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Simple New Method for the Synthesis of 5-Deaza-10-oxaflavin, a Potential Organic Oxidant

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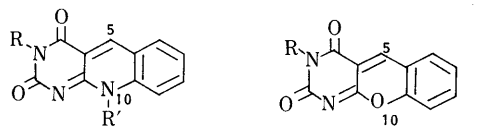
Several 5-deaza-10-oxaflavin (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)dione) derivatives (1) were prepared in satisfactory yields through new, practical routes. These 5-deaza-10-oxaflavins showed a strong redox property in the oxidation of some alcohols to the corresponding carbonyl compounds under slightly acidic conditions, while they were reduced to the stable 1,5-dihydro derivatives. Participation of a direct hydride transfer from the alcohol was demonstrated by an experiment using deuterium-labeled alcohol.

Keywords 5-deaza-10-oxaflavin; barbituric acid; 6-chlorouracil; redox reaction; hetero Diels–Alder reaction; hydride transfer; allylic alcohol; benzylic alcohol

Since the discovery[1] of a 5-deazaflavin derivative as one of the naturally occurring essential redox coenzymes, extensive research in this field has been done to explore its functions in biological systems[2] and to develop a biomimetic model possessing the same basic skeleton.[3] These studies would provide significant information about the function in living systems as well as being useful from a synthetic point of view. In the course of our search for an effective biomimetic model compound, 5-deaza-10-oxaflavin (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione), which can be regarded as a 5-deazaflavin analogue, was selected as a target molecule (Chart 1).

In the 5-deazaflavin molecule, a nitrogen atom at the N(10) position, which forms the central pyridine ring between the pyrimidine and benzene rings, not only makes a significant electrostatic contribution to the whole molecule, but is closely related to redox function. The oxidizing properties of 5-deazaflavin as a two-electron-carrying shuttle have been widely investigated. In connection with this, it might be expected that replacement of the nitrogen atom by oxygen would result in a substantial oxidation potential due to the stronger electronegativity. In consequence, interesting biological activity may also be expected. 5-Deaza-10-oxaflavin possesses a structure both isoelectronic and isosteric with 5-deazaflavin.



5-deazaflavin

1

5-deaza-10-oxaflavin
(2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione)

Chart 1

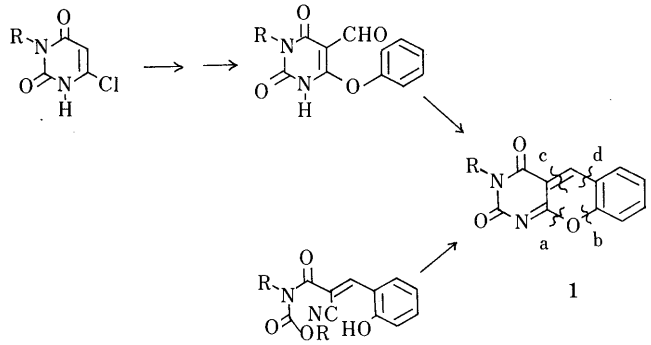


Chart 2. Synthetic Approach to 5-Deaza-10-oxaflavin (**1**)

Some synthetic work on derivatives in this category has been reported, but these precedents did not meet our requirements. In 1980, one of the authors (F.Y.) first reported a synthetic method for 5-deaza-10-oxaflavin,[4] which consists of three synthetic steps including condensation of a phenol to 6-chlorouracil, Vilsmeier–Haack reaction and dehydrative cyclization with polyphosphoric acid (Chart 2). However, isolation of the final product is somewhat troublesome and the overall yield is not so good. Blythin and coworkers published a one-step synthesis of a 5-deaza-10-oxaflavin derivative,[5] but this approach was not so attractive to us because the starting material used, *N*-cyanoacetylurethane, is not easy to prepare (Chart 2). Therefore, an alternative synthetic approach to this interesting molecule was required. In this paper, we describe a new and efficient synthesis of 5-deaza-10-oxaflavin derivatives as well as a detailed investigation of their ability to oxidize alcohols as a coenzyme mimic.[6]

For construction of the central ring of the 5-deaza-10-oxaflavin molecule, three disconnections at a—c can be taken into consideration because a synthetic approach based on a disconnection at bond d has already been unveiled by Yoneda and co-workers[4] (Chart 2). First of all, salicylaldehyde was treated with a barbituric acid derivative (route a in Chart 3). In spite of extensive efforts, this approach turned out to be unfruitful and the only isolated product in this reaction was the 2 : 1 adduct (**2**).

In the second approach based on bond b as a strategic bond (route b in Chart 3), we first prepared the 5-arylidene barbituric acid derivatives. Thus, 5-arylidene barbituric acids were obtained by a condensation of the appropriate *o*-chloro- or *o*-fluorobenzaldehyde with the barbituric acid in 80—95% yield as stable crystalline compounds. After unsuccessful attempts to achieve cyclization to form the central pyran ring under various conditions with solvents, it turned out that intramolecular dehydrohalogenation takes place easily and smoothly simply on heating of the compound at 220—260 °C without using any solvent to furnish the desired 5-deaza-10-oxaflavin derivatives in high yield. In this way, several 5-deaza-10-oxaflavins were prepared as shown in Table I.

In order to examine the last approach (disconnection

This paper is dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March 1989.

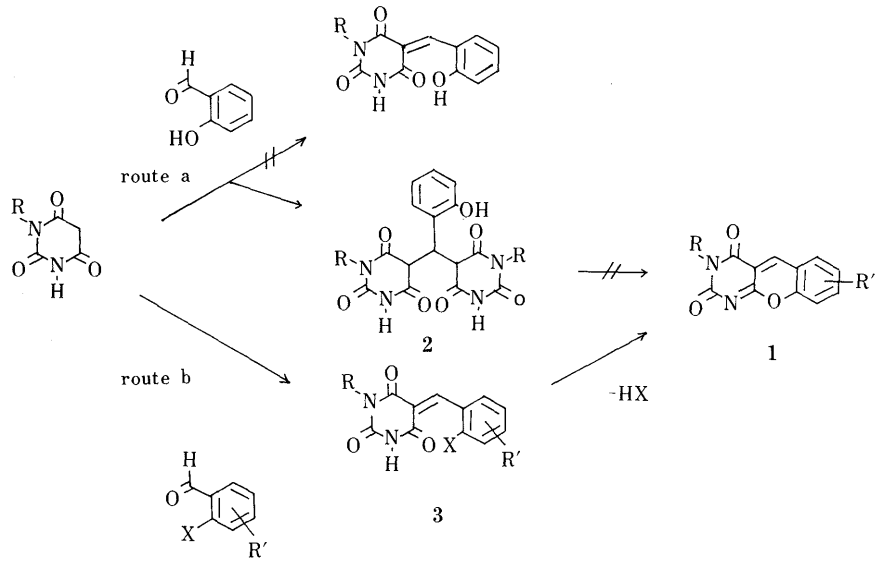


Chart 3. Preparation of 5-Deaza-10-oxaflavin *via* Routes a and b

TABLE I. Yields and Melting Points of **3** and **1** in Route b

	R	R′	X	**3** mp (°C)	**3** Yield (%)	**1** mp (°C)	**1** Yield[a] (%)
a	H	H	Cl	220	87	>300	100
b	Me	H	Cl	187—191	92	>300	80
c	Me	*o*-Cl	Cl	205—210	92	>300	85
d	Me	*p*-Cl	Cl	230	87	>300	60
e	Me	*o*-F	F	285—300	92	>300	75
f	Me	*p*-F	F	270—280	85	>300	63

a) From **3**.

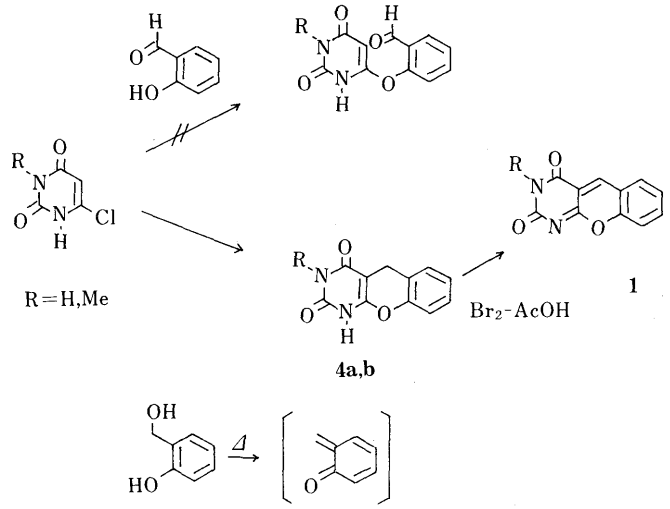


Chart 4. Preparation of 5-Deaza-10-oxaflavin *via* Route c

at bond c, route c in Chart 4), 6-chlorouracil was heated with salicylaldehyde with or without solvent. However, no desired product was obtained due to the lability of the aldehyde under the reaction conditions employed. The aldehyde was changed to *o*-hydroxybenzyl alcohol, a more stable compound to heating, and the condensation reaction was again tried by refluxing in *N*,*N*-dimethylformamide or by heating in nitrobenzene at 200 °C to furnish 1,5-dihydro-5-deaza-10-oxaflavin (**4**), the reduced form of 5-deaza-10-oxaflavin, directly in fairly good yield, as a crystalline compound. It was found that in contrast to conventional 1,5-dihydro-5-deazaflavin, 1,5-dihydro-5-deaza-10-oxaflavin is rather stable toward electrophilic oxidizing agents, including molecular oxygen, *N*-bromosuccinimide and *N*-chlorosuccinimide (NBS, NCS), phenylsulfenyl chloride and diethyl azodicarboxylate (DAD).[7] Transformation to the desired oxidized form, 5-deaza-10-oxaflavin was achieved almost quantitatively by heating with an equivalent amount of bromine in acetic acid. Two routes can be considered as leading to the compound (**4**), one of which is a mechanism involving cyclization initiated by Michael addition of the phenol followed by cyclization concomitant with loss of water, while the other is initial loss of water of *o*-hydroxybenzyl alcohol at an elevated temperature to form 1,2-benzoquinone-2-methide as a reactive intermediate, which spontaneously reacts with the dienophile, 6-chlorouracil. In fact, a reactive dienophile, *N*-phenylmaleimide, smoothly reacted with *o*-hydroxybenzyl alcohol to give the adduct in 55% yield under the same reaction conditions. In both routes, final dehydrochlorination would give the product, 1,5-dihydro-5-deaza-10-oxaflavin. Taking into account the experimental fact that phenol has no tendency to replace the chloride at the C(6) position of 6-chlorouracil under the same reaction conditions, involvement of a [4+2] cycloaddition mechanism is strongly suggested. Although, definitive proof has not been obtained yet, there are some precedents[8] for the 1,4-cycloaddition of dienophiles with a hetero-diene, 1,2-benzoquinone-2-methide.

The present new methods for the preparation of 5-deaza-10-oxaflavin have the advantages of fewer synthetic steps and higher yield compared with previous methods. Additionally in both routes b and c, the procedures, including isolation, are quite simple and convenient. Several derivatives possessing different kinds of substituents on the benzene ring of **1** can be prepared by the new methods, especially by route b.

We next turned our attention to the oxidation of alcohols using a variety of 5-deaza-10-oxaflavin derivatives. Pre-

viously, we reported that some alcohols and thiols are effectively oxidized under neutral conditions with a 5-arylidene barbituric acid derivative,[9] which has an active and electron deficient carbon–carbon double bond, and this method was successfully applied to the synthesis of unsymmetrical disulfides.[10] The oxidation of the alcohol with 5-deaza-10-oxaflavin was tried under the same neutral reaction conditions as used for 5-arylidene barbituric acid, but no redox reaction occurred and only the starting material was recovered. Furthermore, in contrast with 5-deazaflavin, 5-deaza-10-oxaflavin is rather unstable to alkali and substantial decomposition was observed under basic conditions, which are necessary for the activation of alcohols in the case of oxidation with 5-deazaflavin.[11] On the other hand, under acidic conditions protonation on the oxygen atom at the O(10) position might occur and this could make the carbon–carbon double bond more reactive toward nucleophiles due to the greater electron-withdrawing effect. In fact, the oxidation of the alcohol under acidic conditions proceeded with high efficiency, while 5-deaza-10-oxaflavin was hydrogenated to the 1,5-dihydro derivative (Chart 5). The high oxidizing potential of 5-deaza-10-oxaflavin is illustrated by the reactions with some alcohols, especially allylic and benzylic alcohols

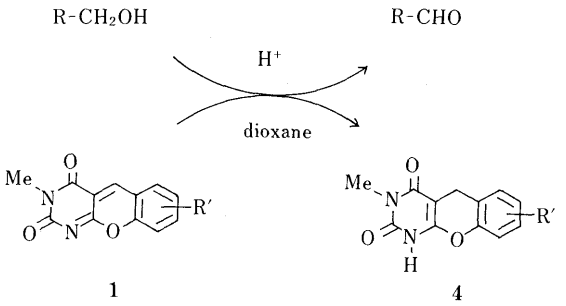
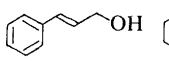
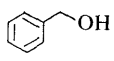
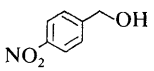
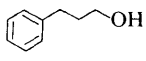


Chart 5. Oxidation of Alcohol with 5-Deaza-10-oxaflavin (**1**)

TABLE II. Oxidation Yields[a] (%) of Some Primary Alcohols with 5-Deaza-10-oxaflavin (**1b**—**f**)[b]

5-Deaza-10-oxaflavin	Alcohol			
				
1b	—100	90	71	20
1c	—100	94	83	40
1d	—100	80	44	10
1e	—100	71	56	2
1f	—100	83	61	13

a) Determined by GLC. *b*) Oxidation was carried out under reflux in dioxane in the presence of *p*-toluenesulfonic acid for 1 h.

(Table II). Experimentally the oxidation was carried out in refluxing dioxane for one hour in the presence of one equivalent amount of *p*-toluenesulfonic acid and the yields of the corresponding carbonyl compounds were determined quantitatively by gas-liquid chromatography (GLC) or if necessary, by isolation. On cooling, the reduced 1,5-dihydro-5-deaza-10-oxaflavin derivative was immediately precipitated from the reaction mixture, and therefore it can be used repeatedly if required. It is worth noting that in spite of a similarity in the structure, neither 5-deazaflavin nor 5-arylidene barbituric acid derivatives show any tendency to oxidize alcohols under acidic conditions, and these three coenzyme models including 5-deaza-10-oxaflavin are complementary each other with respect to oxidation of alcohols. As anticipated from the fact that 1,5-dihydro-5-deaza-10-oxaflavin is too stable to be reoxidized by atmospheric oxygen or other oxidants, 5-deaza-10-oxaflavin can not act as a turn-over catalyst like 5-deazaflavin[12] or pyridodipyrimidine,[13] but acts as a stoichiometric organic oxidant. In addition, it turned out that 5-deaza-10-oxaflavin does not possess any ability to oxidize thiol to disulfide.

As mentioned above, 5-deazaflavin, 5-deaza-10-oxaflavin and 5-arylidene barbituric acid have similar structural units, whereas their oxidation potentials depend upon the reaction conditions, so it is worth studying the differences in reaction mechanism, if any. Mechanistic aspects of the oxidation were investigated using the alcohol labeled with deuterium as a substrate. Thus, α,α-dideuterated benzyl alcohol was oxidized with 5-deaza-10-oxaflavin (**1b**) or its 5-phenyl derivative (**5**) under the same reaction conditions, and the complete incorporation of deuterium at the C(5) position of the corresponding reduced form of 5-deaza-10-oxaflavins was observed. This finding verifies that the redox reaction proceeds through intermolecular hydride shift (Chart 6) in the same manner as with the other two oxidants.[9,14,15]

In conclusion, the present study shows that the new synthetic methods for 5-deaza-10-oxaflavin are practical and convenient, and the 5-deaza-10-oxaflavin is an excellent organic stoichiometric oxidant, which complements other types of coenzyme models, such as 5-deazaflavin and 5-arylidene barbituric acid derivatives.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrophotometer. Unless otherwise specified, the proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in dimethyl sulfoxide-d_6 (DMSO-d_6) at 200 MHz on a JEOL FX 200 instrument with chemical shifts being reported in δ units from tetramethylsilane as an internal standard and couplings in hertz. In the ^{1}H-NMR data of 5-arylidene barbituric acid derivatives, an asterisk indicates the sepa-

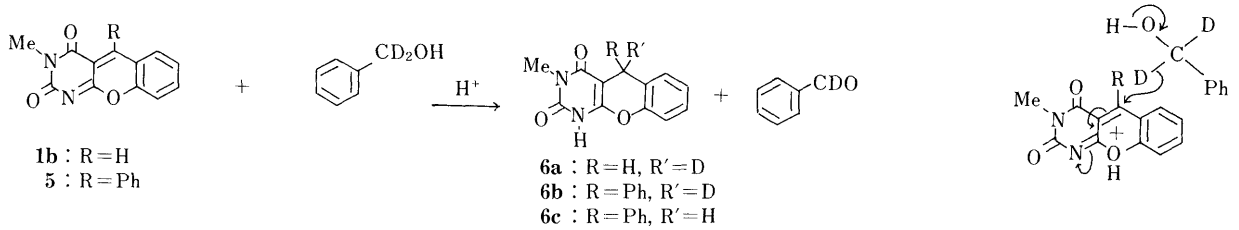


Chart 6. Oxidation Mechanism of 5-Deaza-10-oxaflavin (**1b** and **5**)

rated signals of a minor diastereomer due to *E–Z* isomerism of the double bond. Mass spectra (MS) were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 75 eV. Gas-liquid chromatography (GLC) was done on a Shimadzu GC-7AG with a glass column (3 m) of 5% FFAP.

General Methods for Preparation of 5-Arylidene Barbituric Acid (2) These compounds were generally prepared by means of the reported method.[9]

5-(2′-Chlorobenzylidene)-barbituric Acid (**3a**): Yield 92%, mp 220 °C, IR ν_{max}^{Nujol} cm^{-1}: 3050, 3170, 1740, 1670, 1370; ^{1}H-NMR δ: 11.48 (1H, s, NH), 11.25 (1H, s, NH), 8.33 (1H, s, =CH–), 7.78 (1H, dd, J=7.5, 1.5, Ar-H). *Anal.* Calcd for $C_{11}H_7ClN_2O_3$: C, 52.71; H, 2.58; N, 11.18. Found: C, 52.56; H, 2.79; N, 11.36.

5-(2′-Chlorobenzylidene)-3-methylbarbituric Acid (**3b**): Yield 87%, mp 187—191 °C, IR ν_{max}^{Nujol} cm^{-1}: 3060, 3180, 1720, 1685; ^{1}H-NMR δ: 11.50 (1H, s, NH), *11.72 (1H, s, NH), 8.39 (1H, s, =CH–), 7.75 (1H, dd, J= 8.0, 2.0, Ar-H), 7.50 (1H, dd, J=8.0, 1.5, Ar-H), 7.45 (1H, td, J=8.0, 2.0, Ar-H), 7.35 (1H, td, J=8.0, 1.5, Ar-H), 3.20 (3H, s, N-Me), *3.10 (3H, s, N-Me). (3 : 1 mixture); *Anal.* Calcd for $C_{12}H_9ClN_2O_3$: C, 54.46; H, 3.43; N, 10.58. Found: C, 54.17; H, 3.26; N, 10.52.

5-(2′,6′-Dichlorobenzylidene)-3-methylbarbituric Acid (**3c**): Yield 92%, mp 205—210 °C, IR ν_{max}^{Nujol} cm^{-1}: 3190, 3080, 1690; ^{1}H-NMR δ: 11.60 (1H, s, NH), *11.82 (1H, s, NH), 8.20 (1H, s, =CH–), 7.54 (1H, d, J=10.0, Ar-H), 7.52 (1H, d, J=6.0, Ar-H), 7.54 (1H, dd, J=10.0, 6.0, Ar-H), 3.20 (3H, s, N-Me), *3.08 (3H, s, N-Me). (8 : 1 mixture); *Anal.* Calcd for $C_{12}H_8Cl_2N_2O_3$: C, 48.19; H, 2.70; N, 9.37. Found: C, 48.21; H, 2.59; N, 9.42.

5-(2′,4′-Dichlorobenzylidene)-3-methylbarbituric Acid (**3d**): Yield 87%, mp 230 °C, IR ν_{max}^{Nujol} cm^{-1}: 3190, 3080, 1725, 1685, 1600. ^{1}H-NMR δ: 11.53 (1H, s, NH), *11.72 (1H, s, NH), 8.29 (1H, s, =CH–), 7.75 (1H, d, J=9.0, Ar-H), 7.70 (1H, s, Ar-H), 7.48 (1H, d, J=9.0, Ar-H), 3.21 (3H, s, N-Me), *3.10 (3H, s, N-Me). (3 : 1 mixture); *Anal.* Calcd for $C_{12}H_8Cl_2N_2O_3$: C, 48.19; H, 2.70; N, 9.37. Found: C, 48.18; H, 2.51; N, 9.38.

5-(2′,6′-Difluorobenzylidene)-3-methylbarbituric Acid (**3e**): Yield 92%, mp 285—300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3200, 3070, 1705, 1670; ^{1}H-NMR δ: 11.57 (1H, s, NH), *11.77 (1H, s, NH), 8.10 (1H, s, =CH–), 7.58 (1H, q, J=8.0, Ar-H), 7.17 (2H, t, J=8.0, Ar-H), 3.21 (3H, s, N-Me), *3.11 (3H, s, N-Me). (1 : 1 mixture); *Anal.* Calcd for $C_{12}H_8F_2N_2O_3$: C, 54.14; H, 3.03; N, 11.52. Found: C, 53.48; H, 2.97; N, 11.06.

5-(2′,4′-Difluorobenzylidene)-3-methylbarbituric Acid (**3f**): Yield 85%, mp 270—280 °C, IR ν_{max}^{Nujol} cm^{-1}: 3180, 1705, 1605; ^{1}H-NMR δ: 11.53 (1H, s, NH), *11.70 (1H, s, NH), 8.29 (1H, s, =CH–), *8.25 (1H, s, =CH–), 8.10 (1H, q, J=8.5, Ar-H), 7.35 (1H, td, J=10.0, 2.5, Ar-H). 7.20 (1H, td, J=8.5, 2.5, Ar-H), 3.12 (3H, s, N-Me), *3.20 (3H, s, N-Me). (1 : 1 mixture); *Anal.* Calcd for $C_{12}H_8F_2N_2O_3$: C, 54.14; H, 3.03; N, 11.52. Found: C, 54.09; H, 2.82; N, 10.76.

General Method for Preparation of 5-Deaza-10-oxaflavin (1) from 3 (Route b) A 5-arylidene barbituric acid derivative (**3**) (1.0 g) was heated in a heating mantle at 220—260 °C for 0.5 h. The product **1** was obtained in 60—100% yield after the crystalline mixture was washed with a mixture of chloroform and methanol.

5-Deaza-10-oxaflavin (**1a**): Yield 100%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3150, 3050, 1680, 1640, 1605, 1560; ^{1}H-NMR δ (DMSO): 11.48 (1H, s, NH), 8.97 (1H, s, =CH–), 8.10 (1H, d, J=5, Ar-H), 7.95 (1H, t, J=5.0, Ar-H), 7.70 (1H, d, J=5.0, Ar-H), 7.53 (1H, t, J=5.0, Ar-H); *Anal.* Calcd for $C_{11}H_6N_2O_3$: C, 61.68; H, 2.82; N, 13.08. Found: C, 61.61; H, 2.74; N, 13.04.

3-Methyl-5-deaza-10-oxaflavin (**1b**): Yield 80%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3080, 1705, 1600; ^{1}H-NMR δ (trifluoroacetic acid-d_1–chloroform-d_1, 1 : 4): 9.76 (1H, s, =CH–), 8.40 (1H, t, J=8.0, Ar-H), 8.33 (1H, d, J=8.0, Ar-H), 8.02 (1H, d, J=8.0, Ar-H), 7.79 (1H, t, J=8.0, Ar-H), 3.54 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.91; H, 3.30; N, 13.33.

6-Chloro-3-methyl-5-deaza-10-oxaflavin (**1c**): Yield 85%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1708, 1660, 1630, 1600, 1575; ^{1}H-NMR δ: 8.73 (1H, s, =CH–), 7.92 (1H, t, J=9.0, Ar-H), 7.77 (1H, d, J=9.0, Ar-H), 7.74 (1H, d, J=9.0, Ar-H), 3.28 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_7ClN_2O_3$: C, 54.88; H, 2.69; N, 10.67. Found: C, 54.65; H, 2.64; N, 10.75.

8-Chloro-3-methyl-5-deaza-10-oxaflavin (**1d**): Yield 60%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1655, 1605, 1560; ^{1}H-NMR δ (trifluoroacetic acid-d_1–chloroform-d_1, 1 :4): 9.70 (1H, s, =CH–), 7.85—8.25 (3H, Ar-H), 3.60 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_7ClN_2O_3$: C, 54.88; H, 2.69; N, 10.67. Found: C, 54.63; H, 2.55; N, 10.72.

6-Fluoro-3-methyl-5-deaza-10-oxaflavin (**1e**): Yield 75%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1710, 1655, 1620, 1565; ^{1}H-NMR δ: 9.05 (1H, s, =CH–), 8.22 (1H, dd, J=0.9, 6.5, Ar-H), 7.78 (1H, dd, J=9.0, 2.5, Ar-H), 7.49 (1H, td, J=9.0, 2.5, Ar-H), 3.28 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_7FN_2O_3$: C, 58.54; H, 2.86; N, 11.38. Found: C, 58.51; H, 2.71; N, 11.38.

8-Fluoro-3-methyl-5-deaza-10-oxaflavin (**1f**): Yield 63%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1710, 1650, 1620; ^{1}H-NMR δ: 8.73 (1H, s, =CH–), 7.97 (1H, q, J=9.0, Ar-H), 7.62 (1H, d, J=9.0, Ar-H), 7.47 (1H, t, J=9.0, Ar-H), 3.26 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_7FN_2O_3$: C, 58.54; H, 2.86; N, 11.38. Found: C, 58.17; H, 2.88; N, 11.25.

General Method for Preparation of 5-Deaza-10-oxaflavin (1) from 4 (Route c) A mixture of a 1,5-dihydro-5-deaza-10-oxaflavin (**4**) and bromine (1.0 eq) was refluxed in acetic acid for 0.5 h. After concentration of the mixture, the residue was crystallized from acetic acid or *N,N*-dimethylformamide to give the 5-deaza-10-oxaflavin derivative in 95—98% yield.

1,5-Dihydro-5-deaza-10-oxaflavin (**4**): 6-Chlorouracil (0.29 g, 2.0 mmol) and *o*-hydroxybenzyl alcohol (1.0 g, 8.0 mmol) were heated in hexamethylphosphoramide (HMPA) at 200 °C for 3 h. Concentration of the mixture under reduced pressure gave the residue, which was subjected to a column chromatography on silica gel. Crystallization was carried out from acetic acid and the yield was 35%. mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1710, 1640, 1575; ^{1}H-NMR δ: 11.80 (1H, s, NH), 11.05 (1H, s, NH), 7.00—7.40 (4H, m, Ar-H), 3.55 (2H, s, –CH$_2$–); *Anal.* Calcd for $C_{11}H_8N_2O_3 \cdot CH_3CO_2H$: C, 56.52; H, 4.34; N, 10.14. Found: C, 56.62; H, 4.32; N, 10.17.

1,5-Dihydro-3-methyl-5-deaza-10-oxaflavin (**4b**): The method used for preparation of **4b** was similar to that for **4a** described above except for refluxing in dimethylformamide (DMF) as a solvent and crystallization from methanol. The yield was 80%. mp 282—288 °C, IR ν_{max}^{Nujol} cm^{-1}: 3100, 1720, 1685, 1615; ^{1}H-NMR δ: 12.00 (1H, s, NH), 7.28 (1H, dd, J=7.5, 2.0, Ar-H), 7.25 (1H, td, J=7.5, 2.0, Ar-H), 7.14 (1H, td, J=7.5, 1.5, Ar-H), 7.04 (1H, dd, J=7.5, 1.5, Ar-H), 3.58 (2H, s, –CH$_2$–), 3.19 (3H, s, N-Me); MS *m/z*: 230 (M$^+$), 215, 172, 145; *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.32; H, 4.28; N, 12.04.

General Procedure for Oxidation of Alcohols with 3-Methyl-5-deaza-10-oxaflavin Derivatives (1b—f) A solution of **1** (0.10 mmol), the alcohol (0.10 mmol) and *p*-toluenesulfonic acid monohydrate (0.10 mmol) in 1,4-dioxane (8.0 ml) was refluxed for 1.0 h. The resulting carbonyl compound was identified and quantified by comparison with a known amount of an authentic sample by GLC. The 1,5-dihydro compound (**4**) produced was isolated by usual work-up. Thus, water (50 ml) was added to the mixture, which was extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and then concentrated to give a crystalline residue which was recrystallized from acetic acid. The 1,5-dihydro-5-deaza-10-oxaflavin derivative (**4**) was recovered almost quantitatively.

6-Chloro-1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (**4c**): mp 269—271 °C, IR ν_{max}^{Nujol} cm^{-1}: 1705, 1630, 1530; ^{1}H-NMR δ: 12.19 (1H, s, NH), 7.38 (1H, d, J=4.0, Ar-H), 7.34 (1H, d, J=6.0, Ar-H), 7.06 (1H, dd, J= 6.0, 4.0, Ar-H), 3.51 (2H, s, –CH$_2$–), 3.15 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_9ClN_2O_3 \cdot 1/2H_2O$: C, 52.63; H, 3.65; N, 10.23. Found: C, 52.78; H, 3.33; N, 10.25.

8-Chloro-1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (**4d**): mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3150, 1720, 1685, 1615; ^{1}H-NMR δ: 12.17 (1H, s, NH) 7.40 (1H, d, J=8.5, Ar-H), 7.22 (1H, d, J=8.5, Ar-H), 7.15 (1H, s, Ar-H), 3.53 (2H, s, –CH$_2$–), 3.20 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_9ClN_2O_3$: C, 54.47; H, 3.41; N, 10.59. Found: C, 54.20; H, 3.35; N, 10.64.

6-Fluoro-1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (**4e**): mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3130, 1720, 1685, 1620; ^{1}H-NMR δ: 12.15 (1H, s, NH), 7.38 (1H, dd, J=7.0, 9.0, Ar-H), 7.05 (1H, td, J=9.0, 2.5, Ar-H), 7.00 (1H, dd, J=9.0, 2.5, Ar-H), 3.54 (2H, s, –CH$_2$–), 3.18 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_9FN_2O_3$: C, 58.08; H, 3.64; N, 11.29. Found: C, 57.80; H, 3.58; N, 11.18.

8-Fluoro-1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (**4f**): mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 3080, 1718, 1678, 1608; ^{1}H-NMR δ: 12.18 (1H, s, NH), 7.34 (1H, dd, J=9.0, 16.0, Ar-H), 7.07 (1H, t, J=9.0, Ar-H), 6.97 (1H, d, J=9.0, Ar-H), 3.50 (2H, s, –CH$_2$–), 3.20 (3H, s, N-Me); *Anal.* Calcd for $C_{12}H_9FN_2O_3$: C, 58.08; H, 3.64; N, 11.29. Found: C, 57.79; H, 3.67; N, 11.24.

3-Methyl-5-phenyl-5-deaza-10-oxaflavin (5) This compound (**5**) was obtained by oxidation of **6c** (*vide infra*) with bromine in the same way as used for the oxidation to **1** (*vide supra*). Yield 80%, mp >300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1750, 1705, 1625, 1585; ^{1}H-NMR δ: 7.91 (1H, t, J=8.0, Ar-H), 7.78 (1H, d, J=8.0, Ar-H), 7.56 (3H, m, Ar-H), 7.45 (1H, t, J=8.0, Ar-H), 7.31 (2H, m, Ar-H), 7.11 (1H, d, J=8.0, Ar-H), 3.10 (3H, s, N-Me). MS *m/z*: 304(M$^+$), 289, 275, 262, 229.

1,5-Dihydro-3-methyl-5-phenyl-5-deaza-10-oxaflavin (6c) Phenylmagnesium bromide (4.0 eq), which was prepared from bromobenzene (2.75 g,

17.6 mmol) and magnesium (0.42 g, 17.6 mmol) in dry ethyl ether, was added portionwise to a stirred mixture of **1b** (1.0 g, 4.4 mmol) in tetrahydrofuran (THF) and the mixture was stirred for 5 h at room temperature and then heated at about 50 °C for 10 min. Aqueous hydrochloric acid (5%) was carefully added to the chilled mixture at 0 °C and the resulting mixture was then extracted with chloroform, and the chloroform extract was dried over $MgSO_4$, and concentrated to give a crystalline residue, which was recrystallized from acetic acid. The yield was 0.72 g (54%). mp > 300 °C, IR ν_{max}^{Nujol} cm^{-1}: 1710, 1680, 1650; ^{1}H-NMR δ: 12.31 (1H, s, NH), 7.10—7.35 (9H, m, Ar-H), 5.04 (1H, s, Ph-CH–), 3.08 (3H, s, N-Me). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.38; H, 4.39; N, 9.43.

5-Deuterio-1,5-dihydro-3-methyl-5-deaza-10-oxaflavin (6a) Compound **6a** was derived from the oxidation of α,α-dideuterated benzyl alcohol with **1b**. The thin-layer chromatography (TLC) behavior, IR and ^{1}H-NMR spectra of the deuterio compound (**6a**) were almost the same as those of **4b**, except for the integral of a singlet peak at δ 3.58 ppm (C(5)-H) in the ^{1}H-NMR. Judging from the ^{1}H-NMR analysis, the degree of incorporation of deuterium at the C(5) position is more than 95%.

1,5-Dihydro-3-methyl-5-phenyl-5-deuterio-5-deaza-10-oxaflavin (6b) In the same way as above, **6b** was derived from the oxidation of α,α-dideuterated benzyl alcohol with **5**. This compound was almost identical with **6c** in terms of TLC behavior, IR and ^{1}H-NMR spectra except for the peak at δ 5.04 ppm (C(5)-H) in **6c**, which was absent in the spectrum of **6b**. The mass spectrum of **6b** indicated that the incorporation of deuterium is almost complete (more than 95%). MS *m/z*: 307 (M^+), 230, 173; *Anal.* Calcd for $C_{18}H_{13}DN_2O_3$: C, 70.34; H, 4.92; N, 9.12. Found: C, 69.91; H, 4.73; N, 9.04.

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