1,3,9,11,12,14-Hexa-azapentacene-2,4,8,10(3*H*,9*H*,12*H*,14*H*)-tetraones (Doubled 5-Deazaflavins) with Potential for Oxido Reduction

Fumio Yoneda * **and Masakazu Koga**
Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606, Japan

Condensation of 8-(substituted-amino)1,5-dihydro-5-deazaflavins (**3**) with 6-chloro-5-formyluracils (**4**) gave the 1,5-dihydro doubled 5-deazaflavins (**5**) and 8-(5-formyluracil-6-yl)amino-1,5-dihydro-5-deazaflavins (**6**). The dehydrogenation of compounds (**5**) with diethyl azodicarboxylate or the dehydrative cyclization of compounds (**6**) with Vilsmeier reagent gave the corresponding 1,3,9,11,12,14-hexa-azapentacene-2,4,8,10(3*H*,9*H*,12*H*,14*H*)-tetraones (doubled 5-deazaflavins) (**8**). The latter exhibited strong autorecycling oxidation toward cyclopentanol giving, in sunlight under an oxygen atmosphere, cyclopentanone.

Dihydropyrimidino[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (5-deazaflavins or 5-deazaisoalloxazines) which are regarded as 'flavin-shaped nicotinamide analogues'[1] have acted as organic catalysts in numerous redox reactions in both enzymatic[2] and nonenzymatic model systems.[3] In order to synthesize organic catalysts with stronger redox activities, we designed 'doubled 5-deazaflavins', in which two 5-deazaflavins have a benzene ring in common; this ring system, with two redox centres and extended conjugation, would have increased redox potential compared with the monomeric 5-deazaflavin and heightened oxidizing ability. Here we describe the syntheses of 1,3,9,11,12,14-hexa-azapentacene-2,4,8,10(3*H*,9*H*,12*H*,14*H*)-tetraones (doubled 5-deazaflavins) (**8**) and their use as organic catalysts in the oxidation of cyclopentanol.[4]

The requisite starting materials, 8-alkylamino- and 8-arylamino-5-deazaflavins (**2a**—**h**) were prepared by condensation of the 8-chloro-3-methyl-5-deazaflavins (**1a**—**e**)[5] with an excess of alkylamines and with *p*-toluidine in hexamethylphosphoramide (HMPA) or without solvent according to the literature procedure[6] (Table 1). Compounds (**2a**—**h**) were treated with sodium borohydride to give the corresponding 1,5-dihydro-5-deazaflavins (**3**) which, without purification (being unstable in air), were condensed with 6-chloro-5-formyluracils (**4a,b**) to give the 1,5-dihydro-doubled 5-deazaflavins (**5**). The structures of compounds (**5**)† were established on the basis of satisfactory n.m.r. spectral data, although they were not purified because of their instability during recrystallization.

The above 1,5-dihydro compounds (**5**) were dehydrogenated with an excess of diethyl azodicarboxylate[7] under the conditions indicated in the Experimental section to give the corresponding doubled 5-deazaflavins (**8**). In some cases, the filtrates included considerable amounts of 8-(5-formyluracil-6-yl)amino-1,5-dihydro-5-deazaflavins (**6**) which were oxidized by air to (5-formyluracil-6-yl)amino-5-deazaflavins (**7**) during work-up. The filtrates, which included compounds (**6**) and (**7**), were treated with Vilsmeier reagent ($DMF–POCl_3$) to give the corresponding doubled 5-deazaflavins (**8**).

Compounds (**8a**—**n**) thus obtained showed characteristic 5-H and 7-H signals at lowfield in their ^1H n.m.r. spectra (Table 2). The redox potentials (room temperature, $DMF–LiClO_4$) for the first one-electron transfer of compounds (**8a**—**n**) have been determined to be 500—570 mV *vs.* s.c.e. These potentials are 620—550 mV more positive than those of the monomeric 5-deazaflavins (for example, −1 120 mV for the 10-dodecyl-3-methyl-5-deazaflavin; see Table 3).

As expected, the doubled 5-deazaflavins (**8a**—**n**) were more effective for oxidizing alcohols than the monomeric 5-deazaflavin. For example, compounds (**8**) oxidized cyclopentanol in the dark, in the absence of a base such as potassium carbonate, at 90 °C, to give cyclopentanone. This oxidation was greatly accelerated in sunlight; cyclopentanol was oxidized even lower temperature (10—15 °C) and considerable autorecycling was observed as already reported. Oxidations were also carried out using a sunlamp at 60 °C under an oxygen atmosphere. As reference compounds, photosensitizers such as Methylene Blue and Rose Bengal, and also monomeric 5-deazaflavin, 10-dodecyl-3-methyl-5-deazaflavin, were used for comparison with compounds (**8**). Since the photosensitizer failed completely to catalyze the above alcohol oxidation under the same conditions, compounds (**8**) are shown not to react *via* singlet oxygen. The 5-deazaflavin exhibited some oxidizing ability, although it was less effective than compounds (**8**).

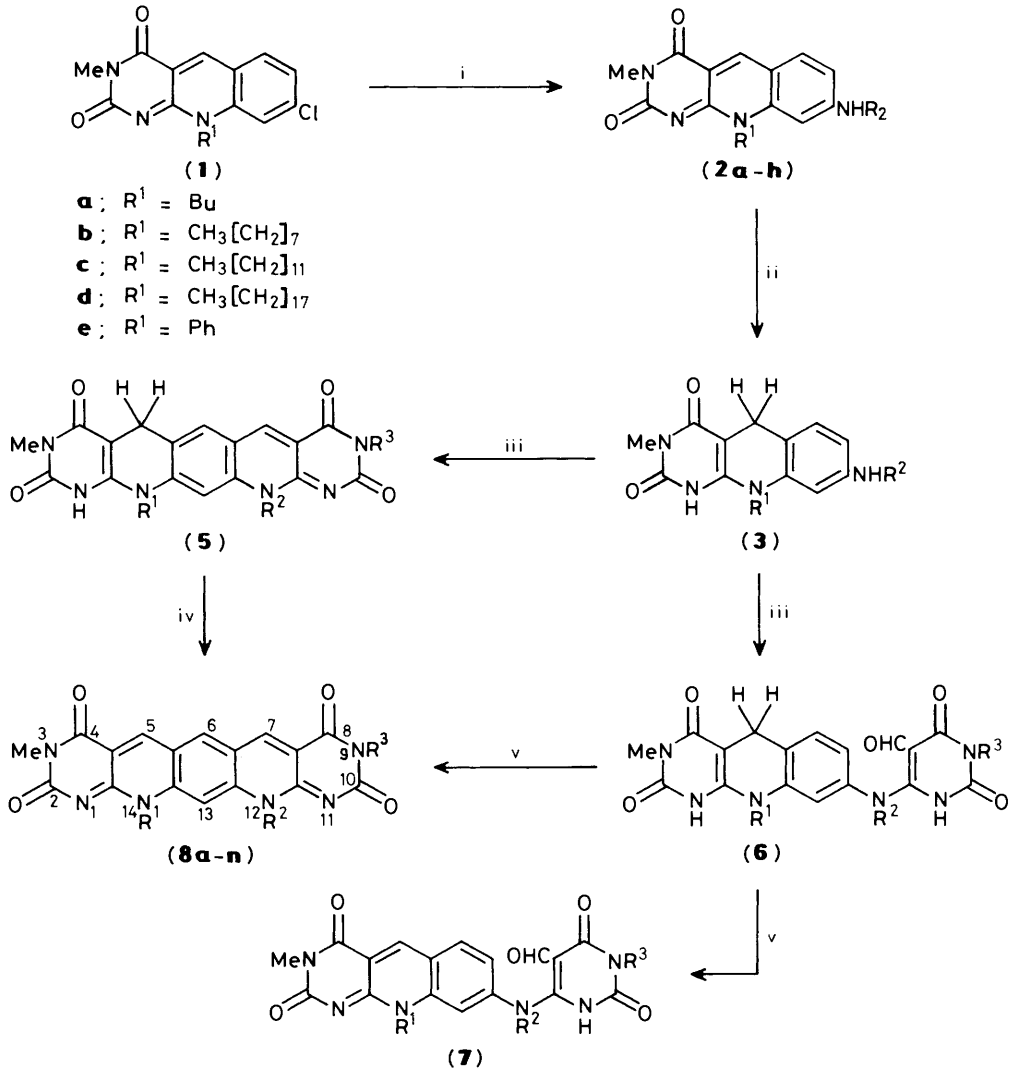
From the above results, compounds (**8**) were shown to dehydrogenate cyclopentanol even under neutral conditions to yield cyclopentanone, while compounds (**8**) were hydrogenated to the corresponding 1,5-dihydro-doubled 5-deazaflavins (**5**) and/or 7,11-dihydro-isomers. Under those conditions the above half-reduced doubled 5-deazaflavins (**5**) were oxidized by oxygen to the original doubled 5-deazaflavins (**8**); they acted as the efficient turnover catalysts upon irradiation with a sunlamp under nonenzymatic conditions.

Experimental

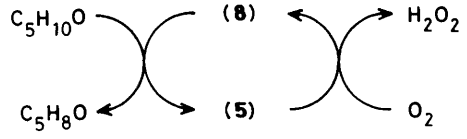
All m.p.s were determined on a Yanagimoto hot-stage apparatus, and are uncorrected. I.r. spectra were obtained on a Shimadzu IR-400 spectrometer and ^1H n.m.r. spectra on a JEOL FX 200 spectrometer. Mass spectra were taken on a JEOL JMS OISG-2 instrument by direct insertion at 70 eV. U.v. and visible spectra were obtained on a Hitachi model 200-20 spectrophotometer. Redox potentials were taken on a MCI model As-O2 cyclic voltammetry analyzer. Column chromatography was carried out with Silica gel 60 (E. M. Merck 230 mesh) and Wakogel-200 and Wakogel-300.

8-Alkylamino- and 8-Arylamino-3-methylpyrimidino[4,5-b]*-quinoline-2,4-(3H,10H)diones* (*5-Deazaflavins*) (**2a**—**h**): *General Procedure.*—A mixture of a 8-chloro-3-methyl-3*H*,10*H*-pyrimidino[4,5-*b*]quinolinediones (**1a**—**e**) (7.7 mmol) and an alkylamine (3—7 equiv.) or *p*-toluidine (3 equiv.) in HMPA (8

† In the earlier communication,[4] these compounds were reported as the fully reduced doubled 5-deazaflavins, whose structures have proved to be wrong.



Scheme 1. *Reagents:* i, R^2NH_2; ii, $NaBH_4$; iii, 6-chloro-5-formyl-3-methyluracil (**4a**) or 6-chloro-5-formyl-3-phenyluracil (**4b**); iv, diethyl azodicarboxylate (DAD); v, DMF–$POCl_3$



Scheme 2. Autorecycling oxidation by doubled 5-deazaflavins (**8**)

ml) or without solvent was heated under the conditions indicated in Table 1. The reaction mixture was cooled and diluted with ether. The precipitate was filtered off, washed with ether or methanol, and either recrystallized from chloroform–methanol or column chromatographed (chloroform–acetone, 9:1) to give the title compounds (**2a**—**h**) (Table 1).

1,3,9,11,12,14-*Hexa-azapentacene*-2,4,8,10(3H,9H,12H,14H)-*tetraones* (*Doubled 5-Deazaflavins*) (**8a**—**n**): *General Procedure.*—A mixture of compounds (**2**) (0.25 mmol) and sodium borohydride (200 mg, 5.28 mmol) in methanol (15 ml) was heated under reflux for 15 min. The reaction mixture was evaporated to dryness under reduced pressure and cooled. Ice–water was added to the residue, which was then neutralized with acetic acid and extracted with chloroform. Immediately, to the chloroform extracts (*ca.* 100 ml) was added 6-chloro-5-formyluracil (**4a,b**) (0.52 mmol), and the mixture was refluxed for 10 h under an argon atmosphere. The reaction mixture was cooled and evaporated to dryness under reduced pressure. To the residue, diethyl azodicarboxylate (DAD) (0.25 ml, 1.6 mmol) was added and the mixture was heated at 100—120 °C for 3—10 h. The reaction mixture was cooled and diluted with methanol or ether. The precipitate was filtered off, washed with methanol, and recrystallized from chloroform–methanol or purified by preparative t.l.c. (chloroform–acetone, 10:2) to give the title compounds (**8**) (Table 2).

Compounds (**8g,h,i**) were also obtained directly by refluxing the chloroform extracts for several hours without adding DAD.

Dehydrative Cyclization of 8-(5-*Formyluracil*-6-*yl*)*amino*-1,5-*dihydro*-(**6**) *and* 8-(5-*Formyluracil*-6-*yl*)*amino-pyrimidino*[4,5-b]*quinoline*-2,4(3H,10H)-*diones* (**7**) *with Vilsmeier Reagent: General Procedure.*—The condensation reaction mixture of 8-(substituted amino)-1,5-dihydropyrimidino[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (**3**) with 6-chloro-5-formyluracil (**4**) in the above general procedure was evaporated to dryness under reduced pressure. Ethanol was added to the residue to precipitate the crude product which was filtered off, washed

Table 1. Synthesis of 8-alkylamino- and 8-*p*-tolylamino-10-alkyl(phenyl)-3-methyl-5-deazaflavins (**2a**—**h**)

No.	R^1	R^2	Reaction solvent	Temp. (°C)	Time (h)	Yield (%)	M.p. (°C)	Appearance[a] ($CHCl_3$–MeOH)	Formula	Found (%) (Required) C	H	N	δ(5-H) (CF_3CO_2H–$CDCl_3$ = 1:1)
(**2a**)	Bu	Bu	HMPA	100	10	56	297	YP	$C_{20}H_{26}N_4O_2$	67.9 (67.75	7.3 7.4	16.0 15.8)	9.02
(**2b**)	$CH_3[CH_2]_7$	Bu	HMPA	100	10	55	290	YP	$C_{24}H_{34}N_4O_2$	70.1 (70.2	8.2 8.35	13.9 13.65)	9.03
(**2c**)	$CH_3[CH_2]_7$	$CH_3[CH_2]_7$	HMPA	100	5	55	276	YP	$C_{28}H_{42}N_4O_2$	71.8 (72.1	9.05 9.1	12.2 12.0)	9.03
(**2d**)	$CH_3[CH_2]_{11}$	$CH_3[CH_2]_{11}$	HMPA	100	2	50	257	YP	$C_{36}H_{58}N_4O_2$	74.8 (74.7	10.2 10.1	9.6 9.7)	9.03
(**2e**)	$CH_3[CH_2]_{17}$	$CH_3[CH_2]_{17}$	HMPA	100	4	49	234	YP	$C_{48}H_{82}N_4O_2$	76.9 (77.15	11.3 11.05	7.6 7.5)	9.03
(**2f**)	Ph	Bu	HMPA	150	4	25	326	YN	$C_{22}H_{22}N_4O_2$	70.65 (70.55	5.7 5.9	15.0 14.95)	9.11
(**2g**)	Ph	$CH_3[CH_2]_7$	Neat	200	1	70	295	YN	$C_{26}H_{30}N_4O_2$	72.25 (72.55	7.0 7.0	13.05 13.0)	9.12
(**2h**)	Ph	*p*-MeC_6H_4	Neat	250	1	70	300	ON	$C_{25}H_{20}N_4O_2$	73.25 (73.5	4.95 4.95	13.45 13.7)	9.18

[a] YP = yellow powder, YN = yellow needles, ON = orange needles.

Table 2. Synthesis of doubled 5-deazaflavins (**8a**—**n**)

No.	R^1	R^2	R^3	Yield (%)	M.p.[a] (°C)	Formula	Found (%) (Required) C	H	N	δ(5-H & 7-H)
(**8a**)	Bu	Bu	Me	28	300	$C_{26}H_{28}N_6O_4$ $+H_2O$	61.85 (61.65	5.65 5.95	16.7 16.6)	9.95
(**8b**)	Bu	Bu	Ph	28	>330	$C_{31}H_{30}N_6O_4$ $+H_2O$	65.1 (65.5	5.3 5.65	14.85 14.8)	9.94 9.90
(**8c**)	$CH_3[CH_2]_7$	Bu	Me	10	>330	$C_{30}H_{36}N_6O_4$	65.75 (66.15	6.8 6.65	14.9 15.45)	9.95
(**8d**)	$CH_3[CH_2]_7$	Bu	Ph	7	272	$C_{35}H_{38}N_6O_4$	69.4 (69.3	6.2 6.3	13.55 13.85)	9.94 9.89
(**8e**)	$CH_3[CH_2]_7$	$CH_3[CH_2]_7$	Me	11	>330	$C_{34}H_{44}N_6O_4$ $+H_2O$	65.9 (66.0	7.15 7.5	13.3 13.6)	9.95
(**8f**)	$CH_3[CH_2]_7$	$CH_3[CH_2]_7$	Ph	9	325	$C_{39}H_{46}N_6O_4$	70.4 (70.65	6.95 7.0	12.5 12.7)	9.94 9.90
(**8g**)	$CH_3[CH_2]_{11}$	$CH_3[CH_2]_{11}$	Me	28	>330	$C_{42}H_{60}N_6O_4$ $+H_2O$	69.15 (69.0	8.5 8.55	11.35 11.5)	9.95
(**8h**)	$CH_3[CH_2]_{17}$	$CH_3[CH_2]_{17}$	Me	27	>330	$C_{54}H_{84}N_6O_4$	73.35 (73.6	9.65 9.6	9.45 9.55)	9.96
(**8i**)	Ph	Bu	Me	16	>330	$C_{28}H_{24}N_6O_4$	66.0 (66.15	4.6 4.75	16.15 16.55)	10.10 9.95
(**8j**)	Ph	Bu	Ph	25	>330	$C_{33}H_{26}N_6O_4$	69.1 (69.45	4.6 4.6	14.2 14.75)	10.10 9.91
(**8k**)	Ph	$CH_3[CH_2]_7$	Me	31	>330	$C_{32}H_{32}N_6O_4$	67.95 (68.05	5.5 5.7	14.8 14.9)	10.10 9.95
(**8l**)	Ph	$CH_3[CH_2]_7$	Ph	21	327	$C_{37}H_{34}N_6O_4$	70.5 (70.9	5.3 5.45	13.1 13.4)	10.09 9.91
(**8m**)	Ph	*p*-MeC_6H_4	Me	11	>330	$C_{31}H_{22}N_6O_4$ $+1/2H_2O$	67.7 (67.5	3.9 4.2	14.75 15.25)	10.08
(**8n**)	Ph	*p*-MeC_6H_4	Ph	9	>330	$C_{36}H_{24}N_6O_4$ $+H_2O$	69.75 (69.45	3.9 4.2	13.3 13.5)	10.11 10.0

[a] All compounds were yellow powders. [b] In CF_3CO_2H–$CDCl_3$.

with boiling ethanol, and recrystallized from acetic acid to give compound (**5**) as a dark yellow powder, sometimes contaminated with compound (**8**). The filtrate which included compound (**6**) was evaporated to dryness under reduced pressure and a small amount of ethanol was added to the residue to give a mixture of compounds (**6**) and (**7**). This was added to Vilsmeier reagent (DMF–$POCl_3$, 5:1) (1 ml) and the mixture was heated at 100 °C for 5 h; it was then cooled and diluted with methanol. The precipitate was filtered off and recrystallized from chloroform–methanol to give compound (**8**). By this procedure, compounds (**8g**), (**8h**), (**8i**), (**8k**), (**8m**), and (**8n**) were obtained in 28, 27, 16, 31, 6, and 9% yields, respectively.

12,14-*Didodecyl*-3,9-*dimethyl*-1,5-*dihydro*-1,3,9,11,12,14-*hexa-azapentacene*-2,4,8,10(3H,9H,12H,14H)-*tetraone* (**5g**).—This compound was isolated as described in the above procedure. During purification by recrystallization it was dehydrogenated to the compound (**8g**). Treatment of compound (**5g**) with DAD also gave immediately compound (**8g**) as a dark yellow powder, m.p. >330 °C; $\nu_{max.}$(Nujol) 1 700, 1 655,

Table 3. Autorecycling oxidation of cyclopentanol by doubled 5-deazaflavins at 60 °C for 25 h with Sunlamp (Toshiba DR 250/TL, *ca.* 60 000 lux) and their redox potentials

Compound	Yield (%)[a] of cyclopentanone A[b]	Yield (%)[a] of cyclopentanone B[c]	Redox potential[d] (mV)
(8a)	41 200	2.03	−530
(8b)	47 300	2.47	−560
(8c)	63 900	3.21	−550
(8d)	42 000	2.14	−560
(8e)	55 700	2.88	−540
(8f)	38 100	1.91	−570
(8g)	48 000	2.20	−550
(8h)	29 000	1.53	−550
(8i)	31 700	1.58	−550
(8j)	40 600	1.96	−520
(8k)	35 700	1.71	−500
(8l)	24 600	1.25	−520
(8m)	36 800	1.79	−500
(8n)	37 900	1.89	−510
Methylene Blue	0	0	
Rose Bengal	0	0	
3-Methyl-10-dodecyl-5-deazaflavin	16 200	0.82	−1 120

[a] Isolated as the 2,4-dinitrophenylhydrazone. [b] Based on the catalyst. [c] Based on the starting cyclopentanol. [d] Room temperature, dimethylformamide–$LiClO_4$, *vs.* s.c.e.

and 1 625 cm^{-1}; δ_H[200 MHz; CF_3CO_2D–$CDCl_3$(1:1)] 4.19 (2 H, s, 5-H_2), 7.41 (1 H, s, 13-H), 8.16 (1 H, s, 6-H), and 9.47 (1 H, s, 7-H) (Found: C, 74.7; H, 10.2; N, 9.7. $C_{36}H_{60}N_4O_2$ requires C, 74.5; H, 10.3; N, 9.65%).

3,9-*Dimethyl*-12,14-*dioctadecyl*-1,5-*dihydro*-1,3,9,11,12,14-*hexa-azapentacene*-2,4,8,10(3H,9H,12H,14H)-*tetraone* (**5h**).—This compound was also isolated as described in the above procedure as a dark yellow powder, m.p. >330 °C; $\nu_{max.}$(Nujol) 1 705, 1 660, and 1 605 cm^{-1}; δ_H[200 MHz; CF_3CO_2D–$CDCl_3$ (1:1)] 4.19 (2 H, s, 5-H_2), 7.42 (1 H, s, 13-H), 8.17 (1 H, s, 6-H), and 9.48 (1 H, s, 7-H) (Found: C, 76.8; H, 11.25; N, 7.4. $C_{48}H_{83}N_4O_3$ requires C, 77.0; H, 11.2; N, 7.5%).

3-*Methyl*-8-[*octyl*(5-*formyl*-3-*methyluracil*-6-*yl*)*amino*]-10-*phenylpyrimidino*[4,5-b]*quinoline*-2,4(3H, 10H)-*dione* (**7k**).—This compound was obtained by preparative t.l.c. (chloroform–acetone 5:1) of the reaction mixture in the second general procedure for the preparation of pyrimidino[4,5-*b*]quinoline-2,4-diones. Recrystallization from acetone–methanol gave the product (**7k**) as a yellow powder, m.p. 312 °C; $\nu_{max.}$(Nujol) 1 680, 1 630, and 1 595 cm^{-1}; δ_H[200 MHz; CF_3CO_2D–$CDCl_3$(1:1)] 6.87 (1 H, s, 9-H), 7.44—8.37 (7 H, m, 6-H, 7-H, and ArH), 9.46 (1 H, s, 5-H), and 9.67 (1 H, s, 5′-CHO) (Found: *m/z* 582.2596. $C_{32}H_{34}N_6O_5$ requires *M*, 582.2591).

The treatment of compound (**7k**) with Vilsmeier reagent (DMF–$POCl_3$ = 5:1) at 100 °C for 5 h gave compound (**8k**).

Autorecycling Oxidation of Cyclopentanol by the Hexa-azapentacenetetraones (**8a**—**n**).—A mixture of compounds (**8a**—**n**) (0.002 mmol) and cyclopentanol (3.83 ml, 40 mmol) was stirred for 25 h at 60 °C whilst being irradiated with a sunlamp (Toshiba, DR 250/TL ; 2 cm distance, *ca.* 60 000 lux) in an oxygen atmosphere. The reaction mixture was cooled and diluted with a saturated solution (200—300 ml) of 2,4-dinitrophenylhydrazine in 2M HCl. The precipitate was filtered off and washed with 2M HCl solution and water to give cyclopentanone 2,4-dinitrophenylhydrazone (Table 3).

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