PYRIDAZINES, 90.[1] ON THE SYNTHESIS OF NOVEL 1,2-DIAZINE CONTAINING TRICYCLIC SYSTEMS: PREPARATION OF TETRA-AZAPHENAZINES

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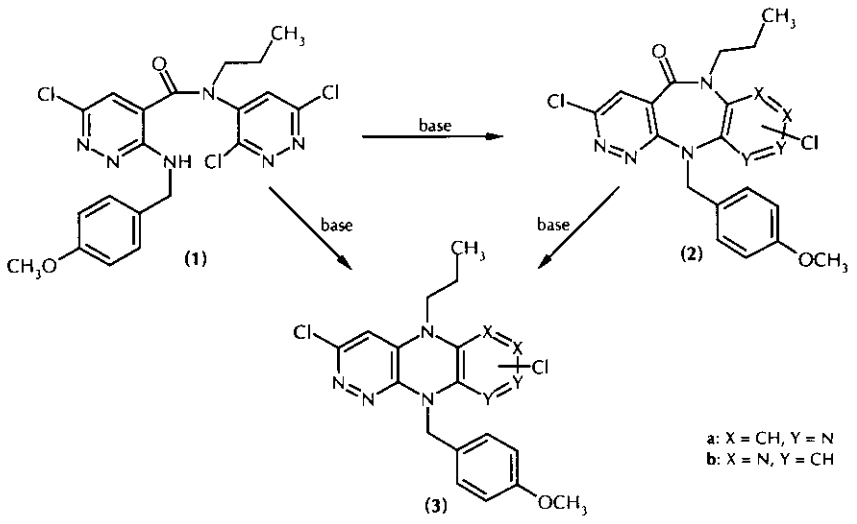
Abstract – Reaction of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzyl-amino)-*N*-propylpyridazine-4-carboxamide (**1**) under strong basic conditions or with a weak base at high temperature was found to result in a ring contraction to give two isomeric tetraazaphenazines. A tentative mechanism is proposed.

Recently we have reported on the reaction of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**1**) under basic conditions (*e.g.* $NaHCO_3$, Na_2CO_3, LiOH, NaOH, KOH, NaH) resulting in a mixture of the expected dipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepinone (**2a**) and the isomeric dipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepinone (**2b**).[2] Moreover, we observed that treatment of **1** with a strong base (*e.g.* NaOH, NaH) in *N*,*N*-dimethylformamide or *N*-methylformamide, respectively, at room temperature results also in the formation of two additional unexpected products exhibiting blue fluorescence. These two compounds could also be obtained by performing the cyclisation of **1** with sodium carbonate in dry dimethyl sulfoxide or *N*,*N*-dimethylformamide at 100 °C or by treatment of the tricyclic compounds (**2a/b**) with a base, respectively. Here we report on structural elucidation of these two fluorescent products. Furthermore we want to postulate a mechanism for this surprising reaction.

The IR spectra of these compounds clearly indicate the absence of a carbonyl group, and MS show that both compounds contain two chloro atoms and exhibit the same molecular mass (M^+ at m/z = 416). The ^{1}H-NMR spectra exhibit signals of two pyridazine protons and of the protons of a propyl and a 4-methoxybenzyl group. Therefore, these reaction products have to be formulated as substituted tetraaza-phenazines (**3a**) and (**3b**). Discrimination between the two isomeric structures follows from NOE difference experiments:[3] a positive NOE was observed for the pyridazine protons in compound (**3a**) upon irradiation of *N*-$C\underline{H}_2$-CH_2-CH_3 (see Figure 1). By contrast, a positive NOE on the pyridazine protons is observed in the isomeric compound (**3b**) not only by irradiation of *N*-$C\underline{H}_2$-CH_2-CH_3 but also by irradiation of *N*-$C\underline{H}_2$-(4-methoxyphenyl) resonances, respectively (see Figure 2).



Scheme 1.

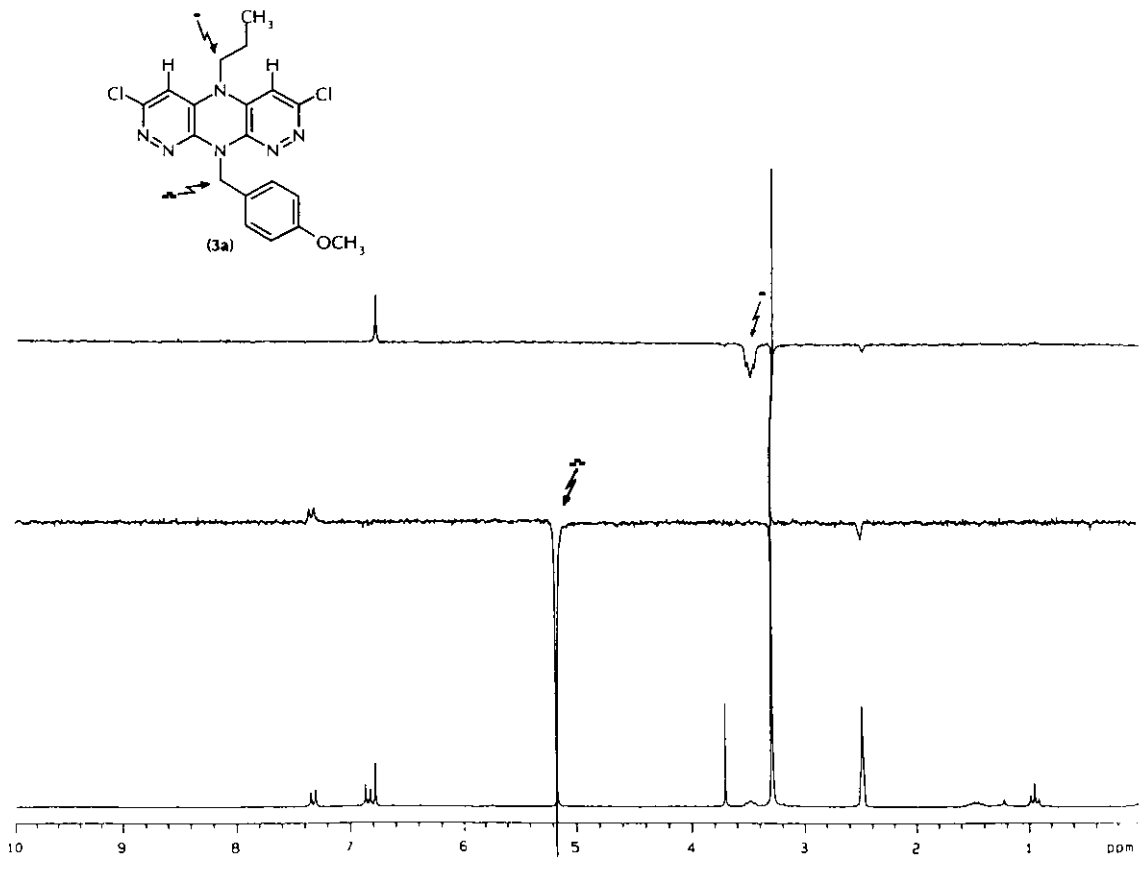


Figure 1. ^{1}H-NMR spectrum of compound (**3a**) and NOE difference spectrum of **3a** resulting from irradiation of *N*-C<u>H</u>$_2$-(4-methoxyphenyl) (**a**) and *N*-C<u>H</u>$_2$CH$_2$CH$_3$ (**b**).

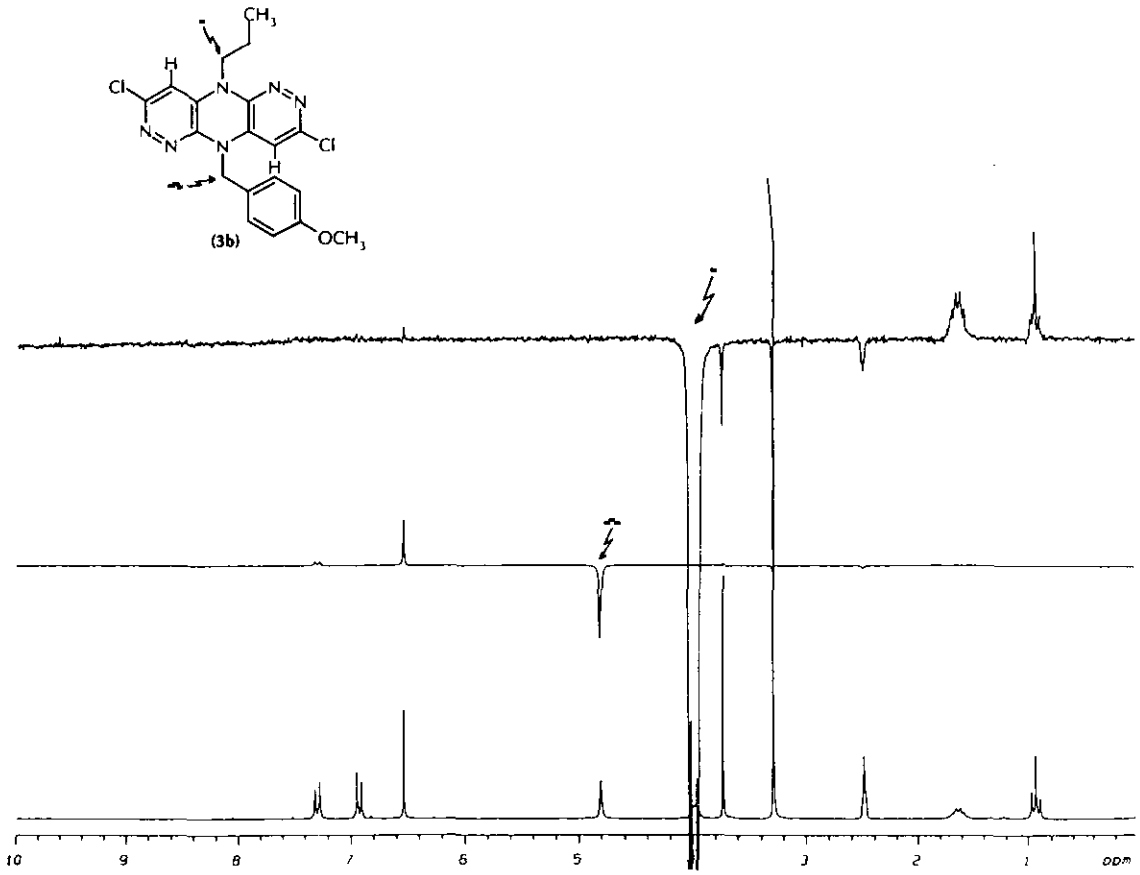
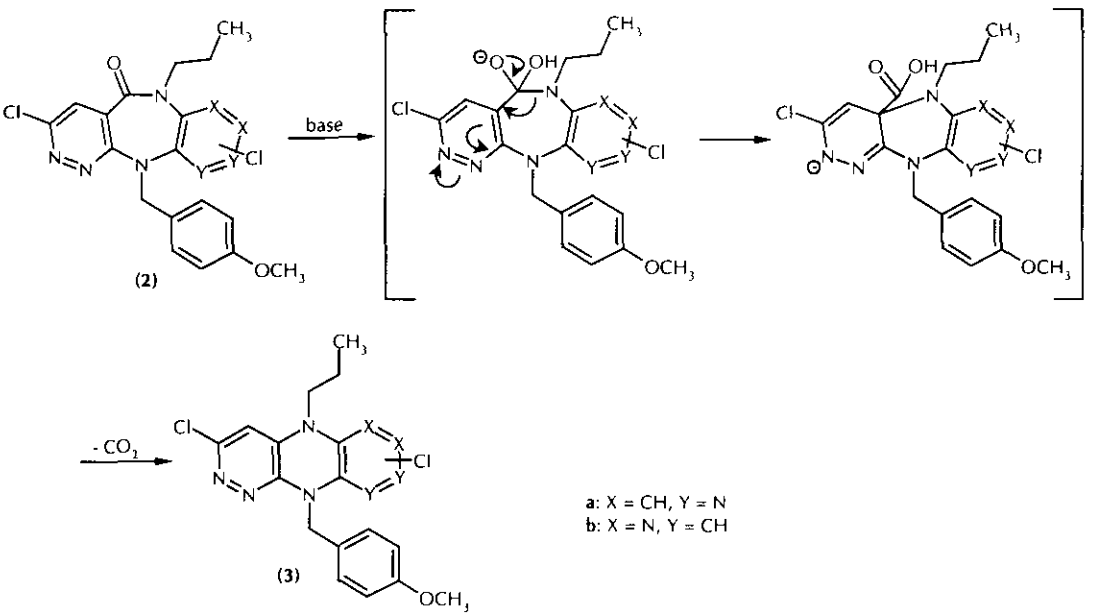


Figure 2. ^{1}H-NMR spectrum of compound (**3b**) and NOE difference spectrum of **3b** resulting from irradiation of *N*-C$\underline{H}_2$-(4-methoxyphenyl) (**a**) and *N*-C$\underline{H}_2$CH$_2$CH$_3$ (**b**).

A tentative mechanism for this ring rearrangement (see Scheme 2) can be formulated in analogy to a imide → lactam ring contraction described in the literature.[4,5] It involves addition of a hydroxyl ion at the carboxamide function, attack of the nitrogen atom at position 4 of the pyridazine-4-carboxamide system, followed by cleavage of the C-N bond of the [1,4] diazepinone. The formation of a six membered ring is accompanied by expulsion of carbon dioxide.

In summary, treatment of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propyl-pyridazine-4-carboxamide (**1**) under strong basic conditions or with a weak base at high temperature leads to tetraazaphthalazine derivatives *via* ring contraction reactions.



Scheme 2.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer from KBr pellets. MS were obtained on a Finnigan MAT SSQ 7000. ^{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 or $CDCl_3$) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm for ^{1}H (DMSO-d_6) or with δ 7.26 ppm for ^{1}H and δ 77.0 ppm for ^{13}C ($CDCl_3$). The standard Varian programme NOEDIF was used to generate NOE.

Reactions were monitored by TLC using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (40-63 μm, Merck), for the MPLC a pre-packed column [LiChroprep® Si (40-63 μm), Merck] was used. Elemental analyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna.

Starting materials: 6-Chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**1**) was prepared as described recently.[2]

General Procedure

Sodium hydride (0.17 g of a 60% dispersion in oil, 4.15 mmol) was added to a solution of 6-chloro-*N*-(4,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**1**) (0.40 g, 0.83 mmol)

in *N,N*-dimethylformamide or *N*-methylformamide (40 mL), respectively, under an atmosphere of nitrogen. The mixture was stirred at rt for 25 h and then poured into cold 0.5 N HCl (100 mL) under a nitrogen atmosphere. The mixture was extracted with dichloromethane, the organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated in *vacuo*.

Purification and separation of the isomers was performed by column chromatography (dichloromethane/ethyl acetate, 9:1 and diisopropyl ether/tetrahydrofuran, 5:1) to yield 0.08 g (14 %) of pure **3b** (using *N*-methylformamide as solvent) or 0.091 g of **3a** and 0.020 g of **3b** (= 32 % of the isomeric mixture, ratio 4.5 : 1) (using *N,N*-dimethylformamide as solvent), respectively.

3,7-Dichloro-5,10-dihydro-10-(4-methoxybenzyl)-5-propyl-1,2,8,9-tetraazaphenazine **(3a)**

yellow powder, mp 228-230 °C (diisopropyl ether/tetrahydrofuran). IR 1597, 1548, 1447. ^{1}H-NMR (DMSO-d_6) δ 7.33 (d, J = 8.7 Hz, 2H, H-2′, H-6′), 6.85 (d, J = 8.7 Hz, 2H, H-3′, H-5′), 6.78 (s, 2H, H-4, H-6), 5.16 (s, 2H, benzyl-CH_2), 3.71 (s, 3H, OCH_3), 3.52-3.45 (m, 2H, N-CH_2), 1.60-1.39 (m, 2H, CH_2), 0.95 (t, J = 7.2 Hz, 3H, CH_3). ^{1}H-NMR ($CDCl_3$) δ 7.66-7.61 (m, 2H, H-2′, H-6′), 6.83-6.79 (m, 2 H, H-3′, H-5′), 6.09 (s, 2H, H-4, H-6), 5.40 (s, 2H, benzyl-CH_2), 3.77 (s, 3H, OCH_3), 3.31-3.23 (m, 2H, N-CH_2), 1.68-1.60 (m, 2H, CH_2), 1.07 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ 159.2 (C-4′), 151.9 (C-9a, C-10a), 147.9 (C-3, C-7), 134.5 (C-4a, C-5a), 131.6 (C-2′, C-6′), 128.2 (C-1′), 113.6 (C-3′, C-5′), 106.0 (C-4, C-6), 55.2 (OCH_3), 45.4, 43.2 (benzyl-CH_2, N-CH_2), 17.4 (CH_2), 11.0 (CH_3). EI MS (70 eV): m/z = 416 [M^+]. *Anal.* Calcd for $C_{19}H_{18}N_6OCl_2$: C, 54.69; H, 4.35; N, 20.14. Found: C, 54.75; H, 4.34; N, 19.90.

3,8-Dichloro-5,10-dihydro-5-(4-methoxybenzyl)-10-propyl-1,2,8,9-tetraazaphenazine **(3b)**

yellow powder, mp 222-226 °C (diisopropyl ether/tetrahydrofuran). IR 1608, 1550, 1445, 1253, 1148. ^{1}H-NMR (DMSO-d_6) δ 7.30 (d, J = 8.8 Hz, 2H, H-2′, H-6′), 6.93 (d, J = 8.8 Hz, 2 H, H-3′, H-5′), 6.54 (s, 2H, H-4, H-9), 4.81 (s, 2H, benzyl-CH_2), 4.02-3.95 (m, 2H, N-CH_2), 3.73 (s, 3H, OCH_3), 1.66-1.61 (m, 2H, CH_2), 0.93 (t, J = 7.4 Hz, 3H, CH_3). ^{1}H-NMR ($CDCl_3$) δ 7.13 (d, J = 8.5 Hz, 2H, H-2′, H-4′), 6.96 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 6.07 (s, 2H, H-4, H-9), 4.57 (s, 2H, benzyl-CH_2), 4.24-4.17 (m, 2H, N-CH_2), 3.83 (s, 3H, OCH_3), 1.83-1.71 (m, 2H, CH_2), 1.00 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ 160.0 (C-4′), 151.7 (C-5a, C-10a), 148.0 (C-3, C-8), 134.9 (C-4a, C-9a), 126.9 (C-2′, C-6′), 124.9 (C-1′), 115.4 (C-3′, C-5′), 106.7 (C-4, C-9), 55.4 (OCH_3), 48.1, 43.2 (benzyl-CH_2, N-CH_2), 18.8 (CH_2), 11.1 (CH_3). EI MS (70 eV): m/z = 416 [M^+]. *Anal.* Calcd for $C_{19}H_{18}N_6OCl_2$: C, 54.69; H, 4.35; N, 20.14. Found: C, 54.92; H, 4.41; N, 20.04.

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REFERENCES AND NOTES

1. For part 89 see ref. 2
2. G. Heinisch, E. Huber, B. Matuszczak, and K. Mereiter, *Heterocycles*, 1999, **51**, 1035.

3. In both types of isomers the two pyridazine protons resonate at the same frequence.

4. H. Langhals and P. v. Unold, *Angew. Chem.*, 1995, **107**, 2436.

5. In this reaction mechanism, the existence of hydroxyl ions seems to be essential. Formation of compounds (**3a**) and (**3b**), however, can also be observed in dry solvents (reactions were performed with about 50 mg of **1** or **2a/b**, respectively). This may be explained by the presence of molar amounts of water.

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