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Syntheses and Properties of 4-Deazatoxoflavins and Related Compounds

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Treatment of 6-(1-methylhydrazino)uracil (I) with phenacyl bromides in methoxyethanol afforded the corresponding 3-aryl-1-methylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-diones (3-aryl-6-demethyl-4-deazatoxoflavins) (II) and 3-aryl-5,7-dioxo-1-methyl-1,4,5,6,7-pentahydropyrimido[4,3-*c*][1,2,4]triazines (III). Methylation of II and III with methyl iodide gave the corresponding 3-aryl-4-deazatoxoflavins (IV) and 1,6-dimethyl-5,7-dioxopyrimido[4,3-*c*][1,2,4]triazines (V). The reaction of IV with *m*-chloroperbenzoic acid in chloroform gave the corresponding 3-aryl-4,4a-epoxy-4-deazatoxoflavins (VI).

The oxidizing abilities of II toward alcohols were examined in comparison with those of IV from both kinetic and synthetic viewpoints.

Treatment of IV with 30% aqueous caustic alkali led to the exclusive formation of 4,8-dihydro-4-deazatoxoflavins (VII) and 4,8-dihydro-4-deazatoxoflavin-4-ones (VIII) *via* intermolecular oxidation–reduction between the initially formed 4-hydroxy-4,8-dihydro-4-deazatoxoflavins (IX) and unchanged IV. Treatment of VI with 10% aqueous sodium hydroxide gave the 6-aryl-4-hydroxy-2-methylpyridazine-3(2*H*)-ones (X).

Keywords——pyrimido[4,5-*c*]pyridazine; pyrimido[4,3-*c*][1,2,4]triazine; 6-demethyl-4-deazatoxoflavin; 4,4a-epoxy-4-deazatoxoflavin; oxidation–reduction; hydrolysis; biomimetic oxidation of alcohol; 4,8-dihydro-4-deazatoxoflavin; 4,8-dihydro-4-deazatoxoflavin-4-one; 4-hydroxy-2-methylpyridazine-3(2*H*)-one

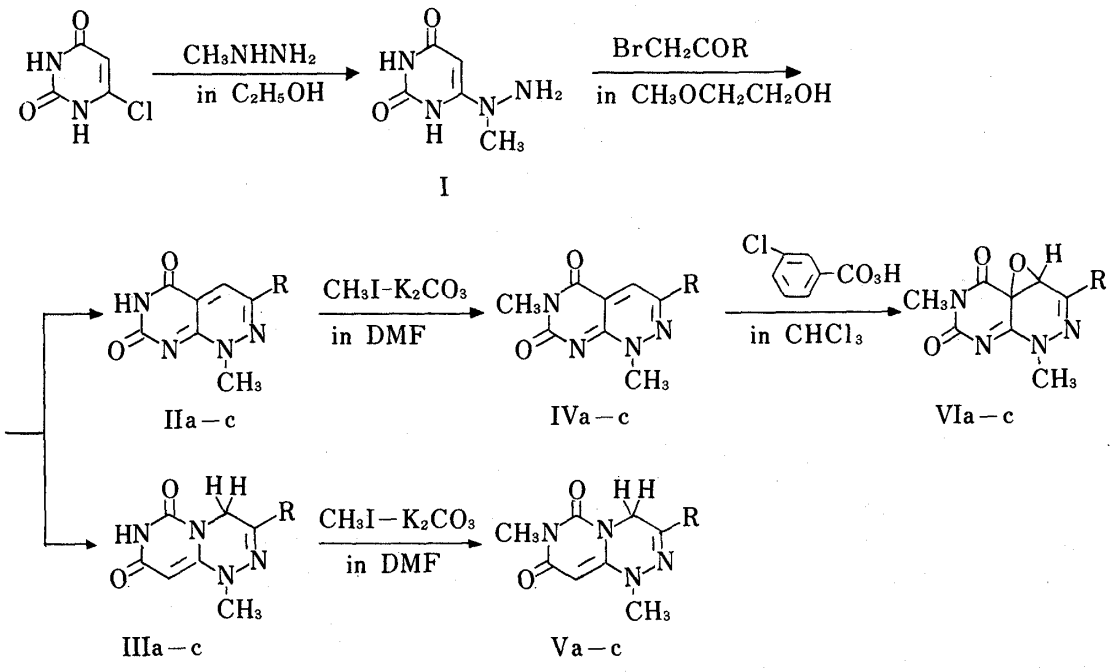
In relation to our studies on the biomimetic oxidations mediated by 5-deazaflavins and analogs, [1–13] we have previously reported the syntheses of 1,6-dimethylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (4-deazatoxoflavin) derivatives and their use in the autorecycling oxidations of alcohols and amines.[14–16] In this paper, we present further information on this series including the preparation of 6-demethyl-4-deazatoxoflavin derivatives and determination of their oxidizing abilities toward alcohols. We also report a synthesis of 4,4a-epoxy-4-deazatoxoflavins and an analysis of their behavior upon alkaline hydrolysis in comparison with that of 4-deazatoxoflavins.

Synthesis of 3-Aryl-1-methylpyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-diones (3-Aryl-6-methyl-4-deazatoxoflavins)

The requisite starting material, 6-(1-methylhydrazino)uracil (I) was prepared by condensation of 6-chlorouracil with methylhydrazine. Refluxing of I with phenacyl bromide in 2-methoxyethanol afforded a mixture of 1-methyl-3-phenylpyrimido[4,5-*c*]pyridazine-5,7-(1*H*, 6*H*)-dione (6-demethyl-3-phenyl-4-deazatoxoflavin) (IIa) (yield 35%) and 5,6-dioxo-1-methyl-3-phenyl-1,4,5,6,7-pentahydropyrimido[4,3-*c*][1,2,4]triazine (IIIa) (yield 60%). Similarly, other 6-demethyl-4-deazatoxoflavins (IIb, c) and pyrimido[4,3-*c*][1,2,4]triazines (IIIb, c) were prepared by the condensation of I with the corresponding phenacyl bromides (Table I).

A remarkable solvent effect was observed during the reaction between I and phenacyl bromides; refluxing of the above mixture in dimethylformamide (DMF) led to the exclusive formation of the corresponding pyrimido[4,3-*c*][1,2,4]triazine (III). Refluxing of the mixture in acetic acid gave mainly III together with a small amount of II.

The structures of II and III were derived on the basis of elemental analyses, molecular weights as determined by mass spectrometry, and nuclear magnetic resonance (NMR) data



a : R=C_6H_5, b : R=4-Br-C_6H_4, c : R=4-Cl-C_6H_4

Chart 1

TABLE I. 3-Aryl-1-methylpyrimido[4,5-*c*]pyridazine-5,7(1*H*, 6*H*)-diones (3-Aryl-6-demethyl-4-deazatoxoflavins) (II) and 3-Aryl-5,7-dioxo-1-methyl-1,4,5,6,7-pentahydropyrimido[4,3-*c*][1,2,4]triazines (III)

Compd. No.	R	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIa	C_6H_5	35	>300	$C_{13}H_{10}N_4O_2$	61.41	3.96	22.04	61.53	3.94	22.24
IIb	4-Br-C_6H_4	49	>300	$C_{13}H_9BrN_4O_2$	46.87	2.72	16.82	46.72	2.94	16.92
IIc	4-Cl-C_6H_4	52	>300	$C_{13}H_9ClN_4O_2$	54.09	3.14	19.41	54.19	3.21	19.56
IIIa	C_6H_5	60	298	$C_{13}H_{12}N_4O_2$	60.93	4.72	21.87	60.91	4.70	21.88
IIIb	4-Br-C_6H_4	43	>300	$C_{13}H_{11}BrN_4O_2$	46.59	3.31	16.72	46.34	3.36	16.66
IIIc	4-Cl-C_6H_4	40	>300	$C_{13}H_{11}ClN_4O_2$	54.09	3.81	19.27	53.75	3.75	18.92

a) All compounds were recrystallized from acetic acid and were obtained as yellow needles.

TABLE II. NMR Data for 6-Demethyl-4-deazatoxoflavins (II), 5,7-Dioxopyrimido[4,3-*c*]-[1,2,4]triazines (III), and 4,4a-Epoxy-4-deazatoxoflavins (VI)

Compd. No.	δ (CF_3COOH) ppm
IIa	4.75 (3H, s, N_1–CH_3), 7.71—8.12 (5H, ArH), 9.38 (1H, s, C_4–H)
IIb	4.73 (3H, s, N_1–CH_3), 7.69—8.09 (4H, ArH), 9.35 (1H, s, C_4–H)
IIc	4.77 (3H, s, N_1–CH_3), 7.57—8.20 (4H, ArH), 9.39 (1H, s, C_4–H)
IIIa	3.74 (3H, s, N_1–CH_3), 4.98 (2H, s, C_4–H_2), 5.73 (1H, s, br, C_9–H_2), 7.49—7.89 (5H, ArH)
IIIb	3.72 (3H, s, N_1–CH_3), 4.93 (2H, s, C_4–H_2), 5.69 (1H, s, br, C_9–H_2), 7.68 (4H, ArH)
IIIc	3.72 (3H, s, N_1–CH_3), 4.96 (2H, s, C_4–H_2), 5.75 (1H, s, br, C_9–H_2), 7.40—7.87 (4H, ArH)
VIa	3.54 (3H, s, N_6–CH_3), 4.22 (3H, s, N_1–CH_3), 5.70 (1H, s, C_4–H), 7.60—8.13 (5H, ArH)
VIb	3.54 (3H, s, N_6–CH_3), 4.20 (3H, s, N_1–CH_3), 5.67 (1H, s, C_4–H), 7.68—8.05 (4H, ArH)
VIc	3.55 (3H, s, N_6–CH_3), 4.20 (3H, s, N_1–CH_3), 5.69 (1H, s, C_4–H), 7.54—8.12 (4H, ArH)

Table III. Ultraviolet (UV) and Visible Maxima of 4-Deazatoxoflavins (IV) and 6-Demethyl-4-deazatoxoflavins (II) in Methanol

Compd. No.	λ_{max}^{MeOH} (log ε)
IVa	392.1(3.49), 275.9(4.45), 209.7(4.32)
IVb	394.9(3.49), 296.8(4.50), 204.8(4.33)
IVc	395.5(3.43), 281.9(4.42), 204.1(4.29)
IIa	335.9(3.91), 295.0(4.26), 204.1(4.25)
IIb	342.1(4.11), 301.0(4.35), 204.3(4.32)
IIc	342.1(3.67), 298.7(4.33), 237.1(3.98), 204.4(4.21)

(Table II). Furthermore, II and III were converted into the known 3-aryl-4-deazatoxoflavins (IV)[16] and 3-aryl-1,6-dimethylpyrimido[4,3-*c*][1,2,4]triazine (V)[16] by conventional methylation with methyl iodide in DMF in the presence of potassium carbonate.

Table III gives ultraviolet absorption data for 6-demethyl-4-deazatoxoflavins (II); hypochromic shifts are apparent as compared with the absorptions of the corresponding 4-deazatoxoflavins (IV).

Synthesis of 4,4a-Epoxy-4-deazatoxoflavins (VI)

It is known that the treatment of 5-deazaflavins with *m*-chloroperbenzoic acid gives 4a,5-epoxy-5-deazaflavins,[17] which show several interesting reactions.[18] This epoxidation has been extended to the 4-deazatoxoflavins (IV), which possess a conjugated system similar to that of 5-deazaflavins. Thus, stirring of IV with *m*-chloroperbenzoic acid in chloroform at room temperature yielded the corresponding 3-aryl-4,4a-epoxy-4-deazatoxoflavins (VIa—c) in good yields, as was expected (Table IV). The structures of VI were established by the analytical and spectral data, particularly by the presence of the characteristic C-4 proton signal in the δ 5.70 ppm region in the NMR (trifluoroacetic acid) (see Table II).

Table IV. 4,4a-Epoxy-4-deazatoxoflavins (VI)

Compd. No.	R	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
VIa	C_6H_5	72	219	$C_{14}H_{12}N_4O_3$	59.15	4.26	19.71	59.24	4.10	19.56
VIb	4-Br-C_6H_4	78	255	$C_{14}H_{11}BrN_4O_3$	46.30	3.05	15.43	46.23	2.92	15.33
VIc	4-Cl-C_6H_4	85	238	$C_{14}H_{11}ClN_4O_3$	52.76	3.48	17.58	52.93	3.40	17.64

a) All compounds were recrystallized from ethanol or chloroform and were obtained as yellow needles.

Autorecycling Oxidations of Alcohols by 4-Deazatoxoflavin Derivatives

Table V shows the apparent oxidation rates of alcohols by the above 6-demethyl-4-deazatoxoflavins (II) and the corresponding 4-deazatoxoflavins (IV) in phosphate buffer (pH 11.0) containing 50 v/v% ethanol, in phosphate buffer (pH 11.0) containing 50 v/v% isopropanol, and in isopropanol alone. In general, some substituent effect was observed in this series and in the phosphate buffer II oxidized alcohols about 10 times more slowly than the corresponding IV. We considered that under these conditions the compounds II were ionized into the corresponding anion, as shown in Chart 2, and their oxidizing abilities decreased, because in isopropanol alone II and IV showed oxidation rates of the same order of magnitude, as shown in Table V. Actually, on a preparative scale and under neutral conditions (without base) II revealed oxidizing abilities toward alcohols comparable to those of IV (Table VI).

Hydrolysis of 4-Deazatoxoflavins and 4,4a-Epoxy-4-deazatoxoflavins

It is known that treatment of 5-deazaflavins with concentrated aqueous potassium hydroxide leads to the exclusive formation of 1,5-dihydro-5-deazaflavins and 1,5-dihydro-5-deazaflavin-5-ones *via* intermolecular oxidation–reduction (disproportionation) between the initially formed 5-hydroxy-1,5-dihydro-5-deazaflavins and unchanged 5-deazaflavins.[8] In connection with this, we have carried out the alkaline hydrolysis of 4-deazatoxoflavins (IV). Treatment of IV with 30% aqueous potassium hydroxide (or sodium hydroxide) gave the 4,8-dihydro-

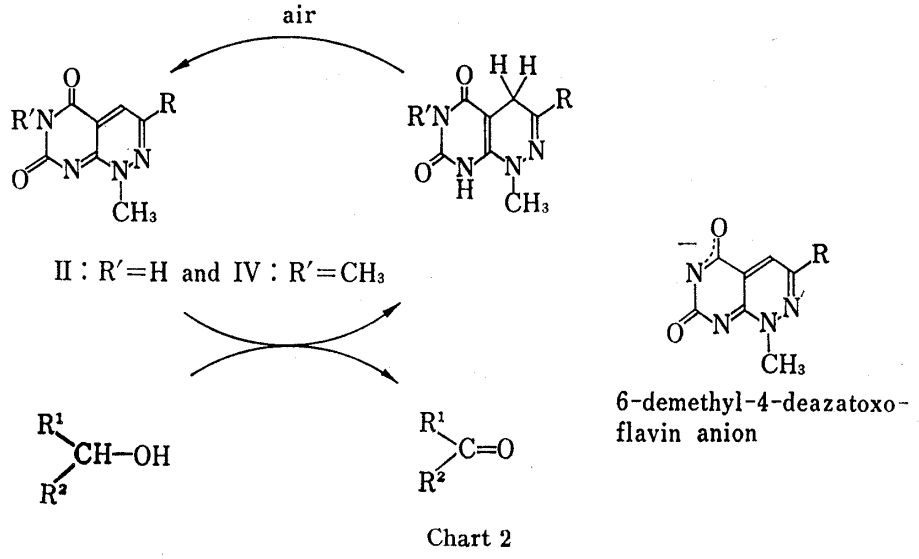


Chart 2

TABLE V. Apparent Oxidation Rates of Alcohols by 4-Deazatoxoflavins (IV) and 6-Demethyl-4-deazatoxoflavins (II)

Compd. No.	R	$k'(min^{-1})^{a)}$	$k'(min^{-1})^{b)}$	$k'(min^{-1})^{c)}$
IVa	C_6H_5	0.0779	0.2108	0.0027
IVb	4-Br-C_6H_4	0.1060	0.5729	0.0036
IVc	4-Cl-C_6H_4	0.1855	0.3480	0.0076
IIa	C_6H_5	0.0033	0.0253	—
IIb	4-Br-C_6H_4	0.0054	0.0559	0.0026
IIc	4-Cl-C_6H_4	0.0053	0.0740	0.0058

a) In phosphate buffer (pH 11.0) containing 50 v/v% ethanol.
b) In phosphate buffer (pH 11.0) containing 50 v/v% isopropanol.
c) In isopropanol alone.

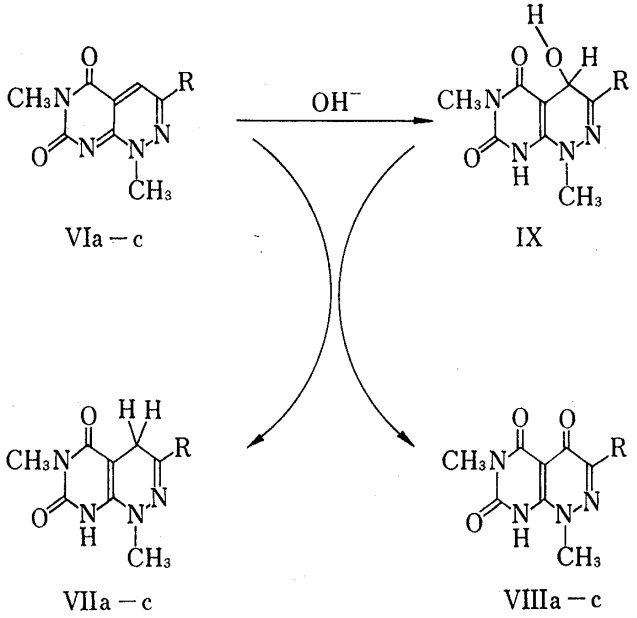
TABLE VI. Oxidations of Benzyl Alcohol and Cyclohexanol by 3-Aryl-6-demethyl-4-deazatoxoflavins (II) at 100°C under Neutral Conditions

Compd. No.	Yield[a] (Yield)[b] (%)			
	Benzaldehyde[c]		Cyclohexanone[c]	
	After 10 h	After 20 h	After 10 h	After 20 h
IIa	120(2.3)	220(4.2)	235(4.1)	363(6.4)
IIb	230(4.4)	1265(23.9)	305(5.3)	493(8.6)
IIc	282(5.3)	888(16.8)	495(8.7)	619(10.8)
IVa	134(2.5)	212(4.0)	—	—

a) Based on the 6-demethyl-4-deazatoxoflavins.
b) Based on the starting alcohols (in parentheses).
c) Isolated as the 2,4-dinitrophenylhydrazone.

4-deazatoxoflavins (VII)[16] and 4,8-dihydro-4-deazatoxoflavin-4-ones (VIII) in a 1:1 ratio, as was expected (Chart 3). This reaction can be rationalized in terms of initial nucleophilic attack of hydroxide ion on the 4-position of one molecule of IV giving 4-hydroxy-4,8-dihydro-4-deazatoxoflavin (IX). Subsequent transfer of hydrogen from the 4-position of IX to the 4-position of another molecule of IV affords the corresponding products VII and VIII (Chart 3). The structures of VIII were determined on the basis of elemental analyses and molecular weight determination by mass spectrometry as well as nuclear magnetic resonance (NMR) data (disappearance of the C-4 proton signal).

Next, the alkaline hydrolysis of 4,4a-epoxy-4-deazatoxoflavins (VI) was carried out. Stirring VI in 10% aqueous sodium hydroxide at room temperature gave 6-aryl-4-hydroxy-2-methylpyridazine-3(2*H*)-ones (X) (Table VIII). The structures of X were derived on the basis of elemental analyses, molecular weights as determined by mass spectrometry and NMR



Starting 4-deazatoxoflavin	Yield (%) VII	VIII	Total
IVa	47	45	92
IVb	44	48	92
IVc	46	43	89

Chart 3. Disproportionation of 4-Deazatoxoflavins with Aqueous Potassium Hydroxide

TABLE VII. 3-Aryl-6,8-dihydro-4-deazatoxoflavin-4-ones (VIII)

Compd. No.	R	mp (°C)[a]	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
VIIIa	C_6H_5	>300	$C_{14}H_{12}N_4O_3$	59.15	4.26	19.71	59.22	4.14	19.78
VIIIb	4-Br-C_6H_4	>300	$C_{14}H_{11}BrN_4O_3$	46.30	3.05	15.43	46.37	3.02	15.09
VIIIc	4-Cl-C_6H_4	>300	$C_{14}H_{11}ClN_4O_3$	52.76	3.48	17.58	52.91	3.28	17.51

a) All compounds were recrystallized from ethanol and were obtained as pale yellow needles.

data (the presence of the C-5 proton in the δ 7.5 ppm region in trifluoroacetic acid) and also by consideration of the mode of formation (Chart 4). An analogous hydrolysis has been reported for the reaction of 4a,5-epoxy-5-deazaflavins with aqueous sodium hydroxide.[18]

This hydrolysis presumably involves initial ring opening by the attack of hydroxide ion on the 7-position. The carbamoyloxy anion could add to the 4a-position, followed by hydrolysis and decarboxylation accompanied by dehydration, to yield the oxazolonopyridazine intermediate (XI).[19] Further hydrolysis of this oxazolonopyridazine would give the final product (X).

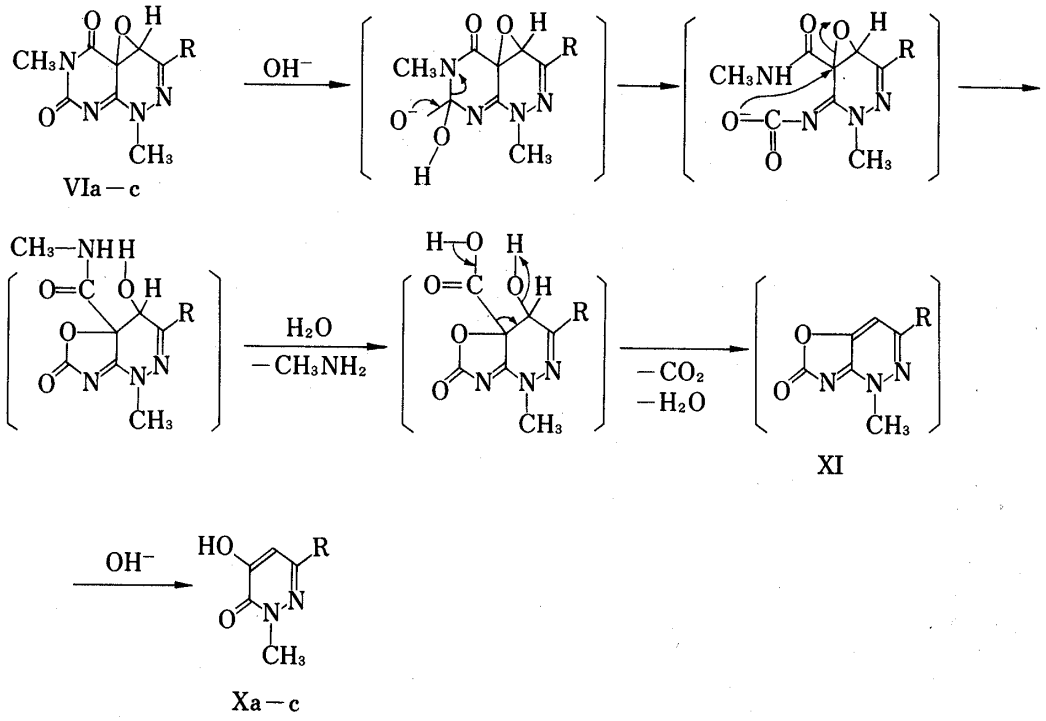


Chart 4

TABLE VIII. 6-Aryl-4-hydroxy-2-methylpyridazine-3(2*H*)-ones (X)

Compd. No.	R	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
Xa	C_6H_5	35	216	$C_{11}H_{10}N_2O_2$	65.33	4.98	13.86	65.17	4.93	13.79
Xb	4-Br-C_6H_4	43	212	$C_{11}H_9BrN_2O_2$	47.00	3.23	9.97	47.18	3.32	9.80
Xc	4-Cl-C_6H_4	50	218	$C_{11}H_9ClN_2O_2$	55.82	3.83	11.84	56.09	3.91	12.01

a) All compounds were recrystallized from ethanol and were obtained as colorless needles.

Experimental[20]

6-(1-Methylhydrazino)uracil (I)——A mixture of 6-chlorouracil (5 g, 0.13 mol) and methylhydrazine (6 g, 0.13 mol) was refluxed in ethanol (40 ml) at 120°C (oil bath) for 2 h. The reaction mixture was filtered to remove the precipitates, then the filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from a mixture of ethanol and dimethylformamide to give a colorless powder (5 g, 94%), mp 272°C. *Anal.* Calcd for $C_5H_8N_4O_2$: C, 38.36; H, 5.16; N, 35.88. Found: C, 38.33; H, 5.12; N, 35.49.

6-Demethyl-4-deazatoxoflavins (IIa—c) and 5,7-Dioxo-1-methyl-1,4,5,6,7-pentahydropyrimido[4,3-*c*]-[1,2,4]triazines (IIIa—c) General Procedure——A phenacyl bromide (0.0064 mol) was added to a solution of I (1 g, 0.064 mol) in methoxyethanol (40 ml), and the mixture was refluxed for 1.5—2 h, then cooled.

The crystals which separated were filtered off, dried and recrystallized from ethanol–dimethylformamide to give the corresponding pyrimido[4,3-*c*][1,2,4]triazines (III) (Table I).

The filtrate was maintained at room temperature for 2—3 d to precipitate crystals, which were collected by filtration and recrystallized from acetic acid to give the corresponding 6-demethyl-4-deazatoxoflavins (II) (Table I).

Methylation of 4-Demethyl-4-deazatoxoflavins (II) and Pyrimido[4,3-*c*][1,2,4]triazines (III). General Procedure——A mixture of II or III (0.001 mol), methyl iodide (0.003 mol) and potassium carbonate (0.003 mol) in dimethylformamide (1 ml) was stirred at 90°C for 3 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 the corresponding 4-deazatoxoflavins (IV) or 1,6-dimethylpyrimido[4,3-*c*][1,2,4]triazines (V) in 80—90% yields.

4,4a-Epoxy-4-deazatoxoflavins (VI). General Procedure——*m*-Chloroperbenzoic acid (0.0015 mol) was added to a solution of IV (0.001 mol) in chloroform (20 ml) and the mixture was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness, the residue was treated with ether, and the crystals thus separated were collected by filtration. Recrystallization from chloroform gave the corresponding 4,4a-epoxy-4-deazatoxoflavin (VI) as colorless needles (Table IV).

Determination of the Oxidation Rates of Alcohols by 4-Deazatoxoflavin Derivatives——The rates of alcohol oxidations by IV and II, giving the corresponding carbonyl compounds, were studied in phosphate buffer (pH 11.0) containing 50 v/v% ethanol, in phosphate buffer (pH 11.0) containing 50 v/v% isopropanol, and in isopropanol alone at 60°C under aerobic conditions and at a concentration of 7.5×10^{-5} mol/l of IV or II. The reaction were performed under pseudo first-order conditions (excess substrate) and the progress of the reaction was followed spectrophotometrically in terms of the decrease in absorbance at 300 nm (for IV) and 287 nm (for II). The pseudo first-order rates (k') were calculated using Eq. 1:

$$\log(A_t - A_\infty) = -\frac{k'}{2.303}t + \log(A_0 - A_\infty) \quad (1)$$

where A_0, A_t and A_∞ are the absorbance at time 0, t, and ∞, respectively.

Oxidation of Alcohols by 6-Demethyl-4-deazatoxoflavins. General Procedure——A solution of II (0.00035 mol) in benzyl alcohol or cyclohexanol (2 ml) was stirred at 100°C under aerobic conditions. The reaction mixture was diluted with ether and the recovered II (usually 50%) was 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 benzaldehyde or cyclohexanone (see Table VI).

Hydrolysis of 4-Deazatoxoflavins (IV)——A suspension of IV (0.0016 mol) in 30% aqueous potassium hydroxide (50 ml) was refluxed for 6 h, then cooled. The crystals which separated were filtered off. The crystals (potassium salts) thus obtained were treated with 10% hydrochloric acid to separate a mixture of free 4,8-dihydro-4-deazatoxoflavins (VII) and 4,8-dihydro-4-deazatoxoflavin-4-ones (VIII), which was collected by filtration. The mixture was extracted with boiling ethanol and the residue was recrystallized from acetic acid to give VII. The ethanol extracts were evaporated to dryness and the residue was recrystallized from ethanol to give VIII (Table VII).

Hydrolysis of 4,4a-Epoxy-4-deazatoxoflavins (VI)——A solution of VI (0.001 mol) in 10% aqueous sodium hydroxide (5 ml) was stirred at room temperature for 6 h. The reaction mixture was neutralized with acetic acid to cause the separation of the corresponding 4-hydroxy-2-methylpyridazine-3(2*H*)-one (X) (Table VIII).

References and Notes

1) F. Yoneda, Y. Sakuma, and P. Hemmerich, *J. Chem. Soc. Chem. Comm.*, **1977**, 825.
2) F. Yoneda, M. Kawazoe, and Y. Sakuma, *Tetrahedron Lett.*, **1978**, 2803.
3) F. Yoneda, Y. Sakuma, Y. Kadokawa, and Y. Nitta, *Chemistry Lett.*, **1979**, 1467.
4) F. Yoneda, T. Asano, K. Tsukuda, and A. Koshiro, *Heterocycles*, **12**, 691 (1979).
5) F. Yoneda, M. Ono, K. Kira, H. Tanaka, and Y. Sakuma, and A. Koshiro, *Chemistry Lett.*, **1980**, 817.
6) F. Yoneda, R. Hirayama, and M. Yamashita, *Chemistry Lett.*, **1980**, 1157.
7) F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama, and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980).
8) *a*) F. Yoneda, Y. Sakuma, and Y. Matsushita, *J. Chem. Soc. Chem. Comm.*, **1978**, 398; *b*) F. Yoneda, Y. Sakuma, and A. Koshiro, *J. Chem. Soc. Perkin I*, **1980**, 293.
9) F. Yoneda, in "Lectures in Heterocyclic Chemistry," Vol. 5, ed. by R.N. Castle and S.W. Schneller, Hetero Corporation, Orem, Utah, S-73.
10) F. Yoneda, K. Mori, M. Ono, Y. Kadokawa, E. Nagao, and H. Yamaguchi, *Chem. Pharm. Bull.*, **28**, 3514 (1980).
11) S. Shinkai, H. Kuroda, O. Manabe, and F. Yoneda, *J. Chem. Soc. Chem. Comm.*, **1981**, 391.
12) F. Yoneda, K. Mori, S. Matsuo, Y. Kadokawa, and Y. Sakuma, *J. Chem. Soc. Perkin I*, **1981**, 1836.

13) F. Yoneda, K. Tsukuda, M. Kawazoe, A. Sone, and A. Koshiro, *J. Heterocyclic Chem.*, **18**, 1329 (1981).
14) F. Yoneda, M. Higuchi, M. Kawamura, and Y. Nitta, *Heterocycles*, **9**, 1571 (1978).
15) F. Yoneda and K. Nakagawa, *J. Chem. Soc. Chem. Comm.*, **1980**, 878.
16) F. Yoneda, K. Nakagawa, M. Noguchi, and M. Higuchi, *Chem. Pharm. Bull.*, **29**, 379 (1981).
17) D. Vargo and M.S. Jorns, *J. Am. Chem. Soc.*, **101**, 7623 (1979).
18) F. Yoneda and Y. Sakuma, *Tetrahedron Lett.*, **1981**, 3977.
19) We have tried to isolate the oxazolonopyridazine intermediate (IX) under various conditions, but without success. It should be noted that in the 4a,5-epoxy-5-deazaflavin series this type of intermediate was isolated.[18]
20) All melting points are uncorrected. NMR spectra were determined with a JEOL-PMX 60 spectrometer with tetramethylsilane as an internal standard. UV spectra were obtained with a JASCO UVIDEC-1 spectrophotometer. The identity of compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IR-A1 spectrometer.