Benzothiazole compounds. XI. Synthesis and antimicrobial activity of 2- and 2,6-substituted benzothiazoles

[a]V. SUTORIS, [b]P. FOLTÍNOVÁ, and [a]G. BLÖCKINGER

[a]*Department of Organic Chemistry, Faculty of Natural Sciences, Komenský University, 816 31 Bratislava*

[b]*Institute of Experimental Biology, Faculty of Natural Sciences, Komenský University, 886 04 Bratislava*

Received 4 March 1976

Accepted for publication 13 August 1976

2-Substituted and 2,6-disubstituted thiobenzothiazoles were synthesized. They were found to show good antimicrobial activities on non-specific bacterial flora, mycobacteria, protozoa, and pathogenic fungi. The highest activity was found with 2-allylthiobenzothiazole (*XIV*), 2-allylthio-6-nitrobenzothiazole (*XV*), 2-allylthio-6-aminobenzothiazole (*XVI*), 2-propargylthiobenzothiazole (*XVIII*), 2-propargylthio-6-nitrobenzothiazole (*XIX*), and 2-propargylthio-6-aminobenzothiazole (*XX*).

Были синтезированы 2-замещенные тиобензтиазолы и 2,6-двух-замещенные тиобензтиазолы. Были определены хорошие противомикробиальные влияния на неспецифическую бактериальную флору, микобактерии, протисты и патогенные грибы. Самая высокая эффективность была определена у 2-аллилтиобензтиазола (*XIV*), 2-аллилтио-6-нитробензтиазола (*XV*), 2-аллилтио-6-аминобензтиазола (*XVI*), 2-пропаргилтиобензтиазола (*XVIII*), 2-пропаргилтио-6-нитробензтиазола (*XIX*) и 2-пропаргилтио-6-аминобензтиазола (*XX*).

2-Alkylthiobenzothiazoles show biological activities in various fields. For instance, defoliant activity was found with 2-butylthiobenzothiazole [1] while 2-alkyl-4,5,6,7-tetrahydrothiobenzothiazoles [2] are used as fungicides. 2-Substituted 5-benzothiazolylacetic acids and their salts have good antipyretic and analgetic properties [3]. 2-Alkylsulfinyl-6-nitrobenzothiazoles [4] and 2-alkylsulfonyl-6-X-benzothiazoles (X = H, Cl, Br, NO_2, NH_2, alkyl amino, and dialkyl amino) [5] were found to have antimicrobial and antifungal activities.

For the study of the relation of the structure and antimicrobial activity some 2-substituted and 2,6-disubstituted thiobenzothiazoles, presented in Table 1, were synthesized. Their preparation was accomplished by the known method [6] from

Table 1

Analytical data of the synthesized 2-R- and 2-R-6-R-substituted benzothiazoles

No.	R	R'	Formula	*M*	Calculated/found % C	% H	% N	% S	Yield %	M.p., °C B.p., °C/Pa (n_D^{20})
I	CH_3	H	$C_8H_7NS_2$	181.0	53.08	3.90	7.73	35.42	80	46—48
					52.90	3.79	7.86	35.58		Ethanol—water (3 : 1)
II	CH_3	NO_2	$C_8H_6N_2O_2S_2$	226.2	42.51	2.67	12.38	28.37	79	131—132
					42.31	2.75	12.40	28.35		Ethanol—water (2 : 1)
III	CH_3	NH_2	$C_8H_8N_2S_2$	196.3	49.02	4.11	14.28	32.71	82	111
					48.87	4.23	14.49	32.71		Ethanol—water (2 : 1)
IV	C_2H_5	H	$C_9H_9NS_2$	195.3	55.43	4.65	7.17	32.88	84	170/1599.84
					55.60	4.51	7.29	32.02		
V	C_2H_5	NO_2	$C_9H_8N_2O_2S_2$	240.3	45.03	3.35	11.66	26.72	89	112
					44.86	3.47	11.79	26.64		Ethanol
VI	C_2H_5	NH_2	$C_9H_{10}N_2S_2$	210.3	51.47	5.71	13.32	30.53	82	74
					51.52	5.60	13.19	30.28		Ethanol
VII	C_2H_5	NHC_2H_5	$C_{11}H_{14}N_2S_2$	238.2	55.50	5.92	11.76	26.94	64	(1.6852)
					55.22	5.80	11.70	27.13		
VIII	C_2H_5	$N(C_2H_5)_2$	$C_{13}H_{18}N_2S_2$	266.4	58.69	6.81	10.53	24.10	58	(1.6647)
					58.84	6.69	10.66	24.28		
IX	C_2H_5	$NHCH_2CH=CH_2$	$C_{12}H_{13}N_2S_2$	249.4	57.87	5.26	11.24	25.75	62	(1.6884)
					57.74	5.39	11.39	25.94		
X	C_2H_4OH	NH_2	$C_9H_{10}N_2OS_2$	226.3	47.82	5.31	12.37	28.33	75	103—104
					47.65	5.18	12.38	28.25		Ethanol
XI	C_3H_7	H	$C_{10}H_{11}NS_2$	209.3	57.46	5.31	6.69	30.67	66	134/133.32
					57.30	5.45	6.82	30.48		
XII	C_3H_7	NO_2	$C_{10}H_{10}N_2O_2S_2$	254.3	47.28	3.96	11.02	25.24	81	93
					47.07	3.82	11.24	25.38		Ethanol—water (3 : 1)
XIII	i-C_3H_7	NO_2	$C_{10}H_{10}N_2O_2S_2$	254.3	47.28	3.96	11.02	25.24	60	74—75
					47.36	4.10	11.22	24.98		Ethanol—water (4 : 1)

Table 1 (Continued)

No.	R	R^1	Formula	*M*	Calculated/found % C	% H	% N	% S	Yield %	M.p., °C B.p., °C/Pa (n_D^{20})
XIV	$CH_2CH=CH_2$	H	$C_{10}H_9NS_2$	207.3	58.02	4.38	6.76	30.97	74	143—145/666.6
					57.84	4.21	6.72	30.85		
XV	$CH_2CH=CH_2$	NO_2	$C_{10}H_8N_2O_2S_2$	252.3	47.65	3.19	11.11	25.44	87	73
					47.69	3.04	11.18	25.32		Ethanol
XVI	$CH_2CH=CH_2$	NH_2	$C_{10}H_{10}N_2S_2$	222.3	54.10	4.54	12.61	28.88	76	48
					54.37	4.77	12.52	28.60		Ethanol
XVII	$CH_2CH=CH_2$	NHC_2H_5	$C_{12}H_{14}N_2S_2$	250.4	57.64	5.64	11.20	25.64	64	(1.6763)
					57.40	5.51	11.07	25.38		
XVIII	$CH_2C\equiv CH$	H	$C_{10}H_7NS_2$	205.3	58.58	3.44	6.82	31.27	73	46
					58.42	3.60	6.80	31.14		Ethanol—water (3 : 1)
XIX	$CH_2C\equiv CH$	NO_2	$C_{10}H_6N_2O_2S_2$	250.3	48.04	2.41	11.20	25.64	89	159
					47.82	2.30	11.11	25.45		Ethanol
XX	$CH_2C\equiv CH$	NH_2	$C_{10}H_8N_2S_2$	220.3	54.59	3.66	12.72	29.14	85	99
					54.32	3.81	12.96	29.20		Ethanol—water (4 : 1)
XXI	$CH_2CH(OH)CH_2Cl$	H	$C_{10}H_{10}ClNOS_2$	259.8	46.15	3.87	5.38	24.68	89	81—82
					46.31	3.72	5.54	24.93		Ethanol
XXII	$CH_2CH=C(Cl)CH_3$	H	$C_{11}H_{10}ClNS_2$	255.8	51.60	3.93	5.46	25.04	53	183/666.6
					51.32	4.08	5.61	25.23		
XXIII	$CH_2CH=C(Cl)CH_3$	NO_2	$C_{11}H_9ClN_2O_2S_2$	300.8	44.03	3.02	9.30	21.30	72	67—69
					44.25	3.18	9.41	21.10		Ethanol
XXIV	$CH_2CH=C(Cl)CH_3$	NH_2	$C_{11}H_{11}ClN_2S_2$	270.8	48.74	4.09	10.33	23.66	57	(1.6910)
					48.49	4.20	10.18	23.54		
XXV	$CH_2C_6H_4Cl$-*p*	H	$C_{14}H_{10}ClNS_2$	309.8	60.04	3.25	4.51	20.68	78	82—83
					60.19	3.28	4.47	20.75		Ethanol
XXVI	$CH_2CH_2SC_6H_4Cl$-*p*	H	$C_{15}H_{12}ClNS_3$	337.9	53.29	3.57	4.14	28.45	86	51
					53.36	3.46	4.21	28.35		Ethanol—water (4 : 1)
XXVII	$CH_2C_6H_3(NO_2)_2$-*o*, *p*	H	$C_{14}H_9N_3O_4S_2$	347.3	48.45	2.61	12.10	18.47	92	125—126
					48.54	2.70	12.06	18.59		Ethanol—tetrahydrofuran (4 : 1)

2-mercaptobenzothiazole, 2-mercapto-6-nitrobenzothiazole, and 2-mercapto-6-aminobenzothiazole in ethanol or acetone by treatment with the appropriate halo derivatives. 2-(2-Hydroxy-3-chloropropylthio)benzothiazole (*XXI*) was prepared from 2-mercaptobenzothiazole and 1-chloro-2,3-epoxypropane under the catalytic action of sulfuric acid. The mixture of tetrahydrofuran and benzene was used as the reaction medium in this case. The p.m.r. spectra of some 2-methylthio-6-*N*-alkylaminobenzothiazoles reported in [6] proved that the compounds were *S* derivatives. As the compounds synthesized in the present work are structurally similar to the mentioned ones and their synthesis was accomplished under the same conditions, it was assumed (without taking their p.m.r. spectra) that they are *S* derivatives as well.

The basic screening of antimicrobial activity was done with all substances. The highest antimicrobial activity was found with 2-allylthio and 2-propargylthio derivatives of benzothiazole and with its 6-nitro and 6-amino derivatives (*XIV—XVI* and *XVIII—XX*). They were active on the strains of non-specific bacterial flora, mycobacteria, protozoa, and pathogenic fungi. Detailed data of their activities are presented in Table 2.

In addition to antimicrobial tests, also orientational determinations of LD_{50} were carried out by single i.p. doses to mice after dissolving the prepared compounds in dimethyl sulfoxide. The following results were obtained: 2-methylthio--6-aminobenzothiazole 500 ± 50 mg/kg, 2-allylthiobenzothiazole 1200 ± 50 mg/kg, 2-allylthio-6-nitrobenzothiazole 1200 ± 50 mg/kg, 2-allylthio-6-aminobenzothiazole 950 ± 50 mg/kg, 2-propargylthiobenzothiazole 900 ± 50 mg/kg, 2-propargylthio-6-nitrobenzothiazole 1200 ± 50 mg/kg, and 2-propargylthio-6-aminobenzothiazole 1200 ± 50 mg/kg.

Experimental

Characterization of the synthesized compounds is given in Table 1. Antimicrobial activity was tested according to the solubility of individual substances as well as specific cultivation conditions of individual test organisms [7]. The obtained values of the chosen compounds are presented in Table 2. The derivatives *VII*, *IX*, and *XII* were prepared by the procedure described in [6].

2-R-6-R'-Thiobenzothiazoles (I—VI, X—XVI, XVIII—XXVII)

Potassium hydroxide (5.6 g; 0.1 mole) and 2-mercapto-6-R'-benzothiazole (R' = H, NO_2, NH_2) (0.1 mole) were dissolved gradually in ethanol or acetone (300 ml) under stirring at 40—50°C. The appropriate halo derivative (0.1 mole) was added dropwise at the same temperature and the reaction mixture was stirred for 2—3 h. Then 2/3 of the solvent was

Table 2. Antimicrobial activity of some synthesized 2- and 2,6-substituted benzothiazoles (μg/ml)

No.	MIC					Bactericidal/bacteriostatical conc.		Lethal conc.			
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida pseudotropicalis*	BCG	*Mycobacterium fortuitum*	*Trypanosoma cruzi*	*Trichomonas foetus*	*Tetrahimena piriforis*	*Euglena gracilis*
II	50		50		100	100/50		100			500
III	10	25	50	300	100	100/50	100/50	100	300	300	500
V	50		100		>100	100/50		>100			>500
VI	50	25	100	300	>100	100/50	100/50	100	500	300	500
VII	50		100		>100	100/50		>100			500
VIII	50		100		>100	100/50		>100			>500
IX	50		100		>100	100/50		>100			>500
X	50		50		>100	50/>10		>100			>500
XII	50		100		>100	100/50		>100			>500
XIII	50		100		>100	100/50		>100			>500
XIV	50	25	100	300	>100	50/10	100/50	100	500	100	250
XV	10	10	50	300	>100	50/10	100/50	100	500	300	>500
XVI	10	10	50	300	>100	50/10	100/50	100	300	100	250
XVII	50		100		>100	100/50		>100			500
XVIII	10	10	10	300	>100	50/10	300/100	100	500	300	250
XIX	50	10	50	300	>100	50/10	300/100	100	500	300	500
XX	10	10	10	300	>100	50/10	300/100	100	500	300	250
XXI	50		50		>100	100/50		100			250
XXII	50		50		>100	50/>10		>100			>500
XXIII	50		50		>100	100/50		>100			>500
XXIV	50		50		>100	50/>10		>100			>500
XXV	>200	>200	>200	>200	>200	100/>100	>500/>500	>100	>800	>800	>500
XXVI	>200	>200	>200	>200	>200	100/>100	>500/>500	>100	>800	>800	>500
XXVII	>200	>200	>200	>200	>200	100/>100	>500/>500	>100	400	>800	>500

distilled off and the residue was poured into water (500—600 ml) from which the compounds *I—III, V, VI, X, XII, XIII, XV, XVI, XVIII—XXI, XXIII, XXV—XXVII* were filtered off as solids. The liquid derivatives (*IV, XI, XIV, XXII,* and *XXIV*), insoluble in water, were extracted with ether. After drying the solution with sodium sulfate, ether was distilled off and the compounds were distilled under reduced pressure. The compound *XXIV* decomposed on distillation (220°C/399.96 Pa); it was purified on a column of aluminium oxide using benzene as eluent.

2-(2-Hydroxy-3-chloropropylthio)benzothiazole (XXI)

A. 2-Mercaptobenzothiazole (16.7 g; 0.1 mole) and 1-chloro-2,3-epoxypropane (9.2 g; 0.1 mole) were added to a mixture of tetrahydrofuran (30 ml), benzene (30 ml), and sulfuric acid (1—2 ml). After 5—10 min staying at room temperature and stirring the exothermic reaction started (dissolution of 2-MBT). The temperature was kept at 50°C. When the exothermic reaction ended, the mixture was allowed to stay for 4 h and then the insoluble portion was filtered off. The solution was washed 3 times with water (100 ml), dried with sodium sulfate and the solvents were distilled off at reduced pressure. The residue, which became solid on staying, was crystallized from ethanol. Yield 22.6 g; 88%.

B. 2-Mercaptobenzothiazole (16.7 g; 0.1 mole), potassium hydroxide (5.6 g; 0.1 mole), and acetone (200 ml) were stirred at 40—60°C until the solution became transparent. After cooling the solution to the room temperature, 1,3-dichloro-2-propanol (12.9 g; 0.1 mole) was added dropwise. The temperature raised to 40°C after 2 h. The cooled reaction mixture was poured into crushed ice (500—700 ml) and 2-(2-hydroxy-3-chloropropylthio)benzothiazole was crystallized from ethanol. Yield 18 g; 70%.

References

1. Umarov, A. A., Rozhkova, K. N., Imamaliev, I. A., Zohirov, S. T., Loi, P. N., and Mirhaidarov, Kh., *USSR* 325957 (1957); *Chem. Abstr.* **77,** 30351 (1972).
2. Usui, Y., *Yakugaku Zasshi* **88,** 1535 (1968); *Chem. Abstr.* **71,** 49836 (1969).
3. Chitosi, V., Tadajuki, S., and Chiroki, M., *Japan.* 36371 (1973); *Ref. Zh. Khim.* 13 N 342 P (1973).
4. Smith, Q. H., *Ger. Offen* 2005529 (1970); *Chem. Abstr.* **74,** 22135 (1971).
5. Popoff, J., Buchholz, B., and Miller, J. H., *US* 3519630 (1970); *Chem. Abstr.* **73,** 76146 (1970).
6. Sutoris, V., Orosová, Ľ., and Foltínová, P., *Chem. Zvesti* **30,** 179 (1976).
7. Raška, K., *Mikrobiologické vyšetřovací methody.* (Microbiological Examination Methods.) Státní zdravotnické nakladatelství. (State Publishing House of Health.) P. 152. Prague, 1958.

Translated by A. Kardošová