

# Synthesis, NMR Spectroscopy, and Molecular Modeling of 2-Methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine

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**Abstract**—A new synthetic approach to fused azepines was demonstrated on an example of the synthesis of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine. The key stage of the synthesis is the formation of the azepine ring under the Eschweiler–Clark reaction conditions. The Gibbs energy of activation for the inversion of the azepine ring was determined by dynamic <sup>1</sup>H NMR spectroscopy. Molecular modeling of the structure and estimation of the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts were performed for 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine. The magnetic shielding tensors were calculated by the standard GIAO method using the B3LYP/6-31G(d,p)-optimized molecular geometry parameters. The solvent effect was taken into account in the PCM approximation. The calculated <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine are in good agreement with the experimental values observed in the spectra of its DMSO-*d*<sub>6</sub> solution.

**Keywords:** fused azepines, Eschweiler–Clark reaction, chemical shift, coalescence, inversion barrier, GIAO

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Heterocyclic compounds with a 2,3-benzodiazepine core are being actively studied as noncompetitive AMPA receptor antagonists [1–4]. The biological activity of such compounds is best demonstrated by the example of Tofisopam, a well-known anxiolytic agent, or Talampanel [5, 6]. Methods for the synthesis of structural analogs of 2,3-benzodiazepines, where the diazepine fragment is fused with indole [7, 8] and benzofuran [9] fragments, are being developed. Related fused heterocyclic systems based on the azepine ring, such as azepino[4,5-*b*]indoles [10], benzofuro[2,3-*c*]azepines [11], and benzothieno[2,3-*c*]azepines [12, 13], can also be considered as promising structural analogs of 2,3-benzodiazepines in drug design. Despite the potent biological properties of these compounds, the methods of their synthesis are limited in number and diversity.

Therefore, the development of an effective strategy for the synthesis of azepines of this type and a comprehensive study of their properties are relevant. Figure 1 shows the structures of known benzothieno[2,3-*c*]azepines [12, 13]. The goal of the present work was to explore the use of the Eschweiler–Clark reaction for forming the azepine ring on an example of the synthesis of a benzothieno[2,3-*c*]azepine derivative, as well as to study the properties of the synthesized compound by means of NMR spectroscopy and molecular modeling.

The approach used in the present work for the synthesis of an azepine fused with a benzothiophene fragment was based on the classical method of 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridines and 1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridines [14] synthesis, which involves the cyclization reaction of 2-(1-benzothien-3-

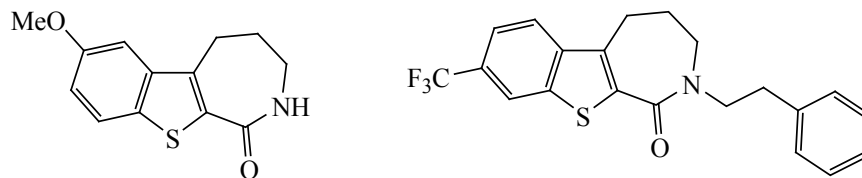


Fig. 1. Structures of known benzothieno[2,3-*c*]azepines [12, 13].

yl)- and 2-(1-benzofuran-3-yl)ethylamines. In our case, we started from 3-(1-benzothien-3-yl)propylamine prepared by the reduction of benzothiophene-3-propanamide (**3**) with diborane (Scheme 1). Amide **3** was synthesized by the reaction of the corresponding acid chloride with an excess of aqueous ammonia. Benzothiophene-3-propionyl chloride was easily obtained by the reaction of the starting acid with phosphorus trichloride in benzene (Scheme 1). The  $^1\text{H}$  NMR spectrum of amide **3** displays a characteristic  $\text{NH}_2$  proton signal at 7.26 ppm and triplet signals of the  $\text{CH}_2$  protons at 2.50 and 3.06 ppm. The proton at the  $\text{C}^2$  atom of the benzothiophene hetero ring appears as a singlet at 6.63 ppm.

Amide **3** was reduced with diborane generated in situ (the reaction proceeding is successful, when freshly distilled and thoroughly dried solvents and reagents are used) to obtain corresponding amine, which was then converted to 3-(1-benzothien-3-yl)propylamine hydrochloride (**4**). The yields of the latter reached 67%.

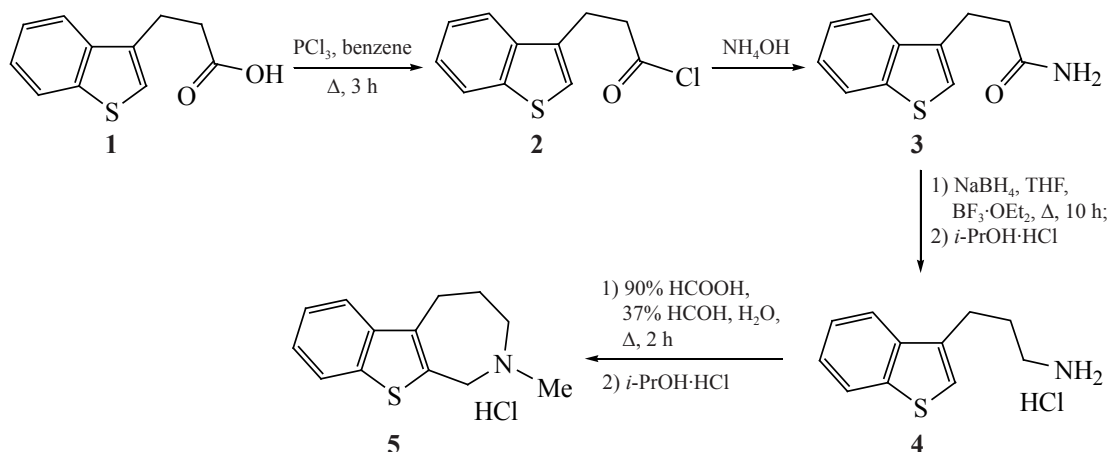
Benzothieno[2,3-*c*]azepine **5** was synthesized by the Eschweiler–Clark reaction with a mixture of formic acid and formaldehyde (Scheme 1). The yields of compound **5** reached 60%.

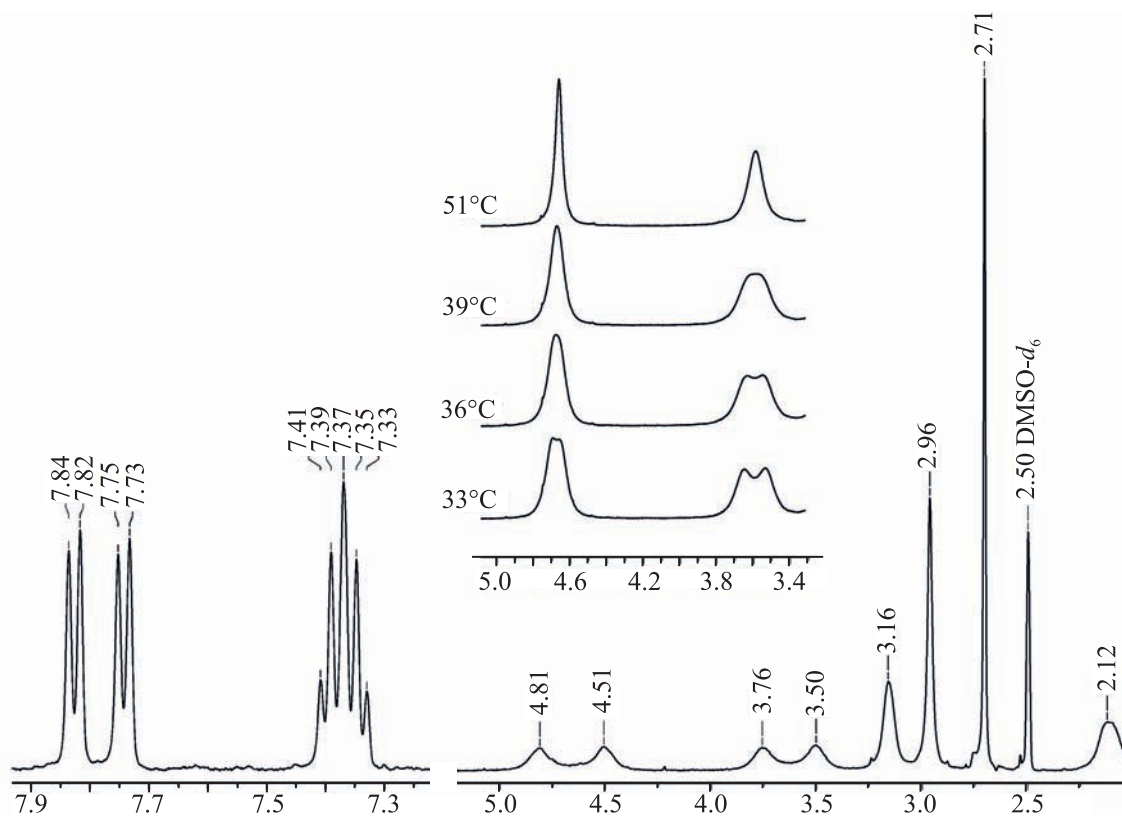
The experimental  $^1\text{H}$  NMR spectrum of azepine **5** in  $\text{DMSO-}d_6$  (Fig. 2) contains groups of signals of the

benzene ring (7.33–7.84 ppm) and azepine ring protons (2.12–4.81 ppm). The  $\text{H}^5$  and  $\text{H}^6$ , as well as  $\text{H}^9$  and  $\text{H}^{10}$  protons (the numbering corresponds to that in Fig. 3) appear as broad signals (3.50, 3.76, 4.51, and 4.81 ppm) indicative of azepine ring inversion. Therewith, the axial and equatorial protons give separate signals.

The structures of the possible conformers of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride (**5**) with different orientations of the azepine ring were studied by molecular modeling. The initial conformational analysis of this compound performed using the Marvin software package [15], revealed two conformers with the lowest energies, which had different mutual orientations of the benzothiene and azepine fragments. Further geometry optimization of these conformers was performed using B3LYP/6-31G(d,p) with the inclusion of nonspecific solvation with DMSO in the GAUSSIAN09 software package [16]. The resulting equilibrium configurations of conformers **C1** and **C2** of azepine hydrochloride **5**, as well as the atom numbering used in the discussion of the results of molecular modeling, are presented in Fig. 3. The geometric parameters of the azepine ring in conformers **C1** and **C2** are listed in Table 1.

Scheme 1. Synthesis of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine.



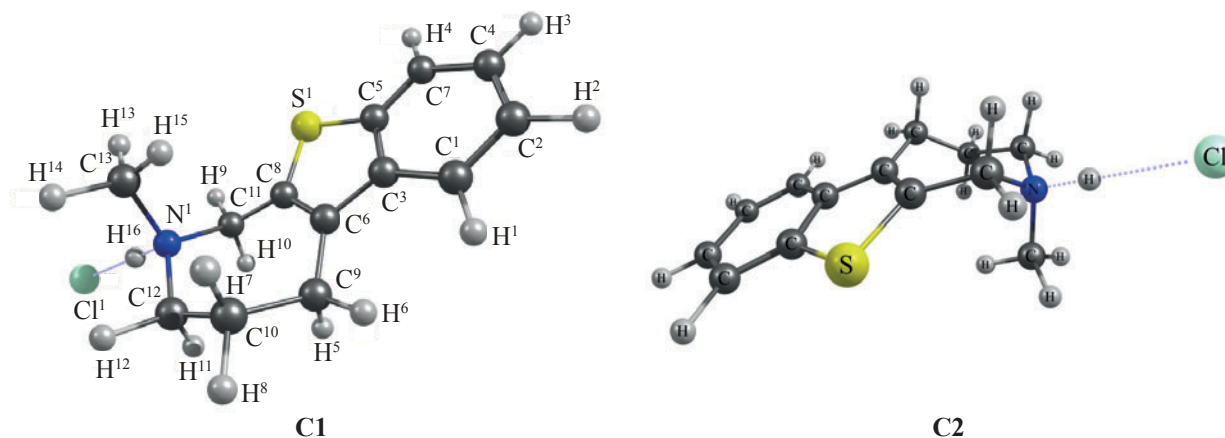


**Fig. 2.**  $^1\text{H}$  NMR spectrum of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride (**5**) in  $\text{DMSO-}d_6$  in the temperature range 24–51°C.

For conformers **C1** and **C2** we also estimated the  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts. The calculated  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts ( $\delta_{\text{calc}}$ , ppm) and the experimental values obtained for a  $\text{DMSO-}d_6$  solution are listed in Table 2 (the  $\delta_{\text{calc}}$  values for magnetically equivalent nuclei are averaged). Note that essential differences in the calculated chemical shifts for conformers **C1** and **C2** are observed between  $\text{H}^5$  and  $\text{H}^6$ , as well as between  $\text{H}^9$

and  $\text{H}^{10}$ , which is due to the inversion of the azepine ring.

The calculated  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of conformers **C1** and **C2** are in good agreement with the experimental chemical shifts in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compound **5** in  $\text{DMSO-}d_6$  (within 0.09–0.66 and 0.4–9.4 ppm, respectively), especially accounting



**Fig. 3.** Equilibrium configurations of and atom numbering in conformers **C1** and **C2** of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride (**5**) [B3LYP/6-31G(d,p)/PCM].

**Table 1.** Geometric parameters of the azepine ring in conformers **C1** and **C2** of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]-benzothieno[2,3-*c*]azepine hydrochloride (**5**) [B3LYP/6-31G(d,p)/PCM]

Atoms	Bond lengths, Å		Atoms	Bond/torsion angles, deg	
	<b>C1</b>	<b>C2</b>		<b>C1</b>	<b>C2</b>
C <sup>6</sup> –C <sup>8</sup>	1.366	1.366			
C <sup>6</sup> –C <sup>9</sup>	1.511	1.511	C <sup>6</sup> –C <sup>9</sup> –C <sup>10</sup>	114.3	114.3
C <sup>9</sup> –C <sup>10</sup>	1.540	1.540	C <sup>9</sup> –C <sup>10</sup> –C <sup>12</sup>	115.9	115.9
C <sup>10</sup> –C <sup>12</sup>	1.528	1.528	C <sup>10</sup> –C <sup>12</sup> –N <sup>1</sup>	116.6	116.6
C <sup>8</sup> –C <sup>11</sup>	1.499	1.499	C <sup>11</sup> –N <sup>1</sup> –C <sup>12</sup>	113.9	113.9
C <sup>11</sup> –N <sup>1</sup>	1.511	1.511	C <sup>8</sup> –C <sup>11</sup> –N <sup>1</sup>	114.2	114.2
C <sup>12</sup> –N <sup>1</sup>	1.511	1.511	C <sup>11</sup> –N <sup>1</sup> –C <sup>13</sup>	113.0	113.0
C <sup>11</sup> –H <sup>10</sup>	1.094	1.091	C <sup>8</sup> –C <sup>6</sup> –C <sup>9</sup> –C <sup>10</sup>	54.4	–54.3
C <sup>12</sup> –H <sup>11</sup>	1.093	1.093	C <sup>6</sup> –C <sup>9</sup> –C <sup>10</sup> –C <sup>12</sup>	72.3	–72.3
C <sup>12</sup> –H <sup>12</sup>	1.092	1.092	C <sup>9</sup> –C <sup>10</sup> –C <sup>12</sup> –N <sup>1</sup>	–66.6	66.5
C <sup>13</sup> –N <sup>1</sup>	1.493	1.493	C <sup>10</sup> –C <sup>12</sup> –N <sup>1</sup> –C <sup>11</sup>	66.7	–66.6
C <sup>9</sup> –H <sup>5</sup>	1.099	1.093	C <sup>12</sup> –N <sup>1</sup> –C <sup>11</sup> –C <sup>8</sup>	–74.1	74.2
C <sup>9</sup> –H <sup>6</sup>	1.093	1.099	N <sup>1</sup> –C <sup>11</sup> –C <sup>8</sup> –C <sup>6</sup>	59.5	–59.6
C <sup>10</sup> –H <sup>7</sup>	1.095	1.095	C <sup>9</sup> –C <sup>6</sup> –C <sup>8</sup> –C <sup>11</sup>	–2.3	2.2
C <sup>10</sup> –H <sup>8</sup>	1.095	1.095	C <sup>8</sup> –C <sup>11</sup> –N <sup>1</sup> –C <sup>13</sup>	57.7	–57.6
C <sup>11</sup> –H <sup>9</sup>	1.091	1.094			
N <sup>1</sup> –H <sup>16</sup>	1.072	1.072			

for the fact that the experimental chemical shifts are affected by such factors as solvent, concentration, and temperature.

Analysis of the data in Table 3 showed that the B3LYP/6-31G(d,p) calculations with the inclusion of nonspecific solvation with DMSO correctly reproduce the <sup>1</sup>H and <sup>13</sup>C chemical shifts for compound **5**. Linear correlations were found between the experimental and calculated (for conformer **C1**) values (Fig. 4) with high correlation coefficients (0.993–0.995). The linear plots are described by Eqs. (1) and (2).

$$^1\text{H NMR: } \delta_{\text{exp}} = (0.93 \pm 0.30) \cdot \delta_{\text{calc}} + (0.44 \pm 0.15), \\ R = 0.9931, n = 15; \quad (1)$$

$$^{13}\text{C NMR: } \delta_{\text{exp}} = (1.01 \pm 0.03) \cdot \delta_{\text{calc}} - (0.11 \pm 3.09), \\ R = 0.9952, n = 13. \quad (2)$$

Evidence for the inversion of the azepine ring in compound **5** and the thermodynamic characteristics of this process were obtained by dynamic NMR

spectroscopy for a solution of this compound in DMSO-*d*<sub>6</sub> in the temperature range 24–51°C. As the temperature of the spectroscopic experiment was raised, the equatorial and axial methylene proton signals shifted closer to each other to coalesce already at 36–39°C (Fig. 2). At higher temperatures these protons appeared as broad singlets at 3.58 and 4.66 ppm, implying fast (on the <sup>1</sup>H NMR scale) azepine ring inversion.

The azepine ring inversion constant  $k_C$  at the coalescence point is given by Eq. (3), where  $\Delta\nu$  is the resonance frequency difference between the signals of the coalescing protons at room temperature [15]:

$$k_C = 2.22\Delta\nu. \quad (3)$$

The Gibbs activation energy of the inversion of the azepine ring at the coalescence point is given by Eq. (4) [17]:

$$\Delta G_C^\ddagger = 4.58T_C[10.32 + \log(\frac{T_C}{k_C})], \quad (4)$$

**Table 2.** Experimental and calculated  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine [B3LYP/6-31G(d,p)/PCM]

Atom	$\delta_{\text{calc}}$ , ppm		$\delta_{\text{exp}}$ , ppm	$ \Delta\delta $ , ppm		Atom	$\delta$ , ppm		$\delta_{\text{exp}}$ , ppm	$ \Delta\delta $ , ppm	
	C1	C2		C1	C2		C1	C2		C1	C2
C <sup>1</sup>	118.31	118.31	121.75	3.44	3.44	H <sup>1</sup>	7.93	7.93	7.74	0.19	0.19
C <sup>2</sup>	120.68	120.68	124.74	4.06	4.06	H <sup>2</sup>	7.64	7.64	7.39	0.25	0.25
C <sup>3</sup>	134.14	134.12	137.70	3.56	3.58	H <sup>3</sup>	7.60	7.60	7.35	0.25	0.25
C <sup>4</sup>	120.97	120.93	124.24	3.27	3.31	H <sup>4</sup>	7.92	7.92	7.83	0.09	0.09
C <sup>5</sup>	141.52	141.54	138.58	2.94	2.96	H <sup>5</sup>	2.90	3.34	3.50	0.60	0.16
C <sup>6</sup>	136.83	136.87	127.39	9.44	9.48	H <sup>6</sup>	3.34	2.90	3.76	0.42	0.86
C <sup>7</sup>	118.46	118.49	122.27	3.81	3.78	H <sup>7</sup>	2.00	2.00	2.12	0.12	0.12
C <sup>8</sup>	131.02	131.05	138.93	7.91	7.88	H <sup>8</sup>	2.00	2.00	2.12	0.12	0.12
C <sup>9</sup>	27.52	27.51	24.36	3.16	3.15	H <sup>9</sup>	3.85	4.49	4.51	0.66	0.02
C <sup>10</sup>	22.76	22.77	22.08	0.68	0.69	H <sup>10</sup>	4.49	3.85	4.81	0.32	0.96
C <sup>11</sup>	53.34	53.36	51.80	1.54	1.56	H <sup>11</sup>	3.35	3.35	3.16	0.19	0.19
C <sup>12</sup>	58.85	58.82	58.41	0.44	0.41	H <sup>12</sup>	3.35	3.35	3.16	0.19	0.19
C <sup>13</sup>	35.41	35.39	40.57	5.16	5.18	H <sup>13</sup>	2.48	2.48	2.71	0.23	0.23
						H <sup>14</sup>	2.48	2.48	2.71	0.23	0.23
						H <sup>15</sup>	2.48	2.48	2.71	0.23	0.23

where  $\Delta G_C^\ddagger$  is the activation Gibbs energy of azepine ring inversion, cal/mol;  $T_C$ , coalescence temperature, K; and  $k_C$ , rate constant of azepine ring inversion,  $\text{s}^{-1}$ .

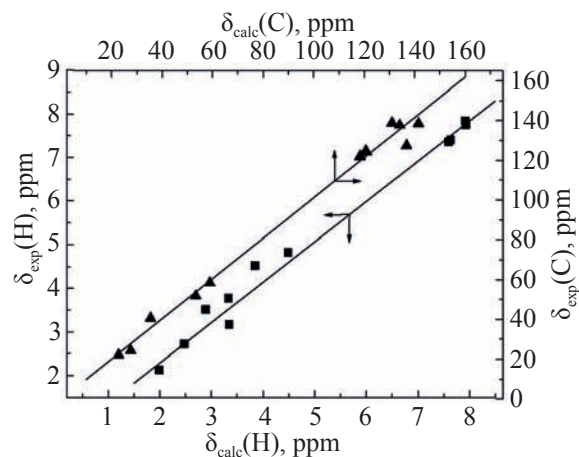
The calculated  $k_C$  and  $\Delta G_C^\ddagger$  values for compound **5** are listed in Table 3. The error of 0.2 kcal/mol specified in Table 3 reflects the uncertainty in the determination of the coalescence point of  $\pm 3$  K [17].

The experimental inversion barrier of the azepine ring (14.8 kcal/mol) in compound **5** is close to those determined for benzazepines in benzene ( $14.2 \pm 0.2$  kcal/mol) [18]. As judged from the coalescence point and  $\Delta G_C^\ddagger$ , azepine **5** is conformationally less mobile than many benzazepines [18, 19] and compares in conformational mobility with benzofurodiazepines [9].

#### EXPERIMENTAL

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance spectrometer at 400 and 100 MHz, respectively, in  $\text{DMSO}-d_6$ , internal reference TMS. The melting points were determined on a Boetius hot stage and are uncorrected. The elemental analyses

were obtained on an Elementar Vario MICRO Cube analyzer. The mass spectra were measured on an Agilent 1100 LC/MSD VL instrument with APCI ionization. Chromatographic separation was performed on a ZORBAX SB-C18 column (length 50 mm, diameter



**Fig. 4.** Linear correlations between the experimental and calculated (for conformer C1) NMR chemical shifts of (■)  $^1\text{H}$  and (▲)  $^{13}\text{C}$  nuclei for 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride.

**Table 3.** Parameters of the  $^1\text{H}$  NMR spectrum for the protons of two methylene groups and parameters of the inversion of the azepine ring in 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride

Protons	$\Delta_{\text{ax}}$ , ppm	$\Delta_{\text{eq}}$ , ppm	$\Delta\nu$ , $\text{s}^{-1}$	$T_{\text{C}}$ , K	$k_{\text{C}}$ , $\text{s}^{-1}$	$\Delta G_{\text{C}}^{\ddagger}$ , kcal/mol
H <sup>5</sup> , H <sup>6</sup>	3.50	3.76	100	309	222	14.8 ± 0.2
H <sup>9</sup> , H <sup>10</sup>	4.51	4.81	120	312	266	14.8 ± 0.2

4.6 mm), mobile phase 95% acetonitrile/5% water/0.1% trifluoroacetic acid at a flow rate of 3.0 mL/min, gradient elution.

**3-(1-Benzothien-3-yl)propionic acid (1).** A mixture 2.2 g (10 mmol) of methyl benzothiophene-3-propionate, 0.6 g (15 mmol) of NaOH, 25 mL of water, and 5 mL of isopropanol was refluxed for 1 h and then cooled, acidified with HCl to pH 2.0–3.0, and allowed to stand for 12 h at room temperature. The precipitate that formed was filtered off, washed with water, dissolved under heating in a solution of 1.3 g (15 mmol) of NaHCO<sub>3</sub> in 25 mL of water, and refluxed for 15 min with the addition of carcoal. The mixture was filtered, cooled, acidified with HCl to pH 2.0–3.0, and allowed to stand for 12 h at room temperature. The precipitate that formed was filtered off, washed with water, and dried. Yield 1.49 g (72%). mp 138–140°C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.66 t (2H, 2-CH<sub>2</sub>,  $J$  8.0 Hz), 3.08 t (2H, 3-CH<sub>2</sub>,  $J$  8.0 Hz), 7.28 br.s (1H, 2-H), 7.33 t (1H, 6-H,  $J$  8.0 Hz), 7.38 t (1H, 5-H,  $J$  8.0 Hz), 7.78 d (1H, 4-H,  $J$  8.0 Hz), 7.86 d (1H, 7-H,  $J$  8.0 Hz), 12.03 br.s (1H, OH). Found, %: C 64.13; H 4.94. C<sub>11</sub>H<sub>10</sub>O<sub>2</sub>S. Calculated, %: C 64.05; H 4.89.  $M$  206.26.

**3-(1-Benzothien-3-yl)propanamide (3).** A mixture of 10.3 g (50 mmol) of acid **1** and 4.4 mL (50 mmol) of PCl<sub>3</sub> in 100 mL of anhydrous benzene was refluxed for 3 h and then cooled, decanted, and evaporated in a vacuum. The residue (benzothiophene-3-propionyl chloride) was dissolved in 30 mL of anhydrous THF, and the solution was added dropwise with stirring to 60 mL of 25% aqueous ammonia at  $\leq 0^\circ\text{C}$ . The reaction mixture was stirred for 1 h, diluted with 200 mL of water, and allowed to stand overnight. The precipitate that formed was filtered off, washed with water (4 × 20 mL), and dried. Yield 7.0 g (68%). mp 78–80°C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.50 t (2H, 2-CH<sub>2</sub>,  $J$  8.0 Hz), 3.06 t (2H, 3-CH<sub>2</sub>,  $J$  8.0 Hz), 6.63 br.s (1H, 2-H,  $J$  8.0 Hz), 7.26 br.s (2H, CONH<sub>2</sub>), 7.32 t (1H, 6-H,  $J$  8.0 Hz), 7.37 t (1H, 5-H,  $J$  8.0 Hz), 7.80 d (1H, 4-H,  $J$  8.0 Hz), 7.84 d (1H, 7-H,  $J$  8.0 Hz). Found, %: C 64.42; H 5.47; N 6.78. C<sub>11</sub>H<sub>11</sub>NOS. Calculated, %: C 64.36; H 5.40; N 6.82.  $M$  205.28.

**[3-(1-Benzothien-3-yl)propyl]amine hydrochloride (4).** Sodium borohydride, 11.4 g (0.3 mol), was added to a solution of 20.5 g (0.1 mol) of amide **3** in 200 mL of anhydrous THF. The mixture was cooled to  $\leq -3^\circ\text{C}$ , followed by the dropwise addition of 64.0 g (0.45 mol) of freshly distilled BF<sub>3</sub>·OEt<sub>2</sub> over the course of 1 h. The resulting mixture was allowed to stand at room temperature for 12 h and then refluxed with stirring for 10 h. The solvent was removed in a vacuum, and the residue was decomposed with a mixture of 500 g of ice and 25 mL of HCl. The solution was filtered, brought to pH 10.0 with an alkali solution, and extracted with benzene (4 × 100 mL). The extract was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in a vacuum. The residual base was dissolved in ether and transformed into hydrochloride by treatment with alcoholic HCl. Yield 15.3 g (67%). mp 153–155°C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.12 quintet (2H, 2-CH<sub>2</sub>,  $J$  8.0 Hz), 2.90 t (2H, 1-CH<sub>2</sub>,  $J$  8.0 Hz), 2.96 t (2H, 3-CH<sub>2</sub>,  $J$  8.0 Hz), 7.31 t (1H, 6-H,  $J$  8.0 Hz), 7.36 t (1H, 5-H,  $J$  8.0 Hz), 7.41 s (1H, 2-H), 7.81 d (1H, 4-H,  $J$  8.0 Hz), 7.83 d (1H, 7-H,  $J$  8.0 Hz), 8.43 br.s (3H, NH<sub>2</sub>, HCl). Found, %: C 58.04; H 6.17; N 6.21. C<sub>11</sub>H<sub>13</sub>NS·HCl. Calculated, %: C 58.01; H 6.20; N 6.15.  $M$  227.75.

**2-Methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride (5).** A mixture of 450 mg (2 mmol) of hydrochloride **4**, 4 mL of 90% formic acid, 4 mL of 37% formaldehyde, and 4 mL of water was refluxed for 2 h, cooled and added into 60 mL of 1 M NaOH solution. The precipitated oily material was extracted with chloroform (4 × 20 mL). The extract was washed with 20 mL of water, dried over MgSO<sub>4</sub>, and evaporated in a vacuum. The residual oil was treated with alcoholic HCl to obtain hydrochloride. Yield 305 mg (60%). mp 244–246°C.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.12 br.s (2H, 4-CH<sub>2</sub>), 2.71 s (3H, N-Me), 3.16 br.s (2H, 3-CH<sub>2</sub>), 3.50 br.s (1H, 5-CH<sub>2</sub>), 3.76 br.s (1H, 5-CH<sub>2</sub>), 4.51 br.s (1H, 1-CH<sub>2</sub>), 4.81 br.s (1H, 1-CH<sub>2</sub>), 7.35 t (1H, 8-H,  $J$  8.0 Hz), 7.39 t (1H, 7-H,  $J$  8.0 Hz), 7.74 d (1H, 6-H,  $J$  8.0 Hz), 7.83 d (1H, 9-H,  $J$  8.0 Hz), 12.66 br.s (1H, HCl).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 22.1, 24.4, 40.6, 51.8, 58.4, 121.8, 122.3, 124.2,

124.7, 127.4, 137.7, 138.6, 138.9. Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 218.2 [ $M + 1$ ]<sup>+</sup>. Found, %: C 61.45; H 6.39; N 5.49. C<sub>13</sub>H<sub>15</sub>NS·HCl. Calculated, %: C 61.52; H 6.35; N 5.52.  $M$  253.79.

**Quantum-chemical calculations of the molecular geometry parameters and <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts of azepine hydrochloride **5**.** The molecular geometry, electronic structure, and thermodynamic parameters of compound **5** were calculated using GAUSSIAN09 software package [16] at the DFT/B3LYP/6-31G(d,p) level of theory [20–22]. The effect of the solvent (DMSO) was taken into account in the PCM approximation [23]. The initial molecular geometry of conformers **C1** and **C2** was generated using the algorithm of complete inclusion of possible geometric and steric factors implemented in the Conformer plugin of the Marvin software package [15]. This algorithm allows generation of molecular structures with complete analysis of the carbon skeleton, functional groups and heteroatoms, geometric isomers, and asymmetric centers. First optimization of the molecular geometry of the conformers was performed, after which harmonic vibrational frequencies and thermodynamic parameters were calculated. The stationary points obtained with the optimized molecular geometry were defined as minima in view of the absence of negative harmonic vibrational frequencies.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the conformers of compound **5** were modeled according to [24]. The <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts were calculated by the standard GIAO method [25] with the inclusion of the nonspecific solvation with DMSO by the PCM model. The equilibrium geometries of the conformers obtained by the B3LYP/6-31G(d,p)/PCM calculations were used. The calculated magnetic shielding tensors ( $\chi$ , ppm) were used to estimate the <sup>1</sup>H and <sup>13</sup>C chemical shifts ( $\delta$ , ppm). For the reference we used TMS, for which full geometry optimization and calculation of  $\chi$  were used at the same level of theory with the same basis set. The <sup>1</sup>H and <sup>13</sup>C chemical shifts were estimated as the differences in the  $\chi$  values for the respective nuclei in TMS and azepine.

## CONCLUSIONS

The example of the synthesis of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride was used to demonstrate the possibility to form the azepine ring under the the Eschweiler–Clark reaction conditions. The proposed approach can be

used for the synthesis of fused azepines. The features of the <sup>1</sup>H NMR spectrum of 2-methyl-2,3,4,5-tetrahydro-1*H*-[1]benzothieno[2,3-*c*]azepine hydrochloride are explained by the inversion of the azepine ring. The barrier to inversion of the azepine ring of  $14.8 \pm 0.2$  kcal/mol was estimated by dynamic NMR. Molecular structure modeling and estimation of the NMR chemical shifts of <sup>1</sup>H and <sup>13</sup>C nuclei were performed for the synthesized compound. The calculated values were in good agreement with those in the experimental spectra obtained for DMSO-*d*<sub>6</sub> solutions.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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