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Studies on the Heterocyclic Compounds. XX.[1] The Reaction of 4-Cyano-3,6-dichloropyridazine with Amines[2]

Mitsuji Yanai, Shigeko Takeda, and Tamao Mitsuoka

Faculty of Pharmaceutical Sciences, Nagasaki University[3]

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4-Cyano-3,6-dichloropyridazine (II) was treated with primary amines in methanol under mild condition (stirring at 0—5°) to give neither the corresponding 3- nor 6-amino derivatives but the corresponding 5-amino derivatives (XVd—m) resulting from nuclear amination. However, when compound II was treated with secondary amines, the corresponding 3- or 6-amino derivatives were obtained.

Keywords——pyridazines; 4-cyano-3,6-dichloropyridazine; nuclear amination; primary amines; 5-aminated-4-cyano-3,6-dichloropyridazine; nucleophilic reaction; under mild condition

In general, two isomers of the corresponding 3-amino and 6-amino compound can be obtained by the reaction of 4-substituted-3,6-dichloropyridazine with ammonia or amines.[4] 4-Cyano-3,6-dichloropyridazine (II), which was obtained by treating 4-carbamoyl-3,6-dichloropyridazine[5] (I) with phosphorous oxychloride, was made to react with amines.

When the compound II was treated with secondary amines (pyrrolidine, piperidine, and morpholine) (2.2 equivalents) in methanol refluxing for 30 minutes, the corresponding 3-amino compounds (IIIa, IIIb, and IIIc) were obtained as major product, accompanied with the corresponding 6-amino compounds (IVa, IVb, and IVc). The isomeric compounds (III and IV) were in the ratios 80:1 (a), 10:1 (b), and 4:1 (c). These compounds (IIIa, IIIb, IVa, and IVb) were also obtained under the ice–cooling condition. The ratios of isomeric compounds were IIIa:IVa=50:1 and IIIb:IVb=20:1. The structures of aminated products (IIIa, IIIb, IIIc, IVa, IVb, and IVc) were established by the elementary analyses and the nuclear magnetic resonance (NMR) spectra of dechlorinated compounds produced from III and IV. That is, the products (IIIa, IIIb, IIIc and IVc) were hydrolyzed to the corresponding 4-carbamoyl compounds (Va, Vb, Vc, and VIIc) with dilute aqueous sodium hydroxide, followed by dechlorination with hydrogen over palladium on charcoal to give compounds (VIa, VIb, VIc, and VIIIc). In the NMR spectra of the compounds (VIa, VIb, and VIc), the coupling constant of two doublet peaks as ring proton showed *ortho* coupling (J=5.0 Hz) and the compound VIIIc showed *meta* coupling (J=2.0 Hz). Moreover, the compound VIc was identified by the mixed melting point test and the comparison of infrared absorption (IR) spectrum with 4-carbamoyl-3-morpholinopyridazine synthesized from 4-cyano-3-morpholinopyridazine (XVIIIc).

The treatment of II with one equivalent of 2-hydroxyethylamine and 3-hydroxypropylamine gave 3-substituted-6-chloro-4-cyanopyridazines (IIId, 19% and IIIe, 15%), which were established by the elementary analyses ($C_7H_7ClN_4O$ and $C_8H_9ClN_4O$) and the similarity of

1) Part XIX: M. Yanai, T. Kinoshita, S. Takeda, and M. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **23**, 1689 (1975).
2) Presented at the 84th Meeting of Kyushu Branch, Pharmaceutical Society of Japan, Fukuoka, Oct. 1973.
3) Location: *1–14 Bunkyo-machi, Nagasaki 852, Japan.*
4) M. Tišler and B. Stanovnik, "Advances in Heterocyclic Chemistry," Vol. 9, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, Inc., New York and London, 1968, p. 270.
5) M. Yanai, T. Kinoshita, H. Watanabe, and S. Iwasaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1849 (1971).

their ultraviolet (UV) spectra to that of 3-amino-6-chloro-4-cyanopyridazine (XXI) which was produced from 3-amino-4-carbamoyl-6-chloropyridazine[5] (XIX). However, when two equivalents of amines were used, 3-substituted-6-chloro-4-(2-oxazolinyl)[and (2-5,6-dihydro-4*H*-1,3-oxazinyl)]pyridazine (IXd and IXe) were obtained in the yields of 26% and 30%, respectively, in which cyano group of 4-position reacted with amines, further. In establishing the structure of the compounds (IXd and IXe) which were equivalent to $C_9H_{11}ClN_4O_2$ and $C_{11}H_{15}ClN_4O_2$ in elementary analyses, respectively, there appeared no absorption in C≡N streching vibration region in IR spectrum; NMR spectrum (in dimethylsulfoxide-d_6 (DMSO-d_6)) of IXd showed one singlet peak at 7.59 ppm (1H) which was assignable to ring proton, and another peaks at 3.75—3.45 ppm (4H, multiplet) and 4.50—3.94 ppm (4H, multiplet), these signals were assignable to ethylene groups. Moreover, the structure was confirmed from the following result. Compound IXd was hydrolyzed to the corresponding carboxy compound (XId) with 3% hydrochloric acid, and dechlorinated with hydrogen over palladium on charcoal to XIId which showed two doublet peaks at 7.51 ppm (J=5.0 Hz) and 8.53 ppm (J=5.0 Hz) in NMR spectrum, the coupling constant indicated *ortho* coupling. When compound IIId was treated with 2-hydroxyethylamine (one equivalent) in methanol refluxing for 40 minutes in the presence of triethylamine (one equivalent), the corresponding methyl carboimidate compound (Xd) was obtained instead of oxazolinyl compound (IXd). This compound Xd was established to methyl 6-chloro-3-(2-hydroxyethylamino)-4-pyridazinecarbo-

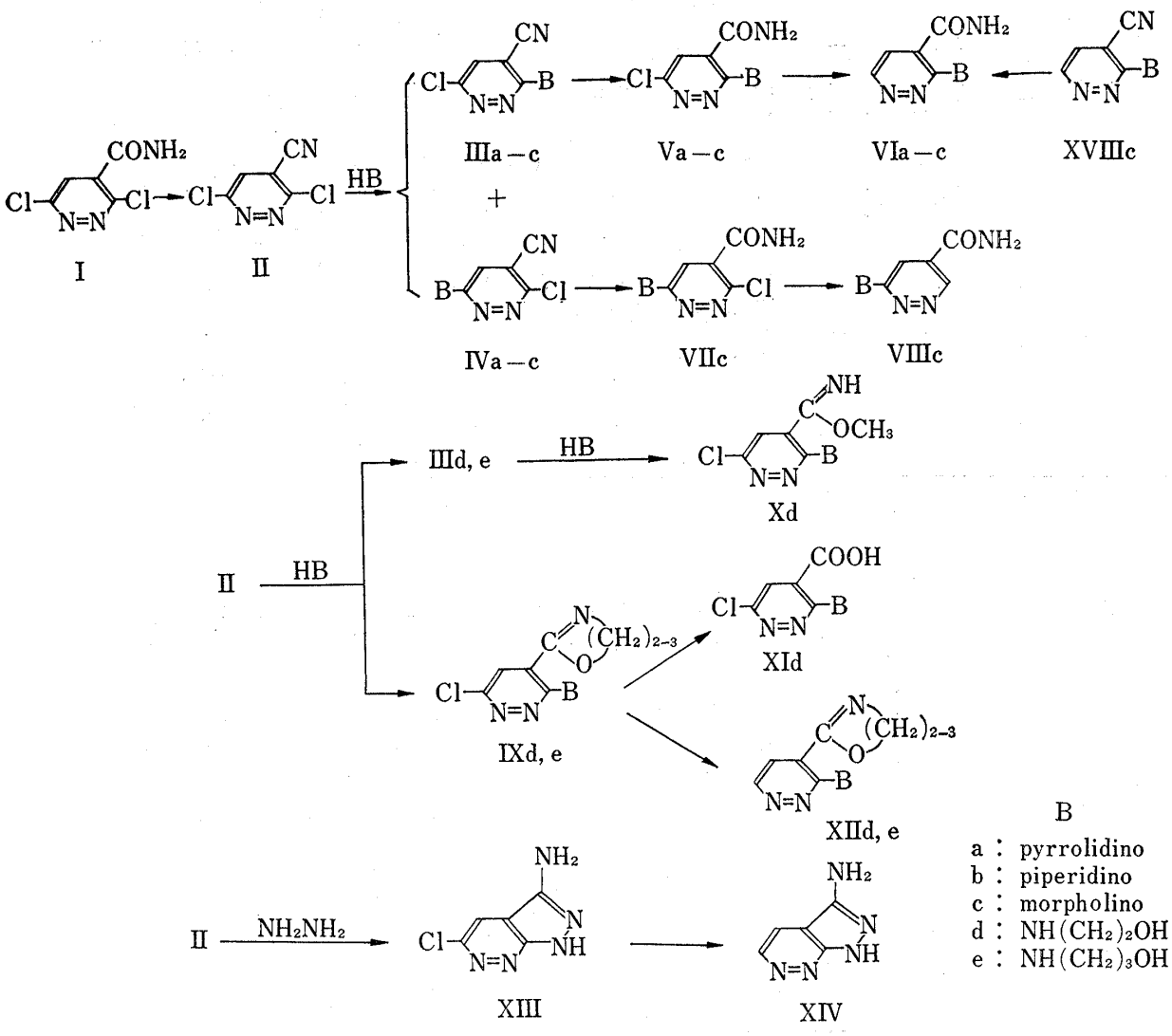
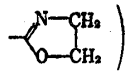
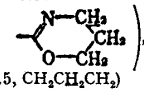
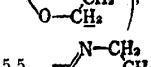
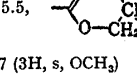
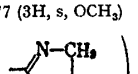
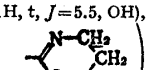
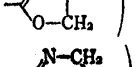
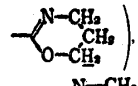
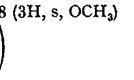


Chart 1

TABLE I. NMR spectra of Pyridazine Derivatives[a)]

Compound No.	3-H	5-H	6-H	B (amino)	Other signals
II	—	8.77(s)[b)] 7.80(s)[c)]	—	—	—
IIId[b)]	—	8.06(s)	—	7.42 (1H, b, NH), 4.74 (1H, t, J=5.5, OH), 3.74—3.40 (4H, m, CH_2CH_2)	—
IIIe[b)]	—	8.12(s)	—	7.59 (1H, t, J=6.0, NH), 4.54 (1H, t, J=5.5, OH), 3.64—3.37 (4H, m, $CH_2CH_2CH_2$), 1.76 (2H, qt (dt), J=6.5, $CH_2CH_2CH_2$)	—
Vd[b)]	—	7.71(s)	—	8.09 (1H, b, NH), 4.74 (1H, b, OH), 3.66—3.38 (4H, m, CH_2CH_2)	8.37, 7.92 (2H, b, $CONH_2$)
VIa[b)]	—	7.20(d) J=5.0	8.48(d) J=5.0	3.64—3.35 (4H, m, ), 2.00—1.70 (4H, m, CH_2CH_2)	8.06, 7.67 (2H, b, $CONH_2$)
VIb[b)]	—	7.41(d) J=5.0	8.77(d) J=5.0	3.52—3.25 (4H, m, ), 1.80 (6H, s(b), $(CH_2)_3$)	8.05, 7.82 (2H, b, $CONH_2$)
VIc[b)]	—	7.46(d) J=5.0	8.84(d) J=5.0	3.84—3.60 (4H, m, ), 3.50—3.25 (4H, m,)	8.15, 7.85 (2H, b, $CONH_2$)
VIIIc[b)]	8.95(d) J=2.0	7.58(d) J=2.0	—	3.88—3.70 (4H, m, ), 3.70—3.50 (4H, m,)	8.36, 7.90 (2H, b, $CONH_2$)
IXd[b)]	—	7.59(s)	—	8.61 (1H, b, NH), 4.80 (1H, b, OH), 3.70—3.48 (4H, m, CH_2CH_2)	4.50—3.94 (4H, m, )
IXe[c)]	—	7.62(s)	—	9.11 (1H, b, NH), 3.91—3.57 (6H, m, $CH_2CH_2CH_2$, ), 1.87 (2H, qt(dt), J=5.5, $CH_2CH_2CH_2$)	4.41 (2H, t, J=5.5, ), 2.03 (2H, qt (dt), J=5.5, )
Xd[b)]	—	7.69(s)	—	9.42 (1H, b, NH), 4.82 (1H, b, OH), 3.70—3.42 (4H, m, CH_2CH_2)	9.32 (1H, b, NH), 3.77 (3H, s, OCH_3)
XIId[b)]	—	7.51(d) J=5.0	8.53(d) J=5.0	8.49 (1H, b, NH), 4.78 (1H, b, OH), 3.68—3.55 (4H, m, CH_2CH_2)	4.50, 3.92 (4H, m, )
XIIe[b)]	—	7.54(d) J=5.0	8.54(d) J=5.0	9.12 (1H, t, J=5.5, NH), 4.56 (1H, t, J=5.5, OH), 3.70—3.38 (6H, m, $CH_2CH_2CH_2$, ), 1.75 (2H, qt(dt), J=5.5, $CH_2CH_2CH_2$)	4.34 (2H, t, J=5.5, ), 1.91 (2H, qt (dt), J=5.5, )
XVd[b)]	—	—	—	8.07 (1H, b, NH), 5.00 (1H, t, J=5.0, OH), 3.96—3.52 (4H, m, CH_2CH_2)	—
XVe[b)]	—	—	—	8.30 (1H, t, J=6.0, NH), 4.75 (1H, b, OH), 3.75 (2H, q, J=6.0, $NHCH_2$), 3.53 (2H, t, J=6.0, CH_2OH), 1.82 (2H, qt(dt), J=6.0, $CH_2CH_2CH_2$)	—
XXIIb[b)]	—	7.70(s)	—	—	9.20 (1H, b, NH), 8.08 (2H, b, NH_2) 3.75 (3H, s, OCH_3)
XXXc[c)]	—	7.76(s)	—	—	9.20 (1H, b, NH), 4.28 (3H, s, OCH_3) 3.92 (3H, s, )

a) δ, ppm from tetramethylsilane; J in Hz; s, singlet; d, doublet; m, multiplet; b, broad; qt, quintet; dt, doublet triplet; q, quartet.
b) Solvent: DMSO-d_6.
c) Solvent: $CDCl_3$.

imidate by the elementary analysis ($C_8H_{11}ClN_4O_2$) and the IR (no absorption for cyano group) and the NMR spectra [7.69 ppm (1H, singlet, 5-position), and 3.77 ppm (3H, singlet, OCH_3) were shown].

Heating of compound II with hydrazine hydrate in absolute ethanol at 50—60° for 30 minutes, compound XIII was obtained. XIII was established to 3-amino-5-chloro-1*H*-pyrazolo[3,4-*c*]pyridazine by dechlorination to XIV, which was identified with 3-amino-1*H*-pyrazolo[3,4-*c*]pyridazine[6)] by the mixed melting point test and the IR comparison.

When compound II was treated with 2-hydroxyethylamine and 3-hydroxypropylamine in methanol stirring vigorously under the ice-cooling condition for three hours, compounds (XVd and XVe), different from above obtained 3-substituted compounds (III and IX), were obtained in the yields of 37% and 33%, respectively. The yields arose about 5%, when the reactions were carried out under aeration. In the case of 2-hydroxyethylamine, a small

6) A. Dornow and W. Abele, *Chem. Ber.*, **97**, 3349 (1964).

Table II. UV Spectra of Pyridazine Derivatives

Compound No.	λ_{max}^{EtOH} nm (log ε)			
II	295 (3.23)			
IIIa	240.5(4.12)	272 (4.30)	354(2.98)[a]	408(3.37)
IIIb	248 (3.91)[a]	275 (4.09)	354(3.05)	408(3.21)
IIIc	224 (3.96)	270 (4.07)	350(3.10)	396(3.18)
IIId	233 (4.18)	256 (4.12)	386(3.46)	
IIIe	233 (4.29)	256 (4.19)	387(3.31)	
IIIg	234 (4.25)	266 (4.13)	378(3.33)	
IIIh	234 (4.22)	267 (4.11)	380(3.27)	
IVb	242.5(4.02)	278 (4.14)	402(3.01)	
IVc	245 (4.03)[a]	272 (4.20)	388(3.22)	
Vd	226 (4.14)	257 (4.15)	380(3.36)	
Vg	225 (4.12)	256 (4.13)	378(3.41)	
Vh	226 (4.08)	257 (4.13)	380(3.39)	
XVd	236 (4.00)	272 (3.89)	332(3.78)	
XVe	236 (4.13)	272 (3.94)	334(3.80)	
XVf	230 (4.29)	259 (3.78)	322(3.83)	
XVg	235.5(4.15)	272 (3.94)	331(3.83)	
XVh	235.5(4.15)	272 (3.95)	331(3.82)	
XVi	237 (4.15)	273 (3.99)	334(3.81)	
XVj	237 (4.21)	272 (3.97)	332(3.81)	
XVk	235.5(4.18)	272 (3.94)	331(3.82)	
XVl	236 (4.13)	273 (3.97)	334(3.80)	
XVm	236 (4.11)	273 (3.95)	334(3.78)	
XVIIIa	226 (4.04)	263.5(4.16)	355(3.32)[a]	393(3.46)
XVIIIb	222 (4.04)	266 (4.06)	345(3.22)	396(3.25)
XVIIIc	222 (4.04)	262 (3.96)	344(3.21)	382(3.19)
XVIIId	221 (4.18)	250 (3.99)	368(3.46)	
XVIIIe	221 (4.34)	250.5(4.11)	370(3.56)	
XIX	248.5(4.08)	357 (3.43)		
XXI	227 (4.13)	247 (4.00)	370(3.27)	

a) Shoulder.

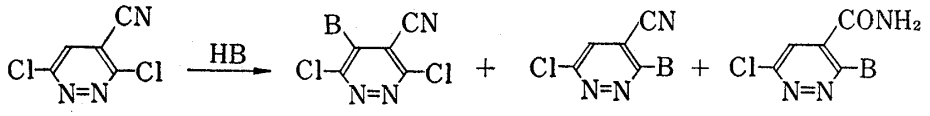
amount of compound Vd was also obtained. The elementary analysis of compound XVd was equivalent to $C_7H_6Cl_2N_4O$; the IR spectrum showed at 2215 cm^{-1} (for cyano group); and the NMR spectrum showed no peak as ring proton of 5-position. Therefore, compound XVd was established to 4-cyano-3,6-dichloro-5-(2-hydroxyethylamino)pyridazine. Similarly, compound XVe was also established to 4-cyano-3,6-dichloro-5-(3-hydroxypropylamino)-pyridazine. Compound Vd was established to 4-carbamoyl-6-chloro-3-(2-hydroxyethyl-amino)pyridazine by the elementary analysis ($C_7H_9ClN_4O_2$) and the similarity of its UV to that of XIX. In these compounds (XVd and XVe) direct nuclear amination occurred under mild condition (stirring at 0—5°).

In the study of nuclear amination, for example, it is known that the famous Chichibabin Reaction, and a reactive aromatic or heterocyclic compound with nitro group reacts with amines to give the compound aminated at *ortho* or *para* position to nitro group.[7] However, our nuclear amination occurred under mild condition, so that it seems not to be similar on the reaction mechanism, which is still unknown.

To further develop this reaction, the compound II was treated with ammonia or primary aliphatic amines (methylamine, ethylamine, cyclohexylamine, benzylamine, aminoaceto-aldehyde diethylacetal, *N*,*N*-dimethylaminopropylamine, and *N*,*N*-diethylaminopropylamine)

7) *a*) J. Meisenheimer and E. Patzig, *Chem. Ber.*, **39**, 2533 (1906); *b*) H.E. Baumgarten, *J. Am. Chem. Soc.*, **77**, 5109 (1955); *c*) M. Hasegawa and T. Okamoto, *Yakugaku Zasshi*, **93**, 1019 (1973).

in methanol with stirring under the ice-cooling condition; as a result, the corresponding 5-amino compounds (XVf—m) were obtained in the yields of 20%—35% like in the case of 2-hydroxyethylamine. Incidentally, in the case of methylamine and ethylamine, the corresponding 3-substituted-4-cyano (and carbamoyl) compounds (IIIg, IIIh, Vg, and Vh) were also obtained in small amount. The structures of compounds (IIIg and IIIh) were established by the elementary analyses ($C_6H_5ClN_4$ and $C_7H_7ClN_4$) and the comparison of their UV with that of XXI. Similarly, compounds (Vg and Vh) were established by the elementary analyses ($C_6H_7ClN_4O$ and $C_7H_9ClN_4O$) and comparison of their UV with that of XIX.



II XV d—m III g, h V d,g,h

B

d : $NH(CH_2)_2OH$ i : NHC_6H_{11}
e : $NH(CH_2)_3OH$ j : $NHCH_2C_6H_5$
f : NH_3 k : $NHCH_2CH(OC_2H_5)_2$
g : $NHCH_3$ l : $NH(CH_2)_3N(CH_3)_2$
h : NHC_2H_5 m : $NH(CH_2)_3N(C_2H_5)_2$

Chart 2

The amination was attempted with the use of 3-chloro-4-cyanopyridazine (XVII), XXI, 6-chloro-4-ethoxycarbonyl-3(2*H*)-pyridazinone[8] (XXIV) and 3-chloro-4-ethoxycarbonyl-6-(1*H*)-pyridazinone[9] (XXVII) as starting materials, no nuclear amination took place in any case. Namely, the reaction of XVII with primary amines (ice–cooling or thermal condition) or secondary amines (thermal condition) gave 3-substituted compounds (XVIIIa—e). XVII was prepared by the chlorination of 4-cyano-3(2*H*)-pyridazinone[10] (XVI) with phosphorus oxychloride. In the reaction of XXI, which was prepared by the treatment of XIX with phosphorus oxychloride in *N*,*N*-dimethylformamide, with primary amine under the ice–cooling condition, no amination reaction took place, but only methyl 3-amino-6-chloro-4-pyridazinecarboimidate (XXII) was obtained. This compound was treated with anthranilic acid to give 4-(2-4-oxo-3*H*-quinazolinyl)pyridazine derivative (XXIII). The structure of XXII was established by the elementary analysis ($C_6H_7ClN_4O$) and the NMR spectrum [7.70 ppm (1H, singlet, 5-position), 8.08 ppm (2H, broad, NH_2), and 3.75 ppm (3H, singlet, OCH_3)]. The reaction of compounds (XXIV and XXVII) with amines gave salt compounds (XXV and XXVIII) at cooling reaction and gave only the corresponding 4-carbamide derivatives (XXVI and XXIX) at thermal reaction.

When compound II was treated with sodium methoxide instead of amine with stirring at room temperature for 30 minutes, methyl 6-chloro-3-methoxy-4-pyridazinecarboimidate (XXX) was obtained, but the corresponding 5-methoxy compound was not obtained. The structure of compound XXX was established according to the following facts. Namely, the hydrolysis of XXX with acetic acid gave 4-carbamoyl-6-chloro-3-methoxypyridazine[5] (XXXI) and its 6-hydroxy derivative (XXXII), and with 2% hydrochloric acid gave 4-carboxy-6-chloro-3(2*H*)-pyridazinone[8] (XXXIII); from the treatment of XXX with anthranilic acid, 4-(2-4-oxo-3*H*-quinazolinyl)pyridazine derivative (XXXIV) was obtained.

As mentioned above, the authors found an interesting fact that 5-position of compound II was nucleophilic reactivity and nuclear amination occurred in the reaction of compound II

8) T. Kuraishi, *Pharm. Bull.* (Tokyo), **5**, 587 (1957).
9) T. Kuraishi, *Chem. Pharm. Bull.* (Tokyo), **6**, 551 (1958).
10) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **37**, 134 (1954).

with primary amines. However, this reaction did not develop in secondary amines and methoxyl anion. In addition to compound II, compounds XVII, XXI, XXIV, and XXVII, having electron-withdrawing group at 4-position, were treated with primary amines, but nucleophilic reaction did not occur to 5-position.

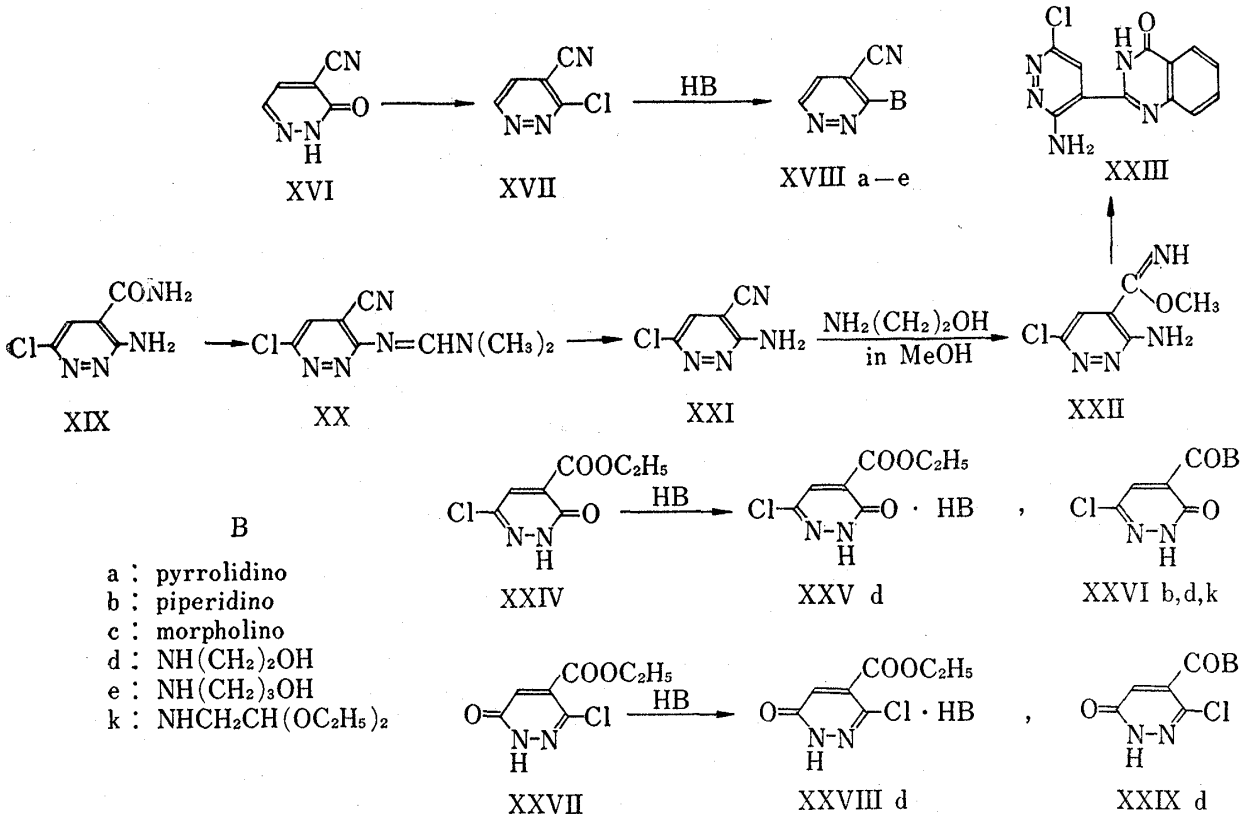


Chart 3

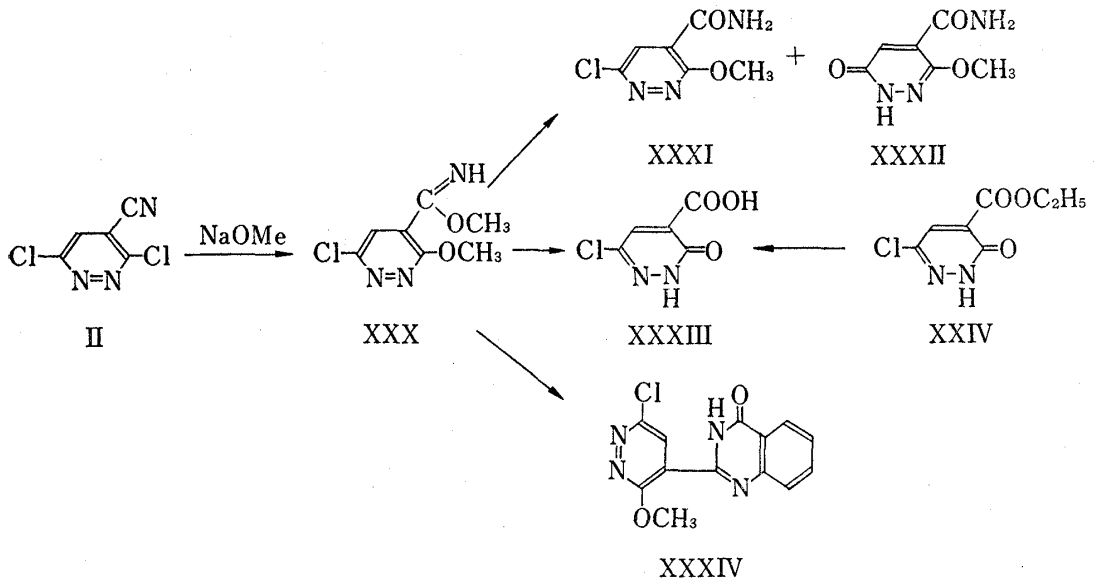


Chart 4

Experimental

Preparation of 4-Cyano-3,6-dichloropyridazine (II)——A mixture of 5.8 g of I and 100 ml of $POCl_3$ was refluxed for 3 hr. The reaction mixture was evaporated to dryness *in vacuo*; the residue was poured on crushed ice, alkalified with $NaHCO_3$, and extracted with $CHCl_3$. The chloroform extract was dried over $MgSO_4$, evaporated to dryness, and the residue was recrystallized to give II. IR ν_{max}^{KBr} cm^{-1}: 2250 (C≡N).

Preparation of 3-Chloro-4-cyanopyridazine (XVII)——A mixture of 1.5 g of XVI, and 12 ml of $POCl_3$ was heated at 100—110° for 1 hr. The reaction mixture was treated as ordinary manner, purified by the distillation under reduced pressure (3 Torr), and recrystallized from ether to give XVII.

Preparation of 3-Amino-6-chloro-4-cyanopyridazine (XXI)——To a solution of 1 g of XIX and 10 ml of absolute *N*,*N*,-dimethylformamide (DMF), a solution of 3 ml of $POCl_3$ and 10 ml of DMF was added dropwise with stirring at 0—5°. The mixture was stirred at room temperature for 3 hr, poured on crushed ice, and neutralized with 10% $NaHCO_3$. The deposited crystals were collected by suction and recrystallized from MeOH to give 0.9 g (74%) of 6-chloro-4-cyano-3-(*N*,*N*-dimethylaminomethylideneamino)pyridazine (XX), yellow needles, mp 151—152°. *Anal.* Calcd. for $C_8H_8ClN_5$: C, 45.83; H, 3.85; N, 33.40. Found: 45.58; H, 3.59; N, 33.61. IR ν_{max}^{KBr} cm^{-1}: 2230 (C≡N). UV λ_{max}^{EtOH} nm (log ε): 302 (4.29).

A mixture of 0.74 g of XX obtained above and 20 ml of 5% HCl was refluxed for 1 hr. The solution was cooled and neutralized with $NaHCO_3$. The deposited crystals were collected. The filtrate was extracted with $CHCl_3$; the extract was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crystals and the residue were combined and recrystallized to give XXI, 0.51 g (92%). Overall yield of XXI from XIX was 68%.

Reactions of II or XVII with Secondary Amines (Pyrrolidine, Piperidine, and Morpholine) (General Procedure)——a) Thermal Reaction: A mixture of 0.01 mol of II or XVII, 12 ml of MeOH, and 0.022 mol of amines was refluxed for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*. After addition of water to the residue; insoluble material was collected by suction, washed with water, and recrystallized to give the corresponding 3-substituted compounds (IIIa, IIIb, IIIc, XVIIIa, XVIIIb, and XVIIIc). The corresponding 6-substituted compounds (IVa, IVb, and IVc) were obtained from the mother liquor of recrystallization.

b) Cooling Reaction: A mixture of 0.005 mol of II, 3.5 ml of MeOH, and 0.0065 mol of amines was stirred vigorously with ice-cooling under aeration. The separated crystals were collected by suction and recrystallized to give the corresponding 3-substituted compound (IIIa). (IIIb: crystals were not separated.) The reaction mother liquor was evaporated to dryness *in vacuo*; the residue was extracted with acetone. The acetone extract was concentrated, passed through an alumina column and the acetone elution was evaporated to dryness. The crystalline mass was recrystallized to give the corresponding 6-substituted compound (IVa). (IIIb and IVb: The crystals were dissolved with ether instead of recrystallizing; the ethereal solution was passed through an alumina column, and eluted with ether. From the first fraction, the corresponding 3-substituted compound (IIIb) was obtained and the corresponding 6-substituted compound (IVb) from the second fraction).

Thermal Reactions of II or XVII with Primary Amines ($NH_2(CH_2)_2OH$, $NH_2(CH_2)_3OH$, and NH_2NH_2)——The following several reactions illustrated the general procedure. a) A mixture of 0.02 mol of II, 25 ml of MeOH, 0.02 mol of $NH_2(CH_2)_2OH$ was refluxed for 30 min. The reaction mixture was evaporated to dryness *in vacuo* and extracted with ether. The ethereal extract was evaporated to dryness; the crystalline mass was recrystallized to give the corresponding 3-substituted compound (IIId). The ethereal insoluble material was dissolved in EtOH and concentrated. The separated crystals ($NH_2(CH_2)_2OH \cdot HCl$, mp 75—81°) were filtered; the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$, passed through an alumina column, and eluted with $CHCl_3$. The starting material was obtained from the first fraction, further the corresponding 3-substituted compound (IIId) from the second fraction. IR ν_{max}^{KBr} cm^{-1} (C≡N): IIId, 2235; IIIe, 2230.

b) A mixture of 0.0115 mol of II, 12 ml of MeOH, 0.023 mol of $NH_2(CH_2)_2OH$, and 0.0127 mol of Et_3N was refluxed for 1 hr. The reaction mixture was concentrated to approximately half in quantity; the separated crystals were collected by suction, and recrystallized to give IXd. Moreover, IXd was obtained from the reaction mother liquor.

c) To a solution of 2 g of II and 14 ml of absolute EtOH, 1.6 g (2.2 eq) of 80% aq. $NH_2NH_2 \cdot H_2O$ was added under ice-cooling. The mixture was allowed to stand at room temperature for a while, heated at 60° for 30 min. The reaction mixture was evaporated to dryness *in vacuo*; to the residue a small amount of water was added; the insoluble material was collected, and recrystallized to give XIII.

Hydrolysis of 4-Cyano-3(or 6)-substituted Pyridazine Derivatives (IIIa, IIIb, IIIc, IVc, and XVIIIc) (General Procedure)——To 0.002 mol of cyano compounds, 2—3 ml of dil. aq. NaOH was added; the mixture was heated for 10 min—4 hr. After cooling, the separated crystals were collected by suction, washed with water, and recrystallized to give the corresponding carbamoyl compounds. In the case of nonseparation of crystals, the reaction mixture was concentrated *in vacuo*; the separated crystals were collected, and recrystallized to give the corresponding carbamoyl compounds.

Dechlorinations of Chloro Compounds (Va, Vb, Vc, VIIc, IXd, IXe, and XIII) (General Procedure)——0.004 mol of chloro compounds in a mixture of 50—100 ml of MeOH and 0.0044—0.0088 mol of 28% aq. ammonia was hydrogenated over 0.5—0.6 g of 5% or 16% Pd–C. After filtration of the catalyst, the filtrate was evaporated to dryness *in vacuo*; to the residue a small amount of water was added; the insoluble crystals were collected, and recrystallized.

Cooling Reactions of II, XVII, or XXI with Ammonia or Primary Amines [$NH_2(CH_2)_2OH$, $NH_2(CH_2)_3OH$, NH_2CH_3, $NH_2C_2H_5$, $NH_2C_6H_{11}$, $NH_2CH_2C_6H_5$, $NH_2CH_2CH(OC_2H_5)_2$, $NH_2(CH_2)_3N(CH_3)_2$, and $NH_2(CH_2)_3N$-

TABLE III

Compound No.	B	mp (°C)	Yield (%)	Appearance[a]	Recryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
II	—	105 —106	91	C.P.	Ether	$C_5HCl_2N_3$	35.06	0.51	24.13	35.06	0.49	23.92
IIIa	Pyrrolidino	152 —154	80[b], 50[c]	Y.R.	MeOH	$C_9H_9ClN_4$	51.79	4.31	26.86	51.80	4.47	26.83
IIIb	Piperidino	57 — 59	75[b], 40[c]	Y.Cl.	Ether	$C_{10}H_{11}ClN_4$	53.94	4.99	25.17	53.88	5.01	24.75
IIIc	Morpholino	134.5—135.5	66[b]	Y.N.	MeOH	$C_9H_9ClN_4O$	48.10	4.00	24.94	48.47	3.98	24.94
IIId	$NH(CH_2)_2OH$	126 —128	19	Y.N.	Ether	$C_7H_7ClN_4O$	42.33	3.55	28.21	42.68	3.46	28.09
IIIe	$NH(CH_2)_3OH$	113.5—115	15	Y.N.	Ether	$C_8H_9ClN_4O$	45.19	4.27	26.34	45.32	4.12	25.97
IIIg	$NHCH_3$	259 —260	3	Y.Cl.	AcOEt	$C_6H_5ClN_4$	42.73	2.97	33.28	43.00	3.08	32.85
IIIh	NHC_2H_5	221 —222	3	Y.Cl.	Acetone	$C_7H_7ClN_4$	46.02	3.82	30.68	46.27	3.84	30.54
IVa	Pyrrolidino	164 —165	1[b] 1[c]	Y.Cl.	MeOH	$C_9H_9ClN_4$	51.79	4.31	26.86	51.99	4.33	26.76
IVb	Piperidino	126 —127	7[b], 2[c]	Y.N.	Ether	$C_{10}H_{11}ClN_4$	53.94	4.99	25.17	53.84	5.06	25.11
IVc	Morpholino	195 —196	17[b]	Y.N.	MeOH	$C_9H_9ClN_4O$	48.10	4.00	24.94	48.61	4.28	24.76
Va	Pyrrolidino	223 —224	77	PY.Cl.	MeOH	$C_9H_{11}ClN_4O$	47.69	4.89	24.72	47.44	4.79	24.79
Vb	Piperidino	144 —145.5	70	Y.N.	MeOH	$C_{10}H_{13}ClN_4O$	49.90	5.41	23.28	50.21	5.06	23.03
Vc	Morpholino	172 —175	50	C.Cl.	AcOEt	$C_9H_{11}ClN_4O_2$	44.53	4.53	23.09	44.84	4.69	23.09
Vd	$NH(CH_2)_2OH$	208 —210	2	Y.Cl.	MeOH	$C_7H_9ClN_4O_2$	38.81	4.19	25.86	38.62	4.54	25.72
Vg	$NHCH_3$	209 —210	2	Y.N.	Water	$C_6H_7ClN_4O$	38.60	3.76	30.26	39.05	3.95	29.80
Vh	NHC_2H_5	185 —186	2	Y.Cl.	Ether	$C_7H_9ClN_4O$	41.89	4.50	27.88	42.09	4.51	27.64
VIa	Pyrrolidino	181 —182	71	PY.Cl.	Acetone	$C_9H_{12}N_4O$	56.23	6.29	29.15	56.42	6.50	29.59
VIb	Piperidino	133.5—134	70	C.P.	AcOEt	$C_{10}H_{14}N_4O$	58.23	6.84	27.17	58.63	6.68	27.01
VIc	Morpholino	156 —158	70[d], 64[e]	C.P.	AcOEt	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	51.87	5.96	27.04
VIIc	Morpholino	255 —257	65	C.N.	MeOH	$C_9H_{11}ClN_4O_2$	44.53	4.53	23.09	44.74	4.78	23.23
VIIIc	Morpholino	216 —217	70	PY.P.	MeOH	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	52.14	5.85	27.02
IXd	$NH(CH_2)_2OH$	201 —203	26	C.N.	MeOH	$C_9H_{11}ClN_4O_2$	44.53	4.54	23.09	44.66	4.72	22.81
IXe	$NH(CH_2)_3OH$	130.5—132	30	C.N.	AcOEt	$C_{11}H_{15}ClN_4O_2$	48.81	5.59	20.70	49.03	5.85	20.20
Xd	$NH(CH_2)_2OH$	165 —166	35	Y.N.	MeOH	$C_8H_{11}ClN_4O_2$	41.66	4.81	24.27	42.10	5.02	23.87
XId	$NH(CH_2)_2OH$	184 —186	70	C.N.	MeOH	$C_7H_8ClN_3O_3$	38.62	3.68	19.30	38.67	3.72	19.68
XIId	$NH(CH_2)_2OH$	218[f]	80	C.N.	MeOH	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	51.61	5.72	26.52
XIIe	$NH(CH_2)_3OH$	114 —115	75	C.N.	AcOEt	$C_{11}H_{16}N_4O_2$	55.91	6.83	23.72	55.92	6.94	23.21
XIII	—	283[f]	67	O.N.	MeOH	$C_5H_4ClN_5$	35.40	2.30	41.29	35.68	2.65	40.74
XIV	—	229 —230.5	55	Y.N.	MeOH	$C_5H_5N_5$	44.44	3.70	51.85	44.55	3.65	51.07
XVd	$NH(CH_2)_2OH$	146 —148	37	C.Cl.	MeOH	$C_7H_8Cl_2N_4O$	36.05	2.59	24.04	35.97	2.57	23.81
XVe	$NH(CH_2)_3OH$	133.5—135.5	33	C.N.	AcOEt	$C_8H_8Cl_2N_4O$	38.86	3.23	22.67	39.17	3.14	22.99
XVf	NH_2	240 —242	20	C.N.	Acetone	$C_5H_2Cl_2N_4$	31.74	1.07	29.63	32.06	1.20	29.90
XVg	$NHCH_3$	164 —165	35	C.Cl.	AcOEt	$C_6H_4Cl_2N_4$	35.99	1.98	27.58	35.99	2.04	27.58
XVh	NHC_2H_5	135 —137	30	C.Cl.	AcOEt	$C_7H_6Cl_2N_4$	38.70	2.77	25.80	39.05	2.88	25.46
XVi	NHC_6H_{11}	117.5—118.5	30	C.N.	Ether	$C_{11}H_{12}Cl_2N_4$	48.70	4.80	20.66	49.03	4.56	21.07
XVj	$NHCH_2C_6H_5$	126 —127	33	C.Cl.	AcOEt	$C_{12}H_8Cl_2N_4$	51.97	2.88	20.07	52.00	3.02	20.01
XVk	$NHCH_2CH(OC_2H_5)_2$	75 — 77	35	C.Cl.	Ether	$C_{11}H_{14}Cl_2N_4O_2$	43.27	4.59	18.36	43.59	4.64	18.51
XVl	$NH(CH_2)_3N(CH_3)_2$	84 — 85.5	25	C.R.	Ether	$C_{10}H_{13}Cl_2N_5$	43.79	4.76	25.54	44.06	4.95	24.87
XVm	$NH(CH_2)_3N(C_2H_5)_2$	76 — 77.5	33	C.Cl.	Ether	$C_{12}H_{17}Cl_2N_5$	47.68	5.63	23.17	48.02	5.77	22.85
XVII	—	41.5— 43	75	C.Cl.	Ether	$C_5H_2ClN_3$	43.01	1.43	30.11	43.32	1.40	29.96
XVIIIa	Pyrrolidino	105 —106	92	PY.N.	MeOH	$C_9H_{10}N_4$	62.05	5.79	32.17	62.44	6.04	31.83
XVIIIb	Piperidino	71 — 72	70	PY.N.	MeOH	$C_{10}H_{12}N_4$	63.81	6.43	29.77	63.80	6.33	29.36
XVIIIc	Morpholino	114 —115	70	PY.N.	MeOH	$C_9H_{10}N_4O$	56.83	5.30	29.46	56.84	5.16	28.93
XVIIId	$NH(CH_2)_2OH$	193 —194	55[b], 30[c]	PY.Cl.	MeOH	$C_7H_8N_4O$	51.21	4.91	34.13	51.20	5.08	34.03
XVIIIe	$NH(CH_2)_3OH$	108 —110	10[c]	PY.Cl.	MeOH	$C_8H_{10}N_4O$	53.92	5.66	31.45	54.02	5.77	30.80
XXI	—	192 —195	92	PY.Cl.	MeOH	$C_5H_3ClN_4$	38.86	1.96	36.24	38.99	1.83	36.89
XXII	—	186 —188[f]	20	PY.N.	MeOH	$C_6H_7ClN_4O$	38.60	3.76	30.02	38.88	3.92	29.15
XXIII	—	>310	30	Y.Cl.	Methyl cellosolve	$C_{12}H_6ClN_5O$	52.64	2.94	25.59	52.40	3.07	25.46
XXVd	$NH(CH_2)_2OH$	126 —127	28	C.N.	EtOH	$C_9H_{14}ClN_3O_4$	41.04	5.35	15.93	40.51	5.77	15.91
XXVb	Piperidino	212 —215	18	C.R.	EtOH	$C_{10}H_{14}ClN_3O_4$	49.68	5.00	17.38	49.75	5.07	17.32
XXVId	$NH(CH_2)_2OH$	182 —184	49[b], 11[c]	C.P.	EtOH	$C_7H_8ClN_3O_3$	38.64	3.75	19.30	38.70	3.60	19.35
XXVIk	$NHCH_2CH(OC_2H_5)_2$	156 —158	57	C.P.	Ether	$C_{11}H_{16}ClN_3O_4$	45.60	5.57	14.54	45.47	5.65	14.55
XXVIIId	$NH(CH_2)_2OH$	93 — 95	51	C.N.	AcOEt	$C_9H_{14}ClN_3O_4$	41.04	5.35	15.93	41.00	5.35	15.94
XXIXd	$NH(CH_2)_2OH$	204 —206	75	C.N.	EtOH	$C_7H_8ClN_3O_3$	38.64	3.75	19.30	38.83	3.64	19.06
XXX	—	97 — 98	63	C.N.	Ether	$C_7H_8ClN_3O_2$	41.70	3.98	20.84	41.74	4.07	20.82
XXXI	—	142 —144	63	C.Cl.	Ether	$C_6H_6ClN_3O_2$	38.42	3.22	22.40	38.43	3.16	22.89
XXXII	—	250 —252	6	C.Pd.	MeOH	$C_6H_7N_3O_3$	42.60	4.17	24.85	42.53	4.10	24.35
XXXIII	—	213 —215	40	C.P.	MeOH	$C_5H_3ClN_2O_3$	34.41	1.73	16.05	34.55	1.76	16.06
XXXIV	—	236 —238	50	C.N.	EtOH	$C_{13}H_9ClN_4O_2$	54.07	3.11	19.42	54.26	3.09	19.33

a) C: colorless, Y: yellow, PY: pale yellow, O: orange, P: plates, R: rhombi, Cl: columns, N: needles, Pd: powder.
b) Thermal reaction.
c) Cooling reaction.
d) From Vc.
e) From XVIIIc.
f) Decomposition.

$(C_2H_5)_2$]——a) General Procedure: A mixture of 0.005 mol of II, XVII, or XXI, 4—7 ml of MeOH, and 0.0055 mol of ammonia or primary amines was stirred vigorously under ice-cooling for 2—3 hr. (In the case of cyclohexylamine and aminoacetoaldehyde diethylacetal, 0.005 mol of Et_3N was added). The separated crystals were collected by suction and recrystallized to give the corresponding 5-amino compounds (XVf, XVj, XVk, XVl, and XVm) or the corresponding 3-substituted compounds (XVIIId and XVIIIe). IR ν_{max}^{KBr} cm^{-1} (C≡N): XVf, 2220; XVj, 2220; XVk, 2240; XVl, 2200; XVm, 2200; XVIIId, 2200; XVIIIe, 2200. In the case of nonseparation of crystals, the reaction mixture was evaporated to dryness at 35—40° *in vacuo*, and extracted with ether or AcOEt. The extract was evaporated to dryness and recrystallized to give the corresponding 5-amino compound (XVi) or XXII. IR ν_{max}^{KBr} cm^{-1} (C≡N): XVi, 2210.

b) A mixture of 0.0058 mol of II, 8 ml of MeOH, and 0.0115 mol of $NH_2(CH_2)_2OH$ was stirred vigorously under ice-cooling for 2 hr. The separated crystals were collected by suction and recrystallized to the corresponding 5-amino compound (XVd). IR ν_{max}^{KBr} cm^{-1} (C≡N): XVd, 2215; XVe, 2225. The reaction mother liquor was evaporated to dryness *in vacuo*; the residue was dissolved in acetone, and passed through an alumina column. The acetone elution was evaporated to dryness; the crystalline mass was recrystallized to give the corresponding 3-substituted-4-carbamoyl compound (Vd).

c) A mixture of 0.005 mol of II, 5 ml of MeOH, 0.006 mol of 40% aq. NH_2CH_3, and 0.005 mol of Et_3N was stirred vigorously under ice-cooling for 2 hr. The separated crystals were collected by suction, dissolved in AcOEt, passed through an alumina column, and eluted with AcOEt. The first elution was concentrated; the separated crystals were collected by suction to give the corresponding 3-substituted compound (IIIg). Mother liquor was concentrated; the separated crystals were collected and recrystallized to give the corresponding 5-amino compound (XVg). IR ν_{max}^{KBr} cm^{-1} (C≡N): XVg, 2220; XVh, 2220. The second elution was evaporated to dryness; the residue was recrystallized to give the corresponding 3-substituted-4-carbamoyl compound (Vg).

Reaction of Methyl 3-Amino-6-chloro-4-pyridazinecarboimidate (XXII) or Methyl 6-Chloro-3-methoxy-4-pyridazinecarboimidate (XXX) with Anthranilic Acid——A mixture of 0.0025 mol of XXII or XXX, 10 ml of MeOH, and 0.0025 mol of anthranilic acid was refluxed for 2 hr. After cooling, the separated crystals were collected and recrystallized to give XXIII or XXXIV.

Reactions of 6-Chloro-4-ethoxycarbonyl-3(2*H*)-pyridazinone (XXIV) or 3-Chloro-4-ethoxycarbonyl-6(1*H*)-pyridazinone (XXVII) with Amines——a) Cooling Reaction: A mixture of 0.0025 mol of XXIV or XXVII, 7 ml of EtOH, 0.0027 mol of $NH_2(CH_2)_2OH$, and 0.0027 mol of Et_3N was stirred under ice–water cooling for 6 hr. The separated crystals were collected by suction and recrystallized to give XXVd (28%) or XXVIIId (51%). XXVId (11%) was obtained from the mother liquor of recrystallization.

b) Reaction at Room Temperature: A mixture of 0.0025 mol of XXIV or XXVII, 1—2 ml of DMSO, 0.0049 mol of $NH_2(CH_2)_2OH$ or $NH_2CH_2CH(OC_2H_5)_2$, and 0.0037 mol of Et_3N was stirred at room temperature for 5—18 hr. After adding ice, the separated crystals were collected and recrystallized to give XXVIk. XXIXd: As the crystals were not separated, the reaction mixture was washed with $CHCl_3$; the aqueous layer was evaporated to dryness *in vacuo*, and the residue was recrystallized to give XXIXd.

c) Thermal Reaction: A mixture of 0.0025 mol of XXIV, 7 ml of EtOH, 0.0027 mol (or 0.0049 mol) of piperidine or $NH_2(CH_2)_2OH$, and 0.0027 mol of Et_3N was refluxed for 4.5 hr. The reaction mixture was evaporated to dryness *in vacuo* and recrystallized to give XXVIb or XXVId.

Methyl 6-Chloro-3-methoxy-4-pyridazinecarboimidate (XXX)——To a solution of NaOMe [0.48 g (1.2 eq) of Na] and 36 ml of absolute MeOH, 3 g of II was added bit by bit with stirring at 0—5°. The mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with $CHCl_3$ after adding 20 ml of ice-water. The chloroform layer was dried over $MgSO_4$, evaporated to dryness and recrystallized to give XXX.

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