New Synthesis of 5-Amino-5-deazaflavin Derivatives by Direct Coupling of 5-Deazaflavins and Amines

Tetsutaro Kimachi and Fumio Yoneda*

Faculty of Pharmaceutical Sciences, Kyoto University,
Sakyo-ky 606, Kyoto, Japan

Takuma Sasaki

Department of Experimental Therapeutics,
Cancer Research Institute, Kanazawa University,
13-1, Takaramachi, Kanazawa 920 Japan

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5-Amino-5-deazaflavin derivatives are newly synthesized by direct coupling of 5-deazaflavins and amines. Some of them revealed potential activity toward tumor cells such as L1210 or KB cells.

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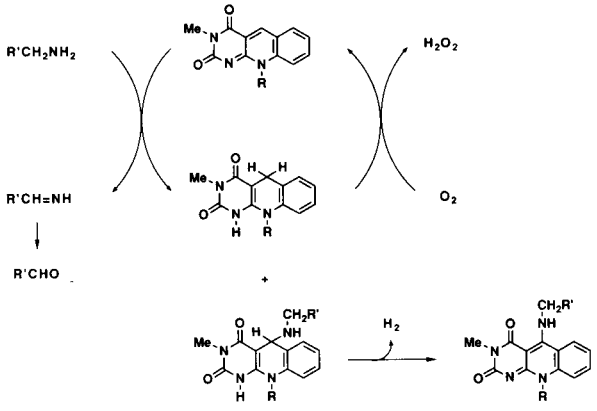
5-Deazaflavins (5-deazaisoalloxazines), in which N-5 of the flavins is replaced by CH, have first been synthesized as potential riboflavin antagonists [1]. 5-Deazaflavins themselves were found to be multifunctional and reactive and to serve as cofactors for several flavin catalyzed reactions [2]. Naturally occurring F_{420} isolated from methane producing bacteria has a 5-deazaflavin skeleton as an 8-hydroxy-5-deazaflavin derivative, and acts as coenzymes in the oxido-reductive system from carbon dioxide to methane [3,4].

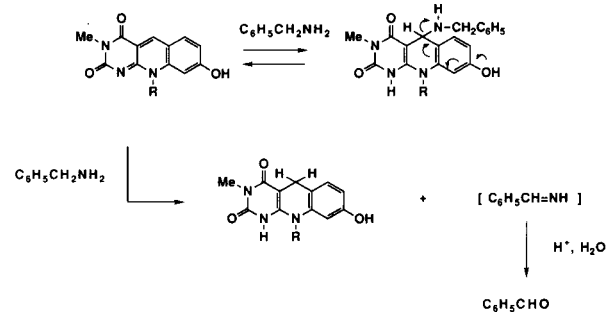
It has been known that 5-deazaflavins have strong oxidizing power which oxidizes alcohols and amines to the corresponding carbonyl compounds and they behave as autorecycling turnover catalysts in the reactions [5,6].

Scheme 1



Previously we have suggested that there are two competitive pathways in the oxidation of amines with 5-deazaflavins [7]. One is the formation of the corresponding imines by hydride or its equivalent transfer agent and the other is the reversible addition of amines into the 5-position of 5-deazaflavins to give 5-amino-1,5-dihydro-5-deazaflavins (Scheme 1). The oxidation of these 5-adducts may give the corresponding 5-amino-5-deazaflavins. Furthermore we have reported that the preferential oxidation of amines occurred when the reaction was carried out with 8-hydroxy-5-deazaflavins having an electron releasing group at the 8-position and that the reason might be because of the destabilization of the above intermediate 5-amino-1,5-dihydro-5-deazaflavins [8] (Scheme 2).

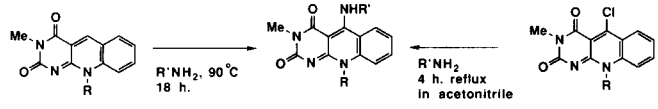
Scheme 2



The 5-amino-5-deazaflavins have usually been obtained from 5-deazaflavins by a few steps syntheses including epoxydation and chlorination, followed by amination [7]. In this paper we describe the direct coupling of 5-deazaflavins with amines which leads to the formation of 5-amino-5-deazaflavin derivatives.

Direct coupling of 5-deazaflavins with amines was car-

Scheme 3 SYNTHESIS OF 5-AMINO-5-DEAZAFLAVINS BY TWO ROUTES

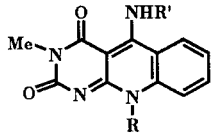


1 a , R = Ethyl,
1 b , = Butyl,
1 c , = Octyl,
1 d , = Dodecyl,

3 a , R = Ethyl, R' = Phenethyl
3 a', R = Ethyl, R' = Octyl
3 b , R = Butyl, R' = Phenethyl
3 b', R = Butyl, R' = Octyl
3 c , R = Octyl, R' = Phenethyl
3 c', R = Octyl, R' = Octyl
3 d , R = Dodecyl, R' = Phenethyl
3 d' , R = Dodecyl, R' = Octyl

2 a, R = Ethyl
2 b , R = Butyl
2 c , R = Octyl
2 d , R = Dodecyl

Table 1



R	R'	Formula	Mw	Ms	mp (°C)	Anal. Calcd./Found C	H	N	Yield (%) Direct	from 5-Cl-5-dFl
Ethyl	Phenethyl	$C_{22}H_{22}N_4O_2$	374	374	220	70.57	5.92	14.96	14.0	80
						70.81	5.98	14.81		
Ethyl	Octyl	$C_{22}H_{30}N_4O_2$	382	382	132	69.08	7.91	14.65	33.7	44
						68.93	7.74	14.70		
Butyl	Phenethyl	$C_{24}H_{26}N_4O_2$	402	402	185	71.62	6.51	13.92	12.8	80
						71.70	6.48	13.72		
Butyl	Octyl	$C_{24}H_{34}N_4O_2$	410	410	130	70.21	8.35	13.65	13.0	84
						70.07	8.35	13.41		
Octyl	Phenethyl	$C_{28}H_{34}N_4O_2$	458	458	163	73.36	7.42	12.23	12.3	78
						73.30	7.49	12.39		
Octyl	Octyl	$C_{28}H_{42}N_4O_2$	460	460	118	72.10	9.01	12.02	28.4	82
						71.90	8.94	12.11		
Dodecyl	Phenethyl	$C_{32}H_{42}N_4O_2$	514	514	153	74.71	8.17	10.89	17.7	70
						74.43	8.25	10.80		
Dodecyl	Octyl	$C_{32}H_{50}N_4O_2$	522	522	121	73.51	9.65	10.72	66.8	59.4
						73.30	9.87	10.72		

ried out by heating 5-deazaflavins with neat amines to afford the corresponding 5-amino-5-deazaflavins in moderate yields. The structures of the 5-amino-5-deazaflavins were established by comparison with the products synthesized by an unequivocal route involving the amination of 5-chloro-5-deazaflavins. The 5-chloro-5-deazaflavins were obtained by epoxidation of 5-deazaflavins with *m*-chloroperbenzoic acid, followed by the treatment with the Vilsmeier reagent (DMF:phosphoryl chloride = 5:1) [9]. The 5-chloro-5-deazaflavins reacted readily with amines in an argon atmosphere to afford the corresponding 5-amino-5-deazaflavins quantitatively (Scheme 3) (Table 1).

The above facts show that the nucleophilic addition of amines to the 5-position of 5-deazaflavins occurs competitively with the proper amine oxidation by the 5-deazaflavins to give the intermediate 5-amino-1,5-dihydro-5-deazaflavins which may be oxidized with another molecule of 5-deazaflavin or air to give the final 5-amino-5-deazaflavins.

The cytotoxities of the 5-amino-5-deazaflavins against L1210 and KB cells are illustrated in Table 2.

Table 2

Cytotoxities of 5-Amino-5-Deazaflavins Against L1210 and KB Cells

R	R'	IC_{50}, ug/ml L1210	KB cell
Ethyl	Phenethyl	3.8	>50
Ethyl	Octyl	2.3	6.2
Butyl	Phenethyl	4.4	13.5
Butyl	Octyl	3.6	9.8
Octyl	Phenethyl	8.8	19
Octyl	Octyl	0.6	>50
Dodecyl	Phenethyl	16	>50
Dodecyl	Octyl	1.8	>50

EXPERIMENTAL

All materials not explicitly discussed were purchased from Wakenyaku Co., Nacalai Tesque Co. and Aldrich chemical Co. The ^1H nmr spectra were obtained with a JEOL JNM-FX 200 fourier transform spectrometer. The ir spectra were measured with a Shimazu IR-400 spectrometer. Melting points were taken using a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra were obtained on a JEOL 01SG-2 instrument (direct inlet) at 70 eV.

Direct Coupling of 5-Deazaflavins **1a-1d** with Amines. General Procedure for Synthesis of **3**.

An amine solution (2.0 ml) containing 5-deazaflavins (0.2 mmole) was heated at 90° for 18 hours. The reaction mixture was diluted with ethyl ether (10 ml) and cooled. The precipitate which formed was filtered off and recrystallized from ethanol (Table 1).

Synthesis of 5-Chloro-5-deazaflavins **2a-2d**. General Procedure.

According to a known procedure [9], 5-chloro-5-deazaflavins were synthesized. A mixture of 5-deazaflavins **1a-1d** (0.1 mmole) with *m*-chloroperbenzoic acid (1.3 equivalents) in chloroform was stirred at room temperature. The yellow fluorescent solution changed to colorless and the starting 5-deazaflavin disappeared.

The reaction mixture was washed with aqueous ammonium chloride solution and extracted with chloroform. The chloroform layer was collected, dried and concentrated to a small volume. The isolated product was used for the next step without further purification.

The 4a,5-epoxy-5-deazaflavin thus obtained was added to the Vilsmeier reagent (DMF:phosphoryl chloride = 5:1) and the mixture was heated at 90° for 2 hours. By cooling the corresponding 5-chloro-5-deazaflavin was obtained as a precipitate.

5-Chloro-10-octyl-5-deazaflavin (**2c**).

This compound was obtained in a yield of 63%, mp >300°.

Anal. Calcd. for $C_{20}H_{24}N_3O_2Cl$: C, 64.26; H, 6.43; N, 11.24. Found: C, 63.98; H, 6.41; N, 11.62.

5-Chloro-10-dodecyl-5-deazaflavin (**2d**).

This compound was obtained in a yield of 58%, mp >300°.

Anal. Calcd. for $C_{24}H_{32}N_3O_2Cl$: C, 67.05; H, 7.45; N, 9.78. Found: C, 66.85; H, 7.25; N, 9.68.

Amination of 5-Chloro-5-deazaflavins. General Procedure.

An excess amount of the amine (2 ml) was added dropwise to a suspension of the requisite 5-chloro-5-deazaflavin **2a-2d** (1 mmole) in acetonitrile under argon atmosphere. The mixture was heated for 3-4 hours. Acetonitrile was removed *in vacuo* and to the residue ethyl ether was added to form a colorless powder, which was recrystallized from ethanol (Table 1).

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