Benzothiazole compounds. XIV. Synthesis and antitubercular activity of some derivatives of *N*-[1-(4-R-2-benzothiazolyl-X)-2,2,2-trichloroethyl]- and *N*-[1-(2-X-6-R-3-benzothiazolinyl-Y)-2,2,2-trichloroethyl]-formamides, -acetamides, -chloroacetamides, and -benzamides

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N-[1-(4-R-2-Benzothiazolyl-X)-2,2,2-trichloroethyl]formamide, -acetamide, -chloroacetamide, and -benzamide (R = H, Cl; X = O, SCH_2CH_2O) and *N*-[1-(2-X-6-R-3-benzothiazolinyl-Y)-2,2,2-trichloroethyl]formamides, -acetamide, -chloroacetamides, and -benzamide (R = H, NH_2, NO_2; X = O, S; Y = −, CH_2CH_2O) were prepared by treatment of 2-mercaptobenzothiazole and some of its derivatives with *N*-(1,2,2,2-tetrachloroethyl)amides. Their structures were proved by interpretation of the i.r. spectra and structural changes of some compounds submitted to pyrolysis were investigated. The synthesized compounds were tested for antitubercular activity.

Воздействием *N*-(1,2,2,2-тетрахлорэтил)амидов на 2-меркаптобензтиазол и некоторые его производные были приготовлены *N*-[1-(4-R-2-бензтиазолил-X)-2,2,2-трихлорэтил]формамид, -ацетамид, -хлорацетамид, -бензамид (R = H, Cl; X = O, SCH_2CH_2O) и *N*-[1-(2-X-6-R-3-бензтиазолинил-Y)-2,2,2-трихлорэтил]формамиды, -ацетамид, -хлорацетамиды, -бензамид (R = H, NH_2, NO_2; X = O, S; Y = −, CH_2CH_2O). Оценкой ИК спектров была подтверждена их структура и у некоторых соединений было обнаружено изменение структуры под влиянием пиролиза. Синтезированные соединения были проверены протитуберкулезным тестом.

On the basis of the results obtained in our previous works [1, 2] we continued the studies on synthesis of benzothiazole compounds. 2-Mercapto-6-R-benzothiazoles

(R = H, NH_2, NO_2), 2-hydroxy-4-R-benzothiazoles (R = H, Cl), 2-X-3-hydroxymethylbenzothiazolines (X = O, S), 2-hydroxyethylthiobenzothiazole, and *N*-(1,2,2,2-tetrachloroethyl)formamide, -acetamide, -chloroacetamide, and benzamide were used as starting components.

The compounds on the basis of *N*-(1,2,2,2-tetrachloroethyl)formamide and its bisderivatives, respectively, exhibit high fungicidal activity [3—5]. We synthesized series of compounds, some of them showing good activity on representatives of atypical mycobacteria, by using the above-mentioned amides [2]. Starting from these results, further compounds *I*—*XI* (Tables 1 and 2) of this type were synthesized and tested for antitubercular activity. With some compounds also the intramolecular rearrangement, occurring during pyrolysis, was investigated.

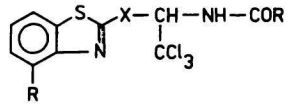
The structures of the compounds *I*—*XII* were proved by their i.r. spectra in the region of 4000—400 cm^{-1} The wavenumbers of some characteristic vibrations are presented in Table 3. The reaction of 2-hydroxybenzothiazole and 3-hydroxymethyl-2-benzothiazolinone, respectively, with *N*-(1,2,2,2-tetrachloroethyl)-formamide resulted in identical products as to the composition and structure. The i.r. spectrum in the region of stretching C = O vibrations revealed besides the absorption band attributed to the carbonyl group in the side chain also the strong absorption band belonging to the carbonyl group of the benzothiazole ring. On the basis of this finding the structure *V* can be ascribed to this compound. In the first case 2-hydroxybenzothiazole reacted with *N*-(1,2,2,2-tetrachloroethyl)-formamide in its tautomeric oxo form and in the second case, after splitting off of formaldehyde, the reaction proceeded again in the position 3 of the benzothiazole ring. Liberation of formaldehyde from 3-hydroxymethyl-2-benzothiazolinone was proved also in a control experiment where 2-hydroxybenzothiazole was formed. Further evidence indicating that the compound resulting from both reactions was an *N*-derivative with the structure *V*, was its stable composition and structure on melting at 200°C.

By contrast, the reaction of *N*-(1,2,2,2-tetrachloroethyl)chloroacetamide with 2-hydroxybenzothiazole proceeded on the oxygen of the hydroxyl group giving the *O*-derivative which had the structure *II*. The strong absorption band belonging to the stretching C = O vibration of the carbonyl group of the oxo form of the benzothiazole ring was absent in the i.r. spectrum. On melting at 200°C, this compound underwent an intramolecular rearrangement resulting in the *N*-derivative of the structure *VI*. Its i.r. spectrum revealed two absorption bands of the stretching C = O vibrations belonging to two different carbonyl groups.

The reaction of *N*-(1,2,2,2-tetrachloroethyl)formamide with 4-chloro-2-hydroxybenzothiazole proceeded analogously and afforded the *O*-derivative *I*. This derivative gave on melting at 200°C a compound which was not the appropriate *N*-derivative. The i.r. spectrum in the region of stretching C = O vibration revealed only one absorption band belonging to the aldehyde group in the side chain. In the

Table 1

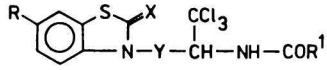
Synthesized *N*-[1-(4-R-2-benzothiazolyl-X)-2,2,2-trichloroethyl]formamide, -acetamide, -chloroacetamide, and -benzamide



Compound	R	R¹	X	Formula	*M*	Calculated/found					Yield %	M.p. °C
						% C	% H	% N	% S	% Cl		
I	Cl	H	O	$C_{10}H_6O_2N_2SCl_4$	360.06	33.35	1.67	7.78	8.90	39.39	61	156—158
						33.36	1.78	7.86	8.98	39.10		
II	H	CH_2Cl	O	$C_{11}H_8O_2N_2SCl_4$	374.09	35.31	2.15	7.48	8.57	37.91	65	126—128
						35.29	2.20	7.48	8.57	38.09		
III	H	C_6H_5	SCH_2CH_2O	$C_{18}H_{15}O_2N_2S_2Cl_3$	461.81	46,81	3.27	6.06	13.88	23.03	58	85—87
						46.95	3.30	6.05	13.73	23.21		
IV	H	CH_3	SCH_2CH_2O	$C_{13}H_{13}O_2N_2S_2Cl_3$	399.74	39.06	3.27	7.00	16.04	26.60	56	129—130
						39.16	3.31	6.90	16.02	26.86		

Table 2

Synthesized *N*-[1-(2-X-6-R-3-benzothiazolinyl-Y)-2,2,2-trichloroethyl]formamides, -acetamide, -chloroacetamides, and -benzamide



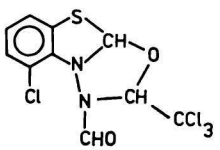
Compound	R	R^1	X	Y	Formula	*M*	Calculated/found					Yield %	M.p. °C
							% C	% H	% N	% S	% Cl		
V	H	H	O	—	$C_{10}H_7O_2N_2SCl_3$	325.61	36.88	2.16	8.57	9.84	32.66	49	161—162
							36.90	2.14	8.62	9.80	32.60		
VI	H	CH_2Cl	O	—	$C_{11}H_8O_2N_2SCl_4$	374.09	35.31	2.15	7.48	8.57	37.91	45	130—132
							35.76	2.53	7.92	8.98	38.20		
VII	H	C_6H_5	S	CH_2CH_2O	$C_{18}H_{15}O_2N_2S_2Cl_3$	461.81	46.81	3.27	6.06	13.88	23.03	46	168—170
							46.50	3.09	5.80	13.49	22.55		
VIII	NO_2	CH_2Cl	S	—	$C_{11}H_7O_3N_3S_2Cl_4$	435.13	30.36	1.62	9.65	14.73	32.59	53	249—251
							30.30	1.76	9.91	14.60	32.34		
IX	H	H	S	—	$C_{10}H_7ON_2S_2Cl_3$	341.67	35.15	2.06	8.19	18.76	31.13	62	144—146
							35.25	2.11	8.32	19.02	31.30		
X	NH_2	CH_3	S	—	$C_{11}H_{10}ON_3S_2Cl_3$	370.70	35.64	2.71	11.33	17.29	28.69	57	151—153
							35.56	2.75	11.22	17.34	28.77		
XI	NH_2	H	S	—	$C_{10}H_8ON_3S_2Cl_3$	356.68	33.67	2.26	11.78	17.97	29.82	60	210 (decomp.)
							33.74	2.29	11.91	17.84	30.00		

Table 3

Wavenumbers of some characteristic vibrations, cm^{-1}

Compound	ν(NH)	ν(C=O) (side chain)	ν(C=O) (ring)
I	3374	1682	—
II	3358	1685	—
III	3290	1649, 1661	—
IV	3190, 3220	1690	—
V	3220	1700	1640
VI	3250	1700	1651
VII	3280	1675, 1700	—
VIII	3210	1678	—
IX	3080, 3130	1672, 1691	—
X	3200	1665	—
XI	3341, 3120	1679	—
XII	—	1680	—

spectrum of this compound, contrary to the spectrum of *I*, the significant absorption band of the stretching N—H vibration at 3374 cm^{-1} was absent. Also the position and the intensity of some characteristic bands of the benzothiazole ring at ≈ 1600 and ≈ 1450 cm^{-1} changed. On the basis of these data the structure presented in the formula can be probably ascribed to the compound *XII* obtained from *I* by melting. The fact that melting of *I* did not result in the appropriate *N*-derivative could be ascribed to steric hindrance of the bulky chlorine atom in the position 4 of the benzothiazole ring. This atom hinders the reagent in approaching the nitrogen atom of the benzothiazole ring.



XII

2-Mercaptobenzothiazole and 3-hydroxymethyl-2-benzothiazolinethione reacted with *N*-(1,2,2,2-tetrachloroethyl)formamide similarly as 2-hydroxybenzothiazole and 3-hydroxymethyl-2-benzothiazolinone. Both reactions resulted in the same product, *i.e.* in the *N*-derivative *IX*. The split absorption bands of stretching C=O and N—H vibrations in the spectrum of this compound as well as

of some other ones (Table 3) are probably connected with conformation in the side chain, formation of hydrogen bonds or with vibrational interactions. Melting did not alter the initial composition and structure of the compound *IX*. The reactions of some 6-substituted 2-mercaptobenzothiazole derivatives with *N*-(1,2,2,2-tetrachloroethyl)acetamide, -formamide, and -chloroacetamide proceeded similarly giving the appropriate *N*-derivatives *X*, *XI*, and *VIII*. The composition and the structure of these compounds did not change on melting at 200—250°C except the compound *VIII* which was decomposed to the starting 6-nitro-2-mercaptobenzothiazole as proved by the i.r. spectra.

2-Hydroxyethylthiobenzothiazole reacted with *N*-(1,2,2,2-tetrachloroethyl)-acetamide and -benzamide on the oxygen atom of the hydroxyl group giving the appropriate *S*-derivatives *IV* and *III*. Melting of the compound *III* at 200°C resulted in the compound *VII* which had the structure of the appropriate *N*-derivative as proved by its i.r. spectrum.

From the obtained activities of both groups of compounds (Table 4) against the tested mycobacteria it is clear that the compounds presented in Table 1 were more active. These activities however, were not so high as those of the known antituberculotics except the activity of the compound *IV* which was in one case equal to that of 2-MBT. The compounds presented in Table 2 were inactive against the tested representatives of typical and atypical mycobacteria.

Table 4

Antimycobacterial activity of the synthesized compounds (MIC μg/ml)

Compound	*M. tuberculosis* $H_{37}R_v$	*M. kansasii* *PKG 18*
I	>100	>100
II	50	100
III	100	>100
IV	50	50
V	>100	>100
VI	—	—
VII	—	—
VIII	>100	>100
IX	—	—
X	—	—
XI	>100	>100
2-MBT	25	50
Isoniazid	1	10
Ethionamide	1	10

Experimental

The results of elemental analysis and physicochemical constants of the synthesized compounds are presented in Tables 1 and 2.

Infrared spectra of the synthesized compounds were measured on a Perkin—Elmer 567 spectrophotometer in the region of 4000—400 cm^{-1} in paraffin oil suspensions. The apparatus was calibrated by polystyrene foil. The results are presented in Table 3.

Antimycobacterial activity was followed by the dilution method in the Šula liquid medium according to the procedure used at screening of the antitubercular activity [6]. Minimal inhibition concentrations (MIC) read after 14-day incubation at 37°C are given in Table 4. Isoniazid (isonicotinohydrazide), 2-MBT (2-mercaptobenzothiazole), and Ethionamide (2-ethylisonicotinothioamide) were used as standards.

2-Mercapto-6-R-benzothiazoles (R = H, NH_2, NO_2) were prepared after [7, 8], 2-hydroxy-4-R-benzothiazoles (R = H, Cl) after [9, 10], 2-X-3-hydroxymethylbenzothiazolines (X = O, S) and 2-hydroxyethylthiobenzothiazole after [11, 12], and *N*-(1,2,2,2-tetrachloroethyl)formamide, -acetamide, -chloroacetamide, and -benzamide after [13—16].

N-[1-(4-Chloro-2-benzothiazolyloxy)-2,2,2-trichloroethyl]formamide (I—V, VIII—XI)

2-Hydroxy-4-chlorobenzothiazole (15 g; 0.080 mol) was dissolved in anhydrous acetone (200—250 ml). After cooling the solution to 30—40°C, 20% excess of anhydrous triethylamine (9.8 g; 0.096 mol) was added and then *N*-(1,2,2,2-tetrachloroethyl)formamide (17 g; 0.080 mol) in anhydrous acetone (80 ml) was added dropwise under continuous stirring. After 3 h stirring at the room temperature the mixture was poured onto crushed ice. The isolated product was crystallized from ethanol.

N-[1-(2-Oxo-3-benzothiazolinyl)-2,2,2-trichloroethyl]chloroacetamide (VI, VII)

To *N*-[1-(2-benzothiazolyloxy)-2,2,2-trichloroethyl]chloroacetamide (*II*, *III*) (1 g; 0.0026 mol) iodine (0.02 g) was added and the mixture was heated under reflux in an oil bath at 200°C for 1 h. The melt was crystallized from the mixture of ethanol—acetone (2 : 1).

2-Hydroxybenzothiazole

Control experiment

3-Hydroxymethyl-2-benzothiazolinone (5 g; 0.027 mol) was dissolved in anhydrous acetone (80 ml) and anhydrous triethylamine (2.7 g; 0.026 mol) was added. The mixture was heated to 60°C and allowed to stay for 3 h. Triethylammonium chloride was precipitated

by addition of diluted hydrochloric acid (1 : 1) and filtered off. The filtrate was poured onto crushed ice and the precipitated product was crystallized from diluted ethanol (1 1). Its melting point 136—138°C was in agreement with that of 2-hydroxybenzothiazole. The mixed melting point did not show depression.

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