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Studies on the Syntheses of N-Heterocyclic Compounds. VI.[1] Monosubstitution of 2-Phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine

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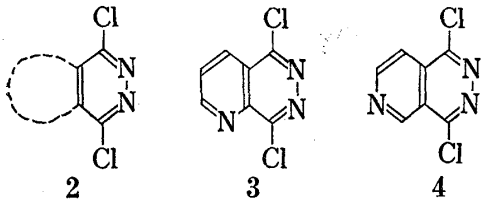
The reaction of 2-phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**) with a variety of primary and secondary amines afforded the corresponding mono-substituted compounds which were mixtures of two isomers, 5-substituted compound (**5**) and 8-substituted compound (**6**). Both isomers were separated and their structures were determined. Only one isomer was obtained by the reaction of **1** with morpholine or aniline under milder condition and its structure was proved to be 8-substituted compound. The reactivity of chlorine atoms at 5- and 8-position in **1** was discussed.

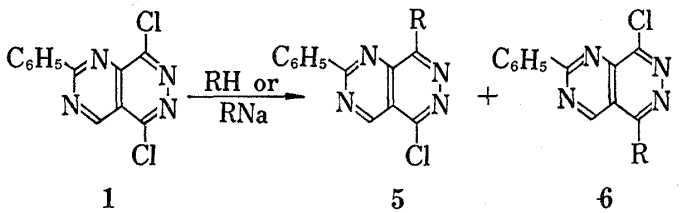
Previously,[1] we reported the synthesis of 2-phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**). The present paper deals with the mono-substitution of the dichlorides (**1**) with nucleophilic reagents. The reaction of **1** with a variety of primary and secondary amines was found to proceed smoothly even in a very mild condition. Allowing to stand at room temperature for 2—4 hr or refluxing in a solvent for several minutes, was enough to give monosubstituted products. Heating for a longer period gave rise to the 5,8-disubstituted products, description of which will be given in the following paper of this series.

In the nucleophilic substitution of dichloride (**2**) of tri- and tetraazanaphthalene which contains condensed pyridazine ring, it is expected that there will be a difference between the reactivities of two chlorine atoms because of the resonance effect[3] brought about by the nitrogens involved in the condensed ring to pyridazine ring. Nitta, *et al.*[4] have compared reactivities of both chlorine atoms in 5,8-dichloropyrido[2,3-*d*]pyridazine (**3**) based on super-delocalizability of chlorine atoms. Matsuura, *et al.*[5] have also estimated the reaction site of 5,8-dichloropyrido[3,4-*d*]pyridazine (**4**) based on the resonance effect by ring nitrogen of the pyridine ring (Chart 1).



2 **3** **4**

Chart 1



1 **5** **6**

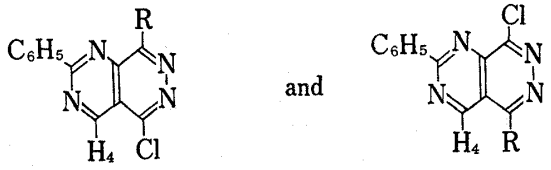
Chart 2

With respect to the mono-substitution of **1**, it is necessary to compare the reactivity of the two chlorine atoms on the pyridazine ring toward nucleophilic attack. In the nuclear magnetic resonance (NMR) spectra (in CF_3COOD) of the mono-substituted products, which

1) Part V: S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1513 (1972).
2) Location: *Jūso, Higashiyodogawa-ku, Osaka.*
3) A.R. Katritzky, A.J. Boulton, and J.M. Lagowski (eds.), "Advances in Heterocyclic Chemistry," Vol. 3, Academy Press, New York and London, 1964.
4) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).
5) I. Matsuura and K. Okui, *Chem. Pharm. Bull.* (Tokyo), **17**, 2266 (1969).

was obtained when **1** was refluxed with aliphatic amines in ethanol or chloroform, the ring proton at 4-position appeared as doublet around 0 τ. This fact suggests that the product may be a mixture of two isomers, namely, 2-phenyl-5-chloro-8-substituted pyrimido[4,5-*d*]-pyridazine (**5**) and 2-phenyl-5-substituted-8-chloropyrimido[4,5-*d*]pyridazine (**6**). The integral value of the two absorptions of the doublet were nearly equal to each other in every derivative, suggesting ratio of the two isomers in the mixture is 1:1. The similar results were observed in the case of mono-substitution of **1** with sodium methoxide. Physical data and yields of the mono-substituted products, the mixture of **5** and **6**, are listed in Table I.

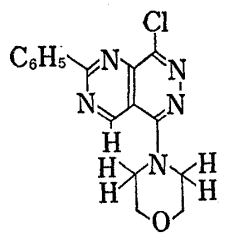
TABLE I. A Mixture of 2-Phenyl-5-chloro-8-substituted pyrimido[4,5-*d*]pyridazine (**5**) and 2-Phenyl-5-substituted-8-chloropyrimido[4,5-*d*]pyridazine (**6**)



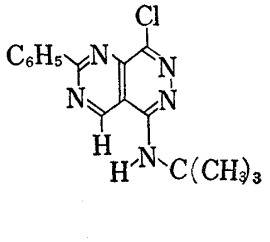
	R	τ of H_4 in NMR (CF_3 COOD)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a		0.00, −0.16	89.0	$C_{16}H_{14}ON_5Cl$	58.63	4.31	21.37	58.71	4.28	21.20
b		0.05, −0.10	85.0	$C_{17}H_{16}N_5Cl$	62.67	4.95	21.50	62.49	4.78	21.23
c	C_3H_7NH	0.06, −0.22	32.4	$C_{15}H_{14}N_5Cl$	60.10	4.67	23.38	60.31	4.46	23.05
d	iso-C_3H_7NH	0.08, −0.21	27.0	$C_{15}H_{14}N_5Cl$	60.10	4.67	23.38	60.40	4.63	23.66
e	C_4H_9NH	0.08, −0.26	97.0	$C_{16}H_{16}N_5Cl$	61.24	5.10	23.33	61.32	5.25	22.62
f	*t*-C_4H_9NH	0.06, −0.16	14.6	$C_{16}H_{16}N_5Cl$	61.24	5.10	23.33	60.87	5.23	22.21
g	 -CH_2NH	0.08, −0.22	72.0	$C_{19}H_{14}N_5Cl$	65.61	4.03	20.14	65.71	4.36	20.01
h	HOC_2H_4NH	0.07, −0.27	75.1	$C_{14}H_{12}ON_5Cl$	55.72	3.98	23.22	55.54	4.04	23.01
i	CH_3O	0.22, 0.01	86.0	$C_{13}H_9ON_4Cl$	57.25	3.30	20.55	58.27	3.22	20.54

The separations of each isomer from the mixtures were carried out on some of the above reaction products by fractional recrystallization or by the technique of column chromatography on silica gel. In the NMR spectra of the compound thus obtained, the signal of the proton at 4-position appeared as a singlet, and the chemical shifts of each pair of isomers were consistent with those of the parent mixture. Physicochemical data of the isomers separated are listed in Table II.

According to Table II, each isomer with a smaller *Rf* value shows higher melting point, a chemical shift to the lower field and a pK_a value slightly larger than the other isomer. The technique of nuclear Overhauser effect (NOE) was applied for the determination of the position of substituent in each isomer. Out of the two isomers (**5a** and **6a**) obtained by the substitution of morpholine, the one with smaller *Rf* value in TLC showed a NOE of 17.6% between the proton (H_4) at 4-position and methylenic protons adjacent to the nitrogen in morpholine. In the NMR spectra of the products substituted with *t*-butylamine, only the one



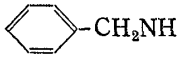
6a



6f

Chart 3

TABLE II. 2-Phenyl-5-chloro-8-substituted Pyrimido[4,5-*d*]pyridazine (**5**) and 2-Phenyl-5-substituted 8-Chloropyrimido[4,5-*d*]pyridazine (**6**)

	R	TLC (acetone:C_6H_6=1:10) larger *Rf* value				TLC (acetone:C_6H_6=1:10) smaller *Rf* value			
		mp (°C)	NMR (τ) H_4 in CF_3COOD	pK_a	UV λ_{max}^{EtOH} mμ (ε)	mp (°C)	NMR (τ) H_4 in CF_3COOD	pK_a	UV λ_{max}^{EtOH} mμ (ε)
a		198—220	0.00	1.9	243.5 (1.6×10^4) 284 (1.99×10^4) 368 (0.66×10^4)	211—213	−0.16	1.8	285 (2.59×10^4)
d	iso-C_3H_7NH	184—186	0.08	2.6	288 (2.0×10^4) 363 (0.7×10^4)	249—250	−0.21	2.9	278 (2.46×10^4) 378 (0.54×10^4)
e	C_4H_9NH	141—142	0.08	2.8	285 (2.02×10^4) 365 (0.7×10^4)	248—250	−0.24	2.9	279 (2.63×10^4) 378 (0.52×10^4)
f	*t*-C_4H_9NH	252—255	0.06	3.4	287 (2.05×10^4) 362 (0.75×10^4)	266—267	−0.16	3.6	288 (2.5×10^4) 377 (0.52×10^4)
g		169	0.04	3.4	283 (2.06×10^4) 365 (0.71×10^4)	245—247	−0.22	3.5	279 (2.79×10^4) 372 (0.54×10^4)
h	HOC_2H_4NH	212—215	0.07	2.8	284 (2.10×10^4) 360 (0.65×10^4)	238—240	−0.27	2.8	278 (2.62×10^4) 370 (0.52×10^4)

with a smaller *Rf* value also showed NOE of 21.4% between H_4 and NH, and 10.2% between H_4 and methyl proton of *t*-butyl group (Chart 3).

Further confirmation of the structures was made by the following chemical modification: Each of the isomers of butylamino-derivative (**5e** and **6e**) separated by column chromatography was treated with sodium hydrosulfide in ethanol to give the corresponding thione derivatives (**7** and **8**), the desulfurization of which with Raney Nickel afforded 2-phenyl-8-butylaminopyrimido[4,5-*d*]pyridazine (**9**) and 2-phenyl-5-butylaminopyrimido[4,5-*d*]pyridazine (**10**), respectively (Chart 4). In the NMR spectra (in d_6-DMSO) of the hydrochloride salts of **9** and **10**, chemical shift of ring proton (H_4) was observed at −0.11 τ in **9** and −0.80 τ

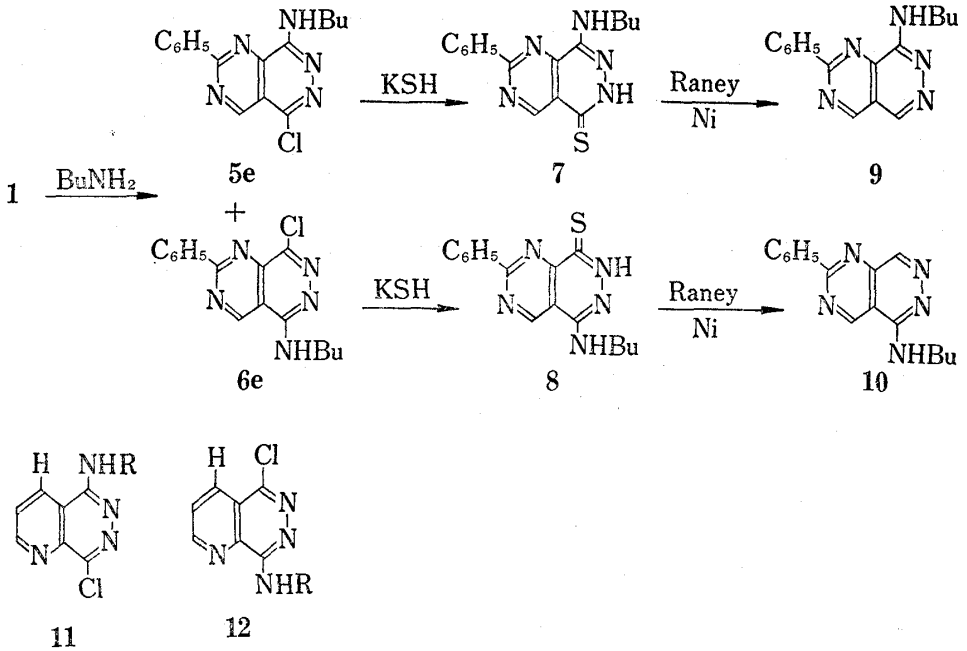


Chart 4

in **10** respectively. A large lower field shift of H_4 in the hydrochloride salt of **10** than that of **9** indicated that butylamino group in **10** is located at *peri* position to H_4. Thus **10** was assigned to 5-butylamino-compound and hence the parent compound (**6e**) which has a smaller *Rf* value in TLC was assigned as 2-phenyl-5-butylamino-8-chloropyrimido[4,5-*d*]pyridazine. Similar observation has been reported by Castle, *et al.*[6] with respect to a structural identification of both isomers in mono-substituted compounds (**11** and **12**) of 5,8-dichloropyrido[2,3-*d*]pyridazine (**3**). This result is also consistent with the above-mentioned rule based on the correlation in the physico-chemical data, and supports the structural assignments to the rest of the three isomeric pairs in Table II. Above results indicate that it is possible to estimate the structure and ratio of components in the product of mono-substitution reaction of dichloride (**1**) based on the chemical shift and integral value of the H_4 proton signal in the NMR spectrum, and that under the reaction condition described earlier, refluxing **1** with two equimolar amines in ethanol or chloroform, the ratio of the 5-amino derivatives to 8-amino derivatives was always nearly 1:1. The latter fact suggests that the difference in the reactivities of the two chlorides was much smaller than we had expected. In order to pursue the small difference, however, the reactions under milder conditions were undertaken.

As a result it was found that the reaction of **1** with morpholine or aniline in chloroform under room temperature yielded only one mono-substituted compound. The produtt of the reaction with morpholine was proved to be identical with 2-phenyl-5-chloro-8-morpholinopyrimido[4,5-*d*]pyridazine (**5a**) by comparing with the authentic sample described above. The structure of the compound (**5j**) obtained by the reaction with aniline was determined in the following way: Treatment of **5j** with morpholine gave a disubstituted product (**13**) which was identical with the compound obtained by the reaction of **6a** with aniline, but **13** was different from the compound (**14**) which was obtained by the reaction of **5a** with aniline (Chart 5). From this result the compound was assigned as 2-phenyl-5-chloro-8-anilinopyrimido[4,5-*d*]pyridazine (**5j**). Reaction of **1** with piperidine or butylamine under the same condition described above, however, gave an isomeric mixture of mono-substituted products in a 1:1 ratio. In these cases no difference in the reactivities of both chlorine atoms was found. These findings led to the conclusion that in the 2-phenyl-5,8-dichloropyrimido-[4,5-*d*]pyridazine (**1**) 8-position is a little more reactive than 5-position toward nucleophilic reagent.

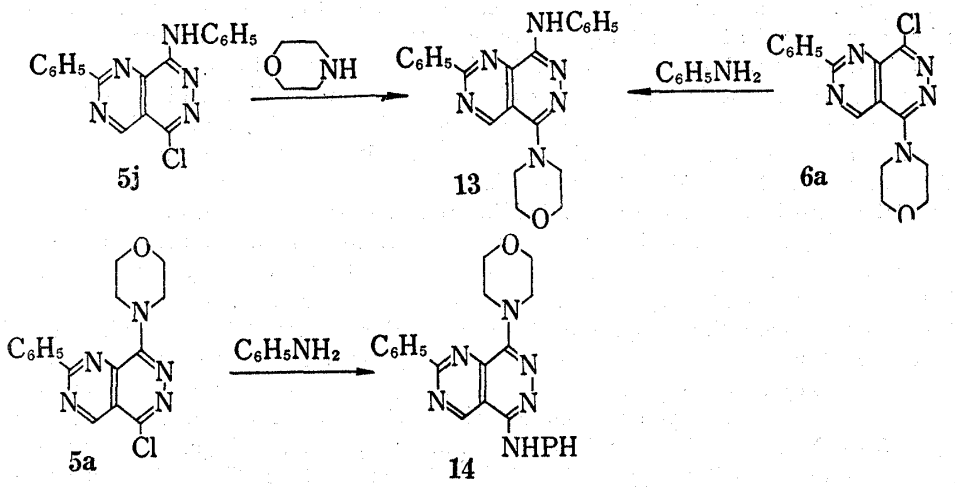


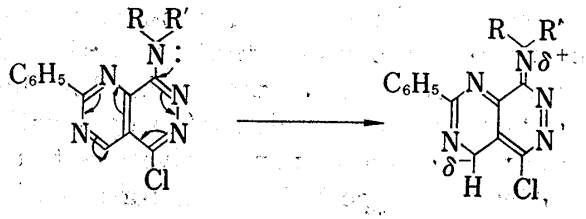
Chart 5

The superdelocalizability ($Sr^{(N)}$)[7] and the frontier electron density ($fr^{(N)}$)[7] of **1** for nucleophilic reagent which might have closer relation to the displacement reaction is shown as

6) N.R. Patel, W.M. Rich, and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 13 (1968).
7) $Sr^{(N)}$ and $fr^{(N)}$ were calculated by ω-technique.

follows: $Sr^{(N)}$ at 5-position=1.31, $Sr^{(N)}$ at 8-position=1.26; $fr^{(N)}$ at 5-position=0.234, $fr^{(N)}$ at 8-position=0.236. Although these data show that the difference in the reactivities of both chlorine atoms will be extremely small or nothing, experimental results show a little difference in the case of weaker basicity of amines such as aniline and morpholine described above. This difference will be caused by a resonance effect of phenyl group.

The interesting physico-chemical correlation found in the series of each isomer of the mono-substituted compound (Table III) leads us to the following speculations about chemical shifts of ring proton (H_4). The difference of chemical shifts of H_4 in both siomers in NMR might be explained as follows; the lone pair on amine nitrogen at 8-position in **5** will increase the electron density on ring carbon atom at 4-position by reasonance effect, while in the case of **6** there will be no effect as in **5** (Chart 6). Therefore it is considered that the nuclear carbon atom at 4-position in **5** would exists in an electron-rich state and as the result the chemical shift of the proton on that carbon has been observed at upper field.



5 **15**

Chart 6

Although a difference of pK_a value in both isomers is not so large, 5-substituted isomer (**6**) shows a little larger pK_a value than that of 8-substituted isomer (**5**). In the case of 8-substituted compound (**5**) an electron density on amine nitrogen will be decreased owing to the resonance effect by phenyl group.

Experimental

2-Phenyl-5-chloro-8-substituted pyrimido[4,5-*d*]pyridazine (5) and 2-Phenyl-5-substituted-8-chloropyrimido[4,5-*d*]pyridazine (6) (Table I)——The general procedure is as follows: a) A mixture of 2-phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**) (5 mmole), aliphatic amine (10 mmole) and EtOH (50 ml) was refluxed for 10—20 min. The end point of the reaction was checked by TLC (acetone:C_6H_6=1:4) on silica gel. After cooling, the resulting crystals were collected by filtration followed by recrystallization from EtOH to give an isomeric mixture (**5** and **6**) of the mono-substituted products as yellow crystals.

b) The same procedure as a) was carried out except that $CHCl_3$ was employed instead of EtOH and that the reaction was carried at room temperature or with cooling. After evaporation of the solvent *in vacuo*, H_2O was added to the residue to give crystals which were recrystallized from EtOH to give the mono-substituted products. An isomeric mixture was obtained when piperidine and benzylamine was used as amine, while only one isomer (5) was obtained in the case of morpholine and aniline.

c) An isomeric mixture of the mono-methoxy compound (**5i** and **6i**) was obtained by reaction of 1 with one mole equivalent of MeONa in MeOH for 3—4 hr under room temperature.

Separation of the Both Isomers from Isomeric Mixture (Table II)——Separation of the mono-substituted compound (**5a** and **6d**, **5e** and **6e**, **5f** and **6f**) was carried out by column chromatography on silica gel, eluted with a solvent system of C_6H_6:acetone (10:1). Separation of the both isomers (**5a** and **6a**, **5g** and **6g**, **5h** and **6h**) was carried out by fractional recrystallization from EtOH or acetone.

2-Phenyl-8-butylamino-5,6-dihydropyrimido[4,5-*d*]pyridazine-5-thione (7)——A mixture of **5e** (1.0 g) and 20% KSH–EtOH (70 ml) was stirred for 8 hr under room temperature. After evaporation of the solvent, the residue was dissolved in H_2O. Indissolved solid was removed by filtration and the filtrate was adjusted to pH 2—3 by conc. HCl to afford **7** as yellow granules (1.0 g, 100%), mp 283—286°. *Anal.* Calcd. for $C_{16}H_{17}N_5S$: C, 61.94; H, 5.16; N, 22.58. Found: C, 61.35; H, 5.38; N, 23.58. IR (in Nujol) cm^{-1}: 1590 (CSNH).

2-Phenyl-5-butylamino-7,8-dihydropyrimido[4,5-*d*]pyridazin-8-thione (8)——A mixture of **6e** (1.5 g) and 20% KSH–EtOH (130 ml) was treated in similar manner as in the case of **7** to give **8** as yellow granules (1.4 g, 95%), mp 235—236°. *Anal.* Calcd. for $C_{16}H_{17}N_5S$: C, 61.94; H, 5.16; N, 22.58. Found: C, 61.69; H, 5.38; N, 22.33. IR (in Nujol) cm^{-1}: 1555, 1520 (CSNH).

1-Phenyl-8-butylaminopyrimido[4,5-d]pyridazine (9)——A mixture of **7** (1.55 g), Raney Nickel (25 g) and acetone (200 ml) was refluxed for 30 min and filtered. The evaporation of the solvent *in vacuo* gave **9** as an oil (0.4 g, 30%). This substance was observed as one spot on TLC (acetone:C_6H_6=1:4) and in IR spectrum (in Nujol) the absorption band at 1590 due to thiolactam structure in **7** disappeared. The NMR spectrum (in $CDCl_3$) of **9** showed the signal of ring proton (H_4) at 0.63 τ (singlet) and H_5 at 1.06 τ. *Anal.* Calcd.

for $C_{16}H_{17}N_5$: C, 68.82; H, 6.09; N, 25.09. Found: C, 68.82; H, 6.03; N, 25.09. This oil (**9**) was dissolved in 10% HCl to afford hydrochloride of **9** as colorless needles, mp 235—236° (decomp.). The signal of H_4 of the hydrochloride salt in NMR (in d_6-DMSO) was observed at -0.11 τ (singlet).

2-Phenyl-5-butylaminopyrimido[4,5-*d*]pyridazine (10)——**8** (1.55 g) was treated in a similar manner as in the case of **9** to afford **10** as colorless granules (0.25 g, 70%). In IR spectrum of this substance, the absorption band at 1555 and 1520 cm^{-1} due to this thiolactam structure in **8** disappeared and in NMR (in $CDCl_3$) of **10** the signal of H_4 and H_5 were observed at 0.02 and 0.96 τ, respectively. **10** was dissolved in 10% HCl to yield hydrochloride of **10** as colorless needles, mp 215—218°. *Anal.* Calcd. for $C_{16}H_{17}N_5HCl$: C, 60.86; H, 5.71; N, 22.19. Found: C, 59.29; H, 5.78; N, 21.41. The signal of H_4 in the hydrochloride salt in NMR (in d_6-DMSO) was observed at -0.80 τ.

2-Phenyl-5-chloro-8-anilinopyrimido[4,5-*d*]pyridazine (5j)——The dichloride (1,1 mmole) was dissolved in $CHCl_3$ (30 ml), to which was added aniline (2 mmole) was dissolved in $CHCl_3$ (30 ml), to which was added aniline (2 mmole) with stirring under room temperature and stirring was continued for 5 hr. After evaporation of the solvent *in vacuo*, H_2O was added to the residue to give crystals which were collected by filtration. Recrystallization from EtOH gave **5j** as colorless needles in 72.7% yeild, mp 209—210°. *Anal.* Calcd. for $C_{18}H_{12}N_5Cl$: C, 64.96; H, 3.59; N, 20.98; Cl, 10.64. Found: C, 64.72; H, 3.44; N, 20.79; Cl, 10.52.

2-Phenyl-5-morpholino-8-anilinopyrimido[4,5-*d*]pyridazine (13)——a) A solution of **6a** (0.5 g) and aniline (1 ml) in EtOH (30 ml) was refluxed for 4 hr. After standing overnight, the resulting crystals were filtered and recrystallized from EtOH to give **13** as orange needles (0.3 g, 52%), mp 262—263°. *Anal.* Calcd. for $C_{20}H_{20}ON_6$: C, 68.75; H, 5.21; N, 21.88. Found: C, 68.80; H, 5.21; N, 21.69. NMR (in CF_2·COOD) τ: -0.01 (1H, singlet, ring proton H_4).

b) A mixture of **5j** (0.5 g) and morpholine (5 ml) was heated at 150—160° for 4 hr. After removal of excess morpholine *in vacuo*, H_2O was added to the residue to give crystals which were filtered and recrystallized from EtOH to give **13** as orange needles (0.4 g, 70%), mp 263°. *Anal.* Calcd. for $C_{22}H_{20}ON_6$: C, 68.75; H, 5.21; N, 21.88. Found. C, 68.77; H, 5.20; N, 21.76. NMR (in CF_3COOD) τ: 0.00 (1H, singlet, ring proton H_4).

2-Phenyl-5-anilino-8-morpholinopyrimido[4,5-d]pyridazine (14)——A solution of **5a** (0.5 g) and aniline (1 ml) in EtOH (30 ml) was refluxed for 4 hr. After standing overnight, the resulting crystals were filtered and recrystallized from EtOH to give **14** as reddish orange needles (0.3 g, 52%), mp 234—235°. *Anal* Calcd for $C_{22}H_{20}ON_6$: C, 68 75; H, 5.21; N, 21.88. Found: C, 68.88; H, 5.25; N, 21.86. NMR (in CF_3·COOD) τ: -0.40 (1H, singlet, ring proton H_4).

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