Physicochemical properties and biological activities of thioureas and thiosemicarbazides derived from ethyl isothiocyanatocarboxylates

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Received 23 December 1982

Accepted for publication 25 July 1983

Preparations of thiourea derivatives of sulfonamides and 6-aminopenicilanic acid and thiosemicarbazide derivatives of isonicotinohydrazide are described and their spectral properties discussed. Some of the prepared derivatives were tested for antimycobacterial activity.

Описано получение тиомочевиновых производных сульфонамидов и 6-аминопеницилановой кислоты и тиосемикарбазидных производных изоникотингидразида и обсуждаются их спектральные свойства. Некоторые полученные производные были испытаны на антимикобактериальную активность.

Thiosemicarbazides of aromatic aldehydes, heterocyclic aldehydes of the pyridine series, and some sulfonamides represent the first true chemotherapeutics for tuberculosis [1]. When preparing isonicotinoaldehyde thiosemicarbazone a very important group of compounds, at present belonging to the most active antituberculotics, was discovered. Isonicotinohydrazide (INH) was introduced into practice for its good therapeutic properties [2, 3].

Compounds containing thiourea grouping were studied in detail. Phenyl- and substituted phenylthioureas [4, 5] were investigated mostly. Of numerous thioureas bis(4-ethoxyphenyl)thiourea (Ethoxid) and bis(4-isoamylphenyl)thiourea (Isoxyl) were introduced into practice [6].

Isothiocyanates derived from esters of amino acids are compounds known for their antimicrobial [7, 8], cytotoxic [9], and antimycobacterial activities [10].

Much attention has been paid to reactions of isonicotinohydrazide, 6-aminopenicilanic acid, and sulfonamides with different isothiocyanates. The effort of

authors was motivated by preparation of new compounds with biological activity or intermediates suitable for synthesis of new heterocyclic compounds. *Ogura* and *Takahashi* [11, 12] and *Wieniawski et al.* [13, 14] devoted attention to reactions of isothiocyanates derived from *O*-acetylated pyranoses with 6-aminopenicilanic acid (6-APA), 7-aminocefalosporanic acid (7-ACA), and isonicotinohydrazide (INH).

Pohloudek-Fabini and *Schroepl* [15] prepared series of 1-isonicotinoyl-4-benzoylsemicarbazides by reaction of acyl isothiocyanates with INH.

In preparation of thioureas derived from sulfonamides the amino groups were replaced by thiourea grouping either on the sulfonamide group [16] or on benzene ring in the position 4 [4, 17].

In spite of the fact that, at present, there is a great amount of compounds known for their antituberculotic activity, resistance of mycobacteria to the used antituberculotics calls for searching of new compounds of this type. Therefore, in the present work we focused our attention to synthesis and antimycobacterial activity of thioureas and thiosemicarbazides of sulfonamides, 6-APA, and INH produced in Czechoslovakia as well as of those derived from esters of isothiocyanatocarboxylic acids. Synthesis and isolation of the described 1-(ethoxycarbonylmethyl)-3-[4-(*N*-R-sulfamoyl)phenyl]thioureas *I*—*VI* and substituted 1-acylthiosemicarbazides *IX*—*XX* proceeded without difficulties.

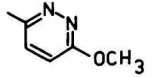
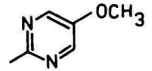
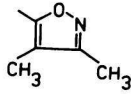
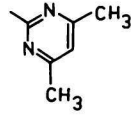
Physicochemical characteristics are summarized in Tables 1 and 2. Preparation and physicochemical properties of thioureas derived from 6-APA are presented in Experimental. In the infrared spectra of thioureas *I*—*VI* the wavenumbers $\tilde{\nu}$(C=O) of the carbonyl group appeared in the region of 1759—1726 cm^{-1} [18] proving the presence of ester group, the wavenumbers $\tilde{\nu}$(N—H) belonged to amino groups of thioureas. For confirmation of structures the results of mass spectrometry and ^{1}H-n.m.r. spectroscopy measurements summarized in Table 3 are important.

The mass spectra of the compounds *I*—*V* did not contain molecular ions. The general fragmentation scheme (Scheme 1), proving the structures of the investigated thioureas, shows two main ways of fission. After elimination of ethyl aminoacetate (way *a*) as a neutral molecule or radical ion and regrouping of hydrogen, fragmentation ions $M^{+\cdot} - 103$ and ions with $m/z = 103$ mostly of high intensity are formed from the basic molecule. The second way (*b*) leads to formation of radical ion of ethyl 2-isothiocyanatoacetate with $m/z = 145$. The base peaks in the spectrum with $m/z = 134$ and $m/z = 72$, respectively are formed by further fission after the ways *a* and *b*. The expected fragmentation ion $M^{+\cdot}$ —C_2H_5OH was observed only with the compound *I* (way *c*).

Very strong absorptions in the i.r. spectra of thiosemicarbazides *IX*—*XX* at $\tilde{\nu} = 1747$—1720 cm^{-1} (Table 2) as well as the triplet and the quartet in the corresponding region of the ^{1}H-n.m.r. spectra proved the presence of ethoxycarbonyl grouping, while the wavenumbers in the region of 1682—1669 cm^{-1} indicated the carbohydrazide grouping [19]. The presence of secondary amines of

Table 1

Physicochemical characteristics of 1-(ethoxycarbonylmethyl)-3-[4-(*N*-R-sulfamoyl) phenyl]thioureas

Compound	R	Formula M_r	w_i(calc.)/w_i(found) % C	% H	% N	M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1} [a] $\tilde{\nu}$(C=O)	$\tilde{\nu}$(N—H)	m/z (relative intensity/%)[b]
I	H	$C_{11}H_{15}N_3O_4S_2$ 317.39	41.63 41.31	7.76 7.67	13.24 13.30	203—205 89	1729	3336	271 (20), 214 (95), 199 (10), 198 (44), 145 (15), 135 (13), 134 (100), 103 (10), 72 (35), 45 (74)
II		$C_{14}H_{16}N_4O_4S_3$ 400.50	41.99 41.66	4.03 4.10	13.99 13.83	184—186 90	1734	3307	297 (19), 198 (18), 145 (57), 135 (14), 134 (37), 103 (29), 73 (27), 72 (100), 45 (49)
III		$C_{16}H_{19}N_5O_5S_2$ 425.49	45.17 44.90	4.50 4.63	16.46 16.30	129—130 96	1759	3287	322 (5), 257 (23), 145 (43), 134 (7), 103 (20), 73 (20), 72 (56), 45 (100)
IV		$C_{16}H_{19}N_5O_5S_2$ 425.49	45.17 45.31	4.50 4.68	16.46 16.55	167—169 87	1754	3345	322 (0.2), 257 (47), 145 (58), 134 (16), 103 (30), 73 (25), 72 (100), 45 (54)
V		$C_{16}H_{20}N_4O_5S_2$ 412.49	46.59 46.41	4.89 4.98	13.58 13.53	144—145 90	1739	3362	309 (36), 245 (15), 199 (18), 198 (89), 150 (30), 145 (34), 135 (26), 134 (100), 103 (15), 90 (33), 73 (15), 72 (54), 45 (44)
VI		$C_{17}H_{21}N_5O_4S_2$ 423.52	48.21 48.04	5.00 5.09	16.54 16.31	118—120 85	1726	3336	—

a) Bands of very high intensity; *b*) chosen fragmentation ions confirming the structures of thioureas *I*—*V*

Table 2

Physicochemical characteristics of 1-acyl-4-R-thiosemicarbazides
R—NH—CS—NH—NH—CO—R′

Compound	R	R′	Formula M_r	w_i(calc.)/w_i(found)			M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1}	
				% C	% H	% N		$\tilde{\nu}$(C=O)	$\tilde{\nu}$(N—H)
IX	$CH_2CO_2C_2H_5$	CH_3O	$C_7H_{13}N_3O_4S$	35.74	5.57	17.86	117—118	1740	3322
			235.26	35.70	5.51	17.96	86		
X	$CH_2COOC_2H_5$	C_6H_5	$C_{12}H_{15}N_3O_3S$	51.23	5.37	14.94	158—159	1669	3318
			281.34	51.55	5.43	15.09	78	1745	
XI	$CH_2COOC_2H_5$	C_6H_4—$NO_2(p)$	$C_{12}H_{17}N_4O_5S$	44.16	4.32	17.17	191—192	1675	3325
			326.33	44.25	4.40	17.22	80	1748	
XII	$CH_2COOC_2H_5$	4-Pyridyl	$C_{11}H_{14}N_4O_3S$	46.80	5.00	19.84	196—198	1674	3257
			282.32	46.57	4.95	19.77	95	1747	
XIII	$CH(CH_3)COOC_2H_5$	4-Pyridyl	$C_{12}H_{16}N_4O_3S$	48.64	5.44	18.91	189—191	1682	3277
			296.35	48.72	5.53	18.63	97	1742	
XIV	$CH(CH_2CH(CH_3)_2)COOC_2H_5$	4-Pyridyl	$C_{15}H_{22}N_4O_3S$	53.24	6.55	16.55	204—206	1682	3297
			338.34	52.88	6.31	16.51	97	1747	
XV	$CH(CH_2C_6H_5)COOC_2H_5$	4-Pyridyl	$C_{18}H_{20}N_4O_3S$	58.05	5.41	15.04	190—192	1679	3304
			372.45	58.21	5.70	15.14	76	1741	
XVI	$CH(CH_2$—C_6H_4—$OH(p))COOC_2H_5$	4-Pyridyl	$C_{18}H_{20}N_4O_4S$	55.66	5.19	14.42	185—186	1672	3427
			388.45	55.43	5.12	14.31	72	1720	

Table 2 (Continued)

Compound	R	R′	Formula M_r	w_i(calc)/w_i(found) % C	% H	% N	M.p./°C Yield/%	$\tilde{\nu}_i$/cm^{-1} $\tilde{\nu}$(C=0)	$\tilde{\nu}$(N–H)
XVII	$CH(COOC_2H_5)CH_2COOC_2H_5$	4-Pyridyl	$C_{15}H_{20}N_4O_5S$	48.90	5.47	15.21	172—174	1681	3302
			368.42	48.56	5.57	15.16	66	1741	
XVIII	$(CH_2)_2COOC_2H_5$	4-Pyridyl	$C_{12}H_{16}N_4O_3S$	48.64	5.44	18.91	170—172	1682	3307
			296.35	48.46	5.47	18.74	95	1737	
XIX	$(CH_2)_3COOC_2H_5$	4-Pyridyl	$C_{13}H_{18}N_4O_3S$	50.31	5.85	18.05	181—182	1676	3312
			310.38	50.41	5.93	17.76	68	1741	
XX	$CH_2C_6H_4Br(p)$	4-Pyridyl	$C_{14}H_{13}N_4BrOS$	46.04	3.59	15.34	216—218	1673	3287
			365.26	46.33	3.67	15.55	90		

Table 3

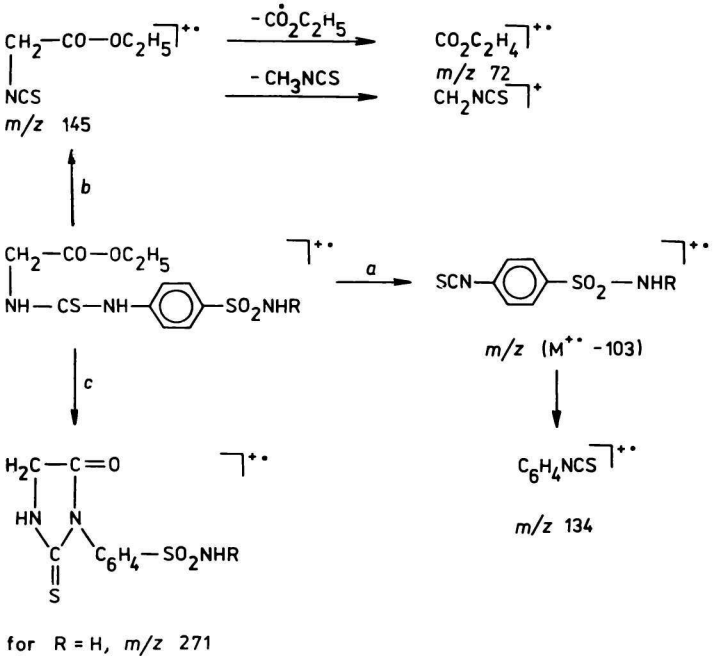
Spectral characteristics of 1-acyl-4-R-thiosemicarbazides

Compound	*m/z* (relative intensity/%)	δ_r/ppm
IX		1.22, 3H (t), $J_{AB}=7$ Hz, $\underline{CH_3}CH_2$; 3.65, 3H (s), CH_3O; 4.00—4.25, 4H (m), $2\times CH_2$; 8.35, 1H (s), $\underline{NH}—CH_2$; 9.24, 1H (s), $\underline{NH}CS$; 9.47, 1H (s), $\underline{NH}CO$
X	281 (3), 231 (18), 106 (9), 105 (100), 85 (6), 83 (9), 77 (44), 72 (9), 51 (14)	
XII	282 (0.2), 236 (26), 145 (20), 137 (16), 122 (15), 107 (16), 106 (100), 79 (13), 78 (90), 73 (13), 72 (43)	1.21, 3H (t), $J_{AB}=7$ Hz, $3\underline{CH_3}CH_2$; 4.00—4.27, 4H (m), $2\times CH_2$; 8.32, 4H (dd), $J_{AB}=5$ Hz, 4-Py; 8.50, 1H (s), $\underline{NH}—CH_2$; 9.75, 1H (s), $\underline{NH}—CS$; 10.82, 1H (s), $\underline{NH}—CO$
XIII	296 (0.6), 250 (41), 222 (8), 164 (5), 106 (100), 86 (9), 79 (9), 78 (63)	
XIV	338 (0.5), 292 (35), 236 (12), 164 (6), 143 (17), 137 (15), 128 (17), 123 (6), 122 (6), 107 (15), 106 (100), 86 (32), 79 (15), 78 (59), 69 (21)	
XV	326 (29), 176 (13), 137 (5), 131 (5), 128 (6), 106 (32), 91 (100), 79 (5), 78 (35), 76 (6)	1.15, 3H (t); 4.10, 2H (q), $J_{AB}=7$ Hz, $\underline{CH_3}CH_2$; 3.13, 2H (d), $J_{AB}=8$ Hz; 5.14, 1H (m), $\underline{CH}CH_2$; 7.25, 5H (m), C_6H_5; 8.31, 4H (dd), $J_{AB}=5$ Hz, 4-Py; 8.20, 1H (d), $J_{AB}=9$ Hz, $\underline{NH}—CH$; 9.72, 1H (s), $\underline{NH}—CS$; 10.75, 1H (s), $\underline{NH}—CO$
XVI	251 (3), 192 (10), 137 (13), 107 (100), 106 (22), 91 (7), 79 (7), 78 (29), 77 (8)	
XVII	368 (0.2), 322 (33), 277 (5), 249 (9), 185 (5), 164 (6), 158 (7), 157 (7), 137 (5), 122 (8), 107 (34), 106 (100), 78 (43)	
XVIII	296 (0.4), 278 (17), 262 (18), 217 (10), 205 (18), 189 (44), 179 (16), 178 (16), 162 (39), 159 (39), 137 (37), 122 (18), 199 (22), 114 (31), 106 (100), 87 (31), 86 (16), 85 (69), 78 (89), 72 (52)	

Table 3 (Continued)

Compound	*m/z* (relative intensity/%)	δ_r/ppm
XIX	310 (0.4), 205 (12), 179 (20), 173 (20), 137 (54), 129 (30), 128 (36), 127 (24), 107 (20), 106 (100), 100 (34), 88 (34), 79 (16), 78 (100), 72 (28)	1.19, 3H (t); 4.05, 2H (q), J_{AB} = 7 Hz, CH_3CH_2O; 1.76, 2H (m), $CH_3CH_2CH_2$; 2.31, 2H (t), J_{AB} = 6 Hz, $\underline{CH_2}NH$; 2.44, 2H (t), J_{AB} = 6 Hz, CH_2CO; 8.23, 1H (s), $\underline{NH}CH_2$; 8.29, 4H (dd), J_{AB} = 5 Hz, 4-Py[a]; 9.40, 1H (s), NH—CS; 10.62, 1H (s), $\underline{NH}$—CO
XX	348 (6), 346 (5), 268 (5), 229 (17), 227 (16)	

a) 4-Pyridyl.

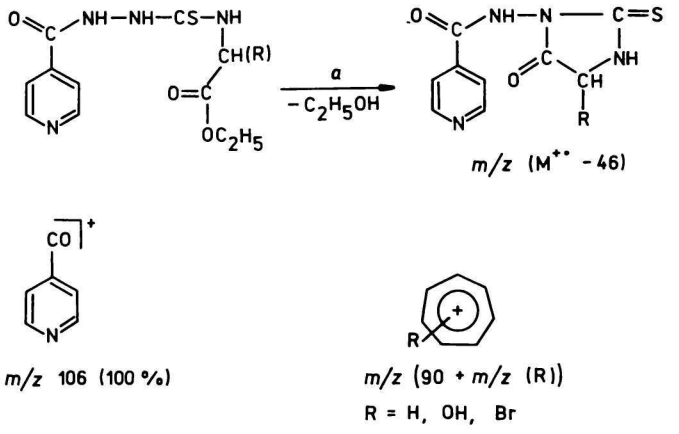


Scheme 1

hydrazides was evidenced by the wavenumbers $\tilde{\nu}$(N—H) at 3427—3257 cm^{-1} as well as by vanishing of the signals assigned to N—H protons in the ^{1}H-n.m.r. spectrum after treatment with D_2O. In the mass spectra of the compounds *X*—*XX* the fragments with $m/z = 106$ (Scheme 2) or tropylium and substituted tropylium cations, formed from the compounds *XV*, *XVI*, and *XX* which contained benzyl arrangement, were most intensive. Majority of compounds give molecular ions of very low intensity and the first more intensive fragment (way *a*) is formed after elimination of ethanol from the thiosemicarbazide molecule.

Elemental analysis, i.r. spectra, and ^{1}H-n.m.r. spectra unambiguously proved that thioureas *VII* and *VIII* derived from 6-aminopenicilanic acid were in the form of triethylammonium salts. The wavenumbers $\tilde{\nu}$(C=O) at 1777—1775 cm^{-1} pointed to β-lactam structure [20]. The results of ^{1}H-n.m.r. measurements were deciding; multiplicity of signals belonging to ethyl groups of triethylammonium salts proved the structures of the compounds *VII* and *VIII*.

Eighteen thioureas and thiosemicarbazides *I*—*VIII*, *X*—*XII*, and *XIV*—*XX* were tested for antimycobacterial activity.



Scheme 2

Of the sulfonamide derivatives of thioureas the derivative *V* showed medium activity against *Mycobacterium tuberculosis* $H_{37}R_v$ (MIC = 25 μg cm^{-3}), the others were less active (MIC > 100 μg cm^{-3}). Thioureas *VII* and *VIII* derived from 6-APA were inactive as well (MIC = 100 μg cm^{-3}). Antimycobacterial activity of 4-isothiocyanatophenyl derivatives derived from the studied sulfonamides was higher (MIC = 10—25 μg cm^{-3}) than that of the synthesized thioureas. Low activity was observed also with thiosemicarbazides *XVIII* and *XIX* prepared from INH and ethyl α- and ω-isothiocyanatocarboxylates, respectively (MIC = 100 μg cm^{-3}). Thiosemicarbazides *XII*, *XIV—XVII* showed the same activity (MIC = 10 μg cm^{-3}). All compounds tested were shown to be inactive against *Mycobacterium Kansasii PKG-8* (MIC > 100 μg cm^{-3}).

The activity of all compounds was compared with that of INH against *M. tuberculosis* $H_{37}R_v$ (MIC = 1 μg cm^{-3}) and *M. Kansasii PKG-8* (MIC = 25 μg cm^{-3}). The activity of thiosemicarbazide *XX* against *M. tuberculosis* $H_{37}R_v$ (MIC = 100 μg cm^{-3}) was compared with that of 4-bromobenzyl isothiocyanate (MIC = 18 μg cm^{-3}).

Experimental

The amino acids used were commercial products: glycine, DL-aspartic acid, DL-phenylalanine (Reanal, Hungary), DL-leucine, β-alanine (Lachema, Brno), L-α-alanine, L-tyrosine (Nutritional Biochemical Corp., Ohio). Sulfonamides Dipron, Sulfatiazol, Sulfometoxidin, Spofadozin, Sulfodimidin, and Sulfisoxazol were obtained from Chemopharma (Ústí n/Labem). γ-Aminobutyric acid and isonicotinohydrazide (INH) were purchased from Koch-Light (England).

The isothiocyanates used were synthesized by the thiophosgene method according to [18]. The optically active ethyl L-2-isothiocyanatopropanate and ethyl L-3-(4-hydroxyphenyl)-2-isothiocyanatopropanate had $[\alpha]_D^{25} = +7.42°$ and $-32.40°$ ($\varrho = 2$ %, CH_3OH), respectively. 6-Aminopenicilanic acid (6-APA) was obtained from Biotika, Slovenská Ľupča.

Infrared spectra were taken with a double-beam Specord 71 IR (GDR) spectrophotometer in NaCl cells or by KBr technique (1 mg sample/30 mg KBr) at room temperature. ^{1}H-N.m.r. spectra were measured with a Tesla BS 487 C apparatus at 80 MHz. Mass spectra were obtained on an MS-902 S spectrometer with direct inlet system at 70 eV and 100 μA.

Minimum inhibitory concentration MIC was followed in liquid Šula medium against strains of *M. tuberculosis* $H_{37}R_v$ (collection of the Department of Mycobacterial Infections, Research Institute of Preventive Medicine) and against atypical strains of *M. Kansasii PKG-8* (collection of Dr. Runyon, Salt Lake City) by the dilution method [21] using dimethyl sulfoxide as solvent. The resulting concentrations of compounds in the medium were (c/μg cm^{-3}): 1, 5, 10, 25, 50, and 100.

1-(Ethoxycarbonylmethyl)-3-[4-(N-R-sulfamoyl)phenyl]thioureas I—VI

Into the solution of the appropriate sulfonamide (0.01 mol) in ethanol (20 cm^3) ethyl isothiocyanatoacetate (1.45 g; 0.01 mol) was added. The products formed after 2 h reflux and cooling were recrystallized from ethanol. Their physicochemical characteristics are presented in Table 1.

1-(Ethoxycarbonylalkyl)-3-(6-aminopenicilanoyl)thioureas VII, VIII

Into the suspension of 6-aminopenicilanic acid (2.16 g; 0.01 mol) in dimethylformamide (10 cm^3) the appropriate isothiocyanate (0.01 mol) was added at 0 °C and triethylamine (1.01 g; 0.01 mol) was added dropwise. After 2 h stirring at 0 °C and 2 h at room temperature the reaction mixture was poured into ether (200 cm^3). The formed thiourea was recrystallized from methanol.

Triethylammonium salt of 1-(ethoxycarbonylmethyl)-3-(6-aminopenicilanoyl)thiourea (*VII*), m.p. = 135—137 °C.

For $C_{19}H_{34}N_4O_5S_5$ ($M_r = 462.62$) w_i(calculated): 49.32 % C, 7.40 % H 12.11 % N; w_i(found): 49.30 % C, 7.55 % H, 12.09 % N. IR spectra ($\tilde{\nu}$/cm^{-1}) in KBr: 3290 $\tilde{\nu}$(N—H), 3080, 2980 (bands of high intensity), $\tilde{\nu}$(C=O) 1777 (β-lactam), 1744 (ester), 1595, 1550 (amide), all bands of very high intensity. ^{1}H-N.m.r. (δ_t/ppm) in DMSO-d_6—acetone-d_6 (volume ratio = 1:1): 1.23 (t), 1.25 (t), 12H, $\underline{CH_3}CH_2O$, $\underline{CH_3}CH_2N$; 3.05 (q) 6H, $J_{AB} = 7$ Hz; 1.54 (s), 3H, 1.62 (s), 3H, $2 \times CH_3$; 4.3—3.99 (m), $O\underline{CH_2}CH_3$, $\underline{CH_2}NH$; 5.89 (dd), 1H, 5.52 (d), 1H, $J_{AB} = 4$ Hz, β-lactam, after D_2O 5.89 (d).

Triethylammonium salt of L-1-(ethoxycarbonylethyl)-3-(6-aminopenicilanoyl) thiourea (*VIII*), m.p. = 111—113 °C, $[\alpha]_D^{25} = +138.60°$.

For $C_{20}H_{36}N_4O_5S_2$ ($M_r = 476.66$) w_i(calculated): 50.39 % C, 7.61 % H, 11.75 % N, 13.45 % S; w_i(found): 49.95 % C, 7.60 % H, 11.68 % N, 13.35 % S. IR spectra ($\tilde{\nu}$/cm^{-1}) in KBr: 3285 $\tilde{\nu}$(N—H), 3080, 2970 (s), 1775 $\tilde{\nu}$(C=O) β-lactam, 1740 $\tilde{\nu}$(C=O) ester, (vs).

1-Acyl-4-R-thiosemicarbazides IX—XX

To the hydrazide of acid (0.01 mol) dissolved in ethanol (20 cm^3) at heating the appropriate isothiocyanate (0.01 mol) in ethanol (5 cm^3) was added dropwise. After 2 h reflux and cooling a crystalline compound was formed and recrystallized from ethanol.

Physical constants and spectral data of the synthesized thiosemicarbazides *IX—XX* are presented in Tables 2 and 3.

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Translated by A. Kardošová