Notes

Chem. Pharm. Bull. 21(4) 885—887 (1973)

UDC 547.852.9.04 : 546.175.04

Studies on Heterocyclic Compounds. XIX.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (7). Nitration of Furo[2,3-*d*]pyridazines in the 5 Position[2]

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(Received March 10, 1972)

Our preceding paper[1] reported that the nitration of 4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (IIIa) with mixed acid gave three products, 2-nitro-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (IV), *trans*-2-nitro-3-hydroxy-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazine (Va) and its *cis*-isomer (Vb). However, the nitration of 4,7-dichlorofuro[2,3-*d*]pyridazine (Ia) with mixed acid resulted in the recovery of unchanged starting material. The present paper describes the nitration of Ia with acetyl nitrate.

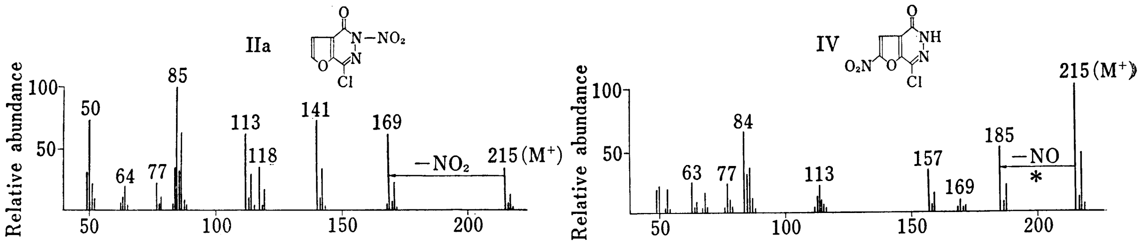

Fig. 1. Mass Spectra of IIa and IV

When Ia was allowed to react with acetyl nitrate, colorless prisms (IIa) of mp 113° (decomp.) were obtained in 58% yield. Both IIa and IV gave the same mass spectral peak at *m*/*e* 215 (molecular ion) but fragmentation of IIa was different from that of IV, as illustrated in Fig. 1. The nuclear magnetic resonance (NMR) spectrum (ppm in DMSO-d_6) of IIa showed the signals at 8.45 (1H, doublet, $J=2$ cps, ring proton 2 pos.) and 7.48 (1H, doublet, $J=2$ cps, ring proton 3 pos.). The infrared (IR) spectrum of IIa showed absorption bands at 1260 cm^{-1} attributed to a nitramino group and 1730 cm^{-1} attributed to a carbonyl group. From these spectral data and elemental analysis it seems reasonable to assume that IIa is 4-oxo-5-nitro-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine. The mechanism of its formation is assumed to be as shown in Chart 1.

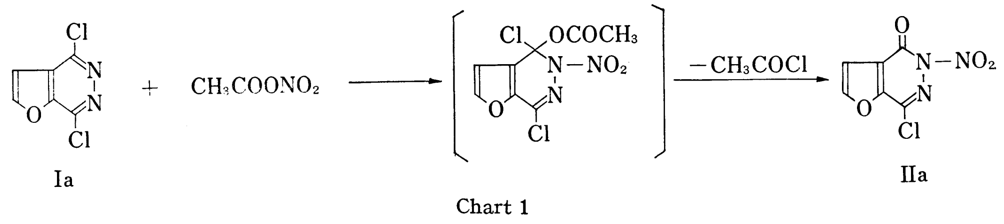

Chart 1

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[1] Part XVIII: S. Yoshina and I. Maeba, *Chem. Pharm. Bull.* (Tokyo), **20**, 936 (1972).

[2] Presented at the 92th Annual Meeting of Pharmaceutical Society of Japan, Osaka, April, 1972.

[3] Location: *Tenpaku-cho, Showa-ku, Nagoya.*

[4] S. Yoshina, I. Maeba, and K. Hirano, *Chem. Pharm. Bull.* (Tokyo), **17**, 2158 (1969).

The nitration of 2-methyl-4,7-dichlorofuro[2,3-*d*]pyridazine[4] (Ib) by the same procedure gave 2-methyl-4-oxo-5-nitro-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (IIb). It was further found that the nitration of IIIa and 2-methyl-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine[4] (IIIb) with acetyl nitrate also gave IIa and IIb, respectively. When IIa was allowed to react with mixed acid at room temperature Va was obtainead instead of the expected 2,5-dinitro-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (VII). Va was proved to be identical with the product obtained by the nitration of IIIa with mixed acid. On the other hand, the reaction of IV with acetyl nitrate afforded the 2,5-dinitro compound (VII).

When Va was allowed to react with acetyl nitrate, colorless prisms (VIa) of mp 115° (decomp.) were obtained in 86% yield. The NMR spectrum (ppm in CD_3COCD_3) of VIa showed the signals at 7.43 (1H, doublet, J=1.5 cps, ring proton 2 pos.) and 7.27 (1H, doublet, J=1.5 cps, ring proton 3 pos.). The signal of hydroxy proton in Va disappeared in the spectrum of VIa. A similar reaction of Vb obtainable from IIIa with mixed acid gave colorless prisms (VIb) of mp 133° (decomp.). The NMR spectrum (ppm in CD_3COCD_3) of VIb showed the signals at 7.62 (1H, doublet, J=7.5 cps, ring proton 2 pos.) and 7.38 (1H, doublet, J=7.5 cps, ring proton 3 pos.), and the signal of hydroxy proton in Vb was not noticed. From these NMR spectra and elemental analysis (see Experimental) it is reasonable to assume that VIa and VIb would be 2,5-dinitro-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazinyl 3-nitrate. They are considered to be stereoisomers. The difference between the coupling constants, J_{AB} of H_A, for VIa and VIb can be explained by the Karplus rule, *i.e.*, the value (J_{AB}=1.5 cps) for VIa suggests that the dihedral angle of H_A–C–C–H_B is about 100°, and that (J_{AB}=7.5 cps) for VIb suggests that the dihedral angle is nearly 0°. Based on above spectral data, the configuration of NO_2 group and ONO_2 group on the furan ring is assigned as *trans*

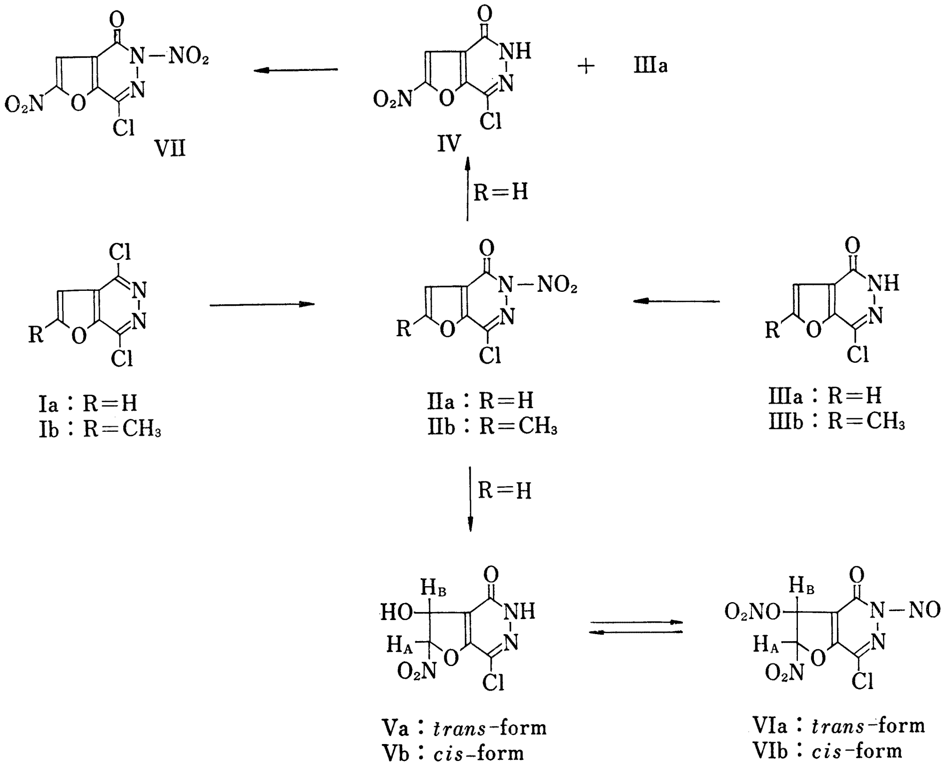

Chart 2

to VIa and *cis* to VIb. VIa and VIb were respectively converted smoothly into Va and Vb on treatment with 70% sulfuric acid.

Relatively little work has been reported concerning nitration of the nitrogen in N-heteroaromatics.5) The synthesis and properties of 1-nitropyrazole and some substituted N-nitropyrazoles have been reported by Hüttel and Büchele.6) They also described the rearrangement of N-nitropyrazoles into 4-nitro derivatives in sulfuric acid solution. We have found that the nitro group in IIa can be undergo rearrangement into the adjoining furan ring. Treatment of IIa with concentrated sulfuric acid at 100° for 8 hours gave two products, rearrangement product (IV) and IIIa, in 18% and 40% yield, respectively.

Experimental7)

4-Oxo-5-nitro-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (IIa)——To a suspension of Ia or IIIa (2.0 g) in 20 ml of Ac_2O, a mixture of Ac_2O and fuming HNO_3 (1:1) (4 ml) was added with stirring at 15°. After the addition, the mixture was stirred for an additional 2 hr at room temperature, poured into ice water, and stirred. The precipitate formed was collected by filtration, washed with some water, and dried over $CaCl_2$ *in vacuo*. The crude product was recrystallized from $CHCl_3$ to IIa as colorless needles, mp 113°. Yield: 58% (from Ia), 91% (from IIIa). *Anal.* Calcd. for $C_6H_2O_4N_3Cl$: C, 33.43; H, 0.94; N, 19.49. Found: C, 33.29; H, 0.77; N, 19.06.

2-Methyl-4-oxo-5-nitro-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (IIb)——This compound was prepared from Ib or IIIb as described above for IIa. The yield of IIb, mp 115° (decomp.), was 62% (from Ib) or 75% (from IIIb). *m/e* 229 (M^+). *Anal.* Calcd. for $C_7H_4O_4N_3Cl$: C, 36.62; H, 1.76; N, 18.30. Found: C, 36.38; H, 1.79; N, 18.01. NMR ppm: 7.62 (1H, quartet, ring proton 3 pos.), 2.63 (3H, doublet, $-CH_3$).

2,5-Dinitro-4-oxo-7-chloro-4,5-dihydrofuro[2,3-*d*]pyridazine (VII)——This compound was prepared from IV as described above for IIa. The yield of VII, mp 137° (decomp.), was 88%. *m/e* 260 (M^+). *Anal.* Calcd. for $C_6HO_6N_4Cl$: C, 27.66; H, 0.39; N, 21.50. Found: C, 27.63; H, 0.54; N, 20.95. NMR ppm: 8.37 (1H, singlet, ring proton 3 pos.).

***trans*-2,5-Dinitro-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazinyl 3-Nitrate (VIa)**——This compound was prepared from Va as described above for IIa. The yield of VIa, mp 115° (decomp.), was 86%. *Anal.* Calcd. for $C_6H_2O_9N_5Cl$: C, 22.27; H, 0.62; N, 21.64. Found: C, 22.28; H, 0.52; N, 21.33.

***cis*-2,5-Dinitro-4-oxo-7-chloro-2,3,4,5-tetrahydrofuro[2,3-*d*]pyridazinyl 3-Nitrate (VIb)**——This compound was prepared from Vb as described above for IIa. The yield of VIb, mp 133° (decomp.), was 80%. *Anal.* Calcd. for $C_6H_2O_9N_5Cl$: C, 22.27; H, 0.62; N, 21.64. Found: C, 22.15; H, 0.73; N, 21.16.

Conversion of VIa and VIb into Va and Vb——A mixture of 0.5 g of VIa or VIb and 5 ml of 70% H_2SO_4 was heated at 80° for 1 hr, poured into ice water, the precipitate formed was collected by filtration and recrystallized from MeOH to give 0.3 g of Va or Vb. Their identity was confirmed by comparing IR spectra and by a mixed melting point.

Treatment of IIa with Concentrated Sulfuric Acid——A mixture of IIa (0.5 g) added to conc. H_2SO_4 was heated at 100° for 8 hr, poured into ice water, and the precipitate formed was collected by filtration. The product was separated by fractional recrystallization from MeOH, and IV and IIIa were obtained in 18% and 40% yield. Their identity was confirmed by comparing IR spectra and by a mixed melting point.

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5) J.W.A.M. Jansen and C.L. Habraken, *J. Org. Chem.*, **36**, 3081 (1971); R. Cohen-Fernandes and C.L. Habraken, *ibid.*, **36**, 3084 (1971).

6) R. Hüttel and F. Büchele, *Chem. Ber.*, **88**, 1586 (1955).

7) 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-data were measured by a Varian A-60-A in CD_3COCD_3 and used Me_4Si as internal standard.