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Studies on the Syntheses of N-Heterocyclic Compounds. XXIV.[1] Oxidation of Dihydrotetraazanaphthalene Derivatives

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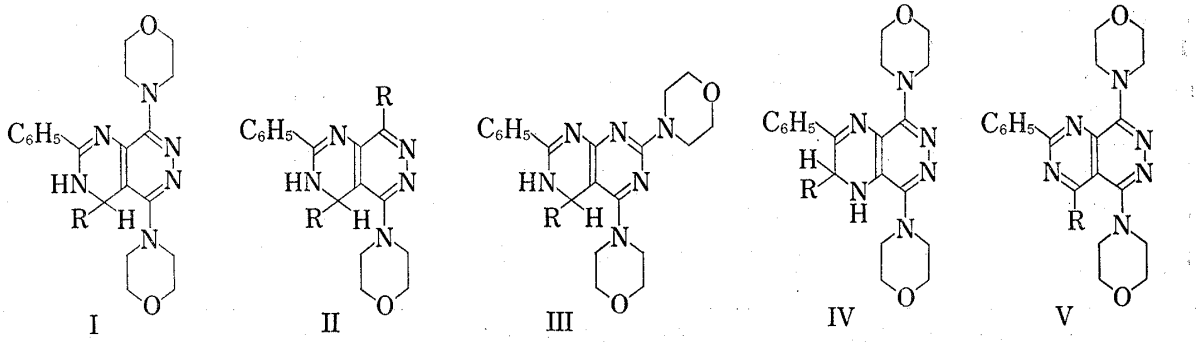
Oxidation of a variety of substituted dihydrotetraazanaphthalene derivatives (I–IV) with 2,3-dichloro-5,6-dicyanoquinone afforded corresponding dehydrogenated aromatic deriva tives (V,VII, IX, and X). However, oxidation with potassium ferricyanide, bromine or nitrobenzene gave rise to oxidative elimination of the substituent in addition to normal dehydrogenation, depending upon the variety of the substituent. The substituents readily removed by this novel C–C bond cleavage were benzyl, allyl, *tert*-butyl, cyclohexyl and α-hydroxyalkyl groups.

In the preceding papers we reported the syntheses of substituted dihydrotetraazanaphthalene derivatives (I—IV) by the reaction of organometallic compounds[3] or photochemical addition of alcohols and ethers[1] to tetraazanaphthalene derivatives. Potential diuretic activities exhibited by a wide variety of the obtained compounds as well as by the parent aromatic compounds[4] led us to assume that 5,8-dimorpholino-2-phenyl-4-substituted pyrimido-[4,5-*d*]pyridazine (V, R≠H), which should be obtainable by oxidation of the corresponding dihydro derivative, would also possess diuretic activity. This paper deals with the oxidations of those dihydrotetraazanaphthalene derivatives leading to aromatized compounds.



I II III IV V

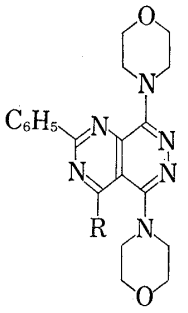
Chart 1

Oxidation of a series of 5,8-dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido-[4,5-*d*]pyridazine (I) with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in benzene afforded desired dehydrogenated products, 5,8-dimorpholino-2-phenyl-4-substituted pyrimido[4,5-*d*]pyridazine (V), regardless of the variety of 4-substituent. (Table I).

It was found, however, that oxidations with other oxidizing reagents such as potassium ferricyanide, bromine or nitrobenzene gave rise to two types of reaction, normal dehydrogenation to V and oxidative elimination leading to 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine

1) Part XXIII: A. Miyake, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1500 (1975).
2) Location: *Juso, Yodogawa-ku, Osaka.*
3) A. Miyake, K. Itoh, N. Tada, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1488 (1975).
4) *a*) S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1528 (1972); *b*) S. Yurugi, A. Miyake, and N. Tada, *J. Takeda Res. Lab.*, **32**, 251 (1973).

TABLE I. 5,8-Dimorpholino-2-phenyl-4-substituted pyrimido[4,5-*d*]pyridazine (V)



V	R	Oxidation method[a]	mp (°C)	Yield	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	$C_6H_5CH_2$	A	163—164	34	$C_{27}H_{28}O_2N_6$	69.21	6.02	17.94	69.33	6.02	18.09
b	CH_3	A	188—190	44	$C_{21}H_{24}O_2N_6$	64.27	6.16	21.42	64.30	6.24	21.59
	CH_3	B	···	64	···	···	···	···	···	···	···
	CH_3	C	···	8	···	···	···	···	···	···	···
c	CH_3CH_2	A	178—180	51	$C_{22}H_{26}O_2N_6$	65.00	6.45	20.68	65.17	6.43	20.57
d	$CH_3(CH_2)_2$	A	158—161	49	$C_{23}H_{28}O_2N_6$	65.69	6.71	19.99	65.94	6.94	19.70
	$CH_3(CH_2)_2$	B	···	74	···	···	···	···	···	···	···
e	$(CH_3)_2CH$	A	191—192	47	$C_{23}H_{28}O_2N_6$	65.69	6.71	19.99	65.89	6.70	19.94
f	$CH_3(CH_2)_3$	A	128—129	50	$C_{24}H_{30}O_2N_6$	66.34	6.96	19.34	66.22	6.97	19.25
g	$(CH_3)_2CHCH_2$	A	167—169	46	$C_{24}H_{30}O_2N_6$	66.34	6.96	19.34	66.46	7.03	19.04
h	$(CH_3)_2CH(CH_2)_2$	A	157—159	55	$C_{25}H_{32}O_2N_6$	66.94	7.19	18.74	67.16	7.20	18.39
i	$CH_3(CH_2)_5$	A	118—119	50	$C_{26}H_{34}O_2N_6$	67.50	7.41	18.17	67.54	7.51	18.06
j		A	221—227	50	$C_{26}H_{32}O_2N_6$	67.80	7.00	18.25	67.70	6.99	18.17
		B	···	18	···	···	···	···	···	···	···
k	$C_6H_5(CH_2)_2$	A	189—191	58	$C_{28}H_{30}O_2N_6$	69.69	6.27	17.42	69.64	6.24	17.35
l	C_6H_5	A	229—230	54	$C_{26}H_{26}O_2N_6$	68.70	5.77	18.48	68.72	5.77	18.47
m		A	254—256	33	$C_{25}H_{25}O_2N_7$	65.93	5.53	21.53	65.92	5.41	21.67
n		A	224—226	59	$C_{24}H_{24}O_2N_6S$	62.60	5.25	18.25	62.59	5.22	18.50
o	$HOCH_2$	A	190—192	43	$C_{21}H_{24}O_3N_6$	61.75	5.92	20.58	61.88	6.00	20.33
p		B	202—204	85	$C_{24}H_{28}O_4N_6$	62.05	6.08	18.09	61.97	6.15	17.88

a) A: oxidation with DDQ B: oxidation with $K_3Fe(CN)_6$-KOH C: oxidation with nitrobenzene

(VI), depending upon the variety of 4-substituent. Thus, the oxidation of 4-benzyl derivative (Ia) (I, R=$C_6H_5CH_2$) with aqueous potassium ferricyanide in alkaline solution gave VI with oxidative liberation of the benzyl group as benzaldehyde. Such an abnormal oxidative elimination was also observed when 4-substituent in I was allyl, *tert*-butyl, cyclohexyl or α-hydroxyalkyl group (Table II). On the other hand, other 4-alkyl, aryl and aralkyl derivatives as well as 4-(1,4-dioxan-2-yl) derivative (I, R= ) gave only normal dehydrogenated product (V). Since dehydrogenated 4-benzyl derivative (V, R=$C_6H_5CH_2$) proved to be stable to the ferricyanide oxidation, it is clear that the elimination occurred prior to the aromatization. Although we have no evidence at present as to whether those ferricyanide oxidations proceed *via* ionic or radical mechanism, it seems that the feasibility of the oxidative elimination reaction is closely related with the stability of carbonium ion or radical on the eliminated species. The oxidative elimination of α-hydroxyalkyl group in I resembles the ferricyanide oxidation of

α-hydroxyethylthiamine (HET) to thiochrome liberating acetaldehyde,[5] though such carbon-carbon bond cleavage is quite rare in literatures.

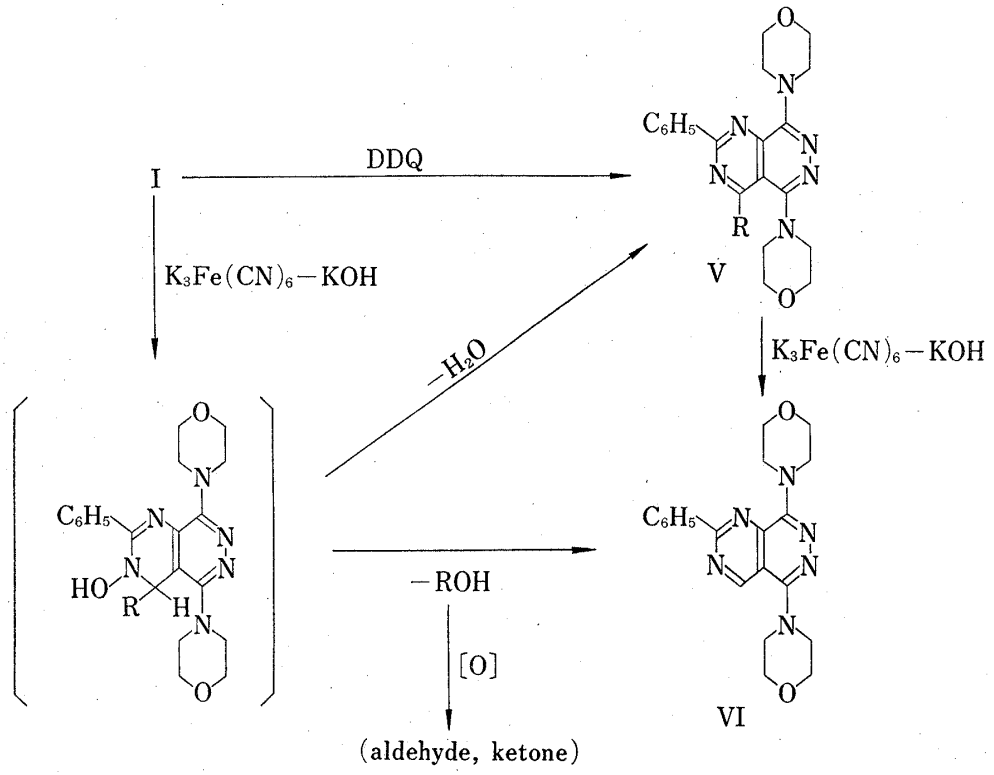


Chart 2

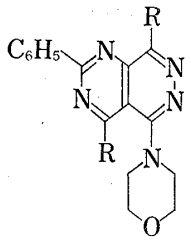
TABLE II. Formation of 5,8-Dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (VI) by Oxidative Elimination of I

R in I	Reaction condition		VI Yield (%)
	Reagent	Solvent	
$C_6H_5CH_2$	Br_2–AcONa	AcOH	33
$C_6H_5CH_2$	nitrobenzene	—	41
$C_6H_5CH_2$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	85
$(CH_3)_3C$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	66
	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	26
CH_2=CH–CH_2	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	29
$HOCH_2$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	74
$CH_3CH(OH)$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	66
$C_6H_5CH(OH)$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	51
$(CH_3)_2C(OH)$	$K_3Fe(CN)_6$–KOH	C_6H_6–H_2O	74

Similar results were obtained by the oxidations of II, III, and IV. Thus, oxidation of 4,8-dibenzyl-5-morpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (II, R=$C_6H_5CH_2$) with DDQ gave dehydrogenated VIIa, while the oxidation with potassium ferricyanide yielded VIII, in which only the benzyl group at 4 position was eliminated. A series of VII obtained by DDQ oxidations of corresponding II is listed in Table III. Ferricyanide oxidation of 4-benzyl-5,7-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (III, R=$C_6H_5CH_2$) resulted in oxidative elimination to give 5,7-dimorpholino-2-phenylpyrimido[4,5-*d*]pyrimidine

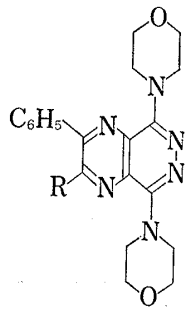
5) H. Asakawa, E. Imamiya, and H. Hirano, *J. Takeda Res. Lab.*, **30**, 705 (1971).

Table III. 5-Morpholino-2-phenyl-4,8-disubstituted pyrimido[4,5-*d*]pyridazine (VII)



VII	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	$C_6H_5CH_2$	33	170—172	$C_{30}H_{27}ON_5 \cdot C_6H_3O_6N_3$	61.56	4.31	15.94	61.51	3.82	16.02
b	$CH_3(CH_2)_2$	34	207—210	$C_{22}H_{27}ON_5$	70.00	7.21	18.55	70.00	7.28	18.58
c	$CH_3(CH_2)_3$	25	70— 73	$C_{24}H_{31}ON_5$	71.08	7.71	17.27	71.00	7.93	17.25
d	$(CH_3)_2CH(CH_2)_2$	15	155—158	$C_{26}H_{35}ON_5 \cdot HCl$	66.49	7.72	14.90	66.47	7.93	14.89
e	$(CH_3)_2CH$	34	143—144	$C_{22}H_{27}ON_5$	70.00	7.21	18.55	69.54	7.51	18.33
f	$CH_3(CH_2)_5$	32	154—155	$C_{28}H_{39}ON_5 \cdot HCl$	67.52	8.09	14.06	67.44	8.07	13.98
g	$C_6H_5(CH_2)_2$	42	202—204	$C_{32}H_{31}ON_5$	76.02	6.23	13.96	76.62	6.14	13.92
h		45	197—200	$C_{28}H_{35}ON_5$	73.49	7.71	15.31	73.27	8.13	15.29

Table IV. 5,8-Dimorpholino-2-phenyl-3-substituted pyrazino[2,3-*d*]pyridazine (X)



X	R	Yield	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
b	CH_3	85	165—168	$C_{21}H_{24}O_2N_6$	64.27	6.16	21.42	64.31	5.89	21.19
c	CH_3CH_2	39	153—156	$C_{22}H_{26}O_2N_6$	65.00	6.45	20.68	64.69	6.43	20.17
d	C_6H_5	66	223—226	$C_{26}H_{26}O_2N_6$	68.70	5.77	18.49	68.93	5.65	18.34
e		90	210—212	$C_{24}H_{28}O_4N_6$	62.05	6.08	18.09	61.97	6.15	17.88

(IXa), while 4-ethyl derivogenative (III, R=C_2H_5) was dehydrogenated to IXb in 95% yield under the same condition. Similarly, 5,8-dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (Xa)[6] was obtained by the ferricyanide oxidation of 3-benzyl or 3-hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]pyridazine (IV, R=$C_6H_5CH_2$, or CH_2OH). On the other hand, normal dehydrogenated product (Xb—e) was obtained when the 4-substituent was methyl, ethyl, phenyl, or 1,4-dioxan-2-yl group.

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

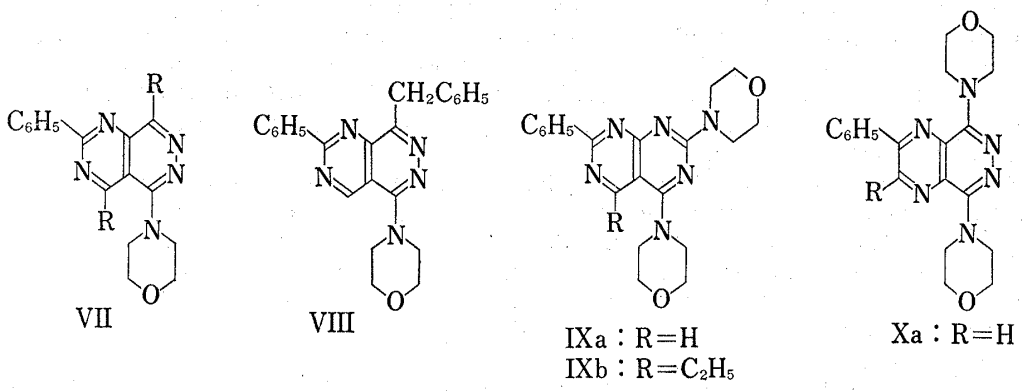


Chart 3

Contrary to our assumption, 5,8-dimorpholino-2-phenyl-4-substituted pyrimido[4,5-*d*]-pyridazines (V, R≠H) showed virtually no diuretic activity. The result is somewhat interesting in view of the fact that 4-unsubstituted derivative (V, R=H) and many of the 4-substituted-3,4-dihydroderivatives (II) are potent diuretics.

Experimental[7]

5,8-Dimorpholino-2-phenyl-4-substituted pyrimido[4,5-*d*]pyridazine (V) (Table I)——a) To a stirred solution of I[3] (1.5 mmole) in C_6H_6 (100 ml) was added a solution of DDQ (1.7 mmole) in C_6H_6 (50 ml) at room temperature. After 0.5—1 hr the reaction mixture was purified by column chromatography on silica gel to give crude product, which was recrystallized from ether or MeOH to give V.

b) To a stirred solution of I (0.2 mmole) in C_6H_6 (200 ml) was added a solution of $K_3Fe(CN)_6$ (6.0 g) in H_2O (40 ml). Then a solution of KOH (3.0 g) in H_2O (7 ml) was added to the reaction mixture at room temperature. After 5—10 hr the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from petroleum ether or ether to give V.

c) A solution of 4-methyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (0.5 g) in nitrobenzene (20 ml) was refluxed for 30 hr. The reaction mixture was chromatographed on silica gel. Elution with C_6H_6–acetone (3:1) gave Vb, mp 188—190°.

5,8-Dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (VI) (Table II)——a) To a stirred solution of Ia[3] (0.2 mmole) in C_6H_6 (40 ml) was added a solution of $K_3Fe(CN)_6$ (6.0 g) in H_2O (40 ml). A solution of KOH (3.0 g) in H_2O (7 ml) was added to the reaction mixture at room temperature. After 5 hr the organic layer was separated, washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with C_6H_6 to give benzaldehyde (0.11 g, 51%) which showed complete identity with an authentic sample in infrared (IR) spectrum. Further elution with C_6H_6–acetone (4:1) gave VI. Recrystallization from ether gave yellow needles, mp 180—182°, which showed complete identity with an authentic sample[4a] in the mixed melting point and IR spectrum.

b) A solution of Ia (1.0 g) in nitrobenzene (50 ml) was refluxed for 8 hr. The reaction mixture was dissolved in C_6H_6 (100 ml) and purified by column chromatography on silica gel eluted with C_6H_6–acetone (9:1) to give VI (0.37 g, 41%).

c) To a solution of Ia (0.9 g) and AcONa (0.5 g) in AcOH (20 ml) was added dropwise 0.5 g of Br_2 with stirring at room temperature. After 3 hr the separated crystalline products were collected by filtration and dissolved in aqueous MeOH. The resulting solution was made alkaline with $NaHCO_3$. The separated crystals were collected by filtration, washed with H_2O, and recrystallized from EtOH to give VI (0.25 g, 33%).

5-Morpholino-2-phenyl-4,8-disubstituted pyrimido[4,5-*d*]pyridazine (VII) (Table III)——To a solution of II (2 mmole) in C_6H_6 (100 ml), was added a solution of DDQ (2.2 mmole) in C_6H_6 (50 ml) with stirring. After 0.5—1 hr, the reaction mixture was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9:1) to give VII, which was recrystallized from petroleum ether or ether. In the case that VII was an oil, it was led to hydrochloride.

8-Benzyl-5-morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (VIII)——To a stirred solution of 4,8-dibenzyl-5-morpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (II)[3] (0.5 g) in C_6H_6 (100 ml) was added a solution of $K_3Fe(CN)_6$ (0.6 g) in H_2O (40 ml). Then a solution of KOH (3.0 g) in H_2O (7 ml) was added to

7) All melting points were taken on a Kofler-type hot-stage apparatus (Yanagimoto Co.) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on Varian HA-100 or A-60 high resolution spectrometers.

the reaction mixture. After 10 hr the organic layer was separated, washed with H_2O, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9:1) to give VIII (0.3 g, 74%), yellow needles, mp 139—140°. *Anal.* Calcd. for $C_{23}H_{21}ON_5$: C, 72.04; H, 5.52; N, 18.27. Found: C, 72.04; H, 5.21; N, 18.17. NMR (in $CDCl_3$) τ: 6.30—6.44 (4H, m, morpholine), 6.03—6.28 (4H, m, morpholine), 5.26 (2H, s, $C\underline{H}_2$–C_6H_5), 2.40—2.90 (8H, m, phenyl), 1.38—1.50 (2H, m, phenyl), 0.50 (1H, s, C_4–H).

5,7-Dimorpholino-2-phenylpyrimido[4,5-*d*]pyrimidine (IXa)——To a stirred solution of 4-benzyl-5,7-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (IIIa)[3] (0.47 g) in C_6H_6 (40 ml) was added a solution of $K_3Fe(CN)_6$ (7.5 g) in H_2O (40 ml). Then a solution of KOH (3.8 g) in H_2O (10 ml) was added to the reaction mixture at room temperature. After 14 hr the organic layer was separated, washed with H_2O, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from C_6H_6–ether to give IXa (0.2 g, 53%) mp 247—249°, which showed complete identity with an authentic sample[4b] in the mixed melting point and IR spectrum.

4-Ethyl-5,7-dimorpholino-2-phenylpyrimido[4,5-*d*]pyrimidine (IXb)——To a stirred solution of 4-ethyl-5,7-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidine (IIIb)[3] (0.2 g) in C_6H_6 (40 ml) was added a solution of $K_3Fe(CN)_6$ (4.5 g) in H_2O (30 ml). Then a solution of KOH (2.0 g) in H_2O (5 ml) was added to the reaction mixture at room temperature. After 10 hr the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from ether to give IXb (0.19 g, 95%), mp 170—173°. *Anal.* Calcd. for $C_{22}H_{26}O_2N_6$: C, 65.00; H, 6.45; N, 20.68. Found: C, 64.89; H, 6.43; N, 20.61. NMR (in $CDCl_3$) τ: 8.65 (3H, t, J=7.2 Hz, CH_3), 6.88 (2H, q, J=7.2 Hz, $C\underline{H}_2$–CH_3), 5.90—6.50 (16H, m, morpholine), 2.44—2.64 (3H, m, phenyl), 1.28—1.52 (2H, m, phenyl).

5,8-Dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (Xa)——a) To a stirred solution of 3-benzyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]pyridazine (IV)[3] (0.47 g) in C_6H_6 (80 ml) was added a solution of $K_3Fe(CN)_6$ (3.0 g) in H_2O (20 ml). Then a solution of KOH (1.5 g) in H_2O (3.5 ml) was added to the reaction mixture at room temperature. After 3 hr the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from C_6H_6–ether to give Xa (0.2 g, 53%) as red prisms, mp 191—192°, which showed complete identity with an authentic sample[6] in the mixed melting point and IR spectrum.

b) To a stirred solution of 3-hydroxymethyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrazino[2,3-*d*]-pyridazine (IV)[1] (0.2 g) in C_6H_6 (20 ml) was added a solution of $K_3Fe(CN)_6$ (3.0 g) in H_2O (20 ml). Then a solution of KOH (2.0 g) in H_2O (8 ml) was added to the reaction mixture at room temperature. After 2 hr the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from C_6H_6–ether to give Xa (0.17 g, 85%).

5,8-Dimorpholino-2-phenyl-3-substituted pyrazino[2,3-*d*]pyridazine (Xb–e)——To a solution of 5,8-dimorpholino-2-phenyl-3-substituted-3,4-dihydropyrazino[2,3-*d*]pyridazine (IV)[1,3] (0.5 mmole) in C_6H_6(40 ml) was added a solution of $K_3Fe(CN)_6$ (1.5 g) in H_2O (10 ml). Then a solution of KOH (0.7 g) in H_2O (3 ml) was added to the reaction mixture at room temperature. After 1—4 hr the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from ether to give X.

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