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Synthesis and Characterization of (–)-Menthyl Containing *N*-Alkyl Cycloimmonium Salts

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Dedicated to Professor Wolfgang Beck on the Occasion of His 80th Birthday

Keywords: *N*-Alkyl cycloimmonium salts; Aminothiazole; α-Bromoacetyl (–)-menthyl ester; Crystal structure; N–H···Br⁻ hydrogen bonds

Abstract. The reaction of 4-phenyl-2-aminothiazole or 2-amino pyridine with α-bromo acetic (–)-menthyl ester (**2c**) yields new *N*-alkyl cycloimmonium bromides (**1c**, **3**) with the chiral (–)-menthyl substituent, which were isolated and fully characterized by ^{1}H and ^{13}C NMR spectroscopy for the first time. In addition, starting from 4-phenyl-2-aminothiazole, two further *N*-alkyl cycloimmonium bromides (**1a**, **1b**) were prepared. The molecular and crystal structures of all three thiazole derived *N*-alkyl cycloimmonium bromides (**1a–c**) were determined by single-crystal X-ray diffraction. In all cases the crystal structures are dominated by N–H···Br hydrogen bonds, which results in the formation of an extensive hydrogen bonded network in the crystal. Interestingly, in all structures S···Br⁻ distances shorter than the sum of the van der Waals radii are observed.

Introduction

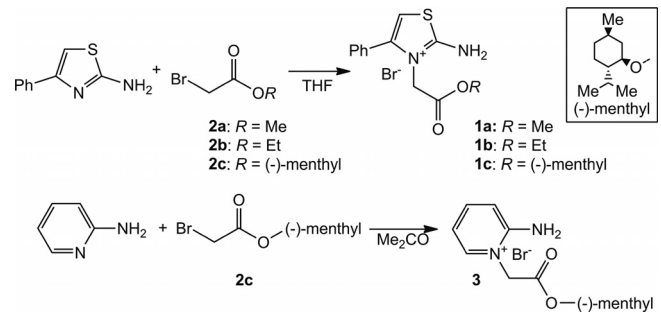
N-Alkyl cycloimmonium salts are of great importance as precursors for the synthesis of heterophospholes.[1] In the course of systematic investigations on the synthesis of heterophospholes containing chiral information we were engaged with the preparation of *N*-alkyl cycloimmonium salts, which contain the chiral (–)-menthyl substituent. No cycloimmonium salts with the (–)-menthyl moiety are known in the literature.

Herein we report the synthesis and characterization of first cycloimmonium salts containing the (–)-menthyl substituent. In addition we report the molecular and crystal structures of three thiazolium bromides. The structures are discussed with respect to the extensive hydrogen bonding found in the crystalline state.

Results and Discussion

Synthesis

Cycloimmonium salts are generally prepared by the alkylation of corresponding 2-amino azoles or azines by appropriate alkyl halides.[1–3] Following this route the thiazolium bromides **1a–c** were obtained by reaction of 2-amino-4-phenylthiazole with the α-bromoesters **2a–c**. While the synthesis of **1a** was described by *Bansal*[1] the thiazolium salt **1c** containing the chiral (–)-menthyl substituent and the thiazolium salt **1b** with the CH_2CO_2Et substituent were obtained herein for the first time (Scheme 1). Similarly reaction of 2-aminopyridine with the α-bromoester **2c** in acetone resulted in the formation of the new pyridinium salt **3**, which was isolated in good yields (Scheme 1).



Scheme 1. Synthesis of 2-amino-4-phenyl thiazolium salts **1a–c** and of the 2-amino pyridinium salt **3**.

2-Amino-4-phenyl-1,3-thiazole can be prepared according to a synthesis published by *Balalaie*[4] from 2-bromo-1-phenylethanone and thiourea in a base catalyzed condensation reaction in good yields.

The synthesis of (1*R*,2*S*,5*R*)-2-(propan-2-yl)-5-methyl-cyclohexyl-2-bromoacetate [(–)-menthyl-2-bromoacetate] (**2c**) by a carbodiimide promoted esterification – using e.g. DCC[5] or EDC/DMAP[6] – or by the condensation of 2-bromoacetyl chloride and (–)-menthol with pyridine[7] as base has been re-

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ported. We prepared **2c** by reaction of 2-bromoacetyl bromide and (–)-menthol using potassium carbonate as the base. This route has the advantage of a much simpler workup and gives the 2-bromoester in very good yields (95%).

The new (–)-menthyl substituted salts **1c** and **3** as well as the esters **1a** and **1b** are isolated as colorless microcrystalline solids, which are easily soluble in DMSO and $CHCl_3$ and sparingly soluble in acetonitrile, THF, and acetone. They are air and water stable. The identities of the salts **1a–c** and **3** result from the ^1H and ^{13}C NMR spectra (see Table 1 and Table 2) and are confirmed by the results of single crystal X-ray diffraction in the case of **1a–c**.

NMR Spectra

The ^1H and ^{13}C NMR spectroscopic data of the cycloimmonium salts **1a–c** and **3** are presented in Table 1 and Table 2, respectively. The *N*-methylene group of the bromoacetates **2** is a good NMR probe for the alkylation reaction as its ^1H and ^{13}C NMR spectroscopic data display the largest changes on alkylation (Table 1 and Table 2).[5,8]

Table 1. ^1H NMR spectroscopic data of compounds **1a–c** and **3**; in $CDCl_3$ except **3** in $[D_6]$DMSO; chemical shifts δ in ppm, coupling constants J in Hz., a = axial, e = equatorial.

	1a	**1b**	**1c**[a)]	**3**[b)]
5-H	7.07	6.67	6.52	6.94 J = 6.9
N–CH_2	4.76	4.98	4.91, 5.28[c)] J_{AB} = 18.1	5.16, 5.27[c)] J_{AB} = 18.1
4-Ph	7.34–7.75	7.27–7.49		
o-H			7.26–7.31	
m-H			7.40–7.45	
p-H			7.46–7.52	
2-NH_2	10.00	9.84	9.94	8.66
R	3.66 (Me)	4.17 (OCH_2) $^3J_{HH}$ = 7.2 1.18 (Me) $^3J_{HH}$ = 7.2		
8′-H			0.65 J = 6.9	0.68 J = 6.9
4′-H[a]			0.73–0.81	0.80–0.89
9′-H			0.79 J = 6.9	0.84 J = 7.0
10′-H			0.87 J = 6.5	0.87 J = 6.5
3′,6′-H[a]			0.90–1.04	0.92–1.08
2′-H			1.23–1.33	1.26–1.34
5′-H			1.34–1.45	1.38–1.50
3′,4′-H[e]			1.53–1.66	1.57–1.66
7′-H			1.79–1.86	1.82–1.91
6′-H[e]			1.96–2.05	1.94–2.00
1′-H			4.67, J = 10.9, J = 4.3	4.65 J = 10.8, J = 4.2

a) Spectrum measured at 40 °C. b) 3-H: δ = 7.13 (d, J = 9.0 Hz, 1 H), 4-H: δ = 7.92 (t, J = 8.0 Hz, 1 H), 6-H: δ = 8.06 (d, J = 6.8 Hz, 1 H). c) N–CH_2: AB spin system.

The corresponding ^1H NMR signals of the *N*-methylene groups in **1c** and **3** show an AB spin system due to the presence of the chiral (–)-menthyl substituent. The ^1H and ^{13}C NMR shifts of **1a–c** compare well with each other and the corresponding shifts of the (–)-menthyl substituents in **1c** and **3** are very similar. Only the ^{13}C NMR shift of C1′ in compounds **1c** and **3** differs by 18.6 ppm.

Table 2. ^{13}C NMR chemical shifts δ /ppm of compounds **1a–c** (in $CDCl_3$) and **3** (in $[D_6]$DMSO).

	1a	**1b**	**1c**[a)]	**3**[b)]
C2	169.6	169.8	169.9	155.3
C4	140.0	140.5	140.9	
C5	105.7	105.9	104.9	
N–CH_2	48.0	49.5	49.4	54.2
C-*i*	128.0	128.2	128.2	
C-*o*	129.2	129.3	129.7	
C-*m*	130.5	130.8	129.2	
C-*p*	129.4	129.7	130.8	
C=O	166.4	165.8	165.2	165.9
R	53.1 (Me)	14.1 (Me) 25.7 (CH_2)		
C1′			68.0	76.6
C2′			46.8	47.0
C3′			23.3	23.2
C4′			34.1	34.1
C5′			31.5	31.4
C6′			40.5	40.9
C7′			21.9	22.4
C8′			16.2	16.7
C9′			25.9	25.8
C10′			20.8	21.3

a) Spectrum measured at 40 °C. b) 113.4 (CH), 115.6 (CH), 141.1 (CH), 143.6 (CH).

Molecular and Crystal Structures of 1a–c

Block-shaped single crystals of **1a–c** suitable for X-ray diffraction studies were obtained by recrystallization of the compounds from dichloromethane.

Compound **1a** crystallizes in the triclinic space group $P\bar{1}$ (No. 2) with two formula units in the unit cell. Figure 1 shows the asymmetric unit of the crystal structure of **1a**, which consists of two crystallographically independent molecules: *molecule A* including sulfur atom S1 and *molecule B* including sulfur atom S2. Both molecules differ in the orientation of their substituents relative to the thiazole ring. The phenyl substituent

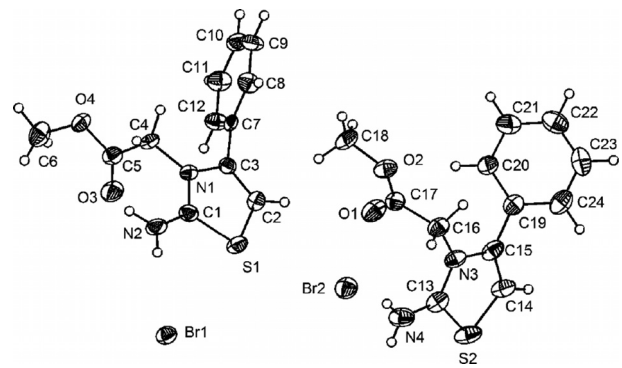

Figure 1. Molecular structure of **1a** in the crystal; ORTEP view of the asymmetric unit showing the two crystallographically independent units *A* and *B*. Thermal ellipsoids are drawn at 50% probability level.

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as well as the CH_2CO_2Me group are both rotated out of the thiazole ring plane. Whereas the phenyl group in *A* is almost perpendicular to the thiazole ring [C2–C3–C7–C12 = 83.7(5)°], in the case of *B* a torsion angle C14–C15–C19–C20 of 132.7(4)° is observed. The corresponding torsion angles for the CH_2CO_2Me groups are C3–N1–C4–C5 = 92.2(3)° for *A* and C15–N3–C16–C17 = 101.3(4)° for *B*, respectively.

In the crystal structure of **1a** N–H···Br hydrogen bonds between the NH_2 groups and the Br^- anions are observed. This results in the formation of dimers, as shown in Figure 2. The bonding parameters of the hydrogen bonds are summarized in Table 3 and compare well to literature values.[9] The dimers are connected by weak intermolecular interactions involving the sulfur atoms S1 and S2 and the bromide anions Br2 and Br1 (Figure 2). This arrangement results in the formation of chains of alternating dimers of molecules *A* and *B*, which are packed to build the crystal. The intermolecular S···Br contacts in the crystal structure of **1a** are also compiled in Table 3.

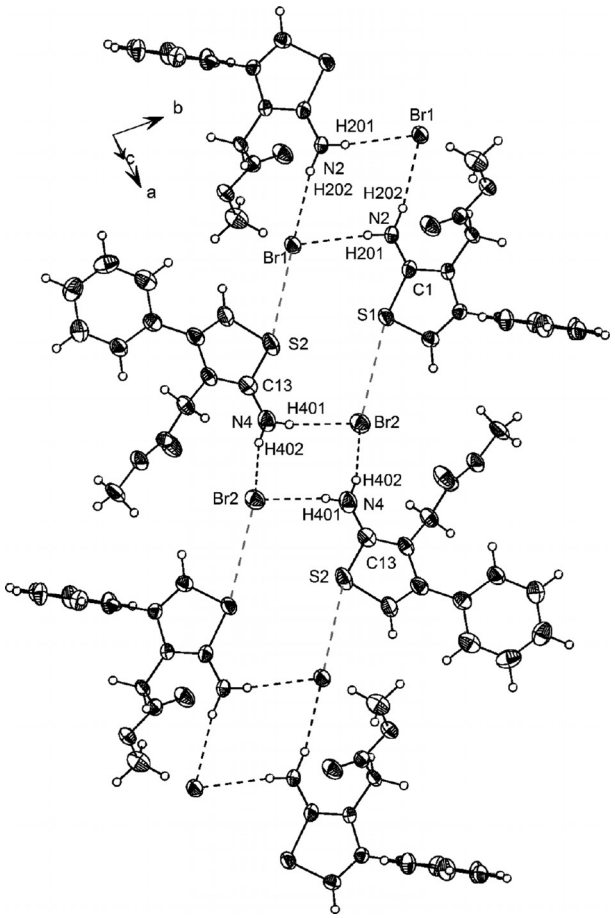

Figure 2. Crystal structure of **1a**; ORTEP view of the hydrogen bonded (black dashed lines) dimers of *molecules A* and *B* linked by weak intermolecular S···Br interactions (grey dashed lines) to form chains. Thermal ellipsoids are drawn at 50% probability level.

Compound **1b** crystallizes in the monoclinic space group $P2_1/n$ (No. 14) with eight formula units in the unit cell. As in the case of **1a** the asymmetric unit of **1b** is formed by two crystallographically independent *molecules A* (containing S1) and *B* (containing S2) and is shown in Figure 3.

Table 3. Atom distances /Å and bond angles /° for the hydrogen bonds and S···Br contacts in compounds **1a–c**.

X–*Y*···Br	*d*(*X*–*Y*)	*d*(*Y*–Br)	*d*(*X*–Br)	*X*–*Y*–Br
1a				
N2–H201···Br1	0.804(4)	2.497(4)	3.295(4)	171.6(4)
N2–H202···Br1	0.925(4)	2.475(4)	3.389(3)	169.6(3)
N4–H401···Br2	0.806(3)	2.501(3)	3.299(3)	169.8(3)
N4–H402···Br2	0.948(3)	2.357(4)	3.287(4)	167.0(3)
C1–S1···Br2	1.720(3)	3.527(9)		168.0(1)
C13–S2···Br1	1.721(3)	3.485(1)		163.0(1)
1b				
N2–H201···Br2[a]	0.848(2)	2.519(2)	3.304(2)	154.3(2)
N2–H202···Br1	0.808(2)	2.587(2)	3.380(2)	168.6(2)
N4[b]–H401[b]···Br2[a]	0.864(3)	2.376(3)	3.202(2)	160.4(3)
N4[b]–H402[b]···Br1[a]	0.897(2)	2.489(2)	3.339(2)	158.4(2)
C2–S1···Br2[a]	1.729(2)	3.604(5)		157.6(7)
C15[b]–S2[b]···Br2[a]	1.726(2)	3.422(5)		171.4(7)
C1–S1···Br1[a]	1.727(2)	3.480(6)		169.2(7)
1c				
N2–H21···Br1[c]	0.859(13)	2.647(17)	3.462(3)	159.0(2)
N2–H22···Br1[d]	0.810(3)	2.503(3)	3.296(3)	166.5(3)
C1–S1···Br1	1.718(3)	3.557(7)		159.6(9)
C2–S1···Br1[d]	1.734(3)	3.639(7)		172.2(0)

Symmetry operators: a) 1+*x*, *y*, *z*; b) 0.5+*x*, 0.5–*y*, 0.5+*z*; c) –1+*x*, *y*, *z*; d) –0.5+*x*, 1.5–*y*, 1–*z*.

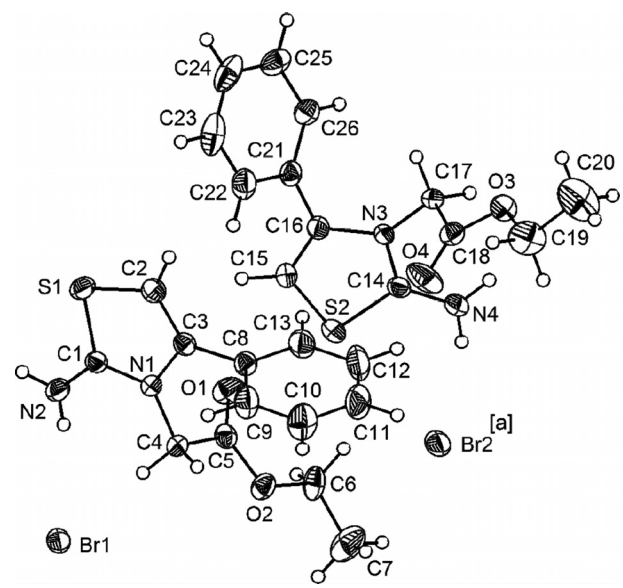

Figure 3. Molecular structure of **1b** in the crystal; ORTEP view of the two crystallographically independent *molecules A* and *B*. [a] 0.5+*x*, 0.5–*y*, –0.5+*z*. Thermal ellipsoids are drawn at 50% probability level.

As in the case of compound **1a** the crystal structure of **1b** is determined by N–H···Br hydrogen bonds. Interestingly the slight change of the substituent at oxygen (from methyl to ethyl) obviously favors an arrangement of the cations and anions to form chains (instead of dimers) along the *a* axis (Figure 4). In this case also intermolecular S···Br distances slightly shorter than the sum of the van der Waals radii are observed. Atom distances and bond angles for all intermolecular interactions in the crystal structure of **1b** are compiled in Table 3.

The two molecules are differing in the orientation of the substituents of the planar thiazole ring. The torsion angles of the phenyl groups are –81.7(3)° (C2–C3–C8–C13) for *molecule A* and 45.7(3)° (C15–C16–C21–C22) for *molecule B*. Also the CH_2CO_2Et groups are twisted out of the plane of the thiazole ring. For *molecule A* the angle C3–N1–C4–C5 is –76.5(2)° and for *molecule B* the torsion angle C16–N3–C17–C18 is 90.3(2)° (Figure 3).

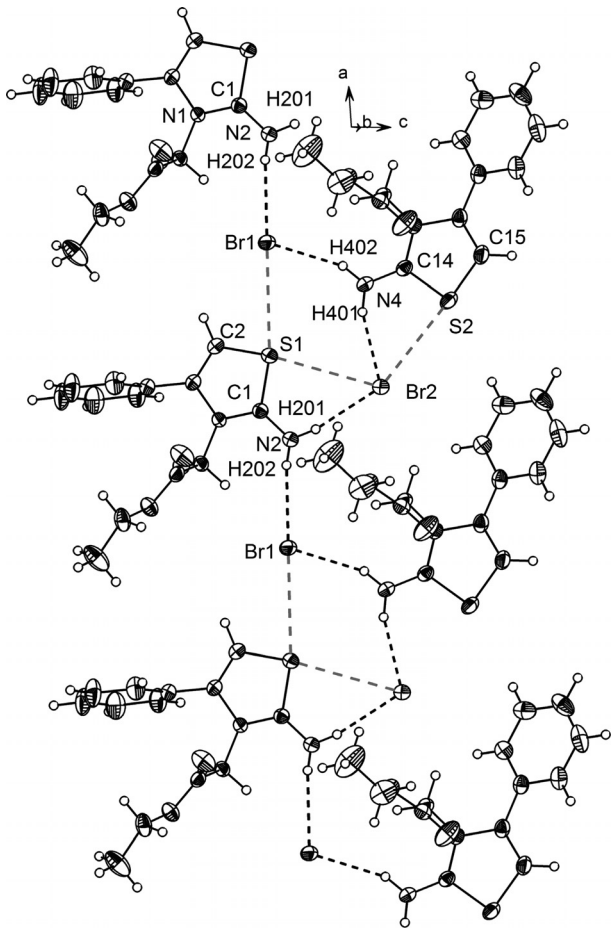

Figure 4. Crystal structure of **1b**; ORTEP view of the hydrogen bonded (black dashed lines) chain, showing also the S···Br contacts (grey dashed lines). Thermal ellipsoids are drawn at 50% probability level.

Compound **1c·CH_2Cl_2** crystallizes in the orthorhombic space group $P2_12_12_1$ (No. 19) with four formula units in the unit cell. The asymmetric unit is shown in Figure 5. As in the case of **1a** and **1b** the thiazole ring in **1c** is planar and both substituents at C3 and at nitrogen are twisted out of the thiazole ring plane. For the phenyl ring a torsion angle C2–C3–C4–C5 of 53.9(4)° and for the ester moiety a torsion angle C3–N1–C11–C10 of –97.3(3)° are observed.

The most interesting feature of the structure of **1c** is the extensive hydrogen bonding involving the amino group of the thiazole ring and the bromide anions. The oxygen atoms of the ester function do not participate to the hydrogen bonding network. The interaction of the NH_2 groups with the Br^- anions results in the formation of zigzag chains along the *a* axis. Figure 6 shows these chains in *a* direction formed by intermolecular hydrogen bonds. In addition within the chains

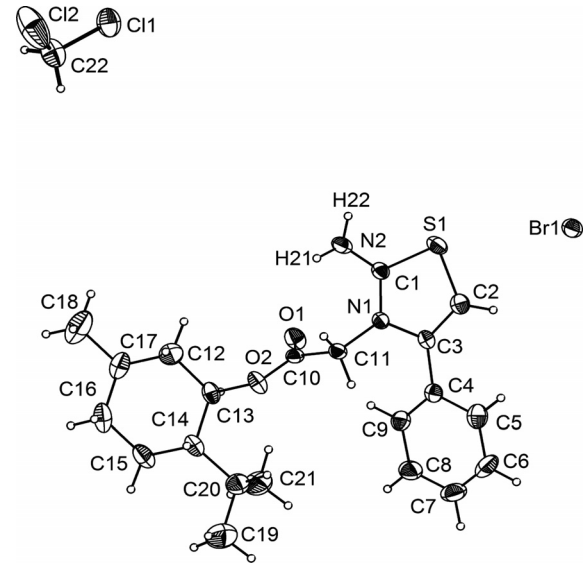

Figure 5. ORTEP drawing of the molecular structure of **1c·CH_2Cl_2** in the crystal. Ellipsoids are drawn at 50% probability level.

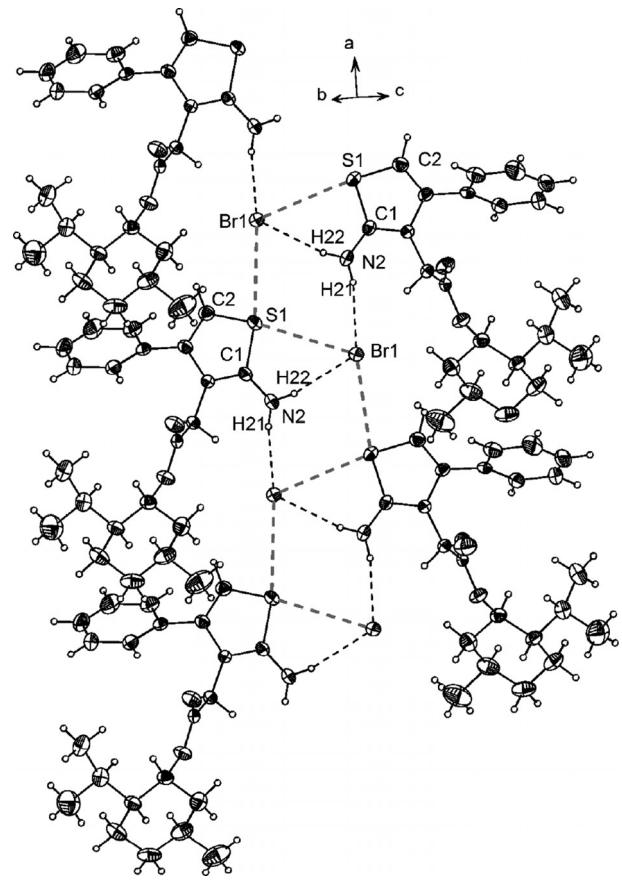

Figure 6. Crystal structure of **1c·CH_2Cl_2**; ORTEP view of the hydrogen bonded chain (black dashed lines), showing also the S···Br contacts (grey dashed lines); solvent molecules omitted for clarity. Thermal ellipsoids are set to 50% probability level.

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S1···Br1 distances of 3.557(7) Å and 3.639(7) Å are observed, which are slightly shorter than the sum of the van der Waals radii (3.65 Å)[10]. This very weak interaction seems to further stabilize the chains. The bond lengths and angles of the hydrogen bonds and the intermolecular S···Br distances are given in Table 3.

Conclusions

Two *N*-alkyl cycloimmonium bromides containing the chiral (–)-menthyl substituent were prepared starting from 4-phenyl-2-aminothiazole and 2-aminopyridine and were fully characterized by ^{1}H and ^{13}C NMR spectroscopy for the first time. In addition the synthesis of two further *N*-alkyl cycloimmonium bromides is described. For all thiazole derivatives the molecular and crystal structures were determined by single-crystal X-ray diffraction. In all cases N–H···Br hydrogen bonds are of crucial importance in determining the crystal structures. Whereas in the case of the methyl ester **1a** hydrogen bonded dimers are formed, in the case of **1b** and **1c** the hydrogen bonds result in the formation of chains throughout the crystal. Remarkably in all structures S···Br distances shorter than the sum of the van der Waals radii are observed. The preparative availability, in particular of the cycloimmonium salts having the chiral (–)-menthyl substituent, opens now the possibility for the synthesis of chiral heterophospholes.

Table 4. Crystal data and structure refinement parameters for **1a–c**.

	1a	**1b**	**1c**
Empirical formula	$C_{24}H_{26}Br_2N_4O_4S_2$	$C_{26}H_{30}Br_2N_4O_4S_2$	$C_{22}H_{31}BrCl_2N_2O_2S$
Formula weight	658.43	686.48	538.36
Cryst. size /mm^3	0.15 × 0.15 × 0.1	0.35 × 0.35 × 0.3	0.4 × 0.1 × 0.1
Crystal system	triclinic	monoclinic	orthorhombic
Space group	$P\bar{1}$ (2)	$P2_1/n$ (14)	$P2_12_12_1$ (19)
a /Å	10.1242(7)	9.432(3)	9.157(3)
b /Å	12.2120(8)	14.273(7)	16.449(5)
c /Å	13.024(1)	22.406(6)	16.690(5)
α /°	62.309(8)	90	90
β /°	74.668(7)	95.00(3)	90
γ /°	87.479(5)	90	90
V /Å^3	1369.18(17)	3004.9(3)	2513.9(14)
Z	2	4	4
ρ_{calcd} /g·cm^{-3}	1.597	1.517	1.422
μ(MoK_α) /cm^{-1}	3.150	2.874	1.951
F(000), e	664	1392	1112
hkl range	$-12 \le h \le 12$, $-14 \le k \le 15$, $-16 \le l \le 15$	$-9 \le h \le 11$, $-7 \le k \le 17$, $-26 \le l \le 27$	$-11 \le h \le 11$, $-20 \le k \le 20$, $-20 \le l \le 20$
Refl. measured	10656	17421	25508
Refl. unique	6201	5865	4927
R_{int}	0.0362	0.0259	0.0404
Param. refined	341	359	279
θ Range /°	$4.18 \le \theta \le 26$	$4.32 \le \theta \le 32.39$	$4.12 \le \theta \le 30.00$
R_1, wR_2 [$I > 2\sigma(I)$][a]	0.0338, 0.0465	0.0252, 0.0446	0.0293,
R_1, wR_2 (all data)[a]	0.0708, 0.0491	0.0467, 0.0459	0.0383,
GooF	0.739	0.813	0.893
δp_{max}, δp_{min} / e·nm^{-3}	0.426, –0.378	0.253, –0.408	0.679, –0.557
x (Flack)			–0.006(6)

Experimental Section

General: All reactions were carried out in an inert gas atmosphere using Schlenk techniques. Argon (Messer Griesheim, purity 4.6 in 50 L steel cylinder) was used as an inert gas. Glass vessels were stored in a 130 °C drying oven and were flame-dried at 10^{-3} mbar vacuum before use. 2-Amino-4-phenyl-1,3-thiazole was prepared according to a literature procedure[4]. All other chemicals were commercially available and were used as received. The solvents were dried using commonly known drying methods and were freshly distilled before use.

NMR Spectroscopy: NMR spectra were recorded with a JEOL EX 400 Eclipse instrument operating at 400.128 MHz (^{1}H) and 100.626 (^{13}C). Chemical shifts are referred to Me_4Si (^{1}H, ^{13}C) as external standards. All spectra were measured, if not mentioned otherwise, at 25 °C. The assignment of the signals in the ^{1}H and ^{13}C NMR spectra is based on 2D (^{1}H,^{1}H-COSY45, ^{1}H,^{13}C-HMQC and ^{1}H,^{13}C-HMBC) spectra for **1c** and comparison with the literature.

Mass Spectrometry: Mass spectrometric data were obtained with a JEOL Mstation JMS 700 spectrometer using the direct EI mode for neutral compounds and the FAB mode for ionic compounds with (4-nitrophenyl)methanol as matrix.

X-ray Crystallography: The molecular structures in the crystalline state were determined with an Oxford Xcalibur3 diffraction instrument with a Spellman generator (voltage 50 kV, current 40 mA) and a Kappa CCD detector with an X-ray radiation wavelength of 0.71073 Å. The data collection was performed with the CrysAlis CCD software[11] and the data reduction with the CrysAlis RED software[12]. The structures were solved with SIR-92, SIR-97, and SHELXS-97 and refined with SHELXL-97 and finally checked using PLATON.[13–17] The absorptions were corrected by SCALE3 ABSPACK multiscan method.[18] All relevant data and parameters of the X-ray measurements and refinements are given in Table 4. The hydrogen atoms were found in the difference Fourier map and refined isotropically.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository numbers CCDC-844692 (**1a**), CCDC-844693 (**1b**), and CCDC-844694 (**1c**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

(1*R*,2*S*,5*R*)-2-(Propan-2-yl)-5-methylcyclohexyl 2-bromo acetate (2c): Compound **2c** was prepared by modification of a literature procedure.[7] In a 100 mL Schlenk flask (–)-menthol [(1*R*,2*S*,5*R*)-2-(propan-2-yl)-5-methylcyclohexanol] (15.63 g, 100 mmol, 1.0 equiv.) and potassium carbonate (6.91 g, 50 mmol, 0.5 equiv.) were poured in dichloromethane (100 mL). The suspension was cooled to 0 °C and 2-bromoacetyl bromide (8.67 mL, 100 mmol, 1.0 equiv.) was added dropwise over a period of 15 min. After warming up to room temperature the reaction mixture was stirred for 12 h. After the addition of water (50 mL), the mixture was extracted three times with diethyl ether (50 mL). The combined organic layers were washed with water (100 mL) and dried over sodium sulfate. After removing the solvent in vacuo **2c** was obtained as colorless, slightly viscous oil (26.44 g, 95 %). The analytic data are in good accordance to the literature known values.[5]

2-Amino-3-(2-methoxy-2-oxomethyl)-4-phenyl-1,3-thiazol-3-ium bromide (1a): To a solution of 2-amino-4-phenyl-1,3-thiazol (3.52 g, 20 mmol, 1.0 equiv.) in THF (20 mL), methyl 2-bromoacetate (**2a**) (1.89 mL, 20 mmol, 1.0 equiv.) was added. The reaction mixture was stirred for five days at room temperature. During this time small

amounts of a colorless solid was formed. To complete the reaction the mixture was heated to reflux for another three days. The precipitate was filtered off, washed with THF (20 mL) and dried in vacuo, yielding **1a** as a colorless solid (3.42 g, 51.9 %). For ^{1}H and ^{13}C NMR spectroscopic data see Table 1 and Table 2, respectively. **MS** (FAB+): *m/z* (%) = 249.1 (100) $[M–Br]^+$. **MS** (FAB–): *m/z* (%) = 80.9 (97) $[Br]^–$, 78.9 (100) $[Br]^–$. **HRMS** (FAB+): *m/z* = 249.0698 (calcd. 249.0692 for $C_{12}H_{13}N_2O_2S^+$, $[M–Br]^+$). **HRMS** (FAB–): *m/z* = 80.9163 (Br-81, 49.3 %), 78.9183 (Br-79, 50.7 %) [calcd. 80.916289 for Br-81 (49.31 %), 78.918336 for Br-79 (50.69 %)].

2-Amino-3-(2-ethoxy-2-oxoethyl)-4-phenyl-1,3-thiazol-3-ium bromide (1b): The compound was prepared following the procedure described for **1a**. Compound **1b** was obtained as a colorless solid (1.19 g, 17.4 %). For ^{1}H and ^{13}C NMR spectroscopic data see Table 1 and Table 2, respectively. **MS** (FAB+): *m/z* (%) = 263.1 (100) $[M–Br]^+$. **MS** (FAB–): *m/z* (%) = 80.9 (97) $[Br]^–$, 78.9 (100) $[Br]^–$. **HRMS** (FAB+): *m/z* = 342.0038 (calcd. 263.0849 for $C_{13}H_{15}N_2O_2S^+$, $[M–Br]^+$). **HRMS** (FAB–): *m/z* = 80.9163 (Br-81, 49.3 %), 78.9183 (Br-79, 50.7 %) [calcd. 80.916289 for Br-81 (49.31 %), 78.918336 for Br-79 (50.69 %)]. Elemental analysis: calcd. C 45.49, H 4.40, N 8.16 %; found C 45.72, H 4.55, N 7.86 %.

2-Amino-3-(2-((1*R*,2*S*,5*R*)-2-(propan-2-yl)-5-methyl-cyclohexyloxy)-2-oxoethyl)-4-phenyl-1,3-thiazol-3-ium bromide (1c): The compound was prepared following the procedure described for **1a**. Compound **1c** was isolated as a colorless solid (1.72 g, 19.0 %). For ^{1}H and ^{13}C NMR spectroscopic data see Table 1 and Table 2, respectively. **MS** (FAB+): *m/z* (%) = 373.2 (100) $[M–Br]^+$. **MS** (FAB–): *m/z* (%) = 80.9 (97) $[Br]^–$, 78.9 (100) $[Br]^–$. **HRMS** (FAB+): *m/z* = 373.1950 (calcd. 373.1944 for $C_{21}H_{29}N_2O_2S^+$, $[M–Br]^+$). **HRMS** (FAB–): *m/z* = 80.9163 (Br-81, 49.3 %), 78.9183 (Br-79, 50.7 %) [calcd. 80.916289 for Br-81 (49.31 %), 78.918336 for Br-79 (50.69 %)]. Elemental Analysis: calcd. C 55.63, H 6.45, N 6.18 %; found C 55.30, H 6.61, N 6.24 %.

2-Amino-1-(2-((1*R*,2*S*,5*R*)-2-(propan-2-yl)-5-methyl cyclohexyloxy)-2-oxoethyl)pyridinium bromide (3): To a solution of 2-aminopyridine (0.471 g, 5 mmol, 1.0 equiv.) in acetone (10 mL), (1*R*,2*S*,5*R*)-2-(propan-2-yl)-5-methyl cyclohexyl 2-bromoacetate (**2c**) (1.39 g, 5 mmol, 1.0 equiv.) was added. From the clear orange solution a colorless solid started to precipitate after 10 min. The mixture was heated to reflux for 12 h. The precipitate formed was separated by filtration, washed with 50 mL of cold acetone and dried in vacuo, yielding compound **3** as colorless powder (1.38 g, 74 %). For ^{1}H and ^{13}C NMR spectroscopic data see Table 1 and Table 2, respectively. **MS** (FAB+): *m/z* (%) = 291.2 (100) $[M–Br]^+$. **MS** (FAB–): *m/z* (%) = 80.9 (97) $[Br]^–$, 78.9 (100) $[Br]^–$. **HRMS** (FAB+): *m/z* = 291.2073 (calcd. 291.2067 for $C_{17}H_{27}N_2O_2^+$, $[M–Br]^+$). **HRMS** (FAB–): *m/z* = 80.9163 (Br-81, 49.3 %), 78.9183 (Br-79, 50.7 %) [calcd. 80.916289 for Br-81 (49.31 %), 78.918336 for Br-79 (50.69 %)] Elemental Analysis: calcd. C 54.99, H 7.33, N 7.54 %; found C 54.79, H 7.49, N 7.84 %.

Supporting Information (see footnote on the first page of this article): Tables of all bond lengths and angles observed in the crystal structures of compounds **1a**–**c**.

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