Synthesis of 1,3,7,9,11,12,14-Heptazapentacene-2,4,8,10-(14*H*,3*H*,9*H*,12*H*)-tetraones (Mixed Flavins) with Oxidizing Ability

Fumio Yoneda* and Masakazu Koga

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

Received August 18, 1987

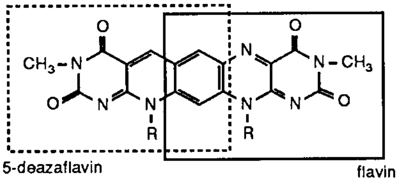
1,3,7,9,11,12,14-Heptazapentacene-2,4,8,10(14*H*,3*H*,9*H*,12*H*)-tetraones (mixed flavins) were synthesized by the cyclization of 1,5-dihydro-8-[*N*-alkyl-*N*-(5-nitrouracil-6-yl)]-amino-5-deazaflavins with the Vilsmeier reagent. The mixed flavins oxidized alcohol under neutral conditions in sunlight.

J. Heterocyclic Chem., **25**, 549 (1988).

It is known that 5-deazaflavins which are regarded as NAD$^+$ analogs in flavin clothing are able to oxidize alcohols [1] and amines [2] non-enzymatically and that they exhibit some autorecycling in the oxidation. However, the reoxidation of the 1,5-dihydro-5-deazaflavins formed initially by molecular oxygen was so slow that these NAD$^+$ analogs could not serve efficiently as a turnover oxidation catalyst. To overcome the shortcoming, Shinkai *et al.* [3] considered that flavins may mediate in the reoxidation step of 1,5-dihydro-5-deazaflavins and constructed an efficient auto-recycling system for the oxidation of benzylamine to benzaldehyde using 5-deazaflavin and FMN. By this system the yield of benzaldehyde reached 3500% as against 170% by 5-deazaflavin alone.

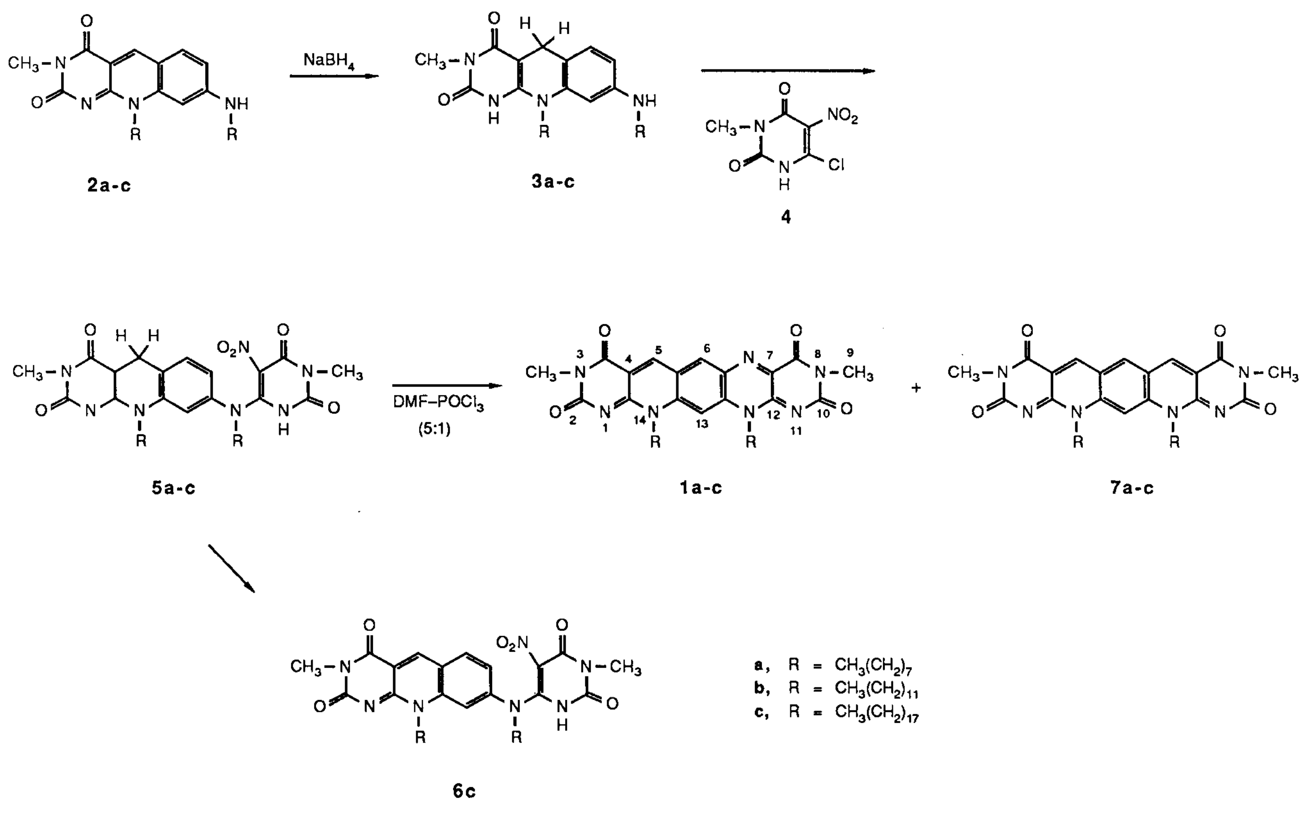
For the purpose of synthesizing the 5-deazaflavin derivatives with stronger oxidizing power, we designed "mixed flavins" which contain both 5-deazaflavin and flavin with a benzene ring in common. In the "mixed flavins", similar cooperation of 5-deazaflavin and flavin moieties to the

Scheme 1



1

Scheme 2



2a-c

3a-c

4

5a-c

1a-c

7a-c

6c

a, R = $CH_3(CH_2)_7$
b, R = $CH_3(CH_2)_{11}$
c, R = $CH_3(CH_2)_{17}$

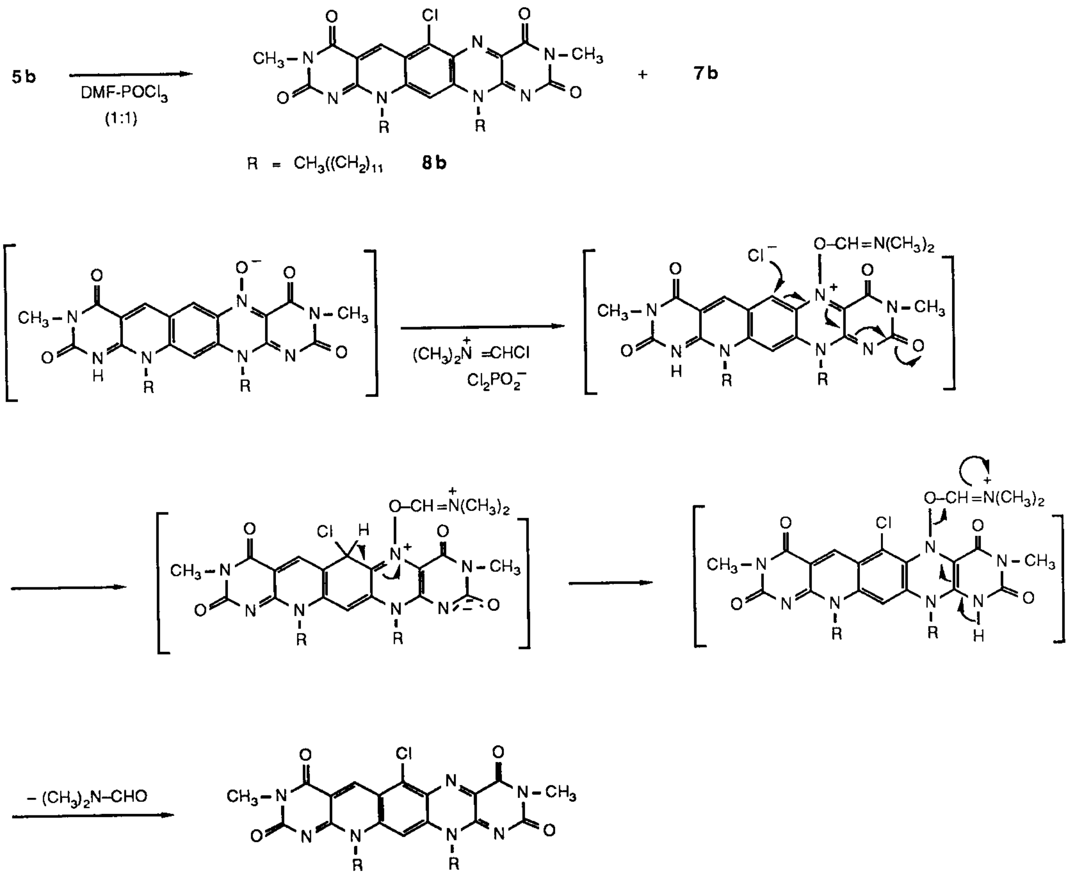
above system may be expected to take place intramolecularly (or intermolecularly). First, we planned to prepare 1,3,7,9,11,12,14-heptazapentacene-2,4,8,10(14*H*,3*H*,9*H*,12*H*)tetraones (**1**) as "mixed flavins". In compounds **1**, the intramolecular (or intermolecular) hydrogen transfer might occur from the initially formed 1,5-dihydro derivatives to 7,11-dihydro derivatives in the oxidation process (Scheme 4). Furthermore, the long conjugation of compounds **1** would increase the redox potentials compared with either monomeric 5-deazaflavins or flavins, considerable oxidizing ability would be expected for compounds **1**. In the present paper we describe the full experimental details of the synthesis of the compounds **1** and their properties [4].

The requisite starting materials, 1,5-dihydro-8-alkylamino-3-methyl-5-deazaflavins **3**, were prepared by the sodium borohydride reduction of 8-alkylamino-3-methyl-5-deazaflavins **2** according to the known procedure [5]. As compounds **3** were extremely unstable in air, 6-chloro-3-methyl-5-nitrouracil (**4**) [6] was added to the chloroform solution of compounds **3**, and the mixture was refluxed in argon atmosphere to give the corresponding 1,5-dihydro-8-[*N*-alkyl-*N*-(3-methyl-5-nitrouracil-6-yl)]-amino-5-deazaflavins **5**. Compounds **5** are also unstable in air and so we used them for the next step without purification.

Treatment of compounds **5** with Vilsmeier reagent (DMF:phosphoryl chloride = 5:1 v/v) in argon atmosphere gave compounds **1** [7] (Table 1), along with the corresponding double-headed 5-deazaflavins **7** [5] in 2-3% yield, and recovered **2** in *ca.* 30% yield. On treatment of **5** with the phosphoryl chloride-rich Vilsmeier reagent (DMF:phosphoryl chloride = 1:1 v/v) gave interestingly 6-chloro-mixed flavin **8**. The formation of **8** would be ascribed to the chlorination *via* reaction of the intermediary flavin *N*-oxide derivative with the Vilsmeier reagent. A similar chlorination was reported in the reaction of flavin *N*-oxide with the Vilsmeier reagent [7]. A plausible mechanism for the chlorination is described in Scheme 3.

Compounds **1** showed characteristic C(5)-proton signal at low field in the ^{1}H nmr spectra (Table 1). The uv and visible spectra of compounds **1** and **8** showed similar absorption patterns with a slight bathochromic shift to that of the corresponding double-headed 5-deazaflavins **7** as seen in Figure 1. This implies that compounds **1** and **8** have the same conjugated system as that of compounds **7**.

Scheme 3



Scheme 4

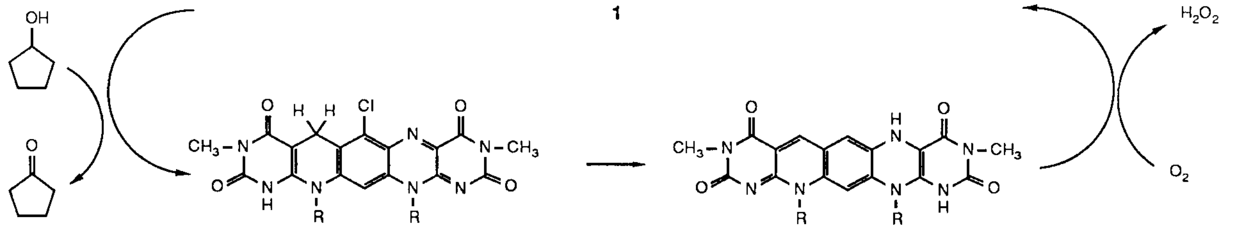


Table 1

Synthesis of 1,3,7,9,11,12,14-Heptazapentacene-2,4,8,10(14*H*,3*H*,9*H*,12*H*)-tetraones (Mixed Flavins) **1a-c**

Compound	R	Yield (%) (Based on compound **2**	Mp (°C)	Formula	Analysis (%) Calcd./(Found)			δ_H(Deuteriochloroform)		
								H-13	H-6	H-5
1a	$CH_3(CH_2)_7$	7	>330	$C_{33}H_{43}N_7O_4 \cdot 2H_2O$	62.14 (62.44)	7.43 (7.09)	15.38 (15.27)	8.20	9.28	9.90
1b	$CH_3(CH_2)_{11}$	12	>330	$C_{41}H_{59}N_7O_4 \cdot 2H_2O$	65.66 (65.27)	8.47 (8.23)	13.07 (13.45)	8.21	9.30	9.92
1c	$CH_3(CH_2)_{17}$	12	>330	$C_{53}H_{83}N_7O_4 \cdot 2H_2O$	69.32 (69.74)	9.55 (9.24)	10.68 (10.74)	8.20	9.28	9.90

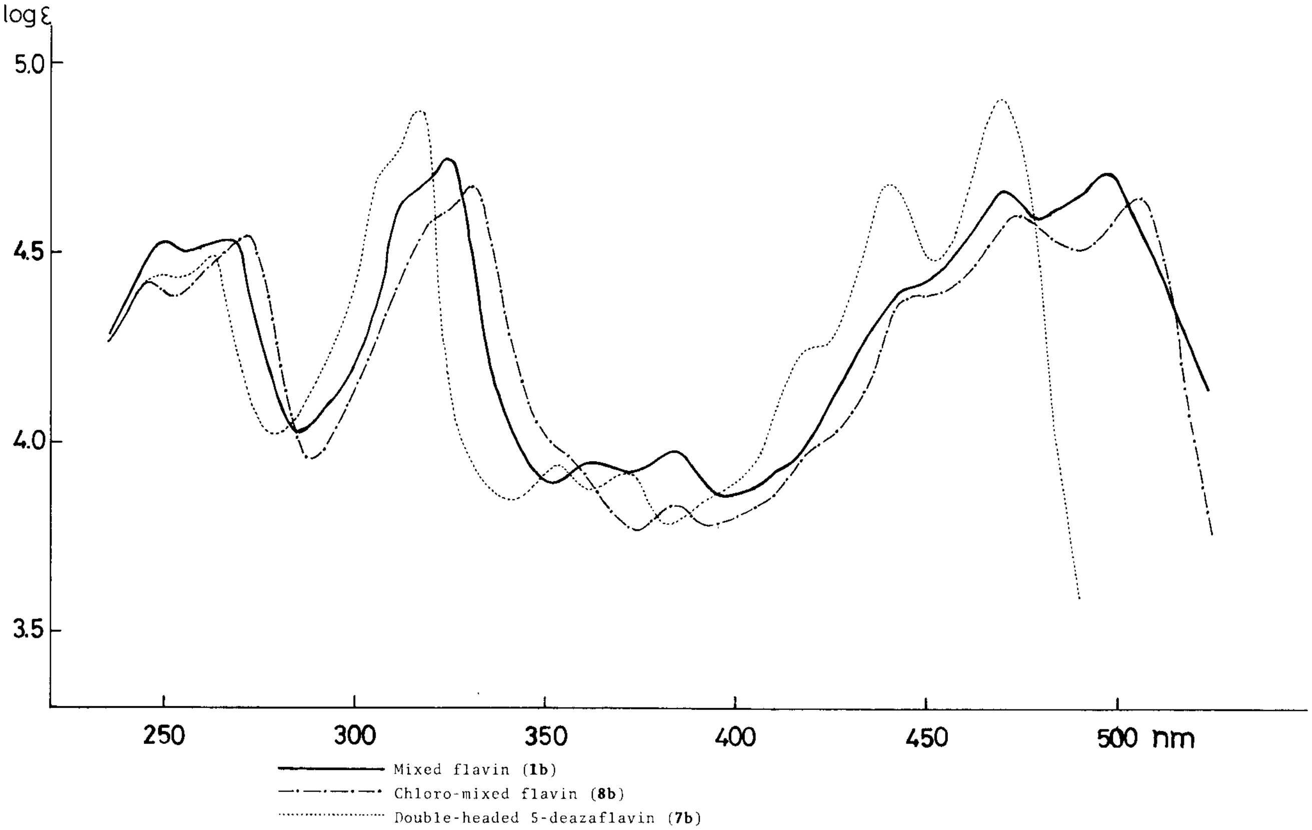


Figure 1. Uv and Visible Spectra in $CHCl_3$-C_2H_5OH (1:1)

The redox potentials (room temperature, DMF-tetrabutylammonium perchlorate) for the first one-electron transfer of compounds **1** were *ca.* -450 mV *vs.* SCE. These potentials are about 700 mV more positive than those of the monomeric 5-deazaflavins (for example, -1150 mV for 10-dodecyl-3-methyl-5-deazaflavin), and furthermore are about 150 mV positive than those of the flavins (for example, -700 mV for 10-ethyl-3-methylflavin).

As expected, compounds **1** thus obtained oxidized cyclopentanol to give cyclopentanone under neutral conditions at 80° (oil bath) in sunlight and a considerable high autorecycling in the oxidation was observed (Table 2).

Table 2

Autorecycling Oxidation of Cyclopentanol (1.5 ml) by Compounds **1** (0.5 mg) at 80° (oil bath) for 25 Hours in Sunlight (Kyoto, February, Cloudless Sky)

Compound	Yield (%) of Cyclopentanone [a]	
1a	83600 [b]	2.5 [c]
1b	119300	5.5
1c	28500	1.1

[a] Isolated as the 2,4-dinitrophenylhydrazone. [b] Based on compounds **1**. [c] Based on the starting cyclopentanol.

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 ^{1}H nmr spectra on a JEOL FX 200 spectrometer. Mass spectra were taken on a JEOL JMS OISG-2 instrument by direct insertion at 70 eV. The uv and visible specta 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 60 GF 254 under *ca.* 1.5 kg/cm^2 pressure [8]. 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 1,3,7,9,11,12,14-Heptazapentacene-2,4,8,10(14*H*,3*H*,9*H*,12*H*)-tetraones (Mixed Flavins) **1a-c**. General Procedure.

A mixture of 3-methyl-8-alkylamino-10-alkyl-5-deazaflavins **2a-c** (0.85 mmole) and sodium borohydride (650 mg, 17.2 mmoles) in methanol (50 ml) was heated under reflux for 1 hour. The reaction mixture was evaporated to dryness under reduced pressure. Ice water was added to the residue, neutralized with formic acid and extracted with chloroform. Immediately, to the chloroform extracts (*ca.* 150 ml) was added 3-methyl-6-chloro-5-nitrouracil (**4**) (2.00 mmoles), and the mixture was refluxed for 6 hours under an argon atmosphere. The reaction mixture was evaporated to dryness under reduced pressure and methanol and ether were added to the residue. The precipitate was filtered off and washed with ether to give crude 1,5-dihydro-3-methyl-10-alkyl-8-[*N*-alkyl-*N*-(3-methyl-5-nitrouracil-6-yl)]amino-5-deazaflavins **6a-c**. A mixture of compounds **6a-c** and Vilsmeier reagent (DMF:phosphoryl chloride = 5:1 v/v, 1.5 ml) was heated at 120° for 3-6 hours under an argon atmosphere. The reaction mixture was cooled and diluted with methanol. The precipitate was filtered off and washed with methanol. The precipitate in DMF (30 ml) was heated under reflux for 30 minutes to 1 hour. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was purified by chromatography technique. The first fraction eluted with chloroform-acetone (9:1) was recrystallized from chloroform-methanol to give the recovered compounds **2a-c** as yellow powders. The second fraction eluted with chloroform-acetone (9:1) was recrystallized from chloroform-methanol to give the corresponding double-headed 5-deazaflavins **7a-c** as yellow powders. The third fraction eluted with chloroform-acetone (9:1) and was recrystallized from chloroform-methanol to give the corresponding mixed flavins **1a-c** as orange powders (Table 1).

6-Chloro-mixed Flavin **8b**.

A mixture of 3-methyl-8-dodecylamino-10-dodecyl-5-deazaflavin (**2b**) (0.85 mmole) and sodium borohydride (650 mg, 17.2 mmoles) in methanol (50 ml) was heated under reflux for 1 hour. The reaction mixture was evaporated to dryness under reduced pressure. The residue was diluted with ice water, neutralized with formic acid and extracted with chloroform. Immediately, to the chloroform extracts (*ca.* 150 ml) was added 3-methyl-6-chloro-5-nitrouracil (**4**) (2.00 mmoles), and the mixture was refluxed for 6 hours under an argon atmosphere. The reaction mixture was cooled and evaporated to dryness under reduced pressure. The residue was diluted with methanol and ether. The precipitate was filtered off and washed with ether to give crude 1,5-dihydro-3-methyl-10-dodecyl-8-[*N*-dodecyl-*N*-(3-methyl-5-nitrouracil-6-yl)]amino-5-deazaflavin (**6b**). A mixture of compound **6b** and Vilsmeier reagent (DMF:phosphoryl chloride = 1:1 v/v, 1.5 ml) was heated at 120° for 6 hours under an argon atmosphere. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was chromatographed. The fraction eluted with chloroform-acetone (9:1) was purified by preparative tlc and recrystallized from chloroform-methanol to give 6-chloro-mixed flavin **6b** (96 mg, 15% yield based on **2b**) as an orange powder, mp 246°; ir (Nujol): 1720, 1705, 1665, 1645 cm^{-1}; pmr (deuteriotrifluoroacetic acid-deuteriochloroform 1:1): 200 MHz δ 3.64 (s, 3H, 3 CH_3), 3.67 (s, 3H, 9 CH_3), 4.68-5.13 (m, 4H, 12 CH_2 and 14 CH_2), 8.04 (s, 1H, H-13), 10.12 (s, 1H, H-5); ms: m/z 747.42659 (M^+).

Anal. Calcd. for $C_{41}H_{58}ClN_7O_4$: C, 65.80; H, 7.81; N, 13.10. Found: C, 65.59; H, 7.80; N, 13.49.

As a by-product, 3,9-dimethyl-12,14-didodecyl-double-headed 5-deazaflavin (**7b**) (21 mg, 3% yield based on **2b**) was obtained.

Structure Identification of 1,5-Dihydro-3-methyl-10-alkyl-8-[*N*-alkyl-*N*-(3-methyl-5-nitrouracil-6-yl)]amino-5-deazaflavins **5**.

As compounds **5** were unstable in air, their structures were identified as follows. For example, a solution of the crude compound **5c** (480 mg) in chloroform (200 ml) was heated under reflux for 2 hours. The reaction mixture was evaporated to dryness under reduced pressure and chromatographed. The fraction eluted with chloroform-acetone-methanol (10:10:1) was recrystallized from chloroform-ether to give 3-methyl-10-stearyl-8-[*N*-stearyl-*N*-(3-methyl-5-nitrouracil-6-yl)]amino-5-deazaflavin (**6c**) as a yellow powder, mp 169°; ir (Nujol): 1695, 1670, 1605 cm^{-1}; pmr (DMSO-d_6): 200 MHz δ 7.03 (1H, s, H-9), 7.08 (1H, d, J = 9 Hz, H-7), 7.93 (1H, d, J = 9 Hz, H-6), 8.82 (1H, s, H-5).

Anal. Calcd. for $C_{53}H_{85}N_7O_6 \cdot 2H_2O$: C, 66.84; H, 9.42; N, 10.30. Found: C, 66.67; H, 9.15; N, 9.95.

Acknowledgement.

Financial support for this work by a Grant-in-Aid for Scientific Research from Ministry of Education, Science and Culture, Japan, is gratefully acknowledged.

REFERENCES AND NOTES

[1] F. Yoneda, K. Mori, S. Matsuo, Y. Kadokawa, and Y. Sakuma, *J. Chem. Soc., Perkin Trans. 1*, 1836 (1981).

[2] F. Yoneda, Y. Sakuma, Y. Kadokawa, and A. Koshiro, *Chem. Letters*, 1467 (1979).

[3] S. Shinkai, H. Kuroda, O. Manabe, and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 391 (1984).

[4] F. Yoneda, M. Koga, and T. Ibuka, *Tetrahedron Letters*, **25**, 5345

(1984), for the preliminary report.

[5a] F. Yoneda, K. Kuroda, K. Koga, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 872 (1984); [b] F. Yoneda and K. Koga, *J. Chem. Soc., Perkin Trans. 1*, in press (1987).

[6] G. D. Daves, R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, **84**, 1724 (1962).

[7] There is a precedent for this type of cyclization leading to the flavin system: F. Yoneda, K. Shinozuka, K. Hiromatsu, R. Matsushita, Y. Sakuma, and M. Hamana, *Chem. Pharm. Bull.*, **28**, 3576 (1980).

[8] W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).