Thiocarbamoylation of amine-containing compounds
4.* Reactions of tetramethylthiuram disulfide with aliphatic amines

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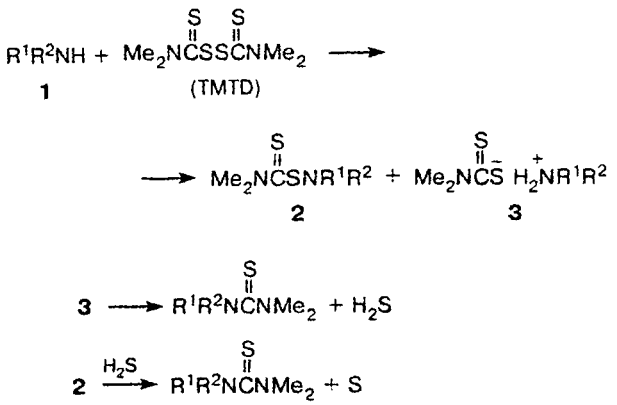
Thiocarbamoylation of primary and secondary aliphatic amines with tetramethylthiuram disulfide in various solvents at different temperatures was studied. At 110 °C, the reactions with primary amines afforded mixed *N,N*-dimethyl-*N'*-alkyl(cycloalkyl)thioureas and symmetrical *N,N'*-dialkyl(cycloalkyl)thioureas as the final products, while the reactions with secondary amines gave mixtures of dithiocarbamate salts with "symmetrical" derivatives predominating.

Key words: tetramethylthiuram disulfide, aliphatic amines, dialkyl(cycloalkyl)ammonium dialkyl(cycloalkyl)dithiocarbamates, *N,N*-dimethylthiocarbamoyl-*N'*-dialkyl(cycloalkyl)-sulfenamides, *N,N'*-dialkyl(dicycloalkyl)thioureas.

Tetramethylthiuram disulfide (TMTD) finds use as a vulcanization accelerator[1] as well as a pesticide.[2] Its analogs are studied as anti-HIV drugs.[3] In scientific practice, TMTD is used, in particular, in studies of clusters.[4,5] Due to the presence of the disulfide group with the enhanced reactivity, TMTD can enter into thiocarbamoylation reactions with amines to form thioureas. An alternative procedure for the synthesis of the latter compounds is based on the use of toxic reagents, such as carbon disulfide or thiophosgene. Thiocarbamoylation is both of practical and theoretical interest. However, it is still poorly developed and studies of the reactions of TMTD with aliphatic amines are scarce in the literature.[6—8] When the reactions are performed in benzene or ethanol with heating, primary aliphatic amines give[6] mixed thioureas, while secondary amines do not react with TMTD. It was demonstrated[7,8] that the reactions of an excess of primary or secondary aliphatic amines (**1**) with TMTD at 20 °C afforded *S*-(thiocarbamoyl)thiohydroxylamines (**2**) and dialkyl(cycloalkyl)ammonium dimethyldithiocarbamates (**3**). In the authors' opinion, an increase in the temperature to 70 °C leads to conversions of the latter compounds into mixed thioureas with elimination of hydrogen sulfide, which catalyzes decomposition of compounds **2** to form the second thiourea molecule and sulfur (Scheme 1).

The above-mentioned studies are not systematic. In some cases, the evidence for the structures of the resulting compounds is not fully convincing. Taking into account the importance of these reactions as a potential route to difficultly accessible thioureas, we studied the reactions of TMTD with primary and secondary aliphatic amines in detail. The reactions were performed both in an excess of amines and in organic solvents (in benzene or ethanol) at 20, 70, or 80 °C as well as in toluene or dioxane at higher temperatures (80—110 °C).

Scheme 1



R^1 = H, R^2 = C_6H_{11}; $R^1 + R^2$ = $(CH_2)_2O(CH_2)_2$; $R^1 + R^2$ = $(CH_2)_5$; $R^1 = R^2$ = Et

First we studied the reactions of TMTD with primary aliphatic amines, *viz.*, with cyclohexylamine (**1a**) and benzylamine (**1b**). The reactions of TMTD with a tenfold excess of amines (**1a,b**) (mixture **I**) (3 h, 20 °C) afforded *N*-cyclohexyl-*S*-(*N,N*-dimethylthiocarbamoyl)-thiohydroxylamine (**2a**) and cyclohexylammonium

* For Part 3, see Ref. 1.

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N,N-dimethyldithiocarbamate (**3a**) along with "symmetrical" cyclohexylammonium *N*-cyclohexyldithiocarbamate (**4a**) or *N*-benzyl-*S*-(*N,N*-dimethylthiocarbamoyl)-thiohydroxylamine (**2b**), benzylammonium *N,N*-dimethyldithiocarbamate (**3b**), and "symmetrical" benzylammonium *N*-benzyldithiocarbamate (**4b**), respectively. The formation of mixtures of dithiocarbamates and their relative compositions were established based on the data of mass spectrometry and ^{1}H NMR spectroscopy (see the Experimental section). The amount of "symmetrical" salts **4a,b** was 10—16% of the total amount of the salts formed. Small amounts (3—6%) of *N'*-cyclohexyl-*N,N*-dimethylthiourea (**5a**) or *N'*-benzyl-*N,N*-dimethylthiourea (**5b**) as well as *N,N'*-dicyclohexylthiourea (**6a**) or *N,N'*-dibenzylthiourea (**6b**) (Scheme 2) were also isolated from mixtures of the products by HPLC. At higher temperature (70 °C, 1 h), mixture **I** afforded sulfur and thioureas **5a,b** and **6a,b**. The yields of thioureas were ~70 and 30%, respectively (see Scheme 2).

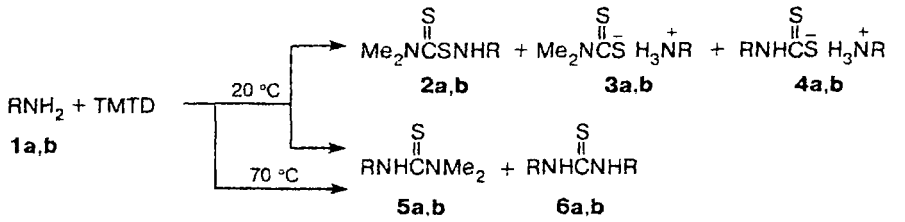
Compounds **5a,b** and **6a,b** were obtained in similar yields in the reactions of amines **1a(b)** with TMTD taken in a ratio of 2 : 1 in boiling toluene (dioxane). The composition of the mixture of the thioureas formed upon refluxing in these solvents strongly depended on the reagent ratio. Thus when the **1a** : TMTD ratio was varied from 1 : 1 to 4 : 1, the yield of **6a** increased from 10 to 80%, while the yield of **5a**, on the contrary, decreased in the reverse order.

The reactions of TMTD with a tenfold excess of secondary amines (**1c—e**) (mixture **II**) gave different results. Thus reactions performed at 20 °C for 3 h yielded *N*-(*N,N*-dimethylaminocarbodithioyl)morpholine (**2c**), *N*-(*N,N*-dimethylaminocarbodithioyl)piperidine (**2d**), or *S*-(*N,N*-dimethylthiocarbamoyl)-*N,N*-dimethylthiohydroxylamine (**2e**), morpholinium or piperidinium dimethylaminocarbodithioates (**3c** or **3d**, respectively), and "symmetrical" morpholinium morpholine-4-carbodithioate (**4c**) or piperidinium piperidine-1-carbodithioate (**4d**), respectively. However, thioureas were not detected in the mixtures of the products. The above-mentioned compounds were identified by mass spectrometry and ^{1}H NMR spectroscopy. When the temperature was increased to 70 °C, salts **3c,d** and **4c—e** were isolated from mixture **II** as the major products in ~70 and 30% yields, respectively (Scheme 3). The reactions of amines **1c(e)** with TMTD (in a ratio of 2 : 1) in boiling toluene (benzene) afforded salts **3c,d** (~10%) and salts **4c—e** (~65%). In both cases, thioureas were isolated only in trace amounts.

The reactions performed with heating afforded also dimethylammonium dimethylaminocarbodithioate (m.p. 128—132 °C, *cf.* the published data[6,14]: m.p. 130—132 °C).

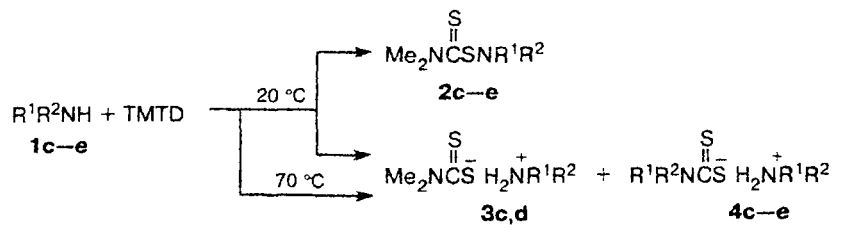
Hence, the results of our studies confirmed only partially the data reported previously.[6—8] Actually, the reactions of TMTD with primary and secondary aliphat-

Scheme 2



R = C_6H_{11} (**a**), $PhCH_2$ (**b**)

Scheme 3



$R^1 + R^2 = (CH_2)_2O(CH_2)_2$ (**c**), $(CH_2)_5$ (**d**), $R^1 = R^2 = Me$ (**e**)

ic amines at 20 °C in media of amines afforded thiohydroxylamine derivatives **2** and salts **3**. When heated (to 110 °C), only primary amines can react with TMTD to form thioureas. In addition, it was found that the mechanism of the reactions of TMTD with aliphatic amines is more complex. The process is always accompanied by symmetrization of intermediates. At 20 °C, a mixture of salts, *viz.*, mixed and "symmetrical" carbodithioates, was also formed, which favored the formation of a mixture of mixed (**5a,b**) and symmetrical (**6a,b**) thioureas upon heating (in the case of primary amines). A repetition of the reaction of TMTD with cyclohexylamine **1a** under conditions reported previously[7] showed that *N,N'*-dicyclohexylthiourea **6a** (m.p. 178—180 °C) rather than *N'*-cyclohexyl-*N,N*-dimethylthiourea **5a** was actually formed. Compound **5a**, which was prepared by us and whose structure was established by mass spectrometry, ^{1}H NMR spectroscopy, and elemental analysis, is characterized by a m.p. of 92—94 °C (rather than 175—178 °C, as was reported previously[7]).

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AM-250 instrument. The chemical shifts were measured relative to Me_4Si. The mass spectra were obtained on an INCOS-50 instrument (EI, 70 eV). TLC was carried out on Silufol UV-254 plates. The plates were inspected under UV light. The reaction products, if required, were isolated by HPLC on a Bruker chromatograph.

TMTD was recrystallized from $CHCl_3$, m.p. 154—156 °C (*cf.* lit.[10]: m.p. 156 °C). Amines **1a—d** were distilled *in vacuo* before use. Reagent-grade dimethylamine (**1e**) was used as a 33% aqueous solution.

Reactions of TMTD with amines 1a—e. *A.* In an excess of amines at 20 °C. Amine 1a. A mixture of TMTD (2.40 g, 10 mmol) and cyclohexylamine (**1a**, 9.90 g, 100 mmol) was stirred for 3 h. After completion of the reaction, the mixture of salts **3a** and **4a** that precipitated was filtered off, washed with ether on a filter, and dried in air. The filtrate was diluted with water. Compound **2a** and a small portion of thioureas that precipitated were filtered off, washed several times with water, and dried under reduced pressure in a desiccator over KOH. Thiohydroxylamine **2a** was purified from thioureas by passing through a column with SiO_2 (a 9 : 1 benzene—ethyl acetate mixture as the eluent) or by HPLC (a 7 : 3 light petroleum—ethyl acetate mixture as the solvent). First product **2a**, then thiourea **6a**, and finally, thiourea **5a** were eluted. Their retention times were 4.00, 4.35, and 6.68 min, respectively. Compounds **2a** and **6a** with close mobilities can be separated by repeated passage through a column with silica gel (hexane as the eluent).

A mixture of thioureas was precipitated from the crude mixture of salts **3a** and **4a** upon dissolution in water. Chro-

Table 1. Yields and selected physicochemical characteristics of the products of the reactions of TMTD with amines **1a—e** in a media of amines (amine : TMTD = 10 : 1) or in toluene (amine : TMTD = 2 : 1)

Amine	Products	R_f[a]	Yield (%)			M.p.[b] /°C	Found (%) / Calculated			Molecular formula
			I[c]	II[d]	III[e]		C	H	N	
1a	**2a**	0.64	78			38—40 (23—24)[7]	49.43 / 49.50	8.07 / 8.31	12.68 / 12.83	$C_9H_{18}N_2S_2$
	5a	0.27	2	70	72	92—94 (175—178)[7]	57.67 / 58.02	9.48 / 9.74	14.75 / 15.04	$C_9H_{18}N_2S$
	6a	0.49	4	30	28	178—180 (180)[12]				
1b	**2b**[f]	0.65	76				53.19 / 53.06	6.33 / 6.23	12.51 / 12.38	$C_{10}H_{14}N_2S_2$
	5b	0.25	3	78	73	98—100 (98.5)[12]				
	6b	0.41	2	22	26.3	146—147 (146—148)[12]				
1c	**2c**	0.65	82			84—86 (84—85)[7]				
	4c		13	29	65	178 (decomp.)	43.32 / 43.17	7.29 / 7.25	11.31 / 11.19	$C_9H_{18}N_2O_2S_2$
1d	**2d**	0.68	93			79—80 (77—79)[12]				
	4d		12	26	60	172 (decomp.) (168—171)[13]				
1e	**2e**	0.68	70			52—54	36.71 / 36.56	7.42 / 7.36	17.19 / 17.05	$C_5H_{12}N_2S_2$
	4e		94			129—132 (130—132)[14]				

[a] C_6H_6 : AcOEt = 1 : 9. [b] The literature data are given in parentheses. [c] In amine, 20° C. [d] At 70° C. [e] In toluene. [f] n_D^{20} 1.6082.

Table 2. Data of ^1H NMR spectroscopy and mass spectrometry of the synthesized compounds

Compound	^1H NMR ($CDCl_3$), δ (*J*/Hz)	Mass spectra (EI, 70 eV), *m/z* (I_{rel} (%))
2a	1.60 (m, 10 H, CH_2 cyclo); 2.78 (m, 1 H, CH cyclo); 3.27 (s, 3 H, MeN); 3.55 (s, 3 H, MeN); 3.80 (s, 1 H, NH)	218 $[M]^+$ (3), 120 [M − 98] (14), 98 [M − 120] (46), 88 [M − 130] (100)
4a	1.55 (m, 20 H, CH cyclo); 3.12 (m, 1 H, CH—NH_3^+); 4.25 (m, 5 H, CH cyclo, NHCS, NH_3^+)	175 [M − 99] (23), 142 [M − 132] (9), 99 [M − 175] (19), 56 [M − 218] (100)
5a	1.60 (m, 10 H, CH_2 cyclo); 3.25 (s, 6 H, Me_2N); 4.30 (m, 1 H, CH cyclo); 5.15 (m, 1 H, NH)	186 $[M]^+$ (55), 98 [M − 88] (100)
6a	1.60 (m, 20 H, CH_2 cyclo); 3.85 (m, 2 H, CH cyclo); 5.60 (m, 2 H, 2 NH)	240 $[M]^+$ (55), 142 [M − 98] (68), 98 [M − 142] (100)
2b	3.23 (s, 3 H, MeN); 3.56 (s, 3 H, MeN); 3.95 (d, 1 H, NH, ^3J = 8.2); 4.10 (d, 2 H, CH_2, ^3J = 8.2); 7.36 (m, 5 H, Ar)	
4b	3.70 (m, 5 H, $\underline{CH_2}$—NH_3^+, NH_3^+); 4.00 (d, 2 H, CH_2, ^3J = 8.0); 4.76 (d, 1 H, NH, ^3J = 8.0); 7.30 (m, 10 H, Ar)	183 [M − 107] (44), 150 [M − 140] (60), 106 [M − 184] (100)
5b	3.28 (s, 6 H, Me_2N); 4.85 (d, 2 H, CH_2, ^3J = 8.5); 5.52 (d, 1 H, NH, ^3J = 8.5); 7.35 (m, 5 H, Ar)	194 $[M]^+$ (85), 106 [M − 88] (100), 91 [M − 103] (68)
6b	4.63 (d, 4 H, CH_2, ^3J = 8.0); 6.08 (d, 2 H, NH, ^3J = 8.0); 7.26 (m, 10 H, Ar)	256 $[M]^+$ (30), 106 [M − 150] (100), 91 [M − 165] (67)
2c	3.28 (m, 10 H, Me_2N, NCH_2); 3.70 (m, 4 H, OCH_2)	206 $[M]^+$ (2), 120 [M − 86] (3), 88 [M − 118] (100)
4c*	3.35 (m, 4 H, $(CH_2)_2NH_2^+$); 3.85 (m, 4 H, OCH_2); 4.05 (m, 4 H, $(CH_2)_2N$—CS); 4.45 (m, 4 H, OCH_2); 4.80 (s, 2 H, NH_2^+)	163 [M − 87] (60), 130 [M − 120] (40), 86 [M − 164] (100)
2d	1.55 (m, 6 H, CH_2 cyclo); 3.45 (m, 10 H, Me_2N, NCH_2 cyclo)	204 $[M]^+$ (2), 120 [M − 84] (12), 88 [M − 120] (100)
4d	1.76 (m, 12 H, CH_2 cyclo); 3.28 (m, 4 H, $(CH_2)_2NH_2^+$); 4.35 (m, 4 H, $(CH_2)_2N$—CS); 8.40 (br.s, 2 H, NH_2^+)	161 [M − 85] (80), 128 [M − 118] (70), 84 [M − 162] (100)
2e	3.13 (m, 9 H, Me_2N—CS, MeN—S); 3.42 (br.s, 3 H, MeN—S)	164 $[M]^+$ (4), 120 [M − 44] (6), 88 [M − 76] (100)
4e	2.79 (s, 6 H, $Me_2NH_2^+$); 3.56 (s, 6 H, Me_2N—CS); 9.05 (br.s, 2 H, NH_2^+)	121 [M − 45] (80), 88 [M − 78] (100)

* In D_2O.

matographic separation of this precipitate gave additional amounts of thioureas **5a** and **6a** (30—40 mg each).

Amines 1b—e. The reactions were performed according to an analogous procedure. After removal of water, oily thiohydroxylamine **2b** was dried with anhydrous Na_2SO_4 and purified as described above.

Thiohydroxylamine **2e** was prepared by mixing TMTD with a 33% aqueous solution of dimethylamine **1e** for 1.5 h. The colorless product that precipitated was filtered off, washed with water, and dried. The aqueous filtrate was concentrated and salt **4e** was obtained.

***B.* In an excess of amines at 70 °C. Amines 1a,b.** A mixture of TMTD (2.40 g, 10 mmol) and amine **1a,b** (100 mmol) was stirred at 70 °C for 1.5 h. After cooling, the reaction mixtures were dissolved in 5% HCl and the yellow precipitates that formed were filtered off and dried. Then the crude products were dissolved in concentrated HCl and sulfur was separated by filtration. The filtrates were diluted with water and white precipitates of thioureas **5a,b** and **6a,b** that formed were filtered off, dried, and chromatographed on a column with silica gel (a 9 : 1 benzene—ethyl acetate mixture as the eluent). First thioureas **6a,b** and then **5a,b** were eluted. Mixtures of **5a,b** and **6a,b** were readily separated by HPLC (a 7 : 3 light petroleum—ethyl acetate mixture as the eluent). Their retention times were 4.35 and 6.68 min, respectively.

Amines 1c,d. The reactions were performed analogously to those of amines **1a,b**. The precipitates of the salts that formed were filtered off and washed on a filter with ether to remove the remaining amines. Then the mixture of the salts was dissolved in a minimum amount of water. Insoluble admixtures were filtered off. The filtrate was cooled and "symmetrical" salts **4c,d** that precipitated were filtered off, dried, and recrystallized from water or aqueous ethanol. Salts **3c,d** were obtained from mother liquors after concentration.

C.* In boiling toluene (dioxane).** A mixture of TMTD (2.40 g, 10 mmol) and amines **1a—d** (20 mmol) in toluene (dioxane) (5 mL) was heated at the boiling temperature of the mixture for 1 h. In the case of amines **1c,d**, the solvent was distilled off from the reaction mixtures and the precipitates of the salts were treated according to procedure ***B. Salts **4c** and **4d** were obtained. After cooling of the reaction mixtures in the case of amines **1a,b**, the precipitates that formed were filtered off and dissolved in concentrated HCl. Insoluble sulfur was separated by filtration. The filtrates were diluted with water and the precipitates of thioureas that formed were filtered off and separated as described in procedure ***B***. Compounds **5a**, **6a**, **5b**, and **6b** were obtained.

The reactions of TMTD with a fourfold excess of amines **1a** or **1c** were performed analogously to obtain thioureas **5a** and **6a** or salt **4c**, respectively.

D. Mixtures of salts **3a—d** and **4a—e** were dried and analyzed by mass spectrometry. Ions of the following acids were detected: dimethyldithiocarbamic (*m/z* 121), cyclohexyldithiocarbamic (*m/z* 175), *N*-benzyldithiocarbamic (*m/z* 183), morpholine-4-carbodithioic (*m/z* 163), and piperidine-1-carbodithioic (*m/z* 161) acids. These signals were observed in the mass spectra of the corresponding acids, which were the anions of the salts unambiguously synthesized according to a known procedure.[11] The relative compositions of the salts in each mixture were calculated from the integrated intensities of the signals for the protons in the ^{1}H NMR spectra recorded in $CDCl_3$. The amounts of "symmetrical" salts **4a—d** in each mixture varied in the range of 10—16%.

The yields and selected physicochemical characteristics of the synthesized compounds are given in Tables 1 and 2.

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