013%,4) respectively. These results clearly show that the substituent on the 4-position of 4-deazatoxoflavins interferes with 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, compound II showed somewhat less oxidizing ability toward cyclohexylamine than toward other amines. This should be attributable to steric hindrance by the bulky cyclohexyl group on the interaction between the 4-deazatoxoflavins and cyclohexylamine.

Next, we carried out the autorecycling oxidation of amines (benzylamine, *n*-octylamine, *n*-dodecylamine, and cyclohexylamine) to the corresponding carbonyl compounds by using the 3,4-disubstituted 4-deazatoxoflavin resin (VII). The yields of the carbonyl compounds thus obtained are listed in Table IV, compared with those obtained by oxidation using the corresponding monomeric 1,3,4-trimethyl-4-deazatoxoflavin (IIh). As shown in Table IV, the resin (VII) showed enhanced oxidizing abilities toward *n*-octylamine and cyclohexylamine in comparison to the monomeric analog (IIh), while it showed weaker oxidizing abilities toward *n*-dodecylamine and particularly toward benzylamine. An advantage of the binding of the 4-deazatoxoflavin (IIh) to polystyrene was that the resin (VII) could be used repeatedly as an oxidizing catalyst in a very convenient operation.

In order to confirm the autorecycling of the catalysts and also the structures of IIc and IIg, the reduction of II was carried out in the usual way. Refluxing of 3,4-disubstituted 4-deazatoxoflavins (II) with sodium dithionite in 7% aqueous ammonia gave the corresponding 4,8-dihydro-4-deazatoxoflavins (IIIa—g) (Chart 2) (Table V). The structures of III were

TABLE V. 3,4-Disubstituted 4,8-Dihydro-4-deazatoxoflavins (III)

Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	CH_3	C_6H_5	C_6H_5	100	300	AcOH	$C_{20}H_{18}N_4O_2$	69.35 (68.74	5.24 5.38	16.18 15.79)
IIIb	CH_3	C_6H_5	CH_3	72	262	EtOH	$C_{15}H_{16}N_4O_2$	63.36 (63.32	5.49 5.49	19.71 19.48)
IIIc	CH_3	CH_3	CH_3	79	239	EtOH	$C_{10}H_{14}N_4O_2$	54.04 (53.94	6.35 6.28	25.21 25.23)
IIId	H	C_6H_5	C_6H_5	49	300	AcOH	$C_{19}H_{16}N_4O_2$	68.66 (67.62	4.85 5.57	16.86 15.40)
IIIe	H	C_6H_5	CH_3	70	290 (dec.)	AcOH	$C_{14}H_{20}N_4O_2$	62.21 (61.58	5.22 5.15	20.78 20.37)
IIIf	H	CH_3	CH_3	81	270 (dec.)	AcOH	$C_9H_{12}N_4O_2$	51.91 (51.98	5.81 5.72	26.91 26.34)
IIIg	C_6H_5	C_6H_5	C_6H_5	77	300	AcOH	$C_{25}H_{20}N_4O_2$	73.51 (73.69	4.94 4.91	13.72 13.58)

TABLE VI. NMR Data for 3,4-Disubstituted 4,8-Dihydro-4-deazatoxoflavins (III)

Compd. No.	δ (CF_3COOH) ppm
IIIa	3.45 (3H, s, N_6–CH_3), 3.82 (3H, s, N_1–CH_3), 5.57 (1H, s, C_4–H), 7.02—7.91 (10H, m, ArH)
IIIb	2.27 (3H, s, C_3–CH_3), 3.40 (3H, s, N_6–CH_3), 3.77 (3H, s, N_1–CH_3), 4.91 (1H, s, C_4–H), 7.32 (5H, s, C_4–C_6H_5)
IIIc	1.51 (3H, d, C_4–CH_3, $J=7.0$ Hz), 2.50 (3H, s, C_3–CH_3), 3.54 (3H, s, N_6–CH_3), 3.75 (3H, s, N_1–CH_3), 4.08 (1H, q, C_4–H, $J=7.0$ Hz)
IIId	3.52 (1H, s, C_4–H), 3.85 (3H, s, N_1–CH_3), 7.08—8.01 (10H, m, Ar)
IIIe	2.25 (3H, s, C_3–CH_3), 3.84 (3H, s, N_1–CH_3), 4.93 (1H, s, C_4–H), 7.47 (5H, s, C_4–C_6H)
IIIf	1.38 (3H, d, C_4–CH_3, $J=6.8$ Hz), 2.38 (3H, s, C_3–CH_3), 3.72 (3H, s, N_1–CH_3), 3.91 (1H, q, C_4–H, $J=6.8$ Hz)
IIIg	3.91 (3H, s, N_1–CH_3), 5.59 (1H, s, C_4–H), 7.00—7.94 (15H, s, ArH)

established by the presence of the characteristic singlet signal of the 4-C proton in the reduced compounds (IIIa—g) in the nuclear magnetic resonance (NMR) spectrum (CF_3COOH) (Table VI). The 3,4-disubstituted 4,8-dihydro-4-deazatoxoflavins (III) were also almost equally effective for the oxidation of amines (Table IV).

Synthesis and Hydrolysis of 3,4-Disubstituted 4,4a-Epoxy-4-deazatoxoflavins (IVa and b)

It is known that the treatment of 5-deazaflavins with *m*-chloroperbenzoic acid gives 4a,5-epoxy-5-deazaflavins$^{11)}$ which show several interesting reactivities.$^{12)}$ We also reported the epoxidation of 4-deazatoxoflavins,$^{8)}$ which possess a conjugated system similar to that of 5-deazaflavins. This epoxidation was extended to the above 3,4-disubstituted 4-deazatoxoflavins (IId and h). Thus, stirring of IId and IIh with *m*-chloroperbenzoic acid in chloroform at room temperature yielded the corresponding 4,4a-epoxy-1,3,4,6-tetramethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-dione (IVa) and 4,4a-epoxy-1,3,4-trimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-dione (IVb), respectively (Chart 2). The structures of IVa and IVb were determined on the basis of elemental analyses and molecular weight determinations by mass spectrometry, as well as NMR data. In contrast, compounds IIa—c, e—g, and i did not react with *m*-chloroperbenzoic acid under the same conditions, and the starting materials were recovered. This result might be due to the steric hindrance of the bulky aryl group at the 4-position.

It is known that treatment of 4a,5-epoxy-5-deazaflavins with aqueous potassium carbonate leads to the formation of the oxazolonoquinoline derivatives.$^{12)}$ An analogous hydrolysis has also been reported for the reaction of 4,4a-epoxy-4-deazatoxoflavins with aqueous sodium hydroxide.$^{8)}$ In connection with these results, we have carried out the alkaline hydrolysis of 3,4-disubstituted 4,4a-epoxy-4-deazatoxoflavins. Thus, treatment of IVa and IVb with 10% aqueous potassium carbonate at room temperature gave the corresponding oxazolonopyridazine derivatives (V) (Chart 2). The structures of V were deduced on the basis of elemental analysis, molecular weight as determined by mass spectrometry, and NMR data.

Experimental

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Hitachi R-24B 60 MHz spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained from Nujol mulls with a JASCO IRA-1 spectrometer.

6-(1-Methylhydrazino)-3-phenyluracil (Ic)——A mixture of 6-chloro-3-phenyluracil (5.0 g, 0.022 mol) and methylhydrazine (4.88 ml, 0.088 mol) was stirred in ethanol (20 ml) at room temperature for 1 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was diluted with water to cause deposition of crystals, which were filtered off, washed with water and recrystallized from ethanol to give 6-(1-methylhydrazino)-3-phenyluracil (Ic) as colorless needles in 82% yield, mp 212 °C. *Anal.* Calcd for $C_{11}H_{12}N_4O_2$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.18; H, 5.12; N, 11.68.

3,4-Disubstituted 4-Deazatoxoflavins (IIa—i). General Procedure——A 6-(1-methylhydrazino)uracil (Ia—c) (0.006 mol) and an α-diketone[13] (0.012 mol) were added to 20 ml of solvent (see Table I). For the syntheses of IIb, f, and i, triethylamine was also added. The mixture was refluxed at 90—160 °C for 6—8 h, then evaporated to dryness *in vacuo*. The residue was treated with ethanol, and the crystals thus separated were collected by filtration. In the syntheses of IIb and IIi, a mixture of the oxidized form and the reduced form was obtained. Therefore, the mixture (1.0 g) was added to excess DAD (1.5 g, 0.009 mol) and the whole was heated at 90—100 °C for 30 min under stirring. After cooling, the reaction mixture was diluted with ether and the crystals which separated were filtered off. Recrystallization from DMF, ethanol, or acetic acid gave the corresponding II in 48—100% yields as indicated in Tables I and II.

Reduction of 3,4-Disubstituted 4-Deazatoxoflavins (IIa, c—e, g—i) with Sodium Dithionite. General Procedure——A 3,4-disubstituted 4-deazatoxoflavin (IIa, c—e, g, h, or i) (0.006 mol) and sodium dithionite (2.5 g, 0.012 mol) were added to 7% aqueous ammonia (30 ml) and the mixture was refluxed for 1—2 h with stirring, then cooled. The separated crystals were filtered off, dried and recrystallized from acetic acid to give the corresponding (III) in 49—100% yields (Table III).

3,4-Disubstituted 4,4a-Epoxy-4-deazatoxoflavins (IVa and b). General Procedure——*m*-Chloroperbenzoic acid (2.1 g, 0.01 mol) was added to a solution of IId or IIh (0.005 mol) in chloroform (20 ml) and the mixture was evaporated to dryness. The residue was treated with ether to precipitate crystals, which were filtered off. Recrystallization of the crystals from chloroform gave IVa and IVb. Yield and physical data are as follows:

Compound IVa: Yield 70%, mp 197 °C, colorless powder. *Anal.* Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.99; H, 4.98; N, 23.57. NMR (CF_3COOH) δ: 2.23 (3H, s, C_4–CH_3), 2.56 (3H, s, C_3–CH_3), 3.47 (3H, s, N_6–CH_3).

Compound IVb: Yield 78%, mp 228 °C (dec.), pale yellow. *Anal.* Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.65. Found: C, 48.52; H, 4.63; N, 25.38. NMR (CF_3COOH) δ: 2.24 (3H, s, C_3–CH_3), 2.27 (3H, s, C_4–CH_3), 4.45 (3H, s, N_1–CH_3).

Hydrolysis of 3,4-Disubstituted 4,4a-Epoxy-4-deazatoxoflavins (IVa and b). General Reaction——Compound IV (0.002 mol) was added to 10% aqueous potassium carbonate (10 ml) and the mixture was stirred at room temperature for 6 h. The reaction mixture was neutralized with acetic acid and the whole was extracted with ethyl acetate. After being dried over anhyd. Na_2SO_4, the ethyl acetate extract was evaporated to dryness and the residue was treated with ether. The precipitated crystals were filtered off. Recrystallization from ethanol gave the corresponding oxazolopyridazine derivative (V) as colorless needles, yield: 45% from IVa; 16% from IVb, mp 174 °C. *Anal.* Calcd for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.25; H, 5.45; N, 23.45. IR ν_{max}^{Nujol} cm^{-1}: 1780 (C=O). NMR (CF_3COOH) δ: 2.61 (3H, s, C_4–CH_3), 2.77 (3H, s, C_3–CH_3), 4.45 (3H, s, N–CH_3).

Oxidation of Amines by 3,4-Disubstituted 4-Deazatoxoflavins (IIa—i and VI). General Procedure——A 3,4-disubstituted 4-deazatoxoflavin (IIa—i or VI) (0.00436 mol) was added to benzylamine (3 ml), *n*-octylamine (3 ml), *n*-dodecylamine (3 ml), or cyclohexylamine (3 ml), and the mixture was maintained at 120 °C with stirring (at 90 °C in the case of benzylamine) under aerobic conditions. After cooling, the reaction mixture was diluted with ether and the crystals which separated were filtered off. The filtrate was treated with a 2 N hydrochloric acid solution of 2,4-dinitrophenylhydrazine to give the corresponding 2,4-dinitrophenylhydrazone of the carbonyl compound (Table IV).

Ethylation of 3,4-Bis(*p*-chlorophenyl)-1-methylpyrido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-dione (VI)——A mixture of IIf (0.3 g, 0.00075 mol), ethyl iodide (0.47 g, 0.003 mol), and potassium carbonate (0.21 g, 0.0015 mol) in DMF (10 ml) was stirred at 90 °C for 2 h. The reaction mixture was filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was treated with ethanol. The crystals thus separated were collected by filtration. Recrystallization from ethanol gave VI as yellow needles in quantitative yield, mp 297 °C (sublim.). *Anal.* Calcd for $C_{21}H_{16}Cl_2N_4O_2$: C, 59.03; H, 3.77; N, 13.11. Found: C, 59.12; H, 3.73; N, 13.00. NMR (CF_3COOH) δ: 1.30 (3H, t, J=7.0 Hz, N_6–$CH_2C\underline{H}_3$), 4.11 (2H, q, J=7.0 Hz, N_6–$C\underline{H}_2CH_3$), 4.69 (3H, s, N_1–CH_3), 6.38—7.56 (8H, m, Ar-H).

Synthesis of 3,4-Disubstituted 4-Deazatoxoflavin Bound to Polystyrene (VII)——A mixture of IIh (0.3 g, 0.00015 mol), chloromethylated polystyrene (divinylbenzene 2%, 100—200 mesh, Cl; 0.93 mmol/g) (1.88 g, Cl; 0.0018 mol) and potassium carbonate (0.4 g, 0.0029 mol) in DMF (10 ml) was refluxed for 3 h. After cooling, the reaction mixture was diluted with water and neutralized with acetic acid. The deazatoxoflavin resin thus obtained was filtered off, purified by washing successively with water and hot ethanol, and dried at room temperature in a vacuum desiccator to give a brown resin. From the analytical values (Found: C, 86.80; H, 7.3; N, 2.69), the amount of 3,4-disubstituted 4-deazatoxoflavin (IIh) groups introduced onto the resin was calculated to be 0.48 mmol/g.

Oxidation of Amines by 3,4-Disubstituted 4-Deazaflavin Resin (VII)——The suspention of the 3,4-disubstituted 4-deazatoxoflavin resin (VII) (90.0 mg) [which contains 9.0 mg (0.0436 mmol) of the 3,4-disubstituted 4-deazatoxoflavin (IIh)] in benzylamine (3 ml) in *n*-octylamine (3 ml), in *n*-dodecylamine (3 g), or in cyclohexylamine (3 ml) was stirred in a flask coupled to a reflux condenser at 120 °C (at 90 °C in the case of benzylamine) for 10 h. After cooling, the reaction mixture was diluted with ether. The resin was recovered quantitatively by filtration and the filtrate was treated with a 2 N HCl solution of 2,4-dinitrophenylhydrazine. The precipitate was filtered off and washed with cold water to give the corresponding 2,4-dinitrophenylhydrazone (Table IV).

References and Notes

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