Benzothiazole compounds. XV. Nucleophilic substitution reactions on benzothiazolium salts

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Treatment of 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium chloride and 2--methylthio-3-methylbenzothiazolium perchlorate with *N*- and *C*-nucleophiles resulted in 3-methyl- and 3-(2-mercaptoethyl)-2-benzothiazolines. The reaction rate with *C*-nucleophiles was directly dependent on the concentration of triethylamine as catalyst. A new method for the preparation of 3-methyl-2-benzothiazolinone hydrazone and 3-methyl-2-(3-methylbenzothiazolinylidenamino)benzothiazolium perchlorate is described. The results of tests for antimicrobial activity were not noticeable.

При действии *N*- и *C*-нуклеофильных частиц на 2,3-дигидротиазоло[2,3-*b*]бензтиазолий хлорид и 2-метилтио-3-метилбензтиазолий перхлорат были синтезированы 3-метил- и 3-(2-меркаптоэтил)-2-бензтиазолины. Скорость реакции с *C*-нуклеофильными реагентами прямо пропорциональна концентрации триэтиламина как катализатора. Описывается новый метод приготовления 3-метил-2-бензтиазолинонгидразона и 3-метил-2-(3-метилбензтиазолинилиденамино)бензтиазолий перхлората. Испытания антимикробиального действия не принесли примечательных результатов.

The reactivity of some quaternary benzothiazolium salts was studied by several authors [1—5]. It was found that in the position 2, where an electron dilution caused by positive charge on the nitrogen atom occurred, nucleophilic substitution reactions proceeded fairly well. The study was focused on the reaction mechanisms and their utilization in syntheses of dyes. Amines, hydrazines, hydrogen sulfide, water, aqueous solution of ammonia, alcoholates, *etc.* were used as nucleophiles.

The aim of the present work was to prepare some 2,3-disubstituted benzothiazoline derivatives which seemed to be interesting from the viewpoint of their antibacterial activity and possible comparison to 2-substituted benzothiazoles [6—9]. We devoted our attention to nucleophilic substitution reactions of 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium chloride (*I*) [10—12] and 2-methylthio-3-methylbenzothiazolium perchlorate (*II*) [5]. Semicarbazide, thiosemicarbazide, hydroxylamine, 4-nitro- and 2,4-dinitrophenylhydrazine, diethyl malonate, nitromethane, acetone, ethanolamine, dry ammonia, isonicotinohydrazide, hydrazides of aliphatic acids and their derivatives were used as reagents.

Experimental

Melting points were determined on a Kofler block. The solvents used for crystallization and analytical data of the synthesized compounds are presented in Table 1 where R and R^1 denote the substituents in the positions 2 and 3, respectively.

The ^{1}H-n.m.r. spectra were measured with a Tesla 487 spectrometer at 80 MHz in 5—10% solutions in deuterated chloroform (using tetramethylsilane as internal standard), dimethyl sulfoxide, and trifluoroacetic acid (using hexamethyldisiloxane as internal standard) according to the solubility of compounds. The chemical shifts were calculated relative to tetramethylsilane with the accuracy of ± 0.02 p.p.m. The molecular weight of *XXVI* was measured on a mass MS-902 spectrometer at 70 eV and 160°C of the ionization chamber. The reaction kinetics of *I* with water in dimethyl sulfoxide was studied at 30 ± 0.1°C; the substrate concentration was 1×10^{-5} M, the concentration of water was 5.55 M, and the concentration of triethylamine varied from 1.43×10^{-2} to 14.38×10^{-2} M. The reaction course (Table 2) was followed by an SF-8 spectrophotometer on the basis of transmittance decrease of the starting compound at 327 nm. The results of the reaction were evaluated by the Guggenheim method [13]. The results of tests for antimicrobial activities of the synthesized 2,3-disubstituted benzothiazoline derivatives are presented in Table 3.

With the microorganisms *1*—*4* and *8* the applied concentrations of the tested compounds were 200, 50, 12.5, and 3.12 μg/disc, with the other microorganisms 800, 200, 50, 12.5, and 3.12 μg/cm^{-3} The activity against the microorganisms *1*—*4* and *6* was investigated by the method of plate diffusion tests and against the other ones by the dilution test-tube method. The cultivation media were chosen according to the growth claims of the individual microorganisms and according to chemical structure of the tested compounds. Detailed procedures of tests are described in [14, 15].

2,3-Dihydrothiazolo[2,3-b]benzothiazolium chloride (I)

2-(2-Hydroxyethylthio)benzothiazole (63.4 g; 0.3 mol) was dissolved in tetrahydrofuran (300 ml) and thionyl chloride (53.3 g; 0.45 mol) in tetrahydrofuran (150 ml) was added dropwise at 20—25°C. The reaction mixture was heated for 2 h at boiling. The cooled solid was filtered off and washed with acetone. Yield 65.3 g (95%), m.p. 225—228°C.

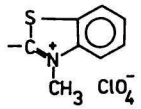
Table 1

Analytical data of the synthesized 3-methyl- and 3-(2-mercaptoethyl)-2-benzothiazolines

Compound	R	R^1	Formula	M	Calculated/found				Yield %	M.p., °C Solvent
					% C	% H	% N	% S		
III	NOH	$(CH_2)_2SH$	$C_9H_{10}N_2OS_2$	226.3	47.76	5.30	12.37	28.33	45	130—132
					47.64	5.27	12.21	28.25		Benzene
IV	NNH_2	CH_3	$C_8H_9N_3S$	179.2	53.60	5.06	23.44	17.88	65	143—144
					53.49	4.92	23.60	18.07		Ethanol
V	$N(CH_2)_2OH$	$(CH_2)_2SH$	$C_{11}H_{14}N_2OS_2$	254.4	51.94	5.54	11.01	25.21	45	110—112
					52.08	5.46	10.95	25.18		Benzene
VI	$CHNO_2$	$(CH_2)_2SH$	$C_{10}H_{10}N_2O_2S_2$	254.3	47.22	3.96	11.01	25.21	30	125—127
					47.26	3.87	10.89	25.14		Nitromethane
VII	$CHNO_2$	CH_3	$C_9H_8N_2O_2S$	208.2	51.91	3.87	13.45	15.39	33	250—252
					51.77	3.98	13.57	15.41		Ethanol—pyridine (2 : 1)
VIII	$CHCOOC_2H_5$	$(CH_2)_2SH$	$C_{13}H_{15}NOS_2$	281.4	55.48	5.37	4.97	22.78	34	149—151
					55.55	5.29	4.87	22.91		Benzene—ether (1 : 1)
IX	$C(COOC_2H_5)_2$	CH_3	$C_{15}H_{17}NO_4S$	307.4	58.61	5.57	4.55	10.43	41	119—120
					58.43	5.61	4.47	10.49		Ethanol
X	$NNHCONH_2$	$(CH_2)_2SH$	$C_{10}H_{12}N_4OS$	268.4	44.75	4.50	20.87	23.89	83	168—169
					44.59	4.41	20.98	23.81		Ethanol—water (1 : 1)
XI	$NNHCONH_2$	CH_3	$C_9H_{10}N_4OS$	222.3	48.63	4.53	25.20	14.42	94	202—205
					48.58	4.41	25.43	14.31		Tetrahydrofuran
XII	$NNHCSNH_2$	$(CH_2)_2SH$	$C_{10}H_{12}N_4S_3$	284.4	42.23	4.25	19.69	33.82	54	188—190
					42.18	4.31	19.59	33.64		Dimethylformamide—ethanol (2 : 1)
XIII	$NNHCSNH_2$	CH_3	$C_9H_{10}N_4S_2$	238.3	45.36	4.22	23.51	26.91	93	200—203
					45.24	4.16	23.69	26.79		Tetrahydrofuran
XIV	*p*-$NNHC_6H_4NO_2$	$(CH_2)_2SH$	$C_{15}H_{14}N_4O_2S_2$	346.4	52.01	4.07	16.17	18.51	78	154—155
					52.12	3.96	16.11	18.71		Acetone—water (3 : 1.5)
XV	*p*-$NNHC_6H_4NO_2$	CH_3	$C_{14}H_{12}N_4O_2S$	300.3	55.98	4.02	18.65	10.67	98	162.5—164
					55.79	4.10	18.51	10.52		Dimethylformamide—ethanol (3 : 1)

Table 1 (Continued)

Compound	R	R^1	Formula	*M*	Calculated/found % C	% H	% N	% S	Yield %	M.p., °C Solvent
XVI	*o,p*-$NNHC_6H_3(NO_2)_2$	$(CH_2)_2SH$	$C_{15}H_{13}N_5O_4S_2$	391.4	46.03	3.34	17.89	16.38	88	above 300
					46.16	3.27	17.77	16.18		Dimethylformamide—ethanol (2 : 1)
XVII	$NNHCOCH_2OC_6H_5$	CH_3	$C_{16}H_{15}N_3O_2S$	313.9	61.22	4.80	13.39	10.21	64	277—278
					61.40	4.61	13.52	10.30		Benzene—petroleum ether (1 : 1)
XVIII	$NNHCOCH_2CN$	CH_3	$C_{11}H_{10}N_4OS$	246.3	53.70	4.09	22.75	13.02	57	224—226
					53.52	4.16	22.51	13.12		Tetrahydrofuran
XIX	$NNHCOCH_2CH_3$	CH_3	$C_{11}H_{13}N_3OS$	235.3	56.22	5.57	17.86	13.63	55	215—217
					56.43	5.41	17.93	13.87		Benzene
XX	$NNHCO(CH_2)_2CH_3$	CH_3	$C_{12}H_{15}N_3OS$	249.3	57.81	6.06	16.85	12.86	80	212—214
					57.73	6.22	17.05	12.59		Benzene
XXI	$NNHCO(CH_2)_3CH_3$	CH_3	$C_{13}H_{17}N_3OS$	263.4	59.27	6.50	15.95	12.17	57	202—203
					59.16	6.39	15.75	12.31		Benzene
XXII	$NNHCO(CH_2)_4CH_3$	CH_3	$C_{14}H_{19}N_3OS$	277.4	60.61	6.90	15.15	11.56	83	198—198
					60.54	6.76	15.32	11.30		Benzene—ethanol (1 : 0.2)
XXIII	$NNHCO(CH_2)_4CH_3$	$(CH_2)_2SH$	$C_{15}H_{21}N_3OS_2$	323.5	55.69	6.54	12.99	19.82	31	182—184
					55.48	6.71	12.98	19.82		Benzene—petroleum ether (1 1)
XXIV	$NNHCOC_5H_4N$	$(CH_2)_2SH$	$C_{15}H_{14}N_4OS_2$	330.4	54.52	4.27	16.95	19.40	33	156—157
					54.69	4.19	16.69	19.34		Benzene
XXV	N—MBTCH*	CH_3	$C_{16}H_{14}ClN_3O_4S_2$	411.9	46.65	3.42	10.20	15.56	46	310—312
					46.81	3.30	10.03	15.59		Triethylene glycol—acetone (1 : 2)
XXVI	NN = MBT**	CH_3	$C_{16}H_{14}N_4S_2$	326.5	58.85	4.32	17.06	19.52	49	262—264
					58.68	4.41	17.00	19.70		Benzene
XXVII	—	CH_3	C_8H_7NOS	165.2	58.16	4.27	8.47	19.40	60	65—67
					58.04	4.38	8.61	19.57		Benzene—petroleum ether (1 : 2)

* = 

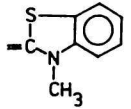
** = 

Table 2

Rate of the nucleophilic substitution reaction in dependence on the concentration of the catalyst

$c_3 \cdot 10^2$ M	1.43,	2.15,	2.87,	3.59,	4.31,	5.75,	7.19,	10.79,	14.38
k 10^3, s^{-1}	1.92,	3.11,	4.71,	6.17,	7.37,	9.65,	11.30,	16.99,	37.70

Table 3

Antimicrobial activity (conc. μg/ml) of 3-methyl- and 3-(2-mercaptoethyl)-2-benzothiazolines

Compound	Microorganisms[a]										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*[b]	*10*[b]	*11*[b]
III	12.5	50	12.5	200	800	200	200	200			
IV	>200	>200	>200	>200	>800	200	800	>200			
V	50	50	200	>200	800	800	800	>200			
VI	12.5	12.5	12.5	>200	800	50	200	>200			
VII	>200	>200	>200	>200	>800	200	800	>200	800/50	800/50	200/50
VIII	>200	>200	>200	>200	>800	200	800	>200			
IX	>200	>200	>200	>200	800	800	800	>200			
X	200	>200	>200	>200	>800	800	800	>200			
XI	>200	>200	>200	>200	>800	800	800	>200			
XII	200	200	>200	>200	>800	800	800	>200			
XIII	>200	>200	>200	>200	>800	800	800	>200			
XIV	200	200	200	200	>800	200	200	200	800/50	800/50	200/50
XV	200	200	200	>200	>800	200	200	200	800/50	800/50	200/50
XVI	200	200	200	>200	>800	200	200	200	200/50	800/50	200/50
XVII	>200	>200	>200	>200	>800	200	200	>200	800/50	800/200	800/200
XVIII	>200	>200	>200	>200	>800	800	200	>200	800/50	800/200	800/200
XIX	>200	>200	>200	>200	>800	800	800	>200	800/50	800/50	200/50
XX	>200	200	200	>200	>800	800	800	>200	800/50	800/50	200/50
XXI	>200	>200	>200	>200	>800	800	800	>200	800/50	800/200	200/50
XXII	>200	>200	>200	>200	>800	800	800	>200	800/50	200/50	200/50
XXIII	>200	>200	>200	>200	>800	800	800	>200	200/50	200/50	200/50
XXIV	>200	>200	>200	>200	800	800	800	>200	200/50	200/50	200/50
XXV	50	50	50	>200					200/50	200/50	200/50
XXVI	>200	>200	200	>200	>800	800	800		800/50	800/50	800/50
XXVII	>200	>200	>200								

a) Microorganisms: *1. Staphylococcus aureus; 2. Bacillus subtilis; 3. Escherichia coli; 4. Pseudomonas aeruginosa; 5. Euglena gracilis; 6. Trichomonas foetus; 7. Trypanosoma cruzi; 8. Candida pseudotropicalis; 9. Microsporum gypseum; 10. Trichophyton rubrum; 11. Epidermophyton floccosum.*

b) Fungicidal/fungistatical concentration.

3-(2-Mercaptoethyl)-2-benzothiazolinone oxime (III) and semicarbazone (X)

To the compound *I* (11.5 g; 0.05 mol) in water (100 ml), portions of hydroxylammonium chloride and semicarbazide chloride solutions, respectively (10.4 g; 0.15 mol) and potassium acetate (17.6 g; 0.2 mol) in water (60 ml) were added. The reaction mixture was stirred at 10—12°C for 1 h. The formed white precipitate was filtered off and washed with water.

3-Methyl-2-benzothiazolinone hydrazone (IV)

To the compound *II* (8.8 g; 0.03 mol) dissolved in triethylene glycol (100 ml) portions of bromoacetohydrazide (4.6 g; 0.03 mol) were added at 40—50°C under stirring. The reaction mixture was heated on a boiling water bath for 10 h and after cooling it was poured into cold water (300 ml). The formed solid was filtered off and purified by crystallization.

^{1}H-N.m.r. spectrum: (C_6H_4) 7.00 (m, 4H); (NH_2) 4.30 (s, 2H); (CH_3) 3.38 (s, 3H).

3-(2-Mercaptoethyl)-2-(2-hydroxyethylamino)benzothiazoline (V)

The compound *I* (11.5 g; 0.05 mol) was dissolved in pyridine (80 ml) and ethanolamine (6.1 g; 0.1 mol). The reaction proceeded exothermically under stirring for 2 h. The reaction mixture was poured into crushed ice (500 ml). The formed precipitate was purified by charcoal and crystallization.

3-(2-Mercaptoethyl)-2-nitromethylenebenzothiazoline (VI)

The compound *I* (4.6 g; 0.02 mol), nitromethane (50 ml), and triethylamine (2.5 g; 0.025 mol) were heated at 45°C for 5 h under stirring. After cooling the crystalline product was washed on the filter by tetrahydrofuran and purified by charcoal and crystallization.

3-Methyl-2-nitromethylenebenzothiazoline (VII), N'-(3-methyl-2-benzothiazolinylidene)propiono- (XIX), -butyro- (XX), -valero- (XXI), -caprono- (XXII), -cyanoaceto- (XVIII), -phenoxyaceto- (XVII), and -isonicotinohydrazide (XXIV), N'-[3-(2-mercaptoethyl)-2-benzothiazolinylidene]capronohydrazide (XXIII)

The compound *II* (5.9 g; 0.02 mol) or the compound *I* (4.6 g; 0.02 mol), triethylene glycol (50 mol), nitromethane (1.8 g; 0.03 mol) or the appropriate hydrazide (0.02 mol), and triethylamine (2 g; 0.02 mol) were heated under stirring at 50°C for 2 h and at 80°C for 4 h. With the compounds *XVII—XXIII* and *XXVI* the reaction mixture was stirred at laboratory temperature for 20 h. At the preparation of *XXIV* the reaction time was 7 h. The crystalline compounds were filtered off after cooling.

^{1}H-N.m.r. spectra: (C_6H_4, NH) 7.40—7.20 (m, 5H); (CH_3) 3.70—3.50 (s, 3H); *XVII* (C_6H_5) 6.93 (m, 5H). The found molecular weight of the compound *XXVI* was 326

(calculated 326.45), m.p. 262—264°C. (Ref. [17] gives 230°C.) At 230°C recrystallization occurred. ^{1}H-N.m.r. spectrum: (C_6H_4) 7.36 (m, 8H); (CH_3) 3.77 (s, 6H).

Ethyl 3-(2-mercaptoethyl)-2-benzothiazolinylideneacetate (VIII)

To the stirred solution of *I* (4.6 g; 0.02 mol) in water (50 ml) diethyl malonate (4 g; 0.025 mol) and triethylamine (2.5 g; 0.025 mol) in ethanol (15 ml) were added during 1 h. The reaction mixture was stirred for 2 h at room temperature. The formed precipitate was filtered off and purified by charcoal and crystallization.

Diethyl 3-methyl-2-benzothiazolinylidenemalonate (IX)

The compound *II* (5.9 g; 0.02 mol) was dissolved in triethylene glycol (50 ml) at 45—50°C. Portions of diethyl malonate (4.8 g) and triethylamine (2 g; 0.02 mol) were added at 20°C under stirring. After 2 h the reaction mixture was poured into crushed ice (150 ml) and the precipitate was isolated and purified by charcoal in ethanol.

^{1}H-N.m.r. spectrum: (C_6H_4) 7.25 (m, 4H); (CH_2) 4.25 (qu, 4H); (CH_3) 3.50 (t, 6H); $J = 7.2$ Hz.

3-Methyl-2-benzothiazolinone semicarbazone (XI), thiosemicarbazone (XIII), 3-methyl-2-benzothiazolone 4-nitrophenylhydrazone (XV)

The compound *II* (7.4 g; 0.025 mol), semicarbazide chloride, thiosemicarbazide chloride or 4-nitrophenylhydrazine (0.05 mol), ethanol (100 ml), and pyridine (5 g) were heated under reflux for 6 h. After cooling the isolated precipitate was washed with water.

3-(2-Mercaptoethyl)-2-benzothiazolinone thiosemicarbanone (XII)

To the compound *I* (11.5 g; 0.05 mol) dissolved in 50% ethanol (80 ml), thiosemicarbazide chloride (6.4 g; 0.05 mol) and potassium acetate (8.8 g; 0.1 mol) in water (30 ml) were added. The reaction mixture was stirred and heated at boiling point for 4 h. After cooling the crystalline product was filtered off, washed with water and purified by crystallization.

3-(2-Mercaptoethyl)-2-benzothiazolone 4-nitro- (XIV) and 2,4-dinitrophenylhydrazone (XVI)

The compound *I* (4.6 g; 0.02 mol) was dissolved in water (70 ml) and 4-nitrophenylhydrazine (0.02 mol) dissolved at heating in ethanol (70 ml) or 2,4-dinitrophenylhydrazine dissolved in tetrahydrofuran was added under stirring. The reaction resulting in a crystalline compound proceeded immediately.

3-Methyl-2-(2-methyl-2-benzothiazolinylidenamino)-benzothiazolium perchlorate (XXV)

The compound *II* (5.9 g; 0.02 mol) in triethylene glycol (50 ml) was heated on a boiling water bath for 2 h in the atmosphere of dry ammonia. After cooling the reaction mixture was poured into cold water (200 ml). The solid was filtered off and purified by crystallization.

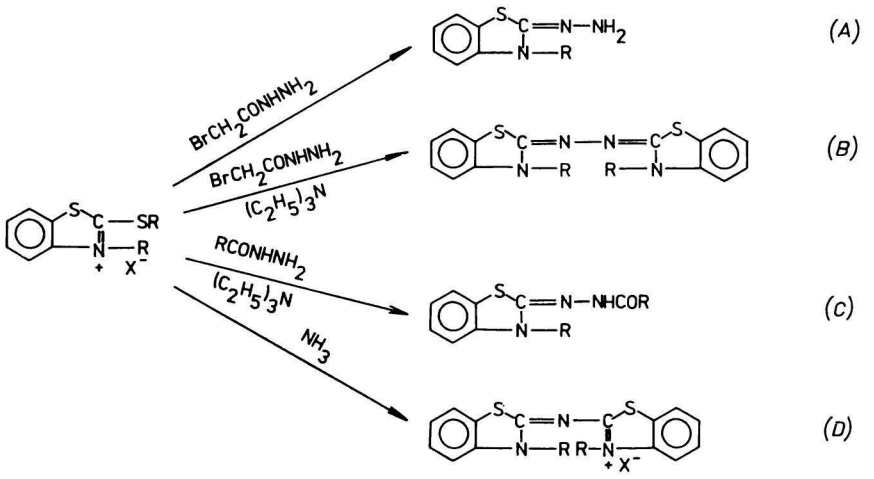
3-Methyl-2-benzothiazolinone (XXVII)

The compound *II* (8.8 g; 0.03 mol) was dissolved in triethylene glycol (130 ml) and acetone (4 g; 0.07 mol) and triethylamine (3 g) were added. The reaction mixture was heated on a water bath for 7 h under stirring until no more methanethiol was liberated. Then it was poured into water (300 ml) and the aqueous solution was extracted with dichloromethane, dried with sodium sulfate and dichloromethane was distilled off. The highly viscous liquid was dissolved in benzene (20 ml) and fractionated on an Al_2O_3 column (according to Brockmann II neutral for chromatography). Benzene was used as eluting agent.

Results and discussion

2,3-Dihydrothiazolo[2,3-*b*]benzothiazolium chloride was prepared after the method modified by us by using tetrahydrofuran instead of chloroform at halogenation of 2-(2-hydroxyethylthio)benzothiazole [10] and cyclization of 2-(2-chloroethylthio)benzothiazole. The yields increased from 50 to 95% and the products were pure and suitable for further syntheses. Water was used as medium for nucleophilic substitution reactions mainly with *I* for good solubility. The optimum reaction temperature was 8—22°C. By increasing the temperature a concurrent reaction with water giving 2-(2-benzothiazolone-3-yl)ethyl disulfide [16] was observed. Triethylene glycol was a suitable solvent for nucleophilic reactions with *I* and *II* under the conditions mentioned in Experimental. In triethylene glycol purer products were formed because the solvent did not enter the reaction even at elevated temperatures. The reactions with *C*-nucleophiles proceeded slowlier than those with *N*-nucleophiles and resulted in lower yields. Therefore, triethylamine or pyridine was used as catalyst in these reactions. Kinetic studies of the reaction of 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium chloride with water in dimethyl sulfoxide in the presence of triethylamine showed that the reaction rate was dependent on the concentration of the catalyst; with increasing concentration the rate constant of the substitution reaction increased. However, with higher concentrations of the catalyst than 11×10^{-2} M the dependence was not linear (Table 2), the reaction proceeded faster than expected.

Treatment of *II* in triethylene glycol with bromoacetohydrazide at elevated temperature resulted in 3-methyl-2-benzothiazolinone hydrazone (*IV*) (Scheme 1*A*). It can be supposed that the liberated methanethiol reacted with the primarily



Scheme 1

formed *N'*-(3-methyl-2-benzothiazolinylidene)bromoacetohydrazide under the formation of *IV* and methyl bromothioacetate. Liberation of methanethiol was not observed in this reaction (contrary to the other reactions). The reaction course was similar in both the commercial and anhydrous triethylene glycol excluding the hydrolysis of *N'*-(3-methyl-2-benzothiazolinylidene)bromoacetohydrazide at elevated temperatures. It is formed [17] by the reaction of 2-methylthio-3-methylbenzothiazolium methyl sulfate with hydrazine hydrate in alcohol as an intermediate (which can be isolated with difficulty) at the preparation of the appropriate azine. When an equivalent amount of triethylamine was added into the reaction mixture and the reaction was carried out at laboratory temperature, 3-methyl-2-benzothiazolinylideneazine (*XXVI*) (*B*) was isolated. The hydrazide of α-bromopropionic, monochloroacetic, dichloroacetic, trichloroacetic, acetic, chloroformic, and formic acids reacted similarly. It is interesting that propiono-, butyro-, valero-, caprono-, cyanoaceto-, phenoxyaceto-, and isonicotinohydrazide with *I* and *II* gave under the same conditions the appropriate 3-(2-mercaptoethyl)- and 3-methyl-2-benzothiazolinylidenehydrazides *XVII*—*XXIV* (*C*). Treatment of *II* with aqueous solution of ammonia resulted in 3-methyl-2-benzolinylidenimine [5]. We have found that by treatment with dry ammonia 3-methyl-2-(3-methylbenzothiazolinylidenamino)benzothiazolium perchlorate *XXV* (*D*) was formed.

It was evident from the intensive liberation of methanethiol that the compound *II* reacted with acetone in the presence of triethylamine. During the isolation procedure water reacted with the product (due to electron dilution in the position

2 caused by the carbonyl group) giving *XXVII*. This compound was prepared also by treatment of *II* with aqueous solution of sodium hydroxide [4]. When studying the effect of triethylamine on the reaction course of *I* with water, where 2-(2-benzothiazolone-3-yl)ethyl disulfide was formed, the synthesis was carried out at the same conditions except the nitrogen atmosphere to exclude oxidation of the primarily formed 3-(2-mercaptoethyl)-2-benzothiazolone. After isolation from water medium and drying, the melting point of 3-(2-mercaptoethyl)-2-benzothiazolone was in a sealed tube 49—52°C. Crystallization of this product from ethanol resulted in 2-(2-benzothiazolone-3-yl)ethyl disulfide.

The data in Table 3 represent the lowest concentrations of the tested compounds which still caused significant inhibition of growth of the appropriate microorganisms. The compound *VI* was found to be most active among the tested compounds on the strains of nonspecific bacterial flora *1, 2, 3* forming a strong zone of growth inhibition in the concentration of 12.5 μg/disc. This compound was most active also against the protozoal strain *Trichomonas foetus* causing total inhibition in concentration of 50 μg/ml. With the other compounds somewhat higher concentrations were necessary for inhibition activity on these microorganisms. With *Euglena gracilis,* besides inhibition activity, also the activity on the plastide system was investigated. Depigmentation activity on the green strain of *Euglena* was not observed with the tested compounds. The tested group of derivatives in higher concentrations acted fungicidally and lower concentrations caused significant fungistatical activity on the microorganisms *9, 10,* and *11.* We tried also to influence the experimental *Trypanosoma cruzi* infection of mice with the compounds *III*, *X*, *XII*, *XIV*, and *XV* but without evident therapeutic effect. On the basis of the obtained results it can be stated that the 2,3-substituted benzothiazolines possess lower antimicrobial activity than the earlier synthesized 2-substituted benzothiazoles.

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