Syntheses of 1,3,8,10,12-Pentazanaphthacene-2,4,7,9-(12*H*,3*H*,8*H*,10*H*)-tetraones (Linear Pyrimidine-Fused 5-Deazaflavins), 1,3,6,8,12-Pentazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (Bent Pyrimidine-Fused 5-Deazaflavins), and Their Flavin Analogs

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1,3,8,10,12-Pentazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused 5-deazaflavins) and 1,3,6,8,12-pentazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (bent pyrimidine-fused 5-deazaflavins) were synthesized by condensation of 7-alkylaminoquinazoline with 6-chloro-5-formyl-3-methyluracil. Also, their flavin analogs, 1,3,5,8,10,12-hexazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused flavins) and 1,3,5,6,8,12-hexazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (bent pyrimidine-fused flavins) were synthesized by cyclization of 7-[*N*-alkyl-*N*-(5-nitrouracil-6-yl)]aminoquinazolines with the Vilsmeier reagent.

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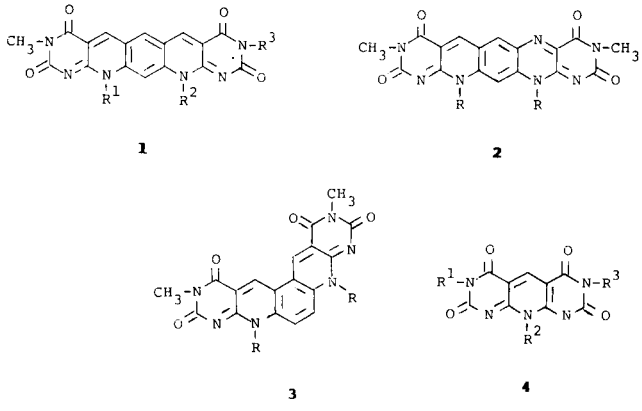
We have recently reported the syntheses of polyazapentacyclic compounds **1**, **2** and **3** of extended conjugation, which include a flavin and/or a 5-deazaflavin moiety in the molecule, and their oxidizing abilities toward cyclopentanol [1-3]. In the present paper we describe the synthesis of two types of tetracyclic pyrimidine-fused 5-deazaflavins, 1,3,8,10,12-pentazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones and 1,3,6,8,12-pentazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones. The former compounds can also be regarded as "stretched-out" derivatives of the pyridodipyrimidines **4** having strong oxidizing ability [4]. Additionally, we will describe the synthesis of the corresponding 5-aza analogs of the above compounds, 1,3,5,8,10,12-hexazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones and 1,3,5,6,8,12-hexazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones.

Scheme 1



The requisite starting material, 7-chloro-3-methylquinazoline (**5**), was prepared by condensation of 2-amino-4-chlorobenzoic acid with *N*,*N*-dimethylurea according to the known procedure [5]. Compounds **5** was treated with excess alkylamines to give the corresponding 7-alkylamino-3-methylquinazolines **6a-c** (Table 1). Compounds **6a-c** were treated with 6-chloro-5-formyl-3-methyluracil (**7**)

Table 1

Synthesis of 7-Alkylamino-3-methylquinazolines **6a-c**

No.	R	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./(Found) C	H	N
6a	$CH_3(CH_2)_7$	36	237	$C_{17}H_{25}N_3O_2$	67.30 (67.14)	8.31 (8.26)	13.85 (13.88)
6b	$CH_3(CH_2)_{11}$	60	225	$C_{21}H_{33}N_3O_2$	70.16 (70.42)	9.26 (9.51)	11.69 (11.40)
6c	$CH_3(CH_2)_{17}$	50	220	$C_{27}H_{45}N_3O_2$	73.09 (73.35)	10.22 (10.58)	9.47 (9.14)

[6] in chloroform under reflux to give a mixture of the corresponding 1,3,8,10,12-pentazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused 5-deazaflavins) **8a-c** and 1,3,6,8,12-pentazabenz[*a*]anthracene-

Scheme 2

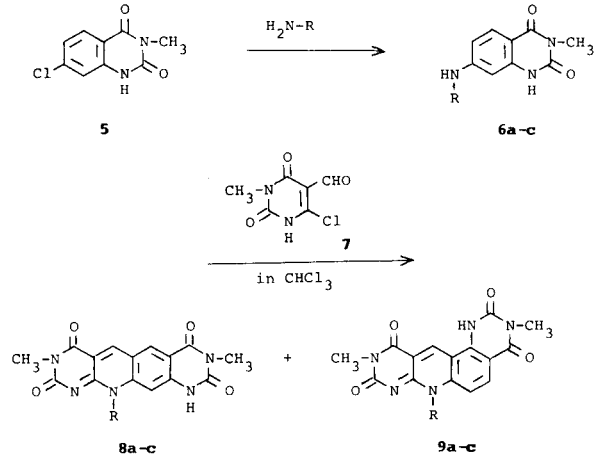


Table 2

Synthesis of Linear Pyrimidine-Fused 5-Deazaflavins **8a-c** and Bent Pyrimidine-Fused 5-Deazaflavins **9a-c**

No.	R	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./(Found) C	H	N	δ H (Deuteriotrifluoroacetic acid-deuteriochloroform, 1:1) H-11	H-6	H-5
8a	$CH_3(CH_2)_7$	6	>330	$C_{23}H_{27}N_5O_4$	63.14 (63.02)	6.22 (6.04)	16.01 (16.11)	7.86	9.33	9.77
8b	$CH_3(CH_2)_{11}$	4	>330	$C_{27}H_{35}N_5O_4$	65.70 (65.44)	7.15 (7.19)	14.19 (14.01)	7.86	9.34	9.78
8c	$CH_3(CH_2)_{17}$	5	>330	$C_{33}H_{47}N_5O_4$	68.60 (68.75)	8.20 (8.31)	12.12 (12.17)	7.84	9.34	9.78
								H-11	H-10	H-5
9a	$CH_3(CH_2)_7$	17	>330	$C_{23}H_{27}N_5O_4$	63.14 (62.92)	6.22 (6.04)	16.01 (16.08)	8.05	9.04 J = 9 Hz [a]	10.31
9b	$CH_3(CH_2)_{11}$	34	>330	$C_{27}H_{35}N_5O_4$	65.70 (65.42)	7.15 (7.14)	14.19 (14.18)	8.04	9.04 J = 8 Hz [a]	10.31
9c	$CH_3(CH_2)_{17}$	33	304	$C_{33}H_{47}N_5O_4$	68.60 (68.61)	8.20 (8.30)	12.12 (12.16)	8.05	9.04 J = 8 Hz [a]	10.31

[a] Coupling constant of H-11 and H-10 of **9a-c**.

2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (bent pyrimidine-fused 5-deazaflavins) **9a-c**, which were separated by chromatography (Table 2).

The structures of compounds **8a-c** and **9a-c** were determined by direct ^1H nmr examination. The signals of C(11)-H and C(6)-H of compound **8b** existed as two sharp singlets at δ 7.86 ppm and δ 9.34 ppm (deuteriotrifluoroacetic acid:deuteriochloroform = 1:1) respectively. The signals of C(11)-H and C(10)-H of compound **9b** existed as two doublets at δ 8.04 ppm and δ 9.04 ppm (deuteriotrifluoroacetic acid:deuteriochloroform = 1:1) respectively. Therefore, the structure of compounds **8** turned out to have a linear form and that of compounds **9** to have a bent form (Table 2).

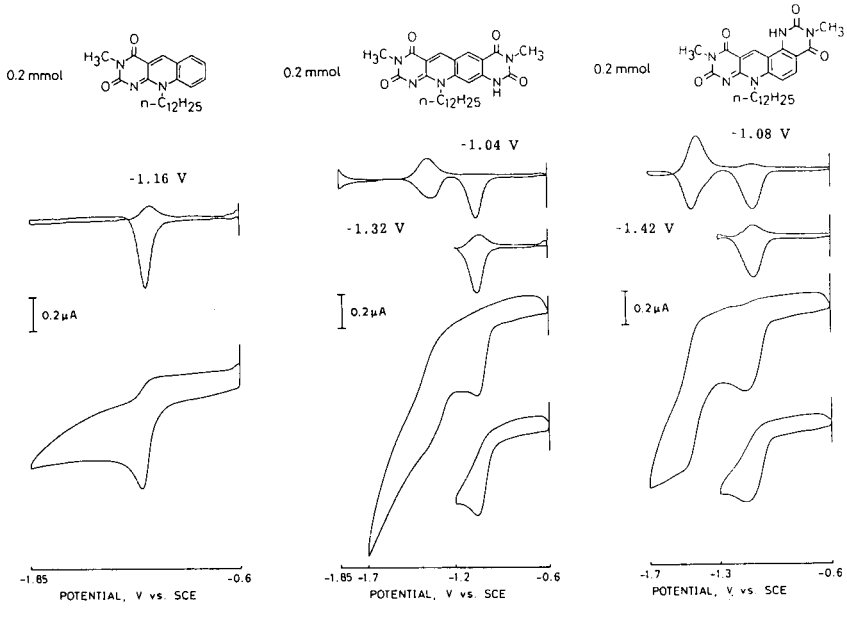


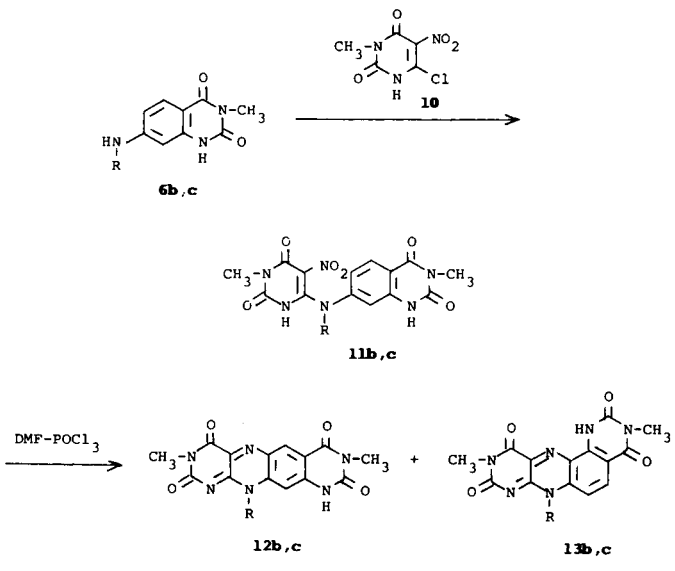
Figure 1. Pulsecyclic Voltammograms and Cyclic Voltammograms in 0.1*M*-(n-C_4H_9)$_4$NClO$_4$/DMF. Measurement was made with a hunging mercury drop electrode (area, 0.89 mm²) at a scan rate of 90 mV/sec; temperature, room temperature; pulse high, 30 mV.

Compounds **8a-c** and **9c-c** showed the characteristic signal of C(5)-H at low field in the ^1H nmr spectra (Table 2). The redox potentials [room temperature, DMF-(tetra-*n*-butylammonium perchlorate)] for the first one electron transfer of compounds **8** and **9** were *ca.* -1050 mV *vs.* SCE. These potentials are about 100 mV more positive than those of the corresponding 5-deazaflavins (for example, -1160 mV for 10-dodecyl-3-methyl-5-deazaflavin) (Figure 1). Therefore, compounds **8** and **9** were expected to have stronger oxidizing ability toward alcohols, however, they showed no appreciable oxidizing ability toward cyclopentanol, contrary to our expectation.

Next, we synthesized the corresponding 5-aza analogs of compounds **8** and **9**, according to a similar procedure to the above synthesis.

Compounds **6b,c** were treated with 6-chloro-5-nitro-3-methyluracil (**10**) [7] in chloroform under reflux to give the corresponding 3-methyl-7-[*N*-alkyl-*N*-(5-nitro-3-methyluracil-6-yl)]aminoquinazolines **11b,c**. Treatment of compounds **11b,c** with Vilsmeier reagent (DMF-phosphoryl chloride) gave a mixture of the corresponding 1,3,5,8,-10,12-hexazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused flavins) **12b,c** and 1,3,5,6,8,12-hexazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,-8*H*)-tetraones (bent pyrimidine-fused flavins) (**13b,c**) along with the corresponding pyrimidine-fused 5-deazaflavins **8b,c** and **9b,c**, which were separated by chromatography (Table 3).

Scheme 3



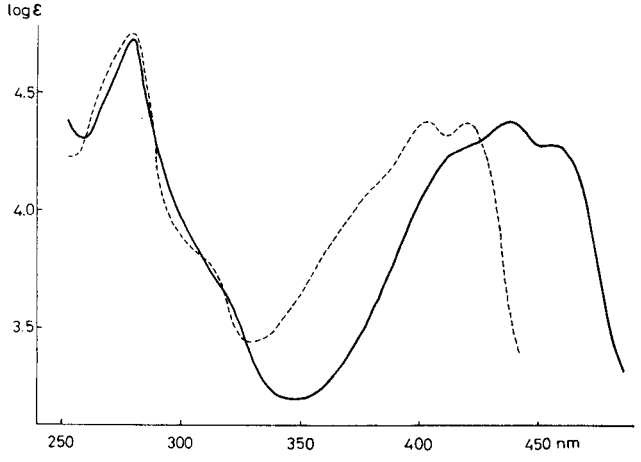


Figure 2. Uv and visible spectra in chloroform-ethanol (1:1).

Table 3

Synthesis of Linear Pyrimidine-Fused Flavins **12b,c** and Bent Pyrimidine-Fused Flavins **13b,c**

No.	R	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./(Found) C	H	N	δ H (Deuteriotrifluoroacetic acid-deuteriochloroform, 1:1)	
								H-11	H-6
12b	$CH_3(CH_2)_{11}$	1	244	$C_{26}H_{34}N_6O_4H_2O$	60.92 (61.17)	7.08 (6.70)	16.39 (16.36)	7.77	9.25
12c	$CH_3(CH_2)_{17}$	1	241	$C_{32}H_{46}N_6O_4H_2O$	64.40 (64.20)	8.36 (8.09)	14.08 (14.26)	7.79	9.26
								H-11	H-10
13b	$CH_3(CH_2)_{11}$	2	240	$C_{26}H_{34}N_6O_4$	63.14 (63.00)	6.93 (6.87)	16.99 (16.83)	7.83 J = 9 Hz [a]	8.87
13c	$CH_3(CH_2)_{17}$	3	224	$C_{32}H_{46}N_6O_4$	66.41 (66.45)	8.01 (7.94)	14.52 (14.54)	7.84 J = 9 Hz [a]	8.87

[a] Coupling constant of H-11 and H-10 of **13b,c**.

The structures of compounds **12b,c** and **13b,c** were likewise determined by direct ^1H nmr examination. The signals of C(11)-H and C(6)-H of **12b** existed as two singlets at δ 7.77 ppm and δ 9.25 ppm (deuteriotrifluoroacetic acid:deuteriochloroform = 1:1) respectively. The signals of C(11)-H and C(10)-H of **13b** existed as two doublets at δ 7.83 ppm and δ 8.87 ppm respectively. Therefore, the structures of compounds **12** and **13** turned out to have a linear form and a bent form respectively.

The uv and visible spectra of compounds **12b** and **13b** showed similar absorption patterns with a slight bathochromic shift in comparison with those of the corresponding 5-deazaflavin derivatives **8b** and **9b** as shown in Figures 2 and 3. This implies that compounds **12** and **13** have the same conjugated systems as those of compounds **8** and **9** respectively.

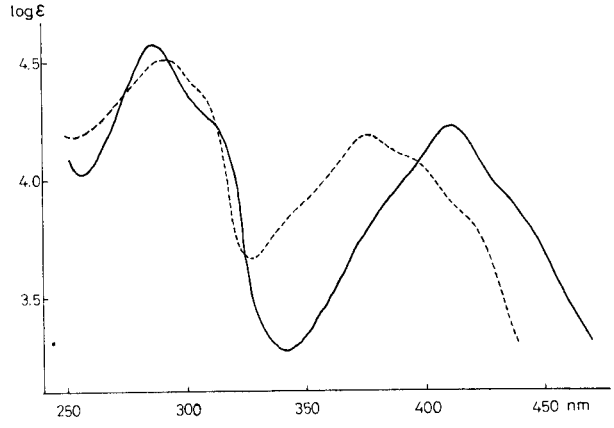


Figure 3. Uv and visible spectra in chloroform-ethanol (1:1).

EXPERIMENTAL

All melting points were determined on a Yanagimoto hot-stage apparatus, and are uncorrected. The ir spectra were obtained on a Shimazu IR-400 spectrometer and the ^1H nmr spectra on a JEOL FX 200 spectrometer. Mass spectra were taken on a JEOL OISG-2 instrument by direct insertion at 70 ev. The uv and visible spectra were obtained on a Hitachi model 200-20 spectrophotometer. Redox potentials were taken on a MCI model AS-02 cyclic voltammetry analyzer. Column chromatography was carried out with Silica gel 60 (E. M. Merck, 230 mesh) and Wakogel-200 and Wakogel-300. Flash column chromatography was carried out with Merck silica gel GF 254 under *ca.* 1.5 kg/cm^2 pressure. Preparative tlc was run on 20 x 20 cm plates coated with a 0.25-0.5 mm layer of Merck silica gel GF 254 and PF 254.

Synthesis of 7-Chloro-3-methylquinazoline (**5**).

A mixture of 2-amino-4-chlorobenzoic acid (5 g, 29 mmoles) and *N,N'*-dimethylurea (15.4 g, 175 mmoles) was heated at 200-240° for 2 hours. The reaction mixture was diluted with methanol. The precipitate was filtered off and purified by column chromatography. The fraction eluted with chloroform was recrystallized from chloroform-methanol to give 7-chloro-3-methylquinazoline (**5**) as a colorless powder, mp 280°; ir (Nujol): 1745, 1640, 1620 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid:deuteriochloroform, 1:1): 200 MHz δ 3.56 (s, 3H, 3-NCH$_3$), 7.31 (d, J = 2 Hz, 1H, H-8), 7.39 (dd, J = 9 and 2 Hz, 1H, H-6), 8.12 (d, J = 9 Hz, 1H, H-5).

Anal. Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.21; H, 3.23; N, 13.47.

Synthesis of 7-Alkylamino-3-methylquinazolines **6a-c**.

General Procedure.

A mixture of 7-chloro-3-methylquinazoline (**5**) (1.5 g, 7.1 mmoles) and alkylamines (21.6 mmoles) was heated at 200-240° for 10 hours under an argon atmosphere. The reaction mixture was diluted with methanol. The precipitate was filtered off, washed with boiling methanol, and recrystallized with chloroform-methanol to give the corresponding 7-alkylamino-3-methylquinazolines **6a-c** as colorless powders (Table 1).

Synthesis of Linear Pyrimidine-Fused 5-Deazaflavins **8a-c** and Bent Pyrimidine-Fused 5-Deazaflavins **9a-c**.

General Procedure.

A mixture of 7-alkylamino-3-methylquinazoline **6a-c** (0.5 g, 1.4 mmoles) and 6-chloro-5-formyl-3-methyluracil (**7**) (0.6 g, 3.2 mmoles) in chloroform (140 ml) was refluxed for 20 hours under an argon atmosphere. The reaction mixture was cooled, evaporated to dryness under reduced pressure, and purified by preparative tlc (chloroform-acetone, 5:1). The polar fraction was recrystallized from chloroform-methanol to give 1,3,8,10,12-pentazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused 5-deazaflavins) **8a-c** as pale yellow powders. The next fraction was recrystallized from chloroform-methanol to give 1,3,6,8,12-pentazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (bent pyrimidine-fused 5-deazaflavins) **9a-c** as yellow needles (Table 2).

Synthesis of 7-[*N*-alkyl-*N*-(5-nitro-3-methyluracil-6-yl)]aminoquinazolines **11b,c**.

General Procedure.

A mixture of 7-alkylamino-3-methylquinazoline **6b,c** (520 mg, 1.45 mmoles) and 6-chloro-5-nitro-3-methyluracil (**10**) (830 mg, 4.04 mmoles) in chloroform (60 ml) was refluxed for 50 hours under an argon atmosphere. The reaction mixture was cooled and chromatographed. The fraction eluted with chloroform-acetone-methanol (5:1:1) was recrystallized from methanol-ether to give the corresponding 7-[*N*-alkyl-*N*-(5-nitro-3-methyluracil-6-yl)]amino-3-methylquinazolines **11b,c** as pale red powders. Compound **11b** had ir (Nujol): 1730, 1710, 1640, 1590 cm^{-1}); ^1H nmr (deuteriotrifluoroacetic acid-deuteriochloroform, 1:1): 200 MHz δ 3.46 (s, 3H, 3'-NCH$_3$), 3.56 (s, 3H, 3-NCH$_3$), 3.92-4.10 (m, 2H, 7-NCH$_2$-), 7.18 (s, 1H, H-8), 7.20 (d, J = 9 Hz, 1H, H-6), 8.27 (d, J = 9 Hz, 1H, H-5).

Compound **11b,c** were unstable in air and we used them for the next steps without purification.

Synthesis of Linear Pyrimidine-Fused Flavins **12b,c** and Bent Pyrimidine-Fused Flavins **13b,c**.

General Procedure.

A mixture of 7-[*N*-alkyl-*N*-(5-nitro-3-methyluracil-6-yl)] amino-3-methylquinazolines **11b,c** (234 mg, 0.44 mmole) and Vilsmeier reagent (DMF:phosphoryl chloride = 5:1 v/v) (0.8 ml) was heated at 90-100° for 37 hours under an argon atmosphere. The reaction mixture was cooled, diluted with methanol, and evaporated to dryness under reduced pressure. The residue was purified by preparative tlc [chloroform-acetone (5:1)] or flash column chromatography [chloroform-acetone (9:1)]. The first fraction was recrystallized from chloroform-methanol to give compounds **8b,c**. The second fraction gave compounds **9b,c** as yellow powders. The third fraction gave the corresponding 1,3,5,8,10,12-hexazanaphthacene-2,4,7,9(12*H*,3*H*,8*H*,10*H*)-tetraones (linear pyrimidine-fused flavins) **12b,c** as yellow powders. The fourth fraction gave the corresponding 1,3,5,6,8,12-hexazabenz[*a*]anthracene-2,4,7,9(12*H*,3*H*,6*H*,8*H*)-tetraones (bent pyrimidine-fused flavins) **13b,c** as yellow needles (Table 3).

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