PYRIDAZINES, 81.[1] A NOVEL 1,2-DIAZINE CONTAINING TRI-CYCLIC SYSTEM: SYNTHESIS OF PYRIDAZINO[3,4-b][1,5]-BENZODIAZEPIN-5-ONES AS POTENTIAL HIV-1 REVERSE TRANSCRIPTASE INHIBITORS

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Abstract - Ring closure reactions of 3-alkylamino-6-chloro-N-phenylpyridazine-4-carboxamides (**7, 10, 13**) bearing a halogen function in ortho position of the carbocyclic moiety were shown to provide convenient access to the pyridazino[3,4-b][1,5]benzodiazepin-5-one system.

INTRODUCTION

Tricyclic systems like dibenzoxazepines, dibenzodiazepines and analogous mono- and dipyrido derivatives represent essential subunits of a wide variety of bioactive compounds.[2] The most interesting therapeutic agents out of this series are nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e]-[1,4]diazepin-6-one) and congeners which have been shown to inhibit HIV-1 reverse transcriptase by allosteric interaction.[3] This enzyme is indispensable for virus replication. Despite numerous efforts to modify the tricyclic core of these anti-AIDS agents,[4] so far no attempts have been made to improve the pharmacological and pharmacokinetic properties by investigating derivatives of the hitherto not accessible isosteric pyridazino[3,4-b][1,5]benzodiazepin-5-one system.

Whereas we succeeded recently in the synthesis of the pyridazino[3,4-b][1,5]benzoxazepin-5(6H)-one system (**3**) by reacting 3,6-dichloro-N-(2-hydroxyphenyl)-pyridazine-4-carboxamide (**1**) with sodium hydride in 1,4-dioxane solution,[5] treatment of the corresponding o-phenylenediamine derived amide (**2**) under analogous conditions surprisingly did not afford the desired pyridazino[3,4-b][1,5]benzodiazepin-5-one system (**4**).[6] Instead a novel type of a 1,2-diazine → 1,2-diazole ring transformation has been found to

take place.[6] This unexpected reaction behavior of **2** had to be explained in terms of initial nucleophilic attack of the aniline nitrogen atom in compound (**2**) at C-4 of the highly π-electron deficient heteroarene.[6] Thus, we envisaged an alternative synthetic strategy for the preparation of our target tricyclic system characterised by the employment of precursors in which the nucleophilic function now is attached to the pyridazine system. Here we report on the synthesis of such precursors and on attempts to achieve ring closure.
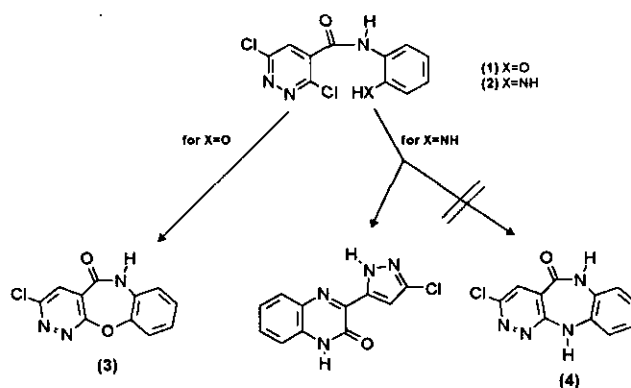
Scheme 1

RESULTS AND DISCUSSION

Based on the reports of Ried and Eichhorn[7] that in 3,6-dichloropyridazine-4-carboxylic acid derivatives the chloro substituent in position 3 can be regioselectively replaced by amino substituents, we were able to prepare the 3-alkylamino derivative (**7**) by reacting 3,6-dichloropyridazine-4-carboxylic acid chloride (**5**)[7] with 2-fluoroaniline and subsequent treatment with n-propylamine.[8] Attempts to convert **7**, an educt now bearing the leaving group in the carbocyclic aromatic system, into the desired tricyclic system by reaction with sodium hydride in dry 1,4-dioxane, however, failed. Even after refluxing the reaction mixture for seven days only unchanged starting material was recovered.
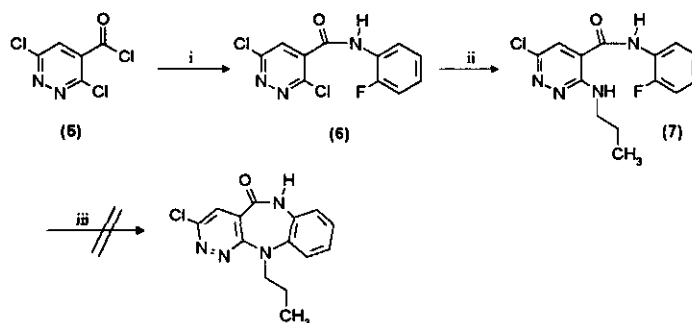

Scheme 2   i) 2-fluoroaniline, triethylamine, CH_2Cl_2; ii) n-$C_3H_7NH_2$, 1,4-dioxane, rt; iii) NaH, 1,4-dioxane, reflux

Assuming that the insufficient reactivity of the fluorine atom in compound (7) is caused by deprotonation of the carboxamide NH thus leading to increased electron density we envisaged an *N*-alkyl derivative like 10 as suitable precursor for the desired tricyclic system. Indeed, treatment of 10 with sodium hydride in 1,4-dioxane afforded smoothly the 3-chloro-6,11-dihydro-6-methyl-11-propyl-5*H*-pyridazino[3,4-*b*][1,5]-benzodiazepin-5-one (11). Compound (10) was conveniently obtained by *N*-alkylation of 6 and subsequent replacement of the 3-chloro substituent by a n-propylamino group.

In order to find access also to *N*(6)-unsubstituted pyridazino[3,4-*b*][1,5]benzodiazepin-5-ones we investigated ring closure reactions of the carboxamide (13). Here, we anticipated that the presence of the electron withdrawing nitro substituent would compensate the electron donating properties of the anion resulting from deprotonation. By refluxing 13 (easily obtained by acylation[9] of 2-chloro-5-nitroaniline[10] with 3,6-dichloropyridazine-4-carboxylic acid chloride (5) and treatment of the resulting 8 with n-propylamine) in dry 1,4-dioxane in the presence of sodium hydride we succeeded the preparation of 3-chloro-6,11-dihydro-8-nitro-11-propyl-5*H*-pyridazino[3,4-*b*][1,5]benzodiazepin-5-one (14) in 58% yield.

As examplified by the transformation of 11 into 12, also pyridazino[3,4-*b*][1,5]benzodiazepin-5-ones without substituents in the aromatic rings are smoothly accessible by reductive dehalogenation.
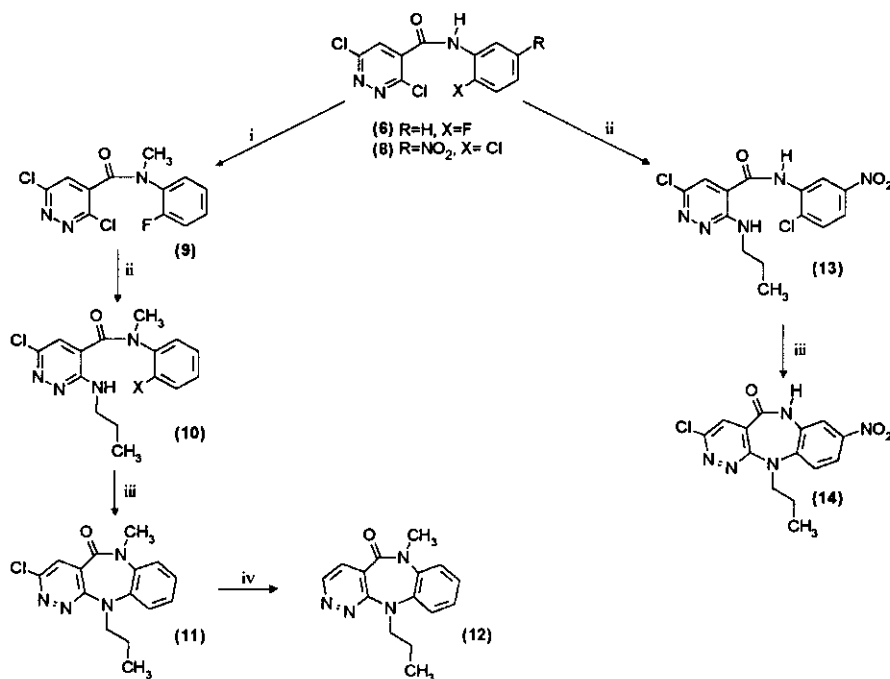
Scheme 3   i) KOH, DMSO, CH₃I, rt; ii) n-C₃H₇NH₂, 1,4-dioxane, rt; iii) NaH, 1,4-dioxane, reflux;
iv) HCOONH₄, Pd-C, methanol, 48°C

All newly prepared compounds were fully characterised by elemental analysis, IR and NMR data which, together with the single crystal X-ray analysis of compound (14) (see Figure 1), provide an unequivocal proof for the pyridazino[3,4-*b*][1,5]benzodiazepin-5-one structure.
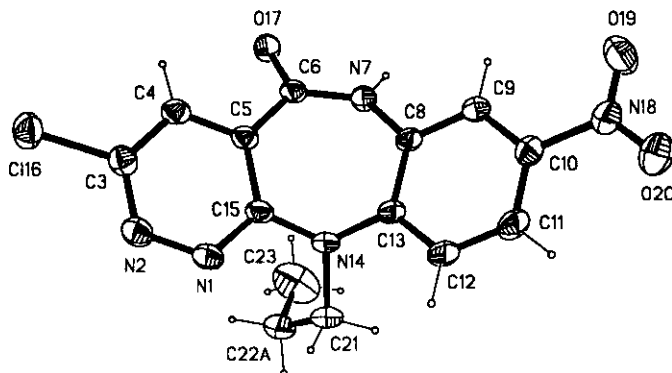

Figure 1   ORTEP-plot (30%-ellipsoids) of $C_{14}H_{12}N_5O_3Cl$ (14) with crystallographic atom numbering scheme. Selected bond
lengths (Å) and bond angles (°): N(1)-N(2) 1.341(3), N(1)-C(15) 1.328(3), N(2)-C(3) 1.314(2), C(3)-Cl(16)
1.730(2), C(5)-C(6) 1.491(3), C(6)-O(17) 1.233(2), C(6)-N(7) 1.338(2), N(7)-C(8) 1.414(2), 1.395(3), C(13)-N(14)
1.413(3), N(14)-C(15) 1.389(2), N(14)-C(21) 1.483(2), C(10)-N(18) 1.456(3), N(18)-O(19) 1.211(3), N(18)-O(20)
1.214(3), C(21)-C(22a) 1.561(5), C(22a)-C(23) 1.429(7), mean aromatic C-C 1.385(3); C(5)-C(6)-N(7) 120.7(2),
C(6)-N(7)-C(8) 129.9(2), C(13)-N(14)-C(15) 118.3(2).

In conclusion, 3-amino-*N*-phenylpyridazine-4-carboxamide derivatives with an activated leaving group in ortho position of the carbocyclic moiety were found to represent suitable precursors for so far not accessible pyridazino[3,4-*b*][1,5]benzodiazepin-5-ones.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were taken on a Mattson Galaxy Series FT-IR 3000 spectrophotometer (KBr pellets). ^{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 and δ 39.5 ppm for [13]C (DMSO-d_6) or with δ 7.26 ppm for ^{1}H and δ 77.0 ppm for [13]C (CDCl$_3$). 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 (0.040-0.063 mm, Merck). Microanalyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna, Austria. Light petroleum refers to the fraction of bp 40-60°C. The yields are not optimised.

Starting materials: 3,6-dichloropyridazine-4-carboxylic acid chloride (5) was available from 3,6-dichloro-4-methylpyridazine[11] by oxidation with $K_2Cr_2O_7$ in H_2SO_4 [12] and subsequent treatment with SOCl$_2$. [7]

Procedures for the Acylation Reactions:

3,6-Dichloro-N-(2-fluorophenyl)pyridazine-4-carboxamide (6)

To an ice-cooled solution of 2-fluoroaniline (8.34 g, 75.00 mmol) and triethylamine (7.60 g, 75.00 mmol) in dry dichloromethane (50 mL) was added dropwise a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (10.60 g, 50.00 mmol) in dry dichloromethane (50 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 4 h, then the crystals which had separated were filtered off, washed with dichloromethane and dried. The dichloromethane phase was washed with $1N$ HCl and extracted three times with $2N$ NaOH. The aqueous solution was washed with dichloromethane and then acidified with *conc.* HCl. The crystals which had separated were collected, washed with water, and subsequently with light petroleum. An analytically pure sample was obtained upon recrystallisation from ethyl acetate.

Yield: 10.35 g (72%) of a light grey powder, mp 187-190 °C. IR 3244-3018, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 10.73 (s, 1 H, NH), 8.40 (s, 1 H, pyridazine H-5), 8.05-7.99 (m, 1 H), 7.35-7.23 (m, 3 H) (phenyl H-3, H-4, H-5, H-6). Anal. Calcd for $C_{11}H_6N_3OCl_2F$: C, 46.18; H, 2.11; N, 14.69. Found: C, 45.96; H, 2.17; N, 14.56.

3,6-Dichloro-N-(2-chloro-5-nitrophenyl)pyridazine-4-carboxamide (8)

To a suspension of 2-chloro-5-nitroaniline (6.40 g, 37.08 mmol) in dry dichloromethane (100 mL) was added at 40 °C dropwise a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (5) (6.50 g, 30.74 mmol) in dry dichloromethane (50 mL) under a nitrogen atmosphere and the mixture was refluxed for 1 h. After dropwise addition of a solution of triethylamine (3.10 g, 30.74 mmol) in dry dichloromethane (10 mL), the mixture was stirred at room temperature for 24 h. The crystals which had separated were filtered off and washed with dichloromethane. To remove the excess 2-chloro-5-nitroaniline the filtrate was extracted three times with $2N$ NaOH and the aqueous extract was washed with ethyl acetate and acidified with $4N$ HCl to pH 1. The resulting crystals were filtered off, washed with water and subsequently with light petroleum. The product thus obtained was used without further purification in the following reaction step. Analytically pure material was obtained by recrystallisation from ethyl acetate.

Yield: 7.59 g (71%) of a colourless powder, mp 161-171°C. IR 3257, 1671 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 10.93 (s, 1 H, NH), 8.82 (d, J_{4-6} = 2.7 Hz, 1 H, phenyl H-6), 8.45 (s, 1 H, pyridazine H-5), 8.13 (dd, J_{3-4} = 8.9 Hz, J_{4-6} = 2.7 Hz, 1 H, phenyl H-4), 7.87 (d, J_{3-4} = 8.9 Hz, 1 H, phenyl H-3). Anal. Calcd for $C_{11}H_5N_4O_3Cl_3$: C, 38.02; H, 1.45; N, 16.12. Found: C, 37.91; H, 1.34; N, 15.91.

Procedure for N-Alkylation

3,6-Dichloro-N-(2-fluorophenyl)-N-methylpyridazine-4-carboxamide (9)

A mixture of **6** (572 mg, 2 mmol) and 4 mmol of powdered potassium hydroxide (224 mg) in dry dimethyl sulfoxide (15 mL) was stirred for 1 h under a nitrogen atmosphere, methyl iodide (710 mg, 5 mmol) was added and stirring continued until the starting material was completely consumed (TLC monitoring, ether, *ca.* 30 min.). Then the reaction mixture was poured into cold $0.5N$ HCl (100 mL). The separated crystals were filtered off,

washed with water and light petroleum. The filtrate was extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulphate and evaporated. The product was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) followed by recrystallisation from diisopropyl ether.

Yield: 510 mg (85%) of colourless crystals, mp 120°C. IR 1657 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 8.40, 8.20 (s, 1 H, pyridazine H-5, 2 rotamers), 7.58-7.13 (m, 4 H, phenyl-H), 3.37, 3.19 (s, 3 H, N-CH$_3$, 2 rotamers). Anal. Calcd for C$_{12}$H$_8$N$_3$OCl$_2$F: C, 48.03; H, 2.69; N, 14.00. Found: C, 48.21; H, 2.66; N, 14.07.

General Procedure for the Preparation of 6-Chloro-N-(2-fluorophenyl)-3-propyl-aminopyridazine-4-carboxamides (7, 10) and 6-Chloro-N-(2-chloro-5-nitrophenyl)-3-propylaminopyridazine-4-carboxamide (13)

To a stirred solution or suspension of 0.5-4.0 mmol of the appropriate 3,6-dichloro-N-(2-fluorophenyl)-pyridazine-4-carboxamide (6) or (9), or 3,6-dichloro-N-(2-chloro-5-nitrophenyl)-pyridazine-4-carboxamide (8) in dry 1,4-dioxane (6 mL/mmol) was added slowly n-propylamine (17-100 mmol) at room temperature under nitrogen. The reaction mixture was stirred until TLC indicated no further conversion (reaction times varied between 12 and 24 h). Then the mixture was poured into 0.5N HCl (ca. 100 mL/mmol). The crystals which had separated were filtered off, washed with water and light petroleum, and dried. The filtrate was extracted with dichloromethane and the organic layer was washed with water and brine, dried over sodium sulphate, and evaporated. The residues thus obtained were purified by column chromatography (dichloromethane/ethyl acetate, 9:1), and the combined solids were recrystallised from diisopropyl ether.

6-Chloro-N-(2-fluorophenyl)-3-propylaminopyridazine-4-carboxamide (7)

Yield: 92% of light yellow crystals, mp 111-113 °C. IR 3358, 3205, 1684/1657 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 10.59 (s, 1 H, NH), 7.90 (s, 1 H, pyridazine H-5), 7.67-7.56 (m, 2 H, NH, phenyl-H), 7.36-7.19 (m, 3 H, phenyl H), 3.48-3.24 (m, 2 H, N-CH$_2$), 1.69-1.51 (m, 2 H, CH$_2$), 0.90 (t, J = 7.4 Hz, 3 H, CH$_3$). Anal. Calcd for C$_{14}$H$_{14}$N$_4$OClF: C, 54.46; H, 4.57; N, 18.15. Found: C, 54.41; H, 4.73; N, 18.01.

6-Chloro-N-(2-fluorophenyl)-N-methyl-3-propylaminopyridazine-4-carboxamide (10)

Yield: 85% of light yellow crystals, mp 79-81 °C. IR 3385, 1659 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 7.35-7.05 (m, 4 H, phenyl-H), 6.61 (s, 1 H, pyridazine H-5), 5.89 (br s, 1 H, NH), 3.57-3.48 (m, 2 H, N-CH$_2$), 3.42 (s, 3 H, N-CH$_3$), 1.80-1.60 (m, 2 H, CH$_2$), 1.01 (t, J = 7.4 Hz, 3 H, CH$_3$). Anal. Calcd for C$_{15}$H$_{16}$N$_4$OClF: C, 55.82; H, 5.00; N, 17.36. Found: C, 55.71; H, 4.87; N, 17.38.

6-Chloro-N-(2-chloro-5-nitrophenyl)-3-propylaminopyridazine-4-carboxamide (13)

Yield: 91% of yellow crystals, mp 165-167 °C. IR 3403, 3295, 1649 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 10.82 (s, 1 H, NH), 8.61 (d, J$_{4-6}$= 2.8 Hz, 1 H, phenyl H-6), 8.14 (dd, J$_{3-4}$ = 8.9 Hz, J$_{4-6}$ = 2.8 Hz, 1 H, phenyl H-4), 7.89 (s, 1H, pyridazine H-5), 7.87 (d, J$_{3-4}$ = 8.9 Hz, 1 H, phenyl H-3), 7.58 (t, J = 5.3 Hz, 1 H, NH), 3.49-3.40 (m, 2

H, N-CH$_2$), 1.70-1.52 (m, 2 H, CH$_2$), 0.91 (t, J = 7.4 Hz, 3 H, CH$_3$). Anal. Calcd for C$_{14}$H$_{13}$N$_5$O$_3$Cl$_2$: C, 45.42; H, 3.54; N, 18.92. Found: C, 45.38; H, 3.32; N, 18.72.

General Procedure for the Cyclisation

Sodium hydride (600 mg of a 60% dispersion in oil, 15.0 mmol) was added at room temperature to a suspension of **10** or **13** (1 mmol) in dry 1,4-dioxane (30 mL) under an atmosphere of nitrogen, and the mixture was refluxed. The reaction was monitored by TLC (ether, reaction times varied between 1 h and 7 days). After cooling to room temperature, the solution was poured under a nitrogen atmosphere into cold 0.5N HCl (100 mL), the resulting crystals were collected, washed with water and subsequently with light petroleum, and dried *in vacuo*. The products were purified by column chromatography [dichloromethane/ethyl acetate, 9:1 (**11**) or ether (**14**)], followed by recrystallisation from diisopropyl ether.

3-Chloro-6,11-dihydro-6-methyl-11-propyl-5H-pyridazino[3,4-b][1,5]benzodiazepin-5-one (11)

Yield: 60% (reaction time: 1 h) of light yellow crystals, mp 146-148 °C. IR 1649 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ 7.75 (s, 1 H, H-4), 7.29-7.22 (m, 4 H, H-7, H-8, H-9, H-10), 4.45-4.31, 3.81-3.68 (m, 2 H, N-CH$_2$), 3.57 (s, 3 H, N-CH$_3$), 1.79-1.62 (m, 2 H, CH$_2$), 0.93 (t, J = 7.4 Hz, 3 H, CH$_3$). ^{13}C NMR (CDCl$_3$) δ 164.9, 161.4 (C-5, C-11a), 152.2 (C-3), 142.6 (C-10a), 136.6 (C-6a), 130.5 (C-4), 128.0 (C-4a), 126.8, 125.8, 123.3, 122.3 (C-7, C-8, C-9, C-10), 50.0 (N-CH$_2$), 37.5 (N-CH$_3$), 20.5 (CH$_2$), 11.3 (CH$_3$). Anal. Calcd for C$_{15}$H$_{15}$N$_4$OCl: C, 59.51; H, 4.99; N, 18.51. Found: C, 59.68; H, 4.96; N, 18.33.

3-Chloro-6,11-dihydro-8-nitro-11-propyl-5H-pyridazino[3,4-b][1,5]benzodiazepin-5-one (14)

Yield: 58% (reaction time: 7 days) of dark yellow crystals, mp 248-253 °C. IR 2972, 2922, 1672 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ 8.57 (s, 1 H, NH), 8.12 (dd, J$_{9-10}$ = 8.9 Hz, J$_{7-9}$ = 2.6 Hz, 1 H, H-9), 7.98 (d, J$_{7-9}$ = 2.6 Hz, 1 H, H-7), 7.88 (s, 1 H, H-4), 7.41 (d, J$_{9-10}$ = 8.9 Hz, 1 H, H-10), 4.20-4.13 (m, 2 H, N-CH$_2$), 1.77-1.62 (m, 2 H, CH$_2$), 0.96 (t, J = 7.4 Hz, 3 H, CH$_3$). ^{13}C NMR (DMSO-d$_6$) δ 163.7, 159.6 (C-5, C-11a), 152.1 (C-3), 145.1 (C-10a), 143.9 (C-8), 132.7 (C-6a), 130.5 (C-4), 127.7, 123.3, 120.4, 117.2 (C-4a, C-7, C-9, C-10), 50.5 (N-CH$_2$), 19.8 (CH$_2$), 10.9 (CH$_3$). Anal. Calcd for C$_{14}$H$_{12}$N$_5$O$_3$Cl: C, 50.39; H, 3.62; N, 20.98. Found: C, 50.16; H, 3.37; N, 20.69.

X-ray Structure Determination of 14

Crystal data: C$_{14}$H$_{12}$N$_5$O$_3$Cl, M_r = 333.74, triclinic, space group P-1 (No. 2), a = 7.921 (2) Å, b = 10.040 (2) Å, c = 10.634 (2) Å, α = 94.65 (1)°, β = 110.97 (1)°, γ = 105.36 (1)°, V = 746.8(3) Å^3, Z = 2, D_x = 1.484 g cm^{-3}, λ = 0.71069 Å, μ = 0.28 mm^{-1}, T = 295K. Cell dimensions were determined from ±θ-scans of 39 reflections (θ = 15 - 20°). The intensities of 2635 independent reflections with θ < 25°, -9 ≤ h ≤ 8, -11 ≤ k ≤ 11, 0 ≤ l ≤ 12, were measured by θ-2θ scans. Three standard reflections showed negligible intensitiy variations (±1.2%). The data were corrected for LP and system instability, but not for absorption.

The structure was solved by direct methods (program *SHELX76*) and was refined by full-matrix least-squares on F^2 (program *SHELXL93*)[12]. Anisotropic temperature factors for non-hydrogen atoms and a correction for extinction were applied. The n-propyl residue showed an orientation disorder for its intermediate carbon atom which was splitted in two separate sites, C(22a) and C(22b) with refined site occupancies of 0.625(5) and 0.375(5), respectively, and a site separation of 1.43(1) Å. The terminal carbon atoms of this group, C(21) and C(23), displayed only single Fourier peaks. Hydrogen atoms were inserted in idealised positions and were refined riding with the atoms to which they were bonded. The final full-matrix least-squares refinement varied 220 parameters and used all 2635 reflections weighted by $w = 1/[\sigma^2(F_o^2) + (0.046P)^2 + 0.22P]$ where $P = (F_o^2 + 2F_c^2)/3$. Final $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.050$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.099$ and $S = 1.04$ for all data; $R1 = 0.037$ for the 2116 refections with $F_o^2 \geq 2\sigma(F_o^2)$. The final difference Fourier map showed minimum and maximum values of -0.18 and 0.22 eÅ^{-3}.[13]

Table 1. Atomic coordinates and equivalent thermal displacement parameters of non-hydrogen atoms for $C_{14}H_{12}N_5O_3Cl$ (14). $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*a_ia_j$.

	x/a	y/b	z/c	Ueq [Å²]
N(1)	0.7343(3)	0.0827(2)	0.7508(2)	0.0559(8)
N(2)	0.9162(3)	0.1054(2)	0.8347(2)	0.0585(8)
C(3)	0.9987(3)	0.2130(2)	0.9383(2)	0.0465(8)
C(4)	0.9073(3)	0.3032(2)	0.9700(2)	0.0422(8)
C(5)	0.7225(3)	0.2810(2)	0.8856(2)	0.0382(7)
C(6)	0.6164(3)	0.3658(2)	0.9281(2)	0.0399(7)
N(7)	0.4672(2)	0.3896(2)	0.8347(1)	0.0429(7)
C(8)	0.3987(3)	0.3613(2)	0.6897(2)	0.0389(7)
C(9)	0.3296(3)	0.4591(2)	0.6220(2)	0.0444(8)
C(10)	0.2515(3)	0.4327(2)	0.4800(2)	0.0472(8)
C(11)	0.2428(3)	0.3113(2)	0.4046(2)	0.0562(9)
C(12)	0.3108(3)	0.2141(2)	0.4721(2)	0.0563(9)
C(13)	0.3877(3)	0.2354(2)	0.6151(2)	0.0428(8)
N(14)	0.4495(2)	0.1315(2)	0.6836(2)	0.0483(7)
C(15)	0.6393(3)	0.1667(2)	0.7730(2)	0.0419(8)
Cl(16)§	1.23374(8)	0.23624(7)	1.04175(6)	0.0633(3)
O(17)	0.6704(2)	0.4139(2)	1.0513(1)	0.0534(6)
N(18)	0.1777(3)	0.5361(2)	0.4091(2)	0.0615(9)
O(19)	0.1763(4)	0.6390(2)	0.4761(2)	0.108(1)
O(20)	0.1217(3)	0.5167(2)	0.2848(2)	0.097(1)
C(21)	0.3423(3)	-0.0186(2)	0.6193(2)	0.058(1)
C(22a)§	0.3364(6)	-0.1115(4)	0.7295(4)	0.065(2)
C(22b)§	0.1851(9)	-0.0615(6)	0.6513(7)	0.064(3)
C(23)	0.2607(6)	-0.0655(3)	0.8222(4)	0.113(2)

Refined site occupation factors for Cl(16) 0.967(3), C(22a) 0.625(5), and C(22b) = 0.375(5)

Synthesis of 6,11-Dihydro-6-methyl-11-propyl-5H-pyridazino[3,4-b][1,5]benzodiazepin-5-one (12) by Reductive Dehalogenation

A mixture of **11** (303 mg, 1 mmol), ammonium formate (315 mg, 5 mmol) and 114 mg of Pd-C (10%) in 20 mL of methanol was stirred under a nitrogen atmosphere at 48°C for 30 min. 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 sulphate and evaporated. The product thus obtained was purified by column chromatography (dichloromethane/ethyl acetate, 9:1), followed by recrystallisation (diisopropyl ether) to give **12** (95%) as light yellow crystals, mp 107-110 °C. IR 1655 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ 8.95 (d, J = 4.5 Hz, 1 H, H-3), 7.74 (d, J = 4.5 Hz, 1 H, H-4), 7.27-7.20 (m, 4 H, H-7, H-8, H-9, H-10), 4.51-4.38, 3.83-3.71 (m, 2 H, N-CH$_2$), 3.57 (s, 3 H, N-CH$_3$), 1.76-1.66 (m, 2 H, CH$_2$), 0.94 (t, J = 7.3 Hz, 3 H, CH$_3$). ^{13}C NMR (CDCl$_3$) δ 166.2, 162.1 (C-5, C-11a), 148.1 (C-3), 143.2 (C-10a), 136.9 (C-6a), 128.9 (C-4), 125.5 (C-4a), 126.6, 125.4, 123.2, 122.3 (C-7, C-8, C-9, C-10), 49.8 (N-CH$_2$), 37.4 (N-CH$_3$), 20.6 (CH$_2$), 11.4 (CH$_3$). Anal. Calcd for C$_{15}$H$_{16}$N$_4$O: C, 67.15; H, 6.01; N, 20.88. Found: C, 66.96; H, 5.80; N, 20.54.

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    in the presence of two equivalents of triethylamine at low temperature (0→25°C) gave the desired amide in
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