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Studies on Heterocyclic Compounds. X.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (1)

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2-Methyl-4,7-dichlorofuro[2,3-*d*]pyridazine (IV) was synthesized and reacted with nucleophiles such as hydroxide, alkoxide and amine to give monosubstituted isomers. The structure assignments of these isomers were described.

Jones[3] reported that the bicyclic compound containing the 1,4-dihydroxypyridazine ring appeared to be effectually for cancer and virus chemotherapy testing, because of the resembrance of their structures and physical and chemical properties with those of certain biologically important purines and pteridines, and such bicyclic compounds were prepared by reaction of hydrazine with dicarboxylic acid esters of furan, thiophene, pyrrole, pyrazole and imidazole.

Moreover, Carbon[4] and Castle, *et al.*[5] reported that a number of imidazopyridazines were prepared for testing as antitumor agents.

This report prompted us to investigate systematic synthesis of pyridazine derivatives including furan ring in an effort to obtain useful pharmacologic agents. A search of the literature revealed that furo[2,3-*d*]pyridazines had been reported by Jones[3] and Robba, *et al.*[6–8]

We synthesized 2-methyl-4,7-dihydroxypyridazine (III) by the method of Jones.[3] Namely, ethyl 2-ethoxalyl-4-ketovalerate was prepared from ethyl levulinate *via* ethyl 4-

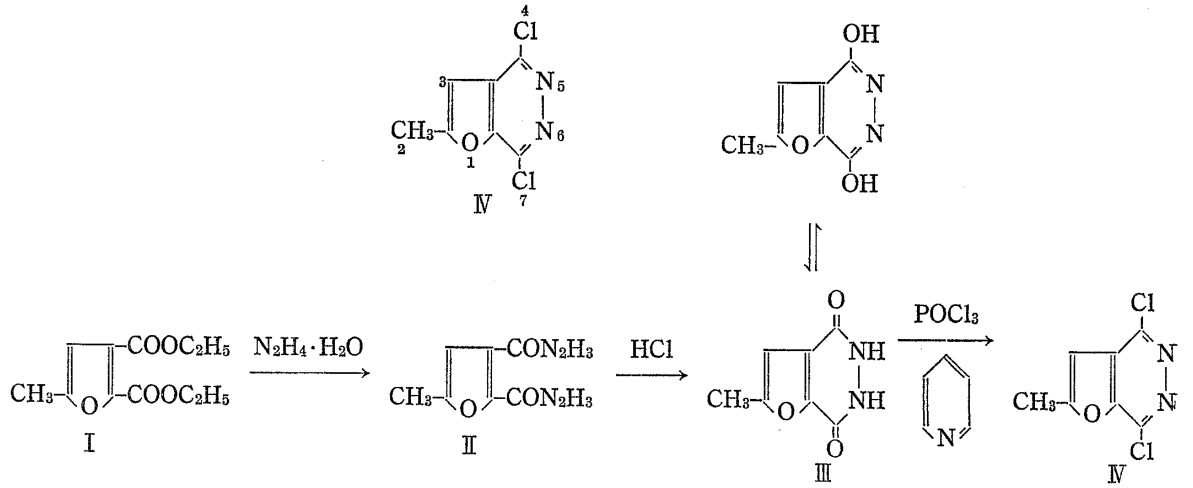

Chart 1

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[1] Part IX: S. Yoshina, A. Tanaka and K. Yamamoto, *Yakugaku Zasshi*, **88**, 997 (1968).
[2] Location: *a*) *Tenpaku-cho, Showa-ku, Nagoya*; *b*) *Aoba, Aramaki, Sendai.*
[3] R.G. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
[4] J.A. Carbon, *J. Am. Chem. Soc.*, **80**, 6083 (1958).
[5] R.N. Castle and T. Kuraishi, *J. Heterocyclic Chem.*, **3**, 218 (1966).
[6] M. Robba, M.C. Zaluski and B. Roques, *Compt. Rend.*, **263**, 814 (1966).
[7] M. Robba, M.C. Zaluski and B. Roques, *Compt. Rend.*, **264**, 413 (1967).
[8] M. Robba and M.C. Zaluski, *Compt. Rend.*, **266**, 31 (1968).

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ethoxy-3-pentenoate and cyclization of ethyl 2-ethoxalyl-4-ketovalerate by the treatment with concentrated sulfuric acid gave dimethyl 5-methyl-2,3-furandicarboxylate (I).

The reaction of I with hydrazine gave the dihydrazide (II) that was converted to III by cyclization with hydrochloric acid solution. 2-Methyl-4,7-dichlorofuro[2,3-*d*]pyridazine (IV) was prepared by refluxing III in a mixture of phosphoryl chloride and pyridine, as shown in Chart 1.

The structure of furo[2,3-*d*]pyridazin-4-ol (V) which was obtained by hydrogenation of 7-chlorofuro[2,3-*d*]pyridazin-4-ol was confirmed by cyclization of 3-carboxy-2-furaldehyde (VI) with hydrazine to give the same product (V). Compound (VI) was obtained from 2,3-dibromofuran *via* 3-bromo-2-furaldehyde.

But they did not describe the details of the experimental such as reaction conditions or yield. In compound (IV), similarly, we considered that the reactivity of the chlorine atoms at position-4 and -7 will differ widely in nucleophilic displacement owing to the influence of furan ring.

For a better view of the relative reactivity of the chlorine atoms at position-4 and -7 in compound (IV), the superdelocalizability for nucleophilic reaction, $S_r(N)$[10) was calculated from the simple Hückel molecular orbital method.

The Coulomb integral, α_x of the hetero atom, X, and the resonance integral, β_{rs}, between the r and s atoms, and the Coulomb integral, α_c ,of the carbon atom adjacent to the hetero atom, X, are expressed as:

$$\alpha_x = \alpha + h\beta \tag{1}$$

$$\beta_{rs} = k\beta \tag{2}$$

$$\alpha_c' = \alpha + 0.1h\beta \tag{3}$$

Here α is the Coulomb integral and β the resonance integral for benzene molecule.

The numerical values of energy parameters used are listed in Table I. In this calculation the hyperconjugation of the methyl group is neglected.

TABLE I. Parameters[9)

Bond	h	k	Bond	h	k
=C–C=		0.9	$\rangle$C=N–		1.0
–C=C–		1.1	=N–N=		1.0[a)
–Ö–	2.0	0.8	–Cl	1.8	0.8
=N–	0.5	1.0			

a) From the ω-β technique[10) k_{N-N} is given as equal to $k_{N-N}=1.031$, so in this calculation $k_{N-N}=1.0$ is adopted.

In Table II the calculated values of the superdelocalizability, $S_r(N)$, listed.

TABLE II. $S_r(N)$

$S_7(N)$	1.039	$S_4(N)$	1.387

As can be seen from Table II, position-4 seemed to be more reactive than position-7 toward nucleophilic reagents.

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9) K. Hirano, S. Yoshina, K. Okamura and I. Suzuka, *Bull. Chem. Soc. Japan*, **40**, 2229 (1967).

10) K. Fukui, T. Yonezawa and C. Nagata, *Bull. Chem. Soc. Japan*, **27**, 423 (1954).

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This was in good agreement with the report of Robba, *et al.*[7] In an attempt to compare theoretical result with experimental result, we were allowed to react the chlorine atoms of IV with nucleophiles such as hydroxide, alkoxide and amine. We were given in this reaction two isomers which was separated by fractional crystallization. As was expected from superdelocalizability, the products which were displaced at position-4 were always afforded more predominantly than another ones displaced at position-7.

Moreover, the two isomers were studied by nulcear magnetic resonance (NMR) and Mass spectra. The experimental results will be mentioned in the following sections.

Hydrolysis

Compound (IV) was found to be stable toward weak acid and alkali at room temperature, but in hot alkali condition hydrolyzed to the isomeric mixture of 2-methyl-7-chlorofuro[2,3-*d*]pyridazin-4-ol (VII) and 2-methyl-4-chlorofuro[2,3-*d*]pyridazin-7-ol (VIII) in the ratio 75:25.

The compound (VII) and (VIII) were identical with the product which was obtained by hydrolysis of IX and X, as shown in Chart 2.

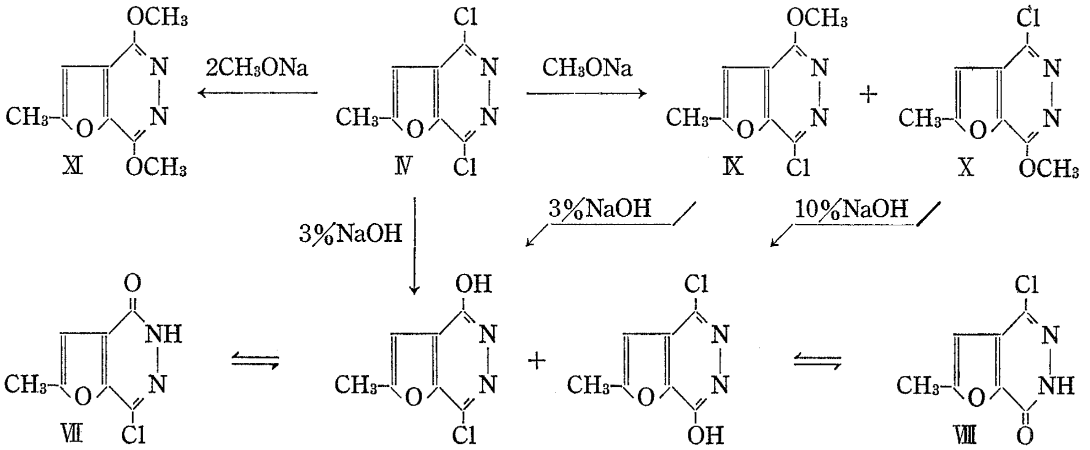

Chart 2

Alkoxylation

Reaction of IV with one mole of sodium methoxide in cold methanol gave the two isomers of 2-methyl-7-chloro-4-methoxyfuro[2,3-*d*]pyridazine (IX) and 2-methyl-4-chloro-7-methoxyfuro[2,3-*d*]pyridazine (X) in the ratio 95:5.

But Robba, *et al.*[8] reported that compound (IV) on treatment with sodium methoxide gave an only product (IX).

Compound (IX) was hydrolyzed to give VII in 3% sodium hydroxide solution. Compound (X) was hydrolyzed to give VIII under the severe condition in concentration and time *i.e.* 10% sodium hydroxide solution and 3 hours. Reaction of IV with two moles of sodium methoxide in methanol gave 2-methyl-4,7-dimethoxyfuro[2,3-*d*]pyridazine (XI), as shown in Chart 2.

Amination

2-Methyl-4-amino-7-chlorofuro[2,3-*d*]pyridazine (XII) was obtained by reaction of IV with the concentrated aqueous ammonia in sealed tube. We could not obtained the other isomer in this reaction.

Compound (XII) was converted to VII with sodium nitrite in hydrochloric acid solution. Reaction of IV with hydrazine hydrate in methanol gave the isomeric mixture of 2-methyl-7-chloro-4-hydrazinofuro[2,3-*d*]pyridazine (XIII) and 2-methyl-4-chloro-7-hydrazinofuro[2,3-*d*]pyridazine (XIV) in the ratio 9:1.

Compound (XII) was converted to VII and 2-methyl-4-bromo-7-chlorofuro[2,3-*d*]pyridazine (XV) by oxidation with sodium hypobromite in hydrochloric acid solution. Moreover, XV was converted to VII and 2-methyl-4-bromofuro[2,3-*d*]pyridazin-7-ol (XVI) by hydrolysis with 3% sodium hydroxide solution, as shown in Chart 3.

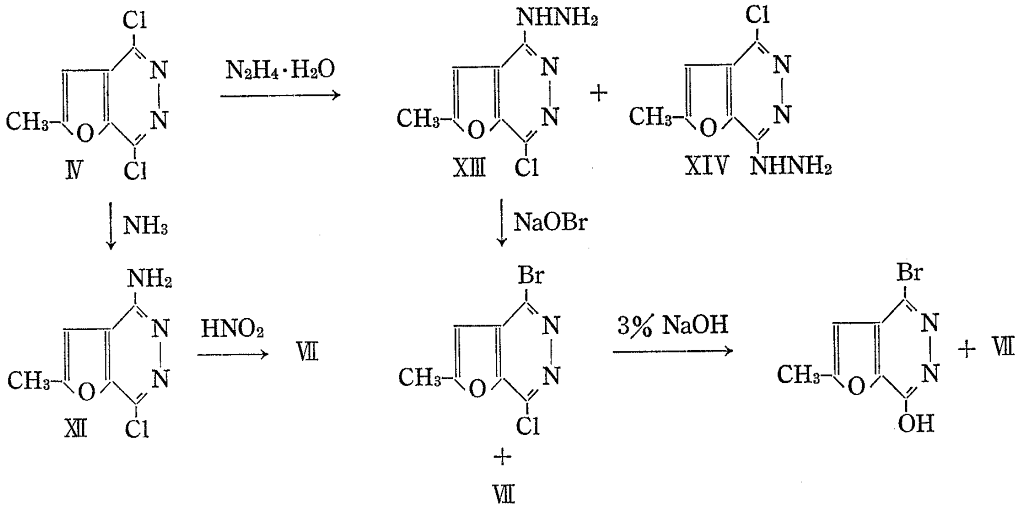

Chart 3

NMR and Mass spectra

The structure of isomers, (VII), (VIII); (IX), (X); and (XIII), (XIV); established almost by our theoretical and experimental studies and synthetic study by Robba, *et al.*[6–8]

Moreover, we discussed in NMR and Mass spectra.

Consequently, it proved that NMR spectrum played an important role in deciding the structure of isomer.

In Mass spectra, isomer which differ in displaced position were similar in fragmentation. Therefore, Mass spectra did not serve to decide the structure of isomer.

We must be careful in fragmentation of structure of compound which differ in displaced position such as above mentioned. In NMR spectra, we were interested in that how hydrogen at C-3 is effected by substituted group at position-7 and -4. The signal of proton H-3 of IV and XI was shown at 6.87 ppm (acetone-d_6) and 6.57 ppm (acetone-d_6).

It suggested that the Cl and OMe group have a different influence on hydrogen at C-3. But the proton H-3 of IX and X showed the same signal at 6.78 ppm (acetone-d_6).

Difference of position between Cl and OMe group almost did not produce different effect on electric density at C-3.

The signal of the proton H-3 of VII at 6.49 ppm appears at a lower field than that of VIII at 6.29 ppm, as shown in Fig. 1. It can be considered that the amide carbonyl group of VII is adjacent to C-3 in comparison with carbonyl group of VIII.

Moreover, the signal of the proton H-3 of XIII at 6.90 ppm (DMSO-d_6) appears at a lower field than that of XIV at 6.69 ppm

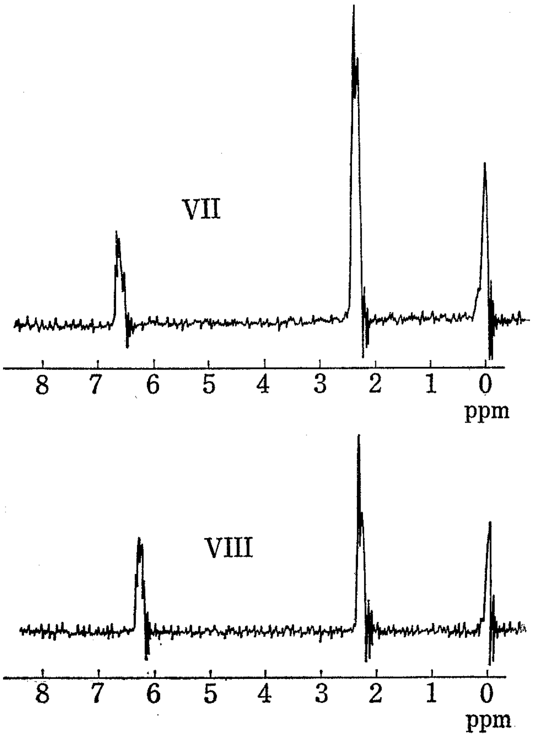

Fig. 1. NMR Spectra of VII and VIII in CF_3COOH

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(DMSO-d_6). As above mentioned, the structure of isomer was confirmed by the superdelocalizability for nucleophilic reaction, the product ratio of isomers and NMR spectra.

Experimental

2-Methyl-4,7-dichlorofuro[2,3-*d*]pyridazine (IV)⁶⁾——Compound (III) (16.6 g), $POCl_3$ (150 g) and pyridine (10 ml) were heated at 130° for 1 hr. The solvent was removed *in vacuo* and the residue was poured into ice. The precipitate was filtered off, washed with cold water and dried over $CaCl_2$ *in vacuo.*

The precipitate was recrystallized from AcOEt to give light yellowish needles 16 g (78.8%), mp 151—153°.

Hydrolysis of (IV). The Formation of 2-Methyl-7-chlorofuro[2,3-*d*]pyridazin-4-ol (VII) and 2-Methyl-4-chlorofuro[2,3-*d*]pyridazin-7-ol (VIII)——Compound (IV) (2.0 g) was added to 3% NaOH (70 ml) and heated at 100° for 2 hr, until a clear solution was obtained. The solution was cooled and acidified with AcOH, and the resulting solid was recrystallized from MeOH.

The isomeric mixture 1.2 g (65.9%), mp 197—215° of compound (VII) and (VIII) was separated by fractional crystallization.

The mixture was dissolved in MeOH (150 ml) and set aside at room temperature for one day. Colorless prisms which separated, was filtered off, and recrystallized from MeOH to yield (VII) 0.8 g, mp 245—246°. The filtrate was concentrated, and cooled to precipitate colorless needles (VIII) 0.3 g, mp 232°. *Anal.* Calcd. for $C_7H_5O_2N_2Cl$: C, 45.53; H, 2.71; N, 15.18. Found (VII): C, 45.50; H, 2.98; N, 15.51. Found (VIII): C, 45.23; H, 2.51; N, 15.45.

2-Methyl-7-chloro-4-methoxyfuro[2,3-*d*]pyridazine (IX) and 2-Methyl-4-chloro-7-methoxyfuro[2,3-*d*]pyridazine (X)——Finely powdered compound (IV) (10 g) was added in small portions to a solution of Na (1.2 g) in anhydrous MeOH (200 ml) with stirring at 10°. Stirring was continued for an additional 1 hr. The reaction mixture was allowed to come to room temperature and then it was refluxed for 1 hr. The solution was filtered off, concentrated, and cooled to give crystalline precipitate.

This isomeric mixture 6.8 g (67%) mp 97—115° of compounds (IX) and (X) was separated by fractional crystallization from MeOH. Colorless needles (IX) 5.5 g, mp 113—114°. Colorless plates (X) 0.7 g, mp 144°. *Anal.* Calcd. for $C_8H_7O_2N_2Cl$: C, 48.36; H, 3.53; N, 14.11. Found (IX): C, 48.49; H, 3.11; N, 14.58. Found (X): C, 48.72; H, 3.46; N, 14.02.

Hydrolysis of IX into VII——Compound (IX) (1.0 g) and 3% NaOH (50 ml) were heated at 100° for 1.5 hr and acidified with AcOH to give precipitate, which on recrystallization from MeOH gave compound (VII) 0.5 g, mp 245—246°. Identity was confirmed by comparing infrared (IR) spectra and mixed melting point.

Hydrolysis of X into VIII——Compound (X) (0.2 g) and 10% NaOH (30 ml) were heated at 100° for 3 hr and acidified with AcOH to give precipitate, which on recrystallization from MeOH gave compound (VIII) 0.1 g, mp 231—232°. Identity was confirmed by comparing IR spectra and mixed melting point.

2-Methyl-4-amino-7-chlorofuro[2,3-*d*]pyridazine (XII)——Compound (IV) (2.0 g) and conc. NH_4OH (50 ml) in a sealed tube were heated at 120° for 5 hr and cooled. The precipitate was collected, and recrystallized from MeOH to give colorless plates 0.5 g (27.6%), mp 208°. *Anal.* Calcd. for $C_7H_6ON_3Cl$: C, 45.78; H, 3.27; N, 22.89. Found: C, 45.70; H, 3.11; N, 22.57.

Action of Sodium Nitrite on XII in conc. HCl. Formation of (VII)——To a solution of XII (0.1 g) in conc. HCl (10 ml) was added excess $NaNO_2$ under cooling in an ice water bath. After 10 min it was heated at 100° on a water bath.

Colorless solid was separated and recrystallized from MeOH to give colorless prisms (VII) 0.03 g, mp 245°.

Action of Hydrazine upon IV. Formation of 2-Methyl-7-chloro-4-hydrazinofuro[2,3-*d*]pyridazine (XIII) and 2-Methyl-4-chloro-7-hydrazinofuro[2,3-*d*]pyridazine (XIV)——Compound (IV) (20 g), 80% hydrazine hydrate (20 ml) and MeOH (400 ml) was heated in a water bath for 5 hr. When cool, the product was filtered off, washed with cold MeOH, and dried to give feathery crystalline (XIII) 11 g (58.7%), mp 210° (decomp.). The filtrate was concentrated, cooled, and recrystallized from MeOH to give yellow prisms (XIV) 1.5 g (7.7%), mp 192° (decomp.). *Anal.* Calcd. for $C_7H_7ON_4Cl$: C, 42.32; H, 3.53; N, 28.21. Found (XIII): C, 42.55; H, 3.31; N, 28.56. Found (XIV): C, 42.51; H, 3.09; N, 28.03.

Action of Sodium Hypobromite on XIII in Hydrochloric Acid Solution. Formation of VII and 2-Methyl-4-bromo-7-chlorofuro[2,3-*d*]pyridazine (XV)——To a solution of (XIII) (4.0 g) in 5N HCl (100 ml) was added dropwise 11% sodium hypobromite (25 ml) at 5°. The precipitate was filtered off, washed with H_2O and dissolved in 3% NaOH. The precipitate which was undissolved was recrystallized from MeOH to give white prisms (XV) 1.2 g, mp 152—153°. *Anal.* Calcd. for $C_7H_4ON_2BrCl$: C, 33.80; H, 1.61; N, 11.28. Found: C, 33.57; H, 1.55; N, 11.52.

The filtrate was acidified with AcOH to give precipitate, which on recrystallization from MeOH gave compound (VII) 0.5 g, mp 245°.

Hydrolysis of XV into VII and 2-Methyl-4-bromofuro[2,3-*d*]pyridazin-7-ol (XVI)——Compound (XV) (0.3 g) and 3% NaOH were heated at 100° for 3 hr and acidified with AcOH to give precipitate, which on fractional recrystallization from MeOH gave compound (VII) 0.1 g, mp 245° and colorless needles (XVI) 0.02 g, mp 223—224°. *Anal.* Calcd. for $C_7H_5O_2N_2Br$: C, 36.52; H, 2.17; N, 12.17. Found: C, 36.18; H, 2.01; N, 12.46.

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