Notes

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Studies on the Synthesis of Pyridazine Derivatives. XII.[1] Synthesis of 4,5-Diaminopyridazine Derivatives[2]

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4,5-Diaminopyridazines are very important starting materials for the syntheses of imidazo[4,5-*d*]- and *v*-triazolo[4,5-*d*] pyridazines as purine analogue, but only several com-

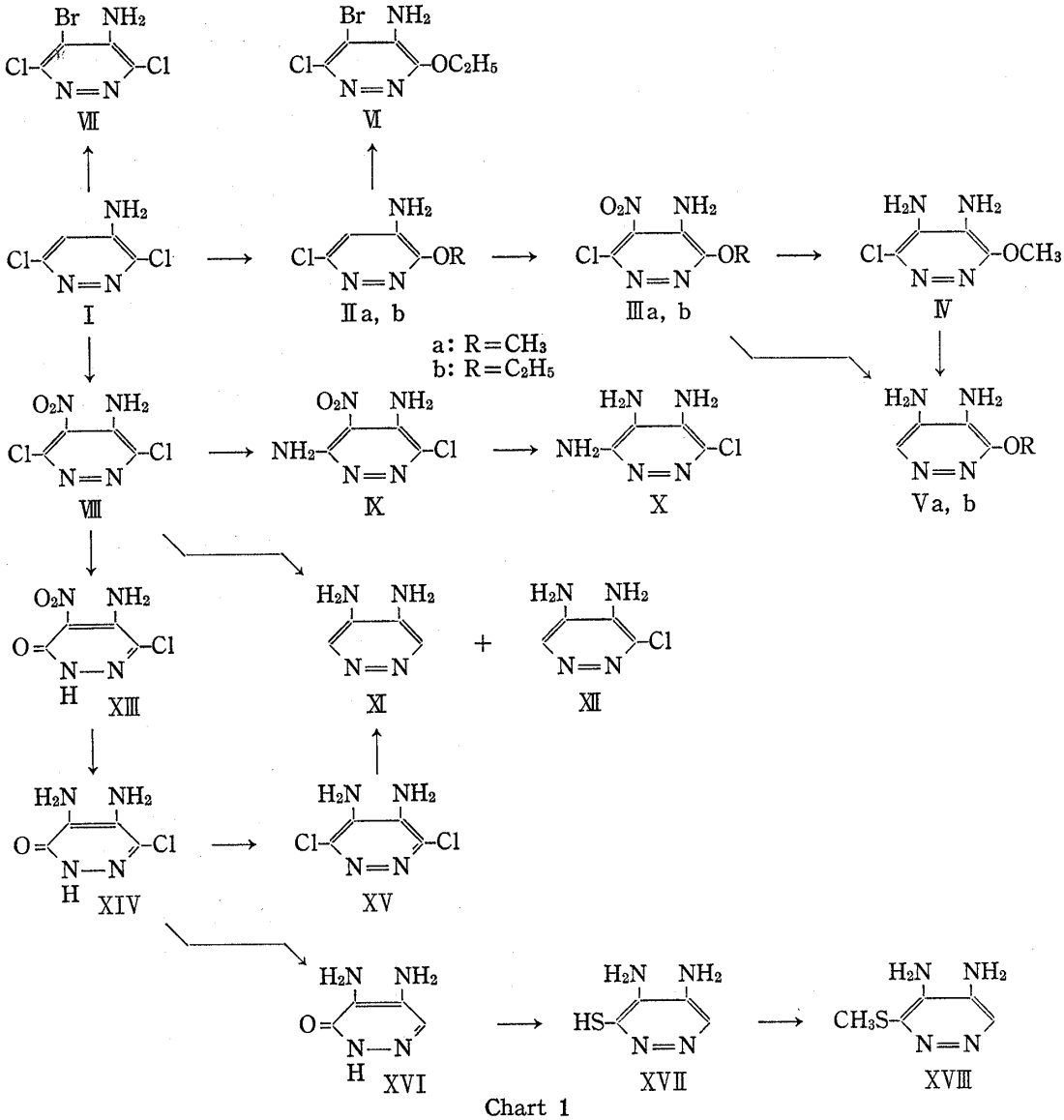

Chart 1

1) Part XI: M. Yanai and M. Yamaguchi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1244 (1968).
2) A part of this paper was presented at Kyushu Branch Meeting of Pharmaceutical Society of Japan, Kumamoto, Des. 8, 1962.
3) Location: *1–14 Bunkyo-machi, Nagasaki, 852, Japan.*

pounds were reported by this time. Three methods have been reported the syntheses of 4,5-diaminopyridazine derivatives.[4]

3-Methoxy (Ethoxy)-4-amino-6-chloropyridazine[5] (IIa, IIb) were nitrated to 3-methoxy-(ethoxy)-4-amino-5-nitro-6-chloropyridazine (IIIa, IIIb) by reaction with nitric acid in a sulfuric acid solution. Hydrogenation of these compounds with palladium on charcoal afforded 3-methoxy(ethoxy)-4,5-diaminopyridazine(Va, Vb). Va was prepared from IVa by same reduction method. Though when Raney nickel was used as catalyst, 3-methoxy-4,5-diamino-6-chloropyridazine (IVa) was obtained. Similarly, reaction of compound I[6] with nitric acid gave successfully 3,6-dichloro-4-amino-5-nitropyridazine (VIII), which is useful intermediate compound for the synthesis of 4,5-diamino-compounds. The bromination of I or IIa with bromine in glacial acetic acid affored 3,6-dichloro-(VII) or 3-ethoxy-6-chloro-4-amino-5-bromopyridazine (VI) in excellent yield. In general, electrophilic reagents attack to 5-position of 4-amino-compounds which have electron donor groups in 3 and 6-position, under comparatively mild condition.

Only recrystallization of VIII from methanol, 3-chloro-4-(or 5)-amino-5(or 4)-nitro-6(1*H*)pyridazinone (XIII) was obtained in excellent yield. Compound VIII was converted to 3,5(or 4)-diamino-6-chloro-4(or 5)-nitropyridazine (IX) with ethanolic ammonia in a sealed tube. Reduction of IX with Raney nickel catalyst afforded 3,4,5-triamino-6-chloropyridazine (X). 4,5-Diaminopyridazine[4b] (XI) was obtained by direct hydrogenation of VIII with palladium on charcoal in only 16% yield, accompanied with 4,5-diamino-6-chloropyridazine (XII). On the other hand, XI was prepared in good yield *via* 3,6-dichloro-4,5-diaminopyridazine (XV). Reaction of 4,5-diamino-3(2*H*)pyridazinone[7] (XVI) with phosphorous pentasulfide affored 4,5-diamino-3-mercaptopyridazine (XVII) which could be 4,5-diamino-3-methylthiopyridazine (XVIII) by usual method.

Compounds XXIII were obtained by same methods *via* corresponding nitro-compounds. Thermal rearrangement of 3-methoxy-4,5-diamino-6-methylpyridazine (XXIIIb) gave 2,6-dimethyl-4,5-diamino-3(2*H*)-pyridazinone (XXV). Compounds XXIIIb and XXIIId were hydrolyzed to 4,5-diamino-6-methyl(ethoxy)-3(2*H*)pyridazinone (XXIVb, XXIVd) with hydrochloric acid.

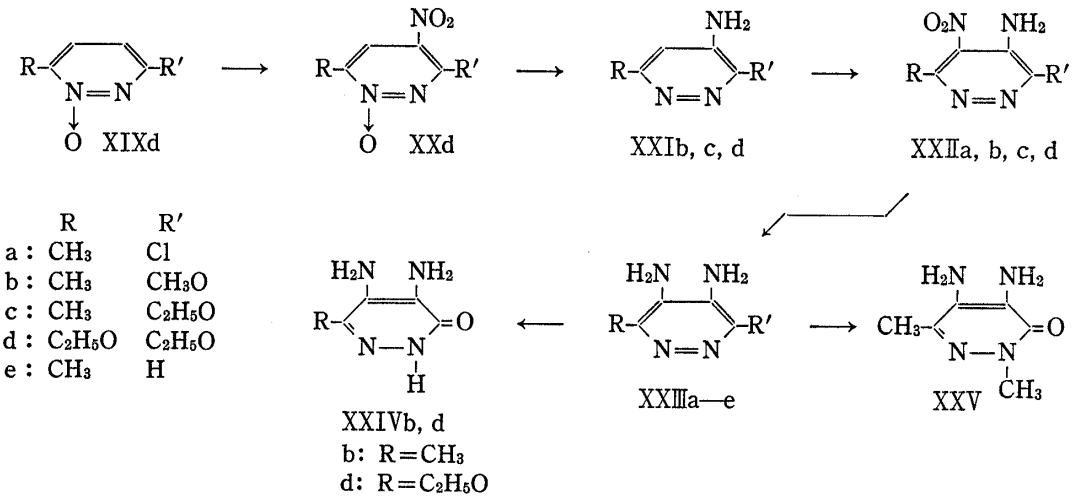

Chart 2

4) *a*) T. Itai and S. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 999 (1960); *b*) W.D. Guither, D.G. Clark and R.N. Castle, *J. Heterocyclic Chem.*, **2**, 67 (1965); *c*) V. Spiro, T. Aiello and I. Fabra, *Ann. Chim.* (Rome), **56**, 866 (1966) [*Chem. Abstr.*, **66**, 10902*v* (1967)].
5) M. Yanai, T. Kuraishi and T. Kinoshita, *Yakugaku Zasshi*, **81**, 708 (1961).
6) T. Kuraishi, *Chem. Pharm. Bull.* (Tokyo), **4**, 137 (1956).
7) Recently this compound was prepared by different route (S.F. Martin and R.N. Castle, *J. Heterocyclic Chem.*, **6**, 93 (1969)).

TABLE I.

No.	Compound R_3	R_5	R_6	mp (°C)	Yield (%)
IIIa	CH_3O	NO_2	Cl	181.5—182	53
IIIb	C_2H_5O	NO_2	Cl	166 —167	69
IV	CH_3O	NH_2	Cl	186.5—187.5[a]	70
Va	CH_3O	NH_2	H	182 —183	66
Vb	C_2H_5O	NH_2	H	155 —156	35
VI	C_2H_5O	Br	Cl	147.5—148.5	35
VII	Cl	Br	Cl	202.5—20.35	95
VIII	Cl	NO_2	Cl	118 —119.5	70
IX	Cl (NH_2)	NO_2	NH_2 (Cl)	258 —259	80
X	Cl	NH_2	NH_2	241 —243	56
XI	H	NH_2	H	270 —271	95
XIII	Cl (HO)	NO_2	HO (Cl)	291 —293	97.5
XIV	Cl	NH_2	HO	314 —318[a]	81
XV	Cl	NH_2	Cl	293 —295[a]	82
XVI	HO	NH_2	H	224 —226	86
XVII	HS	NH_2	H	241 —243	80
XVIII	CH_3S	NH_2	H	193.5—194.5	90
XXIb	CH_3O	H	CH_3	156 —157	81
XXIc	C_2H_5O	H	CH_3	165 —166	56
XXIb	C_2H_5O	H	C_2H_5O	145 —146	90
XXIIa	Cl	NO_2	CH_3	155 —155.5	81
XXIId	CH_3O	NO_2	CH_3	193 —194	64
XXIIc	C_2H_5O	NO_2	CH_3	173 —174	65
XXIId	C_2H_5O	NO_2	C_2H_5O	170.5—171.5	80
XXIIIb	CH_3O	NH_2	CH_3	202 —203	85
XXIIIc	C_2H_5O	NH_2	CH_3	161 —162	85
XXIIId	C_2H_5O	NH_2	C_2H_5O	162 —163	95

No.	Appearance,[b] recryst. solv.		Formula	Analysis Calcd. C	H	N	Found C	H	N
IIIa	Y.N.	$CHCl_3$	$C_5H_5O_3N_4Cl$	29.36	2.46	27.39	29.53	2.42	27.14
IIIb	Y.P.	$CHCl_3$	$C_6H_7O_3N_4Cl$	33.97	3.23	25.63	33.66	3.44	25.69
IV	C.C.	MeOH	$C_5H_7ON_4Cl$	34.38	4.01	32.09	34.11	4.29	32.15
Va	C.P.	MeOH–benzene	$C_5H_8ON_4$	42.85	5.76	39.98	43.02	5.77	39.61
Vb	C.S.	EtOH-benzene	$C_6H_{10}ON_4$	46.74	6.54	36.34	46.86	6.60	36.22
VI	C.R.	acetone	$C_6H_7ON_3BrCl$	28.54	2.79	16.64	28.80	2.71	16.78
VII	C.N.	MeOH	$C_4H_2N_3BrCl$	19.78	0.83	17.30	20.08	0.85	17.53
VIII	Y.P.	$CHCl_3$	$C_4H_2O_2N_4Cl_2$	22.99	0.97	27.00	23.11	0.99	26.81
IX	Y.P.	water	$C_4H_4O_2N_5Cl$	25.34	2.12	36.94	25.59	1.99	36.65
X	C.N.	MeOH	$C_4H_6N_5Cl$	30.09	3.77	43.88	29.82	3.68	43.63
XI	C.P.	EtOH	$C_4H_6N_4$	43.63	5.49	50.88	43.76	5.59	50.32
XIII	Y.P.	MeOH	$C_4H_3O_3N_4Cl$	25.20	1.57		25.26	1.69	
XIV	C.N.	water	$C_4H_5ON_4Cl$	29.90	3.21	34.89	30.20	3.34	34.62
XV	C.N.	water	$C_4H_4N_4Cl_2$	26.82	2.24	31.28	26.96	2.33	31.32
XVI	C.N.	water	$C_4H_6ON_4$	38.09	4.80	44.43	38.04	5.00	44.10
XVII	YB.P.	water	$C_4H_6N_4S$	33.55	4.05	39.43	33.80	4.22	39.14
XVIII	Y.P.	MeOH-water	$C_5H_8N_4S$	38.45	5.13	35.89	38.31	5.10	35.62
XXIb	C.N.	acetone	$C_6H_9ON_3$	51.79	6.52	30.20	51.89	6.45	30.08
XXIc	C.P.	acetone	$C_7H_{11}ON_3$	54.89	7.24	27.43	54.93	7.41	27.19

XXId	C.P.	acetone	$C_8H_{13}O_2N_3$	52.45	7.15	22.94	52.57	7.01	22.58
XXIIa	Y.P.	MeOH	$C_5H_5O_2N_4Cl$	31.84	2.67	29.70	32.16	2.81	29.65
XXIIb	Y.P.	MeOH or water	$C_6H_8O_3N_4$	39.13	4.34	30.43	39.47	4.49	30.40
XXIIc	Y.P.	EtOH	$C_7H_{10}O_3N_4$	42.42	5.09	28.27	42.51	5.04	28.17
XXIId	Y.P.	acetone	$C_8H_{12}O_4N_4$	42.10	5.30	24.55	42.32	5.27	24.36
XXIIIb	C.N.	acetone	$C_6H_{10}ON_4$	46.74	6.54	36.34	47.00	6.55	36.65
XXIIIc	C.P.	acetone	$C_7H_{12}ON_4$	45.15	7.58	30.09	45.29	7.56	30.30
XXIIId	C.P.	acetone	$C_8H_{14}O_2N_4$	48.48	7.07	28.27	48.60	7.20	27.96

a) decomp.
b) Y:yellow, C:colorless, YB:yellowish brown, N:needles, P:prisms, C:crystals, S:scales, R:rhombi

Experimental

3-Methoxy-4-amino-5-nitro-6-chloropyridazine (IIIa)——To a cooling solution of 0.91 g of IIa and 2.5 ml of conc. H_2SO_4, 0.6 ml of fuming HNO_3 ($d=1.52$) was added portionwise, heated at 50—55° for 3 hours. The reaction mixture was poured in crushed ice, the cooling solution was alkalized with $NaHCO_3$ (yellow solid precipitated), extracted with $CHCl_3$, dried over $MgSO_4$, evaporated to dryness.

3-Methoxy-4,5-diamino-6-chloropyridazine (IV)——IIIa (4 g) in 100 ml of MeOH was hydrogenated over 4 g of Raney nickel T-1.[8] The catalyst was filtered, solvent was removed.

3-Methoxy-4,5-diaminopyridazine (Va)——i) IIIa (0.6 g) in 60 ml of EtOH was hydrogenated over 0.25 g of 20% Pd–C. The catalyst was filtered, the filtrate was neutralized with $NaHCO_3$ solution, evaporated to dryness *in vacuo*. The residue was extracted with boiling acetone, solvent was removed to dryness.

ii) IV (4 g) in 100 ml of MeOH was hydrogenated over 0.7 g of 10% Pd–C. The same treatment was employed as above method.

3,6-Dichloro-4-amino-5-bromopyridazine (VII)——A mixture of 0.5 g of I, 0.6 g of bromine, 70 mg of iron powder and 7.5 ml of acetic acid was allowed stand at room temperature overnight. The reaction mixture was poured into 50 ml of water, precipitated crystals were filtered.

3,6-Dichloro-4-amino-5-nitropyridazine (VIII)——To a cooling solution of 40 g of I and 160 ml of conc. H_2SO_4, 32 ml of fuming HNO_3 ($d=1.52$) was added portionwise. The mixture was heated at 50—55° for 2 hours, then 65° for 2 hours. The same treatment was employed as IIIa method.

Reduction of 3,6-Dichloro-4-amino-5-nitropyridazine (VIII) with Pd-C——VIII (4.3 g) in 150 ml of MeOH was hydrogenated over 2.7 g of 20% Pd–C. The catalyst was filtered, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in small amount of water, neutralized with $NaHCO_3$. After removal of solvent under reduced pressure, the residue was extracted with hot AcOEt several times, evaporated to dryness, recrystallized from MeOH–AcOEt (charcoal) to give 35 mg of pale yellow rhombi, mp 207—208° (decomp.). *Anal.* Calcd. for $C_4H_5N_4Cl$ (XII): C, 33.23; H, 3.49; N, 38.75. Found: C, 33.51; H, 3.35; N, 38.91. Insoluble (in AcOEt) residue was dissolved in 20 ml of water, alkalified with 40% NaOH solution. Solvent was evaporated to dryness under reduced pressure, the residue was extracted with hot acetone–MeOH mixture (2:1) several times, evaporated to dryness. The residue was recrystallized from EtOH to give 350 mg (16%) of colorless prisms, mp 270—271°. This compound was identified with an authentic specimen of XI by mixed melting point test and infrared comparison.

3,5(or 4)-Diamino-6-chloro-4(or 5)-nitropyridazine (IX)——A mixture of VIII and 30 ml of ethanolic ammonia was heated at 95—100° for 1.5 hours in a sealed tube (crystals separated). The crystals were filtered, washed with small amount of water.

3,4,5-Triamino-6-chloropyridazine (X)——IX (2 g) in 200 ml of MeOH was hydrogenated over 2 g of Raney nickel T-1. The catalyst was removed, the filtrate was evaporated, the separated crystals were collected by suction.

3-Chloro-4,5-diamino-6(1*H*)-pyridazinone (XIV)——XIII (7 g) in 250 ml of EtOH was hydrogenated over 7 g of Raney nickel T-1. The same treatment was employed as IIIa method.

3,6-Dichloro-4,5-diaminopyridazine (XV)——A mixture of 3 g of XIV, 6 ml of N,N-dimethylaniline and 60 ml of $POCl_3$ was refluxed for 5 hours. The reaction mixture was evaporated under reduced pressure, the residue was poured in crushed ice, alkalized with diluted ammonium hydroxide (precipitate). After removal of N,N-dimethylaniline with ether, the water layer was concentrated, separated crystals were collected.

4,5-Diaminopyridazine (XI)——XV (1.4 g) in a mixture of 70 ml of MeOH, 0.66 g of NaOH and 4 ml of water was hydrogenated over 0.5 g of 20% Pd–C. The catalyst was removed, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with hot acetone–MeOH mixture (2:1) several times, solvent was removed.

8) X.A. Dominguez, I.C. Lopez and P. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

4,5-Diamino-3(2*H*)pyridazinone (XVI)——XIV (6.6 g) in a solution of 100 ml of water and 3.65 g of NaOH was hydrogenated over 1 g of 20% Pd–C. The catalyst was removed, the filtrate was concentrated under reduced pressure, acidified with 10% HCl, separated crystals were collected.

3-Mercapto-4,5-diaminopyridazine (XVII)——To a mixture of 0.5 g of XVI and 40 ml of dry pyridine, 2.7 g of P_2S_5 was added, refluxed for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure. To the residue 50 ml of boiling water was added, filtered. The filtrate was concentrated, separated crystals were collected.

3-Methylthio-4,5-diaminopyridazine (XVIII)——To a cooling solution of 1 g of XVII and 5.5 ml of 10% NaOH, 1.6 g of methyl iodide was added, shaked violently. After few minutes, crystals precipitate, the mixture was allowed stand at room temperature overnight, heated at 80° for 5 minutes. After cooling, the crystals were collected.

Reduction of 3-Chloro-4-nitro-6-methylpyridazine 1-Oxide (XXa) with Raney Nickel——XXa (17.5 g) in 500 ml of MeOH (contained 8.8 ml of acetic acid) was hydrogenated over 15 g of Raney nickel T-1, for 5.75 hours. After addition of 10 g of Raney nickel and 2 ml of acetic acid, hydrogenation was continued for 15 hours (total). The catalyst was removed, the filtrate was evaporated to dryness under reduced pressure. After washing with MeOH–acetone mixture, insoluble material was dissolved in water, alkalized with 15% Na_2CO_3 solution. The separated crystals (4.5 g) were recrystallized from acetone to give 4.06 g of colorless scales, mp 179.5—180°. The mother liquor and the above washing were combined, evaporated to dryness. The residue was dissolved in water, alkalized with 15% Na_2CO_3 solution, the separated crystalline mass was recrystallized fractionally from acetone to give additional 1.67 g of colorless needles, mp 179.5—180° (total 5.73 g, 43.2%) and 0.15 g of pale yellow prisms (mp 223—225°). The alkaline filtrate was evaporated to dryness on a water bath, the residue was extracted with acetone by mean of Soxhlet extractor, 0.21 g of pale yellow prisms (mp 225°) were obtained (total 0.36 g, 2.5%). *Anal.* Calcd. for $C_5H_6N_3Cl$ (mp 179.5—180°, XXIa): C, 41.83; H, 4.21; N, 29.27. Found: C, 41.56; H, 4.19; N, 29.09. *Anal.* Calcd. for $C_5H_6ON_3Cl$ (mp 223—225°, 3-chloro-4-amino-6-methylpyridazine 1-oxide): C, 37.63; H, 3.79; N, 26.33. Found: C, 37.81; H, 3.55; N, 26.26.

3-Ethoxy-4-nitro-6-methylpyridazine 1-Oxide (XXc)——To a cooling solution of 6 g of XIXc and 23 ml of conc. H_2SO_4, 6.3 ml of fuming HNO_3 ($d=1.52$) was added portionwise. The mixture was heated at 50—55° for 4 hours, poured in crushed ice, separated yellow solid was filtered and washed with water. The filtrate and washing were combined, alkalized with $NaHCO_3$, extracted with $CHCl_3$, dried over $MgSO_4$, evaporated to dryness.

3-Methoxy-4-amino-6-methylpyridazine (XXIb)——XXb (10 g) in 400 ml of MeOH was hydrogenated over 10 g of Raney nickel T-1. The catalyst was filtered, the filtrate was evaporated to dryness.

3-Chloro-4-amino-5-nitro-6-methylpyridazine (XXIIa)——To a cooling solution of 0.5 g of XXIa and 2 ml of conc. H_2SO_4, 0.29 ml of fuming HNO_3 ($d=1.52$) was added portionwise, heated at 60° for 4.5 hours. Same treatment was employed as XXc method.

3-Methoxy-4-amino-5-nitro-6-methylpyridazine (XXIIb)——To a solution of 0.5 g of XXIb and 2.5 ml of conc. H_2SO_4, 0.34 ml of fuming HNO_3 ($d=1.52$) was added portionwise with cooling, heated at 50—55° for 3.5 hours. Same treatment was employed as IIIa method.

Reduction of 3-Chloro-4-amino-5-nitro-6-methylpyridazine (XXIIa)——i) With Raney Nickel: XXIIa (1.5 g) in 100 ml of MeOH and 0.5 ml of acetic acid was hydrogenated over 5 g of Raney nickel T-1. The catalyst was removed, washed with MeOH, the filtrate and the washing were combined, evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH–acetone mixture to give 0.86 g (68%) of colorless needles, mp 229—230° (decomp.). *Anal.* Calcd. for $C_5H_7N_4Cl$ (XXIIIa): C, 37.87; H, 4.44; N, 35.33. Found: C, 37.71; H, 4.29; N, 34.99.

ii) With Pd–C: XXIIa (1.5 g) in 100 ml of MeOH and 4 ml of 10% NaOH was hydrogenated over 1 g of 15% Pd–C. The catalyst was filtered, the filtrate was evaporated to dryness under reduced pressure. The residue was dried in a vacuum desiccator over P_2O_5 for two days, extracted with acetone, evaporated to dryness. Two products were obtained by fractional recrystallization of the residue from MeOH–acetone mixture. Product A: mp 213—214°, 0.60 g (61%), colorless needles, *Anal.* Calcd. for $C_5H_8N_4$ (XXIIIe): C, 48.37; H, 6.50; N, 45.13. Found: C, 48.09; H, 6.58; N, 45.33. Product B: mp 229—230.5°, 50 mg (4%), colorless needles. This compound was identified with an authentic specimen of XXIIIa by mixed melting point test and infrared comparison.

4,5-Diamino-6-methyl-3(2*H*)pyridazinone (XXIVb)——A solution of 3.4 g of XXIIIb and 60 ml of 18% HCl was refluxed for 10 hours, evaporated to dryness under reduced pressure. The residue was dissolved in 5% NaOH, acidified with acetic acid, precipitated crystalline mass was filtered. The crystals were recrystallized from water to give 2.4 g (79%) of colorless needles, mp 277—278° (decomp.). *Anal.* Calcd. for $C_5H_8ON_4$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.85; H, 5.72; N, 39.61.

3-Ethoxy-4,5-diamino-6(1*H*)pyridazinone (XXIVd)——A solution of 1 g of XXIIId and 12 ml of 10% HCl was refluxed for 2 hours, alkalized with 18% ammonium hydroxide. The precipitated crystals were collected, recrystallized from EtOH to give 0.71 g (81%) of colorless prisms, mp 224—226.5° (decomp.). *Anal.* Calcd. for $C_6H_{10}O_2N_4$: C, 42.35; H, 5.92; N, 32.92. Found: C, 42.65; H, 6.07; N, 32.68.