Synthesis and Crystal Structures of Two 9-(2-Bromoethyl)-Substituted 7-Deazapurines

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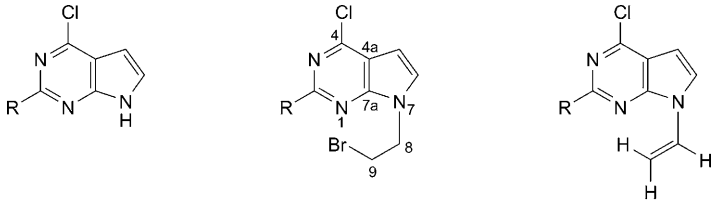
The 7-(2-bromoethyl) derivatives, **2a** and **2b**, of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1a**) and 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine (**1b**) were synthesized by nucleobase anion alkylation (NaH, DMF) and crystallized. X-Ray analyses of both compounds were performed, and they revealed significantly different positioning of the side chain relative to the heterocyclic ring, depending on the substituent (H or NH_2) at C(2).

Introduction. – 7-Deazapurines (= pyrrolo[2,3-*d*]pyrimidines[1])) are of considerable importance, because a series of nucleoside antibiotics comprising tubercidin, toyocamycin, and sangivamycin contains the 7-deazaadenine moiety, while other naturally occurring nucleosides such as queuosine, cadeguomycin, and archaeosine contain a 7-deazaguanine ring [1][2]. 7-Deazapurines of the xanthine type have been prepared as analogues of potent A1- and A2-adenosine receptor antagonists [3]. Functionalized derivatives of 7-deazapurines are of interest, because they can be easily coupled to polymers, dendrimers, lipids, or solid surfaces carrying amino functions, which lend them the functionality of a particular modified nucleobase [4–6]. The coupling of the newly prepared compounds to redox-active dendrimers and their use as electrochromic materials will be published separately.

Results and Discussion. – *Synthesis.* Versatile precursors of 7-deazaadenine and guanine such as compounds **1a** and **1b** are meanwhile available from various providers. Here, these compounds were prepared according to [7] (for **1a**) and [8][9] (for **1b**). Subsequent nucleobase anion alkylation (NaH, DMF) [10] with a 100-fold excess of 1,2-dibromoethane gave the corresponding compounds **2a** and **2b**, respectively, besides small amounts (10–15%) of the corresponding 9-vinyl derivatives **3a** and **3b** which were separated by column chromatography. The latter compounds are also of interest as they can be polymerized to 'polyvinyl(7-deazapurines'; 'plastic nucleic acids') [11]. The structure and integrity of the novel compounds **2a** and **2b** were confirmed by ^{1}H- and ^{13}C-NMR, as well as by UV spectroscopy and by elemental analyses. The assignment of the NMR resonances was established by gradient-selected homo- and

[1]) The atom numbering of the pyrrolo[2,3-*d*]pyrimidine system follows the *IUPAC* rules and is different from the numbering of the purine ring system.



1a R = H
1b R = NH_2

2a R = H
2b R = NH_2

3a R = H
3b R = NH_2

heteronuclear correlation spectroscopy (*Bruker* pulse programs, $^{1}H,^{13}C$: HSQCETGP; $^{1}H,^{1}H$: COSYGPSW). The NMR data exhibit some slight differences between compounds **2a** and **2b**, particularly with respect to the side-chain resonances. Compared to **2a**, the chemical shift $\delta(H)$ of H–C(8) of **2b** is biased to lower field by 0.3 ppm, and the $^{3}J(H,H)$ coupling constants to the corresponding H–C(9) differ by 0.4 Hz. This might be either due to the different group electronegativity values of the different heterocycles, and/or due to their different anisotropic field effects. It is also possible that, in compound **2b**, the side chain is turned into a position which allows the formation of a H-bond between the Br-substituent and one of the amino H-atoms (*Fig. 1*). Such a topological situation is unlikely in case of **2a** because of the missing H-bridge.

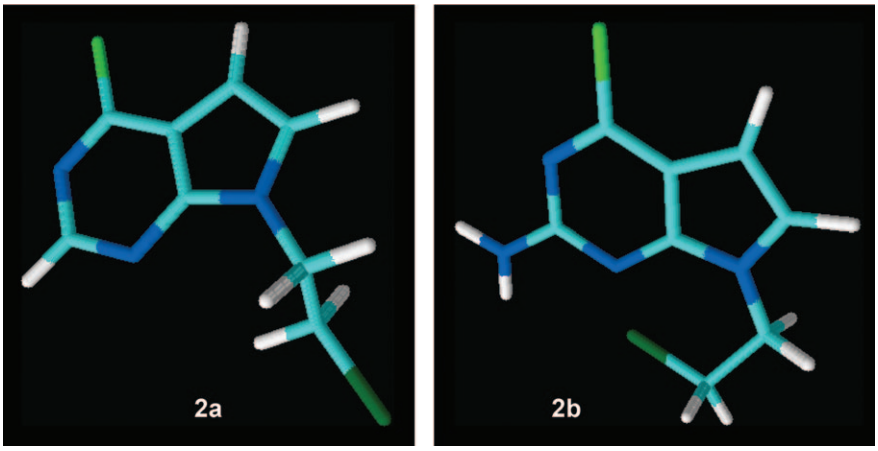


Fig. 1. Left: *3D-Optimized structure of compound* **2a** *using ChemSketch, 3D viewer, version 11.0* (*Advanced Chemistry Developments Inc.*, Toronto). Right: *3D Structure of compound* **2b** *in which the side chain is rotated into a position with a minimized distance of* NH_2–*Br* (2.78 Å).

Crystallography. In *Tables 1–4*, the crystallographic data as well as torsion angles, intramolecular bond distances, and bond angles of compounds **2a** and **2b** are collected. *Fig. 2* displays the ball-and-stick models and the crystal cell of **2a**, while *Fig. 3* shows those for compound **2b**. The data clearly confirm that, for both compounds, the positioning of the side chain relative to the heterocycle is different: while, for **2a**, it is stretched out, it is bent in case of **2b**. The latter allows the formation of a H-bond

Table 1. *Crystallographic Data of Compounds* **2a** *and* **2b**

	2a	**2b**
Empirical formula	$C_8H_7BrClN_3$	$C_8H_8BrClN_4$
Formula weight [g mol^{-1}]	260.53	275.54
Temp. [K]	100(2)	100(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	*Pbca*
a [Å]	6.7567(4)	18.2725(7)
b [Å]	7.1358(4)	5.2455(3)
c [Å]	19.2952(8)	20.5077(9)
V [Å^3]	930.31(9)	1965.63(16)
Z	4	8
D_x [g cm^{-3}]	1.860	1.862
μ(MoK_α) [mm^{-1}]	4.658	4.417
F(000)	512	1088
Crystal size [mm]	$0.47 \times 0.17 \times 0.10$	$0.33 \times 0.31 \times 0.25$
Crystal description	prism	plate
θ Range for data collection [°]	2.11 – 28.00	1.99 – 28.00
Limiting indices	$-8 \le h \le 7$	$-23 \le h \le 24$
	$-8 \le k \le 9$	$-6 \le k \le 6$
	$-25 \le l \le 25$	$-26 \le l \le 26$
Reflection collected/unique	36596/2239	41259/2362
R_{int}	0.0255	0.0361
Completeness to $\theta = 28.00$ [%]	100.0	99.7
Transmission factors [min; max]	0.2182; 0.6531	0.2713; 0.3310
Data/restraints/parameters	2239/0/121	2362/0/129
Goodness-of-fit on F^2	1.109	1.082
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0143$, $wR_2 = 0.0322$	$R_1 = 0.0302$, $wR_2 = 0.0625$
Final R indices (all data)	$R_1 = 0.0156$, $wR_2 = 0.0327$	$R_1 = 0.0380$, $wR_2 = 0.0663$
Largest diff. peak and hole [e Å^{-3}]	0.282 and -0.195	0.496 and -0.605

Table 2. *Intramolecular Bond Distances in Molecules* **2a** *and* **2b**

Bond [Å]	**2a**	**2b**
N(1)–C(2)	1.335(2)	1.345(3)
N(1)–C(7a)	1.339(2)	1.341(3)
C(2)–N(2)	–	1.348(3)
C(2)–N(3)	1.352(2)	1.366(3)
N(3)–C(4)	1.322(2)	1.316(3)
C(4)–C(4a)	1.386(2)	1.374(3)
C(4)–Cl(4)	1.742(2)	1.746(2)
C(4a)–C(7a)	1.417(2)	1.416(3)
C(4a)–C(5)	1.430(2)	1.435(3)
C(5)–C(6)	1.362(2)	1.359(3)
C(6)–N(7)	1.388(2)	1.399(3)
N(7)–C(7a)	1.370(2)	1.367(3)
N(7)–C(8)	1.465(2)	1.446(3)
C(8)–C(9)	1.519(2)	1.512(3)
C(9)–Br(1)	1.954(2)	1.954(2)

Table 3. *Intramolecular Bond Angles in Molecules* **2a** *and* **2b**

Bond angle [°]	**2a**	**2b**
C(2)–N(1)–C(7a)	112.8(1)	112.8(2)
N(1)–C(2)–N(3)	127.9(1)	126.6(2)
C(4)–N(3)–C(2)	116.4(1)	116.8(2)
N(3)–C(4)–C(4a)	123.5(2)	124.1(2)
N(3)–C(4)–Cl(4)	116.5(1)	116.0(2)
C(4a)–C(4)–Cl(4)	120.0(1)	120.0(2)
C(4)–C(4a)–C(7a)	113.5(1)	113.4(2)
C(4)–C(4a)–C(5)	139.0(2)	139.2(2)
C(7a)–C(4a)–C(5)	107.5(1)	107.4(2)
C(6)–C(5)–C(4a)	105.6(1)	106.3(2)
C(5)–C(6)–N(7)	111.4(1)	110.4(2)
C(7a)–N(7)–C(6)	107.4(1)	108.1(2)
C(7a)–N(7)–C(8)	126.8(1)	126.0(2)
C(6)–N(7)–C(8)	125.5(1)	125.7(2)
N(1)–C(7a)–N(7)	126.0(1)	125.8(2)
N(1)–C(7a)–C(4a)	125.9(1)	126.3(2)
N(7)–C(7a)–C(4a)	108.1(1)	107.9(2)
N(7)–C(8)–C(9)	111.0(1)	113.2(2)
C(8)–C(9)–Br(1)	108.2(1)	111.5(2)

Table 4. *Torsion Angles for Molecules* **2a** *and* **2b**

Torsion angle [°]	**2a**	**2b**
C(7a)–N(7)–C(8)–C(9)	– 59.4(2)	– 126.5(2)
C(6)–N(7)–C(8)–C(9)	128.6(2)	59.6(3)
N(7)–C(8)–C(9)–Br(1)	– 175.7(1)	60.9(2)

between the Br-substituent to an amino H-atom of a neighboring **2b** molecule (*Fig. 3*), whereas the molecules of **2a** are held together only by *Van der Waals* forces (*Fig. 2*).

Experimental Part

General. All chemicals were purchased from *Sigma-Aldrich* (*Deisenhofen*, Germany) or from *TCI-Europe* (*Zwijndrecht*, Belgium). Solvents were of laboratory grade. TLC: aluminium sheets, silica gel *60* F_{254}, 0.2 mm layer (*Merck*, Germany). M.p. *Büchi SMP-20*, uncorrected. UV Spectra: *Cary 1E* spectrophotometer (*Varian*, D-Darmstadt); λ_{max} in nm (ε in M^{-1} cm^{-1}). NMR Spectra: *Bruker AMX-500* spectrometer; ^{1}H: 500.14 MHz, ^{13}C: 125.1; chemical shifts δ are given in ppm rel. to Me_4Si as internal standard for ^{1}H and ^{13}C.

*7-(2-Bromoethyl)-4-chloro-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**2a**). *4-Chloro-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**1a**; 2 g, 13 mmol) and 4 g of NaH were suspended in 20 ml of freshly dist. DMF, and 1,2-dibromoethane (242 g, 1,3 mol) was added in 10 ml of DMF. The suspension was stirred at 70° for 3 d under reflux. The mixture was filtered, and the mother liquor was evaporated. The crude product was dissolved in $CHCl_3$ and purified by column chromatography (CC; silica gel, 35 × 3.5 cm, petroleum ether(PE)/AcOEt 4:1). The first fraction contained *4-chloro-7-ethenyl-7*H-*pyrrolo[2,3-*d*]pyrimidine* (**3a**). R_f (PE/AcOEt 4:1) 0.67. ^{1}H-NMR ((D_6)DMSO): 8.66 (*s*, H–C(2)); 8.22 (*d*, ^3J(6,5) = 3.8, H–C(6)); 7.54 (*dd*, $^3J_{(Z)}$(8,9) = 8.9, $^3J_{(E)}$(8,9) = 15.9, H–C(8)); 6.76 (*d*, ^3J(5,6) = 3.8, H–C(5)); 5.84 (*d*, $^3J_{(E)}$(9,8) = 15.9, H–C(9)); 5.09 (*d*, $^3J_{(Z)}$(9,8) = 8.9, H–C(9)).

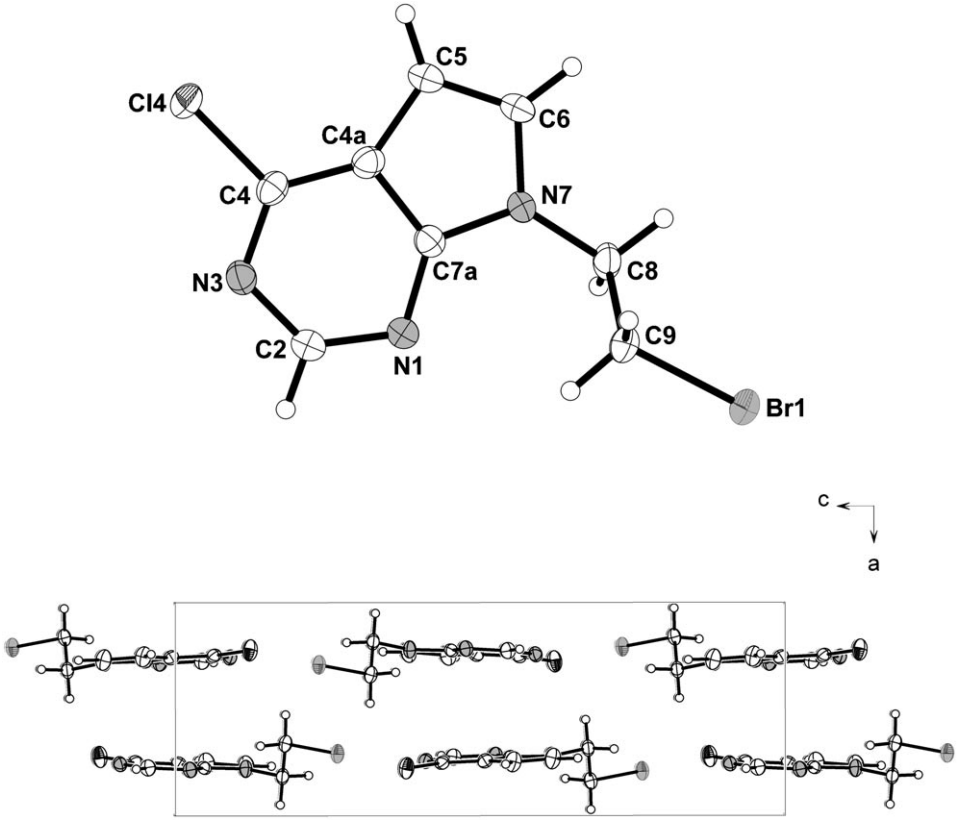


Fig. 2. *Ball-and-stick model of* **2a** *with the atomic numbering scheme used*. With the exception of the H-atoms, which were represented by use of spheres with a common isotropic radius, all other atoms were represented as thermal displacement ellipsoids (one octant: Br-atom = grey, Cl-atom = white; cross: N-atom = grey, C-atom = white) *showing 50% of the probability of the corresponding atom.*

The second fraction contained the title compound **2a**. The product-containing fractions were pooled, and the solvent was evaporated. After drying *in vacuo* (r.t., 24 h) 2.15 g (8.2 mmol, 63%) of **2a** were obtained. Light yellow powder. M.p. 86°. R_f (PE/AcOEt 4:1) 0.42. UV ($CHCl_3$): 239 (18800), 277 (38800). ^{1}H-NMR ((D$_6$)DMSO): 8.58 (*s*, H–C(2)); 7.34 (*d*, ^3J(6,5) = 3.6, H–C(6)); 6.55 (*d*, ^3J(5,6) = 3.6, H–C(5)); 4.70 (*t*, ^3J(8,9) = 5.8, CH_2(8)); 3.76 (*t*, ^3J(9,8) = 5.8, CH_2(9)). ^{13}C-NMR ((D$_6$)DMSO): 150.09 (C(2)); 149.68 (C(7a)); 144.16 (C(4)); 129.74 (C(6)); 121.11 (C(4a)); 100.82 (C(5)); 46.97 (C(8)); 30.00 (C(9)). Anal. calc. for $C_8H_7BrClN_3$ (260.518): C 36.88, H 2.71, N 16.13; found: C 36.60, H 3.10, N 16.09.

Suitable crystals for X-ray analysis were obtained by slow evaporation of a $CHCl_3$ soln. of **2a**.

*7-(Bromomethyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine* (**2b**). *4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine* (**1b**; 2.2 g, 13 mmol) and 4 g of NaH were suspended in 20 ml of freshly dist. DMF, and 1,2-dibromoethane (242 g, 1.3 mol) was added in 10 ml of DMF. The suspension was stirred at 70° for 3 d under reflux. The mixture was filtered, and the mother liquor was evaporated. The crude product was dissolved in $CHCl_3$ and purified by CC (silica gel, 35 × 3.5 cm, PE/AcOEt 4:1). The first fraction contained *4-chloro-7-ethenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine* (**3b**). R_f (PE/AcOEt 4:1) 0.6. ^{1}H-NMR (D$_6$)DMSO): 7.66 (*d*, ^3J(6,5) = 3.3, H–C(6)); 7.33 (*dd*, $^3J_{(Z)}$(8,9)) = 9.4, $^3J_{(E)}$(8,9) = 15.6,

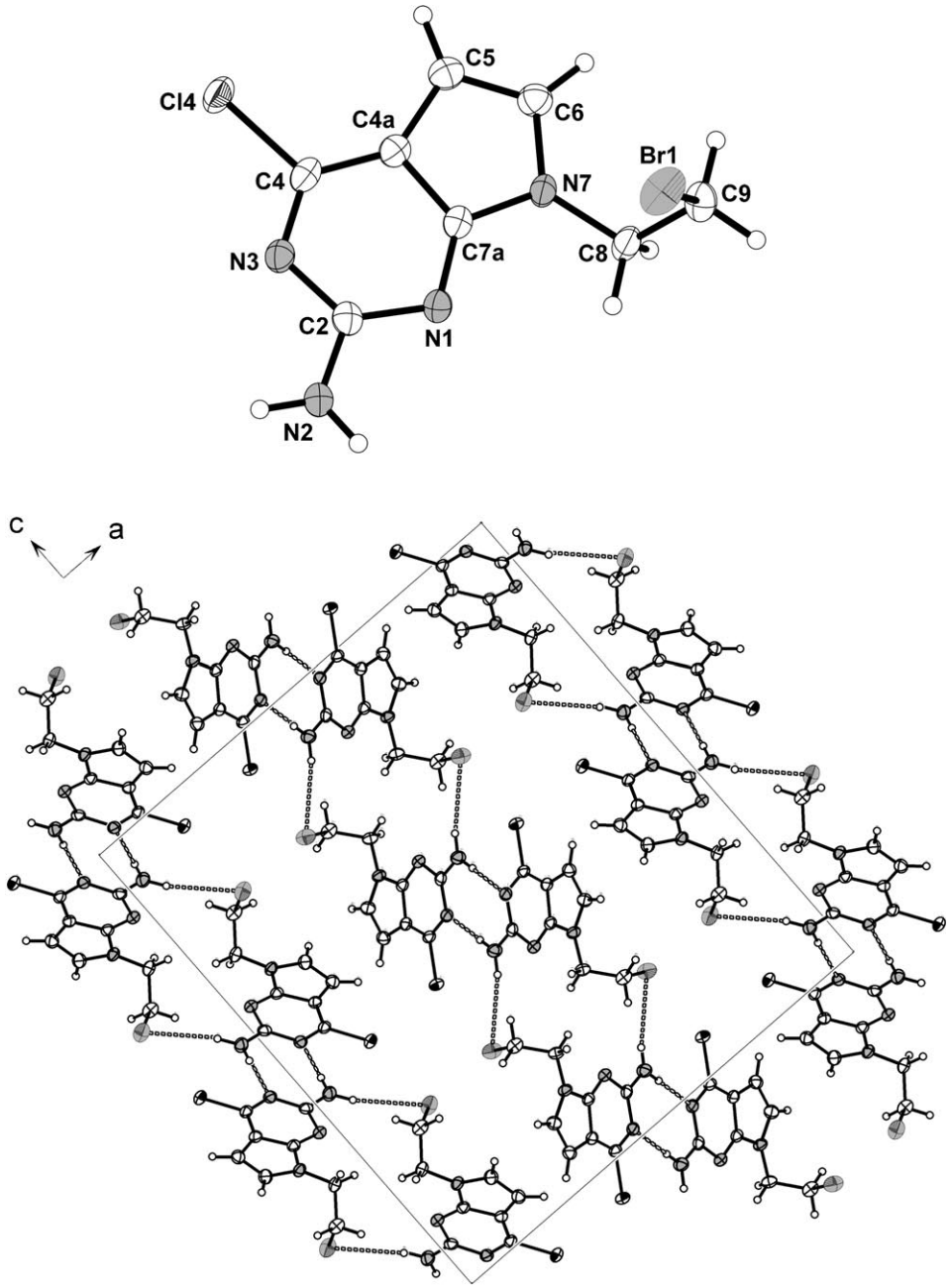


Fig. 3. *Ball-and-stick model of* **2b** *with the atomic numbering scheme used*. With the exception of the H-atoms, which were represented by use of spheres with a common isotropic radius, all other atoms were represented as thermal displacement ellipsoids (one octant: Br-atom = grey, Cl-atom = white; cross: N-atom = grey, C-atom = white) *showing 50% of the probability of the corresponding atom.*

H–C(8)); 6.92 (*s*, NH_2); 6.53 (*d*, $^3J(5,6) = 3.3$, H–C(5)); 5.64 (*d*, $^3J_{(E)}(9,8) = 16.1$, H–C(9)); 4.93 (*d*, $^3J_{(Z)}(9,8) = 9.2$, H–C(9)).

The second fraction containing the title compound **2b** was collected, and the solvent was evaporated. After drying *in vacuo* (r.t., 24 h), 1.84 g (6.6 mmol, 51%) of **2b** were obtained. Yellowish powder. M.p. 121°. R_f (PE/AcOEt 4:1) 0.42. UV ($CHCl_3$): 243 (14500), 312 (5500). ^{1}H-NMR ((D$_6$)DMSO): 7.22 (*d*, $^3J(6,5) = 3.6$, H–C(6)); 6.71 (*s*, NH_2); 6.30 (*d*, $^3J(5,6) = 5.0$, H–C(5)); 4.41 (*t*, $^3J(8,9) = 6.2$, CH_2(8)); 3.83 (*t*, $^3J(9,8) = 6.2$, CH_2(9)). ^{13}C-NMR ((D$_6$)DMSO): 159.33 (C(2)); 153.54 (C(7a)); 151.21 (C(4)); 126.35 (C(6)); 108.63 (C(4a)); 98.55 (C(5)); 45.35 (C(8)); 31.30 (C(9)). Anal. calc. for $C_8H_8BrClN_4$ (275.533): C 34.87, H 2.93, N 20.33; found: C 35.10, H 3.17, N 20.55.

Suitable crystals for X-ray analysis were obtained by slow evaporation of a $CHCl_3$ soln. of **2b**.

X-Ray Crystallography. Suitable single crystals of **2a** and **2b** were selected under a polarization microscope and mounted on a 50-μm *MicroMesh MiTeGen Micromount*™ using *FROMBLIN Y* perfluoropolyether (*LVAC 16/6*, *Aldrich*). The crystallographic data for compounds **2a** and **2b** are given in *Table 1*. All measurements were conducted at 100 K on a *Bruker Kappa APEXII* single-crystal diffractometer with *CCD* area detector using graphite-monochromated MoK_α radiation (λ 0.71073Å) and *KRYO-FLEX Low-Temperature* equipment. Unit cell dimensions were determined using the APEX 2 software suite [12]. The centrosymmetric space group *Pbca* (No. 61) of **2b** was determined unambiguously from the systematic absences 0*kl* with *h* odd, *h*0*l* with *l* odd, and *hk*0 with *h* odd, as was the chiral space group $P2_12_12_1$ (No. 19) of **2a** from the systematic absences *h*00 with *h* odd, 0*k*0 with *k* odd, and 00*l* with *l* odd. In the presence of atoms heavier than Si (Br and Cl), the value of the absolute structure parameter of $x = 0.5095$ [13], however, indicates racemic twinning of **2a** that was taken into account applying twin refinement. Data reduction was performed with SAINT [14]. The intensities were corrected for *Lorentz* and polarization effects. For both compounds, an empirical absorption correction was applied using SADABS [15], which is based on an analysis of symmetry-equivalent reflections in the highly redundant data set. Each structure was solved by direct methods using SHELXS [16], which revealed most of the non-H-atoms of the molecules. All remaining non-H-atoms were located in subsequent difference *Fourier* maps.

The non-H-atoms in each structure were refined anisotropically. All H-atoms including those of the NH_2 group were found in difference *Fourier* maps. To reduce the number of refined parameters, they were placed in geometrically calculated positions and constrained to ride on their parent atoms. Two common isotropic displacement parameters for the H-atoms of the heterocycle and the side chain were refined.

The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. All calculations were performed using SHELXL 97 [16]. The *Figs. 1–3* were drawn using Diamond [17].

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