Benzothiazole compounds. XII. 2-Alkylthio-6-aminobenzothiazoles in the Mannich reaction with 2-mercaptobenzothiazole and 2-mercapto-6-nitrobenzothiazole

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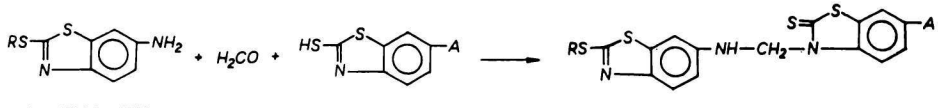
3-(2-Alkylthio-6-benzothiazolylaminomethyl)-2-benzothiazolinethione and its 6-nitro derivatives were prepared by the reaction of 2-mercaptobenzothiazole or its 6-nitro derivative with 2-alkylthio-6-aminobenzothiazoles and formaldehyde. Electronic spectra and antimycobacterial activities of the prepared substances are presented.

3-(2-Алкилтио-6-бензтиазолиламинометил)-2-бензтиазолинтион и его 6-нитропроизводные приготовлялись реакцией 2-меркаптобензтиазола или его 6-нитропроизводного с 2-алкилтио-6-аминобензтиазолами и формальдегидом. Приводятся электронные спектры и антимикобактериальная активность веществ.

The aim of this work was to ascertain the found dependence of the formation of mono and bis derivatives of the Mannich bases on the basicity of primary amines [1] and to compare the antimycobacterial activities of the prepared compounds with those of 2-alkylthio-6-aminobenzothiazoles [2, 3] and of the products of the Mannich reaction of 2-mercaptobenzothiazole (2-MBT) with formaldehyde and primary aliphatic or aromatic amines [4].

By the reaction of both H-active components in the Mannich reaction (2-MBT, 6-nitro-2-MBT) with formaldehyde and amino component (Scheme 1), we pre-



A = H(*I*—*VI*),
NO_2 (*VII*—*XII*).

Scheme 1

pared only mono derivatives of the Mannich bases (Tables 1 and 2). This knowledge is in agreement with the dependence found in [1] because the pK_B value of 2-alkylthio-6-aminobenzothiazoles was in the range 9—10 [5].

Table 1

Characterization of 3-(2-alkylthio-6-benzothiazolylaminomethyl)-2-benzothiazolinethiones

Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
I	CH_3	$C_{16}H_{13}N_3S_4$	375.56	51.17 50.91	3.48 3.57	11.18 11.15	34.15 34.12	75	161—163
II	C_2H_5	$C_{17}H_{15}N_3S_4$	389.59	52.41 52.37	3.88 3.91	10.78 10.78	32.92 32.81	85	157—159
III	C_3H_7	$C_{18}H_{17}N_3S_4$	403.61	53.56 53.37	4.24 4.26	10.41 10.82	31.77 31.70	90	147—149
IV	i-C_3H_7	$C_{18}H_{17}N_3S_4$	403.61	53.56 53.54	4.24 4.15	10.41 10.38	31.77 31.77	80	123—125
V	CH_2=CH—CH_2	$C_{18}H_{15}N_3S_4$	401.60	53.83 53.73	3.76 3.83	10.46 10.43	31.93 32.01	86	151—153
VI	C_6H_5—CH_2	$C_{22}H_{17}N_3S_4$	451.65	58.50 58.54	3.79 3.83	9.30 9.20	28.39 28.52	90	146—148

Table 2

Characterization of 6-nitro-3-(2-alkylthio-6-benzothiazolylaminomethyl)-2-benzothiazolinethiones

Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
VII	CH_3	$C_{16}H_{12}N_4O_2S_4$	420.56	45.69 45.70	2.87 3.01	13.32 13.20	30.49 30.62	82	179—181
VIII	C_2H_5	$C_{17}H_{14}N_4O_2S_4$	434.59	46.98 47.20	3.24 3.52	12.89 13.11	29.51 29.38	58	176—178
IX	C_3H_7	$C_{18}H_{16}N_4O_2S_4$	448.61	48.19 48.15	3.59 3.61	12.48 12.83	28.59 28.40	60	173—175
X	i-C_3H_7	$C_{18}H_{16}N_4O_2S_4$	448.61	48.19 48.50	3.59 3.80	12.48 12.46	28.59 28.59	72	137—139
XI	CH_2=CH—CH_2	$C_{18}H_{14}N_4O_2S_4$	446.60	48.41 48.46	3.15 3.39	12.54 12.52	28.71 29.00	63	163—165
XII	C_6H_5—CH_2	$C_{22}H_{16}N_4O_2S_4$	496.65	53.20 53.05	3.24 3.31	11.28 11.49	25.82 25.76	80	164—166

The obtained values of λ_{max} (log a_{max}) 227.5 nm (4.61) and 322 nm (4.66) for *I* and 226, 295.5, and 336 nm for *VII* (*VII* was little soluble in ethanol) showed that the H-active component in the molecules of the prepared compounds was bound through the position 3 [1].

Table 3

Antimycobacterial activity of the prepared compounds

Compound	MIC in mcg/ml against			
	M. tuberculosis $H_{37}R_v$	*M. kansasii*	*M. avium*	*M. fortuitum*
I	100	100	100	100
II	100	100	100	100
III	50	50	50	50
IV	100	100	100	100
V	100	100	100	100
VI	50	50	50	50
VII	100	100	100	100
VIII	100	100	100	100
IX	50	50	50	50
X	100	100	100	100
XI	100	100	100	100
XII	50	50	50	50

It is evident from Table 3 that substitution had little effect on antimycobacterial activity. Comparison of the activities of *I*—*VI* and *VII*—*XII* showed that the nitro group in the position 6 at the benzothiazolinethione skeleton did not affect the antimycobacterial activity. The alkyl substituent on sulfur at the position 2 was determinant for the activity. However, comparison with 2-alkylthio-6-aminobenzothiazoles showed some differences. While the activity of the propyl and benzyl derivatives decreased a little that of the isopropyl and allyl derivatives decreased essentially. The methyl and ethyl derivatives were approximately equally inactive in both cases. It can be stated that the tested compounds were orderly less active than the starting 2-alkylthio-6-aminobenzothiazoles [2, 3] or the Mannich bases prepared from amines of lower molecular weights [4].

Experimental

The starting 2-alkylthio-6-aminobenzothiazoles were prepared by alkylation of 6-amino-2-mercaptobenzothiazole [2, 3].

The absorption spectra in the u.v. and visible regions were measured on an SF-8 (LOMO Leningrad,

USSR) spectrophotometer. Ethanol was used as a solvent in u.v. spectroscopy (Lachema, Brno). The same solvent was used as the comparative medium.

Antimycobacterial activity was tested against *Mycobacterium (M.) tuberculosis* $H_{37}R_v$ (sensitive to antituberculotics), *M. avium* (both strains are in the collection of the Research Institute of Epidemiology and Microbiology, Department of Tuberculosis, Bratislava), *M. kansasii PKG* (photochromogenic atypical mycobacterium from the collection of Dr E. H. Runyon, Salt Lake City, Utah, USA), and *M. fortuitum* (from the collection of Professor Hauduroy, Faculté de Médicine, Université Lausanne). The classical dilution method [6] in the Šula soil was used. The compounds were dissolved in dimethyl formamide and minimal inhibition concentrations (MIC) were read after 14 days incubation at 37°C against the control. The obtained results are presented in Table 3.

3-(2-Alkylthio-6-benzothiazolylaminomethyl)-2-benzothiazolinethiones (I—VI)

2-Alkylthio-6-aminobenzothiazole (0.02 mole) and a mixture of methanol (26 ml) and acetone (10 ml) were added to 2-MBT (3.3 g; 0.02 mole). The reaction mixture was carefully heated to 40—45°C under stirring and 34% formaldehyde (2 ml; 0.02 mole) was added dropwise. A powdery product precipitated from the transparent solution after 10—20 min. After 15 min the mixture was cooled and the product was sucked and washed with a mixture (40 ml) of ethanol and acetone (2 : 1) on a filter. It could be purified by addition of methanol (30 ml) to the dry substance and careful heating to 30—35°C. The product became almost white while the solution became green. When preparing *IV*, the reaction mixture was heated to 35—40°C and the product precipitated on cooling to 0—5°C and addition of water (3 ml). When preparing *VI*, after the reaction with 2-benzylthio derivative, the product precipitated on cooling of the reaction mixture to 35°C. Characterization of the prepared substances is given in Table 1.

6-Nitro-3-(2-alkylthio-6-benzothiazolylaminomethyl)-2--benzothiazolinethiones (VII—XII)

To 2-alkylthio-6-aminobenzothiazole (0.02 mole) a mixture of methanol (26 ml) and acetone (78 ml) was added. The reaction mixture was heated to 28—33°C and 34% formaldehyde (2 ml; 0.02 mole) was added dropwise; a transparent orange solution was formed. After 2—5 min stirring at the mentioned temperature, 6-nitro-2-MBT (4.2 g; 0.02 mole) was added in portions. A powdery substance began to precipitate from the solution after 30 min. This was sucked after 30 min and washed on a filter with a mixture (40 ml) of methanol and acetone (1 : 3). After the reaction with 2-isopropyl derivative, the product *X* precipitated on cooling the mixture to 20°C and dropwise addition of water (80 ml). After the reaction with 2-benzylthio derivative, the product *XII* began to precipitate on cooling to 18°C. Characterization of the prepared compounds is given in Table 2.

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