[Chem. Pharm. Bull. 13(5) 586~593 (1965)]

UDC 547.852.9

79. Yoshihiro Nitta, Ikutoshi Matsuura, and Fumio Yoneda: Pyridazine Derivatives. VIII.*1 Pyrido[2,3-*d*]pyridazines. I.*2

(*Research Laboratories, Chugai Pharmaceutical Co., Ltd.**3)

In spite of the development of the chemistry of phthalazines, few investigations have been made on the azalogs of phthalazines; pyrido[2,3-*d*]pyridazines and pyrido-[3,4-*d*]pyridazines. This and the fact that a wide variety of phthalazines possess significant pharmacologic activity prompted us to investigate systematic synthesis of these pyridopyridazines in an effort to obtain useful pharmacologic agents. Initial efforts were directed toward the preparation of pyrido[2,3-*d*]pyridazine derivatives derived from 5,8-dichloropyrido[2,3-*d*]pyridazine by nucleophilic displacement reactions and toward the study of influence of a nitrogen atom of pyridine ring on the displacement. The displacement reactions of one of the chlorine atoms of 5,8-dichloropyrido[2,3-*d*]-pyridazine with a variety of nucleophiles such as hydroxide, alkoxides and amines to yield two isomers will be noted.

The starting material, 5,8-dichloropyrido[2,3-*d*]pyridazine, has been prepared by refluxing quinolyl hydrazide in a mixture of phosphoryl chloride and phosphorus pentachloride by means of a long and tedious process.[1] The authors obtained conveniently the compound in much higher yield by heating quinolyl hydrazide[2] in a mixture of phosphoryl chloride and dimethyl aniline.

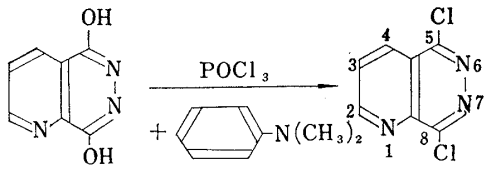


Chart 1.

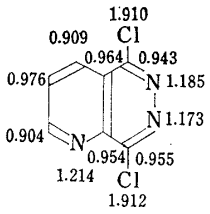


Chart 2.

For a better view of the relative reactivity of the chlorine atoms of 5,8-dichloropyrido[2,3-*d*]pyridazine, π-electronic characters of this compound were calculated from the simple linear-combination-of-atomic-orbitals molecular orbital (LCAO-MO) method. The parameters of the coulomb and resonance integrals for substituent groups were designated as shown in Table I. The distribution of electronic charge in 5,8-dichloropyrido[2,3-*d*]pyridazine was given by Chart 2.

Table I.

Substituent X	a_X[a]	a_r[b]	l[c]
-Cl	1.8	0.18	0.8
=N-	0.6	0.1	1

a) coulomb integral of the substituent X: $\alpha_X=\alpha+a_X\beta$
b) coulomb integral of the carbon atom adjacent to the substituent X: $\alpha_{adj}=\alpha+a_r\beta$
c) resonance integral between that carbon atom and X: $\beta_{c-x}=l\beta$

*1 Part Ⅶ: This Bulletin, **13**, 580 (1965).
*2 This work was presented in part at the 83rd Annual Meeting of the Pharmaceutical Society of Japan, Nov. 2, 1963, Tokyo.
*3 Toshima-ku, Tokyo, Japan (新田義博, 松浦育敏, 米田文郎).
1) W.L.F. Armarego: J. Chem. Soc., **1963**, 6073.
2) G. Gheorghiu: Bull. soc. chim. France, **47**, 630 (1930).

As can be seen from Chart 2, the 5-position which has less density of π-electron seems to be more reactive than the 8-position toward nucleophilic reagents. This view also was supported by the superdelocalizability for nucleophilic reaction ($Sr^{(N)}$),[3] which might have closer relation to the displacement reaction; $S_5^{(N)}=1.319$, $S_8^{(N)}=1.283$. Moreover, this was in good agreement with the experimental results that the products which were displaced at position 5, except in the case of anillino derivatives, were always afforded more predominantly than another ones displaced at position 8. The isomers often showed noticeable differences in physical properties such as solubility and melting point. The foregoing experimental results will be mentioned in the following sections.

Hydrolysis

Compound (I) was found to be stable toward water and weak acid at room temperature, but in hot alkali as well as in hot acid conditions easily hydrolyzed to the isomeric mixture of 8-chloropyrido[2,3-*d*]pyridazin-5-ol and 5-chloropyrido[2,3-*d*]pyridazin-8-ol. The isomers were separated from each other by the different solubility of the sodium salts in dilute sodium hydroxide solution. In the case of alkali hydrolysis, acidification

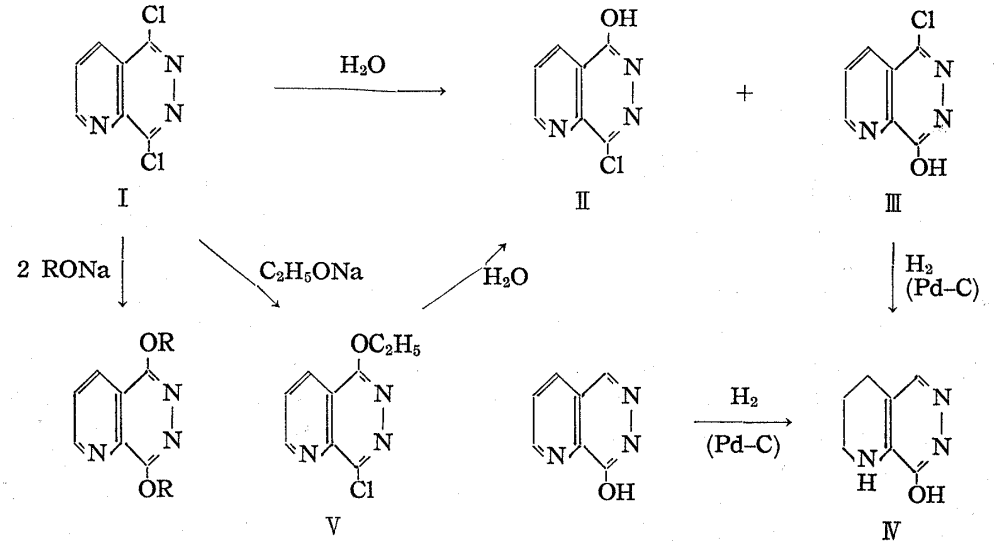


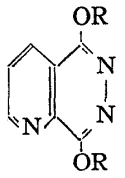
Chart 3.

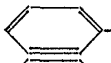
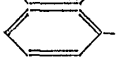
of the sodium salt which was soluble in dilute sodium hydroxide, gave the corresponding free compound (II), in yields of about 70%, and that of the isomeric sodium salt which was insoluble in dilute sodium hydroxide gave the corresponding free compound (III) in yields of about 30%.

The structure of compound (III), 5-chloropyrido[2,3-*d*]pyridazin-8-ol, was confirmed by catalytic dechlorination over palladium-charcoal, followed by unexpected hydrogenation of the pyridine ring to give the compound (IV), which proved to be identical with 1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8-ol that was afforded from the known pyrido-[2,3-*d*]pyridazin-8-ol[4] by a similar catalytic hydrogenation, as shown in Chart 3. The structure of isomeric compound (II) was therefore assigned to be 8-chloropyrido[2,3-*d*]-pyridazin-5-ol, although isolation of the hydrogenated product of II failed. Attempts to obtain pyrido[2,3-*d*]pyridazin-5(or 8)-ol by partial hydrogenation of II or III were unsuccessful.

3) K. Fukui, T. Yonezawa, C. Nagata: Bull. Chem. Soc. Japan, **27**, 423 (1954).
4) F. Bottari, S. Carboni: Gazz. chim. ital., **86**, 990 (1956).

TABLE II.



R	Formula	m.p. (°C)	Recrystallization solvents	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3–	$C_9H_9O_2N_3$	188	MeOH	94	56.54	4.75	21.98	56.60	4.68	22.35
C_2H_5–	$C_{11}H_{13}O_2N_3$	158	EtOH	94	60.26	5.98	19.15	60.38	5.92	19.34
C_3H_7–	$C_{13}H_{17}O_2N_3$	101	dil. MeOH	87	63.14	6.93	16.99	63.11	6.92	16.94
iso-C_3H_7–	$C_{13}H_{17}O_2N_3$	154	MeOH	100	63.14	6.93	16.99	63.21	6.81	17.03
CH_2=CH–CH_2–	$C_{13}H_{13}O_2N_3$	91	〃	55	64.18	5.39	17.28	63.86	5.31	17.29
	$C_{21}H_{17}O_2N_3$	168	〃	65	73.45	4.99	12.24	73.84	4.97	12.44
	$C_{19}H_{13}O_2N_3$	178	〃	80	72.37	4.16	13.33	72.58	4.16	13.62

Alkoxylation

5,8-Dialkoxypyrido[2,3-*d*]pyridazines were prepared by treating I with the corresponding alkoxides. In this way, 5,8-dimethoxy-, -diethoxy-, -di-*n*-propoxy-, -di-isopropoxy-, and -bis(allyloxy)-pyrido[2,3-*d*]pyridazine were obtained. 5,8-Diphenoxy derivative was obtained by heating compound (I) in phenol in the presence of anhydrous potassium carbonate.

Reaction of I with one mole of sodium ethoxide in cold ethanol gave a mixture of isomers of monoethoxychloropyrido[2,3-*d*]pyridazines, from which isomer (V), was isolated in pure condition. Attempts to isolate the other isomer were unsuccessful. The structure of compound (V) was confirmed to be 5-ethoxy-8-chloropyrido[2,3-*d*]pyridazine by hydrolysis in aqueous sodium hydroxide to give compound (II) obtained above.

Mercaptation

Pyrido[2,3-*d*]pyridazin-5,8-dithiol was synthesized by reaction of compound (I) with thiourea, followed by hydrolysis of the bisthiuronium salt with sodium hydroxide solution. As this dimercapto derivative was high-melting solid and did not let itself to further purification, it was converted to 5,8-bis(methylthio)pyrido[2,3-*d*]pyridazine by reaction with methyl iodide and potassium hydroxide in methanol.

Amination

An isomeric mixture of 5-chloro-8-amino- and 5-amino-8-chloropyrido[2,3-*d*]pyridazine was obtained by reaction of I with concentrated aqueous ammonia. The mixture was dissolved in hot dilute hydrochloric acid and the solution was cooled to precipitate crystals, which were neutralized to give compound (VI), and the filtrate was neutralized to give compound (VII). Conversion of VI into 8-chloropyrido[2,3-*d*]pyridazin-5-ol (II) by reaction with sodium nitrite in hydrochloric acid solution established the structure of VI as 5-amino-8-chloropyrido[2,3-*d*]pyridazine. The structure of VII was established in a similar way as 5-chloro-8-aminopyrido[2,3-*d*]pyridazine.

An equimolar mixture of I and aniline was refluxed in alcohol to give compound (VIII) with a small amount of isomeric compound (IX). Compound (VIII) was isolated in a pure form by recrystallization. Compound (IX) was separated from the mixture with VIII by chromatography. The structure of VIII, 5-chloro-8-anilinopyrido[2,3-*d*]pyridazine,

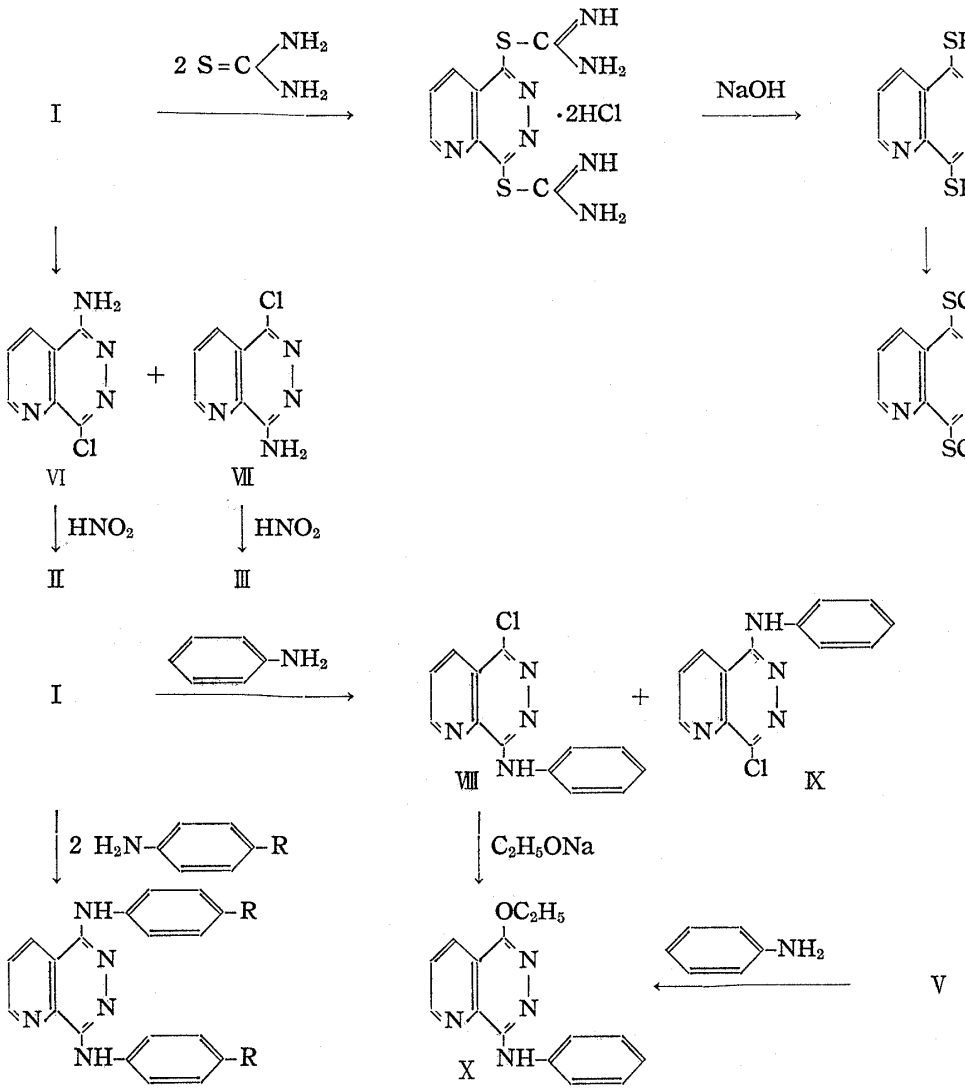
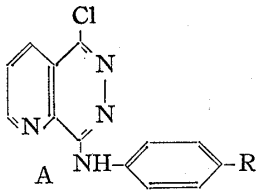


Chart 4.

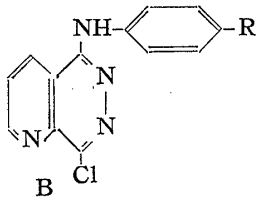
was determined by converting it by reaction with sodium ethoxide to compound (X) which was identical with 5-ethoxy-8-anilinopyrido[2,3-*d*]pyridazine alternatively prepared by the action of aniline on 5-ethoxy-8-chloropyrido[2,3-*d*]pyridazine (V). Compound (IX) was therefore 5-anilino-8-chloropyrido[2,3-*d*]pyridazine. 5-chloro-8-(*p*-substituted-anilino)pyrido[2,3-*d*]pyridazines shown in Table III were prepared in the same manner. 5-(*p*-Chloroanilino)-8-chloropyrido[2,3-*d*]pyridazine was also isolated as the minor isomeric product. These structures were confirmed by comparing their infrared spectra with those of compounds (VIII) and (IX). Reaction of I with two or more moles of aniline in alcohol under refluxing yielded 5,8-dianilinopyrido[2,3-*d*]pyridazine and in this way 5,8-bis(*p*-substituted anilino)pyrido[2,3-*d*]pyridazines shown in Table IV were obtained.

An isomeric mixture of 5-hydrazino-8-chloro- and 5-chloro-8-hydrazinopyrido[2,3-*d*]-pyridazines was obtained in high yields by allowing I to interact with an excess of hydrazine hydrate in methanol at room temperature. A partial separation of these two compounds was effected by crystallization from dilute hydrochloric acid, giving crystalline hydrochloride of compound (XI) and the filtrate gave the isomeric compound (XII) on neutralization. Compounds, XI and XII, were converted to compounds, II and III, respectively, by oxidation with sodium hypobromite in hydrochloric acid solution,

TABLE III.



A

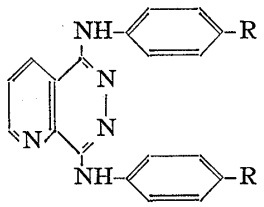


B

R	Formula	Type	m.p. (°C)	Recryst. solvents	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	$C_{13}H_9ClN_4$	A	180	EtOH	78	60.82	3.53	21.83	60.65	3.64	21.63
〃	〃	B	226～227 (decomp.)	MeOH	20	60.82	3.53	21.83	60.62	3.37	21.65
Cl	$C_{13}H_8Cl_2N_4$	A	220	EtOH	79	53.64	2.77	19.25	53.70	2.74	19.58
〃	〃	B	207～208[a] (decomp.)	MeOH	20	53.64	2.77	19.25	53.71	3.05	18.78
Br	$C_{13}H_8BrClN_4$	A	231～233 (decomp.)	Dioxan	81	46.52	2.40	16.70	46.71	2.62	17.02
CH_3	$C_{14}H_{11}ClN_4$	〃	200	MeOH	74	62.12	4.10	20.70	62.29	4.10	20.46
OH	$C_{13}H_9ON_4Cl$	〃	235～236 (decomp.)	EtOH	73	57.24	3.33	20.55	57.59	3.47	20.62
OCH_3	$C_{14}H_{11}ON_4Cl$	〃	199～201	MeOH	70	58.64	3.87	19.54	58.56	4.00	19.30

a) Contaminated with small amount of isomeric type A.

TABLE IV.



R	Formula	m.p. (°C)	Recryst. solvents	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	$C_{19}H_{15}N_5$	217	EtOH	83	72.82	4.83	22.35	73.16	4.96	22.38
CH_3	$C_{21}H_{19}N_5$	250	Dioxan	94	73.88	5.61	20.52	74.10	5.38	20.43
OCH_3	$C_{21}H_{19}O_2N_5$	213～214	MeOH	80	67.54	5.13	18.76	67.78	4.86	18.79

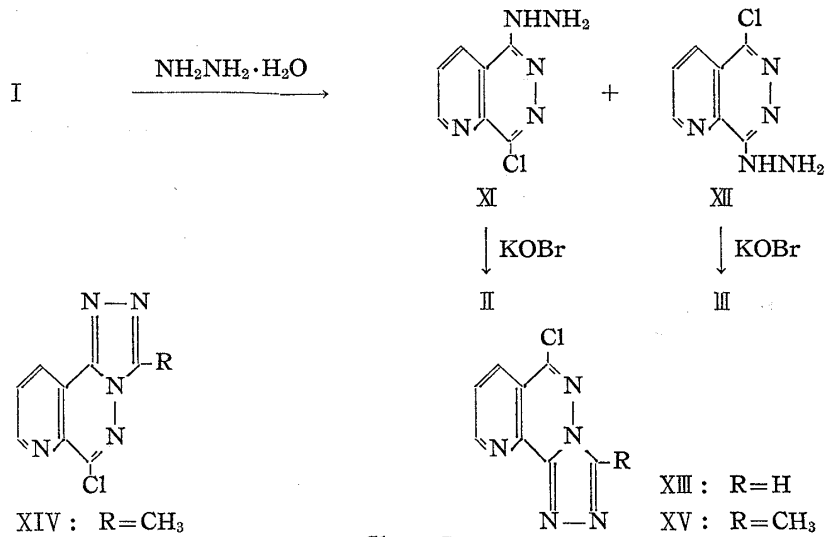


Chart 5.

thus indicating that the structures of XI and XII were 5-hydrazino-8-chloropyrido[2,3-*d*]-pyridazine and 5-chloro-8-hydrazinopyrido[2,3-*d*]pyridazine, respectively. In the case of reactions of I with ammonia and hydrazine, the 5-isomers also were obtained in relatively higher yields than the 8-isomers, as mentioned above.

Triazolopyrido[2,3-*d*]pyridazines were obtained by acylation of the hydrazino derivatives. With 80% formic acid compound (XII) gave a cyclized product, 6-chloropyrido-[2,3-*d*]-s-triazolo[4,3-*b*]pyridazine (XIII), while refluxing the compound (XI) with formic acid failed to give a triazole derivative, and gave only a formyl derivative. Reaction of XI and XII with acetic anhydride afforded the triazolo derivatives, XIV and XV, respectively.

Experimental*4

5,8-Dichloropyrido[2,3-*d*]pyridazine (I)——Quinolyl hydrazide (25 g.), $POCl_3$ (250 ml.) and dimethylaniline (25 ml.) were heated at 100° for 0.5~1 hr. until a clear solution was obtained. The solvent was removed *in vacuo* and the crystalline residue was poured into ice, the temperature being maintained at 0~15°. The precipitate was filtered off, washed with cold H_2O, and dried over $CaCl_2$ *in vacuo* to give yellowish plates (24 g., 78%), m,p, 164°. Recrystallization from acetone raised the m.p. to 169°. (Armarego[2] gave m.p. 163~164°). *Anal.* Calcd. for $C_7H_3Cl_2N_3$: C, 42.04; H, 1.51; N, 21.01. Found: C, 42.27; H, 1.33; N, 21.27.

The crude product was practically pure enough for the following reactions.

Hydrolysis of I. The Formation of 5-Chloropyrido[2,3-*d*]pyridazin-8-ol (III) and 8-Chloropyrido[2,3-*d*]pyridazin-5-ol (II)——Compound (I) (4.0 g.) was added to 2% NaOH (100 ml.) and heated at 100° for 30 min. until a clear solution was obtained. The solution was treated with charcoal, filtered hot, and cooled. The precipitate was collected, and dissolved in H_2O. The solution was acidified with AcOH, and the resulting solid was recrystallized from H_2O to give needles of III, (1.1 g., 30%) m.p. 289°(decomp.). *Anal.* Calcd. for $C_7H_4ON_3Cl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.35; H, 2.27; N, 23.35.

The filtrate of the reaction mixture was acidified with AcOH and the solid obtained was recrystallized from tetrahydrofuran to give prisms of II (2.4 g., 66%), m.p. 275°. *Anal.* Calcd. for $C_7H_4ON_3Cl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.53; H, 2.26; N, 23.18.

Hydrolysis in acid was proceeded in a similar way: compound (I) (2.0 g.) and 1% HCl (35 ml.) were heated at 100° for 2 hr. The precipitate was collected, washed with H_2O, and dried to give a mixture of II and III (1.7 g.). This was dissolved in 2% NaOH (25 ml.), and treated in a manner similar to that described above to give compound (II) (0.7 g.) and compound (III) (1.0 g.).

1,2,3,4-Tetrahydropyrido[2,3-*d*]pyridazin-8-ol (IV)——a) From 5-chloropyrido[2,3-*d*]pyridazin-8-ol (III): III (0.9 g.) was hydrogenated under atmospheric pressure at room temperature over 20% Pd-C (1 g.) in MeOH (30 ml.) and conc. NH_4OH (1 ml.) until absorption had ceased. About 500 ml. of H_2 was absorbed during 12 hr. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The crystalline residue was washed with H_2O, and recrystallized from MeOH to give crystals (0.5 g.), m.p. 226~228°. *Anal.* Calcd. for $C_7H_9ON_3$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.44; H, 6.10; N, 27.74.

b) From pyrido[2,3-*d*]pyridazin-8-ol: Pyrido[2,3-*d*]pyridazin-8-ol was treated just in the same manner as described above to give crystals, m.p. 227~228°. Identity was confirmed through mixed melting point and IR spectra.

General Procedure for 5,8-Dialkoxypyrido[2,3-*d*]pyridazines——Compound (I) (2.0 g.) was added to a solution of sodium (0.02 mole) and the appropriate anhydrous alcohol and heated at 100° on a water bath for 1 hr. The solution was filtered, concentrated, and cooled to give crystalline precipitate. This was filtered off, washed with water, and recrystallized from appropriate solvent to give colorless crystals of 5,8-dialkoxypyrido[2,3-*d*]pyridazine in Table II.

5-Ethoxy-8-chloropyrido[2,3-*d*]pyridazine (V)——A solution of Na (0.5 g.) in EtOH (15 ml.) was added dropwise to the suspension of finely powdered compound (I) (4.0 g.) in EtOH (30 ml.) with stirring at 5~20°. Stirring was continued for an additional 1 hr., and then it was refluxed for 15 min. filtered hot and cooled to give precipitate, which on recrystallization from EtOH gave plates (1.0 g.) m.p. 155°. *Anal.* Calcd. for $C_9H_8ON_3Cl$: C, 51.57; H, 3.85. Found: C, 51.76; H, 3.88.

Hydrolysis of V into II——V (0.25 g.) and 3% NaOH (10 ml.) were heated at 100° for 2 hr., and acidified with AcOH to give precipitate, which on recrystallization from MeOH gave compound (II) (0.15 g.) m.p. 275° (decomp.). *Anal.* Calcd. for $C_7H_4ON_3Cl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.29; H, 2.46; N, 23.06.

*4 All melting points are uncorrected. Infrared spectra of all the compounds prepared were recorded and contribute confirmatory evidence for the structure assigned.

Identity was confirmed by comparing IR spectra.

Pyrido[2,3-*d*]pyridazin-5,8-dithiol——Thiourea (3.0 g.) and I (4.0 g.) were refluxed in EtOH for 20 min., and crystals which separated were collected to give the 5,8-bisthiuronium salt (6.9 g., 95%), m.p. 192° (decomp.). This was heated in 5% NaOH (40 ml.) to give an orange-red solution, which on neutralization with HCl produced yellow high-melting powder of pyrido[2,3-*d*]pyridazine-5,8-dithiol (3.0 g.) (75%) m.p. >260°.

5,8-Bis(methylthio)pyrido[2,3-*d*]pyridazine——I (2.0 g.), KOH (1.2 g.) and CH_3I (1.2 ml.) were heated in methanol in a sealed tube at 100° for 2 hr., the solution was concentrated, and cooled to precipitate needles, which on recrystallization from EtOH gave pale yellow plates (1.7 g.), m.p. 249°. *Anal.* Calcd. for $C_9H_9N_3S_2$: C, 48.41; H, 4.06; N, 18.82. Found: C, 48.69; H, 3.79; N, 18.69.

Amination of I. The Formation of 5-Chloro-8-aminopyrido[2,3-*d*]pyridazine (VII) and 5-Amino-8-chloropyrido[2,3-*d*]pyridazine (VI)——I (5.0 g.) and conc. NH_4OH (50 ml.) in a sealed tube were heated at 100° for 5 hr., and cooled. The precipitate (4.0 g.) was collected and dissolved in 5% HCl (50 ml.). The solution was cooled to precipitate crystals, which were filtered from the filtrate A. The product was dissolved in H_2O, and the solution was neutralized with NH_4OH to give a tan solid, m.p. 225°, which on recrystallization from DMFA yielded crystals of VI, m.p. 229~230° (decomp.). *Anal.* Calcd. for $C_7H_5ClN_4$: C, 46.54; H, 2.79; N, 31.03. Found: C, 46.84; H, 3.01; N, 30.81.

To the filtrate A, 35% HCl (10 ml.) was added and the product which separated was filtered off and dissolved in H_2O. The solution was neutralized with NaOH to give a solid, m.p. 249° (decomp.). This was recrystallized from DMFA to yield colorless crystals of VII, m.p. 258~261° (decomp.). *Anal.* Calcd. for $C_7H_5ClH_4$: C, 46.54; H, 2.79; N, 31.03. Found: C, 46.49; H, 3.00; N, 30.80.

Action of Sodium Nitrite on VI and VII in dilute Hydrochloric Acid. Formation of II and III——To a solution of VI (50 mg., m.p. 225~227°) in 10% HCl (3 ml.) was added excess $NaNO_2$ in H_2O under cooling in an ice-water bath. After 10 min., it was heated at 100°, concentrated, diluted with H_2O, and evaporated. Colorless needles which separated, were collected and recrystallized from MeOH to yield II (30 mg.), m.p. 275° (decomp.).

To a solution of VII (200 mg., m.p. 253~254°) in 5% HCl (10 ml.) was added 2*N* $NaNO_2$ (1 ml.) at room temperature, and it was gradually heated on a water-bath until the evolution of N_2 had ceased. The reaction mixture was evaporated to dryness at 100°, and the residue was recrystallized from H_2O to give needles of III (100 mg.), m.p. 283~285° (decomp.).

5-Chloro-8-anilinopyrido[2,3-*d*]pyridazine (VIII) and 5-Anilino-8-chloropyrido[2,3-*d*]pyridazine (IX)——Compound (I) (1.0 g., 1/200 mole) and aniline (0.46 ml., 1/200 mole) in EtOH were refluxed for 30 min. To the hot reaction mixture was added H_2O until the product began to crystallize. The product was filtered off, and recrystallized from EtOH to yield yellowish needles of compound (VIII) (1.0 g.) m.p. 180°.

The filtrate of the reaction mixture was concentrated and neutralized with NaOH to give precipitate, which was filtered off, dissolved in $CHCl_3$, and the solution passed through Al_2O_3 column with MeOH to isolate needles which on recrystallization from dilute MeOH gave yellowish needles of IX (0.2 g.), m.p. 226~227° (decomp.). The other 5-chloro-8-(*p*-substituted anilino)pyrido[2,3-*d*]pyridazines and the isomers in Table III, were obtained in a similar manner.

5,8-Dianilinopyrido[2,3-*d*]pyridazine——Compound (I) (1.0 g.) and aniline (0.92 ml.) were refluxed for 4 hr. in EtOH. The reaction mixture was neutralized with NH_4OH and the product was collected, washed with H_2O, and recrystallized from MeOH to give yellow needles (1.5 g.), m.p. 217°. The other 5,8-bis(*p*-substituted anilino)pyrido[2,3-*d*]pyridazines in Table IV were prepared in a similar way.

5-Ethoxy-8-anilinopyrido[2,3-*d*]pyridazine——a) From 5-chloro-8-anilinopyrido[2,3-*d*]pyridazine: To excess Na in EtOH was added 5-chloro-8-anilinopyrido[2,3-*d*]pyridazine (1.0 g.) and the mixture was refluxed for 1 hr. The reaction mixture was concentrated, H_2O added, and the precipitate was recrystallized from dilute MeOH to give yellow needles (1.0 g.), m.p. 114~116°. *Anal.* Calcd. for $C_{15}H_{14}ON_3$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.38; H, 5.41; N, 21.04.

b) From 5-ethoxy-8-chloropyrido[2,3-*d*]pyridazine: To a solution of aniline (0.5 ml.) in EtOH (5 ml.) was added compound (V) (0.5 g.) and the mixture was refluxed for 10 min. The reaction mixture was concentrated and cooled. The precipitate was recrystallized from dilute MeOH to give yellow needles (0.4 g.), m.p. 112~113°, mixed m.p. 113~115°.

Action of Hydrazine upon I. Formation of XI and XII——Compound (I) (10.0 g.) was added dropwise under stirring at room temperature to the solution of 80% hydrazine hydrate (6.5 ml.) in MeOH (100 ml.), and stirring was continued for an additional 1 hr. The product was filtered off, washed with water and dried to give an isomeric mixture (9.0 g.) of compounds (XI) and (XII). The mixture was dissolved in 5% HCl (50~100 ml.) and cooled at 0°. The precipitate was collected and dissolved in H_2O. The solution was treated with charcoal, acidified again with HCl, and cooled to precipitate tan needles of hydrochloride of XI (about 4 g.) m.p. 230~232° (decomp.). The hydrochloride was neutralized with NH_4OH to produce compound (XI), m.p. 196~197° (decomp.). As this was difficult to be purified, it was treated with acetone to give yellow crystals of 5-(2-isopropylidenehydrazino)-8-chloropyrido[2,3-*d*]pyridazine, m.p. 135~136° (from MeOH). *Anal.* Calcd. for $C_{10}H_{10}ClN_5$: C, 50.94; H, 4.28; N, 29.71. Found: C, 50.76; H, 4.27; N, 29.29.

The filtrate obtained from the acid solution was neutralized with NH_4OH and the orange-brown precipitate was filtered off, washed with H_2O and dried to give crude product (about 5 g.), which on recrystallization from MeOH gave yellowish plates of XII, m.p. 174~175°. *Anal.* Calcd. for $C_7H_6ClN_5$: C, 42.98; H, 3.09; N, 35.80. Found: C, 43.41; H, 3.39; N, 36.10.

Action of Sodium Hypobromite on XI and XII in Hydrochloric Acid Solution——To a solution of XI or XII (0.002 mole) in 5*N* HCl (4 ml.) was added dropwise 3*M* sodium hypobromite (1.4 ml.) at 0~5°. The precipitate was filtered off, washed with H_2O and dried to give compounds (II) or (III) respectively.

6-Chloropyrido[2,3-*d*]-*s*-triazolo[4,3-*d*]pyridazine (XIII)——Compound (XII) (1 g.) was refluxed in 80% HCOOH (5 ml.) for 15 min. After cooling, the solution was poured into H_2O. The precipitate was filtered off, and recrystallized from MeOH to give colorless plates (0.9 g.), m.p. 271~272°. *Anal.* Calcd. for $C_8H_4ClN_5$: C, 46.73; H, 1.96; N, 34.06. Found: C, 47.00; H, 2.08; N, 34.02.

5-(2-Formylhydrazino)-8-chloropyrido[2,3-*d*]pyridazine——Compound (XI) (1 g.) was refluxed in 80% HCOOH (5 ml.) for 30 min. After cooling, the solution was poured into H_2O. The precipitate was filtered off, and recrystallized from MeOH to give colorless prisms (0.5 g.), m.p. 213~214°. *Anal.* Calcd. for $C_8H_6ON_5Cl$: C, 42.97; H, 2.71; N, 31.32. Found: C, 43.92; H, 2.74; N, 31.55.

3-Methyl-6-chloropyrido[2,3-*d*]-*s*-triazolo[4,3-*d*]pyridazine (XV)——Compound (XII) (1 g.) was refluxed in excess Ac_2O for 30 min. and the solution was cooled. The precipitated crystals were filtered off, washed with H_2O, and recrystallized from EtOH to give colorless crystals (1.1 g.), m.p. 283° (decomp.). *Anal.* Calcd. for $C_9H_6ClN_5$: C, 49.21; H, 2.76; N, 31.88. Found: C, 49.15; H, 2.89; N, 31.76.

3-Methyl-6-chloropyrido[3,2-*d*]-*s*-triazolo[4,3-*d*]pyridazine (XIV)——Compound XI (1 g.) was refluxed in excess Ac_2O for 15 min. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from MeOH to give colorless needles (0.9 g.), m.p. 252~253° (decomp.). *Anal.* Calcd. for $C_9H_6ClN_5$: C, 49.21; H, 2.76; N, 31.88. Found: C, 49.34; H, 2.81; N, 31.61.

The authors express their deep gratitude to Dr. T. Akiba, Director of these Laboratories. Thanks are also due to the members of the Analysis Room for the elemental analysis and to the members of the Section of Physical Chemistry for the spectral data.

Summary

5,8-Dichloropyrido[2,3-*d*]pyridazine was prepared and its reactions with nucleophiles, such as hydroxide, alkoxide, thiourea, ammonia, anilines, and hydrazine were carried out. Monosubstituted isomeric products were isolated, and their isomeric structures were determined by converting them into known structures. Monohydrazino derivatives were cyclized with acid or acid anhydride into triazolo derivatives.

(Received December 15, 1964)