2,4,5,8,9,11-Hexa-azapentaphene-1,3,10,12(2*H*,5*H*,8*H*,11*H*)-tetraones (Angular 5-Deazapteridino-deazaflavins) with Strong Oxidizing Power

Fumio Yoneda * **and Masakazu Koga**
Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan
Yumihiko Yano
Department of Chemistry, Gunma University, Kiryu, Gunma 376, Japan

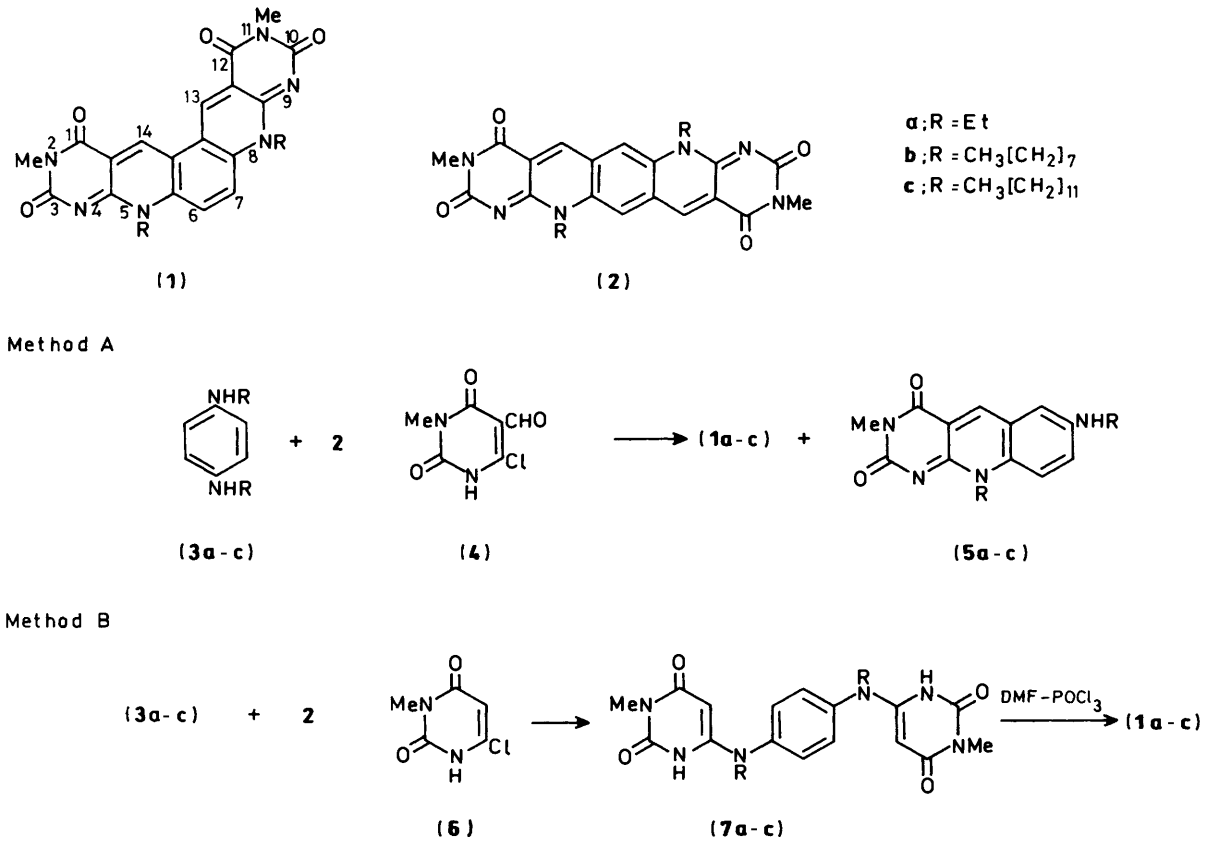
Condensation of *N,N'*-dialkyl-*p*-phenylenediamines with 6-chloro-5-formyl-3-methyluracil, and cyclization of the resulting *N,N'*-dialkyl-*N,N'*-bis(3-methyluracil-6-yl)-*p*-phenylenediamines with Vilsmeier reagent gave the corresponding 2,4,5,8,9,11-hexa-azapentaphene-1,3,10,12(2*H*,5*H*,-8*H*,11*H*)-tetraones, which exhibited a very strong oxidizing ability towards cyclopentanol.

Recently polycyclic flavin derivatives with extended conjugation, consisting of two flavin or two 5-deazaflavin units with a benzo unit in common, have been synthesized.[1,2] A similar mixed system having both flavin and 5-deazaflavin was also synthesized.[3] As expected, these derivatives have shown autorecycling oxidizing activity toward cyclopentanol. In the present paper we describe in full the synthesis of novel derivatives with extended conjugation, the 2,4,5,8,9,11-hexa-azapentaphene-1,3,10,12(2*H*,5*H*,8*H*,11*H*)-tetraones (angular 5-deazapteridino-5-deazaflavins) (**1a**—**c**), and their catalytic activity for the oxidation of cyclopentanol.[4]

The starting materials, the *N,N'*-dialkyl-*p*-phenylenediamines (**3a**—**c**) were prepared according to a known procedure.[5] Compounds (**3a**—**c**) were condensed with 6-chloro-5-formyl-3-methyluracil (**4**) in *N,N*-dimethylformamide (DMF) to give compounds (**1a**—**c**) along with the 10-alkyl-7-alkylamino-3-methyl-5-deazaflavins (**5a**—**c**) (Method A, Scheme 1) (Table 1).

Compounds (**1a**—**c**) were synthesized alternatively as follows (Method B). Compounds (**3a**—**c**) were treated with 6-chloro-3-methyluracil (**6**) to give the corresponding *N,N'*-dialkyl-*N,N'*-bis(3-methyluracil-6-yl)-*p*-phenylenediamines (**7a**—**c**) (Table 3). Treatment of **7a**—**c**) with the Vilsmeier reagent (DMF–$POCl_3$) under argon gave compounds (**1a**—**c**) in better yields than Method A (Table 1) (Scheme 1).

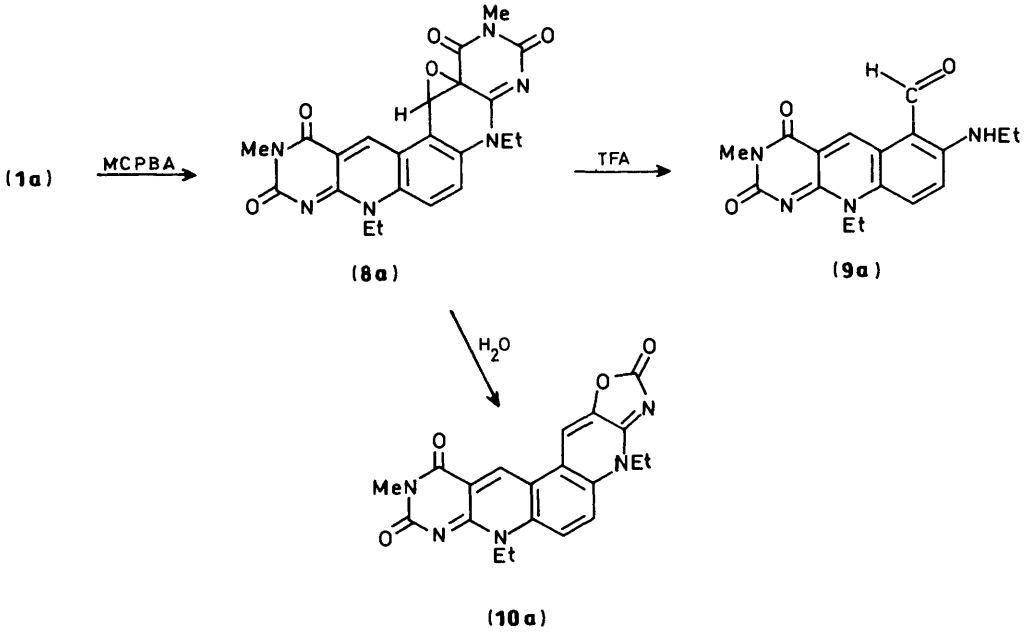
In order to determine whether compounds (**1a**—**c**) have the linear (**2**) or the angular form, we carried out the epoxidation of (**1a**) (the structure could not be determined by direct ^1H n.m.r. examination because of symmetry). Thus, (**1a**) was treated with *m*-chloroperbenzoic acid (MCPBA)[6] to give the corresponding



Scheme 1.

Table 1. Synthesis of angular doubled 5-deazaflavins (**1a**—**c**) and 7-alkylamino-5-deazaflavins (**5a**—**c**)

No.	Yield (%) A	Yield (%) B	M.p. (°C)	Formula	Found (%) (Required) C	H	N	δ[CF_3CO_2D–$CDCl_3$ (1:1)]
								13- and 14-H
(**1a**)	31	34	>330	$C_{22}H_{20}N_6O_4$	60.85 (61.1	4.5 4.65	19.15 19.45)	10.70
(**1b**)	6	36	240	$C_{34}H_{44}N_6O_4$	68.25 (68.0	7.35 7.4	13.7 14.0)	10.70
(**1c**)	2	35	190	$C_{42}H_{60}N_6O_4$	70.65 (70.25	8.25 8.5	11.55 11.8)	10.70
								H-5
(**5a**)	6		318	$C_{16}H_{18}N_4O_2$	64.6 (64.4	6.1 6.1	18.8 18.8)	9.84
(**5b**)	8		215	$C_{28}H_{42}N_4O_2$	71.95 (72.05	9.1 9.05	12.05 12.0)	9.84
(**5c**)	4		188	$C_{36}H_{58}N_4O_2$	74.6 (74.7	10.35 10.1	9.4 9.7)	9.84



Scheme 2.

epoxide (**8a**). The ^1H n.m.r. signal of 6- and 7-H [δ 8.21 ($CDCl_3$) for (**1a**)] was split into two [δ 7.84 (d, *J* 10 Hz) and 7.91 (d, *J* 10 Hz) in the spectrum of the epoxide (**8a**), because of the removal of symmetry. Since (**8a**) was unstable and difficult to purify, it was treated with trifluoroacetic acid (TFA) under reflux to give 10-ethyl-7-ethylamino-6-formyl-5-deazaflavin (**9a**). Furthermore, hydrolysis of (**8a**) with water in refluxing chloroform and acetone gave 1-oxa-3,4,7,8,10-penta-azaindeno-[5,6-*h*]anthracene-2,9,11(4*H*,7*H*,10*H*)-trione (**10a**).* Thus, the angular structure of (**1a**) was verified (Scheme 2).

Compounds (**1a**—**c**) showed characteristic ^1H n.m.r. signals for 13- and 14-H at low field (Table 1). The redox potentials (room temperature, DMF–NBu_4ClO_4) for the first one-electron transfer of compounds (**1a**—**c**) were *ca.* −700 mV *vs.* standard calomel electrode (s.c.e.). These potentials are *ca.* 450 mV more positive than those of the monomeric 5-deazaflavins (*e.g.* −1 150 mV for 10-dodecyl-3-methyl-5-deazaflavin) (Table 2) (Figure 1), and *ca.* 150 mV more negative than those of the linear doubled 5-deazaflavins[1] (*e.g.* −550 mV for the 3,9-dimethyl-12,14-didodecyl derivative). However, it is interesting that the potentials for the second one-electron transfer of compounds (**1a**—**c**) (*ca.* −1 000 mV *vs.* s.c.e.) are *ca.* 300 mV more positive than those of the linear compounds (*ca.* −1 300 mV), and *ca.* 150 mV more positive than the potentials for the first one-electron transfer of the monomeric 5-deazaflavins (Table 2) (Figure 1).

The angular doubled 5-deazaflavins (**1a**—**c**) were more effective for oxidizing alcohols than the monomeric 5-deazaflavins and the linear doubled 5-deazaflavins. They oxidized cyclopentanol to cyclopentanone under neutral conditions at 60 °C in oxygen during irradiation with a sunlamp, with a high level of autorecycling (Table 2). The photosensitizers Methylene Blue and Rose Bengal did not catalyse the alcohol oxidation at all under the same conditions, which implies that singlet oxygen

* A similar hydrolytic ring contraction in the 5-deazaflavin ring system has been reported.[6]

Table 2. Autorecycling oxidation of cyclopentanol by angular doubled 5-deazaflavins at 60 °C for 25 h in light;[a] redox potentials

Compound	Yield (%)[b] of cyclopentanol A[c]	B[d]	Redox potential[e] (mV)	
(**1a**)	53 900	2.80	−950	−700
(**2a**)	63 400	3.11	−1 000	−700
(**3a**)	60 800	3.03	−1 000	−700
Methylene Blue	0	0		
Rose Bengal	0	0		
3-Methyl-10-dodecyl-5-deazaflavin	16 200	0.84	−1 150	
3,9-Dimethyl-12,14-didodecyl-doubled 5-deazaflavin[1]	48 000	2.20	−1 300	−550

[a] Toshiba DR250TL sunlamp, *ca.* 60 000 lux. [b] Isolated as the 2,4-dinitrophenylhydrazone. [c] Based on the catalyst. [d] Based on the starting cyclopentanol. [e] Room temperature; DMF–NBu_4ClO_4; *vs.* s.c.e.

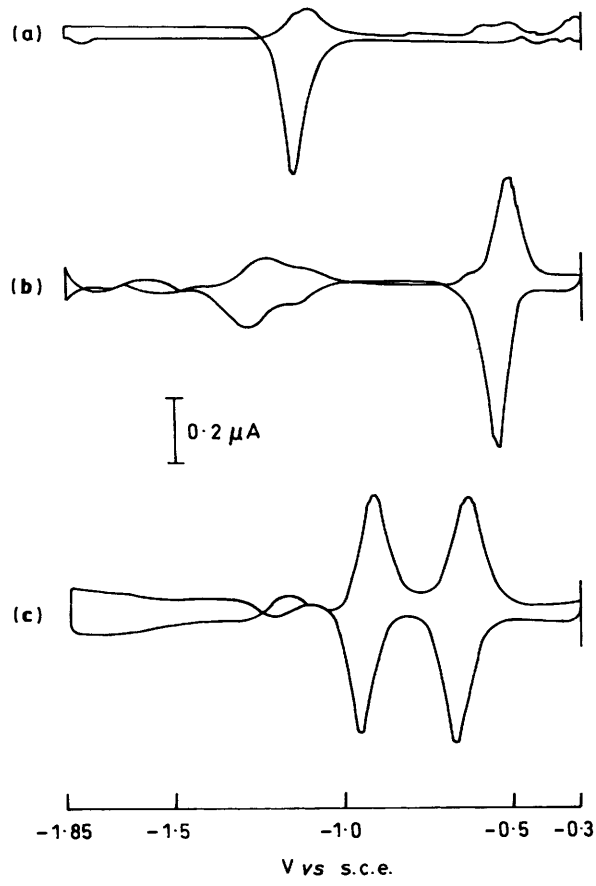
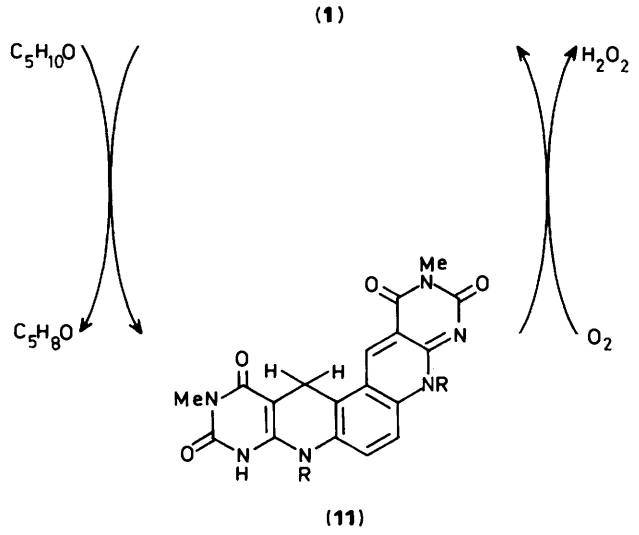


Figure 1. Pulse cyclic voltammograms (DMF–0.1M NBu_4ClO_4) of (a) 0.2mM 3-methyl-10-dodecyl-5-deazaflavin, (b) 0.2mM 3,9-dimethyl-12,14-didodecyl doubled 5-deazaflavin, and (c) 0.2mM angular doubled 5-deazaflavin (**1c**); measurements made with a hanging mercury drop electrode (area 0.89 mm^2) at a scan rate of 90 mV s^{-1}; room temperature; pulse high, 30 mV. Redox potential = $E_p/2$(this chart) − 15 mV

is not involved. These results suggest that compounds (**1**) dehydrogenate cyclopentanol under these conditions, while undergoing hydrogenation to the corresponding 4,14-dihydro derivatives (**11**), and that compounds (**11**) are then reoxidized by oxygen to the original compounds (**1**) (see Scheme 3).



Scheme 3. Autorecycling oxidation by the angular doubled 5-deazaflavins (**1**)

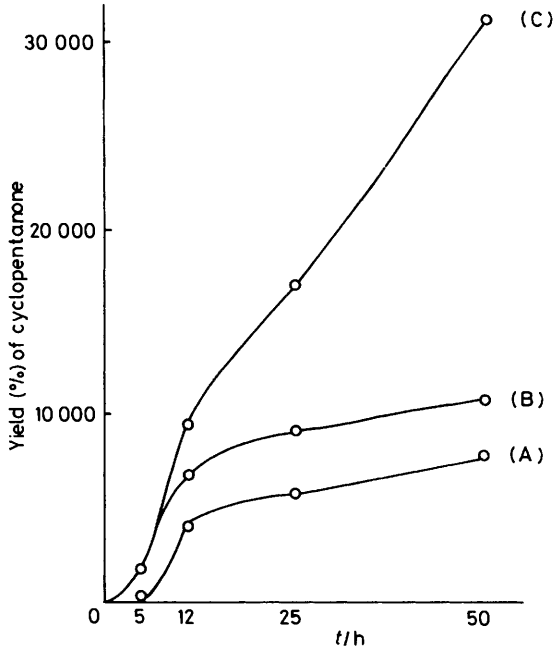


Figure 2. Autorecycling oxidation of cyclopentanol (3.36 ml, 40 mmol) catalysed by (A) 3-methyl-10-dodecyl-5-deazaflavin (0.002 mmol), (B) 3,9-dimethyl-12,14-didodecyl doubled 5-deazaflavin (0.002 mmol), or (C) the angular doubled 5-deazaflavin (**1c**) (0.002 mmol) at 40 °C under irradiation with a sunlamp (Toshiba DR250/TL; *ca.* 27 000 lux) in oxygen; yields are based on the catalyst

We also examined the long-term oxidation of cyclopentanol catalyzed by the angular compound (**1c**) in comparison with a monomeric 5-deazaflavin and linear doubled 5-deazaflavin. As shown in Figure 2, (**1c**) was much the most effective in the autorecycling oxidation towards cyclopentanol. Furthermore compound (**1c**) was stable and stood up to long use even under irradiation with a sunlamp.

In conclusion, the present study has demonstrated that the angular doubled 5-deazaflavins (**1**) are stable in light and act as efficient turnover catalysts for the oxidation of cyclopentanol.

Table 3. Synthesis of *N,N'*-dialkyl-*N,N'*-bis(3-methyluracil-6-yl)-*p*-phenylenediamines (**7a**—**c**)

	Yield (%)	M.p. (°C)	Formula	Found (%) (Required) C	H	N
(**7a**)	60	330	$C_{20}H_{24}N_6O_4$	58.15 (58.25)	5.85 (5.85)	20.2 (20.4)
(**7b**)	29	253	$C_{32}H_{48}N_6O_4$	66.4 (66.2)	8.6 (8.35)	14.35 (14.45)
(**7c**)	28	165	$C_{40}H_{64}N_6O_4$	69.2 (69.35)	9.5 (9.3)	12.0 (12.15)

Experimental

M.ps were determined with a Yanaginoto hot-stage apparatus. I.r. spectra were obtained with a Shimadzu IR-400 spectrometer and ^{1}H n.m.r. spectra with a JEOL FX 200 spectrometer. Mass spectra were taken with a JEOL JMS OISG-2 instrument by direct insertion at 70 eV. Redox potentials were measured with an MCI AS-02 cyclic voltammetry analyser. Column chromatography was carried out with silica gel 60 (Merck; 230 mesh), Wakogel-200, Wakogel-300). Preparative t.l.c. was performed on 20 × 20 cm plates coated with a 0.25—0.5 mm layer of Merck silica gel GF 254 or PF 254.

Synthesis of N,N'-Dialkyl-N,N'-*bis*(3-*methyluracil*-6-*yl*)-p-*phenylenediamines* (**7a**—**c**).—A mixture of *N,N'*-dialkyl-*p*-phenylenediamine (**3a**—**c**) (300 mg, 0.68 mmol) and 3-methyl-6-chlorouracil (**6**) (273 mg, 1.70 mmol) in *N,N*-dimethylaniline (0.3 ml) was heated at 180—200 °C for 5 h under argon. The mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol or column chromatographed (chloroform–acetone, 9:1) to give the N,N'-*dialkyl*-N,N'-*bis*-(3-*methyluracil*-6-*yl*)-p-*phenylenediamine* (**7a**—**c**) as a colourless powder (Table 3).

Synthesis of 2,4,5,8,9,11-*Hexa-azapentaphene*-1,3,10,12-(2H,5H,8H,11H)-*tetraones* (**1a**—**c**).—*Method A.* A mixture of *N,N'*-dialkyl-*p*-phenylenediamine (**3a**—**c**) (400 mg, 1.2 mmol) and 6-chloro-5-formyl-3-methyluracil (**4**) (543 mg, 2.9 mmol) in DMF (10 ml) was heated under reflux for 3—9 h in argon. The mixture was cooled to precipitate the products, which were filtered off, washed with methanol, and column chromatographed. The fraction eluted with chloroform–acetone (15:1) was recrystallized from chloroform–methanol to give the 10-alkyl-7-alkylamino-3-methyl-5-deazaflavin (**5a**—**c**) as red needles (Table 1). The fraction eluted with chloroform–acetone (10:1) was recrystallized from chloroform–methanol to give the *angular doubled 5-deazaflavin* (**1a**—**c**) as orange needles (Table 1).

Method B. A mixture of *N,N'*-dialkyl-*N,N'*-bis(3-methyluracil-6-yl)-*p*-phenylenediamine (**7a**—**c**) (100 mg, 0.17 mmol) and Vilsmeier reagent (DMF–$POCl_3$, 5:1) (0.36 ml) was heated at 90 °C for 5—6 h in argon. The mixture was cooled to precipitate the product, which was filtered off, washed with methanol, and recrystallized from chloroform–methanol to give compounds (**1a**—**c**) as orange needles (Table 1).

The products showed the following spectroscopic data.

^{1}H N.m.r. δ_H[200 MHz; CF_3CO_2D–$CDCl_3$ (1:1)]: (**1a**) 1.82 (6 H, t, *J* 7 Hz, Me of 5- and 8-Et), 3.67 (6 H, s, 2- and 11-Me), 5.14 (4 H, q, *J* 7 Hz, 5- and 8-CH_2), 9.05 (2 H, s, 6- and 7-H), and 10.70 (2 H, s, 13- and 14-H); (**1b**) 0.92 (6 H, t, *J* 7 Hz, Me of 5- and 8-$[CH_2]_7$Me), 1.20—5.10 (24 H, m, $[CH_2]_6$ of 5- and 8-$[CH_2]_7$Me), 3.67 (6 H, s, 2- and 11-Me), 4.85—5.10 (4 H, m, 5- and 8-CH_2), 8.94 (2 H, s, 6- and 7-H), and 10.70 (2 H, s, 13- and 14-H); (**1c**) 0.90 (6 H, t, *J* 7 Hz, Me of 5- and 8-$[CH_2]_{11}$Me), 1.15—2.25 (40 H, m, $[CH_2]_{10}$ of 5- and 8-$[CH_2]_{11}$Me), 3.67 (6 H, s, 2- and 11-Me), 4.82—5.10 (4 H, m, 5- and 8-CH_2), 8.94 (2 H, s, 6- and 7-H), and 10.70 (2 H, s, 13- and 14-H).

I.r. $\nu_{max.}$(Nujol) (**1a**) 1 700 (CO) and 1 650 (CO); (**1b**) 1 705 (CO) and 1 650 (CO); (**1c**) 1 710 (CO) and 1 660 cm^{-1} (CO).

U.v.–visible $\lambda_{max.}$(log ε) [$CHCl_3$–EtOH (1:1)] (**1c**) 289 (5.01), 370sh (4.21), 387 (4.52), 4.08 (4.61), 4.33 (3.94), 460 (4.11), and 490 nm (4.10); (**1a** and **b**) showed the same $\lambda_{max.}$ values.

Structure Determination of the Angular Doubled 5-Deazaflavin (**1a**) *by Oxidative Degradation.*—A mixture of compound (**1a**) (100 mg, 0.23 mmol) and *m*-chloroperbenzoic acid (MCPBA) (100 mg, 0.58 mmol) in chloroform (15 ml) was heated under reflux for 5 h in argon. The mixture was washed with aq. $Na_2S_2O_3$, aq. $NaHCO_3$, and water, dried, and evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. (chloroform–acetone, 10:1) to give the 12a,13-epoxide (**8a**) (19 mg, 18%) as a yellow powder, *m/z* 448 (M^+); $\nu_{max.}$(Nujol) 1 725, 1 680, 1 645, and 1 625 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 5.90 (1 H, s, 14-H), 7.84 (1 H, d, *J* 10 Hz, 7-H), 7.91 (1 H, d, *J* 10 Hz, 6-H), and 9.45 (1 H, s, 13-H). The next fraction was recrystallized from chloroform–methanol to give unchanged (**1a**) (48 mg, 48%).

A mixture of the epoxide (**8a**) (14 mg, 0.03 mmol) and trifluoroacetic acid (TFA) (5 ml) in $CHCl_3$ (5 ml) was heated under reflux for 3 h. The mixture was then cooled and evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. (chloroform–acetone, 10:1), and recrystallized from chloroform–methanol to give 10-*ethyl*-7-*ethylamino*-6-*formyl*-3-*methyl*-5-*deazaflavin* (**9a**) (5 mg, 49%) as a yellow powder, m.p. 330 °C; *m/z* 326 (M^+); $\nu_{max.}$(Nujol) 1 690, 1 620, and 1 590 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.46 (1 H, d, *J* 10 Hz, 9-H), 7.84 (1 H, d, *J* 10 Hz, 8-H), 9.49 (1 H, s, 5-H), 9.63 (1 H, br, 7-NH), and 10.85 (1 H, s, 6-CHO) (Found: C, 62.25; H, 5.5; N, 17.0. $C_{17}H_{18}N_4O_3$ requires C, 62.55; H, 5.55; N, 17.15%).

A mixture of the epoxide (**8a**) (22mg, 0.05 mmol) and water (2 ml) in chloroform (30 ml) and acetone (30 ml) was heated under reflux for 10 h, then cooled and evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. (chloroform–acetone 10:1), and recrystallized from chloroform–methanol to give 1-*oxa*-3,4,7,8,10-*penta-azaindeno*-[5,6-h]*anthracene*-2,9,11(4H,7H,10H)-*trione* (**10a**) (3 mg, 16%) as a yellow powder, m.p. >330 °C, $\nu_{max.}$(Nujol) 1 760, 1 650, and 1 620 cm^{-1}; δ_H[200 MHz; CF_3CO_2D–$CDCl_3$ 1:1)] 8.70—8.79 (1 H, br, 6-H), 8.79—9.09 (1 H, br, 5-H), 9.32 (1 H, s, 13-H), and 10.48 (1 H, s, H-12) (Found: *m/z*, 391.128 18. $C_{20}H_{17}N_5O_4$ requires *M*, 391.128 04).

Autorecycling Oxidation of Cyclopentanol the Angular Doubled 5-Deazaflavins (**1a**—**c**).—Compounds (**1a**—**c**), Methylene Blue, Rose Bengal, 3-methyl-10-dodecyl-5-deazaflavin, or the linear doubled 5-deazaflavin [1] (0.002 mmol each) was stirred with cyclopentanol (3.63 ml, 40 mmol) at 60 °C for 25 h under irradiation with a sunlamp (Toshiba DR250/TL; *ca.* 60 000 lux) in oxygen. To the mixture, a saturated solution (200—300 ml) of 2,4-dinitrophenylhydrazine in 2M HCl was added. The precipitate was filtered off, and washed with 2M HCl and water to give the 2,4-dinitrophenylhydrazone of cyclopentanone (Table 2).

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