Notes

[Chem. Pharm. Bull. 18(2) 379—380 (1970)] UDC 547.852.9.04

Studies on Heterocyclic Compounds. XI.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (2).[2] Carbonyl Bridge Compound of 2-Methyl-4,7-dichlorofuro[2,3-*d*]pyridazine

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(Received June 24, 1969)

In a previous paper,[1] we have reported that the substitution reactions of 2-methyl-4,7-dichlorofuro[2,3-*d*]pyridazine (I) with a variety of nucleophiles such as hydroxide, alkoxide, and amines gave the two isomers. However, the nitrile was not obtained by the reaction of I with cuprous cyanide or potassium cyanide in methanol.

So that, we tried the reaction of I with potassium cyanide in N,N-dimethylformamide or dimethylsulfoxide. Compound (I), potassium cyanide and dimethylsulfoxide were stirred for 6 hours at room temperature, and the resulting brown solution was allowed to stand overnight. The reaction mixture was poured into ice water and filtered.

The filtrate was acidified with hydrochloric acid to give the precipitate, which gave colorless needles (II) on recrystallization from methanol in yield 40%, mp 170—171°. The product can be assigned the carbonyl bridge compound on the basis of the following evidence.

The infrared spectrum of II showed the presence of CO group by absorption band at 1740 cm^{-1}.

In the mass spectrum of II, besides M^+ ion (*m/e* 230), the following ions are remarkable, *m/e* 202 (M-28) and *m/e* 111.

The formulae of M^+ (*m/e* 230) and *m/e* 202 are proved to be $C_8H_4O_2N_2Cl_2$ and $C_7H_4ON_2Cl_2$ with the high resolution mass spectrum.

The peak at *m/e* 202 is due to the loss of a carbonyl group (28 mass unit) from M^+ ion. Moreover, M–CO is supported by the existance of a metastable ion at *m/e* 177.4. In the comparison of mass spectra of I and II, the fragmentation below *m/e* 202 has a strong resemblance, as shown in Fig. 1.

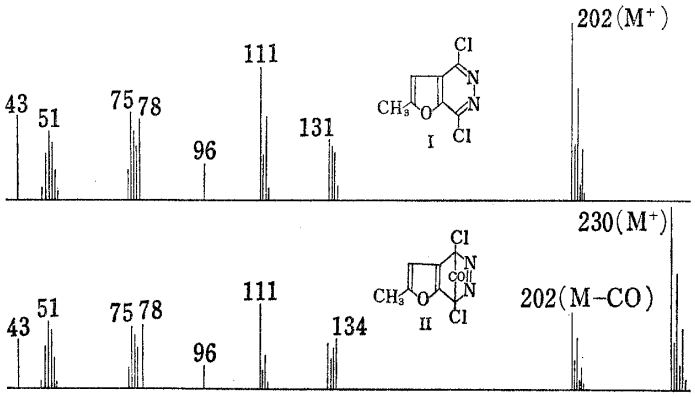

Fig. 1. Mass Spectra of (I) and (II)

The elemental analysis of II supported a molecular formula $C_8H_4O_2N_2Cl_2$. The NMR spectrum (ppm in $CDCl_3$) showed the following signals; 7.70 (1H, q., J=1.5 cps) and 2.40 (3H, d., J=1.5 cps).

Allen, *et al.*[4] reported that the carbonyl bridge compound gives an acid upon alkali treatment. Compound (II) was dissolved in 10% sodium hydroxide solution, and this solu-

1) Part X: S. Yoshina, I. Maeba and K. Hirano, *Chem. Pharm. Bull.* (Tokyo), **17**, 2158 (1969).
2) Presented at the Annual Meeting of Pharmaceutical Society of Japan, April, 1969, Nagoya.
3) Location: *Tenpaku-cho, Showa-ku, Nagoya.*
4) C.F.H. Allen and V. Allan, *J. Org. Chem.*, **11**, (1946).

tion was acidified by dil. hydrochloric acid to give the compound II and III in the approximate ratio of 9:1.

Compound (III) was converted to II by chlorination with phosphorous oxychloride. The expected compound (IV) could not be obtained on alkali treatment. The authors proposed the following mechanism, as shown in Chart 1.

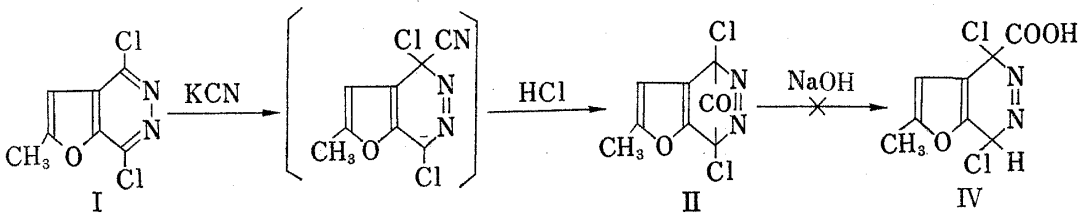

Chart 1

Acid hydrolysis of II in methanol gave the compound (III), mp 245—246°. IR ν_{max}^{KBr} cm^{-1}: 2850 (-OH), 1740 (>CO). NMR $\delta_{ppm}^{DMSO-d_6}$: 13.8 (1H, -OH), 7.85 (1H, q., J=1.5 cps), 2.18 (3H, d., J=1.5 cps). *m/e* 212 (M^+), 184 (M–CO).

Acetylation of III in Ac_2O gave the compound (V), mp 184—186°. IR ν_{max}^{KBr} cm^{-1}: 1770 (-$OCOCH_3$), 1740 (>CO). NMR $\delta_{ppm}^{CDCl_3}$: 7.81 (1H, q., J=1.5 cps), 2.70 (3H, s., J=1.5 cps), 2.27 (3H, d., J=1.5 cps). *m/e* 254 (M^+), 226 (M–CO).

Compound (V) was converted to III by hydrolysis with alkali or acid solution (Chart 2).

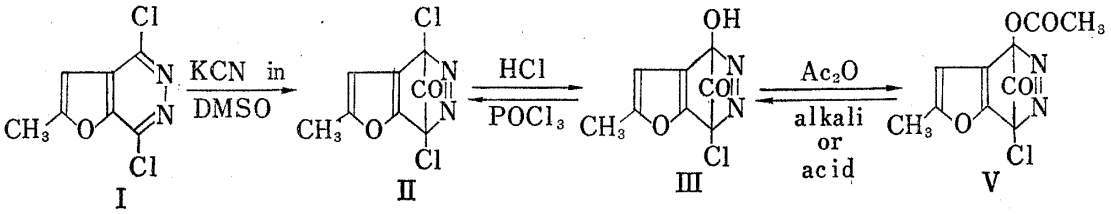

Chart 2

Experimental

Compound II——Compound (I) (2.0 g), KCN (1.3 g), and DMSO (50 ml) were stirred for 6 hr at room temperature, and the resulting brown solution was allowed to stand overnight. And the reaction mixture was poured into ice water and filtered.

The filtrate was acidified with HCl to give the brownish precipitate, which on recrystallization from MeOH gave colorless needles (II) 0.9 g, mp 170—171°. *Anal.* Calcd. for $C_8H_4O_2N_2Cl_2$; C, 41.59; H, 1.75; O, 13.85; N, 12.13. Found: C, 41.90; H, 1.65; O, 14.32; N, 12.04.

Compound III——Compound (II) (1.0 g), conc. HCl (3 drops) and MeOH (50 ml) were heated in a water bath for 3 hr. When cool, the product was filtered off, washed with cold MeOH and recrystallized from MeOH to give colorless needles (III) 0.6 g, mp 245—246°. *Anal.* Calcd. for $C_8H_5O_2N_2Cl$: C, 45.19; H, 2.39; O, 22.58; N, 13.18. Found: C, 45.63; H, 2.21; O, 23.09; N, 13.22.

Compound V——Compound (III) (1.0 g) and Ac_2O (30 ml) were heated under reflux in an oil-bath for 4 hr. After removal of the solvent, the resultant residue was recrystallized from AcOEt to give colorless needles (V) 0.6 g, mp 184—186°. *Anal.* Calcd. for $C_{10}H_7O_4N_2Cl$: C, 47.17; H, 2.77; N, 11.00. Found: C, 46.83; H, 2.51; N, 11.36.

Chlorination of III into II——Compound (III) (0.5 g), $POCl_3$ (10 ml) and pyridine (2 drops) 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. The precipitate was recrystallized from MeOH to give colorless needles, mp 170—171°. Identity was confirmed by comparing IR spectra and mixed melting point.

Hydrolysis of V into III——Compound (V) (0.3 g), MeOH (20 ml) and conc. HCl (2 drops) were heated in a water bath for 30 min. The precipitate was collected, and recrystallized from MeOH to give colorless needles, mp 245—246°. Compound (V) (0.3 g) and 10% NaOH solution were heated in a water bath for 10 min. This solution was acidified with HCl to give the colorless needles, mp 245—246°. Identity was confirmed by comparing IR spectra and mixed melting point.