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Multicomponent heterocyclization of hydrazine, hydrogen sulfide, and formaldehyde

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Multicomponent heterocyclization of hydrazine, hydrogen sulfide, and formaldehyde gave previously unknown bi-, tri-, and tetracyclic nitrogen- and sulfur-containing heterocycles. 3,7-Dithia-1,5-diazabicyclo[3.3.0]octane, 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane, and 4,9,14-trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane were obtained selectively, depending on the reaction temperature (0—60 °C).

Key words: heterocyclization, thiomethylation, hydrazine, formaldehyde, hydrogen sulfide, 3,7-dithia-1,5-diazabicyclo[3.3.0]octane, 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane, 4,9,14-trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane.

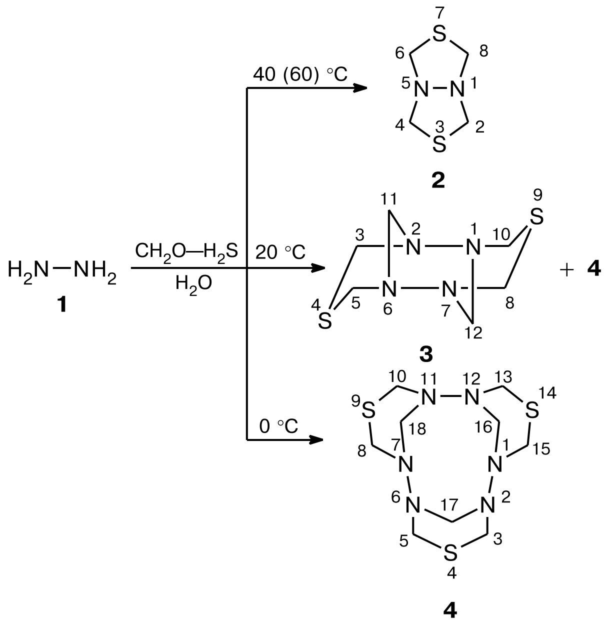
One-pot methods for the synthesis of heterocycles with practically useful properties are of particular interest and hold promise.[1] According to available data,[2—8] multicomponent thiomethylation of primary amines with hydrogen sulfide and formaldehyde yields dithiazines and linear bis(*N*-alkylmethyl) sulfides, while similar reactions with ammonia and hydrazine afford polycyclic systems containing thiadiazine and thiadiazolidine fragments. Thiazaheterocycles exhibit biocidal activity and find use as extractants, complexones, and flotation agents for metals.[9,10]

With the aim of extending the area of application of this method and of synthesizing novel types of nitrogen- and sulfur-containing heterocycles, we studied the reaction of hydrazine with hydrogen sulfide and formaldehyde under different reaction conditions.

Results and Discussion

About half a century ago,[8] the product with the molecular formula $C_4H_8N_2S_2$ was obtained in 11% yield by the reaction of hydrazine with formaldehyde and hydrogen sulfide in the 1 : 2 : 2 ratio at $T < 0$ °C. Later,[11] the 1,3,4-thiadiazolo[3,4-*c*]-1,3,4-thiadiazole structure was assigned to that product, though no confirming spectroscopic data were reported. We studied the effects of the temperature and the ratio of the reagents on the thiomethylation of hydrazine with a $CH_2O—H_2S$ system prepared by bubbling gaseous hydrogen sulfide through a formalin solution. It was found that the heterocyclization of hydrazine **1** with an excess of the $CH_2O—H_2S$ mixture (1 : 6 : 4) in the temperature range from 0 to 60 °C gives bi-, tri-, and tetracyclic nitrogen- and sulfur-containing heterocycles **2**—**4**, depending on the reaction temperature (Scheme 1).

Scheme 1



It turned out that the direction and selectivity of the thiomethylation of hydrazine is substantially affected by the temperature. For instance, at 40 and 60 °C, the reac-

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tion of NH_2NH_2 with H_2S and CH_2O (1 : 4 : 6) exclusively gave 3,7-dithia-1,5-diazabicyclo[3.3.0]octane (**2**) in 30 and 76% yields, respectively. At 20 °C, 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane (**3**) was obtained in 30% yield (it was isolated by extraction with chloroform). Ten to twelve hours after product **3** was separated from the reaction mixture, 4,9,14-trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane (**4**) formed a precipitate; its yield was 30%. Analogously, compound **3** was obtained by the thiomethylation of hydrazine with formaldehyde and hydrogen sulfide in the 1 : 3 : 2 ratio at 20 °C. The yield of compound **4** was 18%. With an increase in the concentration of the thiomethylating mixture ($NH_2NH_2 : CH_2O—H_2S = 1 : 9$), the reaction selectivity decreased significantly and the total yield of the heterocyclization products did not exceed 10%. The optimum conditions for the heterocyclization of hydrazine were experimentally found to occur when NH_2NH_2, CH_2O, and H_2S are used in the 1 : 6 : 4 ratio. Under these conditions, a decrease in the temperature to 0 °C increased the yield of product **4** to 31%. Thus, the direction of the heterocyclization is mainly determined by the reaction temperature.

The structures of heterocycles **2—4** were determined by IR and NMR (^{1}H and ^{13}C) spectroscopy and mass spectrometry. For instance, the mass spectrum of bicyclic compound **2** shows an intense peak of the molecular ion $[M]^+$ with *m/z* 148 and the peaks of ions with *m/z* 102 $[M - CH_2S]^+$ and 46 $[CH_2S]^+$. The ^{1}H and ^{13}C NMR spectra of this compound each contain a single signal at δ_H 4.10 and δ_C 55.61, which were assigned to thiadiazolidine or thiadiazine rings.[12]

To rule out structure **5** isomeric to structure **2**, we performed an additional spectroscopic study. At –20 °C, the signal of geminal protons is split into a doublet of doublets (J = 7.7 Hz), whereas the signal in the room-temperature ^{1}H NMR spectrum is a broadened singlet (Fig. 1). Thus, the ^{1}H NMR spectrum shows a temperature dependence characteristic of dynamic processes. Apparently, 25 °C is a critical temperature (T_c) for conformational equilibrium in solution. Using this temperature, we calculated the experimental inversion barrier by the dynamic NMR method:[12] $\Delta G^{\#} = 14.76$ kcal mol^{-1}. For compound **5**, conformational changes can be due to either the internal vibrations of the four-membered rings or their rotation about the N—N bond. The energies of activation[13] of these processes are ~0.5 to 2 kcal mol^{-1}, which is lower by one order of magnitude than the experimental value. Therefore, structure **2** seems to be more probable. In compound **2**, conformational effects are associated with the inversion of the N atoms, which leads to the conformational equilibrium of thiadiazolidines[14] in solution. However, *N,N′*-di-*tert*-butyloxadiazolidine **6** exists in solution in the symmetrical (C_2) half-chair conformation with the *trans*-arrangement of the N-substituents ($\Delta G^{\#} > 19.4$ kcal mol^{-1}).[12]

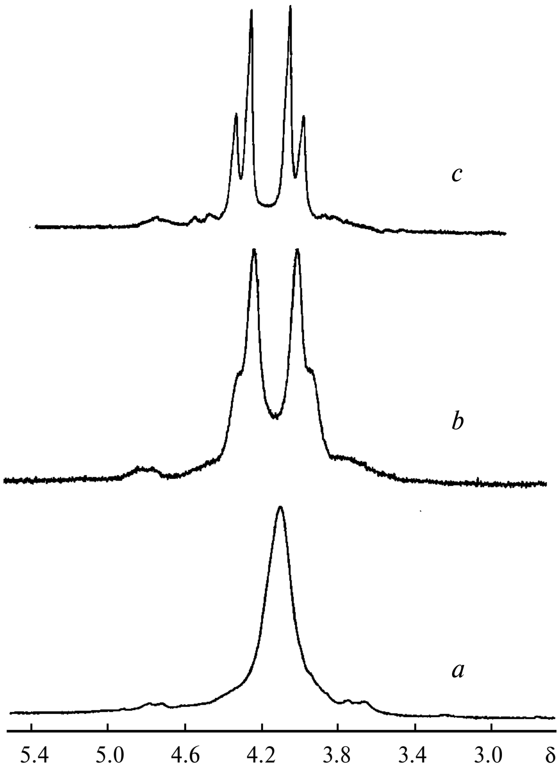
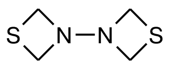


Fig. 1. ^{1}H NMR spectrum of compound **2** at 24.5 (*a*), 0 (*b*), and –20 °C (*c*).



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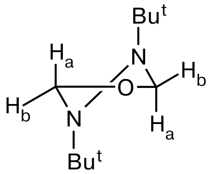

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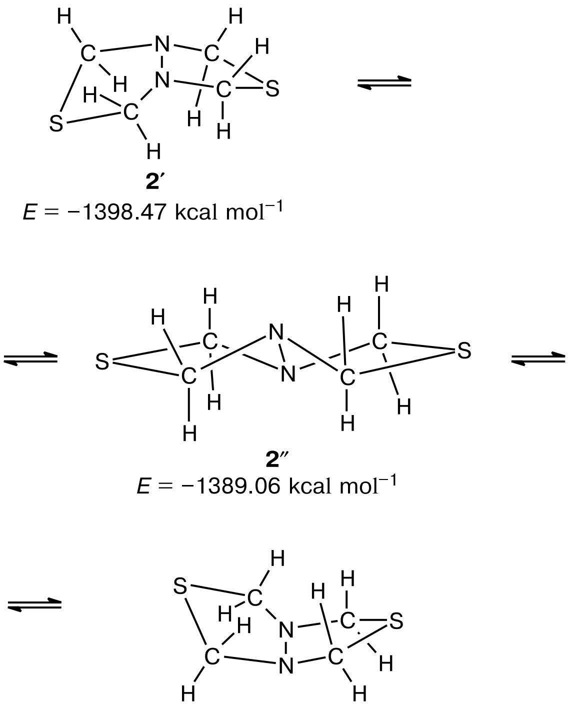
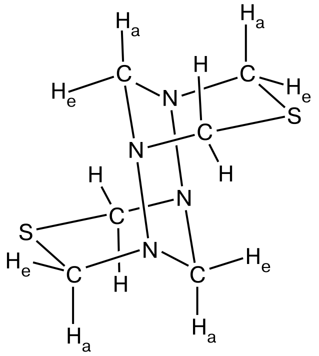
Thus, structure **2** is sterically less hindered. Apparently, the destabilization is due to both the interactions between the lone electron pairs of the adjacent N atoms[15] and the lower torsion barriers for the C—S bond than for the C—O and C—C bonds.[16]

The AM1 calculations of the molecular conformation with the use of the standard Hyperchem 6.0 2000 program package showed that the "cisoid" conformer (**2′**) with the strongly flattened rings is more favorable than the "transoid" conformer (**2″**) with the symmetrical half-chair cycles (Scheme 2). Thus, the experimental spectroscopic data supported by our theoretical calculations allowed compound **2** to be identified as 3,7-dithia-1,5-diazabicyclo[3.3.0]octane.

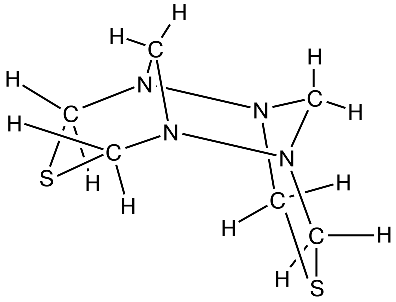
Elemental analysis and mass spectrometric data for the compound **3** obtained correlate with the presence of

Scheme 2





anti-**3**



syn-**3**

four N, two S, six C, and twelve H atoms, which suggests its 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane structure. The mass spectrum of compound **3** contains the peak of the molecular ion $[M]^+$ with *m/z* 204 and characteristic fragmentation ions produced by successive detachment from $[M]^+$ of fragments containing N atoms, methylene groups, and an S atom (*m/z*: 148 $[M - N_2(CH_2)_2]^+$, 116 $[M - N_2(CH_2)_2S]^+$, and 102 $[M - N_2(CH_2)_3S]^+$). The ^{1}H NMR spectrum of compound **3** consists of two pairs of doublets at δ_H 3.60 and 4.65 (geminal spin-spin coupling constant ^2J = 11.8 Hz) and at δ_H 3.95 and 4.45 (^2J = 7.3 Hz). Its ^{13}C NMR spectrum shows two signals at δ_C 52.32 and 61.88. These data suggest that the cyclic structure has a symmetry plane because the NMR spectra contain no signals characteristic of terminal groups. In the molecule, the CH_2 fragments are separated by the heteroatoms, which follows from the analysis of the chemical shifts and the multiplicity of the signals in the ^{1}H and ^{13}C NMR spectra.

The above conditions are satisfied by two structures: *anti*- and *syn*-stereoisomers **3**.

Semiempirical AM1 and PM3 quantum-chemical calculations (standard Hyperchem 6.0 2000 program package) showed that the isomer *anti*-**3** is more favorable than the alternative structure. Apparently, the formation of isomer *syn*-**3** is prevented by steric hindrances between the bridging methylene groups. The binding energies (*E*) in the conformers *anti*-**3** and *syn*-**3** are given below.

Method	*E*(*anti*-**3**)	*E*(*syn*-**3**)	Δ*E*
		kcal mol^{-1}	
AM1	−2119.24	−2104.51	14.63
PM3	−2146.14	−2133.51	12.63

Integration of the ^{1}H NMR spectrum showed that the signal intensity ratio between the pairs of doublets with ^2J = 11.8 Hz and ^2J = 7.3 Hz is 1 : 2. Therefore, the signals at δ_H 3.6 and 4.65 correspond, in the number of protons, to two pairs of geminal protons in the bridges of this heterocycle. The other eight protons are magnetically equivalent in pairs ($H_a(3)$, $H_a(5)$, $H_a(8)$, $H_a(10)$ and $H_e(3)$, $H_e(5)$, $H_e(8)$, $H_e(10)$); in the ^{1}H NMR spectrum, they were assigned to the doublets at δ_H 3.95 and 4.45, respectively. Such a conformationally rigid heterocyclic structure is also evident from the long-range coupling constants of the fourth order ($^4J \approx 1.6$ Hz) observed for the signals of the protons at δ_H 4.45 and 4.65. This suggests the mutual W arrangement of the equatorial protons at the C(3), C(5), and C(11) and C(8), C(10), and C(12) atoms, which confirms the chair conformation of each bicyclic thiadiazine fragment in the molecule. Therefore, the doublet at δ_H 4.46 unambiguously belongs to the equatorial protons at the C(3), C(5), C(8), and C(10) atoms, while the doublet at δ_H 4.65, which also exhibit a long-range constant, was assigned to the $H_e(11)$ and $H_e(12)$

protons, respectively. The signals in the ^{13}C NMR spectrum were unambiguously assigned from the increments characterizing the effects of the N and S atoms on the chemical shifts of carbon atoms.**12** Based on the spectroscopic data obtained, the 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane structure was proposed for compound **3**.

The structure of tetraheterocycle **4** was determined from IR and mass spectra and elemental analysis data. Unfortunately, ^{1}H and ^{13}C NMR spectra were not recorded because of the poor solubility of compound **4**. Its molecular mass determined by cryoscopy with camphor is 306±10. According to the elemental analysis data, the molecular formula of product **4** is $C_9H_{18}N_6S_3$. Its mass spectrum contains a peak of the molecular ion $[M]^+$ with *m/z* 306 and characteristic fragmentation ions produced by successive detachment from $[M]^+$ of fragments containing methylene groups and S and N atoms (*m/z*: 260 $[M - CH_2S]^+$, 204 $[M - (CH_2)_3SN_2]^+$, 148 $[M - N_4(CH_2)_5S]^+$, 116 $[M - N_3(CH_2)_6S_2]^+$, and 102 $[M - N_4(CH_2)_6S_2]^+$). In the range of the vibrations of compound **4**, the IR spectrum shows an absorption pattern identical with that of compound **3**. Based on the data obtained, we identified compound **4** as 4,9,14-trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane.

Thus, the heterocyclization of hydrazine with hydrogen sulfide and formaldehyde opens up a simple and efficient single-step route to nitrogen- and sulfur-containing heterocycles of the unique structures, which are of interest as selective complexones and biologically active substances. It was found that the heterocyclization of hydrazine with an excess of the $CH_2O—H_2S$ mixture (1 : 6 : 4) at 40 and 60 °C yields 3,7-dithia-1,5-diazabicyclo[3.3.0]octane (**2**) predominantly in the *cis*-conformation. The reaction at 20 °C affords an equimolar mixture of 4,9-dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane (**3**) with the chair conformation for each of its tricycles and 4,9,14-trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane (**4**), which is the major product at 0 °C.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) in $CDCl_3$; ^{13}C NMR spectra were recorded on a Jeol FX 90 Q spectrometer (22.50 MHz) in $CDCl_3$. The IR spectrum was recorded on a Specord 75IR spectrophotometer (Nujol). Mass spectra were recorded on a MX 1320 instrument (direct inlet probe, ionization chamber temperature 70—100 °C, ionizing voltage 70 eV).

3,7-Dithia-1,5-diazabicyclo[3.3.0]octane (2). A solution of 37% formalin (25.5 mL, 0.3 mol) was saturated at 40 or 60 °C with H_2S (0.2 mol) for 30 min; then hydrazine (1.6 mL, 0.05 mol) was added dropwise. The reaction mixture was stirred at 40 or 60 °C for 3 h; the crystals of compound **2** that formed were filtered off, washed with water, and dried. The yields of heterocycle **2** were 2.2 g (30%) at 40 °C and 5.6 g (76%) at 60 °C, m.p. 65—66 °C. Found (%): C, 32.00; H, 5.19; N, 18.51; S, 44.30. $C_4H_8N_2S_2$. Calculated (%): C, 32.43; H, 5.40; N, 18.92; S, 43.24. IR, ν/cm^{-1}: 520, 650, 670, 710, 780, 1100, 1370, 1450. ^{1}H NMR (−20 °C), δ: 3.97 (d, 4 H, $H_b(2)$, $H_b(4)$, $H_b(6)$, $H_b(8)$, ^2J = 7.7 Hz); 4.29 (d, 4 H, $H_a(2)$, $H_a(4)$, $H_a(6)$, $H_a(8)$, ^2J = 7.7 Hz). ^{13}C NMR, δ: 55.61 (s, C(2), C(4), C(6), C(8)). MS, *m/z* (I_{rel} (%)): 148 $[M]^+$ (52), 102 $[M - CH_2S]^+$ (40), 46 $[CH_2S]^+$ (61).

4,9-Dithia-1,2,6,7-tetraazatricyclo[5.3.1.1^{2,6}]dodecane (3). ***A.*** A solution of 37% formalin (25.5 mL, 0.3 mol) was saturated at 20 °C with H_2S (0.2 mol) for 30 min; then hydrazine (1.6 mL, 0.05 mol) was added dropwise. The reaction mixture was stirred at 20 °C for 3 h. The product was extracted with chloroform (2×30 mL) and the extract was dried with $CaCl_2$ and concentrated to give heterocycle **3** (1.5 g, 29%), m.p. 157—158 °C. Found (%): C, 35.48; H, 5.76; N, 27.34; S, 31.42. $C_6H_{12}N_4S_2$. Calculated (%): C, 35.29; H, 5.88; N, 27.45; S, 31.38. IR, ν/cm^{-1}: 640, 770, 1100, 1370, 1450. ^{1}H NMR, δ: 3.60 (d, 2 H, $H_a(11)$, $H_a(12)$, ^2J = 11.8 Hz); 3.95 (d, 4 H, $H_a(3)$, $H_a(5)$, $H_a(8)$, $H_a(10)$, ^2J = 7.3 Hz); 4.45 (dd, 4 H, $H_e(3)$, $H_e(5)$, $H_e(8)$, $H_e(10)$, ^2J = 7.3 Hz, ^4J = 1.6 Hz); 4.65 (dd, 2 H, $H_e(11)$, $H_e(12)$, ^2J = 11.8 Hz, ^4J = 1.6 Hz). ^{13}C NMR, δ: 52.32 (s, C(3), C(5), C(8), C(10)); 61.88 (s, C(11), C(12)). MS, *m/z* (I_{rel} (%)): 204 $[M]^+$ (32), 148 $[M - N_2(CH_2)_2]^+$ (36), 116 $[M - N_2(CH_2)_2S]^+$ (48), 102 $[M - N_2(CH_2)_3S]^+$ (60).

B. Heterocycle **3** (1.5 g, 30%) was also obtained from 37% formalin (12.25 mL, 0.15 mol) and hydrazine (1.6 mL, 0.05 mol) as described in procedure ***A***. The IR, ^{1}H and ^{13}C NMR, and mass spectra of the product were identical with the data given above for compound **3**.

4,9,14-Trithia-1,2,6,7,11,12-hexaazatetracyclo[10.3.1.1^{2,6}.1^{7,11}]octadecane (4). ***A.*** Ten to twelve hours after product **3** was separated from the reaction mixture, the crystals of compound **4** that formed were filtered off, washed with water, and dried. The yields of heterocycle **4** were 1.6 g (30%) from the filtrate in procedure ***A*** and 0.95 g (18%) from the aqueous layer in procedure ***B***; m.p. 254—255 °C. Found (%): C, 35.48; H, 5.76; N, 27.34; S, 31.42. $C_9H_{18}N_6S_3$. Calculated (%): C, 35.29; H, 5.88; N, 27.45; S, 31.38. MS, *m/z* (I_{rel} (%)): 306 $[M]^+$ (4), 260 $[M - CH_2S]^+$ (8), 204 $[M - (CH_2)_3SN_2]^+$ (89), 148 $[M - N_4(CH_2)_5S]^+$ (44), 116 $[M - N_3(CH_2)_6S_2]^+$ (4), 102 $[M - N_4(CH_2)_6S_2]^+$ (100). IR, ν/cm^{-1}: 640, 770, 1100, 1370, 1450. M_{cr} = 306±10.

B. Heterocycle **4** (1.65 g, 31%) was also obtained from 37% formalin (25.5 mL, 0.3 mol) and hydrazine (1.6 mL, 0.05 mol) at 0 °C as described for compound **2**. The product was identical with compound **4** obtained according to procedure ***A***.

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