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Pyridopyridazines. III.[1] Pyrido[3,4-*d*]pyridazines. I.

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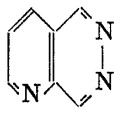
Improved syntheses of 1,4-dihydroxypyrido[3,4-*d*]pyridazine (II) and 1,4-dichloropyrido[3,4-*d*]pyridazine (I) were described. Reaction of I with alcohol and alkali gave 1,4-dialkoxypyrido[3,4-*d*]pyridazines (IIIa—c). Hydrolysis of I gave an isomeric mixture of 1-chloro-4-hydroxy- and 1-hydroxy-4-chloropyrido[3,4-*d*]pyridazines (IV and V). Reaction of I with hydrazine hydrate afforded also an isomeric mixture of 1-chloro-4-hydrazino- and 1-hydrazino-4-chloropyrido[3,4-*d*]pyridazines (VIII and IX). The structures of these compounds were determined by an alternative synthesis of V from known 1-hydroxy-4-aminopyrido[3,4-*d*]pyridazine (VI) and by conversion of IX into V. Also described were the preparations of 1-hydroxypyrido[3,4-*d*]pyridazine (VII) and isopropylidene derivatives (X and XI) of VIII and IX, and improved syntheses of 1,4-dichlorophthalazine and ethyl 3-cyanoisonicotinate.

In the previous papers,[1,3] the preparations, reactions and some pharmacological properties of pyrido[2,3-*d*]pyridazine derivatives were described. In this paper, efforts were directed toward the preparation of pyrido[3,4-*d*]pyridazine compounds derived from 1,4-dichloropyrido-[3,4-*d*]pyridazine (I). The reactivity of the chlorine atoms at positions 1 and 4 of this compound was discussed and compared with that of 1,4-dichlorophthalazine.



pyrido[2,3-*d*]pyridazine

pyrido[3,4-*d*]pyridazine

Chart 1

The chemistry of pyrido[3,4-*d*]pyridazines began only recently to be developed[4] and very few compounds were known. The preparation of the parent pyrido[3,4-*d*]pyridazine was recently reported.[4]

As the starting material, 1,4-dihydroxypyrido[3,4-*d*]pyridazine (II) was prepared. Although some methods[5] were reported for the preparation of II, they were found to be unsuitable for the larger scale preparation since the crude product was often mixed with the uncyclized hydrazides and purified with difficulty. Two different synthetic ways were now developed. In the first way, cinchomeronic acid was converted with acetic anhydride into cinchomeronic anhydride, which was then treated with two molar equivalents of hydrazine hydrate in acetic acid to give an almost quantitative yield of II. In this case, the treatment of the anhydride with one molar equivalent of hydrazine in acetic acid on the analogy of the preparation of 5,8-dihydroxypyrido[2,3-*d*]pyridazine[5b] was not successful in giving the cyclized product II, but the uncyclized hydrazides were obtained. Similar observation was reported in the preparation of 1,4-dihydroxy-5,8-dichlorophthalazine,[6] where two molar equivalents of hydrazine hydrate were necessary. In the second way, cinchomeronimide was treated

1) Part II: I. Matsuura, F. Yoneda, and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), **14**, 1010 (1966).
2) Location: *Takada-3-41-8, Toshima-ku, Tokyo.*
3) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).
4) *a*) G. Queguiner and P. Pastour, *Compt. Rend. Ser. C*, **262**, 1335 (1966); *b*) D.B. Paul and H.J. Rodda, *Australian J. Chem.*, **21**, 1291 (1968).
5) *a*) H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912); *b*) G. Gheorghiu, *Bull. Soc. Chim. France*, **53**, 151 (1933); *c*) H.L. Yale, K. Losee, J. Martins, M. Holsing, F.M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
6) H.D.K. Drew and F.H. Pearman, *J. Chem. Soc.*, **1937**, 26.

with an equimolar hydrazine hydrate in water to give II in good yield. Crude product of II thus obtained by the both ways was practically pure for the further synthesis and the contamination by the uncyclized hydrazides or N-aminocinchomeronimide was not detected by infrared spectroscopy.

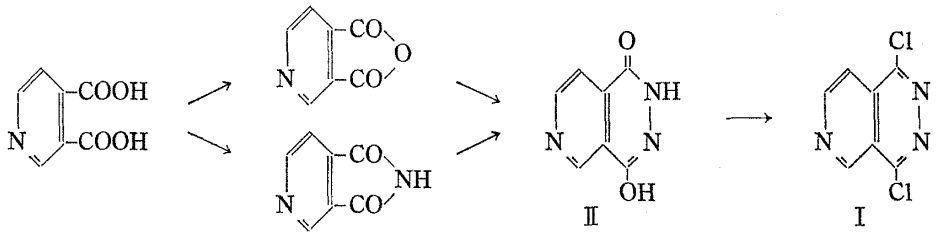


Chart 2

The preparation of I by treatment of II with phosphorus oxychloride was patented by the authors[7] and later reported independently by Paul and Rodda.[4b] Improvement of this method was successful when pyridine type base, such as pyridine, picoline or quinoline was added. Dimethylaniline and triethylamine were however not effective as catalysts. This special utility of the pyridine type catalyst was also demonstrated in the quantitative (99%) preparation of 1,4-dichlorophthalazine from phthalhydrazide by treatment with phosphorus oxychloride and pyridine.

Reactions of I with nucleophilic agents were studied on alkoxylation, hydrolysis and hydrazination. In these reactions, the chlorine atoms of I are expected to be more reactive than those of 1,4-dichlorophthalazine owing to the electron withdrawing effect of pyridine nitrogen, and when one chlorine atom of I is displaced, some higher reactivity of position 4 over that of position 1 will be expected due to the orientation of this effect as shown in Chart 3. The experimental results are indicated in the following sections.

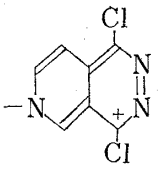


Chart 3

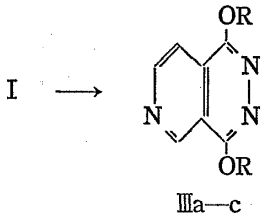


Chart 4

Alkoxylation

Reactions of I with two molar equivalents of alkoxides in the corresponding alcohols or with alcohols in the presence of two equivalents of alkali hydroxide afforded 1,4-dialkoxypyrido[3,4-*d*]pyridazines (IIIa—c) in good yields. It was found that the reaction condition was similar to that of 5,8-dichloropyrido[2,3-*d*]pyridazine[3] and much milder than in the case of 1,4-dichlorophthalazine.[8] Datas are presented in Table I. These compounds IIIa—c showed some interesting pharmacological effects as antipyretics, analgesics and anticonvulsants. Reactions of I with an equimolar sodium alkoxide in alcohol was unsuccessful in giving the alkoxychloro derivatives owing to the difficulty in separating the products.

Hydrolysis

Hydrolysis of I proceeded rapidly in both alkaline and acidic conditions. It was reported that hydrolysis of 1,4-dichlorophthalazine[9] did not proceed in alkaline condition, and repeti-

7) Y. Nitta, F. Yoneda, and I. Matsuura, Japan. Patent 16476 (1966).
8) *a*) J.A. Elvidge and A.P. Redman, *J. Chem. Soc.*, **1960**, 1710; *b*) E. Hayashi, T. Higashino, C. Iijima, Y. Kono, and T. Doihara, *Yakugaku Zasshi*, **82**, 584 (1962).
9) R.D. Haworth and S. Robinson, *J. Chem. Soc.*, **1948**, 777.

Table I

Compd.	R	Reactants	Recryst. solvt.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	CH_3	CH_3ONa	CH_3OH	100	139—140	$C_9H_9O_2N_3$	56.54	4.75	21.98	56.33	4.97	21.42
IIIa	CH_3	$CH_3OH+KOH$	CH_3OH	85	138—139							
IIIb	C_2H_5	C_2H_5ONa	dil. CH_3OH	89	96—97	$C_{11}H_{13}O_2N_3$	60.26	5.98	19.15	60.08	6.06	19.23
IIIb	C_2H_5	$C_2H_5OH+KOH$	C_2H_5OH	74	96—97							
IIIc	$CH(CH_3)_2$	$(CH_3)_2CHONa$	dil. CH_3OH	89	80—81	$C_{13}H_{17}O_2N_3$	63.14	6.93	16.99	63.49	6.91	17.33

tion of the acid hydrolysis showed that it needed longer heating than in the case of I. Alkali hydrolysis of I afforded a mixture of 1-chloro-4-hydroxypyrido[3,4-*d*]pyridazine (IV) and 1-hydroxy-4-chloropyrido[3,4-*d*]pyridazine (V) in the ratio of 45:55, and acid hydrolysis of I in trifluoroacetic acid afforded a mixture of IV and V in the ratio 55:45 as shown in Fig. 1. The same tendency was found in the case of the hydrolysis of I in dilute hydrochloric acid. This increase of the ratio of IV may be explained that the substrate I was protonated at position 3 or 6 in the acidic condition to activate the position 4 to the nucleophilic attack as shown in Chart 5. Such catalytic effect of proton has been noted on many occasions in N-heteroaromatic chemistry.[10] The ratio of the products was determined by nuclear magnetic resonance (NMR) spectroscopy in trifluoroacetic acid or sulfuric acid solutions. Protonation of pyridine nitrogen at position 6 of IV and V was observed in the sulfuric acid solutions.

The structures of IV and V were determined by an alternative synthesis of V by

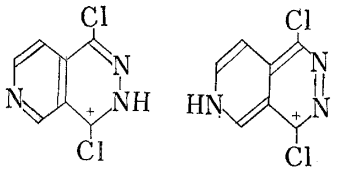


Chart 5

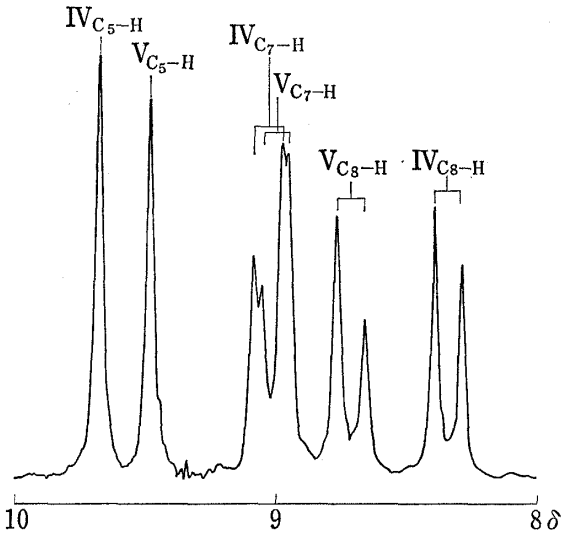


Fig. 1. NMR Spectrum (60 Mc) of the Mixture of IV and V prepared by dissolving I in CF_3COOH

reaction of the known 1-hydroxy-4-aminopyrido[3,4-*d*]pyridazine (VI) with nitrous acid in hydrochloric acid. The compound VI was synthesized by the method of Novacek, *et al.*[11] from ethyl 3-cyanoisonicotinate, which was now conveniently synthesized in 52% yield in one step from 3-carbamoylisonicotinic acid by an application of Sauers and Cotter cyanoester synthesis.[12] It will be the first application of this synthesis in the heteroaromatic field. The lactam structures of IV and V were determined by infrared spectroscopy, since both IV and V exhibited a strong carbonyl band at 1680 cm^{-1}. Reductive dehalogenation of V

10) R.G. Shepherd and J.L. Fedrick, "Advances in Heterocyclic Chemistry," Vol. 4, ed. by A.R. Katritzky, Academic Press Inc., New York, N.Y., 1965, p. 145.
11) L. Novacek, K. Palat, M. Celadnik, and E. Matuskova, *Ceskoslov. Farm.*, **11**, 76 (1962); *Chem. Abstr.*, **57**, 15067 (1962).
12) C.K. Sauers and R.J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).

on palladium charcoal afforded the normal dechlorination product, 1-hydroxypyrido[3,4-*d*]-pyridazine (VII), in contrast to the case of pyrido[2,3-*d*]pyridazine derivatives, of which the pyridine ring was hydrogenated to give the tetrahydro derivatives under the same reductive condition.[1,3] The infrared spectrum of VII also showed a strong carbonyl band at 1660 cm^{-1} in favor of its lactam structure.

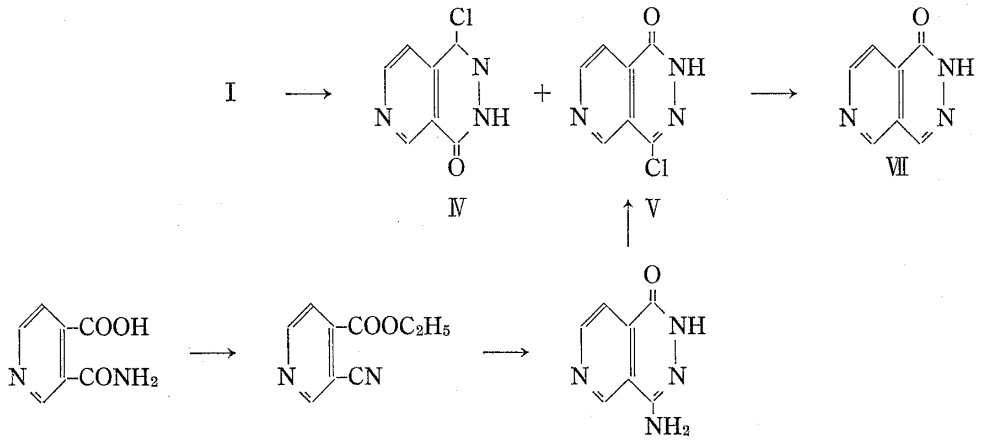


Chart 6

Hydrazination

Reaction of I with two molar equivalents of hydrazine hydrate in methanol at room temperature afforded an isomeric mixture of 1-chloro-4-hydrazinopyrido[3,4-*d*]pyridazine (VIII) and 1-hydrazino-4-chloropyrido[3,4-*d*]pyridazine (IX) in a quantitative yield. The reaction condition is similar to the case of 5,8-dichloropyrido[2,3-*d*]pyridazine[3] and much milder than the case of 1,4-dichlorophthalazine.[13] In order to separate VIII and IX from the reaction mixture, it was converted to a mixture of 1-chloro-4-isopropylidenehydrazino-pyrido[3,4-*d*]pyridazine (X) and 1-isopropylidenehydrazino-4-chloropyrido[3,4-*d*]pyridazine (XI) by treatment with acetone, and recrystallization of the mixture effected the separation of X and XI. Treatment of X and XI with hydrazine hydrate provided the isomers VIII and IX respectively. Attempts of direct separation of VIII and IX by recrystallization of the mixture of the free bases or the hydrochlorides were unsuccessful. The structures of VIII and IX were determined by conversion of IX into V by oxidation with sodium hypobromite in dilute sulfuric acid.

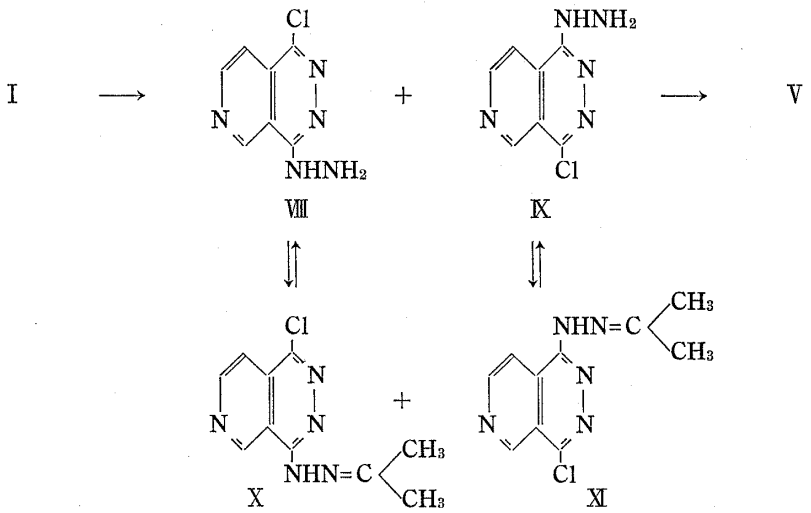


Chart 7

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

The ratio of VIII and IX in the reaction mixture was determined to be almost 50:50 by use of NMR spectroscopy in trifluoroacetic acid solution, where VIII was converted into a compound tentatively assumed on the analogy of pyrido[2,3-*d*]pyridazine derivatives[3] to be 3-trifluoromethyl-6-chloropyrido[3,4-*d*]triazolo[4,3-*b*]pyridazine, and IX into a mixture of IX protonated at position 6 and 3-trifluoromethyl-6-chloropyrido[4,3-*d*]triazolo[4,3-*b*]pyridazine. The NMR spectrum of the mixture of X and XI in deuterochloroform showed the same ratio.

In conclusion, the chlorine atoms of I were found to be more reactive to the nucleophiles than those of 1,4-dichlorophthalazine, and the orientation of the reaction of I was found to depend on the condition of the reactions due to the effects as protonation, hydrogen bonding and solvation involved in the reactions.

Experimental[14]

1,4-Dihydroxypyrido[3,4-*d*]pyridazine (II)——a) A mixture of cinchomeronic acid (134 g) and acetic anhydride (336 g) was heated under reflux for 1 hr to make a solution, to which a mixture of 80% $NH_2NH_2 \cdot H_2O$ (100 ml) and glacial acetic acid (200 ml) was added dropwise with stirring at reflux temperature. The mixture was heated under reflux for additional 3 hr and cooled. The precipitate was collected, washed with H_2O and dried to give powdery crystals of II (123 g, 95%), mp *ca.* 365° (decomp.). Recrystallization from a large amount of H_2O gave a powder, mp *ca.* 365° (decomp.). *Anal.* Calcd. for $C_7H_5O_2N_3$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.11; H, 3.48; N, 25.60. Purification was also possible by sublimation under 20 mmHg.

b) To a solution of 80% $NH_2NH_2 \cdot H_2O$ (24 ml) in H_2O (350 ml) was added powdered cinchomeronimide (50 g) and heated under reflux for 4 hr. The solution was treated with active charcoal and filtered. The filtrate was acidified with acetic acid to give a precipitate, which was collected and dried to give pale yellow powder of II (51.3 g, 91%), mp>350°. It was identical (IR spectrum) with a specimen prepared by method a.

1,4-Dichloropyrido[3,4-*d*]pyridazine (I)——a) To a mixture of pyridine (32.2 ml) and $POCl_3$ (200 ml) was added II (32.6 g) and heated at 100° for 2 hr. The solution was concentrated under reduced pressure and allowed to stand overnight at room temperature to give a crystalline residue, which was poured on crushed ice, collected and washed thoroughly with H_2O and dried under reduced pressure to give pale tan prisms of I (25.9 g, 65%), mp 153—155°. Recrystallization from acetone gave colorless prisms of I, mp 159°. *Anal.* Calcd. for $C_7H_3N_3Cl_2$: C, 42.04; H, 1.51; N, 21.01. Found: C, 42.01; H, 1.67; N, 21.19.

b) By procedures identical to method a except that two molar equivalents of the following base catalysts were used in place of pyridine, I was obtained in the following yields. α-Picoline, 76%; lutidine, 58%; quinoline, 66%; dimethylaniline, 0%; triethylamine, 15%.

1,4-Dichlorophthalazine——To a mixture of $POCl_3$ (300 ml) and pyridine (145 g) was added portionwise with stirring phthalhydrazide (145 g). In the course of the reaction, the mixture began to reflux. It was heated at 100° for 1 hr and allowed to stand overnight at room temperature. The crystalline reaction mixture was poured portionwise with stirring on crushed ice, collected and washed thoroughly with H_2O to give colorless needles of 1,4-dichlorophthalazine (183 g, 99%), mp 160—162°. Recrystallization from acetone gave colorless needles, mp 164°, which were identical (IR spectrum and mixed mp) with an authentic sample prepared by another method.[9]

1,4-Dialkoxypyrido[3,4-*d*]pyridazines (IIIa—c)——a) To a solution of sodium alkoxide prepared from Na (0.5 g) in the corresponding alcohol (25—50 ml) was added I (2.0 g) and heated under reflux for 15 min and concentrated to dryness. The residue was washed with H_2O and recrystallized from an appropriate solvent to give colorless crystals of IIIa—c presented in Table I.

b) To a solution of KOH (0.7 g) in the corresponding alcohol (20 ml) was added I (1.0 g). The mixture was treated in the same manner as the method a to give colorless crystals of IIIa—b.

Alkali Hydrolysis of I——A suspension of I (5.0 g) in 15% aqueous NaOH (50 ml) was heated at 100° for 20 min to give a solution, which was cooled overnight at 0°. The precipitate was collected, washed with MeOH, dissolved in H_2O (400 ml), neutralized with HCl, refluxed and filtered while hot. The insoluble residue (1.48 g, 33%), mp 293—294°, was recrystallized from acetic acid to give colorless crystals of V, mp 293—294°. *Anal.* Calcd. for $C_7H_4ON_3Cl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.23; H, 2.55; N, 22.95. NMR spectra: δ in conc. H_2SO_4; 10.05 (C_5–H, doublet), 14.50 (N_6–H, broad), 9.42 (C_7–H, triplet), 9.33 (C_8–H,

14) All melting points were uncorrected. Infrared spectra of all the compounds prepared were recorded in KBr disk and contribute confirmatory evidence for the structures assigned. NMR spectra were recorded at 60 Mc or 100 Mc. Chemical shifts (δ) are given in ppm from internal Me_4Si and coupling constants (J) in cps.

doublet); $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$, *ca.* 6 cps: δ in CF_3COOH: 9.45 (C_5–H, singlet), 8.95 (C_7–H, doublet), 8.71 (C_8–H, doublet); $J_{7,8}$, 6.3 cps. The filtrate was allowed to stand at room temperature and filtered. The precipitate was collected to give an additional amount of V (0.38 g, 8%), mp 273°. The filtrate was concentrated and cooled to give needles of the hydrate of IV (1.65 g, 33%), mp 200°. Recrystallization from H_2O gave needles, mp 202—203°. *Anal.* Calcd. for $C_7H_4ON_3Cl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.68; H, 2.57; N, 22.94. NMR spectra at 60 Mc: δ in conc. H_2SO_4; 10.18 (C_5–H, doublet), 14.25 (N_6–H, broad), 9.57 (C_7–H, triplet), 9.10 (C_8–H, doublet); $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$, 6.3 cps: δ in CF_3COOH; 9.65 (C_5–H, singlet), 9.00 (C_7–H, doublet), 8.40 (C_8–H, doublet); $J_{7,8}$, 6.3 cps.

Acid Hydrolysis of I——a) A suspension of I (5.0 g) in 5% HCl (50 ml) was heated at 100° for 1 hr. It was filtered after standing overnight at room temperature. The precipitate was washed with H_2O to give V (2.1 g, 46%), mp 295—298°. The filtrate was concentrated to give the hydrochloride of IV (2.7 g), mp 235—243° (decomp.), which was neutralized with sodium acetate in H_2O to give colorless crystals, mp 189—192°, which was recrystallized from H_2O to give IV, mp 194—196°, identical (IR spectrum and mixed mp) with a specimen prepared by the alkali hydrolysis.

b) Compound I was dissolved with warming in CF_3COOH containing H_2O, and the NMR spectrum of the solution was measured at 60 Mc. This is shown in Fig. 1, indicating that I was completely hydrolyzed to the mixture of IV and V.

Ethyl 3-Cyanoisonicotinate——To a mixture of 3-carbamoylisonicotinic acid (24.9 g, 0.15 mole) and triethylamine (45.6 g, 0.45 mole) in CH_2Cl_2 was added with stirring ethyl chlorocarbonate (48.6 g, 0.45 mole), the temperature being maintained between 0 and 5°. The reaction mixture was allowed to stand overnight at room temperature, and filtered. The filtrate was washed with H_2O, concentrated under reduced pressure to give a black viscous residue, which was extracted 4 times with refluxing petroleum ether (500 ml). The combined extracts were cooled to −20° and filtered to give pale yellow flakes of ethyl 3-cyanoisonicotinate (13.8 g, 52%), mp 58—59°. Recrystallization from petroleum ether gave colorless plates, mp 64—65° (lit.,[11] mp 64°). *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.07; H, 4.75; N, 15.72.

1-Hydroxy-4-aminopyrido[3,4-*d*]pyridazine (VI)——The solution of the cyanoisonicotinate in 0.5N ethanolic $NH_2NH_2 \cdot H_2O$ (20 ml) was allowed to stand 2 days at room temperature. The precipitate was collected, washed with H_2O to give yellowish powder of VII (1.300 g, 80%). Recrystallization from H_2O gave yellowish needles, mp >360° (lit.,[11] mp 343° (decomp.)). *Anal.* Calcd. for $C_7H_6ON_4$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.46; H, 3.86; N, 34.48.

Reaction of VI with Nitrous Acid——To a solution of VI (300 ml) in conc. HCl (50 ml) was added dropwise $NaNO_2$ (140 mg) in H_2O (10 ml) with stirring at 0° and it was stirred for 1 hr and concentrated to dryness to give a solid residue, which was washed with H_2O, and recrystallized from H_2O to give a product (230 mg, 67%), mp 287—292° (decomp.), identical (IR spectrum and mp) with V prepared by the method described above.

1-Hydroxypyrido[3,4-*d*]pyridazine (VII)——Compound V (1.0 g) suspended in MeOH (50 ml) was hydrogenated over 5% Pd–C at room temperature. The mixture was extracted with hot H_2O (200 ml) and cooled to give needles of VII, mp 290°. Recrystallization from H_2O gave colorless needles of VII, mp 292—293°. *Anal.* Calcd. for $C_7H_5ON_3$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.15; H, 3.79; N, 28.81.

Reaction of I with Hydrazine Hydrate——To a solution of 80% $NH_2NH_2 \cdot H_2O$ (13 ml) in MeOH (200 ml) was added I (20 g) portionwise under stirring at room temperature, and stirring was continued for additional few hr. The reaction mixture was allowed to stand overnight. The orange-red precipitate was collected, washed thoroughly with cold H_2O and dried to give cream-colored crystals of the mixture of VIII and IX (19.1 g, 97.6%), decomp. point 183—184°.

Partial Separation of X and XI——The mixture of VIII and IX (20 g) was added to acetone (20 ml) in MeOH (600 ml), refluxed for 15 min and filtered while hot. The insoluble part was recrystallized from MeOH to give yellow needles of X, mp 198—199°. *Anal.* Calcd. for $C_{10}H_{10}N_5Cl$: C, 50.94; H, 4.28; N, 29.71. Found: C, 51.18; H, 4.51; N, 29.92. NMR spectrum at 100 Mc: δ in $CDCl_3$; 9.57 (C_5–H, singlet), 8.85 (C_7–H, doublet), 7.53 (C_8–H, doublet), 2.15 (CH_3, singlet), 2.07 (CH_3, singlet); $J_{7,8}$, 6 cps. The hot soluble part was allowed to cool to separate a precipitate, which was collected and recrystallized several times from MeOH to give yellow flakes of XI, mp 201—202°. *Anal.* Calcd. for $C_{10}H_{10}N_5Cl$: C, 50.94; H, 4.28; N, 29.71. Found: C, 50.93; H, 4.14; N, 29.71. NMR spectrum at 100 Mc: δ in $CDCl_3$; 9.11 (C_5–H, singlet), 8.83 (C_7–H, doublet), 8.09 (C_8–H, doublet), 2.15 (CH_3, singlet), 2.07 (CH_3, singlet); $J_{7,8}$, 6 cps. The combined filtrates of recrystallization were concentrated to recover the isomeric mixture of X and XI, which by repeating the above mentioned procedure gave an additional amount of isolated X and XI. The total yields of X (5—6 g) and XI (3—4 g) were obtained.

1-Chloro-4-hydrazinopyrido[3,4-*d*]pyridazine (VIII)——To a solution of 80% $NH_2NH_2 \cdot H_2O$ (0.500 ml) in MeOH was added X (1.000 g), and the mixture was refluxed for 10 min to give dark red needles (0.746 g, 90%), decomp. point 190°. Recrystallization from MeOH gave dark red needles of VIII, decomp. point 190°. *Anal.* Calcd. for $C_7H_6N_5Cl$: C, 42.98; H, 3.09; N, 35.80. Found: C, 42.72; H, 3.08; N, 36.06. NMR spectrum at 100 Mc: δ in CF_3COOH as 3-trifluoromethyl-6-chloropyrido[3,4-*d*]triazolo[4,3-*b*]pyridazine; 8.37 (C_7–H, doublet), 9.11 (C_8–H, doublet), 10.01 (C_{10}–H, singlet); $J_{7,8}$, 6 cps. When this colored needles were

thoroughly washed with H_2O, almost colorless crystals were obtained as the case of the mixture of VIII and IX.

1-Hydrazino-4-chloropyrido[3,4-*d*]pyridazine (IX)——To a solution of 80% $NH_2NH_2 \cdot H_2O$ (0.500 ml) in MeOH (20 ml) was added I (1.000 g) and refluxed for a few min to give orange–yellow crystals of IX (0.780 g, 94%), decomp. point 186°. Recrystallization from MeOH gave IX, decomp. point 186°. *Anal.* Calcd. for $C_7H_6N_5Cl$: C, 42.98; H, 3.09; N, 35.80. Found: C, 42.72; H, 3.08; N, 35.80. NMR spectrum at 100 Mc: δ in CF_3COOH as a mixture of protonated IX; 9.67 (C_5–H, doublet), 9.04 (C_7–H, triplet), 8.27 (C_8–H, doublet); $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$, 6 cps and 3-trifluoromethyl-6-chloropyrido[4,3-*d*]triazolo[4,3-*b*]pyridazine; 9.57 (C_7–H, singlet), 9.05 (C_9–H, doublet), 8.66 (C_{10}–H, doublet); $J_{9,10}$, 6 cps.

Oxidation of IX with Hypobromite——To a solution of IX (196 mg) in 0.5N H_2SO_4 (20 ml) was added dropwise with stirring at room temperature aqueous NaBrO, prepared from NaOH (130 mg), Br_2 (330 mg) and H_2O (to 1 ml). The reaction mixture was allowed to stand for 30 min to give purple–red crystals of crude V (113 mg, 62%), mp 280° (decomp.). This was dissolved in aqueous NaOH and filtered. The filtrate was acidified with HCl to give a colorless precipitate of V, mp 290°, identical (IR and mixed mp) with the sample prepared from VI.

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