

**PYRIDAZINES, 71.<sup>1</sup> A NOVEL TYPE OF 1,2-DIAZINE → 1,2-DIAZOLE  
RING CONTRACTION**

Gottfried Heinisch,<sup>a</sup> Barbara Matuszczak,<sup>a\*</sup> and Kurt Mereiter<sup>b</sup>

<sup>a</sup> Institute of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a,  
A-6020 Innsbruck, Austria

<sup>b</sup> Institute of Mineralogy, Crystallography and Structural Chemistry, Technical  
University of Vienna, Getreidemarkt 9, A-1060 Vienna, Austria

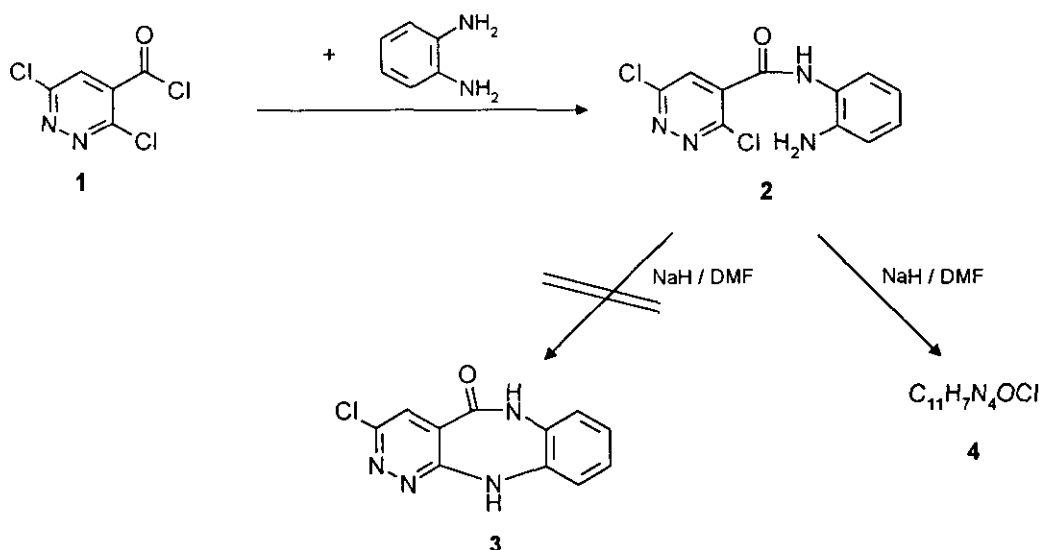
**Abstract** - Reaction of the 3,6-dichloro-4-pyridazinecarboxamide derivative (**2**) with sodium hydride in dimethylformamide does not afford a pyridazino[3,4-*b*]-[1,5]benzodiazepine system (**3**) but results in a ring transformation to give the quinoxaliny-substituted pyrazole derivative (**4**). The structure of this unexpected reaction product could be elucidated by means of a crystal structure determination, a mechanistic interpretation of this novel type of a pyridazine → pyrazole ring contraction is proposed

In the course of our ongoing studies aimed at the synthesis of so far not accessible pyridazine-containing bi- and tricyclic ring systems of potential pharmaceutical relevance<sup>2</sup> the 6,11-dihydropyridazino[3,4-*b*][1,5]benzodiazepin-5-one system became an object of interest. In view of the reported smooth cyclisation of 2-chloro-nicotinic acid chloride with *o*-phenylenediamine derivatives yielding pyrido[2,3-*b*][1,5]benzodiazepinones,<sup>3</sup> *N*-(2-aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide (**2**) was considered as an appropriate precursor for the desired tricyclic system (**3**). Compound (**2**) could be prepared conveniently by reaction of 3,6-dichloro-4-pyridazinecarboxylic acid chloride (**1**)<sup>4</sup> with an excess of *o*-phenylenediamine.<sup>5</sup>

Treatment of **2** with sodium hydride in dimethylformamide for 10 minutes at 100 °C followed by work-up under acidic conditions indeed gave a product (**4**) with the expected elemental composition C<sub>11</sub>H<sub>7</sub>N<sub>4</sub>OCl in >80%

yield. The spectroscopic data of this compound, however, were not consistent with the structure of our target compound (3). As shown by tlc monitoring the reaction course cannot be altered by using 1,4-dioxane as the solvent.<sup>6</sup> This attempt was undertaken in view of a recent report<sup>7</sup> on the pyridine congeneric series. Here, employment of an ether as the solvent is required in order to achieve ring closure to a dipyrido[3,2-*b* 2',3'-*e*]-[1,4]diazepin-6-one, whereas in dimethylformamide an alternative cyclisation product (a 2-substituted oxazolo[5,4-*b*]pyridine) is formed exclusively

Scheme I



Whereas the infrared spectrum of the new compound (4) clearly indicates the presence of an oxo function ( $\nu_{C=O}$ :  $1671\text{ cm}^{-1}$ ), the nmr data ( $^1H$ ,  $^{13}C$ ) did not provide sufficient information to permit the elucidation of its structure. This, however, could be achieved by a X-ray structure determination using material obtained by crystallisation from dioxane-water. These crystals were found to be the  $\frac{1}{2}$ -dioxane solvate of 4 which is subsequently designated 4a (see Figure 1 and Table 1).

Thus, under our experimental conditions, transformation of the pyridazinecarboxamide derivative (2) into the quinoxalanyl-substituted pyrazole (4) had taken place

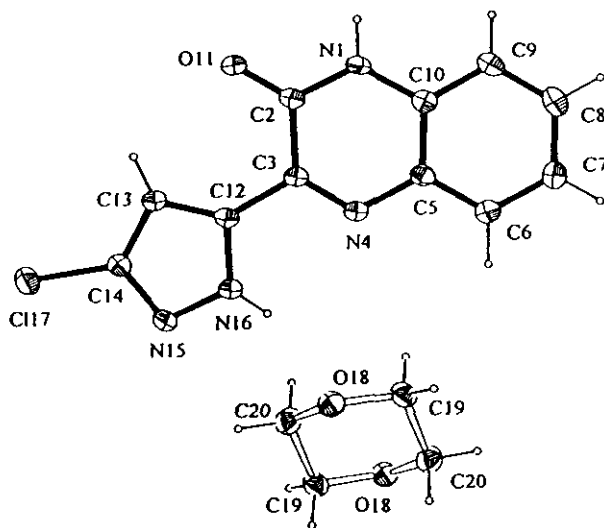


Figure 1 ORTEP plot (30%-ellipsoids) of  $C_{11}H_7N_4OCl \cdot \frac{1}{2}C_4H_8O_2$  (4a) with crystallographic atom numbering scheme. Selected bond lengths (Å) are: N1-C2=1.355(2), N1-C10=1.377(3), C2-C3=1.485(3), C2-O11=1.232(3), C3-N4=1.298(3), C3-C12=1.459(2), N4-C5=1.383(2), C12-C13=1.373(3), C12-N16=1.351(3), C13-C14=1.391(2), C14-N15=1.319(3), C14-Cl17=1.725(2), N15-N16=1.347(2).

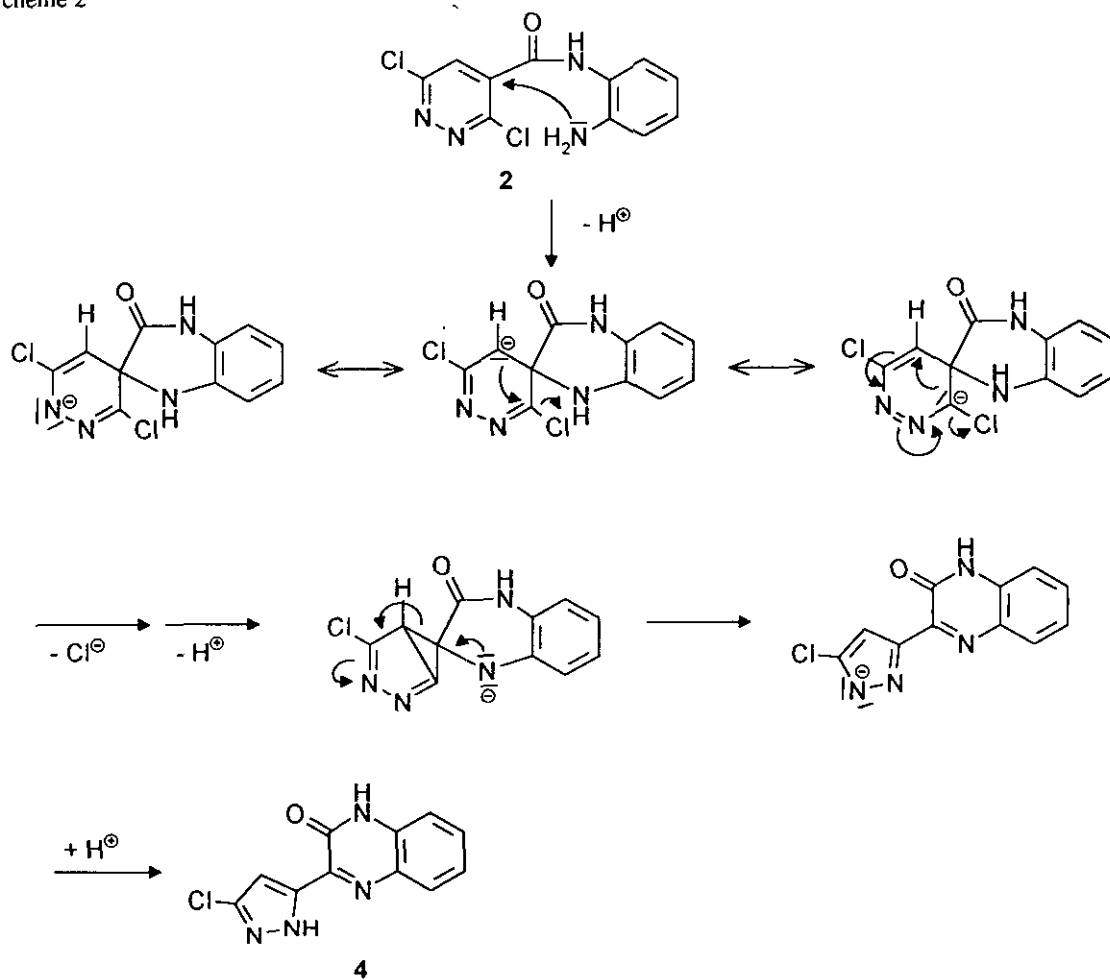
Table 1. Atomic coordinates and equivalent thermal displacement parameters of non-hydrogen atoms for  $C_{11}H_7N_4OCl \cdot \frac{1}{2}C_4H_8O_2$  (4a).  $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$ .

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	$U_{eq}[\text{Å}^2]$
N1	0.06727(9)	-0.1030(3)	0.4469(1)	0.0351(6)
C2	0.1122(1)	0.0991(4)	0.5041(1)	0.0329(7)
C3	0.1925(1)	0.1530(4)	0.4995(1)	0.0295(6)
N4	0.21746(8)	0.0225(3)	0.4450(1)	0.0319(6)
C5	0.1679(1)	-0.1794(4)	0.3878(1)	0.0313(6)
C6	0.1937(1)	-0.3209(5)	0.3284(1)	0.0397(8)
C7	0.1447(1)	-0.5215(5)	0.2712(1)	0.0447(8)
C8	0.0686(1)	-0.5838(5)	0.2723(1)	0.0446(8)
C9	0.0420(1)	-0.4487(4)	0.3297(1)	0.0396(7)
C10	0.0914(1)	-0.2460(4)	0.3880(1)	0.0323(7)
O11	0.08776(8)	0.2267(3)	0.55460(9)	0.0450(6)
C12	0.24715(9)	0.3622(4)	0.5592(1)	0.0296(6)
C13	0.2443(1)	0.5345(4)	0.6255(1)	0.0331(7)
C14	0.3190(1)	0.6737(4)	0.6569(1)	0.0323(6)
N15	0.36592(8)	0.6011(3)	0.6149(1)	0.0372(6)
N16	0.32026(9)	0.4096(4)	0.5549(1)	0.0356(6)
Cl17	0.35513(3)	0.9160(1)	0.74245(3)	0.0446(2)
O18	0.06677(7)	0.1873(3)	0.01862(9)	0.0418(5)
C19	0.0752(1)	-0.0779(5)	0.0635(2)	0.0421(8)
C20	-0.0040(1)	-0.1649(6)	0.0685(2)	0.0466(8)

A variety of 1,2-diazine  $\rightarrow$  1,2-diazole ring transformations have been reported in the literature.<sup>8</sup> Furthermore we have shown previously that phenyl(4-pyridazinyl)methanol under acidic conditions is converted into a C-4 substituted pyrazole derivative.<sup>9</sup> The transformation of the pyridazine derivative (2) into the pyrazole derivative (4), as observed in the present investigation, however, obviously represents an unprecedented type of ring contraction.

A tentative reaction mechanism is displayed in Scheme 2. It involves nucleophilic attack of the aromatic amino group of compound (2) at position 4 of the 1,2-diazine system resulting in the formation of a spiro compound. Expulsion of the chloro substituent from C-3 and deprotonation followed by ring opening of the postulated intermediate C3-C5-bridged pyridazine system finally permits to explain the formation of the pyrazole ring. Considering the findings of Adembri *et al.*<sup>10</sup> in the course of investigations of the reactivity of pyridazine-4,5-dicarboxylates towards 1,3-binucleophiles (attack of an *N*-nucleophile at C-4 of the 1,2-diazine system yielding a spiran), it appears reasonable to assume spirocyclisation of 2 as the initial reaction step. The high tendency of the  $\beta$ -positions in a pyridazine ring bearing electron withdrawing substituents to add nucleophiles is obvious also from recent observations in Grignard reactions of 4-cyano-substituted pyridazines (attack of the carbanionic species at the heteroaromatic ring rather than at the cyano function).<sup>11</sup> Moreover, we had demonstrated that cyclisation of 3-(2-aminophenylthio)-4-pyridazinecarbonitrile leads to a diazaphenothiazine system but not to a pyridazino[3,4-*b*][1,5]benzothiazepinone.<sup>12</sup> Also this type of reaction requires addition of the amino group to the  $\beta$ -position of the pyridazine system as the initial step. The assumed intermediate [3.1.0] system is outside the scope of Bredt's rule in its original interpretation.<sup>13</sup> However, it should be emphasised that a large variety of "anti-Bredt compounds" including species containing a bridgehead imine functionality have been reported.<sup>14</sup> Moreover, there is an indirect proof for the intermediate formation of the analogous bicyclo[3.1.0]-hex-1-ene system upon elimination of hydrogen chloride from 1-chloro-2,6-dimethylhepta-1,5-diene.<sup>15</sup>

Scheme 2



## EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected. Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer from KBr pellets. Mass spectra were obtained on a Varian MAT 44/S. <sup>1</sup>H and <sup>13</sup>C nmr spectra were recorded on a Varian Gemini 200 spectrometer (<sup>1</sup>H: 199.98 MHz, <sup>13</sup>C: 50.29 MHz). The centre of the solvent multiplet (DMSO-*d*<sub>6</sub>) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm for <sup>1</sup>H and δ 39.50 ppm for <sup>13</sup>C. The assignment of the <sup>13</sup>C nmr data for compound (4) was based on comparison with values reported for

3-substituted quinoxalinones.<sup>16</sup> Reactions were monitored by tlc using Polygram SIL G/UV<sub>254</sub> (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Elemental analyses were performed by Mag. J. Theiner, Institute of Physical Chemistry, University of Vienna, Austria. We thank Doz. Dr. K.-H. Ongania, Institute of Organic Chemistry, University of Innsbruck for recording the mass spectra.

### *N*-(2-Aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide (2)

To a solution of *o*-phenylenediamine (0.649 g, 6.0 mmol) and triethylamine (0.202 g, 2.0 mmol) in dry dichloromethane (20 ml) was added a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (1) (0.423 g, 2.0 mmol) in dry dichloromethane (15 ml) under a nitrogen atmosphere at 0°C. The mixture was then stirred for 4 h at room temperature. The resulting crystals were filtered off and washed with dichloromethane and water to give 0.352 g of 2. To remove the excess of *o*-phenylenediamine and the resulting *N,N*-diheteroarylated product, the dichloromethane layer was extracted three times with 2 *N* NaOH (25 ml) and the aqueous extract was acidified with 4 *N* HCl to pH 1. The resulting crystals (the *N,N*-diheteroarylated phenylenediamine) were filtered off and the filtrate was washed twice with dichloromethane (30 ml). Then the aqueous phase was neutralised with saturated aqueous NaHCO<sub>3</sub> and extracted exhaustively with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, and evaporated in vacuo to give additional 0.135 g of 2. Recrystallisation of 2 from ethanol afforded 0.437 g (77% yield), instant mp 200-205°C (decomposition from about 150°C). Ms: *m/z* (rel. int.) 282/284/286 (62/42/7%, M<sup>+</sup>), 107 (100%). Ir (cm<sup>-1</sup>): 3340, 3252, 3175, 2935, 2812, 1672, 1595. <sup>1</sup>H-Nmr (DMSO-*d*<sub>6</sub>) δ: 5.04 (s, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 6.55-6.63 (m, 1H, benzene H-5), 6.77 (dd, *J*<sub>3,4</sub> = 8.1 Hz, *J*<sub>3,5</sub> = 1.4 Hz, 1H, benzene H-3), 6.95-7.04 (m, 1H, benzene H-4), 7.26 (dd, *J*<sub>5,6</sub> = 7.8 Hz, *J*<sub>4,6</sub> = 1.5 Hz, 1H, benzene H-6), 8.49 (s, 1H, pyridazine H-5), 9.99 (s, 1H, NH, D<sub>2</sub>O exchangeable). <sup>13</sup>C-Nmr (DMSO-*d*<sub>6</sub>) δ: 115.8, 116.1 (benzene C-3, C-5), 121.0 (benzene C-1), 126.0, 127.3 (benzene C-4, C-6), 129.2 (pyridazine C-5), 138.2 (benzene C-2), 142.8 (pyridazine C-4), 152.3 (pyridazine C-6), 156.1 (pyridazine C-3), 160.4 (C=O). Anal. Calcd for C<sub>11</sub>H<sub>8</sub>N<sub>4</sub>OCl<sub>2</sub>: C, 46.67, H, 2.85; N, 19.79; Cl, 25.04. Found C, 46.95, H, 3.05, N, 19.79, Cl, 25.22.

**3-(3-Chloro-1H-pyrazol-5-yl)-1H-quinoxalin-2-one (4)**

Sodium hydride (0.240 g of a 60% dispersion in oil, 6.0 mmol) was added at room temperature to a solution of **2** (0.568 g, 2.0 mmol) in dry dimethylformamide (10 ml) under a nitrogen atmosphere. The reaction mixture was heated at 100°C for 10 min and poured into 2 *N* HCl (150 ml). The resulting yellow crystals were collected and washed with water and subsequently with light petroleum ether (boiling fraction: 40-60 °C). The product was recrystallised from tetrahydrofuran to yield 0.432 g (87 %) of yellow needles, mp 318°C. Ms: *m/z* (rel. int.) 246/248 (100/35%,  $M^+$ ) Ir ( $\text{cm}^{-1}$ ): 3217, 2849, 1671, 1612.  $^1\text{H-Nmr}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 7.22 (s, 1H, pyrazole H-4), 7.31-7.82 (m, 4H, benzene-H), 12.80 (br s, 1H, quinoxalinone NH,  $\text{D}_2\text{O}$  exchangeable), 13.76 (s, 1H, pyrazole NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-Nmr}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 107.1 (pyrazole C-4), 115.5 (quinoxalinone C-8), 123.7 (quinoxalinone C-6), 128.5 (quinoxalinone C-5), 130.8 (quinoxalinone C-7), 131.5 (quinoxalinone C-4a/C-8a), 131.9 (quinoxalinone C-4a/C-8a), 138.7, 139.4 (pyrazole C-3, C-5), 144.6 (quinoxalinone C-3), 153.1 (C=O). Anal. Calcd for  $\text{C}_{11}\text{H}_7\text{N}_4\text{OCl}$ : C, 53.57; H, 2.68; N, 22.71; Cl, 14.37. Found: C, 53.44; H, 3.08; N, 22.46; Cl, 14.18.

**Crystal structure determination of  $\text{C}_{11}\text{H}_7\text{N}_4\text{OCl} \cdot \frac{1}{2}\text{C}_4\text{H}_8\text{O}_2$  (**4a**) (dioxane solvate of **4**)**

A prismatic crystal of **4a** with dimensions of 0.19 x 0.33 x 0.49 mm was used for X-ray diffraction work with a Philips PW1100 four-circle diffractometer and graphite monochromatized Mo  $K\alpha$  radiation. Crystal data are:  $\text{C}_{13}\text{H}_{11}\text{N}_4\text{O}_2\text{Cl}$ ,  $M_r = 290.71$ , monoclinic, space group  $P2_1/n$  (non-standard setting of No. 13),  $a = 17.863(2) \text{ \AA}$ ,  $b = 4.700(1) \text{ \AA}$ ,  $c = 16.394(2) \text{ \AA}$ ,  $\beta = 113.00(1)^\circ$ ,  $V = 1265.0(4) \text{ \AA}^3$ ,  $Z = 4$ ,  $D_x = 1.526 \text{ g cm}^{-3}$ ,  $\lambda = 0.71069 \text{ \AA}$ ,  $\mu = 0.305 \text{ mm}^{-1}$ ,  $T = 297 \text{ K}$ . Cell dimensions from  $\pm\Theta$ -scans of 27 reflections ( $\Theta = 15 - 23^\circ$ ). The intensities of 2614 reflections ( $\Theta < 25^\circ$ ,  $-21 \leq h \leq 19$ ,  $0 \leq k \leq 5$ ,  $0 \leq l \leq 19$ ,  $\Theta$ - $2\Theta$  scans) were measured, corrected for  $LP$  but not for absorption, and were then merged to 2240 independent  $F_{hkl}$ , of which 1750 had  $F_o \geq 6\sigma(F_o)$ .

The structure was solved with direct methods and refined by full-matrix least-squares using the program *SHELX76*<sup>17</sup> (Sheldrick, 1976), weights  $w = 1/[\sigma^2(F_o)^2 + 0.0002F_o^2]$ , anisotropic temperature factors for non-hydrogen atoms, and a correction for extinction. All hydrogen atoms were located from a difference Fourier synthesis and were refined in positional parameters and isotropic temperature factors. Final Refinement on  $F$  gave  $R = 0.030$ ,  $wR = 0.035$ , and  $S = 1.42$  for 1749 reflections and 225 parameters. Maximum and minimum residual densities 0.19 and  $-0.14 \text{ e \AA}^{-3}$ . Atomic coordinates of non-hydrogen atoms are given in Table 1.<sup>18</sup> A

view of the molecular structure is shown in Figure 1. The structure is built up in a 2:1 ratio from flat  $C_{11}H_7N_4OCl$  molecules and puckered dioxane solvent molecules having  $\bar{1}$  symmetry. These two constituents are crosslinked via N-H...O type hydrogen bonds: each two bonds N(1)-H(1)...O(11) [N...O = 2.816(2) Å] link pairs of  $C_{11}H_7N_4OCl$  molecules related by inversion, moreover each  $C_{11}H_7N_4OCl$  molecule is bonded via the hydrogen bond N(16)-H(16)...O(18) [N...O = 2.916(2) Å] to a dioxane molecule, which is thus well-anchored in the structure by each two H bonds. Both kinds of hydrogen bonds give rise to a continuous chain-like connection parallel to the  $a$ -axis. The  $C_{11}H_7N_4OCl$  molecule is almost planar having a r.m.s. deviation of 0.035 Å from a common least-squares plane fitted to all non-hydrogen atoms. Segmented least-squares plane fits show that the 5-membered ring is slightly inclined at an angle of 2.2(1)° to the two six-membered rings. Bond lengths (Fig. 1) and angles within the  $C_{11}H_7N_4OCl$  molecule are fully consistent with the chemical structure of compound 4 in Scheme 2.

?

## REFERENCES AND NOTES

- 1 Part 70: N. Haider, G. Heinisch, and J. Moshuber, *Pharmazie*, in the press.
- 2 For a recent review see N. Haider and G. Heinisch, *Heterocycles*, 1993, **35**, 519.
- 3 K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. McNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlein, T. D. Saboe, S. J. Campbell, A. S. Rosenthal, and J. Adams, *J. Med. Chem.*, 1991, **34**, 2231.
- 4 W. Ried and T. A. Eichhorn, *Arch. Pharm. (Weinheim)*, 1988, **321**, 527.
- 5 Whereas reaction of 1 with equimolar amounts of the diamine results mainly in an *N,N'*-diheteroalylated phenylenediamine, employment of a twofold excess of the nucleophile affords analytically pure 2 in 77% yield.
- 6 Also the use of dimethyl sulfoxide or the replacement of sodium hydride by sodium carbonate resulted in the formation of compound (4). Likewise 4 results from 2 upon heating in dimethylformamide solution (1h, 100°C) in the absence of a base.
- 7 M. H. Norman, D. J. Minick, and G. E. Martin, *J. Heterocycl. Chem.*, 1993, **30**, 771.
- 8 For a review see H. C. van der Plas, 'Ring Transformations of Heterocycles', Vol. 2, Academic Press, Inc., London, 1973, pp. 146-150.



- 9 a) G. Heinisch and R. Waglechner, *J. Heterocycl. Chem.*, 1984, **21**, 1727; b) G. Heinisch, T. Huber, C. Langer, W. Gössler, and G. Kollenz, *J. Heterocycl. Chem.*, 1989, **26**, 1009.
- 10 G. Adembri, S. Chimichi, R. Nesi, and M. Scotton, *J. Chem. Soc., Perkin Trans. I*, **1977**, 1020
- 11 N. Haider, G. Heinisch, and J. Moshuber, *Tetrahedron*, 1991, **47**, 8573.
- 12 K. Czech, N. Haider, and G. Heinisch, *Monatsh. Chem.*, 1991, **122**, 413
- 13 J. Brecht, *Ann. Chem.*, 1924, **437**, 1.
- 14 a) G. Köbrich, *Angew. Chem.*, 1973, **85**, 494; b) R. S. Sheridan and G. A. Ganzer, *J. Am. Chem. Soc.*, 1983, **105**, 6158.
- 15 G. Köbrich and H. Heinemann, *Chem. Comm.*, **1969**, 493
- 16 L. Cazaux, M. Faher, C. Picard, and P. Tisnès, *Can. J. Chem.*, 1993, **71**, 2007
- 17 Sheldrick, G.M (1976): *SHELX76*. Program for crystal structure determination. Univ of Cambridge, England.
- 18 Full details on the structure determination including anisotropic temperature factors and H-atom coordinates can be obtained from the authors.

Received, 24th May, 1994