

## PYRIDAZINES, 90.<sup>1</sup> ON THE SYNTHESIS OF NOVEL 1,2-DIAZINE CONTAINING TRICYCLIC SYSTEMS: PREPARATION OF TETRAAZAPHENAZINES

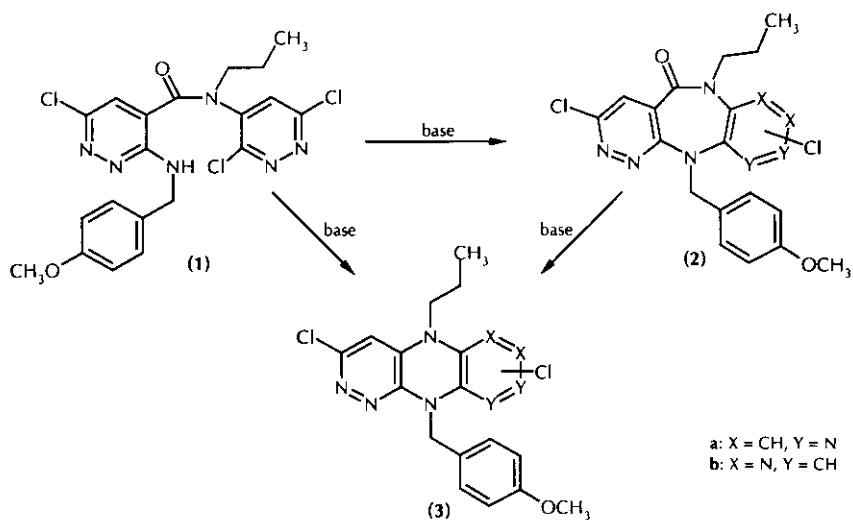
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**Abstract** – Reaction of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**1**) under strong basic conditions or with a weak base at high temperature was found to result in a ring contraction 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<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, 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**).<sup>2</sup> 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 <sup>1</sup>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 tetraazaphenazines (**3a**) and (**3b**). Discrimination between the two isomeric structures follows from NOE difference experiments:<sup>3</sup> a positive NOE was observed for the pyridazine protons in compound (**3a**) upon irradiation of *N*-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub> (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*-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub> but also by irradiation of *N*-CH<sub>2</sub>-(4-methoxyphenyl) resonances, respectively (see Figure 2).



Scheme 1.

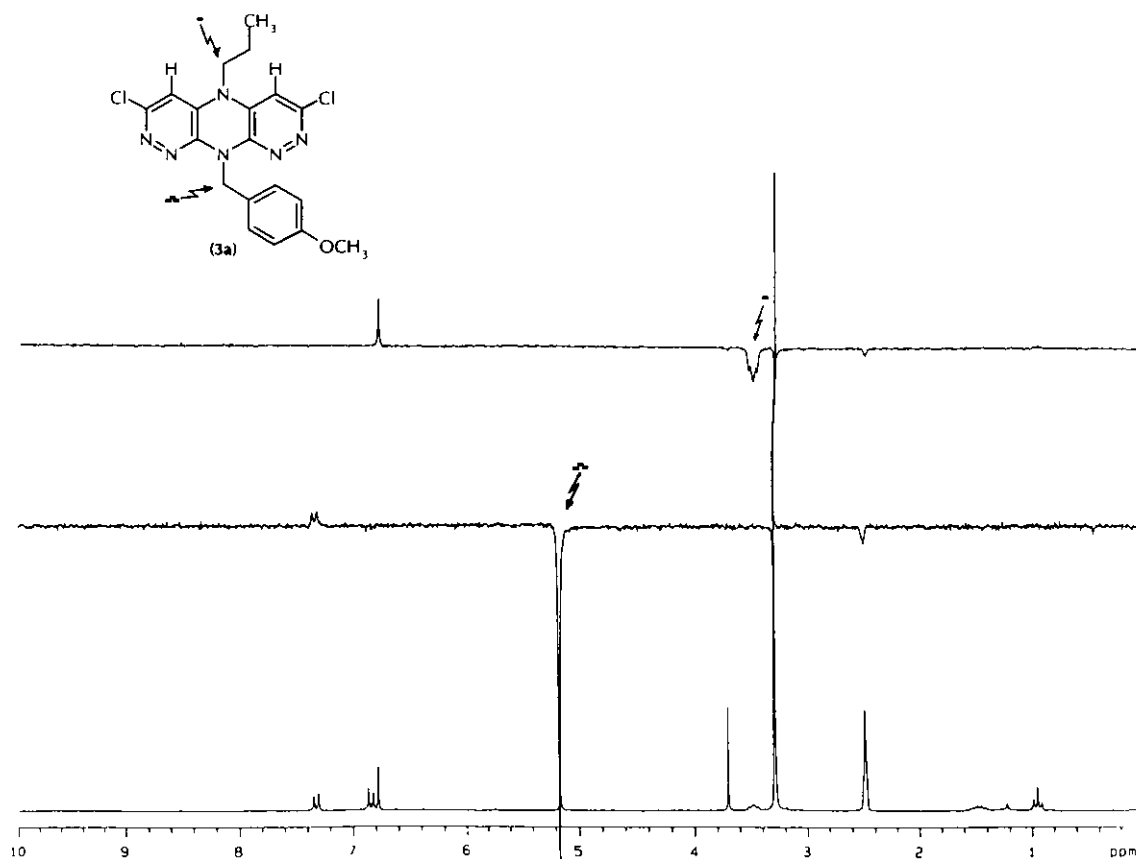


Figure 1.  $^1\text{H-NMR}$  spectrum of compound (3a) and NOE difference spectrum of 3a resulting from irradiation of  $N\text{-CH}_2\text{-(4-methoxyphenyl)}$  (a) and  $N\text{-CH}_2\text{CH}_2\text{CH}_3$  (b).

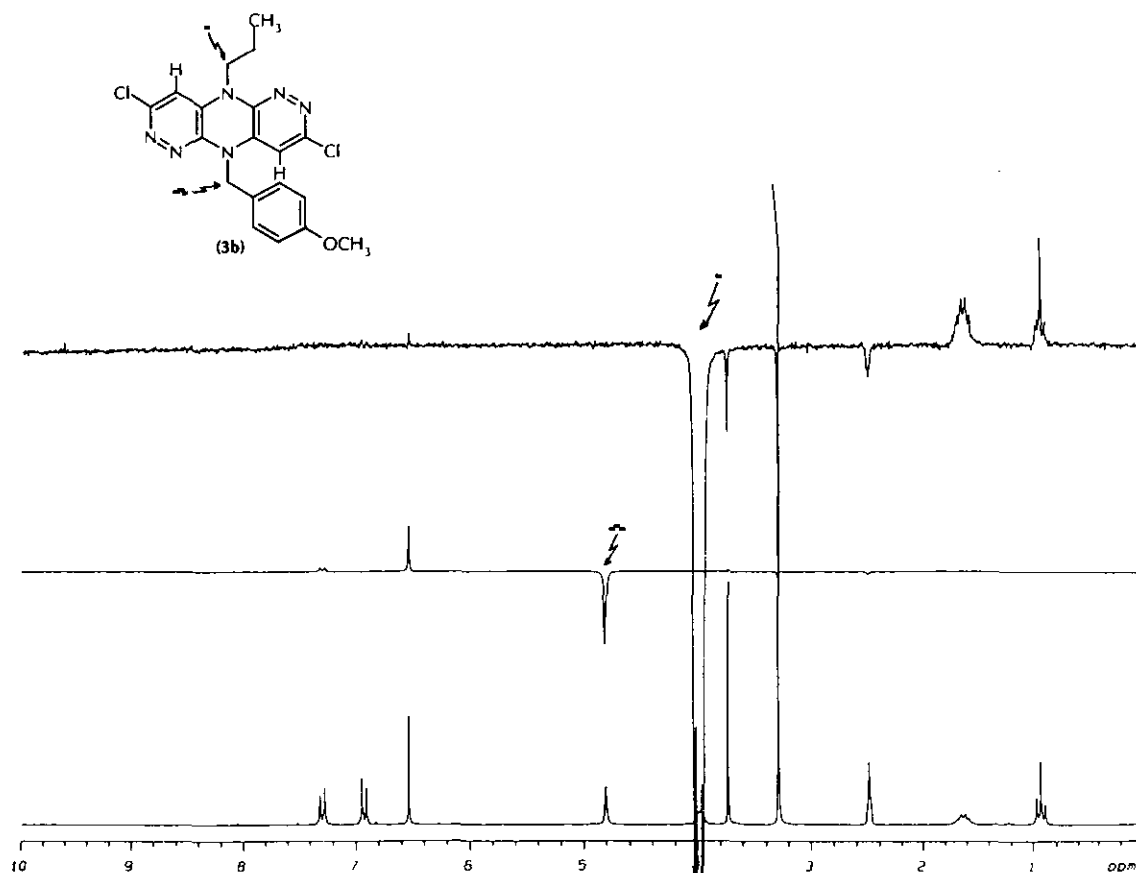
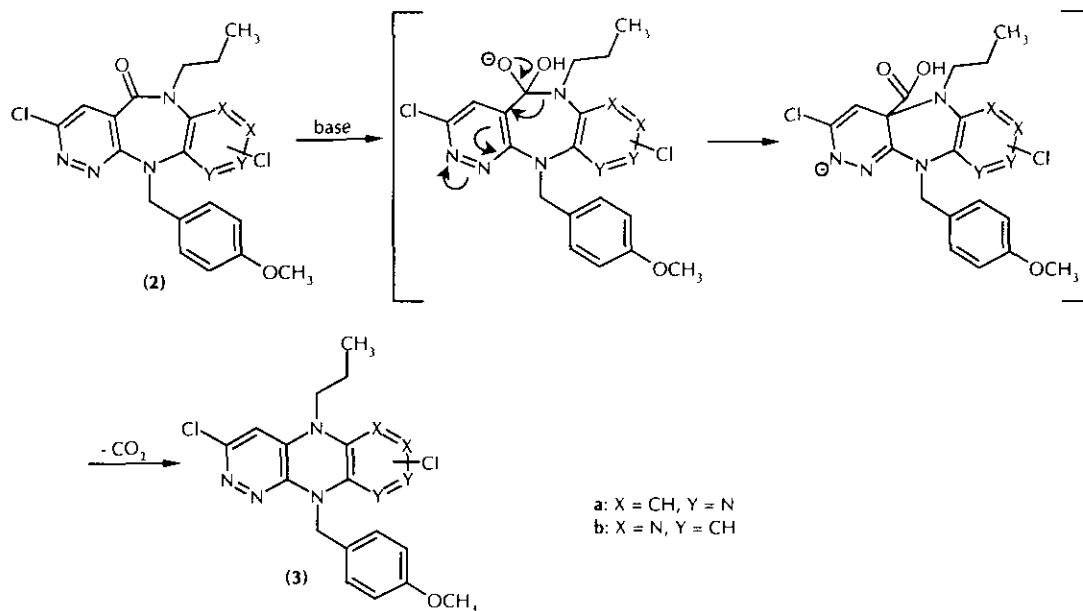


Figure 2.  $^1\text{H-NMR}$  spectrum of compound (3b) and NOE difference spectrum of 3b resulting from irradiation of  $N\text{-CH}_2\text{-(4-methoxyphenyl)}$  (a) and  $N\text{-CH}_2\text{CH}_2\text{CH}_3$  (b).

A tentative mechanism for this ring rearrangement (see Scheme 2) can be formulated in analogy to a imide  $\rightarrow$  lactam ring contraction described in the literature.<sup>4,5</sup> 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*-propylpyridazine-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. <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> or CDCl<sub>3</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 (DMSO-d<sub>6</sub>) or with δ 7.26 ppm for <sup>1</sup>H and δ 77.0 ppm for <sup>13</sup>C (CDCl<sub>3</sub>). The standard Varian programme NOEDIF was used to generate NOE.

Reactions were monitored by TLC using Polygram<sup>®</sup> SIL G/UV<sub>254</sub> (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<sup>®</sup> 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.<sup>2</sup>

### 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. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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<sub>2</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.52-3.45 (m, 2H, N-CH<sub>2</sub>), 1.60-1.39 (m, 2H, CH<sub>2</sub>), 0.95 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.66-7.61 (m, 2H, H-2', H-6'), 6.83-6.79 (m, 2H, H-3', H-5'), 6.09 (s, 2H, H-4, H-6), 5.40 (s, 2H, benzyl-CH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.31-3.23 (m, 2H, N-CH<sub>2</sub>), 1.68-1.60 (m, 2H, CH<sub>2</sub>), 1.07 (t, *J* = 7.3 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sub>3</sub>), 45.4, 43.2 (benzyl-CH<sub>2</sub>, N-CH<sub>2</sub>), 17.4 (CH<sub>2</sub>), 11.0 (CH<sub>3</sub>). EI MS (70 eV): *m/z* = 416 [M<sup>+</sup>]. *Anal.* Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>6</sub>OCl<sub>2</sub>: 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. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 7.30 (d, *J* = 8.8 Hz, 2H, H-2', H-6'), 6.93 (d, *J* = 8.8 Hz, 2H, H-3', H-5'), 6.54 (s, 2H, H-4, H-9), 4.81 (s, 2H, benzyl-CH<sub>2</sub>), 4.02-3.95 (m, 2H, N-CH<sub>2</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 1.66-1.61 (m, 2H, CH<sub>2</sub>), 0.93 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>), 4.24-4.17 (m, 2H, N-CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 1.83-1.71 (m, 2H, CH<sub>2</sub>), 1.00 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 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<sub>3</sub>), 48.1, 43.2 (benzyl-CH<sub>2</sub>, N-CH<sub>2</sub>), 18.8 (CH<sub>2</sub>), 11.1 (CH<sub>3</sub>). EI MS (70 eV): *m/z* = 416 [M<sup>+</sup>]. *Anal.* Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>6</sub>OCl<sub>2</sub>: C, 54.69; H, 4.35; N, 20.14. Found: C, 54.92; H, 4.41; N, 20.04.

## ACKNOWLEDGEMENT

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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 frequency.
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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