Synthesis of Some 8-Substituted 5-Deazaflavins

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Treatment of 8-fluoro-3,10-dimethyl-5-deazaflavin (Ia) with ethyl cyanoacetate in ethanol in the presence of potassium carbonate gave the corresponding 8-(1-cyano-1-ethoxycarbonylmethyl)-5-deazaflavin, which was converted into 3,8,10-trimethyl-5-deazaflavin by refluxing in aqueous dimethylformamide. Treatment of Ia with sodium azide in ethanol yielded 8-azido-3,10-dimethyl-5-deazaflavin (V). Compound V was converted into the corresponding 8-amino-, 8-acetamido-, and 8-benzamido-5-deazaflavins by heating in high boiling alcohols, acetic anhydride, and benzoic anhydride, respectively. Fusion of compound V with dimethyl acetylenedicarboxylate yielded 4,5-bis(methoxycarbonyl)-1-(3,10-dimethyl-5-deazaflavin-8-yl)-1,2,3-triazole.

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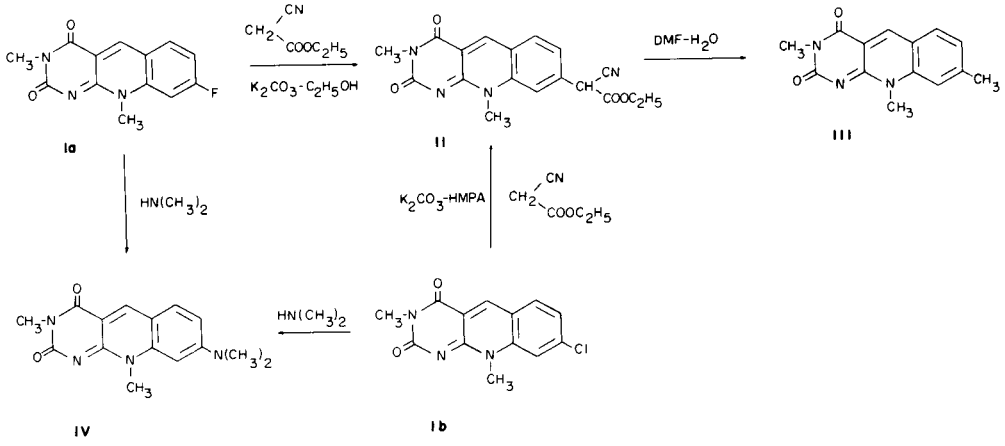
We have recently been engaged in a program to prepare several kinds of pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (5-deazaflavins) and to investigate their oxido-reductive properties (1). As an entry into this area, we previously explored a novel synthetic method for the preparation of 7- and 8-substituted 5-deazaflavins by the oxidative cyclization of aryl-bis(6-alkylaminouracil-5-yl)methanes with diethyl azodicarboxylate (2) and examined their abilities to oxidize alcohol (3). An extension of this work was the preparation of a series of 10-aryl-5-deazaflavins (4) which had strong abilities to reduce benzaldehyde to benzyl alcohol (5). In order to extend these studies, we have now prepared some 8-substituted 5-deazaflavins by using 8-fluoro-3,10-dimethyl-5-deazaflavin as the starting material.

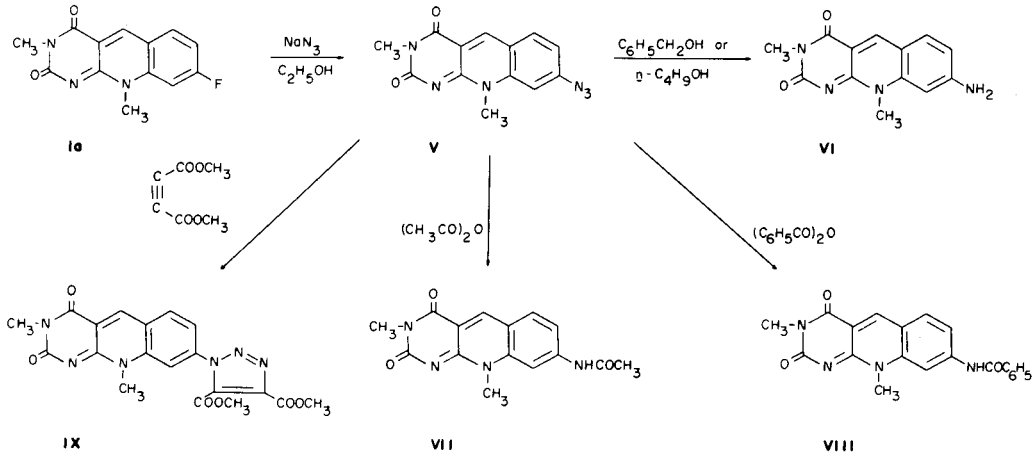
8-Fluoro-3,10-dimethyl-5-deazaflavin (Ia) was synthesized by the oxidative coupling of *p*-fluorophenyl-bis-(3-methyl-6-methylaminouracil-5-yl)methane with diethyl azodicarboxylate (3). Compound Ia has been shown to be more reactive than 8-chloro-3,10-dimethyl-5-deazaflavin (Ib) (2) toward nucleophilic substitution. For example, refluxing of Ia with ethyl cyanoacetate in ethanol in the presence of potassium carbonate gave 8-(1-cyano-1-ethoxycarbonylmethyl)-3,10-dimethyl-5-deazaflavin (II), which could not be obtained from Ib and ethyl cyanoacetate under the same conditions. However, the condensation of Ib with ethyl cyanoacetate proceeded by using hexamethyl phosphoramide (HMPA) as solvent to give also II. On refluxing of II in dimethylformamide including water, hydrolysis and decarboxylation of II occurred to give rise to 3,8,10-trimethyl-5-deazaflavin (III), which was identical with the authentic sample (2). Also Ia readily reacted with aqueous dimethylamine to give 8-dimethylamino-3,10-dimethyl-5-deazaflavin (IV). On the other hand, it was not until the use of HMPA as solvent that the reaction of Ib and dimethylamine proceeded to give IV.

Next, Ia was converted into 8-azido-3,10-dimethyl-5-deazaflavin (V) by refluxing with sodium azide in ethanol.

Scheme I



Scheme 2



Compound V was fairly stable, but on refluxing in both benzyl alcohol and l-butanol, 8-amino-3,10-dimethyl-5-deazaflavin (VI) was obtained. This may imply the formation of the intermediary (5-deazaflavin-8-yl)nitrene by thermal decomposition of V followed by hydrogen abstraction from solvents to give the 8-amino-5-deazaflavin (VI). Refluxing V in acetic anhydride gave 8-acetamido-3,10-dimethyl-5-deazaflavin (VII). Furthermore, heating V with benzoic anhydride gave 8-benzamido-3,10-dimethyl-5-deazaflavin (VIII).

Fusion of V in excess dimethyl acetylenedicarboxylate afforded the corresponding triazole, 4,5-bis(methoxycarbonyl)-1-(3,10-dimethyl-5-deazaflavin-8-yl)-1,2,3-triazolo (IX).

The 5-deazaflavins thus obtained oxidized cyclopentanol at 120° under neutral conditions (without base) to yield cyclopentanone, particularly compounds I and IX showed considerable strong oxidizing abilities. Under these conditions, the 1,5-dihydro-5-deazaflavins initially formed are reoxidized to the original 5-deazaflavins by adventitous air, and thus the 5-deazaflavins acted as a turover catalyst. In control experiments without the 5-deazaflavins in the cyclopentanol oxidation, no cyclopentanone was detected. The results obtained are summarized in Table I.

Table 1

Oxidation of Cyclopentanol to Cyclopentanone by the 5-Deazaflavins (a)

Compound No.	Yield of Cyclopentanone (b)	
I	1134	(1.98) (c)
II	200	(0.26)
IV	303	(0.48)
IX	1089	(1.16)

(a) At 120° for 25 hours. (b) Based on the 5-deazaflavins. (c) Based on the starting cyclopentanol given in parentheses.

EXPERIMENTAL (6)

8-(1-Cyano-1-ethoxycarbonylmethyl)-3,10-dimethyl-5-deazaflavin (II).

Method A.

A mixture of 8-fluoro-3,10-dimethyl-5-deazaflavin (Ia) (0.26 g, 0.001 mole), ethyl cyanoacetate (0.57 g, 0.005 mole) and potassium carbonate (0.3 g) in ethanol (40 ml) was gently refluxed for 5 hours. After the reaction mixture was evaporated *in vacuo*, the residue was diluted with water and neutralized with acetic acid to precipitate crystals, which were filtered off, washed with water and dried. Recrystallization from acetic acid gave violet powder (0.35 g, 98%), mp 329°, ms: m/e 352 (M^+); nmr (trifluoroacetic acid): δ ppm 1.39 (3H, t, J = 7, OCH_2CH_3), 3.67 (3H, s, N_3-CH_3), 4.46 (2H, q, J = 7, OCH_2CH_3), 4.62 (3H, s, N_{10}-CH_3), 5.57 (1H, s, $CH(CN)COOC_2H_5$), 8.06-8.70 (3H, m, aromatic protons), 9.83 (1H, s, C_5-H); ir (nujol): ν max 2165 (C≡N) and 1721 ($COOC_2H_5$) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.29; H, 4.56; N, 15.69.

Method B.

A mixture of 8-chloro-3,10-dimethyl-5-deazaflavin (Ib) (0.28 g, 0.001 mole), ethyl cyanoacetate (0.57 g, 0.005 mole), and potassium carbonate 0.3 g) in hexamethyl phosphoramide (HMPA) (3 ml) was heated at 90° for 5 hours. After cooling, the reaction mixture was diluted with water and neutralized with acetic acid. The crystals thus separated were filtered off and recrystallized from acetic acid to give violet powder (0.32 g, 94%), mp 329°.

3,8,10-Trimethyl-5-deazaflavin (III).

8-(Cyano-1-ethoxycarbonylmethyl)-3,10-dimethyl-5-deazaflavin (II) (0.26 g, 0.001 mole) was refluxed in a mixture of dimethylformamide and water (10:1) (20 ml) for 3 hours. After the reaction mixture was evaporated *in vacuo*, the residue was recrystallized from acetic acid to give yellow needles (0.18 g, 71%), mp 309°; ms: m/e 255 (M^+); nmr (trifluoroacetic acid): δ ppm 2.86 (3H, s, C_8-CH_3), 3.67 (3H, s, N_3-CH_3), 4.53 (3H, s, N_{10}-CH_3), 7.80-8.45 (3H, m, aromatic protons), 9.68 (1H, s, C_5-H). This compound was in all respects identical with the authentic sample (2).

8-Dimethylamino-3,10-dimethyl-5-deazaflavin (IV).

Method A.

A mixture of Ia (0.26 g, 0.01 mole) and 40% aqueous dimethylamine (0.5 ml, 0.005 mole) was heated at 90° for 1 hour under refluxing. After cooling, the reaction mixture was diluted with water and the crystals which separated were filtered off and recrystallized from acetic acid to

give yellow needles (0.27 g, 94%), mp > 360°; ms: m/e 284 (M^+); nmr (trifluoroacetic acid): δ ppm 3.47 (6H, s, 8-N(CH_3)$_2$), 3.65 (3H, s, N_3-CH_3), 4.26 (3H, s, N_{10}-CH_3), 6.90-8.14 (3H, s, aromatic protons), 9.09 (1H, s, C_5-H).

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.25; H, 5.50; N, 19.50.

Method B.

A mixture of Ib (0.5 g, 0.0018 mole) and 40% aqueous dimethylamine (0.6 ml, 0.0054 mole) in HMPA (3 ml) was heated at 100° for 1 hour. After cooling, the reaction mixture was diluted with water and the crystals thus separated were filtered off. Recrystallization from acetic acid gave yellow needles (0.47 g, 91%), mp > 360°.

8-Azido-3,10-dimethyl-5-deazaflavin (V).

A mixture of Ia (2.59 g, 0.01 mole) and sodium azide (0.98 g, 0.015 mole) in ethanol (10 ml) was heated at 110° (oil bath temperature) for 8 hours. After cooling, the crystals which separated were collected by filtration, washed with water and dried. Recrystallization from ethanol gave yellow crystals (2.29 g, 81%), mp 334°; nmr (trifluoroacetic acid): δ ppm 3.66 (3H, s, N_3-CH_3), 4.48 (3H, s, N_{10}-CH_3), 7.62-8.50 (3H, m, aromatic protons), 9.64 (1H, s, C_5-H); ir (nujol): ν max 2110 (N_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_6O_2$: C, 55.31; H, 3.57; N, 29.78. Found: C, 55.27; H, 3.69; N, 30.01.

8-Amino-3,10-dimethyl-5-deazaflavin (VI).

Method A.

The azide (V) (0.28 g, 0.001 mole) was heated in benzyl alcohol (2 ml) at 120° for 5 hours. After cooling, the crystals which separated were filtered off and recrystallized from dimethylformamide to give yellow powder (0.22 g, 85%), mp > 350°; ms: m/e 256 (M^+); nmr (trifluoroacetic acid): δ ppm 3.64 (3H, s, N_3-CH_3), 4.23 (3H, s, N_{10}-CH_3), 7.10-8.07 (3H, m, aromatic protons), 9.11 (1H, s, C_5-H); ir (nujol): ν max 3330 (NH) and 3180 (NH) cm^{-1}.

Method B.

Compound V (0.28 g, 0.001 mole) was refluxed in 1-butanol (15 ml) at 130° for 6 hours, and then treated as above to give VI (0.20 g, 77%).

8-Acetamido-3,10-dimethyl-5-deazaflavin (VII).

Compound V (0.56 g, 0.002 mole) was refluxed in acetic acid (8 ml) at 160° for 8 hours. After cooling, the crystals which separated were filtered off and recrystallized from dimethylformamide to give yellow powder (0.34 g, 57%), mp > 360°C, ms: m/e 298 (M^+); nmr (trifluoroacetic acid): δ ppm 2.52 (3H, s, $COCH_3$), 3.55 (3H, s, N_3-CH_3), 4.51 (3H, s, N_{10}-CH_3), 7.80-8.50 (3H, m, aromatic protons), 9.20 (1H, s, C_5-H).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.44; H, 4.69; N, 18.56.

8-Benzamido-3,10-dimethyl-5-deazaflavin (VIII).

Compound V (0.56 g, 0.002 mole) was heated with benzoic anhydride (2.26 g, 0.01 mole) at 110° for 4 hours. After cooling, the reaction mixture was diluted with ethanol (40 ml) and the crystals which separated were filtered off and recrystallized from dimethylformamide to give yellow powder (0.37 g, 51%), mp > 360°; ms: m/e 360 (M^+); nmr (trifluoroacetic acid): δ ppm 3.67 (3H, s, N_3-CH_3), 4.58 (3H, s, N_{10}-CH_3), 7.45-8.50 (8H, m, aromatic protons), 9.44 (1H, s, C_5-H).

Anal. Calcd. for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.71; H, 4.47; N, 15.23.

4,5-Bis(methoxycarbonyl)-1-(3,10-dimethyl-5-deazaflavin-8-yl)-1,2,3-triazole (IX).

A mixture of V (0.28 g, 0.001 mole) and dimethyl acetylenedicarboxylate (0.7 g, 0.005 mole) was heated at 120° for 10 hours. The reaction mixture was treated with a small amount of acetic acid to separate yellow crystals, which were filtered off, washed with water and dried. Recrystallization from acetic acid gave yellow needles (0.29 g, 69%), mp 284°; ms: m/e 424 (M^+); nmr (trifluoroacetic acid): δ ppm 3.69 (3H, s, N_3-CH_3), 4.08 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 4.65 (3H, s, N_{10}-CH_3), 8.14-8.85 (3H, m, aromatic protons), 9.98 (1H, s, C_5-H); ir (nujol); ν max 1743 ($COOCH_3$) and 1721 ($COOCH_3$) cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}N_6O_6$: C, 53.76; H, 3.80; N, 19.81. Found: C, 53.59; H, 3.73; N, 19.90.

Oxidation of Cyclopentanol by 5-Deazaflavins.

A 5-deazaflavin (15 mg) was added to cyclopentanol (3 ml) and the mixture was heated at 120° for 25 hours under stirring. The reaction mixture was diluted with ether and the precipitate (a mixture of 5-deazaflavin and 1,5-dihydro-5-deazaflavin) thus separated was filtered off. The filtrate was treated with a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid to cause the separation of cyclopentanone 2,4-dinitrophenylhydrazine, mp 135°.

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(6) Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. The nmr spectra were determined with a Hitachi R-24 B spectrometer (tetramethysilane as internal standard) and ir spectra were obtained in nujol with a JASCO IR-Al spectrometer.