SYNTHESIS OF A 5-DEAZA-10-SELENAFLAVIN DERIVATIVE, A NEW TYPE OF 5-DEAZAFLAVIN REDOX COENZYME MODEL

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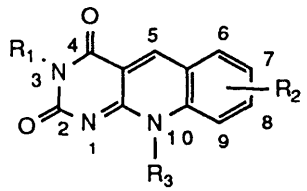
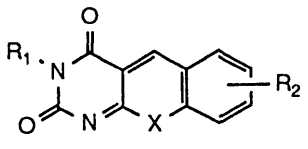
A new class of 5-deazaflavin derivatives, 3-methyl-5-deaza-10-selenaflavin (1), in which the nitrogen at the N(10) position of the 5-deazaflavin is replaced by a selenium atom, was synthesized via two different routes. Spectroscopic properties of the 5-deaza-10-selenaflavin are also discussed comparing with those of the known related 5-deazaflavin coenzyme models such as the parent 5-deazaflavin, 5-deaza-10-oxaflavin, and 5-deaza-10-thiaflavin derivatives.

KEYWORDS 5-deaza-10-selenaflavin; synthesis; 5-deazaflavin; coenzyme model; organoselenium; chemical shift; red shift

Before the advent of Factor 420 in 1978,[2] 5-deazaflavin (pyrido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione), in which the nitrogen at the N(5) of flavin is replaced by CH, had been only an artificial compound prepared for the purpose of searching for antagonists or elucidation of the redox mechanism involved in the flavin coenzymes.[3,4] Discovery of a redox active coenzyme Factor 420 in nature stimulated researchers to investigate 5-deazaflavins and related compounds from the chemical, biological and pharmaceutical points of view.[4] In the course of our intensive investigation for development of an efficient coenzyme model[5] and enzyme-coenzyme model systems,[6] the syntheses and chemical properties of 5-deaza-10-oxaflavin[7] (2*H*-chromeno[2,3-*d*]-pyrimidine-2,4(3*H*)-dione) and 5-deaza-10-thiaflavin[8] (1-benzothiopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione) derivatives have already been reported. In these compounds, the nitrogen atom existing in a 5-deazaflavin derivative at the N(10) position is replaced by oxygen and sulfur, respectively. In spite of being isoelectronic and isosteric with the parent 5-deazaflavin, an introduction of the heteroatom into the fused ring system caused a significant change in the inherent chemical character of the 5-deazaflavin. Furthermore, it is interesting that some of these compounds revealed potential biological activity including anti-tumor and anti-viral activities.[9]



5-deazaflavins

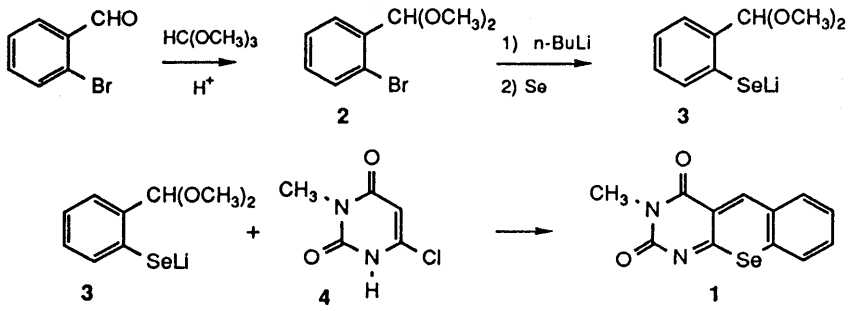


X = O ; 5-deaza-10-oxaflavins
X = S ; 5-deaza-10-thiaflavins
X = Se; 5-deaza-10-selenaflavins

In connection with this series of studies, we describe here the preparation of selenium variation of 5-deazaflavin derivative, 1-benzoselenopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione. Though selenium belongs to the group IV atoms in the same column as that of sulfur and oxygen in the periodic table, some different redox functionalities and biological activities might be expected.

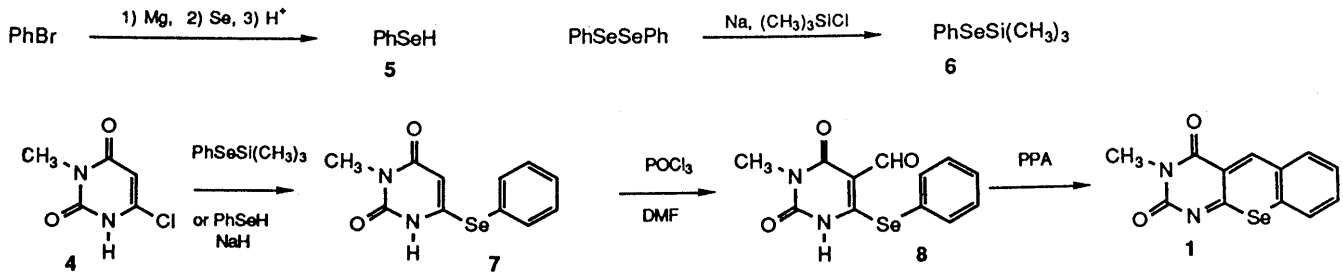
Several synthetic methods for an approach to the 5-deazaflavin skeleton are available,[8,10] and two of them were successfully applied to the construction of a 5-deaza-10-selenaflavin skeleton. Thus, 3-methyl-5-deaza-10-selenaflavin (**1**) was synthesized by two different synthetic routes, as shown in Chart I and II.[11] By using metal-halogen exchange reaction, the aryllithium was first prepared from *o*-bromobenzaldehyde *via* **2**, and the selenium atom was inserted to the aromatic ring[12] at the position *ortho* to the protected aldehyde group to afford the lithium areneselenolate **3**. Without isolation the reactive organoselenium compound **3** was subsequently condensed with 3-methyl-6-chlorouracil (**4**) to yield **1**[13] in rather low yield (7 %) (Chart I). Appearance of a characteristic

Chart I



singlet at δ 8.77 ppm due to the proton at the C(5) position in the ^{1}H-NMR spectrum of the product supports the structure of the 5-deazaflavin-related derivative. Alternatively, **1** was prepared in improved overall yield by using nucleophilic organoselenium reagents **5**[14] or **6**.[15] The reactions of the selenolate anion derived from **5** or **6** with 3-methyl-6-chlorouracil (**4**) furnished 3-methyl-6-phenylselenouracil (**7**) as a result of an addition-elimination sequence. In this case, sodium benzene selenolate generated *in situ* by the reduction of diphenyldiselenide with sodium borohydride was proven to be less reactive, probably due to the boron complexation.[16] Introduction of the C_1 unit into the uracil ring was achieved by the treatment with Vilsmeier's reagent to give the crude formylated compound **8**, which was successfully cyclized by heating in PPA[17] to give **1** in a satisfactory overall yield (53-58 % from **4**) (Chart II). This product in hand was completely identical with that obtained *via* the former route in all spectroscopic respects.

Chart II



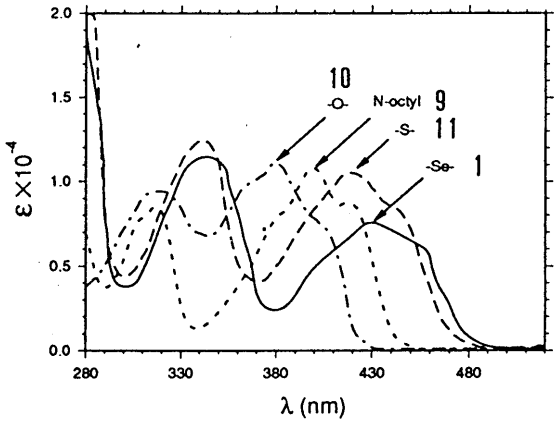
Hückel MO calculation indicates that the C(5) position of the 5-deazaflavin ring system is very π-electron deficient in the same way as is the C(4) position of NAD.[18] The redox potential of the coenzyme is closely related to the electron density at the reaction center involved, which is the C(5) for 5-deazaflavin and the C(4) for NAD. Since the chemical shift in NMR spectrum and the absorption position in ultraviolet spectrum may roughly provide a quick guide to the electronic situation of the particular position, ^{1}H-, ^{13}C-NMR and UV spectra of **1** were taken to compare the electron density at the C(5) with those of the other related models including **9**,[19] **10**,[7] and **11**.[8] The chemical shifts of the C(5) and the proton attached are tabulated (Table I). The UV spectra of these related compounds show slightly splitting absorption bands consisting of three peaks, which are characteristic of 5-deazaflavins, in a range of about 350 to 480 nm (Fig. 1). The maximal absorption positions are also shown in Table I. As can be seen from the figure and table, replacement of the nitrogen atom by oxygen, sulfur and selenium atoms causes a significant shift (blue shft for O, and red shift for S and Se), and its degree is well consistent with the order of electronegativity of the atom (O > N> S > Se). Furthermore, a good correlation of electronegativity to the chemical shift of the C(5) carbon in ^{13}C-NMR is observed.

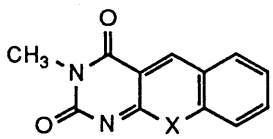
An investigation of the relative redox potential, biological activity and the more detailed electronic structure of the model is currently in progress.

Table I. Some Spectroscopic Data of 5-Deazaflavin Related Coenzyme Models [a)]

Models	λ_{max} (nm)	Chemical shift	
		^{1}H at the C(5) (∂, ppm)	^{13}C at the C(5) (ppm)
9	399.8	8.896	142.74
10	382.0	8.776	136.66
11	420.0	8.807	147.60
1	432.2	8.770	149.36

a) The UV spectra were taken in acetonitrile and ^{1}H-, ^{13}C-NMR were in chloroform-d_1.





X = N-*n*Oct **9**
X = O **10**
X = S **11**
X = Se **1**

Fig. 1. Ultraviolet Spectra of 5-Deazaflavin Related Compounds in Acetonitrile

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13) Compound **1**: mp 258-262°C. ^{1}H-NMR ($CDCl_3$) δ3.45 (3H,s), 7.57 (1H,s), 7.68 (1H,s), 7.81 (1H,s), 8.03 (1H,s), 8.77 (1H,s). IR ($CHCl_3$) 1705 and 1650 cm^{-1}. *Anal.* Calcd for $C_{12}H_8N_2O_2Se$: C, 49.53; H, 2.77; N, 9.63. Founf: C, 49.70; H, 2.85; N, 9.55.
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