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Studies on Heterocyclic Compounds. XVIII.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (6).[2] Nitration of 4-Oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine[3]

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Nitration of 4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (V) with 96% sulfuric acid and fuming nitric acid gave 2-nitro-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (VII) and *trans*-2-nitro-3-hydroxy-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]-pyridazine (VIII). Nitration of V with 75% sulfuric acid and fuming nitric acid gave three products; VII, VIII and *cis*-2-nitro-3-hydroxy-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazine (IX). The structure assignment of this *trans-cis* isomers were described.

A variety of nitro heterocyclic systems have been demonstrated to possess useful therapeutic properties. Nitrofurans for example have been extensively investigated[5] and several are useful clinically in man. These reports prompted us to investigate the synthesis of 2-nitrofuro[2,3-*d*]pyridazine derivatives in an effort to obtain useful pharmacologic agents.

We report here some investigation into the nitration of furo[2,3-*d*]pyridazine derivatives. Nitration of furan derivatives has been extensively discussed in the literature,[6] but in the furo[2,3-*d*]pyridazine ring system only Marquet, *et al.*[7] reported that the nitration of 4-oxo-4,5-dihydrofuro[2,3-*d*]pyridazine with mixed acid gave 2-nitro-4-oxo-4,5-dihydrofuro[2,3-*d*]-pyridazine.

For the synthesis of 2-nitrofuro[2,3-*d*]pyridazine derivatives, 4,7-dichlorofuro[2,3-*d*]-pyridazine-2-carboxylic acid (I)[2] served as the starting material. Attempts to convert I to 4,7-dichlorofuro[2,3-*d*]pyridazine (II) by decarboxylation were unsuccessful. However, we have prepared II from I in three steps as described below. Treatment of I with acetic acid gave the two isomeric products, 4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine-2-carboxylic acid (III) and 4-chloro-7-oxo-6,7-dihydrofuro[2,3-*d*]pyridazine-2-carboxylic acid (IV), in the ratio 95: 5.

Decarboxylation of III with quinoline in the presence of copper powder gave colorless needles (V) of mp 282°, in 82% yield. Both the melting points and comparison on nuclear magnetic resonance (NMR) spectra confirmed the identity of V with 4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine, whose structure has been established by Robba, *et al.*[8] On the other hand, decarboxylation of IV under the similar reaction condition did not give VI. Reaction of V with phosphoryl chloride gave II in good yield.

Attempts to obtain 2-nitro-4,7-dichlorofuro[2,3-*d*]pyridazine from II were unsuccessful. Nitration of V with 96% sulfuric acid and fuming nitric acid at 50° gave two products, yellow

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[1] Part XVII: S. Yoshina and K. Yamamoto, *Yakugaku Zasshi*, 92, 359 (1972).
[2] Part (5): S. Yoshina, I. Maeba and V. Laohathai, *Chem. Pharm. Bull.* (Tokyo), 20, 584 (1972).
[3] Presented at the Third International Congress of Heterocyclic Chemistry, August 1971, Sendai, Japan.
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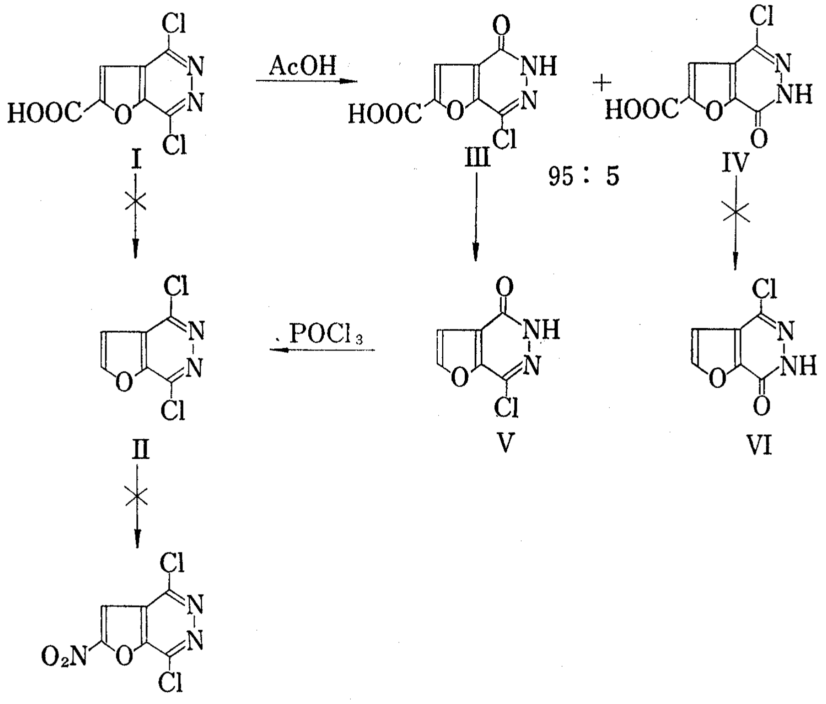

Chart 1

prisms of mp 196—197° (VII) and colorless prisms of mp 246—247° (VIII), in yields of 40% and 36.6%, respectively.

In the mass spectrum of VII, parent peak was recognized at *m/e* 215. The infrared (IR) spectrum (nujol) showed the absorption band at 1555 cm^{-1} attributed to a nitro group. In the NMR spectrum (ppm in DMSO-d_6), VII showed the following signals; 8.38 (1H, singlet, ring proton 3 pos.) and 13.50 (1H, broad, NH). These spectral data are consist with 2-nitro-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (VII).

In the mass spectrum of VIII, parent peak was recognized at *m/e* 233. The IR spectrum (nujol) showed the absorption band at 1555 cm^{-1} attributed to a nitro group. In the NMR

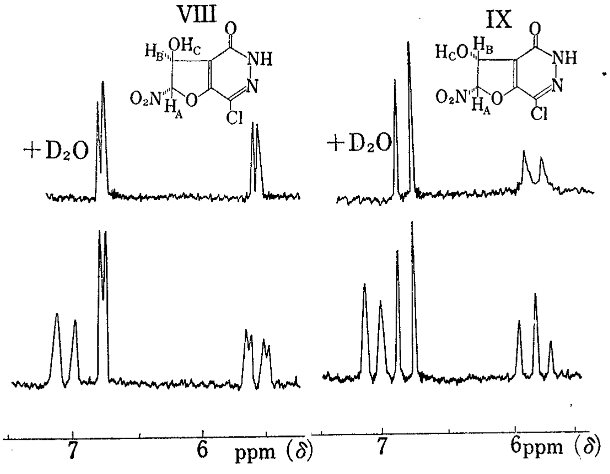

Fig. 1. NMR Spectra of VIII and IX in DMSO-d_6

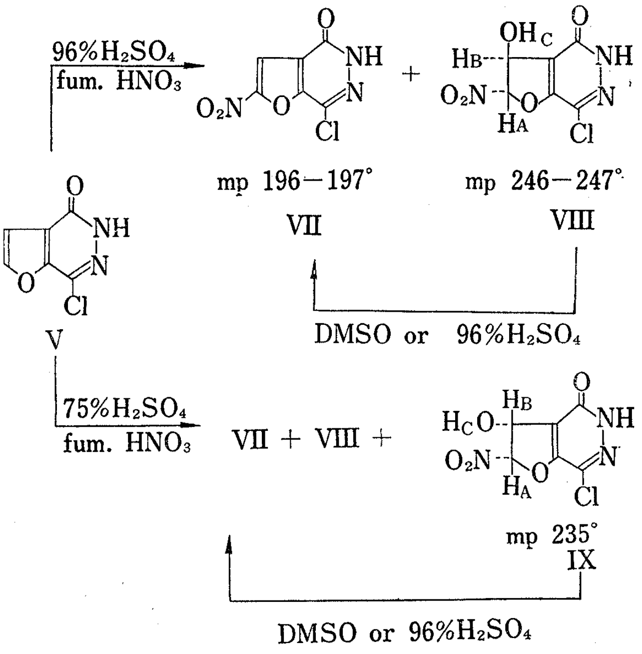

Chart 2

spectrum (ppm in DMSO-d_6), VIII showed the following signals; 5.55 (1H, doublet of doublet, $J_{AB}=1.5$ cps, $J_{BC}=7.5$ cps, ring proton 3 pos.), 6.76 (1H, doublet, $J_{AB}=1.5$ cps, ring proton 2 pos.), 7.07 (1H, doublet, $J_{BC}=7.5$ cps, -OH) and 13.42 (1H, broad, NH), and the signals of the last two protons disappeared on the addition of deuterium oxide and the signal of C-3 proton became doublet as shown in Fig. 1.

From these spectra it is reasonable to assume that VIII would be 2-nitro-3-hydroxy-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazine. Moreover, VIII was converted smoothly into VII on treatment with dimethyl sulfoxide or 96% sulfuric acid.

Nitration of V with 75% sulfuric acid and fuming nitric acid gave three products, VII, VIII, and colorless prisms of mp 235° (IX), in yields of 4%, 45.6%, and 3.7%, respectively. In the mass spectrum of IX, the fragmentation pattern very closely resembled to that of VIII. Both VIII and IX have the same empirical formula $C_6H_4O_5N_3Cl$ and they showed only slight differences in the finger print region in their IR spectra. IX was converted smoothly into VII on treatment with dimethyl sulfoxide or 96% sulfuric acid.

Therefore they are well considered to be stereoisomers to each other. The configuration of VIII and IX will be discussed in the comparative studies of their NMR spectra. In the NMR spectrum (ppm in DMSO-d_6), IX showed the following signals; 5.78 (1H, triplet, $J_{AB}=J_{BC}=7.5$ cps, ring proton 3 pos.), 6.81 (1H, doublet, $J_{AB}=7.5$ cps, ring proton 2 pos.), 7.06 (1H, doublet, $J_{BC}=7.5$ cps, -OH) and 13.40 (1H, broad, NH), and the signals of the last two protons disappeared on the addition of deuterium oxide and the signal of C-3 proton became doublet (Fig. 1).

The difference between the coupling constants, J_{AB} of H_A, for VIII and IX can be explained by Karplus rule,[9] *i.e.* the value ($J_{AB}=1.5$ cps) for VIII suggests that the dihedral angle of H_A-C-C-H_B is about 110°, and the value ($J_{AB}=7.5$ cps) for IX suggests that the dihedral angle is nearly 0°. Based on above spectral finding, the configuration of nitro group and hydroxy group on the furan ring is effectively assigned as *trans* for VIII and *cis* for IX.

It was obvious that the production of VII was highly affected by the concentration of sulfuric acid employed and the reaction proceeded *via* intermediate VIII or IX.

Experimental[10]

Hydrolysis of I. The Formation of 4-Oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine-2-carboxylic Acid (III) and 4-Chloro-7-oxo-6,7-dihydrofuro[2,3-*d*]pyridazine-2-carboxylic Acid (IV)——A mixture of I (14 g) and AcOH (300 ml) were heated at 120° for 3 hr. After cooling, the product was filtered off, washed with cold MeOH, and recrystallized from dioxane to give 10 g (77%) of colorless prisms (III), mp 293°. *Anal.* Calcd. for $C_7H_3O_4N_2Cl$: C, 39.19; H, 1.41; N, 13.06. Found: C, 39.38; H, 1.53; N, 12.83. *m/e* 214 (M^+). NMR$\delta_{ppm}^{DMSO\text{-}d_6}$: 13.20 (1H, br., NH) and 7.73 (1H, s, ring proton 3 pos.).

The filtrate was concentrated and the residue was recrystallized from MeOH to give 0.4 g (4%) of pale yellow prisms (IV), mp 281°. *Anal.* Calcd. for $C_7H_3O_4N_2Cl$: C, 39.19; H, 1.41; N, 13.06. Found: C, 39.02; H, 1.75; N, 12.96. *m/e* 214 (M^+). NMR$\delta_{ppm}^{DMSO\text{-}d_6}$: 13.20 (1H, br., NH) and 7.60 (1H, s, ring proton 3 pos.).

Decarboxylation of III——When a mixture of 10 g of III, 150 ml of quinoline and 0.1 g of active copper powder were heated at about 200°, carbon dioxide was evolved at a moderate rate and the reaction was completed in 10 min. After cooling, the reaction mixture was poured into 10% HCl solution and filtered. The product was recrystallized from dioxane to give 6.5 g (82%) of colorless needles (V), mp 282°.

Chlorination of V——A mixture of V (1.0 g), $POCl_3$ (10 ml) and pyridine (one drop) was 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 recrystallized from MeOH to give 1.0 g (90%) of colorless needles (II), mp 118°. *Anal.* Calcd. for $C_6H_2ON_2Cl_2$: C, 38.12; H, 1.06; N, 14.82. Found: C, 38.25; H, 1.09; N, 15.03. NMR$\delta_{ppm}^{CDCl_3}$: 7.08 (1H, d., ring proton 3 pos.) and 8.07 (1H, d, ring proton 2 pos.).

Nitration of V with 96% Sulfuric Acid and Fuming Nitric Acid. Formation of VII and VIII——To a solution of V (2.0 g) in 96% H_2SO_4 (10 ml), a mixture of 96% H_2SO_4 and fuming HNO_3 (1:1; 4 ml) was added

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[9] M.T. Karplus, *Chem. Phys.*, **30**, 11 (1959); M.T. Karplus and D.H. Anderson, *ibid.*, **30**, 6 (1959).

[10] All melting points were not corrected. Mass spectra were obtained with a Hitachi RMU-6 mass spectrometer using the direct introduction probe and ionizing voltage of 70 eV. The NMR spectra were taken on a Varian A-60-A spectrometer with tetramethylsilane as an internal standard.

with stirring at 10°. After the addition, the mixture was stirred for an additional 5 hr at 50°. The mixture was poured into ice and neutralized to pH 7 with $NaHCO_3$ to precipitate 2.1 g of crude products. The precipitate was dissolved in MeOH (150 ml) and set aside at room temperature for one day. Colorless prisms which separated were filtered off and recrystallized from MeOH to give 1.0 g (40%) of VIII, mp 246—247°. *Anal.* Calcd. for $C_6H_4O_5N_3Cl$: C, 30.86; H, 1.73; N, 17.99. Found: C, 30 52; H, 1.47; N, 18.21.

The filtrate was concentrated and the residue was recrystallized from MeOH to give 1.0 g (36.5%) of yellow prisms (VII), mp 196—197°. *Anal.* Calcd. for $C_6H_2O_4N_3Cl$: C, 33.43; H, 0.94; N, 19.49. Found: C, 33.64; H, 1.27; N, 19.38.

Nitration of V with 75% Sulfuric Acid and Fuming Nitric Acid. Formation of VII, VIII and IX——To a solution of V (4.0 g) in 75% H_2SO_4 (20 ml), a mixture of 75% H_2SO_4 and fuming HNO_3 (1:1; 8 ml) was added with stirring at 10°. After the addition, the mixture was stirred for an additional 5 hr at 50°. The mixture was poured into ice and neutralized to pH 7 with $NaHCO_3$ to precipitate 3.0 g of crude product. The precipitate was dissolved in MeOH (200 ml) and set aside at room temperature for one day. Colorless prisms which separated were filtered off and recrystallized from MeOH to give 2.5 g (45.6%) of VIII, mp 246—247°.

The mother liquor contained VII and IX, which on fractional recrystallization from MeOH gave 0.2 g (4%) of VII and 0.18 g (3.3%) of colorless prisms (IX), mp 235°. *Anal.* Calcd. for $C_6H_4O_5N_3Cl$: C, 30.86; H, 1.73; N, 17.99. Found: C, 30.76; H, 1.64; N, 18.18.

Dehydration of VIII and IX into VII——VIII or IX (0.5 g) was added to 96% H_2SO_4 or dimethyl sulfoxide (5 ml) and heated at 100° for 2 hr. The mixture was poured into ice and the precipitate was filtered off and recrystallized from MeOH to give 0.4 g (87%) of VII, mp 196—197°. Identity was confirmed by comparing IR spectra and mixed melting point.