Synthesis and tuberculostatic properties of *S*-alkyl 2-(α-naphthothiazolyl)dithiocarbamates

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The tuberculostatic properties of the synthesized *S*-alkyl 2-(α-naphthothiazolyl)dithiocarbamates were compared with those of *S*-alkyl 2-alkylthiobenzothiazolyldithiocarbamates. All substances were found to exhibit a very good effect against *M. tuberculosis* $H_{37}R_v$; moreover, substances of the first type are also effective against *M. tuberculosis INH-R*.

Были приготовлены *S*-алкил 2-(α-нафтотиазолил)дитиокарбаматы и сравнены их туберкулостатические свойства с действием *S*-алкил 2-алкилтиобензотиазолилдитиокарбаматов. Все вещества оказывают очень хорошее воздействие относительно *M. tuberculosis* $H_{37}R_v$ и вещества первого типа также по отношению к *M. tuberculosis INH-R*.

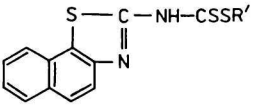
Dithiocarbamates are used in agriculture and their effect in human medicine is also known [1]. Both their sodium and copper(II) salts [2] show an antimicrobial effect. Their inhibition effect on *Mycobacterium tuberculosis, Trichophyton gypsum,* and other bacteria has been also reported [3, 4].

This paper deals with the preparation and characterization of *S*-alkyl 2-mercapto-6-benzothiazolyldithiocarbamates [5] with potential fungicide and herbicide properties. As found, only methyl and ethyl esters exhibited weak fungicidal properties. Orientation tests on antimicrobial effect showed the esters under study to have good tuberculostatic properties (see Table 3).

Aiming to discover the relationship between the bacteriostatic activity and structure of the amine [6] a series of *S*-alkyl 2-(α-naphthothiazolyl)dithiocarbamates listed in Table 1 were synthesized and the size of the molecule was contrasted with the antimicrobial effect. The esters were prepared by reacting the sodium

Table 1

Characteristic data of *S*-alkyl 2-(α-naphthothiazolyl)dithiocarbamates



Compound	Alkyl	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
I	CH_3	$C_{13}H_{10}N_2S_3$	290.36	53.79	3.34	9.65	33.10	65.2	187—189
				53.91	3.52	9.49	32.58		
II	C_2H_5	$C_{14}H_{12}N_2S_3$	304.37	55.26	3.95	9.21	31.57	68.7	174—176
				55.09	4.07	8.95	31.21		
III	C_3H_7	$C_{15}H_{14}N_2S_3$	318.38	56.60	4.40	8.80	30.18	63.9	151—153
				56.83	4.42	8.57	29.89		
IV	iso-C_3H_7	$C_{15}H_{14}N_2S_3$	318.38	56.60	4.40	8.80	30.18	36.3	168—171
				56.42	4.29	9.01	29.74		
V	C_4H_9	$C_{16}H_{16}N_2S_3$	332.39	57.82	4.81	8.43	28.90	62.2	130—131
				57.72	4.63	8.30	28.61		
VI	$C(CH_3)_3$	$C_{16}H_{16}N_2S_3$	332.39	57.82	4.81	8.43	28.91	45.6	156—158
				57.63	4.59	8.38	28.53		
VII	C_8H_{17}	$C_{20}H_{24}N_2S_3$	372.43	61.85	6.18	7.47	24.74	51.8	103—104
				61.57	6.21	7.23	24.77		

2-(α-naphthothiazolyl)dithiocarbamate with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and octyl iodide at room temperature. The measure of the bactericide activity of the prepared compounds was the minimum inhibition concentration (MIC) in μg/ml needed for the complete inhibition of reproduction of mycobacteria after 14 or 21 days of incubation (according to the kind of mycobacteria).

Results of testing are summarized in Table 2. The starting compound, *i.e.* 2-amino-α-naphthothiazole does not exhibit tuberculostatic effect similarly as methyl 2-(α-naphthothiazolyl)dithiocarbamate. Ethyl, propyl, isopropyl, butyl, isobutyl, and octyl esters inhibit the growth of typical mycobacteria already in a 10—25 μg/ml concentration. A considerable effect was found against a resistant tribe of *M. tuberculosis*. The investigated esters were found not to be efficient against atypic mycobacteria.

On the basis of comparison of the activity tests of *S*-alkyl 2-mercapto-6-benzothiazolyldithiocarbamates on *M. tuberculosis* (Table 3) with those of *S*-alkyl

Table 2

Antimycobacterial efficacy of the prepared substances

Compound	*M. tuberculosis* $H_{37}R_v$	*M. tuberculosis* *INH-R*	*M. bovis*	*M. avium*	*M. kansasii*	*M. fortuitum*
I	50	100	50	100	100	100
II	25	10	25	100	100	100
III	25	10	25	100	100	100
IV	25	10	25	100	100	100
V	25	10	25	50	100	50
VI	50	10	25	50	100	100
VII	25	1	50	100	100	100
VIII	100	100	100	100	100	100

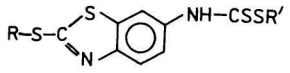
2-(α-naphthothiazolyl)dithiocarbamates (Table 2) we anticipate the structure of the amine to be of no decisive effect on the biological activity of the molecule, but more probably subject to the presence of an ester group irrespective of its position.

Experimental

2-Amino-α-naphthothiazole (*VIII*) was prepared according to [7], *S*-alkyl 2-alkylthiobenzothiazolyldithiocarbamate according to [5].

Table 3

Minimum concentration against mycobacteria



Compound	R	R′	*M. tuberculosis* $H_{37}R_v$	*M. kansasii*
IX	H	CH_3	10	100
X	CH_3	CH_3	10	100
XI	C_2H_5	C_2H_5	25	100
XII	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$	25	100
XIII	$(CH_3)_2CH$	$(CH_3)_2CH$	10	100
XIV	H	$CH_3(CH_2)_3$	10	100
XV	$CH_3(CH_2)_3$	$CH_3(CH_2)_2$	25	100
XVI	$CH_3(CH_2)_2$	$(CH_3)_2CH$	10	100
XVII	Na	Na	25	100

S-Alkyl 2-(α-naphthothiazolyl)dithiocarbamate (I—VII)

Sodium hydroxide (15 mmoles; 0.6 g) dissolved in water (4 ml) was added to a solution of 2-amino-α-naphthothiazole (10 mmoles; 2 g) in dimethylformamide (DMF) (25 ml); after 10 min carbon disulfide (25 mmoles; 1.9 g) was poured into the reaction mixture which turned redbrown. Finally, alkyl iodide (10 mmoles) was added after 5 h of reaction, and the mixture was allowed to stand for 6 h at room temperature. The yellow precipitate was then filtered off, washed with a little amount of water, dissolved in DMF, clarified with charcoal and poured onto ice. Characteristic data of the reaction products are listed in Table 1.

Testing methods

The efficiency of substances tested *in vitro* against various kinds of bacteria was determined according to [8]. Substances to be tested dissolved in dimethyl sulfoxide were added to the cultivation medium of the Šula substrate. Used were *M. tuberculosis* $H_{37}R_v$ sensitive against antituberculotics (AT), *M. tuberculosis INH* resistant tribe (No. 3161), *M. bovis 59 Z 73, M. avium, M. kansasii PKG* photochromogenic atypic mycobacteria, and *M. fortuitum.*

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