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Studies on the Syntheses of N-Heterocyclic Compounds. XXIII.[1] The Photochemical Reaction of Polyazanaphthalene Derivatives

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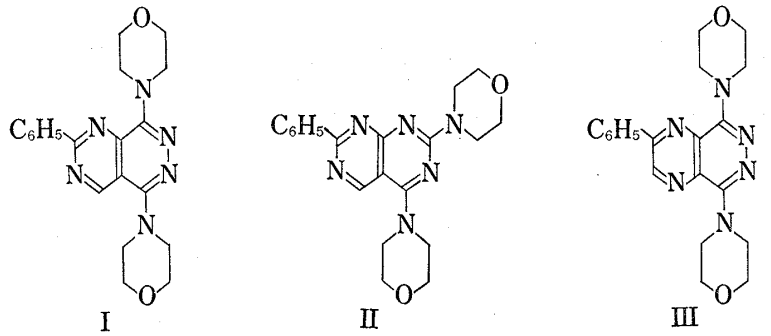
Photochemical reactions of tetraazanaphthalene derivatives, I, II, and III, with alcohols and cyclic ethers in the presence of photosensitizer resulted in selective addition at the 3,4 C=N bond to give substituted-3,4-dihydro derivatives. Potential diuretic activity was shown by many of the obtained compounds.

Although several reports have been published on the photochemical addition of alcohols and ethers to nitrogen containing aromatic compounds,[3] the reaction with tetraazanaphthalene derivatives has scarcely been studied.

In the preceding paper, we reported the reaction of tetraazanaphthalene derivatives, 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (I), 5,7-dimorpholino-2-phenylpyrimido-[4,5-*d*]pyrimidine (II) and 5,8-dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (III), with a variety of Grignard reagents.[1] In view of the remarkable diuretic activity exhibited by a wide variety of the obtained dihydrotetraazanaphthalene derivatives, it was speculated that more potent compounds might be expected by employing photochemical addition reaction of alcohols and ethers.



I II III

Chart 1

Irradiation of I in methanol with a 300 W high-pressure mercury lamp under nitrogen afforded yellow needles, $C_{21}H_{25}O_3N_6$, in 55% yield. Similarity of ultraviolet (UV) spectrum of the compound to that of 4-methyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]-pyridazine (V)[1] and an absorption at 3350 cm^{-1} in infrared (IR) spectrum, together with a triplet at 5.40 τ due to methine proton at 4 position, a hydroxyl proton at 5.30 τ and an imino proton at 1.76 τ in nuclear magnetic resonance (NMR) spectrum, led to assign the structure 4-hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IVa) to

1) Part XXII: A. Miyake, K. Itoh, N. Tada, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1488 (1975).
2) Location: *Juso, Yodogawa-ku, Osaka.*
3) *a*) F.R. Stermitz, C.C. Wei, and C.M. O'Donnell, *J. Am. Chem. Soc.*, **92**, 2745 (1970); *b*) H. Goth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965); *c*) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1970**, 3839; *d*) E.C. Taylor, Y. Maki, and B.E. Evans, *J. Am. Chem. Soc.*, **91**, 5181 (1969); *e*) M. Natsume and M. Wada, *Tetrahedron Letters*, **1971**, 4503.

the compound. It was found that this reaction was markedly accelerated in the presence of photosensitizer such as acetone and acetophenone, which was indicative of a photosensitized addition reaction. The reaction conditions and the results are summarized in Table I.

It has been reported that photochemical addition of alcohols to quinoline,[3a] phthalazine,[4] pyrimidine[5] and pyrazolopyrimidine[5] in acidic conditions afforded dehydrated addition products, and that 1-hydroxymethyl-1,2-dihydrophthalazine prepared by the photochemical addition of methanol to phthalazine in a neutral condition readily underwent dehydration to give 1-methylphthalazine upon heating in an acidic condition.[4] However, the photochemical reaction of I with methanol in an acidic condition also gave IVa along with 5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido [4, 5 - *d*] pyridazine (VI),[6] affording no dehydrated product (VII). Moreover IV resisted the dehydration even under heating in 20% hydrogen chloride-methanol solution. Similar results were obtained in the photochemical reactions of I with ethanol, isopropanol and benzylalcohol (Table II).

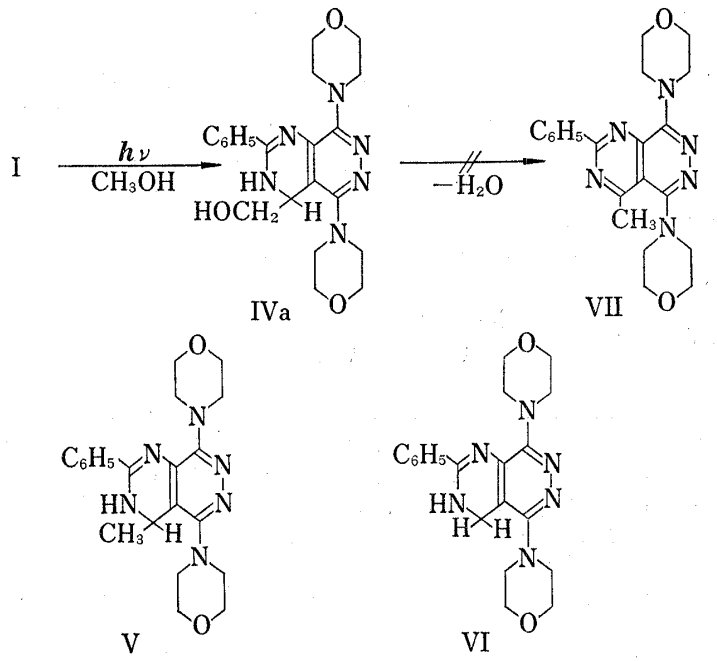


Chart 2

Table I. Photochemical Reactions of 5,8-Dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (I)

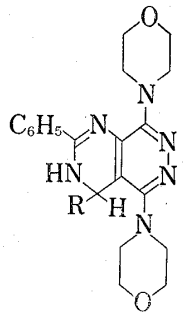
No.	Irradiation condition		Time (hr)	Recovered starting material (%)	Product (%)[a]	
	Solvent	Light source			IVa	VI
1	MeOH	HPL[b]	2	90	0	0
2	MeOH	HPL	40	20	55	0
3	MeOH–acetone	HPL	2	0	55	0
4	MeOH–acetophenone	HPL	2	0	46	10
5	MeOH–2%HCl	HPL	16	5	19	15
6	MeOH–acetone–2%HCl	HPL	6	15	38	5
7	MeOH–2%HCl	LPL[c]	16	5	35	13

a) based on total amount of starting material
b) 300 W high pressure lamp.
c) low pressure lamp

Reaction of I with ethers were subsequently undertaken. Photochemical reaction of I with dioxane under the above-mentioned condition afforded pale yellow needles, $C_{24}H_{30}O_4N_6$, in 43% yield, which was assigned as 4-(1,4-dioxanyl)-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IVe) by spectroscopic data (IR, UV, and NMR). Tetrahydrofuran

4) Y. Otsuji, S. Wake, and E. Imoto, Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Sendai, 1971, p. 194.
5) *a*) M. Ochiai and K. Morita, *Tetrahedron Letters*, **1967**, 2349; *b*) M. Ochiai, E. Mizuta, Y. Asahi, and K. Morita, *Tetrahedron*, **24**, 5861 (1968).
6) S. Yurugi, T. Fushimi, and M. Hieda, *Yakugaku Zasshi*, **92**, 1316 (1972).

Table II. 5,8-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyridazine (IV) by the Photochemical Reaction of I with Alcohols and Ethers



IV	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	CH_2OH	55	251—253	$C_{21}H_{26}O_3N_6$	61.44	6.39	20.49	61.28	6.25	20.19
b	$CH(CH_3)OH$	31	250—252	$C_{22}H_{28}O_3N_6$	62.24	6.65	19.80	62.57	6.80	19.65
c	$CH(C_6H_5)OH$	35	amorphous	$C_{27}H_{30}O_3N_6$	66.65	6.22	17.27	66.94	5.99	16.90
d	$C(CH_3)_2OH$	35	100—102	$C_{23}H_{30}O_3N_6$	62.99	6.90	19.17	63.25	7.03	19.39
e		43	227—229	$C_{24}H_{30}O_4N_6$	61.78	6.48	18.02	61.42	6.51	17.72
f		27	245—247	$C_{24}H_{30}O_3N_6$	63.98	6.71	18.65	63.78	6.76	18.71

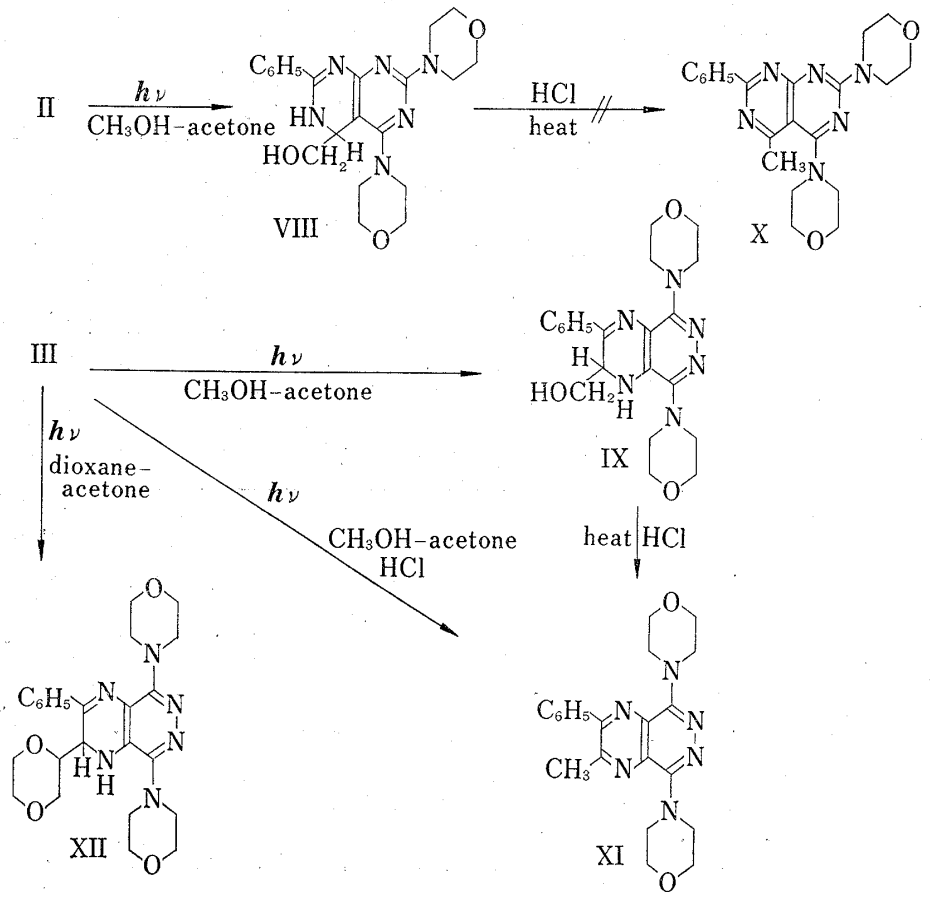


Chart 3

was similarly reacted to give IVf, while reactions with aliphatic ethers such as ethyl ether effected polymerization.

Similar reactions were carried out with other tetraazanaphthalene analogues, II and III. The photochemical reaction of II with methanol gave 4-hydroxymethyl-5,7-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (VIII) in 8% yield, accompanied by considerable polymerization. 3-Hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]-pyridazine (IX) was similarly afforded by the reaction of III with methanol. VIII also resisted dehydration to X when heated with hydrogen chloride in ethanol, whereas IX was converted to dehydrated 3-methyl-5,8-dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (XI) under the same condition. XI could also be obtained directly by the photochemical reaction of III with methanol in the presence of hydrogen chloride. The structure of XI was confirmed by comparison with an authentic sample prepared by an alternative method.[7] The reaction of III with dioxane gave 3-(1,4-dioxanyl)-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]-pyridazine (XII).

As shown above, photochemical reaction of those tetraazanaphthalene derivatives with alcohols and ethers resulted in selective addition at the 3, 4 C=N bond as in the case with Grignard reagents. In accord with our expectation, many of the obtained derivatives, *e.g.* IVa, IVb, IVc and IVe showed potential diuretic activity.

Experimental[8]

4-Hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IVa)——a) A solution of I[9] (1.0 g) in MeOH (500 ml) was irradiated with a 300 W high-pressure mercury lamp under nitrogen at room temperature for 40 hr. The reaction mixture was evaporated *in vacuo*. The residue was chromatographed on silica gel eluted with C_6H_6–acetone (1: 1) to give recovered I (0.2 g, 20%) and IVa (0.6 g, 55%) as yellow needles, mp 251—253°. IR ν_{max}^{Nujol} 3340 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 245 (20000), 363 (7600). NMR (in $CDCl_3$) τ: 6.60—7.15 (4H, m, morpholine), 6.10—6.50 (14H, morpholine and $C\underline{H}_2$–OH), 5.40 (1H, t, $J=5$ Hz, C_4–H), 5.30 (1H, s, OH), 2.50—2.64 (3H, m, phenyl), 1.99—2.10 (2H, m, phenyl), 1.70 (1H, s, NH).

b) A solution of I (1.0 g) in MeOH (400 ml) and acetone (100 ml) was irradiated with a 300 W high-pressure lamp under nitrogen at room temperature for 2 hr. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with C_6H_6–acetone (1: 1) gave IVa (0.6 g, 55%).

c) A solution of I (1.0 g) and acetophenone (3.6 g) in MeOH (500 ml) was irradiated with a 300 W high-pressure mercury lamp under nitrogen at room temperature for 2 hr. The reaction mixture was evaporated *in vacuo*. The residue was chromatographed over silica gel eluted with C_6H_6–acetone (1: 1) to give VI (0.1 g, 10%), mp 247—248°, which was identical with an authentic sample.[6] Further elution with the same solvent gave IVa (0.5 g, 46%).

d) A solution of I (1.0 g) in MeOH (500 ml) containing 2% dry hydrogen chloride was irradiated with a 300 W high-pressure mercury lamp under nitrogen at room temperature for 16 hr. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O (100 ml), and the resulting solution was made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed over silica gel eluted with C_6H_6–acetone (1: 1) to give IVa (0.12 g, 11%) and VI (0.05 g, 5%).

5,8-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyridazine (IV)——General Procedure: A solution of I (1.0 g) in alcohol or cyclic ether (400 ml) and acetone (100 ml) was irradiated with a 300 W high-pressure mercury lamp under nitrogen at room temperature for 0.5—2 hr. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with C_6H_6–acetone (1: 1) or C_6H_6–acetone (4: 1) gave IV, which was recrystallized from AcOEt or MeOH.

4-Hydroxymethyl-5,7-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (VIII)——A solution of II[10] (1.0 g) in MeOH (400 ml) and acetone (100 ml) was irradiated with 300 W high-pressure mercury

7) A. Miyake, K. Itoh, N. Tada, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1505 (1975).
8) All melting points were taken on a Kofler-type hot-stage apparatus (Yanagimoto Co.) and are uncorrected. NMR spectra were measured in $CDCl_3$ on Varian HA-100 or A-60 high resolution spectrometer.
9) S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1528 (1972).
10) S. Yurugi, A. Miyake, and N. Tada, *J. Takeda Res. Lab.*, **32**, 251 (1973).

lamp under nitrogen at room temperature for 1 hr. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with C_6H_6–acetone (1: 1) gave VIII (0.1 g, 8%), mp 200—203°, as colorless prisms. *Anal.* Calcd. for $C_{21}H_{26}O_3N_6 \cdot 1/2C_6H_6$: C, 64.24; H, 6.29; N, 18.74. Found: C, 64.15; H, 6.46; N, 18.74. UV λ_{max}^{EtOH} nm (ε): 237 (31000). NMR (in $CDCl_3$) τ: 6.28—6.90 (18H, m, morpholine and $C\underline{H}_2$–OH), 4.97 (1H, t, J=4 Hz, C_4–H), 2.70 (3H, s, phenyl), 2.26—2.38 (2H, m, phenyl), 2.08—2.14 (3H, m, phenyl).

3-Hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]pyridazine (IX)——A solution of III (1.0 g) in MeOH (400 ml) and acetone (100 ml) was irradiated with a 300 W high-pressure mercury lamp under nitrogen at room temperature for 3 hr. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (1: 1) to give IX (0.6 g, 55%), which was recrystallized from EtOH to give yellow needles, mp 216—219°. *Anal.* Calcd. for $C_{21}H_{26}O_3N_6$: C, 61.44; H, 6.39; N, 20.49. Found: C, 61.33; H, 6.46; N, 20.32. UV λ_{max}^{EtOH} nm (ε): 235 (29000), 380 (9000). NMR (in $CDCl_3$) τ: 6.70—7.06 (4H, m, morpholine), 5.98—6.50 (14H, m, morpholine and $C\underline{H}_2$-OH), 4.79—4.98 (2H, m, C_4–H and NH), 4.28 (1H, s, OH), 2.46—2.54 (3H, m, phenyl), 1.98—2.10 (2H, m, phenyl).

3-Methyl-5,8-dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (XI)——a) A solution of III[11] (1.0 g) in MeOH (400 ml) and acetone (100 ml) containing 2% dry HCl was irradiated with high-pressure mercury lamp under nitrogen at room temperature for 5 hr. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O (100 ml) and made alkaline with 10% NaOH. The resulting solution was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with C_6H_6–acetone (1: 1) gave dark orange needles, XI (0.3 g, 29%), mp 165—168°. *Anal.* Calcd. for $C_{21}H_{24}O_2N_6$: C, 64.27; H, 6.16; N, 21.42. Found: C, 64.31; H, 5.89; N, 21.19. NMR (in $CDCl_3$) τ: 7.14 (3H, s, CH_3), 6.09 (16H, s, morpholine), 2.30—2.53 (5H, m, phenyl).

b) A solution of IX (0.9 g) in MeOH (5 ml) containing 20% dry HCl was refluxed for 2 hr. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O (10 ml). The resulting solution was made alkaline with 10% NaOH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was crystallized from ether to give XI (0.9 g, 94%).

3-(1,4-Dioxanyl)-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]pyridazine (XII)——A solution of III (1.0 g) in dioxane (400 ml) and acetone (100 ml) was irradiated with a 300 W high-pressure lamp under nitrogen at room temperature for 2 hr. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with C_6H_6–acetone (2: 1) gave XII (0.5 g, 40%) as yellow oil, which was crystallized from ether to give yellow needles, mp 134—136°. *Anal.* Calcd. for $C_{24}H_{30}O_4N_6$: C, 61.78; H, 6.48; N, 18.02. Found: C, 61.62; H, 6.41; N, 17.68. NMR (in $CDCl_3$) τ: 6.79—6.89 (8H, m, morpholine), 5.98—6.50 (15H, m, morpholine and dioxane), 5.20 (1H, d, J=8 Hz, C_3–H), 4.96 (1H, s, NH), 2.59—2.64 (3H, m, phenyl), 2.02—2.14 (2H, m, phenyl).

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11) S. Yurugi and M. Hieda, *Yakugaku Zasshi*, **92**, 1322 (1972).