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Studies on the Syntheses of N-Heterocyclic Compounds. VII.[1] 2-Aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine

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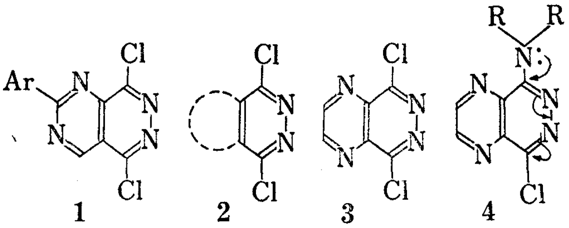
When 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**) was reacted with a variety of nucleophiles, such as amines, sodium methoxide, sodium azide, sodium sulfide *etc.*, 5,8-disubstituted compounds (**5**) were obtained. Treatment of 2-phenyl-5-chloro-8-morpholinopyrimido[4,5-*d*]pyridazine (**9**, $^{R}_{R}{>}N$: morpholino) or 2-phenyl-5-morpholino-8-chloropyrimido[4,5-*d*]pyridazine (**10**, $^{R}_{R}{>}N$: morpholino) with nucleophiles gave the corresponding products with a different kind of substituents at 5- and 8-position (**12** and **13**). The phenyl group at 2-position seems to accelerate the substitution at position **5** and **8**. The reaction of 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazine (**5**) with chlorine afforded the dichloride (**1**, Ar: phenyl). Among the synthesized disbstituted compounds, **5v**, **5h**, **5i**, **5j**, **5k**, **5m**, **5C**, **5E**, **5F**, **5K**, **5M** and **5O** showed diuretic activity.

In the preceding paper[1] nucleophilic mono-substitution of 2-aryl-5,8-dichloropyrimido-[4,5-*d*]pyridazine (**1**)[3] has been reported. This paper deals with the disubstitution reaction of **1** with various nucleophiles.

In regard to the nucleophilic substitution of 1,4-dichloropyridazine system (**2**), several papers are found in the literatures,[4-8] but none of them have succeeded in the disubstitution by aliphatic amine. On the other hand, the disubstitution of the dichloride (**2**) with arylamines occurs smoothly. According to Castle, *et al.*,[8] the difference in the reactivity between aliphatic and aromatic amines with 5,8-dichloropyrazino[2,3-*d*]pyridazine (**3**) can be explained on the basis of the higher electron donating capacity of aliphatic amines at C_5 which becomes effective after monosubstitution has taken place; *i.e.* the carbon atom at 8-position becomes more electronegative, which prevents the second nucleophilic attack to 8-position (Chart 1).



1 2 3 4

Chart 1

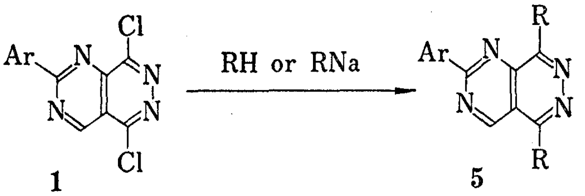


Chart 2

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[1] Part VI: S. Yurugi and M. Hieda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1522 (1972).

[2] Location: *Jûso, Higashiyodogawa-ku, Osaka.*

[3] S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1513 (1972).

[4] S. Robinson and R.D. Haworth, *J. Chem. Soc.*, **1948**, 777.

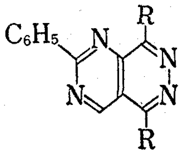
[5] J. Druey and B.H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

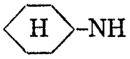
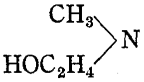
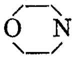
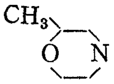
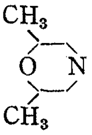
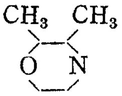
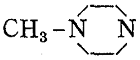
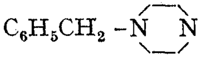
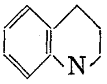
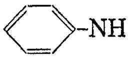
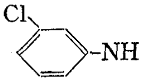
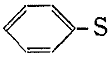
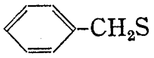
[6] Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).

[7] I. Matsuura and K. Okui, *Chem. Pharm. Bull.* (Tokyo), **17**, 2266 (1969).

[8] N.R. Patel and R.N. Castle, *J. Heterocyclic Chem.*, **3**, 512 (1966).

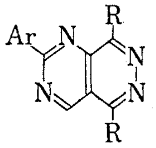
TABLE I. 2-Phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (5)

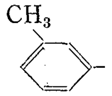
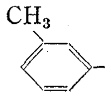
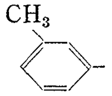
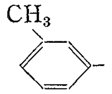
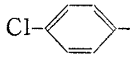
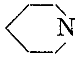
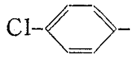
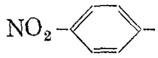
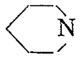
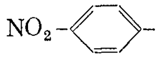
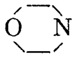
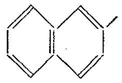
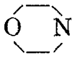
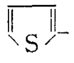
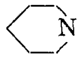
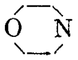
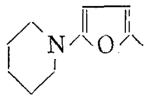
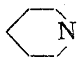
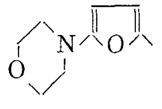
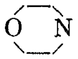


	R	mp (°C)	Yield (%)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
a	C_3H_7NH	227—229	80.0	$C_{18}H_{22}N_6$	67.08	6.83	26.09	66.15	6.55	25.72
b	iso-C_3H_7NH	265	37.6	$C_{18}H_{22}N_6$	67.08	6.83	26.09	66.75	6.65	25.93
c	$CH_3OC_2H_4NH$	116—117	46.8	$C_{18}H_{22}O_2N_6$	63.88	6.55	24.84	61.10	6.30	24.07
d	$C_2H_5OC_2NH$	125—127	29.0	$C_{20}H_{26}O_2N_6$	62.80	6.85	21.98	62.45	6.78	21.96
e		223—226	68.5	$C_{24}H_{30}N_6$	71.61	7.51	20.88	71.65	7.69	20.81
f	$C_6H_5CH_2NH$	85—87	72.0	$C_{26}H_{22}N_6$	74.62	5.30	20.08	74.33	5.41	20.30
g	 $\left.\begin{matrix}CH_3\\HOC_2H_4\end{matrix}\right\rangle N$	119—121	78.2	$C_{18}H_{22}O_2N_6$	61.02	6.22	23.73	60.50	6.16	23.47
h		141—142	80.0	$C_{20}H_{22}N_6$	69.34	6.40	24.26	68.52	6.46	23.77
i		144	80.0	$C_{22}H_{26}N_6$	70.56	7.00	22.44	70.26	7.03	22.30
j		180—182	90.0	$C_{20}H_{22}N_6O_2$	63.47	5.86	22.21	63.49	6.02	22.23
k		165—167	68.0	$C_{22}H_{26}O_2N_6$	65.02	6.40	20.69	65.30	6.38	20.64
l		209—212	43.0	$C_{24}H_{30}O_2N_6$	66.33	6.95	19.34	65.98	6.93	19.26
m		149—153	64.0	$C_{24}H_{30}O_2N_6$	66.33	6.95	19.34	66.55	6.99	19.21
n		152—154	73.0	$C_{20}H_{28}N_8$	63.16	7.37	27.74	64.49	6.89	27.10
o		181—182	20.0	$C_{34}H_{36}N_8$	73.35	6.52	20.13	73.50	6.41	19.92
p		198—200	68.0	$C_{22}H_{22}N_6S_2$	58.54	5.37	20.49	58.25	5.28	20.33
q		219—221	55.3	$C_{30}H_{26}N_6$	76.60	5.53	17.87	61.68	4.19	16.64
r		273	85.2	$C_{24}H_{18}N_6$	73.83	4.65	21.53	73.58	4.49	21.40
s		127—128	84.3	$C_{24}H_{16}N_6Cl_2$	62.75	3.51	18.30	61.93	3.58	17.44
t	N_3	214—216	97.0	$C_{12}H_6N_{10}$	49.66	2.07	48.28	49.53	2.35	48.01
u	CH_3O	204—206	93.0	$C_{14}H_{12}O_2N_4$	62.76	4.48	20.80	62.65	4.53	21.04
v	HS	269—272	100	$C_{12}H_8N_4S_2$	52.94	2.94	20.59	49.82	2.59	19.19
w	CH_3S	174—176	92.0	$C_{14}H_{12}N_4S_2$	56.00	4.00	18.67	55.52	4.03	18.63
x	C_3H_7S	103—105	89.2	$C_{18}H_{20}N_4S_2$	60.66	5.66	15.72	60.93	5.66	15.77
y		209—212	100	$C_{24}H_{16}N_4S_2$	67.92	3.80	13.20	67.86	3.63	13.18
z		189—192	87.7	$C_{26}H_{20}N_4S_2$	68.17	4.58	12.72	67.93	4.46	12.81

However, the reaction of **1** with excess of aliphatic amines under heating over 100° gave the corresponding 2-aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**) in high yields. The reaction also proceeded under milder conditions, *e.g.* by refluxing with amines in ethanol, or even under room temperature in the case of the reaction with potassium hydrosulfide and sodium mercaptan. A variety of 2-phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**)

Table II. 2-Aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (5)



	Ar	R	mp (°C)	Yield (%)	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
A		iso-C_3H_7NH	273—274	66.0	$C_{19}H_{24}N_6$	67.86	7.14	25.00	67.92	7.11	25.41
B			226—228	70.0	$C_{23}H_{28}N_6HCl$	65.02	6.83	19.79	64.24	6.87	19.78
C			160—162	74.0	$C_{21}H_{22}O_2N_6$	64.29	6.12	21.43	64.31	6.20	21.45
D		N_3	214—216	97.0	$C_{13}H_8N_{10}$	51.32	2.63	46.05	51.32	2.52	46.15
E			180—181	40.6	$C_{22}H_{25}N_6Cl$	64.62	6.16	20.55	64.45	6.20	20.50
F			216—217	37.8	$C_{20}H_{21}O_2N_6Cl$	58.18	5.13	20.36	57.88	5.34	20.22
G			221—223	51.3	$C_{22}H_{25}O_2N_7$	62.99	6.01	23.73	62.90	6.21	23.10
H			269—270	50.8	$C_{20}H_{21}O_4N_7$	56.73	5.00	23.16	56.63	4.82	23.28
I			216—218	40.0	$C_{24}H_{24}O_2N_6$	67.28	5.65	19.63	67.22	5.69	19.51
J			133	24.0	$C_{21}H_{25}N_7$	67.17	6.71	26.12	67.25	6.51	26.52
K			197	46.0	$C_{19}H_{21}O_2N_2\cdot{}^1/_2H_2O$	58.59	5.58	25.70	58.98	5.58	25.70
L			158—159	52.6	$C_{20}H_{24}N_6S$	63.14	6.36	22.09	63.31	6.35	21.59
M			200—203	57.5	$C_{18}H_{20}O_2N_6S\cdot H_2O$	53.72	5.51	20.89	53.66	5.55	20.95
N			185	32.0	$C_{25}H_{33}ON_7\cdot{}^1/_2H_2O$	65.76	7.50	21.47	65.69	7.37	21.46
O			222	66.5	$C_{22}H_{27}O_4N_7$	58.28	6.00	21.62	58.03	5.96	21.57

and 2-aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**) was synthesized by those methods expecting pharmacological activities. The resulting compounds are listed in Table I and Table II.

Among those compounds 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazines (**5w**, **5x**, and **5z**) were synthesized by alkylation of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]-pyridazine-5,8-dithione (**5v**) with alkyl halide. 2-Aryl-5,8-diazidopyrimido[4,5-*d*]pyridazines (**5t** and **5D**) were obtained by reaction of **1** with sodium azide in dimethylsulfoxide under cooling. It has been reported that one of the azide group in 3,6-diazidopyridazine⁹⁾ and 5,8-diazidopyrazino[2,3-*d*]pyridazine¹⁰⁾ exist in the form of tetrazolopyridazine structure. Therefore one of the azide groups in **5t** and **5D** is expected to cylize with pyridazine ring to form tetrazole ring. Two possible structures for the cyclized product can be proposed, namely 6-azido-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (**6**) and 6-azido-8-phenylpyrimido-[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (**7**). The nuclear magnetic resonance (NMR) spectra of **5t** and **5D** showed a signal of ring proton (H_4) at 4-position as a singlet, which indicated that each product consisted of single compound. When **5t** was heated with tetraline, a product (**8a**) which has one amino group in place of azido group was obtained, and the reaction of **5t** with sodium methoxide gave a monomethoxy compound (**8b**). In the IR spectrum of those products the absorption band due to azido group, which was observed at 2130 cm^{-1} in **5t** and **5D**, disappeared. This implies that another azido group which did not participate in the reaction had been cyclized to tetrazole ring.

In the NMR spectrum of **8b**, the nuclear Overhauser effect (NOE) of 13.8% was observed between methyl protons of methoxy group and ring proton at 4-position. From these results the structure of **8b** was assigned as 6-methoxy-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*d*]pyridazine. Therefore the parent compound (**5t**) was assigned as **6** (Ar=phenyl) (Chart 3).

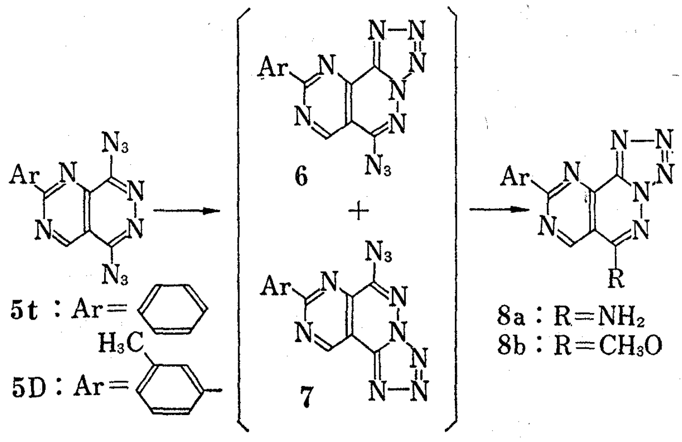


Chart 3

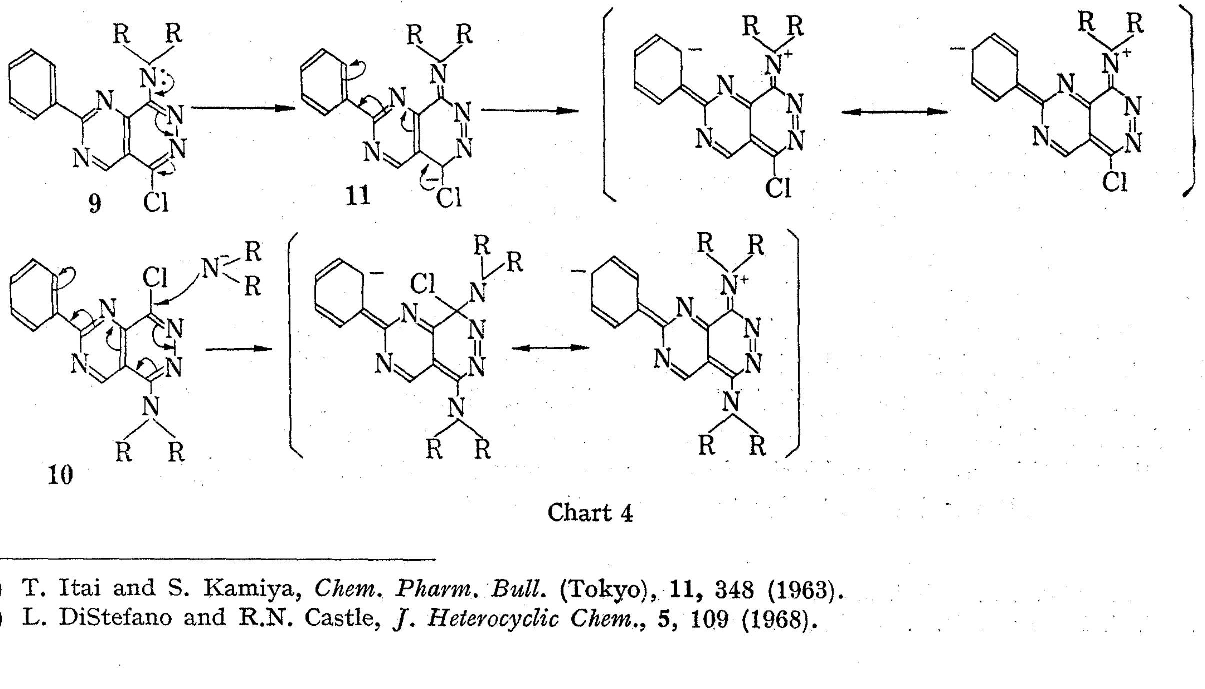


Chart 4

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9) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 348 (1963).

10) L. DiStefano and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 109 (1968).

As described above the nucleophilic disubstitution of 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**) was found to proceed quite smoothly probably because of the effect by the aryl group at 2-position. It has already been mentioned in the preceding paper that a mixture of monosubstituted compounds which consists of nearly equal amount of 5- and 8-amine (**9** and **10**) was obtained when the reaction of **1** with amines was stopped halfway.[1] Therefore the assisting effect of the phenyl group is considered to work on the further substitution reaction of both **9** and **10**. In the compound **9**, 5-position is supposed to be an unfavorable position for the nucleophilic attack because of the electron donating effect of the amino nitrogen at 8-position leading to the structure like (**11**). The resonance effect of the 2-phenyl group, however, would be instrumental in delocalizing the electron at 5-position, which assists the nucleophilic attack. On the other hand in the case of **10**, the resonance effect of the phenyl group makes 8-position electron-poor, which would assist the nucleophilic attack overcoming the reverse effect by the amine nitrogen at 5-position.

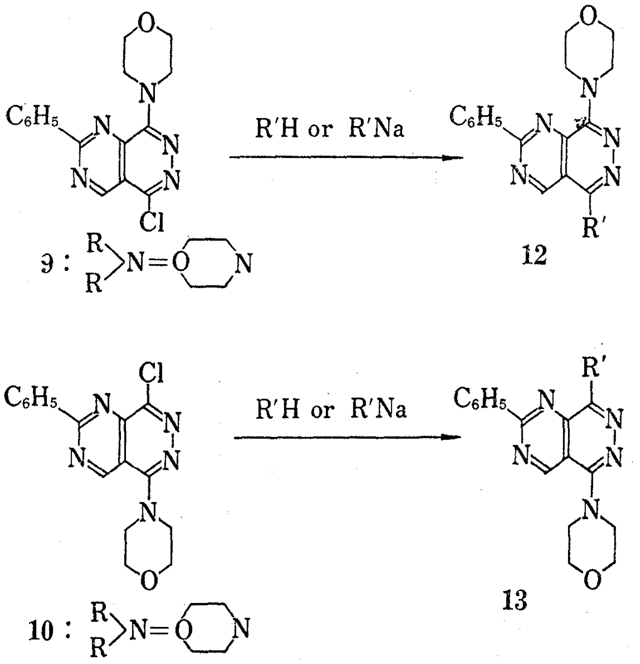

Chart 5

2-Phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazines (**12** and **13**) which have different substitutents at 5- and 8-position were obtained by the reaction of 2-phenyl-5-chloro-8-morpholinopyrimido[4,5-*d*]pyridazine (**9**, $^{R}_{R}{>}N$: morpholino) and 2-phenyl-5-morpholino-8-chloropyrimido[4,5-*d*]pyridazine (**10**, $^{R}_{R}{>}N$: morpholino)[1] with nucleophiles such as piperidine, sodium ethoxide and sodium hydroxide. Their physical data and yields is presented in Tables III and IV.

2-Phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (**5v**) which was obtained by reaction of **1** with potassium hydrosulfide (Table I) could alternatively be prepared by reaction of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**14**)[3] with phosphorus pentasulfide in pyridine. **5v** was recognized to exist in thiolactam form in solid state by infrared (IR) spectrum (3125, 1563, 1553, and 1240 cm^{-1} in Nujol). The treatment of **5v** with methyliodide, propylbromide, and benzylchloride in alkaline solution gave the corresponding 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazine (**5w**, **5x**, and **5z**). 2-Phenyl-5,8-bis(phenylthio)pyrimido[4,5-*d*]pyridazine (**5y**) was obtained by the reaction of **1** with sodium thiophenolate.

Although attempts to oxidize 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazines (**5**) expecting the formation of the corresponding sulfoxide or sulfone were made, no expected compounds were obtained. When the 5,8-bis(substituted thio) compounds (**5w**, **5x**, **5y**, and **5z**) and the 5,8-dithione compound (**5v**) were treated with chlorine as oxidizing agent, 2-phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**, Ar: phenyl) was obtained (Chart 5). Similar results have also been reported related to the displacement reaction of mercapto or substituted thio groups by chlorine in other heterocyclic systems.[11,12] This method may be useful as an alternative route for the preparation of **1**.

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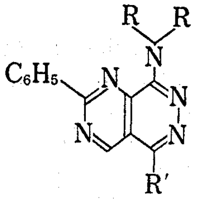
11) G.S. Shidhn, S. Naqui, and D.L. Lyengar, *J. Heterocyclic. Chem.*, **3**, 158 (1966).
12) C.W. Noell and R.K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

Table III. 2-Phenyl-5,8-disubstitutedpyrimodo[4,5-*d*]pyridazine (**12**)



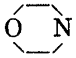
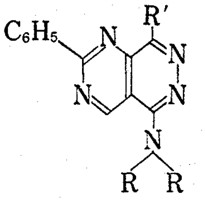
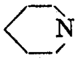
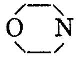
	R >N- R	R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a			156—158	65	$C_{21}H_{24}ON_6$	67.02	6.38	22.34	67.05	6.52	22.10
b		C_2H_5O	156—157	60	$C_{18}H_{19}O_2N_5$	64.10	5.64	20.77	64.41	5.58	20.96
c		HO	>305	70	$C_{16}H_{15}O_2N_5$	62.14	4.85	22.65	62.12	4.92	22.85

Table IV. 2-Phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**13**)



	R >N- R	R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a			159—161	52	$C_{21}H_{24}ON_6$	67.02	6.38	22.34	67.06	6.49	22.13
b		C_2H_5O	143—144	60	$C_{18}H_{19}O_2N_5$	64.10	5.64	20.77	63.75	5.62	20.85
c		HO	303—305	84	$C_{16}H_{15}O_2N_5$	62.14	4.85	22.65	62.19	4.63	22.84

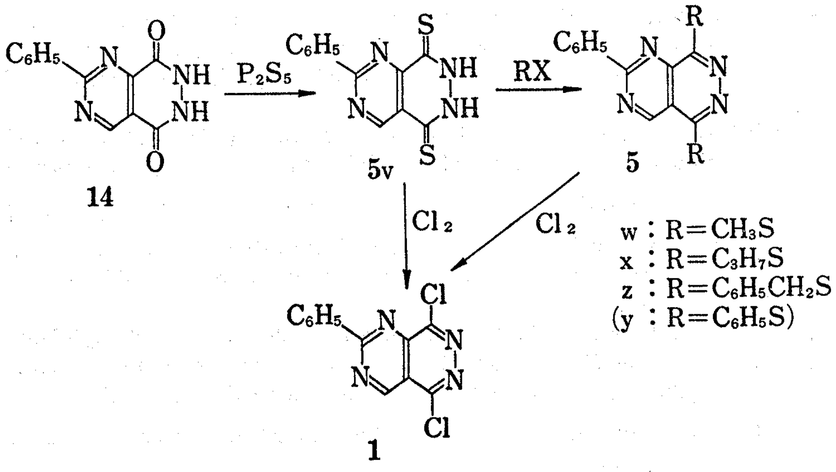


Chart 6

Experimental

2-Phenyl-5,8-disbsutitutedpyrimido[4,5-*d*]pyridazine (5) (Table I and Table II)——The general procedure is as follows: a) A mixture of 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (1) (1.0 g) and aliphatic amines (10 g) was heated at 100—150° for 4—8 hr. After removal of the excess amine *in vacuo*, H_2O (about 100 ml) was added to the residue. The resulting crystals were filtered and recrystallized from EtOH to give **5**.

b) A solution of **1** (1.0 g) and arylamines (4 mole eq.) in EtOH (50 ml) was refluxed for 1 hr. After evaporation of the solvent, H_2O (about 100 ml) was added to the residue. The resulting solid was filtered and recrystallized from the appropriate solvent such as EtOH, AcOEt, and ether to give **5**.

c) To a solution of MeONa prepared from Na (460 mg) and MeOH (50 ml) was added the dichloride (1) (10 mmole) and the mixture was refluxed for 2—4 hr. After evaporation of the solvent *in vacuo*, H_2O (about 100 ml) was added to the residue. The resulting crystals were filtered and recrystallized from MeOH to give 2-phenyl-5,8-dimethoxypyrimido[4,5-*d*]pyridazine (**5u**).

d) To 10% KSH–EtOH (500 ml) was added the dichloride (**1**) (3.0 g) and the mixture was stirred for 5 hr under room temperature. After standing overnight, the solvent was evaporated *in vacuo*. The residue was dissolved in H_2O and the undissolved substance was removed by filtration. The filtrate was acidified was acidified with conc. HCl to yiel crystals, filtration and recrystallization of which from MeOH gave 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (**5v**). IR (in Nujol) cm^{-1}: 3125 (NH), 1563, 1553 (CSNH), 1240 (C=S).

e) The dichloride (**1**) (1.0 g) was suspended in MeOH (200 ml) with stirring under room temperature and to the suspension was added the solution of sodium thiophenolate in MeOH (containing 2.5 mole equivalents of thiophenol). After stirring for 3 hr, the solvent was removed *in vacuo*. H_2O was added to the residue to yield yellow crystals which were filtered and washed with H_2O several times. Recrystallization from AcOEt gave 2-phenyl-5,8-bis(phenylthio)pyrimido[4,5-*d*]pyridazine (**5y**) as yellow needles (1.5 g).

2-Phenyl-5,8-bis(alkylthio)pyrimido[4,5-*d*]pyridazine (5w, 5x and 5z) (Table I)——To a solution of 2-phenyl 5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (**5v**) (1 mmole) in 10% NaOH was added alkylhalide (CH_3J, C_3H_7Br and $C_6H_5CH_2Cl$) (2 mmole) with stirring under room temperature or at 50—60° for 3 hr. The resulting crystals were filtered and recrystallized from EtOH to give the corresponding 5,8-bis(alkylthio) compounds (**5x**, **5y**, and **5z**) as yellow needles.

6-Azido-9-arylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (5t and 5D) (Table I and Table II)——The general procedure is as follows: DMSO (60 ml) was added to a mixture of the dichloride (**1**, Ar=phenyl, 3-tolyl) (3.0 g) and NaN_3 (2 mole eq.) with stirring under cooling. After stirring at room temperature overnight, the reaction mixture was poured into H_2O. The resulting crystals were collected by filtration and recrystallized from $CHCl_3$ to give **5t** and **5D** as cololess granules. Physical data of **5t** is as follows: IR (in Nujol) cm^{-1}: 2150 (N_3). NMR (in d_6-DMSO) τ: −0.10 (1H, singlet, ring proton), (in CF_3COOD): −0.47 (1H, singlet, ring proton).

6-Amino-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (8a)——A mixture of **5t** and tetraline (10 ml) was heated at 160° for 5 hr. After cooling, the resulting crystals were collected by filtration and recrystallized from THF gave **8a** (0.5 g, 47%), mp 218—219°. IR (in Nujol) cm^{-1}: 3300, 3460 (NH). An absorption band of azido group at 2150 cm^{-1} in the starting material (5t) disappeared. *Anal.* Calcd. for $C_{12}H_8N_8$: C, 54.55; H, 3.03; N, 42.42. Found: C, 54.63; H, 2.97; N, 42.70.

6-Methoxy-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (8b)——To a solution of sodium methoxide prepared from Na (100 mg) and MeOH (50 ml) was added **5t** (1.0 g), and the mixture was refluxed for 3 hr. After evaporation of the solvent *in vacuo*, H_2O (about 100 ml) was added to the residue to give crystals, which were filtered and recrystallized from THF to give **8b** (0.8 g), mp 241—242°. The absorption band at 2150 cm^{-1} (N_3) in 8t disappeared. NMR (in d_6-DMSO) τ: −0.19 (1H, singlet, ring proton). NOE (in d_6-DMSO, 100 Mc): NOE (13.8%) was observed between the ring proton (0.21 τ) and the methyl protons of methoxy group at 5-position (5.68 τ). *Anal.* Calcd. for $C_{13}H_9ON_7$: C, 55.91; H, 3.23; N, 35.13. Found: C, 56.10; H, 3.26; N, 35.23.

2-Phenyl-5-piperidino-8-morpholinopyrimido[4,5-*d*]pyridazine (12a) and 2-Phenyl-5-morpholino-8-piperidinopyrimido[4,5-*d*]pyridazine (13a) (Table III and Table IV)——The general procedure is as follows: The monosubstituted compound (9 and **10**, $\genfrac{}{}{0pt}{}{R}{R}{>}N$: morpholino) (0.5 g) was heated with piperidine (5 ml) at 140—150° for 4—6 hr. After removal of excess amine, H_2O (about 50 ml) was added to the residue. The resulting crystals were collected by filtration and recrystallized from EtOH to give the corresponding disubstituted product (**12a** and **13a**).

2-Phenyl-5-ethoxy-8-morpholinopyrimido[4,5-*d*]pyridazine (12b) and 2-Phenyl-5-morpholino-8-ethoxypyrimido[4,5-*d*]pyridazine (13b) (Table III and Table IV)——The general procedure is as follows: To a solution of EtONa prepared from Na (230 mg) and EtOH (50 ml) was added the monosubstituted compound (**9** and **10**, $\genfrac{}{}{0pt}{}{R}{R}{>}N$: morpholino) (10 mmole) and the solution was refluxed for 1 hr. After evaporating the solvent, H_2O (about 200 ml) was added to the residue to give crystals, which were filtered and recrystallized from EtOH to give the corresponding disubstituted product (**12b** and **13b**).

2-Phenyl-5,6-dihydro-8-morpholinopyrimido[4,5-*d*]pyridazin-5-one (12c) and 2-Phenyl-5-morpholino-7,8-dihydropyrimido[4,5-*d*]pyridazin-8-one (13c)——The general procedure **8i** as follows: The monosubstituted compound (**9** and **10**, $^{R}_{R}{>}N$: morpholino) (0.3 g) was refluxed with a mixture of 10% NaOH (3 ml) and EtOH (30 ml) for 5 hr. After evaporation of the solvent, H_2O (about 50 ml) was added to the residue. H_2O (about 50 ml) was added to the residue. An indissolved substance was removed by filtration and the filtrate was acidified with dil. HCl to yield crystals, which were filtered and recrystallized from dioxane to give the corresponding disubstituted product (12c and 13c). IR (in Nujol) cm^{-1}: 1650 (CONH) *in* both products.

2-Phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (5v)——To a mixture of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**14**) (1.2 g) and pyridine (50 ml) was added P_2S_5 (2.22 g) under reflux with stirring and the stirring was continued under reflux for 1 hr. After cooling, the solvent was evaporated *in vacuo* and the residue was poured into ice-water (50 ml). The resulting solution was heated on water bath for 2 hr. After cooling, the solution was filtered and the filtrate was adjusted to pH 2 with conc. HCl. The above procedure was repeated twice on the resulting precipitates and the precipitates were refluxed with 95% EtOH for 1.5 hr. The resulting crystals were collected by filtration to give to give **5v** as reddish orange granules (180 mg, 14%), mp 269—272°. The structure of this substance was confirmed by comparing its infrared spectrum (in Nujol) with that of authentic sample.

2-Phenyl-5, 8-dichloropyrimido [4,5-*d*] pyridazine (1)——a) 2-Phenyl-5, 6, 7, 8-tetrahydropyrimido [4,5-*d*]-pyridazine-5,8-dithione (**5v**) (1.0 g) was suspended in a mixture of AcOH (20 ml) and H_2O (1.2 ml) and chlorine gas was bubbled into the suspension under cooling for 2 hr. After excess chlorine was removed by passing N_2 to the solution, the solution was poured into ice-water (100 ml) with stirring. The resulting crystals were filtered to give the dichloride (**1**) (1.02 g, 68.5%), mp 211—213°. *Anal.* Calcd. for $C_{12}H_6N_4Cl_2$: C, 51.99; H, 2.17; N, 20.22; Cl, 25.49. Found: C, 52.22; H, 2.06; N, 20.57; Cl, 25.49. IR spectrum (in Nujol) of this substance showed complete identity with authentic sample.

b) To a solution of 2-phenyl-5,8-bis(methylthio)pyrimido[4,5-*d*]pyridazine (**5w**) (1.5 g) in $CHCl_3$ (50 ml) was passed chlorine gas under cooling for 2 hr. After evaporation of the solvent and excess chloride *in vacuo*, the dichloride (**1**) was obtained as crystalline residue (1.28 g, 70.3%). This substance was identified by comparing its IR spectrum (in Nujol) with that of authentic sample. 2-Phenyl-5,8-bis(substituted thio)-pyrimido[4,5-*d*]pyridazines (**5x**, **5y**, and **5z**) were treated just in the same manner as described above to give the dichloride (**1**) in following yields: **5x** ($R=C_3H_6S$), 54%; **5y** ($R=C_6H_5S$), 78%; **5z** ($C_6H_5CH_2S$), 70%.

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