Thiocarbamoylation of amine-containing compounds
3.* 5-(*N'*,*N'*-Dimethylthioureido)salicylic acid. Synthesis and reactions

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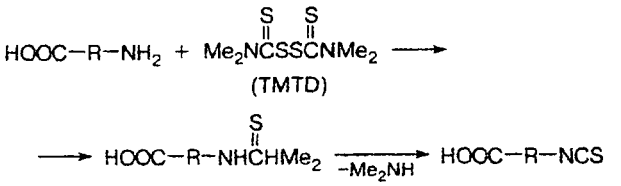
Thiocarbamoylation of 5-aminosalicylic acid with tetramethylthiuram disulfide afforded 5-(*N'*,*N'*-dimethylthioureido)salicylic acid. Treatment of the latter with mineral acids or Ac_2O gave 5-isothiocyanatosalicylic acid, whose reaction with ethanolamine yielded 5-[*N'*-(2-hydroxyethyl)thioureido]salicylic acid. The latter underwent cyclization under the action of TsOH to form 5-(2-thiazolin-2-ylamino)salicylic acid.

Key words: tetramethylthiuram disulfide, 5-aminosalicylic acid, 5-(*N'*,*N'*-dimethylthioureido)salicylic acid, 5-isothiocyanatosalicylic acid, 5-[*N'*-(2-hydroxyethyl)thioureido]salicylic acid, 5-(2-thiazolin-2-ylamino)salicylic acid.

Isothiocyanatobenzoic acids exhibit a broad spectrum of biological activities and find use in medicine and agriculture.[2–5] Due to the presence of the isothiocyanate group, these compounds can be transformed into compounds of various classes with new biological properties.[6–8] Derivatives of isothiocyanatobenzoic acids are difficultly accessible and poorly studied. A procedure for their synthesis based on the reactions of the corresponding aminobenzoic acids with thiophosgene[8,9] is rather laborious and often gives unsatisfactory yields. Previously,[10,11] we have reported a new preparative procedure for the synthesis of isothiocyanato carboxylic acids by thiocarbamoylation of amino carboxylic acids with tetramethylthiuram disulfide (TMTD) followed by decomposition of the resulting *N'*,*N'*-dimethylthioureido derivatives under the action of Ac_2O, AcCl, or mineral acids (HCl or H_2SO_4) (Scheme 1). The method for the preparation of isothiocyanato carboxylic acids developed by us is characterized by simplicity and high yields of the target products (>90%). In addition, this method allows one to avoid the use of toxic compounds, such as thiophosgene.

In continuation of our studies and considering specific biological properties of salicylic acid and its derivatives,[8] in this work we studied thiocarbamoylation of 5-aminosalicylic acid (**1**) under the action of TMTD with the aim of preparing 5-(*N'*,*N'*-dimethylthioureido)salicylic acid (**2**). The reactions of the latter with Ac_2O, AcCl, HCl, or H_2SO_4 afforded 5-isothiocyanatosalicylic acid (**3**). Thiourea **2** and isothiocyanate **3a**

Scheme 1



R — alkylarylene or aryloxyalkanediyl

obtained according to this procedure are substantially cheaper than those synthesized by other methods. These compounds can serve as starting materials in the synthesis of other organic compounds, in particular, of thiazole derivatives (**4**) (Scheme 2).

Unlike arylamines containing electron-donating substituents, whose reactions with TMTD in benzene or toluene give thioureas in high yields,[12] aminosalicylic acid **1** contains the amino group with reduced basicity, which hinders the reaction. We succeeded in performing this reaction only in polar solvents, *viz.*, in propanol, dioxane, or DMF. When the reaction was carried out at 100 °C and the reagents were taken in an equimolar ratio, thiourea **2** was obtained in 90% yield. When the amount of TMTD was halved, the yield of thiourea **2** decreased to 76%, unlike the analogous reactions of nonsubstituted aminobenzoic acids[10] or nitroanilines,[13] in which the yields of the final products decreased to 50% when the amount of TMTD was halved. The less

* For Part 2, see Ref. 1.

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Scheme 2

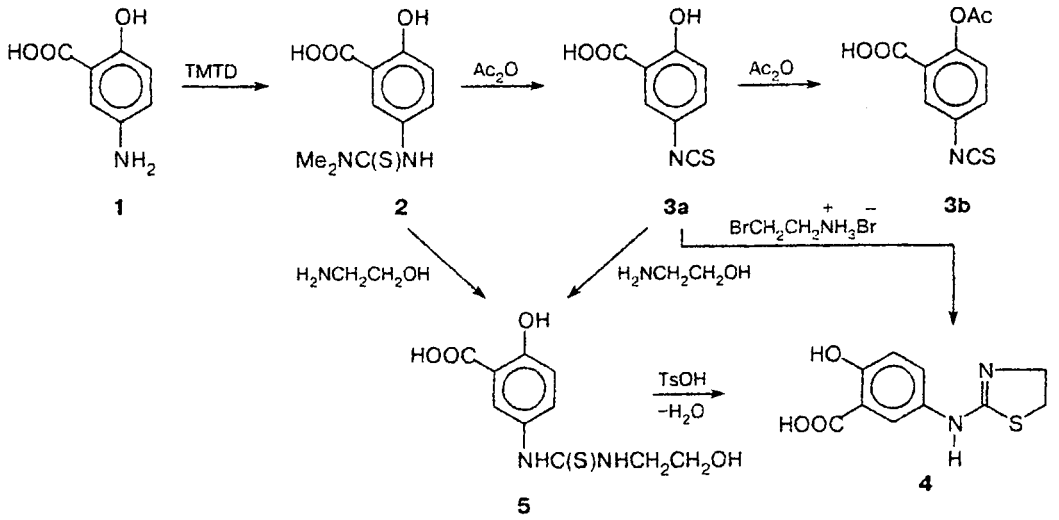

Table 1. The yields and selected physicochemical characteristics of the synthesized derivatives of 5-aminosalicylic acid

Compound	Procedure	Yield (%)	M.p./°C	R_f	Solvent system	Found / Calculated (%) C	H	N	Molecular formula
2		90	166—168	0.24	C_6H_6—Me_2CO (2 : 1)	50.19 / 49.99	5.16 / 5.03	11.89 / 11.66	$C_{10}H_{12}N_2O_3S$
3a	***A***	56	176—178	0.57	C_6H_6—Me_2CO (2 : 1)	49.08 / 49.23	2.72 / 2.56	7.34 / 7.18	$C_8H_5NO_3S$
	B	85							
	C	87							
3b	***A***	18	151—153	0.48	C_6H_6—Me_2CO (2 : 1)	51.12 / 50.63	3.08 / 2.95	6.13 / 5.91	$C_{10}H_7NO_4S$
	D	83							
4	***A***	81	240 (decomp.)	0.34	C_6H_6—AcOEt—Me_2CO (1 : 3 : 1)	50.21 / 50.42	4.12 / 4.20	11.64 / 11.76	$C_{10}H_{10}N_2O_3S$
	B	71							
5	***A***	85	179—181	0.50	EtOH—AcOEt (3 : 1)	48.51 / 48.32	4.76 / 4.73	9.62 / 9.39	$C_{12}H_{14}N_2O_5S$
	B	82							

significant decrease in the yield of thiourea **2** is apparently associated with the fact that the electron-withdrawing effect of the carboxy group in amine **1** is partially compensated by the electron-donating effect of the hydroxy group.

Heating of thiourea **2** with Ac_2O, AcCl, HCl, or H_2SO_4 afforded isothiocyanate **3a** (see Scheme 2). In the case of Ac_2O, 2-acetoxy-5-isothiocyanatobenzoic acid (**3b**) was obtained as a by-product, whose structure was confirmed by an independent synthesis, *viz.*, by acetylation of isothiocyanatosalicylic acid **3a**.

The use of mineral acids (HCl or H_2SO_4) instead of Ac_2O led to an increase in the yield of isothiocyanate **3a**. From the viewpoint of the efficiency, H_2SO_4 is the reagent of choice. The reaction of H_2SO_4 with thiourea **2** is characterized by simplicity and high purity of the target product.

With the aim of going to thiazole derivatives, we synthesized [*N'*-(2-hydroxyethyl)thioureido]salicylic acid (**5**) by the reactions of thiourea **2** or isothiocyanate **3a** with ethanolamine. In both cases, good yields (82 and 85%, respectively) were attained with a twofold molar excess of ethanolamine.

2-Hydroxyethylthiourea **5** underwent cyclization upon heating in the presence of TsOH to form 5-(2-thiazolin-2-ylamino)salicylic acid (**4**). The latter was synthesized also by the reaction of isothiocyanate **3a** with 2-bromoethylamine hydrobromide. Preference should be given to the latter procedure because thiazole **4** prepared from 2-bromoethylamine is purer and it can readily be additionally purified by recrystallization from a mixture of ethanol and DMF.

The yields and selected physicochemical characteristics of the synthesized compounds **2**—**5** are given in Tables 1 and 2.

Table 2. ^{1}H NMR spectra and mass spectra of the synthesized compounds

Compound	Solvent	^{1}H NMR, δ (*J*/Hz)	Mass spectrum, *m*/*z* (I_{rel} (%))
2	DMSO-d_6	3.26 (s, 6 H, NMe_2); 6.97 (d, 1 H, C(3)H, ^3J = 11.7); 7.15 (s, 1 H, C(6)H); 7.70 (d, 1 H, C(4)H, ^3J = 11.7); 9.19 (s, 1 H, NH)	240 $[M]^+$ (7), 195 (71), 177 (100)
3a	DMSO-d_6	7.00 (d, 1 H, C(3)H, ^3J = 10.5); 7.51 (d, 1 H, C(4)H, ^3J = 10.5); 7.69 (s, 1 H, C(6)H)	195 $[M]^+$ (65), 177 (100), 149 (43)
3b	$CDCl_3$	2.42 (s, 3 H, MeCO); 6.95 (d, 1 H, C(3)H, *J* = 11.9); 7.47 (d, 1 H, C(4)H, *J* = 11.9); 7.70 (s, 1 H, C(6)H); 11.30 (br.s, 1 H, OH)	237 $[M]^+$ (4), 194 (57), 176 (100)
4	DMSO-d_6	3.32 (t, 2 H, SCH_2, *J* = 7.5); 4.05 (t, 2 H, $=NCH_2$, *J* = 7.5); 6.95 (d, 1 H, C(3)H, *J* = 11.5); 7.25 (s, 1 H, C(6)H); 7.60 (d, 1 H, C(4)H, *J* = 11.5)	238 $[M]^+$ (100), 220 (90), 195 (55)
5	DMSO-d_6	3.40 (t, 2 H, OCH_2, *J* = 8.5); 3.96 (t, 2 H, NCH_2, *J* = 8.5); 6.92 (d, 1 H, C(3)H, *J* = 11.5); 7.47 (s, 1 H, C(6)H); 7.68 (d, 1 H, C(4)H, *J* = 11.5); 9.89 (s, 1 H, NH)	256 $[M]^+$ (2), 238 (3), 195 (71), 177 (100)

Experimental

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

TMTD was recrystallized from $CHCl_3$, m.p. 154–156 °C (*cf.* lit[14]: m.p. 156 °C). Reagent-grade 5-aminosalicylic acid was used. Ethanolamine was distilled *in vacuo* before use.

5-(*N'*,*N'*-Dimethylthioureido)salicylic acid (2). A mixture of amine **1** (1.53 g, 10 mmol) and TMTD (2.40 g, 10 mmol) in PrOH (2 mL) was heated at 100 °C for 1 h. The solvent was distilled off *in vacuo*. Then water (5 mL) and a 5% aqueous solution of $NaHCO_3$ were added to the residue until the reaction mixture became alkaline. Sulfur and insoluble admixtures were filtered off. The filtrate was acidified with HCl to pH 5. Thiourea **2** was obtained in a yield 2.16 g (90.3%).

The reactions in dioxane and DMF were carried out similarly with the use of **1** and TMTD taken in a molar ratio of 2 : 1. Thiourea **2** was obtained in 76% yield.

5-Isothiocyanatosalicylic acid (3a) and 2-acetoxy-5-isothiocyanatobenzoic acid (3b). ***A.*** A solution of thiourea **2** (2.40 g, 10 mmol) and Ac_2O (1.02 g, 10 mmol) in dioxane (8 mL) was heated at 90 °C for 2 h. After completion of the reaction, the solvent was distilled off *in vacuo* and the residue was washed with water and dried. Chromatography on a column with SiO_2 (benzene as the eluent) afforded isothiocyanates **3a** and **3b** in yields of 1.08 g (55.6%) and 0.42 g (18%), respectively. Trace amounts of the initial amine **1** were eluted with a 7 : 3 benzene–acetone mixture.

Treatment of thiourea **2** with a twofold excess of Ac_2O afforded isothiocyanate **3b** in 80% yield.

B. A solution of thiourea **2** (2.40 g, 10 mmol) and concentrated H_2SO_4 (0.98 g, 10 mmol) in dioxane (8 mL) was heated at 100 °C for 3 h and then the solvent was distilled off *in vacuo*. The residue was washed with water and dried. Isothiocyanate **3a** was obtained in a yield of 1.65 g (85%).

C. A solution of thiourea **2** (2.40 g, 10 mmol) and hydrogen chloride (0.73 g, 20 mmol) in dioxane (10 mL) was heated in a sealed tube at 90 °C for 3 h. The tube was opened and the solution was heated to boiling. After cooling, the precipitate that formed was filtered off, washed with water, and dried. Isothiocyanate **3a** was obtained in a yield of 1.36 g (70%). After removal of the solvent, an additional amount of the product (0.33 g) was obtained from the filtrate. The total yield of isothiocyanate **3a** was 87%.

D. **Independent synthesis of 3b.** A solution of isothiocyanate **3a** (1.95 g, 10 mmol) and Ac_2O (2.04 g, 20 mmol) in dioxane (6 mL) was heated at 100 °C for 2 h. Then the reaction mixture was diluted with water and cooled. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from benzene. Isothiocyanate **3b** was obtained in a yield of 1.96 g (83%).

5-[*N'*-(2-Hydroxyethyl)thioureido]salicylic acid (5). ***A.*** Isothiocyanate **3a** (1.95 g, 10 mmol) was added to a solution of ethanolamine (1.22 g, 20 mmol) in water (4 mL). The reaction mixture was kept at ~20 °C for 30 min and then heated at 40–50 °C for 10 min. After cooling, the solution was acidified with HCl to pH 4 and the precipitate that formed was filtered off, washed with water, and dried. (2-Hydroxyethyl)thiourea **5** was obtained in a yield of 2.17 g (85%).

B. A solution of thiourea **2** (2.40 g, 10 mmol) and ethanolamine (1.22 g, 20 mmol) was heated at 100 °C for 1 h. Then water (4 mL) was added to the reaction mixture and the mixture was acidified with 10% HCl to pH 4. The precipitate that formed was filtered off. (2-Hydroxyethyl)thiourea **5** was obtained in a yield of 2.05 g (82%).

A mixture of samples of 2-hydroxyethylthiourea prepared according to procedures ***A*** and ***B*** did not give melting point depression.

5-(2-Thiazolin-2-ylamino)salicylic acid (4). ***A.*** A solution of (2-hydroxyethyl)thiourea **5** (2.56 g, 10 mmol) and TsOH (0.17 g, 1 mmol) in dioxane (8 mL) was heated at 80 °C for 1.5 h. Then the solvent was distilled off under reduced pressure. A saturated aqueous solution of $NaHCO_3$ (1 g) was added to the residue and the mixture was filtered. The filtrate was acidified with AcOH and the precipitate that formed was filtered off, washed with water, and dried. Thiazole **4** was obtained in a yield of 2.10 g (81%).

B. A solution of isothiocyanate **3a** (1.95 g, 10 mmol), 2-bromoethylamine hydrobromide (2.05 g, 10 mmol), and

$NaHCO_3$ (0.84 g, 10 mmol) in water (8 mL) was heated at 70 °C for 1 h. Then NaOH (0.40 g, 10 mmol) was added to the resulting solution and the mixture was kept at ~20 °C for 4 h. The precipitate that formed was filtered off, washed with water, and dried. Recrystallization from a mixture of ethanol and DMF afforded thiazole **4** in a yield of 1.80 g (71%).

A mixture of samples of thiazole **4** prepared according to procedures ***A*** and ***B*** did not give melting point depression.

The yields of the synthesized compounds **2**—**5** and their selected physicochemical characteristics are given in Tables 1 and 2.

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