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Aminomethylation of Thiourea with Formaldehyde and Cyclic Amines

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Abstract—Three-component condensation of thiourea with equimolar amounts of formaldehyde and morpholine afforded *N*-(morpholin-4-ylmethyl) derivative, whereas analogous reaction with 2 equiv of formaldehyde and amine gave symmetrical *N*,*N*′-bis(morpholin-4-ylmethyl)thiourea. In the condensation of thiourea with piperidine and formaldehyde, only symmetrical *N*,*N*′-bis(piperidin-1-ylmethyl)thiourea was isolated, regardless of the reactant ratio.

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Thiourea and its derivatives have long been known, and they have found wide application in industry [1]. Nevertheless, the synthesis of new compounds containing a thiourea fragment attract increasing interest, since thiourea derivatives are expected to exhibit diverse biological activity, including inhibitory effect on NO synthase [2, 3] and adaptogenic (antihypoxic) activity [4].

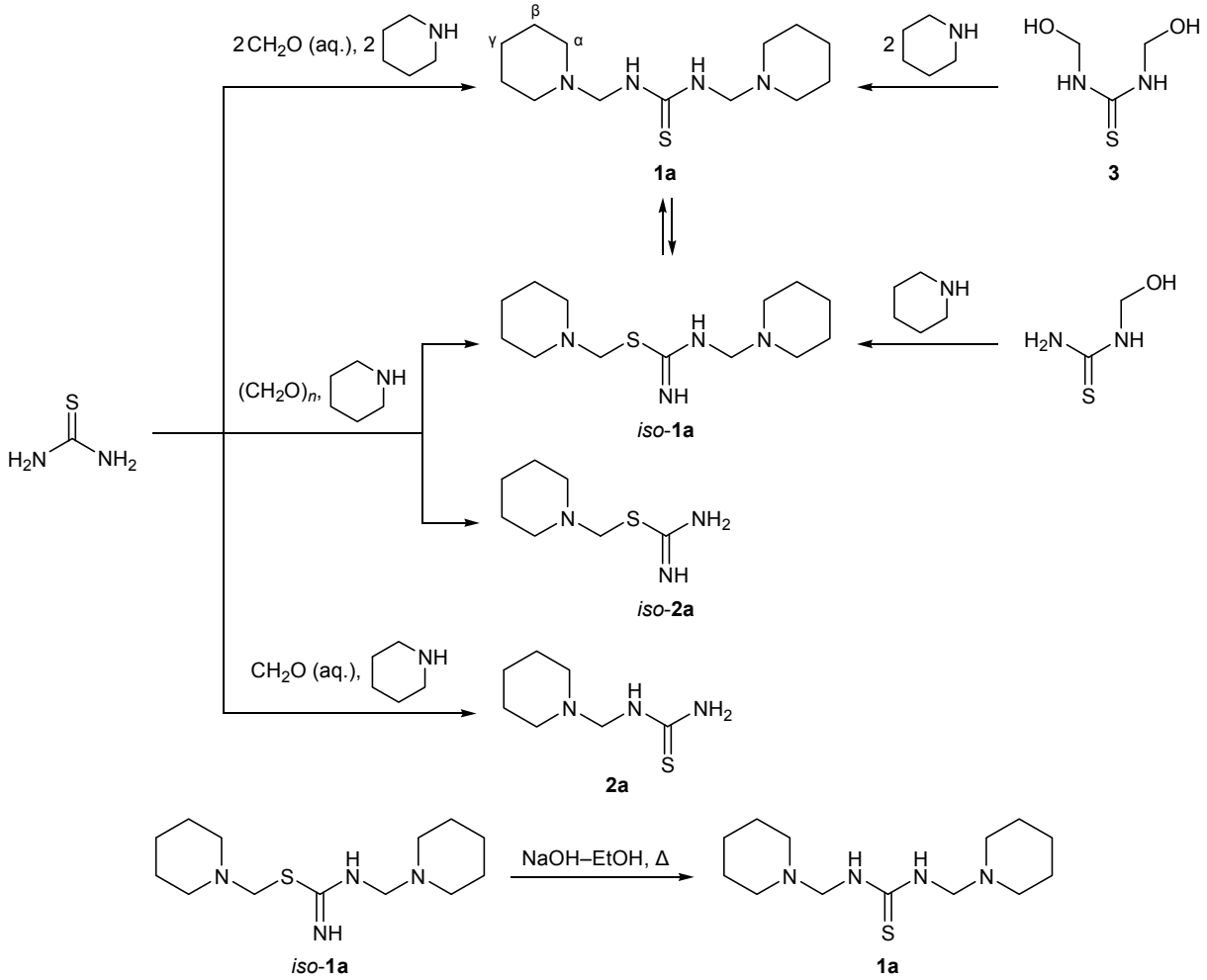
In the synthesis of new biologically active compounds involving complication of the molecular structure, the structure of relatively simple initial compounds should be determined unambiguously. However, one cannot contend the same for the aminomethylation products of thiourea with formaldehyde and secondary amines. Although the first publication on this topic has appeared more than 80 years ago, analysis of relevant literature data showed that the available information is often contradictory and/or insufficiently convincing.

The first products of aminomethylation of thiourea with piperidine were noted in patent [5] on the synthesis of symmetrical *N*,*N*′-bis(piperidin-1-ylmethyl)-thiourea (**1a**) via three-component condensation of thiourea with equimolar amounts of aqueous formaldehyde and piperidine on heating (Scheme 1). It was also noted that thiourea is capable of thione–thiol tautomerism and emphasized that thiourea reacts in the thione form under the given conditions.

The reaction of equimolar amounts of thiourea with paraformaldehyde and piperidine gave both *S*-mono- (iso-**2a**, mp 140°C) and unsymmetrical *N*,*S*-bis(piperidin-1-ylmethyl) derivatives (iso-**1a**, mp 142–143°C) [6]. The latter was also synthesized later from *N*-(hydroxymethyl)thiourea and piperidine taken at a ratio of 1 : 1, and the author differentiated the product from isomeric symmetrical *N*,*N*′-bis(piperidin-1-ylmethyl)-derivative **1a** prepared according to [5], as well as by the condensation of *N*,*N*′-bis(hydroxymethyl)thiourea (**3**) with 2 equiv of piperidine (Scheme 1). All reactions were carried out at room temperature (except for the condensation performed as described in [5]) under solvent-free conditions. The authors [6] stated that *N*,*S* derivative iso-**1a** can be converted to *N*,*N*′ isomer **1a** by heating in alcoholic alkali (Scheme 1). The melting points of **1a** given in [5] and [6] were fairly similar (152–154°C and 152–153°C, respectively), whereas *N*,*S* isomer iso-**1a** melted at 142–143°C [6].

Singh et al. [7] reported the synthesis of pure *N*-(piperidin-1-ylmethyl)thiourea (**2a**) with mp 120°C by reaction of thiourea with equimolar amounts of

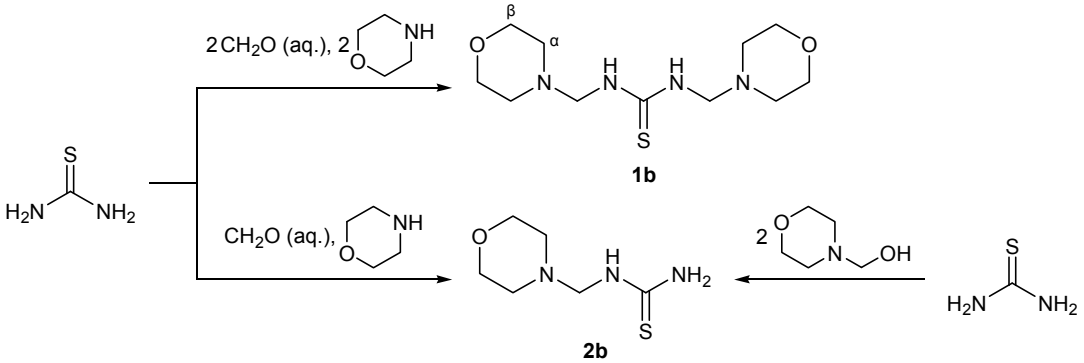
Scheme 1.



aqueous formaldehyde and piperidine in ethanol on cooling with ice (Scheme 1); however, no convincing proofs of its structure and purity were given (neither elemental analysis nor TLC data were supplied).

Symmetrical *N*,*N*′-bis(morpholin-4-ylmethyl)thiourea (**1b**) was described in two patents [5, 8]. The three-component condensation of thiourea with 2 equiv of aqueous formaldehyde and morpholine was carried out on heating under reflux [5] (the product melted at 124–125°C) or at 10–20°C [8] (mp 130°C) (Scheme 2). The synthesis of *N*-(morpholin-4-ylmethyl)thiourea (**2b**) was also reported in [7, 9]. In the first case, a solution of equimolar amounts of thiourea, aqueous formaldehyde, and morpholine in ethanol was kept on

Scheme 2.



cooling with ice [7], and in the second case, a mixture of thiourea and 2 equiv of morpholin-4-ylmethanol in water was heated at the boiling point [9] (Scheme 2). The melting points of the isolated monomorpholinomethyl derivatives were close to each other, 140 [7] and 141–142°C [9]. As noted above for the reaction with piperidine, no convincing proofs of the formation of just *N*,*N*′-bis- or *N*-mono(morpholin-4-yl)methyl derivatives rather than their *N*,*S*- or *S*-isomers were given in these publications.

Thus, the available data on the products of piperidinomethylation of thiourea are contradictory, and the proofs given in [5, 6, 8, 9] in favor of their structure and purity, as well as of the structure and purity of morpholinomethyl analogs, cannot be regarded as unambiguous because of the lack of reliable structural and chromatographic methods at the time of these publications. Moreover, the reported data do not allow a relation to be drawn between the reactant ratio and product structure. The aminomethylation temperature reported in different sources varies over a wide range, from 0 to 100°C. The above stated contradictions, unconvincing structural proofs, and data that are difficult to explain prompted us to revise reactions of thiourea with formaldehyde and cyclic amines.

The goal of the present work to reliably determine the structure of products of thiourea aminomethylation with formaldehyde and piperidine or morpholine at different reactant ratios with the aid of modern instrumental methods with account taken of lability of aminomethyl derivatives of thiourea and their ability to undergo S,N isomerizations, dimerization, and prototropic tautomerism in solution.

We have synthesized *N*,*N*-bis(piperidin-1-ylmethyl)thiourea (**1a**) in two ways: (1) by heating a mixture of thiourea, aqueous formaldehyde, and piperidine at a ratio of 1:2:2 [5] but with addition of isopropyl alcohol and (2) by reaction of *N*,*N*′-bis(hydroxymethyl)thiourea (**3**) with 2 equiv of piperidine at room temperature [6] but with addition of methanol. The structure of **1a** as symmetrical *N*,*N*′-disubstituted thiourea was unambiguously confirmed by X-ray analysis (Fig. 1). However, its ^{1}H NMR spectra were unusual. The spectrum of **1a** in DMSO-d_6 showed a signal from two NH protons with a reduced intensity (~1.7H instead of 2.0H), as well as a broadened asymmetric signal from the NHC**H**$_2$N methylene protons at δ 4.34 ppm with an intensity somewhat lower than 4H. The complex pattern of the CH_2 resonance may be related to three factors: (1) restricted rotation about the C(S)–N bond and different populations of rotamers, (2) monomer–dimer equilibrium, and/or (3) tautomeric equilibrium in solution (Scheme 3). The possibility of dimerization follows from the X-ray diffraction data (Fig. 1), and the formation of dimer should facilitate tautomerization.

The ^{1}H NMR spectrum of *N*,*N*′-bis(piperidin-1-ylmethyl) derivative (**1a**) in $CDCl_3$ was even more unusual. At first glance, it corresponded better to unsymmetrical *N*,*S*-isomer iso-**1a**: it displayed two broadened downfield signals at δ 8.79 and 6.45 ppm, each with an intensity of ~0.8H instead of 1H, and two broadened signals of exocyclic methylene protons at δ 4.53 and 3.73 ppm (2H each). A simple explanation may be shift of the conformational equilibrium in DMSO-d_6 toward one rotamer and complete association to dimer in $CDCl_3$. Tautomeric equilibrium can be ruled out,

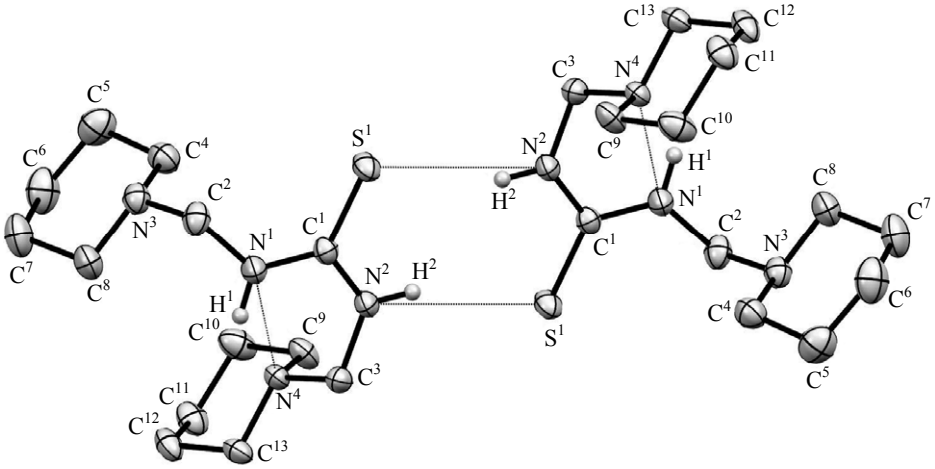
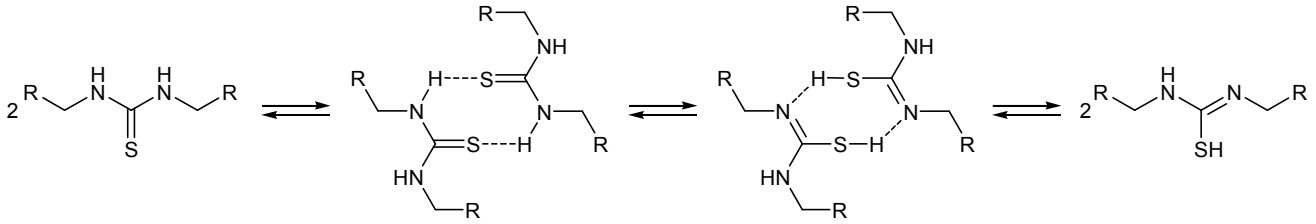


Fig. 1. Structure of the centrosymmetric dimer formed by molecules of *N*,*N*′-bis(piperidin-1-ylmethyl)thiourea (**1a**) in crystal. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%. Methylene hydrogen atoms are not shown.

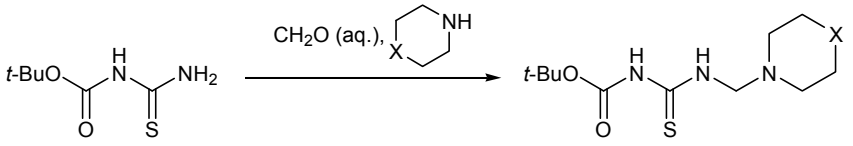
Scheme 3.



1a, **1b** Dimer **1a**-SH, **1b**-SH

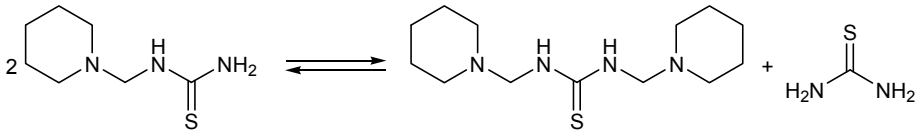
R = piperidn-1-yl (**a**), morpholin-4-yl (**b**).

Scheme 4.



4 **5a**, **5b**

X = CH_2 (**a**), O (**b**).



2a **1a**

since the ^{13}C NMR spectra in both solvents contained no signals assignable to thiol structure **1a**-SH.

We failed to obtain *S*-(piperidin-1-ylmethyl)isothiourea (iso-**2a**) by different procedures, including those described in [6, 7]. Despite variation of the solvent, temperature, source of formaldehyde (formalin, 1,3,5-trioxane, paraformaldehyde), and order of reactant addition, the reactions with equimolar amounts of the reactants in all cases afforded compound **1a** instead of monopiperidinomethyl derivative. According to the TLC and MS data, the reaction mixtures contained unreacted thiourea, *N*,*N*′-bis(piperidin-1-ylmethyl)thiourea (**1a**), and mono-piperidinomethylthiourea, but we did not succeed in isolating the latter by recrystallization, column chromatography, preparative thin-layer chromatography, or washing with chloroform. Neither transaminomethylation (reaction of thiourea with **1a**) nor deprotection of specially prepared *N*-(*tert*-butoxycarbonyl)-*N*′-(piperidin-1-ylmethyl)thiourea (**5a**)[1] (Scheme 4) was successful. A probable reason is disproportionation of the monopiperidinomethyl derivative in protic solvent (Scheme 4), namely fast establishment of the disproportionation equilibrium and its shift toward **1a**.

In fact, in our numerous attempts to extract monopiperidinomethyl derivative from its mixture with thiourea (such mixture can be prepared by washing with chloroform of the solid residue isolated from the reaction mixture), rapid formation of compound **1a** in solution was detected by TLC. It is also possible that the predominant formation of **1a** instead of monopiperidinomethyl derivative is favored by much lower solubility of the former in the reaction mixture; its precipitation from the solution induced shift of the disproportionation equilibrium toward its formation.

N,*N*′-Bis(morpholin-4-ylmethyl)thiourea (**1b**) was synthesized according to a modified procedure [5], by three-component condensation of thiourea with aqueous formaldehyde and morpholine at a ratio of 1:2:2, but at room temperature rather than under reflux as in [5]. The X-ray diffraction data unambiguously showed that the product had symmetrical *N*,*N*′-disubstituted structure; the independent part of its unit cell also contained one acetone molecule. The ^1H NMR spectra of **1b** displayed the same features as those observed in the spectra of bis-piperidinomethyl derivative **1a**; they can be interpreted in a similar way, i.e., assuming either restricted rotation about the C(S)–N bond with different rotamer populations in DMSO-d_6 or complete dimerization in $CDCl_3$ (Scheme 2). As with compound

[1] The deprotection was accompanied by elimination of the piperidinomethyl group with the formation of thiourea.

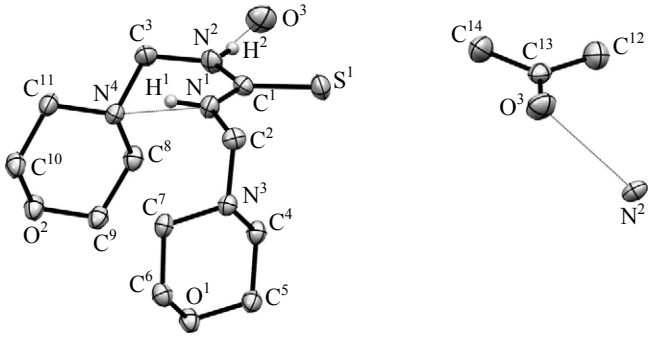


Fig. 2. Structure of the independent part of a unit cell of *N*,*N*′-bis(morpholin-4-ylmethyl)thiourea (**1b**) in crystal (1 : 1 solvate with acetone). Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%. Methylene hydrogen atoms are not shown. Hydrogen bond is shown with dotted line.

1a, the ^{13}C NMR spectra of **1b** in DMSO-d_6 and $CDCl_3$ contained no signals assignable to thiol tautomer **1b**-SH, indicating its symmetrical structure. The ^{13}C NMR spectra of **1b** in DMSO-d_6 and $CDCl_3$ were similar, except for the considerably lower intensity of the C=S signal in DMSO-d_6.

Our attempts to synthesize compound **1b** from bis(hydroxymethyl)thiourea **3b** in different solvents at different temperatures resulted in the formation of oily reaction mixtures from which no crystalline product separated even after a long time (up to 30 days).

N-(Morpholin-4-ylmethyl)thiourea (**2b**) was synthesized according to the procedure described in [7], by three-component condensation of thiourea with equimolar amounts of aqueous formaldehyde and morpholine, but the reaction was carried out at room temperature without addition of ethanol. We failed to obtain a single crystal of **2b**, and the product structure was confirmed by combination of its mass spectra, ^{1}H and ^{13}C NMR spectra in DMSO-d_6, and IR spectra of a solid sample. The position of signal from the exocyclic methylene protons in the ^{1}H NMR spectrum of **2b** (δ 4.29 ppm) was similar to the position of the corresponding signal of **1b** (δ 4.40 ppm). The IR spectrum showed a band at 1190 cm^{-1} due to C=S stretching vibrations [10], whereas no S–H stretching band was observed (2450 cm^{-1}) [11]. These findings indicated that the morpholinomethyl group in **1b** is located on the nitrogen atom. The same also follows from almost complete similarity of the ^{13}C NMR spectra of **1b** and **2b**.

We failed to obtain compound **2b** by removal of the Boc protection from preliminarily prepared *N*-(*tert*-butoxycarbonyl)-*N*′-(morpholin-4-ylmethyl)thiourea (**5b**) (Scheme 3). As in the reaction with piperidine analog **5a**, elimination of the protecting group was accompanied by deaminomethylation to give initial thiourea.

In the examined three-component condensations with both morpholine and piperidine, only two products, *N*,*N*′-bis- and *N*-monoaminomethyl derivatives, were detected by TLC in the solid materials isolated from the reaction mixtures. This fact convincingly shows that in no case isomeric *N*,*S*-bis- and *S*-monoaminomethyl derivatives are formed.

According to the X-ray diffraction data, *N*,*N*′-bis(aminomethyl)thioureas **1a** and **1b**, as well as thiourea itself and its other *N*-substituted derivatives, have thione structure in crystal (Figs. 1. 2). The C=S bond lengths in molecules **1a** and **1b** almost coincide with the C=S bond length in thiourea (1.706 Å [12]). The C^1–N^1 and C^1–N^2 bond lengths in both compounds are similar and close to the C–N bond length in thiourea (1.340 Å [12]). Insignificant asymmetry of the C–N bond may be rationalized by asymmetric hydrogen bonding (Table 1). The thione structure of **1a** and **1b** is confirmed by the presence of C=S stretching bands at 1050–1250 cm^{-1} in their IR spectra [10].

The piperidine rings in **1a** adopt a *chair* conformation (Fig. 1). Molecules **1a** in crystal form centrosymmetric dimers through two intermolecular hydrogen bonds N^2–$H^2\cdots S^1$ 3.319 Å. These hydrogen

Table 1. Hydrogen bond parameters in the crystal structures of compounds **1a** and **1b**

D–H···A	D–H, Å	H···A, Å	D···A, Å	∠DHA, deg	*d* – vdW, Å
1a, symmetry operation (*i*): $-x, 1-y, -z$					
N^1–$H^1\cdots N^4$	0.860	2.430	2.953(2)	119.80	–0.147
N^2–$H^2\cdots S^{1i}$	0.860	2.494	3.319(2)	161.09	–0.031
1b, symmetry operation (*i*): $x, -y+5/2, z-1/2$					
N^1–$H^1\cdots N^4$	0.86	2.33	2.8842(18)	122.9	–0.216
N^2–$H^2\cdots O^{3i}$	0.86	2.11	2.9473(16)	165.0	–0.123

bonds close a planar six-membered ring provided that hydrogen atoms are not taken into account. Two piperidine rings of one molecule are almost parallel to each other.

N,*N*′-Bis(morpholin-4-ylmethyl)thiourea (**1b**) crystallized as solvate with one acetone molecule (Fig. 2) which is linked to molecule **1b** through the intermolecular hydrogen bond N^2–$H^2\cdots O^3$ 2.947 Å. The sulfur atom is not involved in hydrogen bonding, and no dimer is formed. Two morpholine rings in a single molecule have *chair* conformation and are less coplanar to each other than piperidine rings in the crystal structure of **1a**.

The $C^2N^1C^1(=S^1)N^2C^3$ fragment of both molecules is planar, and the three-dimensional structure is formed only through van der Waals interactions. In addition, intramolecular hydrogen bond N^1–$H^1\cdots N^4$ (2.953 and 2.884 Å) and intramolecular contact $H^3\cdots S^1$ (2.654 and 2.691 Å, respectively were found in the crystal structures of **1a** and **1b**. Analogous interactions in solution could hinder rotation of the exocyclic methylene groups, which could lead to broadening of signals in the ^{1}H NMR spectra.

Thus, we have shown that neither *S*-(piperidin-1-ylmethyl)urea nor *S*-(morpholin-4-ylmethyl)urea exist. The reaction of thiourea with aqueous formaldehyde and piperidine or morpholine gives only *N*-aminomethylation products. *N*,*N*′-Bis(aminomethyl) derivatives are formed in the reactions of thiourea with 2 equiv of formaldehyde and amine. *N*-(Morpholin-4-ylmethyl)thiourea can be obtained at an equimolar reactant ratio, whereas analogous *N*-monopiperidinomethyl derivatives could not be isolated. *N*,*N*′-Bis(aminomethyl)ureas in solution ($CDCl_3$ and DMSO-d_6) exist as thione tautomers, and dimeric structures are formed in $CDCl_3$.

Table 2. Principal crystallographic parameters of compounds **1a** and **1b** and conditions of X-ray diffraction experiments

Parameter	**1a**	**1b**
Formula	$C_{13}H_{26}N_4S$	$C_{11}H_{22}N_4O_2S\cdot C_3H_6O$
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a, Å	13.3687(10)	17.829(11)
b, Å	9.7031(8)	6.186(4)
c, Å	11.4726(9)	16.073(10)
β, deg	92.442(2)	95.790(14)
V, Å^3	1486.8(2)	1763.7(19)
Z	4	4
μ, mm^{-1}	0.21	0.20
Crystal dimensions, mm	0.26×0.19×0.14	0.21×0.16×0.09
$T_{min.}$, T_{max}	0.205, 0.304	0.189, 0.322
Total number of reflections	16108	20568
Number of independent reflections	4330	6532
Number of reflections with [$I > 2\sigma(I)$]	3843	4959
R_{int}	0.066	0.054
$(\sin\theta/\lambda)_{max}$, Å^{-1}	0.703	0.772
R [$F^2 > 2\sigma(F^2)$]	0.037	0.037
wR (F^2)	0.110	0.103
Goodness of fit *S*	1.06	1.01
Number of variables	163	201
$\Delta\rho_{max}$, $\Delta\rho_{min.}$, e·Å^{-3}	0.37, –0.33	0.34, –0.31

EXPERIMENTAL

The IR spectra were recorded from samples prepared as KBr discs on a Shimadzu FTIR-8400S spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III-400 spectrometer at 400.13 and 100.62 MHz, respectively. The chemical shifts were referenced to the residual proton and carbon signals of the deuterated solvent (DMSO-d_5, δ 2.51 ppm; $CHCl_3$, δ 7.28 ppm; DMSO-d_6, δ_C 39.91 ppm; $CDCl_3$, δ_C 77.25 ppm). The mass spectra were obtained at the Chemical Analysis and Materials Research Center (St. Petersburg State University) on a Bruker Daltonik MaXis 62 instrument (electrospray ionization, quadrupole time-of-flight mass analyzer; positive ion detection; capillary voltage 4.5 kV; solvent methanol or methylene chloride); characteristic isotope peak distributions coincided with the theoretical values.

The progress of reactions was monitored, and the purity of the isolated compounds was checked, by TLC on Kieselgel TLC 60 F254 plates (Merck) which were preliminarily deactivated by treatment with hexane–triethylamine (10:1), followed by washing with hexane; a 10:1 mixture of methylene chloride and methanol was used as eluent. The melting points were measured on a PTP (M) melting point apparatus.

Thiourea. ^{1}H NMR spectrum, δ, ppm: 6.98 s (DMSO-d_6), 6.40 s ($CDCl_3$) (NH_2).

***N*,*N*′-Bis(piperidin-1-ylmethyl)thiourea (1a).** *a*. Piperidine, 3.41 g (0.04 mol), was added dropwise

with stirring to a mixture of 1.52 g (0.02 mol) of thiourea and 3.24 g (0.04 mol) of 37% aqueous formaldehyde in 15 mL of isopropyl alcohol. The mixture was refluxed for 1 h with stirring and cooled, and the white finely dispersed solid was filtered off, dried, and recrystallized from isopropyl alcohol. Yield 2.71 g (50%), transparent crystals, mp 142–144°C; published data: mp 152–154°C [5], 152–153°C [6], 142–143°C [6]. IR spectrum, ν, cm^{-1}: 3306 (NH), 1254, 1224, 1190 (C–N), 1160, 1120, 1091, 1063 (C=S), 1035. ^{1}H NMR spectrum, δ, ppm: in DMSO-d_6: 1.39 m (4H, γ-H), 1.49 m (8H, β-H), 2.50 m (8H, α-H, overlapped by the residual proton signal of the solvent), 4.34 br.s (4H, NHC**H**$_2$N), 7.85 br.s (2H, NH); in $CDCl_3$: 1.37 m (4H, γ-H), 1.61 m (8H, β-H), 2.55 m (8H, α-H), 3.73 br.s and 4.53 br.s (2H each, NHC**H**$_2$N), 6.45 br.s and 8.79 br.s (1H each, NH). ^{13}C NMR spectrum, δ_C, ppm: in $CDCl_3$: 24.3 (2C, C^{γ}), 25.8 (4C, C^{β}), 51.2 (4C, C^{α}), 67.8 (2C, $NHCH_2N$), 184.6 (C=S); in DMSO-d_6: 24.4 (2C, C^{γ}), 25.9 (4C, C^{β}), 51.2 (4C, C^{α}), 66.5 (2C, $NHCH_2N$), 184.0 (C=S). Found: *m*/*z* 271.1942 $[M + H]^+$. $C_{13}H_{27}N_4S$. Calculated: *M* + H 271.1951.

b. The procedure was the same as in *a*, but 3.04 g (0.04 mol) of thiourea was used. Yield 2.42 g (45%), transparent prisms, mp 143–144°C (from *i*-PrOH). The IR and ^{1}H NMR spectra were identical to those of a sample prepared as described in *a*.

c. Piperidine, 1.25 g (14.68 mmol), was added dropwise to a solution of 1.00 g (7.34 mmol) of *N*,*N*′-bis(hydroxymethyl)thiourea (**3**) in 8 mL of methanol maintained at 35–40°C, and the mixture was stirred for 1 h at 34–36°C. The mixture was cooled, and the finaly crystalline precipitate was filtered off, dried, and recrystallized from isopropyl alcohol. Yield 1.21 g (61%), mp 142–144°C. The IR and ^{1}H NMR spectra were identical to those of a sample prepared as described in *a*.

***N*,*N*′-Bis(morpholin-4-ylmethyl)thiourea (1b).** Morpholine, 3.48 g (0.04 mol), was added dropwise with stirring to a mixture of 1.52 g (0.02 mol) of thiourea and 3.24 g (0.04 mol) of 37% aqueous formaldehyde, and the mixture was stirred for 1 h at room temperature and left to stand for 48 h. The white finely dispersed solid was filtered off and recrystallized from acetone. Yield 2.22 g (40%), transparent crystals which turned white on exposure to air, mp 123–124°C; published data: mp 124–125°C [5], 130°C [8]. IR spectrum, ν, cm^{-1}: 3210 (N–H), 1232, 1167 (C–N), 1110, 1088, 1071 (C=S). ^{1}H NMR spectrum, δ, ppm: in DMSO-d_6: 2.51 m (8H, α-H), 3.57 m (8H, β-H), 4.40 br.s (4H, NHC**H**$_2$N), 7.89 br.s (2H, NH); in $CDCl_3$: 2.59 m (8H, α-H), 3.76 m (10H, NHC**H**$_2$N, β-H), 4.55 br.s (2H, NHC**H**$_2$N), 6.91 br.s and 8.47 br.s (1H each, NH). ^{13}C NMR spectrum, δ_C, ppm: in $CDCl_3$: 50.4 (4C, C^{α}), 66.7 (4C, C^{β}), 67.1 (2C, $NHCH_2N$), 185.1 (C=S); in DMSO-d_6: 50.5 (4C, C^{α}), 65.6 (4C, C^{β}), 66.6 (2C, $NHCH_2N$), 184.5 (C=S). Found: *m*/*z* 275.1537 $[M + H]^+$. $C_{11}H_{23}N_4O_2S$. Calculated: *M* + H 275.1536.

***N*-(Morpholin-4-ylmethyl)thiourea (2b)** was synthesized as described above for compound **1b** using 3.04 g (0.04 mol) of thiourea. Yield 5.75 g (82%), white finely dispersed solid, mp 140–141°C (from acetone); published data: mp 141–142°C [9], 140°C [7]. IR spectrum, ν, cm^{-1}: 3298 (N–H), 1642 (NH_2), 1253, 1215, 1172 (C–N), 1136, 1109, 1071 (C=S). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 m (4H, α-H), 3.58 m (4H, β-H), 4.29 s (2H, NHC**H**$_2$N), 7.06 br.s (2H, NH_2), 7.85 br. unsym. s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 50.5 (2C, C^{α}), 66.2 (2C, C^{β}), 66.5 ($NHCH_2N$), 184.5 (C=S). Compound **2b** was almost insoluble in $CDCl_3$. Found: *m*/*z* 176.0856 $[M + H]^+$. $C_6H_{14}N_3OS$. Calculated: *m*/*z* 176.0852.

***N*,*N*′-Bis(hydroxymethyl)thiourea (3)** was synthesized as described in [13]. mp 94°C; published data [13]: mp 92–94°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.85 (4H, CH_2), 5.40 (2H, OH), 8.01 (2H, NH).

***tert*-Butyl carbamothioylcarbamate (4, *N*-*tert*-butoxycarbonylthiourea)** was synthesized as described in [14]. mp 143°C; published data [14]: mp 145°C. ^{1}H NMR spectrum, δ, ppm: in DMSO-d_6: 1.44 (9H, *t*-Bu), 8.97 and 9.17 (1H each, NH), 10.53 (1H, N**H**Boc); in $CDCl_3$: 1.51 (9H, *t*-Bu), 7.07 and 8.19 (1H each, NH), 9.23 (1H, N**H**Boc).

***tert*-Butyl [(piperidin-1-ylmethyl)carbamothioyl]carbamate [5a, *N*-(*tert*-butoxycarbonyl)-*N*′-(piperidin-1-ylmethyl)thiourea] (5a).** To a mixture of 0.94 g (6 mmol) of compound **4** and 1 mL of isopropyl alcohol we added in succession 0.487 g (6 mmol) of 37% aqueous formaldehyde and 0.511 g (6 mmol) of piperidine. After the addition of piperidine, the mixture became homogeneous, and abundant yellow–white solid precipitated in the next 2 min. The precipitate was filtered off, washed with isopropyl alcohol, and dried in a vacuum desiccator. Yield 1.48 g (90%), mp 123–124°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 m (2H, γ-H), 1.46 s (9H, *t*-Bu), 1.46 m (4H, β-H), 2.50 m (4H, α-H, overlapped by the residual proton signal of the solvent), 4.47 s (2H, NHC**H**$_2$N),

10.00 br.s (1H, N**H**CH_2N), 10.67 br.s (1H, N**H**Boc). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 24.09 (C^{γ}), 25.84 (2C, C^{β}), 28.18 (3C, CH_3), 51.50 (2C, C^{α}), 67.51 (NHCH_2N), 82.67 (C–O), 153.22 (C=O), 180.77 (C=S). Found: *m*/*z* 274.1578 $[M + H]^+$. $C_{12}H_{23}N_3O_2S$. Calculated: *M* + H 274.1584.

***tert*-Butyl [(morpholin-4-ylmethyl)carbamothioyl]carbamate [5b, (*N*-*tert*-butoxycarbonyl)-*N*′-(morpholin-4-ylmethyl)thiourea]** was synthesized in a similar way using 0.523 g (6 mmol) of morpholine. The product separated from the reaction mixture after 2 h as abundant white solid. Yield 0.97 g (59%), mp 143–145°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.46 s (9H, *t*-Bu), 2.53 m (4H, β-H, overlapped by the residual proton signal of the solvent), 3.57 m (4H, α-H), 4.51 s (2H, NHC**H**$_2$N), 10.04 s (1H, N**H**CH_2N), 10.71 s (1H, N**H**Boc). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.18 (3C, CH_3), 50.69 (2C, C^{β}), 66.48 (2C, C^{α}), 66.56 (NHCH_2N), 82.74 (C–O), 153.17 (C=O), 181.17 (C=S). Found: *m*/*z* 276.1380 $[M + H]^+$. $C_{11}H_{21}N_3O_3S$. Calculated: *M* + H 276.1376.

The X-ray diffraction data for compounds **1a** and **1b** were obtained at the Center for X-Ray Diffraction Studies of the St. Petersburg State University on a Bruker APEX-II CCD single crystal diffractometer (Mo K_α radiation) at 150 and 293 K, respectively. The principal crystallographic parameters and conditions of X-ray diffraction experiments are given in Table 2. Primary data processing was done using CrysAlisPro (version 1.171.36.20, release 27-06-2012, Agilent Technologies). A correction for absorption was applied by the Multiscan method (SADABS, Bruker, 2007). The structures were solved by the direct method and were refined by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms (SIR2014) [15]. The positions of hydrogen atoms were calculated geometrically and were refined in the rigid body approximation. The molecular structures were plotted using Mercury 3.7 [16]. The X-ray diffraction data for compounds **1a** and **1b** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry nos. 1517961 and 1517960, respectively). The interatomic distances and bond and dihedral angles are available upon request.

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