

PYRIDAZINES, 89.¹ ON THE SYNTHESIS OF NOVEL 1,2-DIAZINE CONTAINING TRICYCLIC SYSTEMS: PREPARATION OF DIPYRIDAZINODIAZEPINONES

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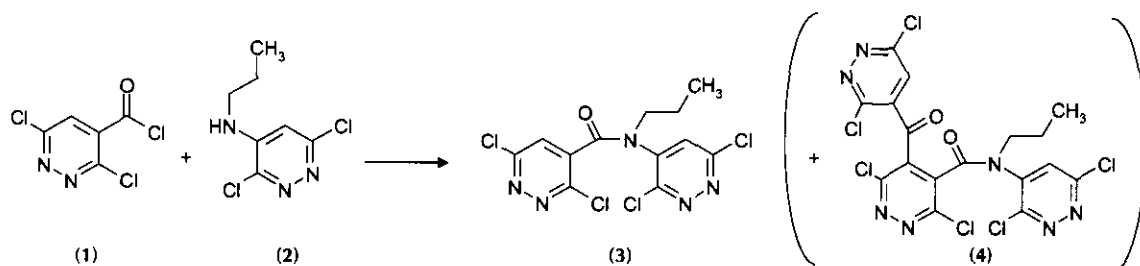
Abstract – A synthetic method for the so far unknown dipyridazino[4,3-*b*:3',4'-*e*][1,4]-diazepinone system (**7a**) was elaborated. Cyclisation of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**5**) under basic conditions was found to yield in addition to the expected compound (**7a**) an isomeric dipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepinone (**7b**) resulting from *Smiles* rearrangement. The **7a/7b** ratio was found to be influenced by the nature of the base and the solvent.

Diannelated 1,4-diazepin(on)es represent essential subunits of a wide variety of bioactive compounds. Whereas substituted dibenzodiazepin(on)es and analogous mono- and dipyrdo derivatives are known to exhibit antidepressive,^{2a/b, 3} psychotropic,^{2a/b, 4a-d} antihistaminic,^{2a/b, 5} antimuscarinic,^{2a/b, 6a-d} analgesic,^{2b} and antiviral^{7a/b} activities, comparatively little is known about congeners containing the pyridazine system. In continuation of our efforts towards the preparation of condensed pyridazines as aza-isosters of pharmaceutically relevant tricycles,⁸ we here want to report on work aimed at the synthesis of dipyridazinodiazepinones.

Based on our previous results^{9a-d} we considered a substituted 3-amino-6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide as a suitable precursor for the hitherto unknown dipyridazinodiazepinone system. Whereas initial attempts to prepare the 3,6-dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (**3**) under reaction conditions used for the synthesis of the corresponding benzo and pyrdo compounds^{9a-d} (*i.e.* reaction in dry dichloromethane in the presence of

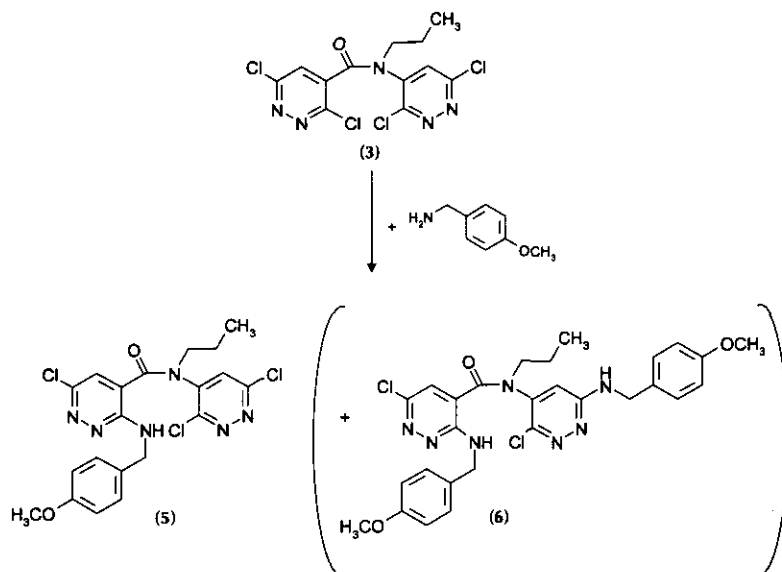
triethylamine at 0 °C to room temperature) failed,¹⁰ treatment of **1** with **2** at 40 °C led to product (**3**) in 40 % yield. In order to increase the yield of the target carboxamide, an alternative synthetic method was chosen. Thus, 3,6-dichloro-4-(propylamino)pyridazine (**2**) was reacted with sodium hydride in dry *N,N*-dimethylformamide, then a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (**1**) in dry *N,N*-dimethylformamide was added slowly. Using this procedure, **3** became accessible in 56 % yield. However, under these conditions also a by-product was formed in *ca.* 7 % yield. The elemental composition of the latter (C₁₇H₉N₇O₂Cl₆) indicated that this compound results from reaction of initially formed **3** with another mol of **1** under the strong basic conditions applied. The spectroscopic data did not permit to distinguish unequivocally between the two possible isomers (attachment of the dichloropyridazinecarbonyl group at C-5 of the pyridazinecarboxylic acid part or at C-5 of the aminopyridazine part of **3**). However, considering the pyridazine-4-carboxamide core to be the more π -electron deficient part we may assume structure **4** for this unexpected product. It should be emphasised that to our knowledge attack of an acid chloride at a β -carbon atom of a 3,6-dichloropyridazine system so far is unprecedented.¹¹

Our assumption that the formation of **4** is initiated by deprotonation of a pyridazine system in **3** under the conditions of the above mentioned procedure is supported by the fact that **4** is not formed when a mixture of the substituted amine and sodium hydride in dry *N,N*-dimethylformamide was added slowly to a solution of the carboxylic acid chloride derivative in dry *N,N*-dimethylformamide.



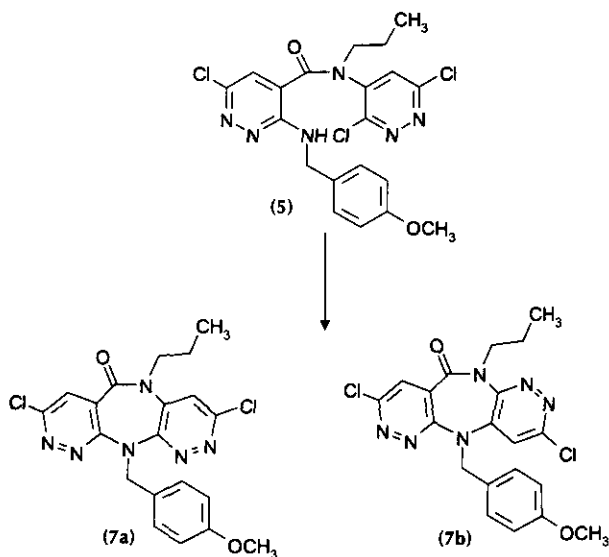
Scheme 1.

For the synthesis of the desired dipyridazinodiazepinone system, **3** was then treated with 4-methoxybenzylamine. This *N*-nucleophile was chosen in view of envisaged structural modifications since the 4-methoxybenzyl moiety is known to be smoothly removed upon treatment with trifluoroacetic acid. Reaction in 1,4-dioxane solution at 100 °C led to a mixture of the desired product (**5**) (73 % yield) and a disubstituted derivative (6-chloro-*N*-[6-chloro-3-(4-methoxybenzylamino)pyridazin-4-yl]-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**6**), 13 %). Structural elucidation of this by-product could be performed by NMR spectroscopy (see Experimental) after reductive dehalogenation (ammonium formate/palladium on charcoal).¹²



Scheme 2.

Finally, we expected to achieve cyclisation of **5** in analogy to our recently reported procedure^{9a-d} under basic conditions. However, to our surprise, a mixture of two reaction products (**7a/b**) which could be separated by column chromatography (diisopropyl ether/tetrahydrofuran, 5:1) was obtained. From NMR experiments (NOE), the slower eluted compound turned out to be the desired reaction product (**7a**) whereas the second had to be formulated as the isomer (**7b**) (see Figures 1 and 2). An unequivocal proof for both structures was achieved by single crystal X-Ray analysis (see Figures 3 and 4).



Scheme 3.

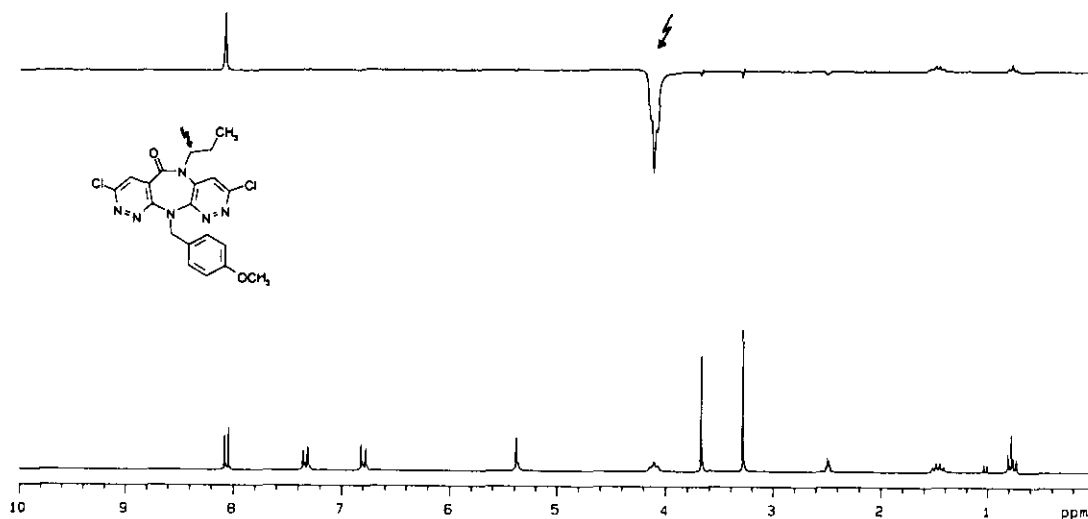


Figure 1. ^1H -NMR spectrum of compound (7a) and NOE difference spectrum of 7a resulting from irradiation of $N\text{-CH}_2\text{-CH}_2\text{-CH}_3$.

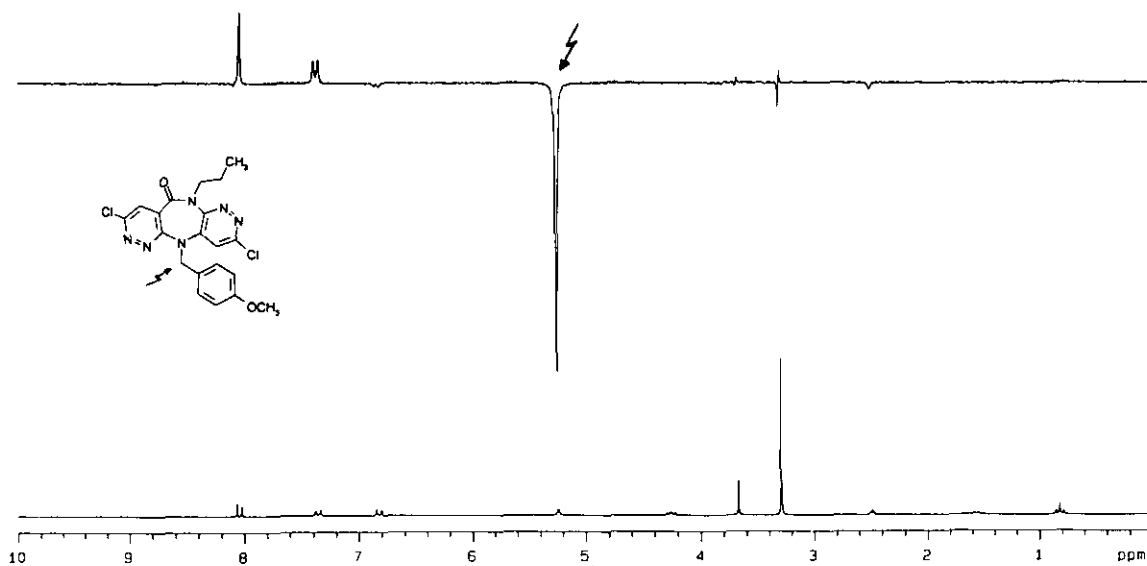


Figure 2. ^1H -NMR spectrum of compound (7b) and NOE difference spectrum of 7b resulting from irradiation of $N\text{-CH}_2\text{-(4-methoxy)phenyl}$.

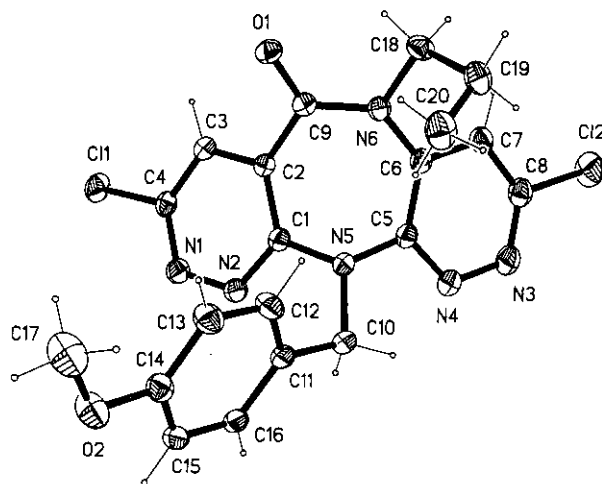


Figure 3. Molecular structure of **7a** in crystalline state (20% ellipsoids). Only first of the two independent molecules in the crystal structure is shown. Selected bond lengths and angles (Å, deg): C(4)-Cl(1) = 1.733(2), C(8)-Cl(2) = 1.728(3), N(1)-N(2) = 1.349(3), N(3)-N(4) = 1.358(3), C(4)-N(1) = 1.311(3), C(1)-N(2) = 1.328(3), C(1)-N(5) = 1.411(3), C(8)-N(3) = 1.313(4), C(5)-N(4) = 1.319(3), C(5)-N(5) = 1.409(3), C(1)-N(2)-N(1) = 119.5(2), C(4)-N(1)-N(2) = 118.4(2), C(5)-N(4)-N(3) = 120.2(2), C(8)-N(3)-N(4) = 117.7(2).

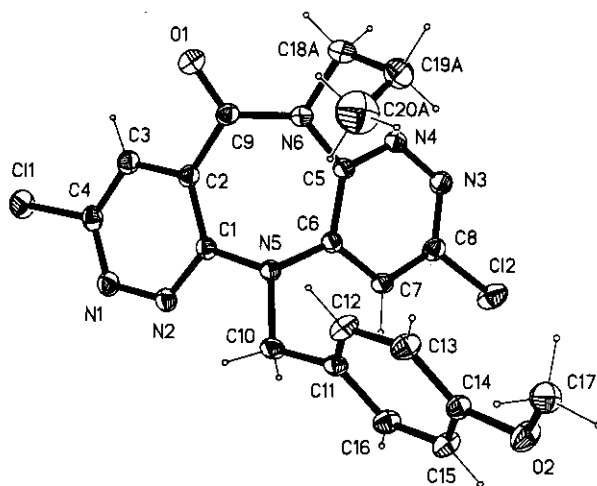
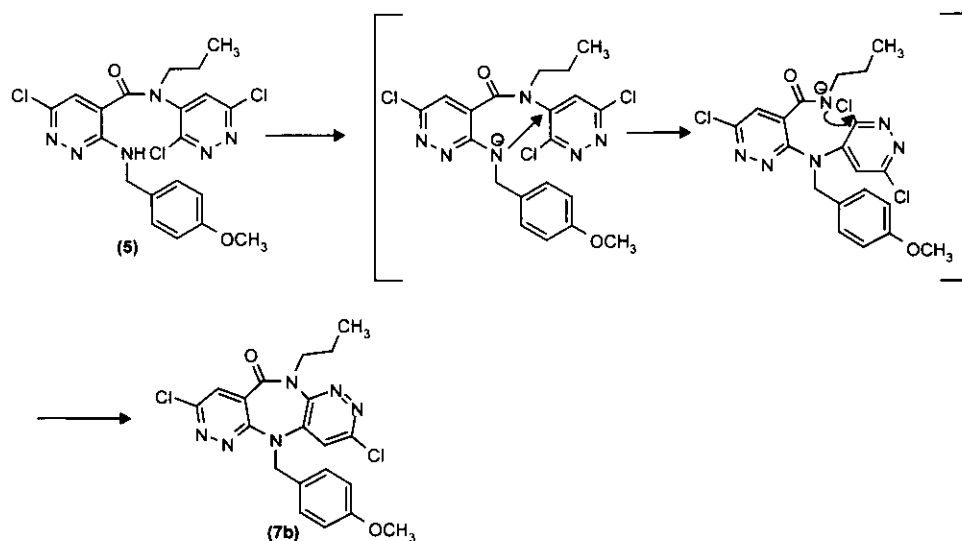


Figure 4. Thermal ellipsoid plot (20% ellipsoids) of $C_{20}H_{18}N_6O_2Cl_2$ (**7b**) shown with the predominant 'a'-orientation of the disordered propyl group. Selected bond lengths and angles (Å, deg): C(4)-Cl(1) = 1.734(2), C(8)-Cl(2) = 1.722(3), N(1)-N(2) = 1.345(3), N(3)-N(4) = 1.343(3), C(4)-N(1) = 1.313(3), C(1)-N(2) = 1.330(3), C(1)-N(5) = 1.412(3), C(8)-N(3) = 1.312(4), C(5)-N(4) = 1.323(3), C(5)-N(6) = 1.415(3), C(6)-N(5) = 1.406(3), C(1)-N(2)-N(1) = 119.9(2), C(4)-N(1)-N(2) = 118.1(2), C(5)-N(4)-N(3) = 120.9(2), C(8)-N(3)-N(4) = 117.0(2).

Formation of the unexpected product (**7b**) can be explained by a *Smiles* rearrangement. It has to be noted that analogous reactions have been observed in the course of synthesis of substituted dipyridodiazepinones.¹³ A tentative reaction mechanism is displayed in Scheme 4. It involves nucleophilic attack of the deprotonated 3'-nitrogen at position 4 of the second pyridazine ring resulting in displacement of a carboxamide anion. Subsequent ring closure gives the tricyclic compound (**7b**).



Scheme 4.

We now investigated the influence of the reaction conditions on the formation of the isomeric dipyridazinediazepinones. The ratio of the isomers was detected by ¹H-NMR spectroscopy after work up of the reaction mixtures obtained. The results shown in Table 1 indicate that there is an effect of the solvent: whereas performing the reaction in dimethyl sulfoxide/sodium carbonate leads to a 1 : 1 mixture, the ratio could be shifted to compound (**7a**) by using *N,N*-dimethylformamide/sodium carbonate (ratio **7a** : **7b** = 1.3 : 1). On the other hand, the product formed *via Smiles* rearrangement dominates in the system 1,4-dioxane/sodium hydride (ratio **7a** : **7b** = 1 : 3), and treatment of **5** with sodium carbonate in *N*-methylformamide yields the isomer (**7b**) exclusively.

Table 1

solvent	base	temp.	reaction time	ratio of the isomers*
dimethyl sulfoxide	Na ₂ CO ₃	rt 100 °C	3 d 2.5 h	1 : 1 (7a : 7b)
<i>N,N</i> -dimethylformamide	Na ₂ CO ₃	rt	20 h	1.3 : 1 (7a : 7b)
1,4-dioxane	NaH	100 °C	4 h	0.4 : 1 (7a : 7b)
<i>N</i> -methylformamide	Na ₂ CO ₃	rt	4 d	only 7b

* The assignment of the ratios of the isomers was performed by ¹H NMR spectroscopy after work up of the reaction mixtures and column chromatography (yields of the mixture of isomers: 80-100 %).

Moreover, the influence of the base on the product distribution in the reaction in *N,N*-dimethylformamide was investigated (see Table 2): using sodium hydrogencarbonate instead of sodium carbonate results in a **7a** : **7b** mixture of 1.5 : 1. Employment of a stronger base led to ratios of 0.9 : 1 (sodium hydroxide) and 0.8 : 1 (potassium hydroxide). Cyclisation in the presence of lithium hydroxide resulted in the formation of a **7a** : **7b** mixture of 1.2 : 1. In summary, these results show that performing the cyclisation of **5** in the presence of a strong base favours the formation of the rearrangement product.¹⁴

Table 2

solvent	base	temp.	reaction time	ratio of the isomers*
<i>N,N</i> -dimethylformamide	Na ₂ CO ₃	rt	20 h	1.3 : 1 (7a : 7b)
<i>N,N</i> -dimethylformamide	NaHCO ₃	50 °C	5 h	1.5 : 1 (7a : 7b)
<i>N,N</i> -dimethylformamide	NaOH	0 °C → rt	30 min	0.9 : 1 (7a : 7b)
<i>N,N</i> -dimethylformamide	KOH	0 °C → rt	30 min	0.8 : 1 (7a : 7b)
<i>N,N</i> -dimethylformamide	LiOH	rt	100 min	1.2 : 1 (7a : 7b)

* The assignment of the ratios of the isomers was performed by ¹H NMR spectroscopy after work up of the reaction mixtures and column chromatography (yields of the mixture of isomers: 80-100 %).

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. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini 200 spectrometer (¹H: 199.98 MHz, ¹³C: 50.29 MHz). The centre of the solvent multiplet (DMSO-d₆ or CDCl₃) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm for ¹H and δ 39.5 ppm for ¹³C (DMSO-d₆) or with δ 7.26 ppm for ¹H and δ 77.0 ppm for ¹³C (CDCl₃). The standard Varian programme NOEDIF was used to generate NOE. Reactions were monitored by TLC using Polygram® SIL G/UV₂₅₄ (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. Light petroleum refers to the fraction of bp 40-60°C. The yields are not optimised.

3,6-Dichloro-4-propylaminopyridazine (2)

3.50 g (15.36 mmol) of 4-bromo-3,6-dichloropyridazine was suspended in 30 mL of a *n*-propylamine solution (40 % in water) and the mixture was stirred 10 min at room temperature. The resulting crystals were filtered, washed with water and dried in vacuo. The product was purified by recrystallisation from diisopropyl ether/tetrahydrofuran to yield 2.56 g (81 %) of **2**.

Colourless crystals, mp 107-110 °C. IR 3297 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 6.52 (s, 1H, pyridazine-H-5), 5.18 (s, br, 1H, NH), 3.24-3.14 (m, 2H, CH_2), 1.83-1.65 (m, 2H, CH_2), 1.04 (t, $J = 7.3$ Hz, 3H, CH_3). EI MS (70 eV): $m/z = 205$ [M^+]. *Anal.* Calcd for $\text{C}_7\text{H}_9\text{Cl}_2\text{N}_3 \times 0.2 \text{ HCl}$: C, 39.41; H, 4.35; N, 19.69. Found: C, 39.48; H, 4.08; N 19.48.

Procedures for *N*-Acylation Reaction: Synthesis of 3,6-Dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (3):

Method A:

To a solution of 3,6-dichloro-4-propylaminopyridazine (3.00 g, 14.56 mmol) in dry dichloromethane (50 mL) was added triethylamine (2.21 g, 21.84 mmol) under a nitrogen atmosphere. A solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (3.08 g, 14.56 mmol) in dichloromethane (20 mL) was added dropwise at 40 °C and the mixture was stirred at this temperature for 72 h. After cooling to rt, the dichloromethane solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The product was purified by column chromatography (dichloromethane/ethyl acetate, 19:1) followed by recrystallisation from diisopropyl ether/ethyl acetate to yield 2.22 g (40 %) of 3.

Method B:

To an ice-cooled suspension of sodium hydride (60 %, 0.582 g, 14.56 mmol) in 60 mL of dry *N,N*-dimethylformamide was added 3,6-dichloro-4-propylaminopyridazine (3.00 g, 14.56 mmol). The mixture was stirred at rt for 1 h. 3,6-Dichloropyridazine-4-carboxylic acid chloride (3.08 g, 14.56 mmol) was added dropwise at 0 °C. After stirring at rt for 15 min, the mixture was poured into cold 0.5 N HCl (100 mL). The resulting crystals were filtered off and washed with water and light petroleum. The product was purified by column chromatography (dichloromethane/ethyl acetate, 19:1), followed by recrystallisation from diisopropyl ether/ethyl acetate to yield 3.11 g (56 %) of 3 and 0.57 g (7 %) of 4.

Method C:

To an ice-cooled suspension of sodium hydride (60 %, 0.388 g, 9.71 mmol) in dry *N,N*-dimethylformamide (40 mL) was added 3,6-dichloro-4-propylaminopyridazine (2.00 g, 9.71 mmol). After stirring at rt for 1 h this mixture was added dropwise at 0 °C to solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (2.05 g, 9.71 mmol) in dry *N,N*-dimethylformamide (40 mL). After 1 h of stirring, the mixture was poured into cold 0.5 N HCl (100 mL) and the product thus obtained was treated as described in method B to yield 1.70 g (46 %) of 3 and 0.60 g (30 %) of 2.

3,6-Dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (3)

Colourless crystals, mp 125-128 °C. IR 1585 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 7.58 (s, 1H, pyridazine-H-5), 7.53 (s, 1H, pyridazine-H-5'), 3.51-3.45 (m, 2H, N-CH_2), 1.55-1.75 (m, 2H, CH_2), 1.05-0.85 (m, 3H, CH_3). EI MS

(70 eV): $m/z = 381$ [M^+]. *Anal.* Calcd for $C_{12}H_9N_5OCl_4$: C, 37.83; H, 2.38; N, 18.38. Found: C, 38.08; H, 2.46; N, 18.27.

3,6-Dichloro-*N*-(3,6-dichloropyridazin-4-yl)-5-[3,6-dichloropyridazin-4-ylcarbonyl]-*N*-propylpyridazine-4-carboxamide (4)

Colourless crystals, mp 155–158 °C. IR 1743 cm^{-1} . 1H -NMR ($CDCl_3$) δ 6.59 (s, 1H), 5.14 (s, 1H) (pyridazine-H-5', pyridazine-H-5''), 3.68–3.61 (m, 2H, N-CH₂), 1.83–1.72 (m, 2H, CH₂), 1.01 (t, $J=7.3$ Hz, 3H, CH₃). 1H -NMR (DMSO- d_6) δ 8.55 (s, 1H), 5.87 (s, 1H) (pyridazine-H-5', pyridazine-H-5''), 4.00–3.93 (m, 2H, N-CH₂), 1.74–1.63 (m, 2H, CH₂), 0.91 (t, $J=7.3$ Hz, 3H, CH₃). ^{13}C -NMR ($CDCl_3$) δ 170.4 (ketone C=O), 159.9, 156.2, 151.0, 150.7, 143.0, 139.6, 136.4, 135.4, 129.2, 124.6 (amide C=O, C-3, C-4, C-5, C-6, C-3', C-4', C-6', C-3'', C-4'', C-6''), 127.6, 103.1 (C-5', C-5''), 44.3 (N-CH₂), 23.0 (CH₂), 10.7 (CH₃). ^{13}C -NMR (DMSO- d_6) δ 170.1 (ketone-C=O), 159.0, 155.7, 150.0, 149.3, 143.5, 139.2, 136.2, 135.4, 126.2, 124.1 (amide-C=O, C-3, C-4, C-5, C-6, C-3', C-4', C-6', C-3'', C-4'', C-6''), 128.5, 104.2 (C-5', C-5''), 43.2 (N-CH₂), 21.9 (CH₂), 10.1 (CH₃). CI MS (70 eV, methane): $m/z = 556$ [$M+1^+$]. *Anal.* Calcd for $C_{17}H_9N_7O_2Cl_6 \times 0.3$ diisopropyl ether: C, 38.49; H, 2.27; N, 16.71. Found: C, 38.23; H, 2.17; N 16.69.

Procedures for the Reaction of 3,6-Dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide with 4-Methoxybenzylamine: Synthesis of 6-Chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (5) and 6-Chloro-*N*-[6-chloro-3-(4-methoxybenzylamino)pyridazin-4-yl]-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (6)

Method A:

A solution of 3,6-dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (3) (3.00 g, 7.87 mmol) and 4-methoxybenzylamine (3.00 g, 21.87 mmol) in dry 1,4-dioxane (100 mL) was refluxed for 72 h. The 1,4-dioxane was evaporated *in vacuo* and the residue was taken up in dichloromethane, the solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residue thus obtained was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) to give a total yield of 3.45 g of 5 and 6. Separation of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (5) (yield: 2.88 g, 76 %) and 6-chloro-*N*-[6-chloro-3-(4-methoxybenzylamino)pyridazin-4-yl]-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (6) (yield: 0.575 g, 13 %) was achieved by MPLC with diisopropyl ether/ethyl acetate, 1:1 as eluent.

Method B:

A solution of 3,6-dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (3) (3.00 g, 7.87 mmol) and 4-methoxybenzylamine (3.00 g, 21.87 mmol) in dry dichloromethane (100 mL) was refluxed for 72 h. The mixture was cooled to rt, washed with water and brine, dried over anhydrous sodium sulfate and

evaporated. The residue was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) followed by crystallisation from diisopropyl ether/ethyl acetate to yield 2.88 g (76 %) of **5**.

6-Chloro-N-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-N-propylpyridazine-4-carboxamide (5)

Colourless powder, mp 110–115 °C. IR 3349, 3258, 1659 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 7.58 (s, 1H, pyridazine-H-5), 7.28–7.22 (m, 2H), 7.18 (s, 1H), 6.85–6.80 (m, 2H) (benzyl-H-2, -H-3, -H-5, -H-6; pyridazine-H-5'), 6.46–6.38 (m, 1H, NH), 5.23 (s, 2H, N-CH₂-benzyl), 3.77 (s, 3H, OCH₃), 3.12–3.02 (m, 2H, N-CH₂), 1.48–1.33 (m, 2H, CH₂), 0.88 (t, J = 7.4 Hz, 3H, CH₃). EI MS (70 eV): m/z = 480 [M^+]. *Anal.* Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_6\text{O}_2\text{Cl}_3 \times 0.2$ diisopropyl ether: C, 50.70; H, 4.38; N, 16.73. Found: C, 50.79; H, 4.05; N, 16.71.

6-Chloro-N-[3-chloro-6-(4-methoxybenzylamino)pyridazin-4-yl]-3-(4-methoxybenzylamino)-N-propylpyridazine-4-carboxamide (6)

Light yellow crystals, mp 70–75 °C. IR 3384, 3304, 1657 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 7.32–7.18 (m, 4H), 6.91–6.83 (m, 4H), 6.72 (s, 1H), 6.31 (s, 1H) (benzyl-H-2, -H-3, -H-5, -H-6, -H-2', -H-3', -H-5', -H-6', pyridazine-H-5, -H-5'), 6.06–6.00 (m, 1H, NH), 5.28 (t, J = 5.5 Hz, 1H, NH), 4.67 (d, J = 5.4 Hz, 2H, N-CH₂-benzyl), 4.46 (d, J = 5.6 Hz, 2H, N-CH₂-benzyl), 3.80 (s, 3 H, OCH₃), 3.77 (s, 3H, OCH₃), 3.71–3.58 (m, 2H, N-CH₂), 1.55–1.43 (m, 2H, CH₂), 0.86 (t, J = 7.3 Hz, 3H, CH₃). EI MS (70 eV): m/z = 581 [M^+]. *Anal.* Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_7\text{O}_3\text{Cl}_2 \times 0.2$ diisopropyl ether: C, 58.17; H, 5.32; N, 16.26. Found: C, 58.15; H, 5.12; N, 16.24.

Reductive Dehalogenation of 6 in Order to Determine the Substitution Position: N-[3-(4-Methoxybenzylamino)pyridazin-5-yl]-3-(4-methoxybenzylamino)-N-propylpyridazine-4-carboxamide

A mixture of **6** (0.07 g, 0.12 mmol), 0.152 g (2.40 mmol) of ammonium formate and 0.060 g of Pd/C (10%) in 20 mL of methanol was stirred under a nitrogen atmosphere at 48 °C for 20 h. The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The product thus obtained was purified by column chromatography (ethyl acetate) to yield 0.018 g (29 %) of an oily product.

$^1\text{H-NMR}$ (CDCl_3) δ 8.40 (d, J = 4.7 Hz, 1H, pyridazine-H-6), 8.34 (d, J = 2.2 Hz, 1H, pyridazine-H-6'), 7.35–7.17 (m, 4H), 6.89–6.84 (m, 4H) (benzyl-H-2, -H-3, -H-5, -H-6, -H-2', -H-3', -H-5', -H-6'), 6.57 (d, J = 4.7 Hz, 1H, pyridazine-H-5), 6.17 (t, J = 5.3 Hz, 1H, NH), 6.02 (d, J = 2.2 Hz, 1H, pyridazine-H-4'), 5.11 (t, J = 6.5 Hz 1H, NH), 4.73 (d, J = 5.4 Hz, 2H, N-CH₂-benzyl), 4.39 (d, J = 5.8 Hz, 2H, N-CH₂-benzyl), 3.81 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.80–3.68 (m, 2H, N-CH₂), 1.72–1.48 (m, 2H, CH₂), 0.90 (t, J = 7.4 Hz, 3H, CH₃). EI MS (70 eV): m/z = 513 [M^+].

Procedure for the Cyclisation Reaction: Synthesis of 3,8-Dichloro-5,11-dihydro-11-(4-methoxybenzyl)-5-propyldipyridazino[4,3-b:3',4'-e][1,4]diazepin-6-one (7a) and 3,8-Dichloro-5,11-dihydro-5-(4-methoxybenzyl)-11-propyldipyridazino[3,4-b:3',4'-e][1,4]diazepin-10-one (7b)

To a solution of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**5**) (0.05-0.50 g, 0.10-1.04 mmol) in 5-50 mL of the appropriate solvent (see Tables 1 and 2) was added 0.52-5.20 mmol of base (see Tables 1 and 2) under an atmosphere of nitrogen. The mixture was stirred at the temperature given in Tables 1 and 2, then poured into 0.5 N HCl (20-100 ml), and extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) to 71-88 % of the isomeric mixture (**7a/b**). Separation of the isomers was achieved by recrystallisation from tetrahydrofuran to yield pure **7b**. The residue remaining after recrystallisation was chromatographed (diisopropyl ether/tetrahydrofuran, 5:1), the pure isomers **7a/b** were recrystallised from diisopropyl ether/ethyl acetate.

3,8-Dichloro-5,11-dihydro-11-(4-methoxybenzyl)-5-propyldipyridazino[4,3-b:3',4'-e][1,4]diazepin-6-one (7a)

Yellow crystals, mp 145-148 °C. IR 1665 cm⁻¹. ¹H-NMR (DMSO-d₆) δ 8.07 (s, 1H), 8.04 (s, 1H) (H-4, H-7), 7.33 (d, J = 8.8 Hz, 2H, H-2', H-6'), 6.79 (d, J = 8.8 Hz, 2H, H-3', H-5'), 5.38 (s, 2H, benzyl-CH₂), 4.15-4.05 (m, 2H, N-CH₂), 3.67 (s, 3H, OCH₃), 1.51-1.44 (m, 2H, CH₂), 0.77 (t, J = 7.4 Hz, 3H, CH₃). ¹H-NMR (CDCl₃) δ 7.78 (s, 1H), 7.25 (s, 1H) (H-4, H-7), 7.38-7.33 (m, 2H, H-2', H-6'), 6.79-6.74 (m, 2H, H-3', H-5'), 5.55 (s, 2H, benzyl-CH₂), 4.05-3.99 (m, 2H, N-CH₂), 3.74 (s, 3H, OCH₃), 1.69-1.57 (m, 2H, CH₂), 0.89 (t, J = 7.5 Hz, 3H, CH₃). ¹³C-NMR (CDCl₃) δ 163.1, 159.0, 158.0, 155.5, 153.5, 153.3 (C-3, C-6, C-8, C-10a, C-11a, C-4'), 136.2, 128.6, 126.5 (C-1', C-4a, C-6a), 130.7, 120.7 (C-4, C-7), 130.5 (C-2', C-6'), 113.7 (C-3', C-5'), 55.2 (OCH₃), 51.0, 50.8 (benzyl-CH₂, N-CH₂), 20.8 (CH₂), 11.0 (CH₃). EI MS (70 eV): m/z = 444 [M⁺]. Anal. Calcd for C₂₀H₁₈N₆O₂Cl₂: C, 53.94; H, 4.07; N, 18.87. Found: C, 54.17; H, 3.92; N, 18.88.

X-Ray Structure Determination of 7a

Crystal data: C₂₀H₁₈N₆O₂Cl₂, *M_r* = 445.30, monoclinic, space group *P*2₁/n (No. 14), *a* = 15.390 (4) Å, *b* = 16.906 (4) Å, *c* = 16.552 (4) Å, α = 90°, β = 99.97 (2)°, γ = 90°, *V* = 4241.5 (18) Å³, *Z* = 8, *D_x* = 1.395 Mg m⁻³, λ = 0.71073 Å, μ = 0.336 mm⁻¹, *T* = 299 K. X-Ray data collection with a Siemens Smart CCD area detector 3-circle diffractometer (sealed X-Ray tube, Mo Kα radiation, λ = 0.71073 Å, graphite monochromator, 0.3° ω-scan frames covering the complete reciprocal space with θ ≤ 25°, 45259 reflections collected, 7446 reflections independent, data corrections included absorption). The structure was solved with direct methods and was refined on *F*² with program SHELXL97.¹⁵ Hydrogen atoms were inserted in calculated positions and were refined riding at their carrier atoms. The final refinement with 7446 reflections and 546 varied parameters converged at *R*1 = Σ||*F*_o| - |*F*_c||/Σ|*F*_o| = 0.058, *wR*2 = [Σ(*w*(*F*_o² - *F*_c²)²)/Σ(*w*(*F*_o²)²)]^{1/2} = 0.115 for all data; and at *R*1 = 0.0425 for the 5858 data with *F* ≥ 4σ(*F*). Excursions in final difference Fourier map between -0.31 and 0.47 e Å⁻³.¹⁶

The crystal structure of **7a** is remarkable by containing two crystallographically independent molecules in the unit cell. The two molecules (Table 3) are very similar in bond lengths, bond angles, and conformation and show stereochemically only minor, but crystallographically significant differences in the orientations of the 4-

methoxybenzyl and propyl groups relative to the dipyridazinodiazepine moieties. Therefore, only molecule 1 is shown in Fig. 3. The background for this similarity of two crystallographically independent molecules in **7a** is that both are packed in separate molecular chains extending along the 2_1 screw axes, *i.e.* parallel to *b*. Thus, molecule 1 forms chains along $x=\frac{1}{4}$, $y, z=\frac{3}{4}$ and $x=\frac{3}{4}$, $y, z=\frac{1}{4}$, whereas molecule 2 forms chains along $x=\frac{1}{4}$, $y, z=\frac{1}{4}$ and $x=\frac{3}{4}$, $y, z=\frac{3}{4}$. Both chains are in their internal structure practically identical but the orientations they mutually adopt upon stacking are different and lead to the observed moderate conformation differences without giving rise to a pronounced lattice pseudosymmetry.

Table 3. Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the non-hydrogen atoms of $\text{C}_{20}\text{H}_{18}\text{N}_6\text{O}_2\text{Cl}_2$ (**7a**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
molecule 1				
Cl(1)	0.01268(4)	0.24120(5)	0.55674(4)	80(1)
Cl(2)	0.40090(7)	0.69482(5)	0.66217(7)	107(1)
O(1)	0.13897(11)	0.40325(10)	0.82804(10)	65(1)
O(2)	0.39977(15)	0.01650(11)	0.86400(12)	86(1)
N(1)	0.18207(13)	0.24718(12)	0.59102(12)	62(1)
N(2)	0.26113(12)	0.27606(12)	0.62683(12)	60(1)
N(3)	0.43274(16)	0.54560(14)	0.65030(15)	78(1)
N(4)	0.41867(14)	0.46740(13)	0.66150(13)	68(1)
N(5)	0.34942(11)	0.36229(11)	0.71446(12)	54(1)
N(6)	0.25589(11)	0.47292(11)	0.80057(11)	53(1)
C(1)	0.26448(13)	0.33373(13)	0.68174(13)	49(1)
C(2)	0.18985(13)	0.36389(12)	0.70929(12)	46(1)
C(3)	0.10967(14)	0.33454(13)	0.67188(13)	51(1)
C(4)	0.11065(14)	0.27812(14)	0.61109(13)	55(1)
C(5)	0.35969(14)	0.44447(13)	0.70569(14)	53(1)
C(6)	0.30997(14)	0.49772(13)	0.74458(13)	52(1)
C(7)	0.32317(16)	0.57662(14)	0.73129(16)	64(1)
C(8)	0.38404(18)	0.59633(16)	0.68267(17)	71(1)
C(9)	0.19301(14)	0.41519(13)	0.78388(13)	50(1)
C(10)	0.42456(14)	0.31060(14)	0.70602(16)	62(1)
C(11)	0.41641(13)	0.23310(14)	0.74935(15)	56(1)
C(12)	0.39397(17)	0.23051(15)	0.82632(16)	69(1)
C(13)	0.38705(18)	0.16025(16)	0.86692(16)	72(1)
C(14)	0.40401(16)	0.08980(15)	0.83001(15)	62(1)
C(15)	0.42628(14)	0.09121(14)	0.75294(16)	60(1)
C(16)	0.43224(14)	0.16180(14)	0.71313(15)	59(1)
C(17)	0.3749(3)	0.0122(2)	0.94236(19)	108(1)
C(18)	0.26140(16)	0.51898(16)	0.87815(14)	65(1)
C(19)	0.35471(18)	0.52102(17)	0.92739(16)	74(1)
C(20)	0.3934(2)	0.44102(19)	0.9494(2)	90(1)
molecule 2				
Cl(1')	0.18021(6)	0.33317(5)	-0.00180(4)	82(1)
Cl(2')	0.09593(5)	-0.12823(4)	0.30767(6)	87(1)
O(1')	0.40509(11)	0.15892(12)	0.20597(14)	85(1)
O(2')	0.30949(12)	0.55531(11)	0.41871(13)	82(1)
N(1')	0.13900(14)	0.32036(12)	0.14190(12)	64(1)
N(2')	0.14255(12)	0.28867(12)	0.21707(11)	60(1)
N(3')	0.07991(13)	0.01979(14)	0.33934(14)	70(1)
N(4')	0.10353(12)	0.09696(13)	0.34142(12)	64(1)
N(5')	0.19786(11)	0.20018(11)	0.32094(10)	51(1)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
N(6')	0.32240(11)	0.08756(11)	0.27957(12)	55(1)
C(1')	0.19888(13)	0.23080(12)	0.24202(12)	48(1)
C(2')	0.25893(13)	0.20082(12)	0.19477(13)	49(1)
C(3')	0.25378(15)	0.23234(13)	0.11798(14)	57(1)
C(4')	0.19136(16)	0.29095(14)	0.09488(14)	59(1)
C(5')	0.17858(13)	0.11850(13)	0.31920(12)	51(1)
C(6')	0.23814(13)	0.06391(13)	0.29450(13)	50(1)
C(7')	0.21310(15)	-0.01384(14)	0.29133(14)	59(1)
C(8')	0.13287(15)	-0.03139(15)	0.31345(15)	63(1)
C(9')	0.33414(14)	0.14715(14)	0.22738(15)	57(1)
C(10')	0.15677(16)	0.24964(15)	0.37800(14)	61(1)
C(11')	0.20077(15)	0.32912(15)	0.39036(13)	58(1)
C(12')	0.29146(17)	0.33840(17)	0.41182(18)	77(1)
C(13')	0.33087(17)	0.41208(17)	0.42222(19)	80(1)
C(14')	0.27880(16)	0.47932(15)	0.41148(15)	63(1)
C(15')	0.18813(16)	0.47124(16)	0.39020(15)	66(1)
C(16')	0.15055(16)	0.39731(16)	0.37952(15)	64(1)
C(17')	0.40200(19)	0.56793(19)	0.4322(2)	92(1)
C(18')	0.40016(15)	0.03956(16)	0.31640(17)	72(1)
C(19')	0.4244(4)	0.0500(4)	0.4021(3)	222(4)
C(20')	0.4127(4)	0.1058(4)	0.4532(3)	201(3)

3,8-Dichloro-5,11-dihydro-5-(4-methoxybenzyl)-11-propyldipyridazino[3,4-b:3',4'-e][1,4]diazepin-10-one (7b)

Colourless crystals, mp 237–242 °C. IR 1669 cm⁻¹. ¹H-NMR (DMSO-d₆) δ 8.07 (s, 1H), 8.03 (s, 1H) (H-4, H-9), 7.36 (d, *J* = 8.8 Hz, 2H, H-2', H-6'), 6.83 (d, *J* = 8.8 Hz, 2H, H-3', H-5'), 5.24 (s, 2H, benzyl-CH₂), 4.26 (t, *J* = 7.0 Hz, 2H, N-CH₂), 3.68 (s, 3H, OCH₃), 1.63–1.52 (m, 2H, CH₂), 0.83 (t, *J* = 7.4 Hz, 3H, CH₃). ¹H-NMR (CDCl₃) δ 7.88 (s, 1H), 7.23 (s, 1H) (H-4, H-9), 7.30–7.25 (m, 2H, H-2', H-6'), 6.83–6.79 (m, 2H, H-3', H-5'), 5.21 (s, 2H, benzyl-CH₂), 4.44–4.37 (m, 2H, N-CH₂), 3.77 (s, 3H, OCH₃), 1.78–1.66 (m, 2H, CH₂), 0.95 (t, *J* = 7.4 Hz, 3H, CH₃). ¹³C-NMR (CDCl₃) δ 162.7, 159.6, 157.6, 154.4, 153.6, 152.0 (C-3, C-4a, C-5a, C-8, C-10, C-4'), 143.8, 127.3, 126.0 (C-9a, C-11a, C-1'), 131.3, 119.7 (C-4, C-9), 129.7 (C-2', C-6'), 114.4 (C-3', C-5'), 55.3 (OCH₃), 51.4, 50.4 (benzyl-CH₂, N-CH₂), 21.3 (CH₂), 11.3 (CH₃). EI MS (70 eV): *m/z* = 444 [M⁺]. *Anal.* Calcd for C₂₀H₁₈N₆O₂Cl₂: C, 53.94; H, 4.07; N, 18.87. Found: C, 54.31; H, 4.04; N, 18.88.

X-Ray Structure Determination of 7b

Crystal data: C₂₀H₁₈N₆O₂Cl₂, *M_r* = 445.30, triclinic, space group P $\bar{1}$ (No. 2), *a* = 9.279 (2) Å, *b* = 9.809 (2) Å, *c* = 11.764 (4) Å, α = 90.66°, β = 109.49 (1)°, γ = 95.03°, *V* = 1004.5 (5) Å³, *Z* = 2, *D_x* = 1.472 Mg m⁻³, λ = 0.71073 Å, μ = 0.354 mm⁻¹, *T* = 299 K. X-Ray data collection with a Siemens Smart CCD area detector 3-circle diffractometer (Mo *K*α radiation, 0.3° ω-scan frames covering the reciprocal space with θ ≤ 25°, 10925 reflections collected, 3516 reflections independent, data corrections included absorption). The structure was solved with direct methods and was refined on *F*² with program SHELXL97. Hydrogen atoms were inserted in calculated positions and were refined riding at their carrier atoms. The final refinement with 3516

reflections and 287 varied parameters converged at $R1 = 0.0706$, $wR2 = 0.114$ for all data, and at $R1 = 0.0418$ for the 2427 data with $F \geq 4\sigma(F)$. Excursions in final difference Fourier map between -0.34 and $0.31 \text{ e } \text{\AA}^{-3}$. The molecular structure is shown in Fig. 4. All bond lengths and bond angles are in good agreement with expected values. The geometry and conformation of the dipyrizidinodiazepinone moiety is similar to **7a** (Fig. 3), except the orientation of the 4-methoxybenzyl residue which is here *cisoid* to the propyl group (Fig. 4). In the crystal lattice the stacking of the molecules of **7b** is layerlike and differs distinctly from the molecular chains in **7a**.

Table 4. Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the non-hydrogen atoms of $\text{C}_{20}\text{H}_{18}\text{N}_6\text{O}_2\text{Cl}_2$ (**7b**).

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
Cl(1)	0.49781(9)	0.81482(7)	0.50021(7)	71(1)
Cl(2)	-0.38934(7)	0.33846(9)	-0.05852(7)	78(1)
N(1)	0.2762(2)	0.6275(2)	0.4817(2)	51(1)
N(2)	0.1852(2)	0.5116(2)	0.4363(2)	47(1)
N(3)	-0.1164(2)	0.3426(2)	-0.0672(2)	52(1)
N(4)	0.0361(2)	0.3369(2)	-0.0201(2)	49(1)
N(5)	0.1036(2)	0.3201(2)	0.3052(2)	40(1)
N(6)	0.2620(2)	0.3064(2)	0.1309(2)	46(1)
O(1)	0.5108(2)	0.3710(2)	0.2395(2)	60(1)
O(2)	-0.2656(2)	-0.2734(2)	0.2780(2)	58(1)
C(1)	0.2089(2)	0.4370(2)	0.3501(2)	39(1)
C(2)	0.3308(2)	0.4689(2)	0.3065(2)	40(1)
C(3)	0.4247(3)	0.5860(2)	0.3549(2)	46(1)
C(4)	0.3884(3)	0.6621(2)	0.4399(2)	48(1)
C(5)	0.1040(2)	0.3255(2)	0.0973(2)	39(1)
C(6)	0.0242(2)	0.3233(2)	0.1806(2)	36(1)
C(7)	-0.1321(2)	0.3221(2)	0.1316(2)	41(1)
C(8)	-0.1942(3)	0.3332(2)	0.0078(2)	47(1)
C(9)	0.3749(3)	0.3777(2)	0.2233(2)	44(1)
C(10)	0.0154(3)	0.2697(2)	0.3839(2)	45(1)
C(11)	-0.0572(2)	0.1254(2)	0.3495(2)	39(1)
C(12)	0.0292(3)	0.0189(2)	0.3461(2)	51(1)
C(13)	-0.0350(3)	-0.1156(2)	0.3211(2)	50(1)
C(14)	-0.1894(2)	-0.1446(2)	0.3006(2)	41(1)
C(15)	-0.2772(3)	-0.0396(2)	0.3050(2)	51(1)
C(16)	-0.2121(3)	0.0932(2)	0.3286(2)	49(1)
C(17)	-0.1818(3)	-0.3852(2)	0.2718(2)	58(1)
C(18a) [#]	0.3089(3)	0.2164(3)	0.0498(3)	63(1)
C(19a) [#]	0.2368(8)	0.0671(5)	0.0432(6)	78(2)
C(20a) [#]	0.2843(13)	0.0038(12)	0.1676(9)	119(3)
C(18b) [#]	0.3089(3)	0.2164(3)	0.0498(3)	63(1)
C(19b) [#]	0.3534(16)	0.0935(10)	0.0978(11)	89(4)
C(20b) [#]	0.2188(19)	0.0070(3)	0.1190(3)	119(3)

[#] Propyl group disordered over two alternative orientations, 'a' and 'b', with refined site occupancies of 0.65(1) for 'a'-sites and 0.35(1) for 'b'-sites.

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10. This failure may be explained by the insufficient nucleophilicity of the amino function in compound (2).
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12. Separation of **6** from **5** requires tedious chromatography. By performing the reaction at 40 °C in dichloromethane solution we, however, succeeded in suppressing the formation of **6**.
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