PYRIDAZINES, 90. ON THE SYNTHESIS OF NOVEL 1,2-DIAZINE CONTAINING TRICYCLIC SYSTEMS: PREPARATION OF TETRAAZAPHENAZINES

Gottfried Heinisch, Elisabeth Huber, and Barbara Matuszczak*

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

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. NaHCO₃, Na₂CO₃, 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). 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 ¹H-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: a positive NOE was observed for the pyridazine protons in compound (3a) upon irradiation of N-CH₂-CH₂-CH₃ (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-CH₂-CH₂-CH₃ but also by irradiation of N-CH₂-(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 $N$-$\text{CH}_2$-(4-methoxyphenyl) (a) and $N$-$\text{CH}_2$CH$_2$CH$_3$ (b).
Figure 2. $^1H$-NMR spectrum of compound (3b) and NOE difference spectrum of 3b resulting from irradiation of $N$-CH$_2$-(4-methoxyphenyl) (a) and $N$-CH$_2$CH$_2$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.$^{4,5}$ 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)-$N$-propylpyridazine-4-carboxamide (1) under strong basic conditions or with a weak base at high temperature leads to tetraazaphthalazine derivatives $via$ ring contraction reactions.
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 $\delta$ ppm), which was related to TMS with $\delta$ 2.49 ppm for $^1$H (DMSO-d$_6$) or with $\delta$ 7.26 ppm for $^1$H and $\delta$ 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$^\text{v}$ SIL G/UV$_{254}$ (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (40-63 $\mu$m, Merck), for the MPLC a pre-packed column [LiChroprep$^\text{R}$ Si (40-63 $\mu$m), 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)-1,2,8,9-tetraazaphenazine (3a)

yellow powder, mp 228-230 °C (diisopropyl ether/tetrahydrofuran). IR 1597, 1548, 1447. 1H-NMR (DMSO-d6) 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, t, J = 7.2 Hz, 3H, CH3). 13C-NMR (CDCl3) δ 159.2 (C-4a, C-10a), 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 (OCH3), 45.4, 43.2 (benzyl-CH2, N-CH2), 17.4 (CH2), 11.0 (CH3). EI MS (70 eV): m/z = 416 [M+]. Anal. Calcd for C19H14N6O2Cl2: 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. 1H-NMR (DMSO-d6) 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-CH2), 4.02-3.95 (m, 2H, OCH3), 3.73 (s, 2H, OCH3), 1.66-1.61 (m, 2H, CH2), 0.93 (t, J = 7.4 Hz, 3H, CH3). 1H-NMR (CDCl3) 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-CH2), 4.24-4.17 (m, 2H, N-CH2), 3.83 (s, 3H, OCH3), 1.83-1.71 (m, 2H, CH2), 1.00 (t, J = 7.4 Hz, 3H, CH3). 13C-NMR (CDCl3) 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 (OCH3), 48.1, 43.2 (benzyl-CH2, N-CH2), 18.8 (CH2), 11.1 (CH3). EI MS (70 eV): m/z = 416 [M+]. Anal. Calcd for C19H14N6O2Cl2: C, 54.69; H, 4.35; N, 20.14. Found: C, 54.92; H, 4.41; N, 20.04.

ACKNOWLEDGEMENT

The authors are very grateful to Dr. Dietmar RAKOWITZ (Institute of Pharmaceutical Chemistry, University of Innsbruck) for recording the MS.

REFERENCES AND NOTES

1. For part 89 see ref. 2
3. In both types of isomers the two pyridazine protons resonate at the same frequency.


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.

Received, 12th February, 1999