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Studies on the Syntheses of N-Heterocyclic Compounds. XXII.[1] The Reaction of Polyazanaphthalene Derivatives with Organometallic Reagents

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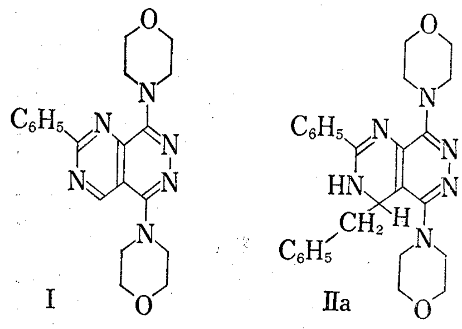
Reaction of 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (I) with Grignard reagent or organolithium afforded 4-substituted-3,4-dihydro derivatives (II). The use of an excess of the reagent gave rise to further substitution at 8-position to afford 4,8-disubstituted-3,4-dihydro derivatives (III and VII). Similar results were observed in the reaction of Grignard reagents with analogous tetraazanaphthalene derivatives, 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyrimidine (XX) and 5,8-dimorpholino-2-phenylpyrazino[2,3-*d*]pyridazine (XXII), to afford 4-substituted-3,4-dihydro derivatives (XXI) and 3-substituted-3,4-dihydro derivatives (XXIII), respectively. Among the obtained derivatives, IIa and IIj exhibited significant diuretic activity.

In spite of the extensive studies on the reaction of organometallic reagents with nitrogen containing aromatic compounds,[3] relatively little have been reported on the reaction with tetraazanaphthalene derivatives.

During the course of our studies on the previously reported novel diuretics, 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine[4] (I) and 4-benzyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IIa),[5] reactions of I with Grignard reagent or benzyllithium were undertaken in an attempt to explore a facile synthetic route to IIa.



I IIa

Chart 1

In accord with our assumption, the reaction of I with benzylmagnesium chloride in tetrahydrofuran (THF) under room temperature afforded needles, mp 220—221°, in 78% yield, which showed complete identity with an authentic sample of IIa in spectral data (nuclear magnetic resonance (NMR,) infrared (IR) and ultraviolet (UV) spectra), elemental analysis and mixed melting point.

The reaction of I with other Grignard reagents similarly proceeded to afford a variety of 5,8-dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyridazine derivatives (II), which are listed in Table I.

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1) Part XXI: A. Miyake, Y. Oka, and S. Yurugi, *J. Takeda Res. Lab.*, 33, 155 (1974).

2) Location: *Juso, Yodogawa-ku, Osaka.*

3) *a*) A.R. Katritzky ed., "Advances in Heterocyclic Chemistry," Vol. 6, Academin Press, New York and London, 1963, p. 229; *b*) W.K. Detweiler and E.D. Amstutz, *J. Am. Chem. Soc.*, 73, 5451 (1951); *c*) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), 7, 297 (1957); *d*) H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.*, 79, 1245 (1957); *e*) A. Marxer, F. Hofer, and U. Salzmann, *Helv. Chim. Acta*, 52, 1376 (1969).

4) S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), 20, 1528 (1972).

5) S. Yurugi, K. Itoh, A. Miyake, and K. Omura, *Yakugaku Zasshi*, 93, 1043 (1973).

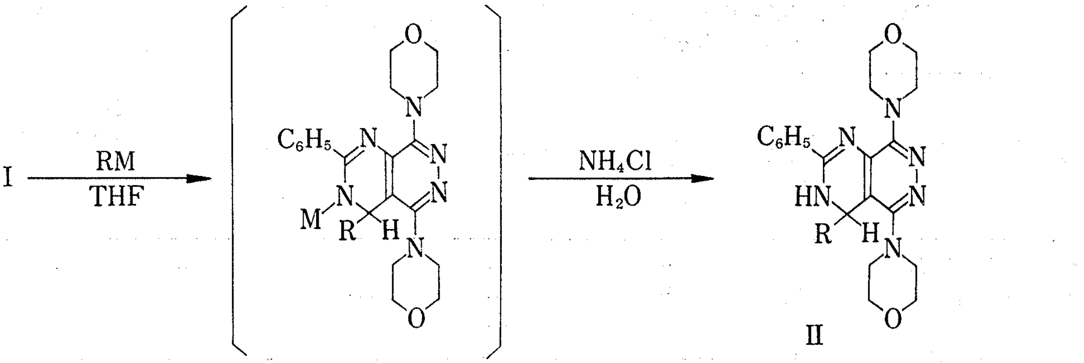
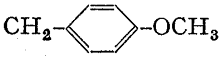
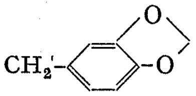


Chart 2

Table I. 5,8-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyridazine (II) by the Reaction of Grignard Reagents with I

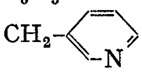
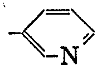
II	R	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	$CH_2C_6H_5$	221—223	$C_{27}H_{30}O_2N_6$	68.91	6.43	17.86	69.12	6.65	17.69
b	CH_3	275—277	$C_{21}H_{26}O_2N_6$	63.94	6.64	21.31	63.50	6.73	21.07
c	C_2H_5	159—161	$C_{22}H_{28}O_2N_6 \cdot$ 1/2EtOH	63.85	7.22	19.43	64.02	7.30	19.16
d	C_3H_7	228—230	$C_{23}H_{30}O_2N_6$	65.38	7.16	19.89	65.40	7.27	19.20
e	C_4H_9	193—195	$C_{24}H_{32}O_2N_6$	66.03	7.39	19.25	66.16	8.38	19.19
f	C_6H_{13}	173—176	$C_{26}H_{36}O_2N_6$	67.21	7.81	18.09	67.27	8.17	17.94
g	$CH(CH_3)_2$	132—136	$C_{23}H_{30}O_2N_6$	65.38	7.16	19.89	65.39	7.18	20.03
h	$CH_2CH(CH_3)_2$	297—302	$C_{24}H_{32}O_2N_6$	66.03	7.39	19.25	66.07	7.26	19.20
i	$C_2H_4CH(CH_3)_2$	206—208	$C_{25}H_{34}O_2N_6$	66.64	7.16	18.65	66.77	7.63	18.48
j	$C(CH_3)_3$	297(decomp.)	$C_{24}H_{32}O_2N_6$	66.03	7.39	19.25	66.30	7.39	19.02
k		251—254	$C_{26}H_{34}O_2N_6$	67.50	7.41	18.17	67.40	7.23	18.03
l	$C_2H_4C_6H_5$	208—211	$C_{28}H_{32}O_2N_6 \cdot$ 1/2AcOEt	68.03	7.04	15.87	67.60	6.88	15.84
m		159—163	$C_{28}H_{32}O_3N_6$	67.18	6.44	16.79	67.39	6.37	17.14
n		222—224	$C_{28}H_{30}O_4N_6$	65.35	5.88	16.33	65.66	5.89	16.01
o		220—223	$C_{28}H_{32}O_2N_6$	68.40	6.18	18.71	68.24	6.21	18.99
p	C_6H_5	225—227	$C_{26}H_{28}O_2N_6$	69.40	6.66	17.34	69.85	6.67	17.35

It was found that addition of benzyllithium to I also occurred selectively at the 3, 4 C=N bond to afford II. The results together with the derivatives prepared by the reactions with various organolithium compounds are listed in Table II.

When a large excess of benzylmagnesium chloride (*e.g.* 20 equivalent) was employed in the above reaction, an unexpected product (IIIa), mp 116—120°, was yielded along with 11% of IIa. Empirical formula of the compound, $C_{30}H_{29}ON_5$, as well as the presence of two benzyl and one morpholino groups in the NMR (Fig. 1) indicated that one of the two morpholino groups in IIa had been replaced by a benzyl group.

In order to elucidate which of the two morpholino groups, 5 or 8 position, was replaced by the benzyl group, the reaction of ethylmagnesium bromide with structurally established

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

II	R	Yield (%)	mp (°C)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
a	$CH_2C_6H_5$	85	a)	…	—	—	—	—	—	—
e	C_4H_9	39	a)	…	—	—	—	—	—	—
p	C_6H_5	64	a)	…	—	—	—	—	—	—
q		55	195—196	$C_{26}H_{29}O_2N_7$	66.22	6.19	20.79	66.39	6.07	20.80
r		61	162—164	$C_{24}H_{26}O_2N_6S$	62.32	5.67	18.17	62.39	5.60	17.50
s		26	164—166	$C_{25}H_{27}O_2N_7 \cdot$ AcOEt	63.81	6.47	17.97	63.73	6.43	18.12

a) refer to Table I

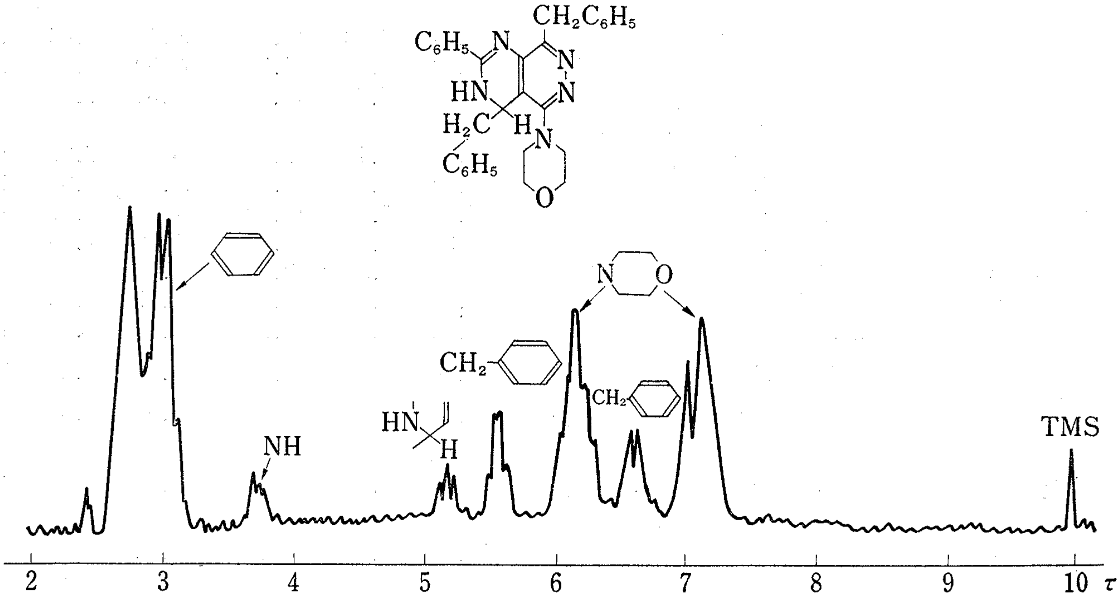
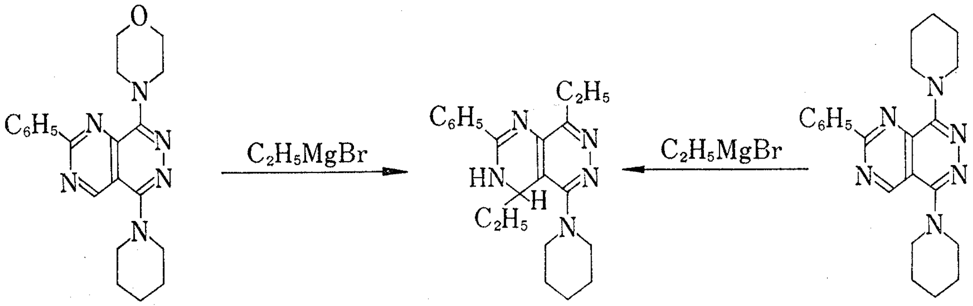


Fig. 1. NMR Spectrum of IIIa (in $CDCl_3$ 100 MHz)

8-morpholino-5-piperidino-2-phenylpyrimido[4,5-*d*]pyridazine (IV)[4] was carried out as a model experiment to obtain 4,8-diethyl-2-phenyl-5-piperidino-3,4-dihydropyrimido[4,5-*d*]pyridazine (V), in which substituted moiety was not 5-piperidino, but 8-morpholino group. V was also afforded by the reaction of excess ethylmagnesium bromide with 5,8-dipiperidino-2-phenylpyrimido[4,5-*d*]pyridazine (VI).[4]

Hence the structure of IIIa was assigned as 4,8-dibenzyl-5-morpholino-2-phenylpyrimido-[4,5-*d*]pyridazine. In Table III are listed several homologues of III obtained by the similar reaction of I with 4—20 equivalent Grignard reagents.

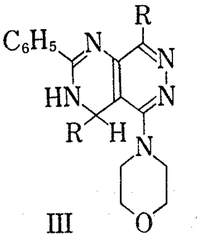
Furthermore, a third type of substituted product was discovered when a large excess of unbranched alkyl magnesium bromide was employed in the reaction. Thus the reaction of I with 10 equivalent ethylmagnesium bromide afforded an unknown compound VIIa, mp 204—207°, along with 21% of IIIc. The empirical formula of VIIa, $C_{22}H_{29}ON_5$, suggested



IV V VI

Chart 3

Table III. 5-Morpholino-2-phenyl-4,8-disubstituted-3,4-dihydropyrimido-[4,5-*d*]-pyridazine (III) by the Reaction of Grignard Reagents with I



III

III	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	$CH_2C_6H_5$	116—120	$C_{30}H_{29}ON_5$	75.76	6.15	14.73	75.37	6.22	14.32
b	CH_3	243—246	$C_{18}H_{21}ON_5$	66.85	6.55	21.66	66.81	6.51	21.75
c	C_2H_5	198—200	$C_{20}H_{35}ON_5$	68.35	7.17	19.93	68.21	7.25	19.62
d	C_3H_7	217—218	$C_{22}H_{29}ON_5$	69.63	7.70	18.46	69.98	7.83	18.37
e	C_4H_9	210—212	$C_{24}H_{33}ON_5$	70.73	8.16	17.19	70.73	8.03	17.20
f	C_6H_{13}	137—139	$C_{28}H_{41}ON_5$	72.53	8.91	15.11	72.59	8.98	14.94
g	$CH(CH_3)_2$	252—255	$C_{22}H_{29}ON_5$	69.63	7.70	18.46	69.71	7.72	18.39
h	$CH_2CH(CH_3)_2$	264—266	$C_{24}H_{33}ON_5$	66.03	7.39	19.25	66.07	7.26	19.20
i	$C_2H_4CH(CH_3)_2$	139—142	$C_{26}H_{37}ON_5$	71.69	8.58	16.07	71.39	8.57	15.96
j		236—237	$C_{28}H_{37}ON_5 \cdot 1/2(C_2H_5)_2O$	72.55	8.53	14.10	72.36	8.28	14.34
k	$C_2H_4C_6H_5$	93— 99	$C_{32}H_{33}ON_5$	76.31	6.60	13.91	76.34	6.45	13.78
l	C_6H_5	222—224	$C_{28}H_{25}ON_5$	75.14	5.63	15.65	75.03	5.47	15.48

that three ethyl groups were involved in the molecule and the NMR spectrum (Fig. 2) showed that the third ethyl group had been substituted at the α position of the 8-ethyl group was in IIIc. The structure of VIIa, therefore, was assigned as 8-*sec*-butyl-4-ethyl-5-morpholino-2-phenylpyrimido[4,5-*d*]pyridazine.

In Table IV are listed derivatives of VII, prepared by the similar reaction of I with alkylmagnesium halides.

As described above, the reaction of I with Grignard reagents resulted in three types of product, and the ratio of each varied with the reaction condition or the amount of the reagent employed (Table V): (1) Addition of the reagent to 3, 4 C=N bond to give II. (2) Subsequent addition to 7, 8 C=N bond followed by elimination of morpholine to give III. (3) Further addition to the α position of the substituted alkyl group to give VII. It should be noted that reaction 2 and 3 were significantly influenced by steric factor. For instance the reaction 2

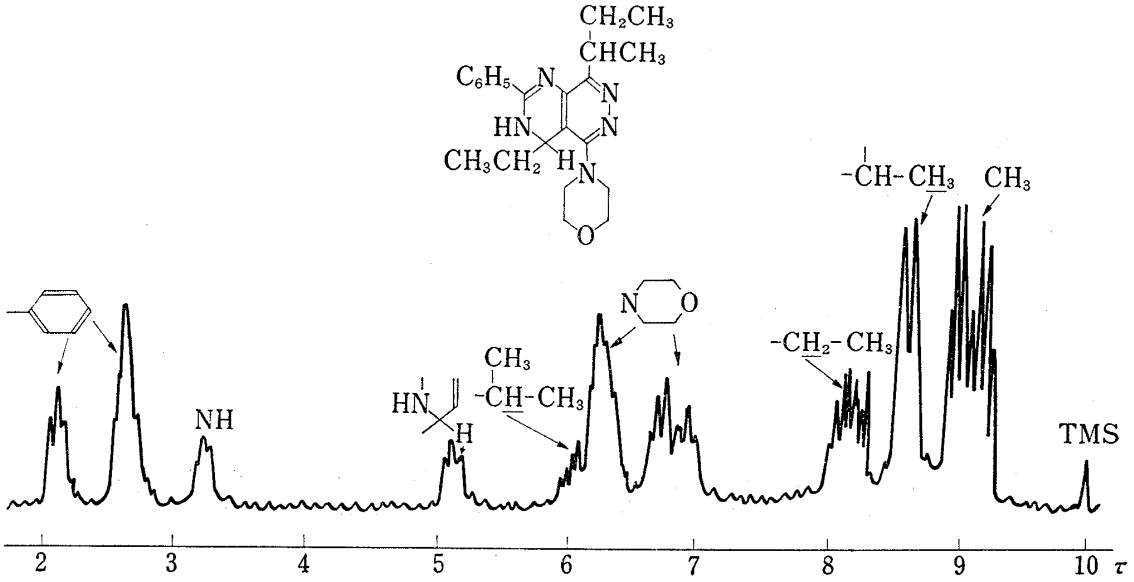
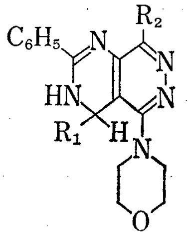


Fig. 2. NMR Spectrum of VIIa (in $CDCl_3$ 100 MHz)

Table IV. 5-Morpholino-2-phenyl-4,8-disubstituted-3,4-dihydropyrimido[4,5-*d*] pyridazine (VII) by the Reaction of Grignard Reagents with I



VII	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	C_2H_5	C_2H_5 $-CHCH_3$	204—207	$C_{22}H_{29}ON_5$	69.50	7.84	18.01	69.16	7.79	18.09
b	n-C_3H_7	C_3H_7 $-CHC_2H_5$	233—235	$C_{25}H_{35}ON_5$	71.22	8.37	16.61	71.22	8.25	16.07
c	n-C_4H_9	C_4H_9 $-CHC_3H_7$	203—204	$C_{28}H_{41}ON_5$	72.53	8.91	15.11	72.76	9.05	14.91
d	n-C_6H_{13}	C_6H_{13} $-CHC_5H_{11}$	128—130	$C_{34}H_{53}ON_5$	74.54	9.75	12.79	74.58	10.02	12.70

hardly proceeded when *tert*-butylmagnesium bromide was employed, and the reaction 3 was restricted to the case of unbranched alkyl magnesium halide.

Mechanisms of those reaction might be explained as illustrated in Chart 4. In all the compounds submitted to the above reaction, however, 5 and 8 positions of the pyrimido[4,5-*d*]-pyridazine skeleton had been substituted by morpholino group, although 3, 4 C=N bond was reacted in preference to 7, 8 C=N bond. In order to compare the reactivities between unsubstituted C=N bonds in the nucleus toward Grignard reagent, compounds X and XIII, in which position 5 and 8 are free from morpholino group, were synthesized starting with 5-chloro-8-

Table V. Reaction Condition and Product Distribution of the Reaction of I with Grignard Reagents

$$I \xrightarrow{RMgX} I, II+III+VII$$

R	Ratio of reagent RMgX/I	X	Reaction time (hr)	Solvent	Product (%)			
					II	III	VII	I
CH_3	2	I	1	THF–$(C_2H_5)_2O$	57	0	0	18
CH_3	20	I	1	THF–$(C_2H_5)_2O$	22	26	0	0
C_2H_5	2	Br	1	THF–$(C_2H_5)_2O$	43	0	0	32
C_2H_5	10	Br	0.5	THF	0	23	21	0
C_2H_5	20	Br	1	THF	0	0	61	0
C_3H_7	2	Br	1	THF	47	0	0	13
C_3H_7	20	Br	1	THF	0	34	21	0
C_3H_7	20	Br	22	THF	0	0	61	0
C_4H_9	2	Br	1	THF–$(C_2H_5)_2O$	41	0	0	37
C_4H_9	10	Br	1	THF	0	45	0	0
C_4H_9	20	Br	1	THF	0	23	37	0
C_6H_{13}	2	Br	1	THF	34	0	0	11
C_6H_{13}	4	Br	1	THF	6	29	0	0
C_6H_{13}	20	Br	1	THF	0	31	20	0
$CH(CH_3)_2$	2	Br	1	THF	33	0	0	0
$CH(CH_3)_2$	4	Br	1	THF	5.7	37	0	0
$CH(CH_3)_2$	20	Br	1	THF	0	68	0	0
$CH_2CH(CH_3)_2$	2	Br	1	THF	55	0	0	10
$CH_2CH(CH_3)_2$	20	Br	1	THF	0.7	38	0	2
$C_2H_4CH(CH_3)_2$	2	Cl	1	THF	49	0	0	23
$C_2H_4CH(CH_3)_2$	20	Cl	1	THF	0	64	0	0
	2	Br	1	THF	52	0	0	11
	4	Br	1	THF	46	0	0	0
	20	Br	1	THF	8.6	68	0	0
$C(CH_3)_3$	4	Br	1	THF	78	0	0	0
$C(CH_3)_3$	20	Br	1	THF	78	0	0	0
$C_2H_4C_6H_5$	2	Br	1	THF	43	0	0	9
$C_2H_4C_6H_5$	20	Br	1	THF	0	52	0	0
$CH_2C_6H_5$	2	Cl	1	THF–$(C_2H_5)_2O$	63	0	0	0
$CH_2C_6H_5$	4	Cl	1	THF	78	0	0	0
$CH_2C_6H_5$	20	Cl	1	THF	11	14	0	0
C_6H_5	2	Br	1	THF–$(C_2H_5)_2O$	36	0	0	40
C_6H_5	20	Br	1	THF	39	31	0	0

morpholino and 8-chloro-5-morpholino derivatives6) respectively by the scheme shown in Chart 5. The reaction of XIII with phenylmagnesium bromide gave 4-phenyl-3,4-dihydro derivative (XIV) as the major product in 46% yield, accompanied by minor products, IIIl (7%) and XV (4%), while the reaction of X under the same condition afforded only 4-phenyl-3,4-dihydro derivative (XVI) in 82% yield. Moreover, while 4-ethyl-3,4-dihydro derivative (XVII) was afforded by the reaction of X with 10 moles of ethylmagnesium bromide, enhancement of the reagent (20 moles) and prolonged reaction period gave rise to 8-*sec*-butyl-4-ethyl-3,4-dihydro derivative (XIX) (reaction 3) by way of 4,8-diethyl-3,4-dihydro derivative (XVIII) (reaction 2), leaving 5 position unattacked.

From those results, it is suggested that the reactivity towards nucleophilic attack by Grignard reagents in the 2-phenylpyrimido[4,5-*d*]pyridazine ring is in the order of 4>8>5 position.

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6) S. Yurugi and M. Hieda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1522 (1972).

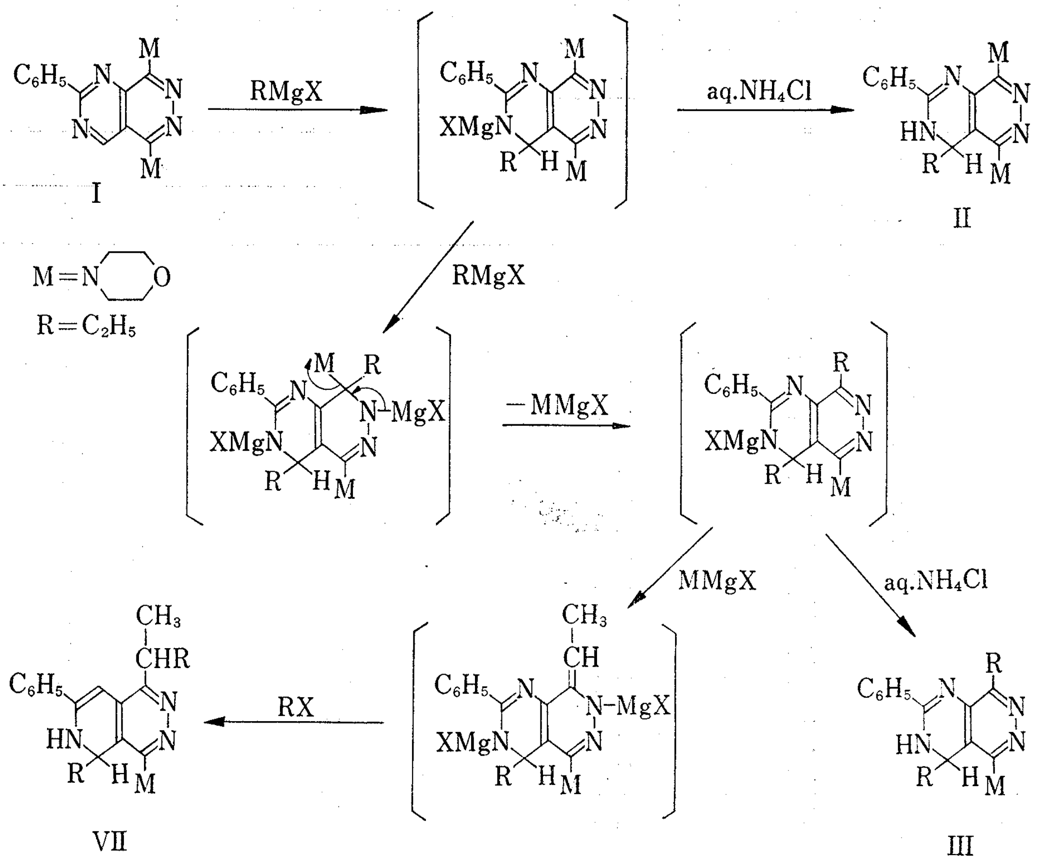

Chart 4

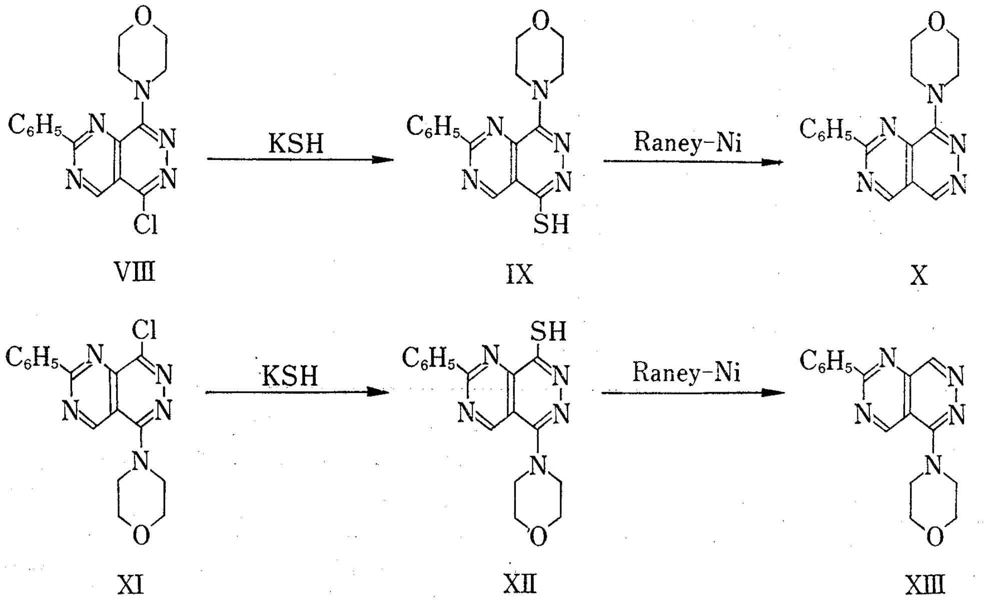

Chart 5

Subsequently, similar reactions with other analogous tetraazanaphthalene derivatives were undertaken. The reaction of Grignard reagents with 5,7-dimorpholino-2-phenylpyrimido-[4,5-*d*]pyrimidine (XX)[7] also occurred at 3, 4 C=N bond to provide 5,7-dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyrimidine (XXI). The results are summarized in Table VII.

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[7] S. Yurugi, A. Miyake, and N. Tada, *J. Takeda Res. Lab.*, 32, 251 (1973).

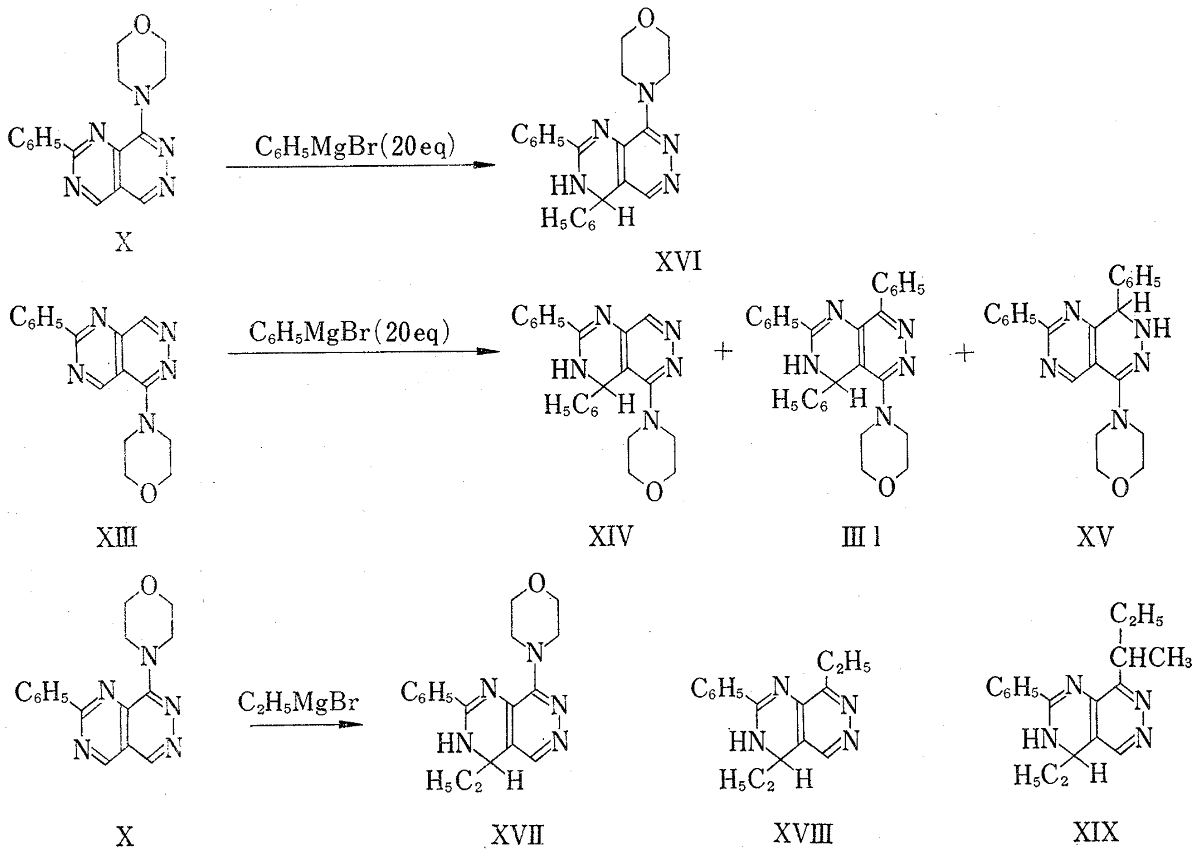


Chart 6

TABLE VI. Reaction Condition and Product Distribution of the Reaction of X with Ethylmagnesium Bromide

Ratio of reagent EtMgBr/X	Reaction time (hr)	Solvent	Product (%)		
			XVII	XVIII	XIX
10	1	THF	69	0	0
20	1	THF	0	43	15
20	5	THF	0	0	50

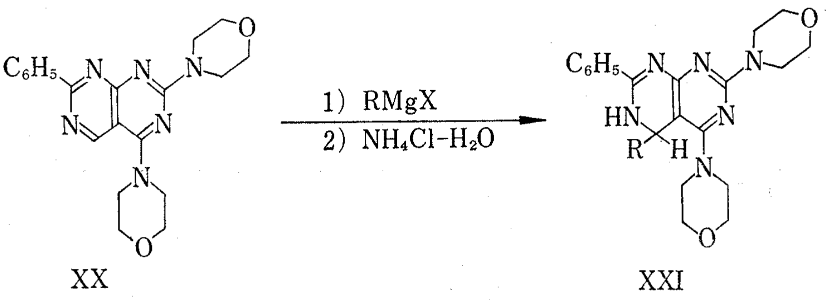
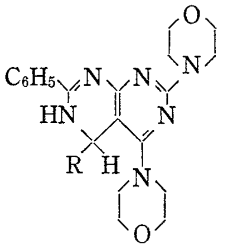
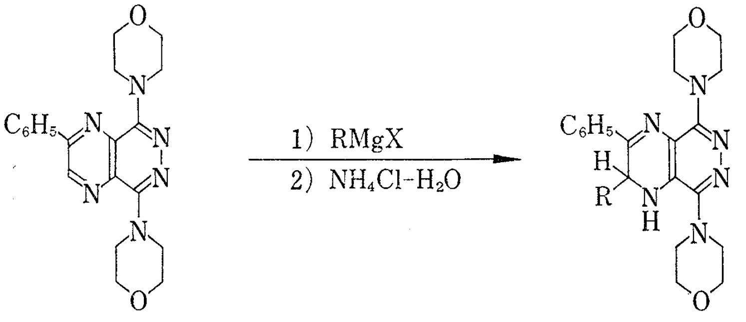


Chart 7

Table VII. 5,7-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyrimidine (XXI)



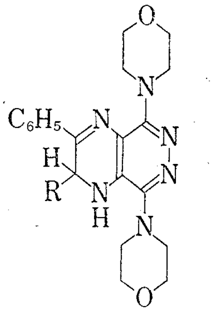
XXI	R	Yield	mp (°C)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
a	$CH_2C_6H_5$	87	98—100	$C_{27}H_{30}O_2N_6$	68.91	6.43	17.86	68.56	6.29	17.64
b	CH_3	23	222—223	$C_{21}H_{26}O_2N_6$	63.94	6.64	21.31	63.84	6.66	21.28
c	C_2H_5	59	192—194	$C_{22}H_{28}O_2N_6$	64.68	6.91	20.58	64.64	6.92	20.23
d	C_4H_9	55	103—105	$C_{24}H_{32}O_2N_6$	66.03	7.39	19.25	66.10	7.33	19.24
e	C_6H_5	50	221—222	$C_{26}H_{28}O_2N_6$	68.40	6.18	18.41	68.37	6.15	18.43



XXII XXIII

Chart 8

Table VIII. 5,8-Dimorpholino-2-phenyl-3-substituted-3,4-dihydropyrazino[2,3-*d*]pyridazine (XXIII)



XXIII	R	Yield (%)	mp (°C)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
a	$CH_2C_6H_5$	68	225—226	$C_{27}H_{30}O_2N_6$	68.91	6.43	17.86	68.72	6.69	17.61
b	CH_3	61	198—200	$C_{21}H_{26}O_2N_6$	63.94	6.64	21.31	63.71	6.70	21.28
c	C_2H_5	44	133—135	$C_{22}H_{28}O_2N_6$	64.68	6.91	20.58	64.71	6.76	20.48
d	C_6H_5	84	133—135	$C_{26}H_{28}O_2N_6\cdot$ AcOEt	66.15	6.66	15.43	65.95	6.67	15.45

Moreover, similar reaction proceeded in the case with 5,8-dimorpholino-2-phenylpyrazino-[2,3-*d*]pyridazine (XXII)[8] giving rise to 3-substituted-3,4-dihydro derivatives (XXIII). (Table VIII).

In the reaction of XX and XXII, no such product as III and VII was observed even when a large excess of the reagent was used.

Among the derivatives obtained by the above reaction potential diuretic activity in rat was observed in compounds IIa and IIj, moderate activity in IIm, IIo, IIq, and XXIa, and weak activity in IIi, IIk, IIn, and IIr.

Experimental[9]

5,8-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyridazine (II)——General Procedure: a) To a stirred solution of I (1 mmole) in THF (50 ml) was added dropwise a solution of the Grigaard reagent (2—4 mmole) in THF (50 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl and the resulting solution was extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from EtOH, MeOH or AcOEt to give II (Table I).

b) To a stirred solution of I (1 mmole) in THF (50 ml) was added dropwise a solution of organolithium compound (2—5 mmole) in ether (30 ml) at 0—5°. After 0.5—1 hr the reaction mixture was hydrolyzed with H_2O, and the resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (4: 1) and recrystallized from EtOH to give II (Table II).

4-Benzyl-5,8-dimorpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IIa)——To a stirred solution of I (1 mmole) in THF (50 ml) was added a solution of benzylmagnesium chloride (4 mmole) in THF (50 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl (100 ml) and the resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from EtOH to give IIa.

5-Morpholino-2-phenyl-4,8-disubstituted-3,4-dihydropyrimido[4,5-*d*] pyridazine (III)——General Procedure: To a stirred solution of I (1 mmole) in THF (50 ml) was added dropwise a solution of Grignard reagent (4—20 mmole) in THF (50 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl and resulting solution was extracted with $CHCl_3$ and the extract was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (4: 1) to give III. III was recrystallized from EtOH, AcOEt or C_6H_6. Further elution with C_6H_6–acetone (4: 1) afforded II.

4,8-Dibenzyl-5-morpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (IIIa)——To a stirred solution of I (3.8 g) in THF (50 ml) was added dropwise a solution of benzylmagnesium chloride. prepared from 25.4 g of benzyl chloride and 4.8 g of magnesium in THF (50 ml), at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6 to give IIIa (0.65 g, 14%), colorless needles, mp 116—120°. NMR (in $CDCl_3$) τ: 6.20—7.20 (10H, m, morpholine), 5.56 (2H, s, $C\underline{H}_2$–Ph), 5.06—5.28 (1H, m, C_4-H), 3.60—3.80 (1H, s, NH), 2.26—3.02 (15H, m, Ph).

Further elution with C_6H_6–acetone (9: 1) gave IIa (0.5 g, 11%).

4,8-Diethyl-5-piperidino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (V)——a) To a stirred solution of IV (0.5 g) in THF (20 ml) was added a solution of ethylmagnesium bromide, prepared from 0.17 g of magnesium and 0.8 g of ethyl bromide in THF (10 ml), at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt to give V (0.25 g, 54%), pale yellow needles, mp 215—216°. *Anal.* Calcd. for $C_{21}H_{27}N_5$: C, 72.17; H, 7.79; N, 20.04. Found: C,

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

9) 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 spectrometers. Organolithium compounds, benzyl-,[10] butyl-,[11] picolinyl-,[12] 3-pyridyl-,[13] and thienyllithium,[14] were all prepared by the methods described in literatures.

10) H. Gilmann and G.L. Schwebkes, *J. Org. Chem.*, **27**, 4259 (1962).

11) H. Gilmann, *J. Am. Chem. Soc.*, **54**, 1957 (1923).

12) N.N. Goldberg, L.B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

13) H.F. French, B.M. Perfetti, and R. Levine, *J. Am. Chem. Soc.*, **75**, 3843 (1953).

14) N.M. Lofgren and C. Tegner, *Acta Chem. Scand.*, **6**, 1020 (1952).

72.28; H, 7.73; N, 19.80. NMR (in $CDCl_3$) τ: 9.03 (3H, t, $J=7$ Hz, CH_3), 8.16 (3H, t, $J=7.5$ Hz, CH_3), 8.20—8.44 (8H, m, CH_2), 6.70—7.20 (4H, m, CH_2), 5.38 (1H, t, $J=6$ Hz, C_4-H), 1.60—2.60 (5H, m, Ph).

b) To a stirred solution of VI (0.5 g) in THF (20 ml) was added a solution of ethylmagnesium bromide in THF (10 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl (100 ml). The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt to give V (0.3 g, 65%).

5-Morpholino-2-phenyl-4,8-disubstituted-3,4-dihydropyrimido[4,5-*d*]pyridazine (VII)——General Procedure: To a stirred solution of I (1 mmole) in THF (50 ml) was added a solution of Grignard reagent (10—20 mole) at room temperature. After 0.5 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. VIIa and VIIb were obtained by the recrystallization of the residue. In the case of VIIc and VIId. the residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (4: 1). (Table IV)

8-*sec*-Butyl-4-ethyl-5-morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (VIIa)——To a stirred solution of I (3.87 g) in THF (50 ml) was added a solution of ethylmagnesium bromide (20 mmole) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt to give VIIa (2.3 g, 61%). UV λ_{max}^{EtOH} nm (ε): 244 (19000), 345 (8800). NMR (in $CDCl_3$) τ: 9.04 (6H, q. $J=7.2$ Hz, CH_3), 8.59 (3H, d, $J=7.2$ Hz, CH_3), 8.00—8.40 (4H, m, $C\underline{H}_2$–CH_3), 6.16—7.10 (9H, m, morpholine and C–H), 3.25—3.50 (1H, s, NH), 2.06—2.64 (5H, m, Ph).

8-Morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (X)——5-Chloro-8-morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (VIII)⁶⁾ (5.0 g) was added to a stirred solution of 10% KSH–EtOH (60 ml) at room temperature and set aside overnight. After removal of the solvent *in vacuo*, the residue was dissolved in H_2O and acidified with AcOH. The resulting precipitate was collected by filtration to give IX (5.0 g) which was used for the subsequent step without further purification. To a solution of IX (5.0 g) in acetone (500 ml), Raney nickel (*ca.* 50 g) was added and the suspension was heated under reflux for 30 min. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1) to give X (2.9 g, 65%), mp 183—185°. *Anal.* Calcd. for $C_{16}H_{15}ON_5$: C, 65.51; H, 5.15; N, 23.88. Found: C, 65.59; H, 5.33; N, 23.65. NMR (in $CDCl_3$) τ: 5.60—6.21 (8H, m, morpholine), 2.32—2.50 (3H, m, Ph), 1.40—1.61 (2H, m, Ph), 0.94 (1H, s, C_5–H), 0.58 (1H, s, C_4–H).

5-Morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (XIII)——8-Chloro-5-morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (XI)⁶⁾ (5.0 g) was added to a solution of 10% KSH–EtOH (60 ml) at room temperature and set aside overnight. After removal of the solvent *in vacuo* the residue was dissolved in H_2O and acidified with AcOH. The resulting precipitate was collected by filtration to give XII (4.8 g) which was used for subsequent step without further purification. To a solution of XII (4.8 g) in acetone (500 ml) Raney nickel (*ca.* 50 g) was added and the suspension was heated under reflux for 30 min. The mixture was filtered and filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1) to give XIII (2.3 g, 52%), mp 234—236°. *Anal.* Calcd. for $C_{16}H_{15}ON_5$: C, 65.51; H, 5.15; N, 23.88. Found: C, 65.88; H, 5.08; N, 23.62. NMR (in $CDCl_3$) τ: 5.90—6.34 (8H, m, morpholine), 2.34—2.50 (3H, m, Ph), 1.30—1.46 (2H, m, Ph), 0.60 (1H, s, C_8–H), 0.40 (1H, s, C_4–8).

8-Morpholino-2,4-diphenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (XVI)——To a stirred solution of X (0.59 g, 0.2 mmole) in THF (30 ml) was added a solution of phenylmagnesium bromide (4 mmole) in THF (20 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel to give XVI (0.61 g, 82%), mp 225—227°, pale yellow needles. *Anal.* Calcd. for $C_{22}H_{21}ON_5$: C, 71.14; H, 5.70; N, 18.86. Found: C, 70.92; H, 5.75; N, 18.63. NMR (in $CDCl_3$) τ: 6.80 (4H, s, morpholine), 6.05—6.30 (4H, m, morpholine), 4.24 (1H, s, C_4–H), 2.50—2.70 (8H, m, Ph), 2.00—2.12 (2H, m, Ph), 1.86 (1H, s, C_8–H).

Reaction of 5-Morpholino-2-phenylpyrimido[4,5-*d*]pyridazine (XIII) with Phenylmagnesium Chloride——To a stirred solution of XIII (0.59 g) in THF (30 ml) was added a solution of phenylmagnesium bromide (4 mmole) in THF (20 ml) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solutions was extracted with $CHCl_3$. Removal of solvent gave an oil, which was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1) to give XIV (0.28 g, 46%), mp 195—197°. *Anal.* Calcd. for $C_{22}H_{21}ON_5$: C, 71.14; H, 5.70; N, 18.86. Found: C, 71.33; H, 5.61; N, 18.59. NMR (in $CDCl_3$) τ: 6.86—7.00 (4H, m, morpholine), 6.16—6.28 (4H, m, morpholine,) 4.74 (1H, s, C_4–H), 2.52—2.70 (8H, m, Ph), 1.30 (1H, s, C_8–H), 1.08—1.24 (2H, m, Ph). Elution was further continued with the same solvent to give IIIl (0.05 g, 7%), mp 222—224°, which showed complete identity with an authentic sample in mixed melting point and IR spectrum, and further elution with C_6H_6–acetone (3: 2) gave XV (0.025 g, 4%), mp 245—248°. *Anal.* Calcd. for $C_{22}H_{21}ON_5$: C, 71.14; H, 5.70; N, 18.86. Found: C, 71.19; H, 5.55; N, 18.80. NMR (in $CDCl_3$) τ: 6.82—7.10 (4H, m, morpholine), 6.26—6.38 (4H, m, morpholine), 4.10 (1H, s, C_8–H), 2.52—2.72 (8H, m, Ph), 2.12—2.22 (2H, m, Ph), 1.13 (1H, s, C_4–H).

4-Ethyl-8-morpholino-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (XVII)——To a stirred solution of X (0.59 g) was added a solution of ethylmagnesium bromide (2 mmole) at room temperature. After

1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt-$(C_2H_5)_2O$ to give XVII (0.45 g, 69%), mp 186—188°. *Anal.* Calcd. for $C_{18}H_{21}ON_5$: C, 66.85; H, 6.55; N, 21.36. Found: C, 66.86; H, 6.69; N, 21.36. NMR (in $CDCl_3$) τ: 9.02 (3H, t, J=6 Hz, CH_3), 8.26 (2H, q, J=6 Hz, $\underline{CH_2}$-CH_3), 6.13 (8H, s, morpholine), 5.30 (1H, J=5.5 Hz, C_4-H), 2.44—2.56 (3H, m, Ph), 1.98—2.14 (2H, m, Ph), 1.70 (1H, s, C_5-H).

4,8-Diethyl-2-phenyl-3,4-dihydropyrimido[4,5-*d*]pyridazine (XVIII) and 8-*sec*-Butyl-4-ethyl-2-phenylpyrimido[4,5-*d*]pyridazine (XIX)——To a stirred solution of X (0.5 g) in THF (20 ml) was added a solution of ethylmagnesium bromide (4 mmole) at room temperature. After 1 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (4: 1) to give XIX (0.1 g, 15%), mp 147—149°. *Anal.* Calcd. for $C_{18}H_{22}N_4$: C, 73.43; H, 7.53; N, 19.03. Found: C, 72.93; H, 7.57; N, 18.73. NMR (in $CDCl_3$) τ: 8.98—9.17 (6H, m, CH_3), 8.60 (3H, d, J=7 Hz, CH_3), 7.40—7.96 (4H, m, $\underline{CH_2}$-CH_3), 6.16—6.34 (1H, m, C–H), 5.30 (1H, t, J=5 Hz, C_4-H), 2.56—2.66 (3H, m, Ph), 2.00—2.10 (2H, m, Ph), 1.58 (1H, s, C_5-H). Further elution of the column with C_6H_6–acetone (3: 2) gave XVIII (0.28 g, 43%), mp 196—198°. *Anal.* Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.82; H, 6.77; N, 20.74. NMR (in $CDCl_3$) τ: 9.01 (3H, t, J=7 Hz, CH_3), 8.60 (3H, t, J=7 Hz, CH_3), 8.24 (2H, q, J=7 Hz, $\underline{CH_2}$-CH_3), 6.78 (2H, q, J=7 Hz, $\underline{CH_2}$-CH_3), 5.30 (1H, t, J=5 Hz, C_4-H), 2.44—2.60 (3H, m, Ph), 1.92—2.06 (2H, m, Ph), 1.47 (1H, s, C_5-H).

5,7-Dimorpholino-2-phenyl-4-substituted-3,4-dihydropyrimido[4,5-*d*]pyrimidine (XXI)——To a stirred solution of XX (1 mmole) in THF (50 ml) was added a solution of Grignard reagent (8—20 mmoles) in THF (50 ml) at room temperature. After 2 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from C_6H_6 to give XXId and XXIe. In the case of XIXa, XXIb, and XXIc, the residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1). (Table VII).

5,8-Dimorpholino-2-phenyl-3-substituted-3,4-dihydropyrazino[2,3-*d*]pyridazine (XXIII)——To a stirred solution of XXII (0.5 mmole) in THF (25 ml) was added a solution of Grignard reagent (2 mmoles) in THF (25 ml) at room temperature. After 2 hr the reaction mixture was hydrolyzed with aqueous NH_4Cl. The resulting solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt to give XXIIIa. In cases that the product failed to crystallize, the residue was chromatographed on silica gel with C_6H_6–acetone (9: 1) as eluent to give XXIIIb, XXIIIc, and XXIIId (Table VIII).

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