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Synthesis and Spectral Characteristics of *N*-(2,2,2-Trichloro-1-Thioureidoethyl)Carboxamides and 2-(1-Carboxamido-2,2,2-Trichloroethyl)Isothiouronium Chlorides

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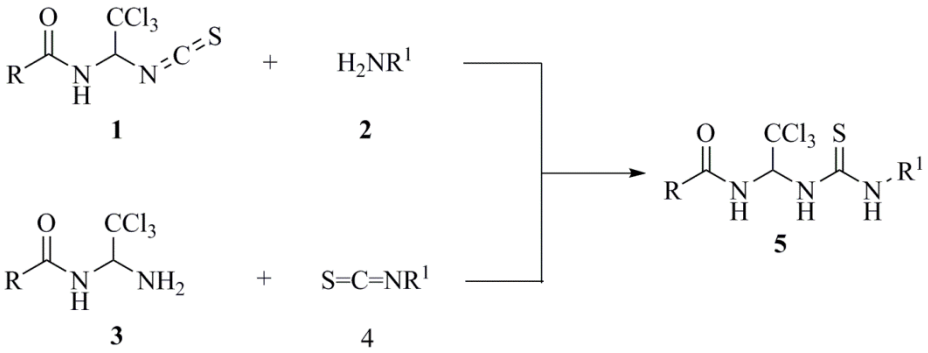
Abstract: Monosubstituted thioureas have found wide application in various fields of science and technology. They are widely used in organic synthesis to obtain various heterocyclic and acyclic compounds and are also of great interest in medicine, pharmacy, and agriculture as biologically active substances. In this work, we reported the synthesis of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides obtained by hydrazinolysis of the starting acylated thioureas. Target products were obtained in 87-91% yields. The paper also reported on the synthesis of a series of 2-(1-carboxamido-2,2,2-trichloroethyl)isothiouronium chlorides by S-amido alkylation of thiourea with N-(1,2,2,2-tetrachloroethyl)carboxamides. Attempts to synthesize *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides based on the obtained isothiuronium salts by their dehydrochlorination with triethylamine were unsuccessful. The structure of all obtained compounds was confirmed by ^{1}H, ^{13}C NMR, IR spectroscopy, and mass spectrometry data.

Keywords: synthesis; thiourea; isothiouronium salts; hydrazinolysis; solvent-free.

1. Introduction

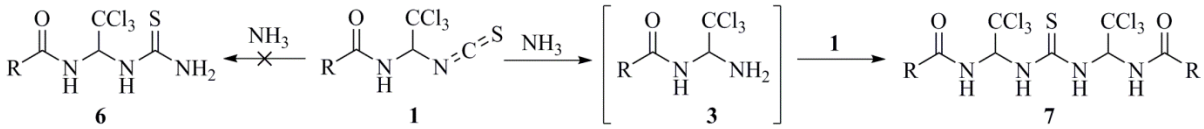
Monosubstituted thioureas are classical reagents for the synthesis of 2-amino-1,3-thiazole derivatives [1,2], pyrimidine-2-thiones [3-5], imidazole-2-thione [6-8], and other heterocyclic and acyclic systems. In addition, the thiourea fragment is an active pharmacophore group and is a component of many drugs [9-12].

Amidoalkylated *N*,*N'*-substituted thioureas are fairly well described in the scientific literature. These compounds are obtained by adding amines **2** to *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides (**1**) or *N*-(1-amino-2,2,2-trichloroethyl)carboxamides (**3**) to isothiocyanates **4** (Scheme 1) [13-19]. Due to the presence of several reaction centers in thioureas **5**, they are successfully used for the synthesis of heterocyclic [13,16-19], acyclic [20], and complex [21] compounds. In addition, some thioureas **5** show high or moderate biological activity. Among these compounds, effective inhibitors of the GADD34:PP1 holoenzyme complex are known, for example, Salubrinal [22], Sal003 [23] and their structural analogs [14,15,24], as well as moderate inhibitors of the hERG potassium channel [25] and some enzymes of the CYP family [26].



Scheme 1. Synthesis of amido alkylated *N,N'*-substituted thioureas.

The attempts to synthesize monosubstituted *N*-amido alkylated thioureas were unsuccessful. Thus, in the interaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides (**1**) with ammonia, the formation of monosubstituted thioureas **6** was not observed, but symmetrical *N,N'*-diamido alkylated thioureas **7** were obtained [27] (Scheme 2). It is assumed that *N*-(1-amino-2,2,2-trichloroethyl)carboxamide (**3**) was formed at the first stage of this transformation, which was then added to the initial isothiocyanate **1**.



Scheme 2. The reaction of *N*-(2,2,2-trichloro-1-isothiocyanatoethyl)carboxamides (**1**) with ammonia.

In this work, we reported the synthesis of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides **6**, which were obtained by hydrazinolysis of the starting acylated thioureas [28], as well as the synthesis of the 2-(1-carboxamido-2,2,2-trichloroethyl)isothiouronium chlorides as the product of another unsuccessful attempt to synthesize monosubstituted *N*-amido alkylated thioureas **6**.

2. Materials and Methods

IR spectra were recorded on KBr pellets using a Spectrum BX II spectrometer. The FAB mass spectra were recorded on a VG7070 instrument. Ions were desorbed from samples in meta-nitrobenzyl alcohol by an 8-keV argon beam. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured for solutions in DMSO-d_6 using a Varian VXR-400 spectrometer. Residual solvent signals were used as standards. Elemental analysis was performed on a LECO CHNS-900 instrument. The reaction and purity of the compounds were monitored by TLC on Silufol UV-254 plates. A mixture of chloroform/acetone (3:1) was used as an eluent for thioureas **6a-d**, and a mixture of chloroform/acetone/methanol (3:1:1) was used for isothiuronium salts **12a-d**.

*2.1. Synthesis of 2-(1-carboxamido-2,2,2-trichloroethyl)isothiouronium chlorides (**12a-d**).*

$SOCl_2$ (12 mmol) was added to 10 mmol of the corresponding *N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamide (**8**) [29] in 25 mL of CCl_4. The mixture was refluxed for 1.5-2 hours, then the reaction mass was cooled, and the solvent was evaporated on a rotary evaporator. Dry residue **9** was washed with 10 mL of hexane, filtered, and dried for 10-15 minutes. Then, chlorine derivative **9** was dissolved in 15 mL of dry acetonitrile, and 10 mmol

(0.76 g) of thiourea (**11**) was added to the resulting solution. The mixture was left for 2 hours. The precipitated isothiuronium salt **12** was filtered and purified by recrystallization from acetonitrile.

*2.2. 2-(1-Acetamido-2,2,2-trichloroethyl)isothiouronium chloride (**12a**).*

White crystals; yield 84% (2.53 g); mp 124-126 °C (MeCN); R_f = 0.33. IR: ν_{max} 3331, 3287, 3042 (NH), 2874, 2774 (CH), 1664 (C=O), 1652 (C=N) cm^{-1}. ^1H NMR: δ 8.58 (br. s, 1H, NH), 6.57 (br. s, 4H, NH), 5.73 (d, J = 9.3 Hz, 1H, CH), 1.92 (s, 3H, CH_3). ^{13}C NMR: δ 167.9 (C=O), 164.6 ($H_2N-\underline{C}=NH_2^+$), 102.1 ($CCl_3$), 72.6 (CH), 23.4 ($CH_3$). FAB-MS: m/z 300 $[M+H]^+$. Anal. Calcd (%) for $C_5H_9Cl_4N_3OS$ (301.01): C, 19.95; H, 3.01; N, 13.96; S, 10.65. Found: C, 19.90; H, 2.98; N, 13.99; S, 10.69.

*2.3. 2-(2,2,2-Trichloro-1-cinnamamidoethyl)isothiouronium chloride (**12b**).*

White crystals; yield 86% (3.35 g); mp 172-174 °C (MeCN); R_f = 0.24. IR: ν_{max} 3292, 3108, 3058 (NH), 2858, 2728 (CH), 1659 (C=O), 1551 (C=N) cm^{-1}. ^1H NMR: *δ* 9.87 (d, *J* = 8.8 Hz, 1H, NH), 8.92 (br. s, 4H, NH), 7.58-7.56 (m, 2H, $H_{arom.}$), 7.51 (d, *J* = 15.8 Hz, 1H, =CH-*cis*), 7.40-7.36 (m, 3H, $H_{arom.}$), 6.80 (d, *J* = 15.8 Hz, 1H, =CH-*trans*), 6.42 (d, *J* = 8.8 Hz, 1H, CH). ^{13}C NMR: *δ* 168.1 (C=O), 165.4 ($H_2N-\underline{C}=NH_2^+$), 141.2 ($C_6H_5\underline{C}H=CH$), 135.8, 129.9, 129.6, 127.9 ($C_{arom.}$), 121.0 ($C_6H_5CH=\underline{C}H$), 101.9 (CCl_3), 72.8 (CH). FAB-MS: m/z 388 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_{13}Cl_4N_3OS$ (389.12): C, 37.04; H, 3.37; N, 10.80; S, 8.24. Found: C, 37.00; H, 3.33; N, 10.84; S, 8.29.

*2.4. 2-(1-Benzamido-2,2,2-trichloroethyl)isothiouronium chloride (**12c**).*

White crystals; yield 89% (2.34 g); mp 146-148 °C (MeCN); R_f = 0.40. IR: ν_{max} 3336, 3183, 3151, 3030, 2982 (NH), 2858, 2765 (CH), 1673 (C=O), 1651 (C=N) cm^{-1}. ^1H NMR: *δ* 10.04 (d, *J* = 9.3 Hz, 1H, NH), 9.70 (br. s, 4H, NH), 7.91-7.89 (m, 2H, $H_{arom.}$), 7.55-7.53 (m, 3H, $H_{arom.}$), 7.06 (d, *J* = 9.3 Hz, 1H, CH). ^{13}C NMR: *δ* 168.8 (C=O), 165.9 ($H_2N-\underline{C}=NH_2^+$), 135.7, 131.8, 131.5, 129.9 ($C_{arom.}$), 101.9 (CCl_3), 74.5 (CH). FAB-MS: m/z 362 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_{11}Cl_4N_3OS$ (363.08): C, 33.08; H, 3.05; N, 11.57; S, 8.83. Found: C, 33.02; H, 3.02; N, 11.61; S, 8.87.

*2.5. 2-(2,2,2-Trichloro-1-(4-methylbenzamido)ethyl)isothiouronium chloride (**12d**).*

White crystals; yield 88% (3.32 g); mp 114-116 °C (MeCN); R_f = 0.38. IR: ν_{max} 3352, 3109 (NH), 2973, 2871, (CH), 1662 (C=O), 1652 (C=N) cm^{-1}. ^1H NMR: *δ* 10.02 (d, *J* = 9.1 Hz, 1H, NH), 9.67 (br. s, 4H, NH), 7.76-7.74 (d, *J* = 7.8 Hz, 2H, $H_{arom.}$), 7.34-7.31 (m, *J* = 7.8 Hz, 2H, $H_{arom.}$), 6.84 (d, *J* = 9.1 Hz, 1H, CH). ^{13}C NMR: *δ* 168.2 (C=O), 165.7 ($H_2N-\underline{C}=NH_2^+$), 141.6, 131.4, 128.7, 127.9 ($C_{arom.}$), 102.1 (CCl_3), 74.4 (CH), 21.8 (CH_3). FAB-MS: m/z 376 $[M+H]^+$. Anal. Calcd (%) for $C_{11}H_{13}Cl_4N_3OS$ (377.11): C, 35.04; H, 3.47; N, 11.14; S, 8.50. Found: C, 35.00; H, 3.44; N, 11.19; S, 8.54.

*2.6. Synthesis of N-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides (**13a-d**).*

Acylated thioureas **13a-d** were obtained by the addition of amino derivatives **6a-d** to benzoyl isothiocyanate in acetonitrile, as described in [30]. Compounds **13a-d** had been described before [14,30].

*2.7.Synthesis of N-(2,2,2-trichloro-1-thioureidoethyl)acetamides (**6a-e**).*

1.5 mL of hydrazine hydrate was added to 10 mmol of one of the acylthioureas **13**. The mixture was heated to 25 °C for 10-15 minutes with vigorous stirring. The resulting pasty mass was left for 2 hours at room temperature, then treated with 40 mL of water and filtered. The product was dried and purified by recrystallization from ethanol.

*2.8. N-(2,2,2-Trichloro-1-thioureidoethyl)acetamide (**6a**).*

White solid; yield 89% (2.35 g); mp 231-233 °C (EtOH); R_f = 0.22. IR: ν_{max} 3331, 3048 (NH), 2927, 2869 (CH), 1668 (C=O) cm^{-1}. ^1H NMR: δ 8.74 (d, J = 8.8 Hz, 1H, NH), 8.00-7.93 (m, 2H, NH), 7.56 (br. s, 1H, NH), 7.10 (br. s, 1H, CH), 1.92 (s, 3H, CH_3). ^{13}C NMR: δ 182.1 (C=S), 167.9 (C=O), 102.1 (CCl_3), 75.6 (CH), 23.7 (CH_3). FAB-MS: m/z 264 $[M+H]^+$. Anal. Calcd (%) for $C_5H_8Cl_3N_3OS$ (264.55): C, 22.70; H, 3.05; N, 15.88; S, 12.12. Found: C, 22.73; H, 3.01; N, 15.92; S, 12.18.

*2.9. N-(2,2,2-Trichloro-1-thioureidoethyl)cinnamamide (**6b**).*

White solid; yield 87% (3.07 g); mp 228-230 °C (EtOH); R_f = 0.19. IR: ν_{max} 3329, 3054 (NH), 2918, 2871 (CH), 1664 (C=O) cm^{-1}. ^1H NMR: 9.22 (d, J = 6.8 Hz, 1H, NH), 8.08-7.96 (m, 5H, 3NH+2$H_{arom.}$), 7.64-7.61 (m, 3H, $H_{arom.}$), 7.46 (d, J = 14.7 Hz, 1H, =CH-*cis*), 7.35 (br. s, 1H, CH), 6.78 (d, J = 14.7 Hz, 1H, =CH-*trans*). ^{13}C NMR: δ 182.4 (C=S), 168.2 (C=O), 140.8 (C_6H_5CH=CH), 135.5, 129.7, 129.4, 128.4 ($C_{arom.}$), 120.4 (C_6H_5CH=CH), 103.0 (CCl_3), 74.8 (CH). FAB-MS: m/z 352 $[M+H]^+$. Anal. Calcd (%) for $C_{12}H_{12}Cl_3N_3OS$ (352.66): C, 40.87; H, 3.43; N, 11.92; S, 9.09. Found: C, 40.83; H, 3.40; N, 11.95; S, 9.12.

*2.10. N-(2,2,2-Trichloro-1-thioureidoethyl)benzamide (**6c**).*

White solid; yield 91% (2.97 g); mp 214-216 °C (EtOH); R_f = 0.18. IR: ν_{max} 3341, 3052 (NH), 2929, 2882 (CH), 1667 (C=O) cm^{-1}. ^1H NMR: δ 9.21 (d, J = 6.8 Hz, 1H, NH), 8.00-7.86 (m, 5H, 3NH+2$H_{arom.}$), 7.61-7.57 (m, 1H, $H_{arom.}$), 7.53-7.50 (m, 2H, $H_{arom.}$), 7.37 (br. s, 1H, CH). ^{13}C NMR: δ 181.8 (C=S), 168.6 (C=O), 135.6, 132.0, 131.4, 130.3 ($C_{arom.}$), 102.8 (CCl_3), 77.6 (CH). FAB-MS: m/z 326 $[M+H]^+$. Anal. Calcd (%) for $C_{10}H_{10}Cl_3N_3OS$ (326.62): C, 36.77; H, 3.09; N, 12.87; S, 9.82. Found: C, 36.74; H, 3.05; N, 12.92; S, 9.88.

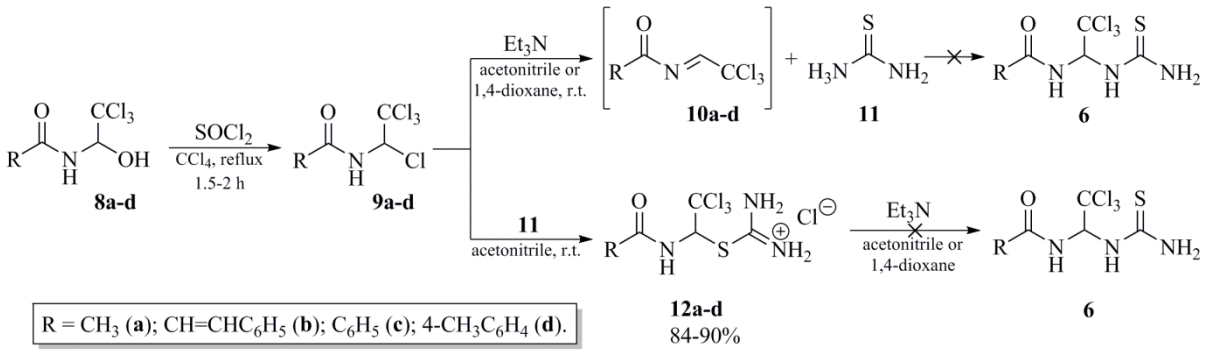
*2.11. 4-Methyl-N-(2,2,2-trichloro-1-thioureidoethyl)benzamide (**6d**).*

White solid; yield 90% (3.07 g); mp 211-213 °C (EtOH); R_f = 0.27. IR: ν_{max} 3334, 3108, 3047 (NH), 2958, 2881 (CH), 1665 (C=O) cm^{-1}. ^1H NMR: δ 9.02 (br. s, 1H, NH), 7.84-7.78 (m, 5H, 3NH+2$H_{arom.}$), 7.33-7.31 (m, 3H, 2$H_{arom.}$+CH). ^{13}C NMR: δ 184.1 (C=S), 165.6 (C=O), 141.7, 131.7, 128.9, 128.2 ($C_{arom.}$), 102.7 (CCl_3), 75.0 (CH), 21.6 (CH_3). FAB-MS: m/z 340 $[M+H]^+$. Anal. Calcd (%) for $C_{11}H_{12}Cl_3N_3OS$ (340.65): C, 38.79; H, 3.55; N, 12.34; S, 9.41. Found: C, 38.82; H, 3.51; N, 12.37; S, 9.47.

3. Results and Discussion

Monosubstituted *N*-amidoalkylated thioureas, *N*-(2,2,2-trichloro-1-thioureidoethyl) carboxamides (**6**) are of great interest for organic and coordination chemistry due to the presence of several reaction centers in their molecule. We made several attempts to synthesize these compounds in this investigation. The first approach was based on the interaction of *N*-

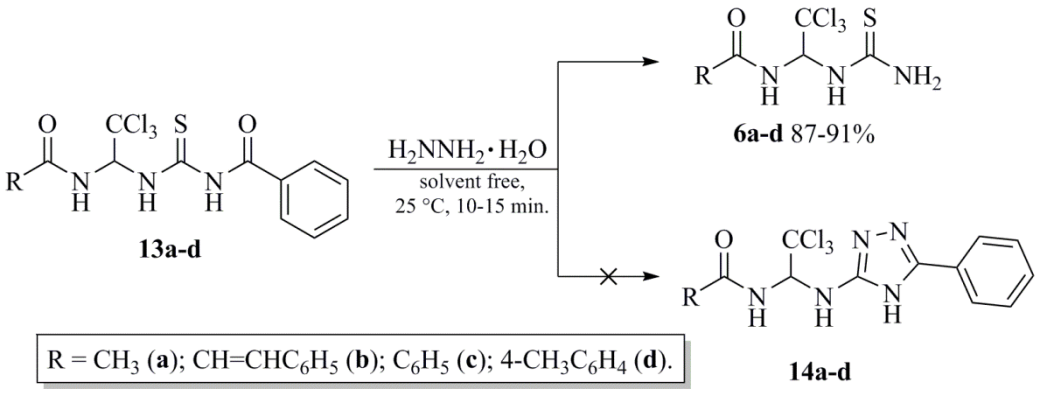
(1,2,2,2-tetrachloroethyl)carboxamides **9a-d** with thiourea with or without triethylamine (Scheme 3). The interaction of chlorine derivatives **9a-d** with triethylamine in anhydrous acetonitrile or dioxane led to the formation of acylimines **10a-d** [31,32]. After the addition of thiourea (**11**) to the resulting acylimines, the reaction mass was strongly resinified, and monosubstituted thioureas 6 or any other products could not be isolated. In turn, the interaction of *N*-(1,2,2,2-tetrachloroethyl)carboxamides **9a-d** with thiourea in dry acetonitrile led to the formation of *S*-amidoalkylation products corresponding to 2-(1-carboxamido-2,2,2-trichloroethyl)isothiouronium chlorides (**12a-d**). Further interaction of isothiuronium salts **12a-d** with triethylamine in acetonitrile or 1,4-dioxane also led to resinification of the reaction mixture and thiourea **6** [33], and no other products were isolated.



Scheme 3. The reaction of *N*-(1,2,2,2-tetrachloroethyl)carboxamides **9** with thiourea.

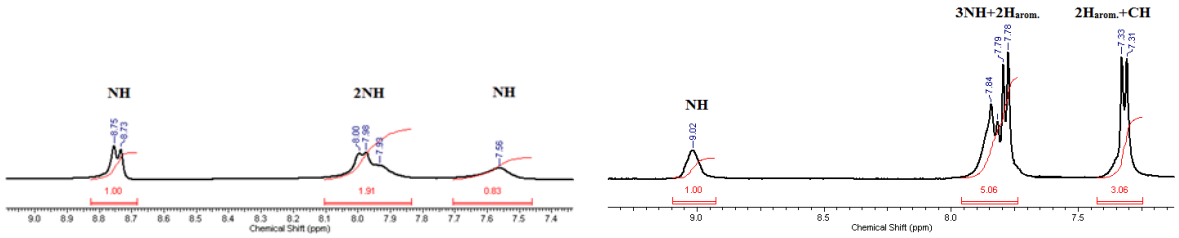
Isothiuronium salts **12a-d** were colorless crystalline substances that were easily isolated from the reaction mixture. Their structure was reliably proven by complex spectral investigations. In the ^{1}H NMR spectra of compounds **12a-d**, the signals of the amide NH proton were characteristic and appeared at 10.0-8.6 ppm as a doublet or broadened singlet, a doublet signal appeared at 7.1-5.7 ppm of the CH proton, as well as a broadened singlet signal of four protons appeared at 9.7-6.6 ppm corresponding to isothiuronium group [34-36]. In the ^{13}C NMR spectra of compounds **12a-d**, the signals of the C=O group were characteristic at 168.8-167.9 ppm, the signals of the carbon $H_2N{-}C{=}NH_2^+$ group – at 165.9-164.6 ppm, and the signals of the CCl_3 group and carbon CH – at 102.1-101.8 ppm and 74.5-70.8 ppm, respectively. In the IR spectra of the obtained isothiuronium salts, broad, intense absorption bands of NH bonds were observed at 3330-3040 cm^{-1}, absorption bands corresponding to the C=O group – at 1670-1660 cm^{-1} and absorption bands of the C=N bond of isothiuronium fragment – at 1655-1650 cm^{-1} [35,36]. Mass spectrometry data confirmed the molecular weight of compounds **12a-d**.

N-(2,2,2-Trichloro-1-thioureidoethyl)carboxamides **6a-d** were prepared using a different approach. We took *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides **13a-d** as initial reagents. At room temperature and without solvent, hydrazinolysis of these compounds led to the formation of target products **6a-d**. In contrast, the formation of amido alkylated derivatives of 2-amino-1,3,5-triazole **14a-d** [37] did not occur (Scheme 4).



Scheme 4. Synthesis of *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides **6a-d**.

The structure of thioureas **6a-d** was proven by complex spectral investigations. In the 1H NMR spectra of compounds 6a-d, the signals of four NH protons were characteristic. The amide proton appeared as a doublet or a broadened singlet at 9.2-8.7 ppm; the signals of the remaining NH protons shifted to the aromatic region and were mainly part of the multiplet signals with aromatic hydrogens. The exception was compound 6a, which had no aromatic ring in its structure. In this case, the NH_2 group appeared as a multiplet, and the third NH proton of the thioureide fragment appeared as a broadened singlet (Figure 1).



(**a**) (**b**)

Figure 1. Comparison of the NH proton signals positions of compounds **6a (a)** and **6d (b)** in the ^{1}H NMR spectra.

In the ^{13}C NMR spectra of compounds **6a-d**, the C=S and C=O carbon signals appeared at 184.1-181.8 ppm and 168.6-165.6 ppm, respectively. The signals of the CCl_3 group and CH carbon appeared at 103.0-102.1 ppm and 77.6-75.0 ppm, respectively. In the IR spectra of the obtained thioureas, absorption bands of NH bonds were observed at 3340-3050 cm^{-1}, and absorption bands corresponding to the C=O group were observed at 1670-1665 cm^{-1}. Mass spectrometry data confirmed the molecular weight of compounds **6a-d**.

4. Conclusions

In this work, we have proposed a method for the synthesis of monosubstituted *N*-amido alkylated thioureas – *N*-(2,2,2-trichloro-1-thioureidoethyl)carboxamides. The method for preparing these compounds is based on the hydrazinolysis of *N*-((1-carboxamido-2,2,2-trichloroethyl)carbamothioyl)benzamides in the absence of a solvent. It has also been shown that the interaction of *N*-(1,2,2,2-tetrachloroethyl)carboxamides with thiourea in dry acetonitrile leads to the formation of *S*-amido alkylation products corresponding to 2-(1-

carboxamido-2,2,2-trichloroethyl) isothiouronium chlorides. The complex spectral investigation data confirmed the synthesized compounds' structure.

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Conflicts of Interest

The authors declare no conflict of interest.

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