PYRIDAZINES, 71.[1] A NOVEL TYPE OF 1,2-DIAZINE → 1,2-DIAZOLE RING CONTRACTION

Gottfried Heinisch,[a] Barbara Matuszczak,[a*] and Kurt Mereiter[b]

[a] Institute of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

[b] Institute of Mineralogy, Crystallography and Structural Chemistry, Technical University of Vienna, Getreidemarkt 9, A-1060 Vienna, Austria

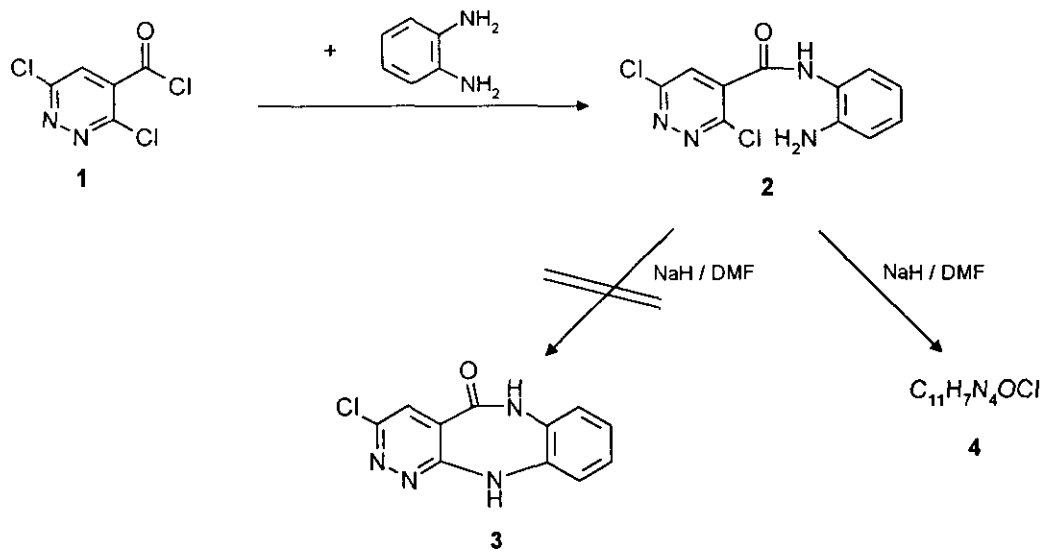
Abstract - Reaction of the 3,6-dichloro-4-pyridazinecarboxamide derivative (**2**) with sodium hydride in dimethylformamide does not afford a pyridazino[3,4-*b*]-[1,5]benzodiazepine system (**3**) but results in a ring transformation to give the quinoxalinyl-substituted pyrazole derivative (**4**) The 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[2] 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-chloronicotinic acid chloride with *o*-phenylenediamine derivatives yielding pyrido[2,3-*b*][1,5]benzodiazepinones,[3] *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**)[4] with an excess of *o*-phenylenediamine [5]

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 $C_{11}H_7N_4OCl$ 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.[6] This attempt was undertaken in view of a recent report[7] 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 1



1 **2** **3** **4**

Whereas the infrared spectrum of the new compound (**4**) clearly indicates the presence of an oxo function ($\nu_{C=O}$: 1671 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 ½-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 quinoxalinyl-substituted pyrazole (**4**) had taken place

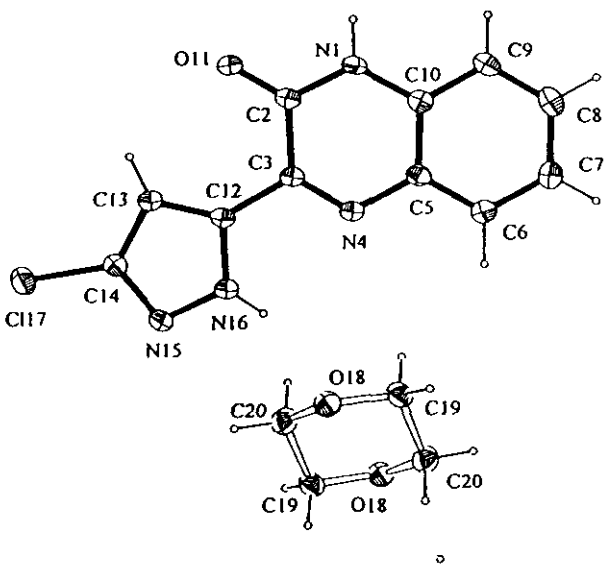


Figure 1 ORTEP plot (30%-ellipsoids) of $C_{11}H_7N_4OCl{\cdot}½C_4H_8O_2$ (**4a**) with crystallographic atom numbering scheme. Selected bond lengths (Å) are: N1-C2=1.355(2), N1-C10=1.377(3), C2-C3=1.485(3), C2-O11=1 232(3), C3-N4=1.298(3), C3-C12=1.459(2), N4-C5=1.383(2), C12-C13= 1 373(3), C12-N16=1.351(3), C13-C14=1.391(2), C14-N15=1 319(3), C14-Cl17=1 725(2), N15-N16=1.347(2).

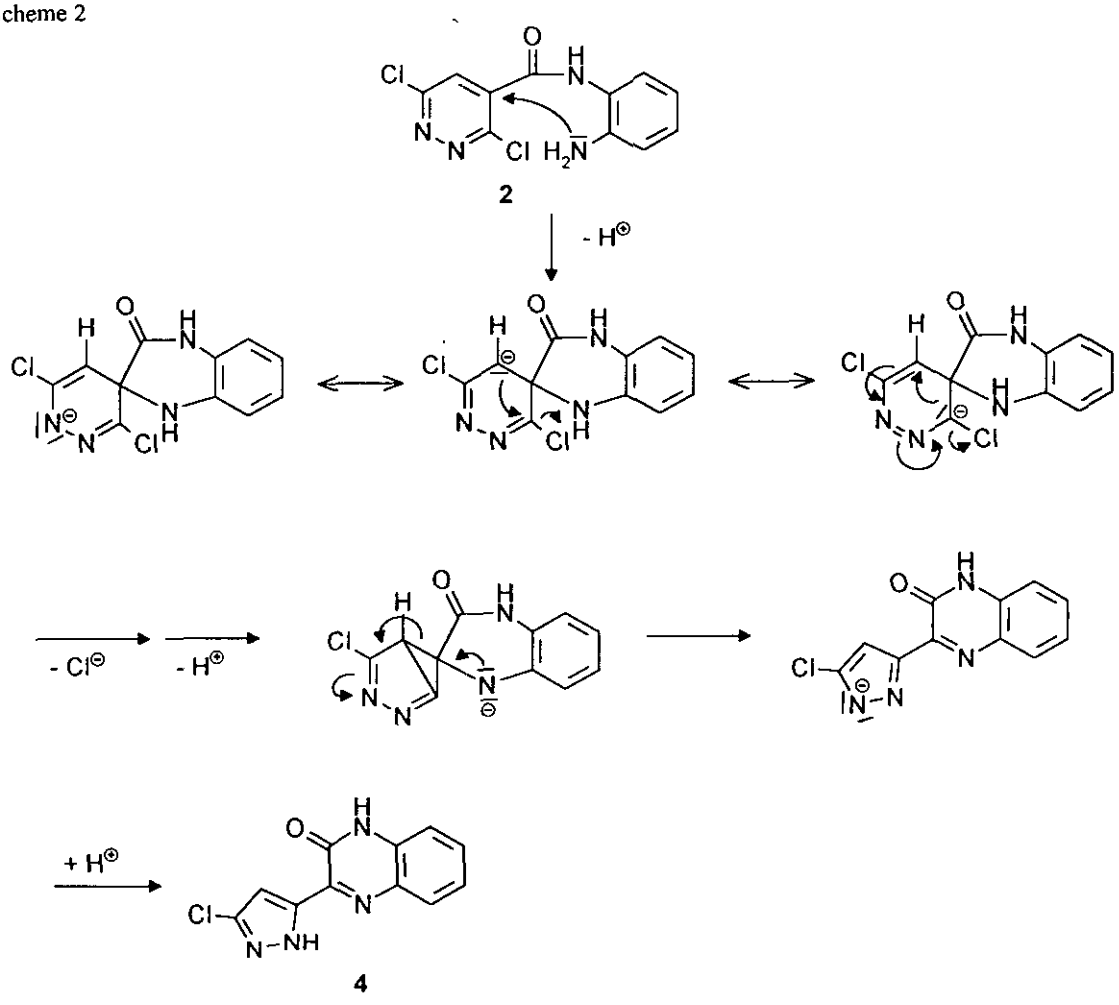
Table 1. Atomic coordinates and equivalent thermal displacement parameters of non-hydrogen atoms for $C_{11}H_7N_4OCl\ ½C_4H_8O_2$ (**4a**). $U_{eq} = (1/3)\ \Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i\ a_j$.

	x/a	*y/b*	*z/c*	U_{eq}[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 → 1,2-diazole ring transformations have been reported in the literature [8] Furthermore we have shown previously that phenyl(4-pyridazinyl)methanol under acidic conditions is converted into a C-4 substituted pyrazole derivative [9] 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.*[10] 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 β-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).[11] 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.[12] Also this type of reaction requires addition of the amino group to the β-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.[13] However, it should be emphasised that a large variety of "anti-Bredt compounds" including species containing a bridgehead imine functionality have been reported.[14] 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 [15]

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. ^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H· 199 98 MHz, ^{13}C 50 29 MHz). The centre of the solvent multiplet (DMSO-d_6) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2 49 ppm for ^{1}H and δ 39.50 ppm for ^{13}C The assignment of the ^{13}C nmr data for compound(**4**)was based on comparison with values reported for

3-substituted quinoxalinones.[16] Reactions were monitored by tlc using Polygram SIL G/UV$_{254}$ (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*'-dihetaroylated 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*'-dihetaroylated phenylenediamine) were filtered off and the filtrate was washed twice with dichloromethane (30 ml) Then the aqueous phase was neutralised with saturated aqueous $NaHCO_3$ 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^+), 107 (100%). Ir (cm^{-1}): 3340, 3252, 3175, 2935, 2812, 1672, 1595. ^{1}H-Nmr (DMSO-d_6) δ: 5.04 (s, 2H, NH_2, D_2O exchangeable), 6.55-6 63 (m, 1H, benzene H-5), 6.77 (dd, $J_{3,4}$= 8.1 Hz, $J_{3,5}$= 1.4 Hz, 1H, benzene H-3), 6 95-7.04 (m, 1 H, benzene H-4), 7.26 (dd, $J_{5,6}$= 7.8 Hz, $J_{4,6}$= 1 5 Hz, 1H, benzene H-6), 8.49 (s, 1H, pyridazine H-5), 9 99 (s, 1H, NH, D_2O exchangeable). ^{13}C-Nmr (DMSO-d_6) 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 $C_{11}H_8N_4OCl_2$· 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-1*H*-pyrazol-5-yl)-1*H*-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 (cm^{-1}): 3217, 2849, 1671, 1612. ^{1}H-Nmr (DMSO-d_6) δ: 7 22 (s, 1H, pyrazole H-4), 7.31-7.82 (m, 4H, benzene-H), 12.80 (br s, 1H, quinoxalinone NH, D_2O exchangeable), 13 76 (s, 1H, pyrazole NH, D_2O exchangeable). ^{13}C-Nmr (DMSO-d_6) δ: 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 $C_{11}H_7N_4OCl$: 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 $C_{11}H_7N_4OCl$ ½$C_4H_8O_2$ (**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 Kα radiation. Crystal data are: $C_{13}H_{11}N_4O_2Cl$, M_r = 290 71, monoclinic, space group *P2/n* (non-standard setting of No. 13), a = 17.863 (2) Å, b = 4 700 (1) Å, c = 16 394 (2) Å, β = 113 00 (1)°, V = 1265.0 (4) Å^3, Z = 4, D_x = 1 526 g cm^{-3}, λ = 0.71069 Å, μ = 0.305 mm^{-1}, T = 297 K Cell dimensions from ±Θ-scans of 27 reflections (Θ = 15 - 23°) The intensities of 2614 reflections (Θ < 25°, $-21 \le h \le 19$, $0 \le k \le 5$, $0 \le l \le 19$, Θ-2Θ scans) were measured, corrected for *LP* but not for absorption, and were then merged to 2240 independent F_{hkl}, of which 1750 had $F_o \ge 6\sigma(F_o)$.

The structure was solved with direct methods and refined by full-matrix least-squares using the program *SHELX*76[17] (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 e Å^{-3} Atomic coordinates of non-hydrogen atoms are given in Table 1 [18] 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, moreoever 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.

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5 Whereas reaction of **1** with equimolar amounts of the diamine results mainly in an *N,N'*-dihetaroylated 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

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18 Full details on the structure determination including anisotropic temperature factors and H-atom coordinates can be obtained from the authors.

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