Benzothiazole compounds

XXXIX. Synthesis of 3-substituted 2-phenyl- and 2-(2-phenylethyl)benzothiazolium salts

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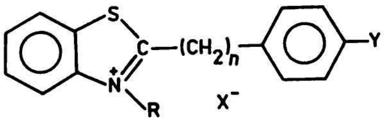
Trimethylsilyl ester of polyphosphoric acid was used as a cyclocondensation agent to prepare 2-phenylbenzothiazole and 2-(2-phenylethyl)benzothiazole from 2-aminothiophenol, benzoic acid, and 3-phenylpropanoic acid, respectively. Quaternary salts were prepared by alkylation of these compounds. It was proved that the electronic effect of phenyl group in 2-phenylbenzothiazole makes the course of quaternization difficult. 2-Phenyl-3-allylbenzothiazolium triiodide was isolated by treating 2-phenylbenzothiazole with an excess of allyl iodide. The structure of 3-substituted 2-phenyl- and 2-(2-phenylethyl)benzothiazolium salts was confirmed by UV and ^{1}H NMR spectroscopy. A high-noticeable growth-regulating activity was found for 2-[2-(4-nitrophenyl)ethyl]-3-methylbenzothiazolium iodide when tested on *Triticum aestivum* L.

Триметилсилиловый эфир полифосфорной кислоты был использован в качестве циклоконденсирующего агента при получении 2-фенилбензотиазола и 2-(2-фенилэтил)бензотиазола из 2-аминотиофенола, бензойной кислоты и 3-фенилпропионовой кислоты, соответственно. Посредством алкилирования этих соединений были получены четвертичные соли. Показано, что электронный эффект фенильной группы в 2-фенилбензотиазоле затрудняет ход квартернизации. После действия избытка аллилиодида был выделен трииодид 2-фенил-3-аллилбензотиазолия. Строение 3-замещенных 2-фенил- и 2-(2-фенилэтил)бензотиазолиевых солей было подтверждено с помощью УФ и ^{1}H ЯМР спектроскопии. У иодида 2-[2-(4-нитрофенил)этил]-3-метилбензотиазолия была обнаружена высоко заметная активность в качестве регулятора роста *Triticum aestivum* L.

The activity of some 3-substituted 2-benzylbenzothiazolium salts in the region of stimulation of growth of *Triticum aestivum* L. [1] gave rise to the need

Table 1

Characterization of the synthesized compounds



Compound	R	n	X	Y	Formula	M_r	w_i(calc.)/% w_i(found)/%					Yield	M.p.
							C	H	N	S	Halogen	%	°C
I	CH_3	0	I	H	$C_{14}H_{12}INS$	353.22	47.61	3.42	3.97	9.08	35.33	42	227—231
							47.28	3.22	3.61	8.90	35.05		
II	CH_3	0	ClO_4	H	$C_{14}H_{12}ClNO_4S$	325.77	—	—	—	9.84	10.88	65	225—228
							—	—	—	9.80	10.99		
III	CH_3	0	BF_4	H	$C_{14}H_{12}F_4BNS$	313.12	—	—	—	10.24	—	58	203—207
							—	—	—	10.09	—		
IV	C_2H_5	0	I	H	$C_{15}H_{14}INS$	367.28	49.05	3.84	3.82	8.73	34.55	20	190—195
							49.22	3.69	4.05	8.49	34.12		
V	$CH_2CH{=}CH_2$	0	I_3	H	$C_{16}H_{14}I_3NS$	633.07	30.36	2.22	2.21	5.06	60.14	15	135—138
							30.67	2.10	2.28	4.95	59.86		
VI	CH_3	2	I	H	$C_{16}H_{16}INS$	381.28	50.40	4.23	3.67	8.41	33.28	76	199—202
							50.34	4.03	3.70	8.26	32.96		
VII	CH_3	2	I	OCH_3	$C_{17}H_{18}INOS$	411.30	49.64	4.41	3.41	7.79	30.85	53	193—196
							49.36	4.22	3.28	7.48	30.81		
VIII	CH_3	2	I	NO_2	$C_{16}H_{15}IN_2O_2S$	426.27	45.08	3.55	6.57	7.52	29.77	65	225—229
							45.27	3.52	6.63	7.48	29.82		
IX	C_3H_7	2	I	H	$C_{18}H_{20}INS$	409.33	52.82	4.92	3.42	7.83	—	47	128—130
							52.67	5.08	3.28	7.99	—		
X	C_4H_9	2	I	H	$C_{19}H_{22}INS$	423.35	53.91	5.24	3.31	7.57	29.98	45	159—163
							53.69	5.19	3.17	7.61	29.57		

Table 1 (Continued)

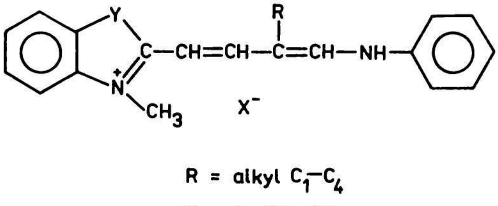
Compound	R	*n*	X	Y	Formula	M_r	w_i(calc.)/% w_i(found)/%					Yield	M.p.
							C	H	N	S	Halogen	%	°C
XI	$CH_2CH{=}CH_2$	2	I	H	$C_{18}H_{18}INS$	406.42	53.11	4.46	3.45	7.89	31.23	62	165—168
							53.53	4.44	3.18	7.77	31.09		
XII	$CH_2C_6H_5$	2	Br	H	$C_{22}H_{20}BrNS$	410.42	64.38	4.91	3.42	7.81	19.47	59	181—185
							64.26	4.69	3.41	7.70	19.67		
XIII	CH_2COOCH_3	2	Br	NO_2	$C_{18}H_{17}BrN_2O_4S$	437.31	49.44	3.92	6.41	7.33	18.27	58	192—195
							49.18	3.86	6.20	7.00	18.17		
XIV	$CH_2COOC_2H_5$	2	Br	H	$C_{19}H_{20}BrNO_2S$	406.39	56.16	4.96	3.46	7.89	19.66	56	201—204
							55.94	5.13	3.26	7.69	19.44		
XV	$CH_2COOC_3H_7$	2	Br	H	$C_{20}H_{27}BrNO_2S$	420.36	57.15	5.27	3.33	7.63	19.01	54	193—197
							57.27	5.29	3.16	7.48	19.37		
XVI	$CH_2COOC_3H_7$-i	2	Br	H	$C_{20}H_{22}BrNO_2S$	420.36	57.15	5.27	3.33	7.63	19.01	50	208—211
							57.07	5.39	3.15	7.70	19.39		
XVII	$CH_2COOCH_2C_6H_5$	2	Br	H	$C_{23}H_{22}BrNO_2S$	456.40	60.53	4.86	3.07	7.01	17.51	62	159—163
							60.27	4.73	2.93	6.98	17.15		

of the synthesis of further homologues, *i.e.* 3-substituted 2-phenyl- and 2-(2-phenylethyl)benzothiazolium salts.

For the synthesis of these compounds the starting 2-phenylbenzothiazole was prepared from 2-aminothiophenol and benzoic acid in 1,2-dichloroethane by treating with trimethylsilyl ester of polyphosphoric acid as a cyclocondensation agent. 2-(2-Phenylethyl)benzothiazole was obtained by treating of 3-phenylpropanoic acid with 2-aminothiophenol. The steric or electronic effect of substituent in position 2 of benzothiazole skeleton can make the course of quaternization difficult [2]. In the case of 2-phenylbenzothiazole, besides steric effect, owing to the significant influence of conjugation the basicity of the nitrogen as well as the rate of quaternization decreases.

3-Substituted 2-phenylbenzothiazolium salts were prepared in the yield of 15—42 % only with methyl iodide (*I*), ethyl iodide (*IV*), and allyl iodide (*V*) (Table 1). By the reaction of 2-phenylbenzothiazole with dimethyl sulfate a yellow crystalline compound is formed, which owing to the atmospheric moisture changes for a dark-brown pitchy matter the structure of which could not be ascertained. To compare the influence of anion on the biological activity, analogues with perchlorate (*II*) and tetrafluoroborate anion (*III*) were prepared from 2-phenyl-3-methylbenzothiazolium iodide. The structure of *I* was confirmed by ^{13}C NMR spectra: δ/ppm: 177.23 (C-2), 144.45 (C-3a), 118.85 (C-4), 132.75 (C-5), 131.57 (C-6), 125.58 (C-7), 131.73 (C-7a), 126.56 (C-8), 132.09 (C-9), 131.88 (C-10), 136.56 (C-11), 39.51 (CH_3).

Treating 2-phenylbenzothiazole with a great excess of allyl iodide 2-phenyl-3-allylbenzothiazolium triiodide (*V*) is generated in a small yield (15 %). The structure of this compound was proved by ^{1}H NMR and UV spectra (Table 2). The multiplicity and integral intensities of signals of its protons were found to be comparable with those of allyl group in 2-benzyl-3-allylbenzothiazolium iodide [1]. These values confirm that the structure of compound corresponds to 2-phenyl-3-allylbenzothiazolium cation and that I_2 generated *in situ* in the reaction medium does not undergo addition on the C═C bond of allyl moiety. *Hirsch et al.* [3] in their paper on chemistry of dyes reported on a triiodide with benzothiazolium cation (Formula 1). *Gordon* and *Ware* [4] claimed that some



R = alkyl C_1–C_4
Y = S, CH═CH
X = I, ClO_4, I_3

Formula 1

Table 2

UV and ^{1}H NMR spectra of the synthesized benzothiazolium salts

Compound	λ/nm log (ε/(m^2 mol^{-1}))		δ/ppm
I	245 3.30	300 3.04	4.49 (s, 3H, $\overset{+}{N}$—CH_3), 7.8—8.4 (m, 9H, H_{arom})
IV	240 3.48	290 3.98	4.94 (q, 2H, $\overset{+}{N}$—CH_2, $J = 7$ Hz), 1.81 (t, 3H, CH_3, $J = 7$ Hz), 7.9—8.4 (m, 9H, H_{arom})
V	290 3.78	360 3.39	5.0—5.5 (m, 4H, $\overset{+}{N}$—CH_2, =CH_2), 5.85—6.2 (m, 1H, —CH=), 7.7—8.4 (m, 9H, H_{arom})
VI	240 3.11	280 3.69	3.9 (s, 3H, $\overset{+}{N}$—CH_3), 3.17 (t, 2H, C_6H_5—CH_2, $J = 7$ Hz), 3.67 (t, 2H, Z, $J = 7$ Hz), 7.1—7.8 (m, 9H, H_{arom})
VII	240 3.48	280 3.97	3.8 (s, 3H, $\overset{+}{N}$—CH_3), 2.75 (t, 2H, C_6H_5—CH_2, $J = 7$ Hz), 3.4 (t, 2H, Z, $J = 7$ Hz), 3.45 (s, 3H, O—CH_3), 6.6—7.8 (m, 8H, H_{arom})
VIII	240 3.50	280 3.29	4.09 (s, 3H, $\overset{+}{N}$—CH_3), 3.28 (t, 2H, C_6H_5—CH_2, $J = 8$ Hz), 3.68 (t, 2H, Z, $J = 8$ Hz), 7.27—8.1 (m, 8H, H_{arom})
IX	240 3.35	280 3.93	4.3 (t, 2H, $\overset{+}{N}$—CH_2, $J = 7$ Hz), 0.7 (t, 3H, CH_3, $J = 7$ Hz), 1.4—1.75 (m, 2H, CH_2—CH_3), 3.15 (t, 2H, C_6H_5—CH_2, $J = 8$ Hz), 3.6 (t, 2H, Z, $J = 8$ Hz), 6.9—7.7 (m, 9H, H_{arom})
X	240 3.42	280 3.99	4.2 (t, 2H, $\overset{+}{N}$—CH_2, $J = 8$ Hz), 0.7—1.8 (m, 7H, CH_2—CH_2), 2.95 (t, 2H, C_6H_5—CH_2, $J = 8$ Hz), 3.35 (t, 2H, Z, $J = 8$ Hz), 6.9—7.8 (m, 9H, H_{arom})
XI	240 3.48	285 2.99	5.0—5.5 (m, 4H, $\overset{+}{N}$—CH_2, =CH_2), 5.8—6.1 (m, 1H, —CH=), 3.4 (t, 2H, Z, $J = 8$ Hz), 2.9 (t, 2H, C_6H_5—CH_2, $J = 8$ Hz), 6.85—7.7 (m, 9H, H_{arom})
XII	240 3.24	285 3.02	5.75 (s, 2H, $\overset{+}{N}$—CH_2), 3.05 (t, 2H, C_6H_5—CH_2, $J = 9$ Hz), 2.7 (t, 2H, Z, $J = 8$ Hz), 6.8—7.8 (m, 14H, H_{arom})

Table 2 (Continued)

Compound	λ/nm log (ε/(m^2 mol^{-1}))		δ/ppm
XIII	240 3.34	280 3.24	5.5 (s, 2H, $\overset{+}{N}$—CH_2), 3.1 (t, 2H, C_6H_5—CH_2, J = 8 Hz), 3.35 (s, 3H, O—CH_3), 3.45 (t, 2H, Z, J = 8 Hz), 7.0—7.9 (m, 8H, H_{arom})
XIV	235 3.38	290 3.01	5.2 (s, 2H, $\overset{+}{N}$—CH_2), 0.85 (t, 3H, CH_3, J = 8 Hz), 2.9 (t, 2H, C_6H_5—CH_2, J = 8 Hz), 3.5 (t, 2H, Z, J = 8 Hz), 3.95 (q, 2H, O—CH_2, J = 8 Hz), 6.8—7.7 (m, 9H, H_{arom})
XV	235 3.32	285 2.96	5.4 (s, 2H, $\overset{+}{N}$—CH_2), 0.7 (t, 3H, CH_3, J = 7 Hz), 1.4—1.85 (m, 2H, $CH_3\underline{CH_2}$), 3.05 (t, 2H, C_6H_5—CH_2, J = 8 Hz), 3.6 (t, 2H, Z, J = 8 Hz), 3.95 (t, 2H, O—CH_2, J = 7 Hz), 6.9—7.7 (m, 9H, H_{arom})
XVI	235 3.35	285 3.04	5.2 (s, 2H, $\overset{+}{N}$—CH_2), 0.8 (d, 6H, CH_3, J = 7 Hz), 2.9 (t, 2H, C_6H_5—CH_2, J = 8 Hz), 3.45 (t, 2H, Z, J = 8 Hz), 5.0 (sp, 1H, O—CH, J = 7 Hz), 6.85—7.7 (m, 9H)
XVII	235 3.27	285 2.97	5.2 (s, 2H, $\overset{+}{N}$—CH_2), 2.8 (t, 2H, C_6H_5—CH_2, J = 8 Hz), 4.85 (s, 2H, O—CH_2), 3.4 (t, 2H, Z, J = 8 Hz), 6.8—7.7 (m, 14H, H_{arom})

Z =  CH_2.

organic molecules form CT complexes with iodine, which regularly behaves as an acceptor. Such complexes can be investigated mainly by UV spectroscopy, which however was not possible in our case, because the compound lost iodine during dissolution. The compound strongly absorbs in the near UV region and the absorption band exhibits a large half-width, which makes impossible to use this method. Although it is not possible to exclude completely the rise of a CT complex of 2-phenyl-3-allylbenzothiazolium iodide with I_2 molecule, we regard the origin of a salt of 2-phenyl-3-allylbenzothiazolium triiodide (*V*) as most probable. It is known that some inorganic iodides create with solution of iodine corresponding triiodides, *e.g.* KI_3 [5].

In the molecule of 2-(2-phenylethyl)benzothiazole the methylene groups in position 2 restrain the conjugation between the π-electrons of C=N bond in benzothiazole ring and those of the aromatic ring of substituent. Consequently the nitrogen of heterocycle is not deactivated and the quaternization reactions take place relatively easily in the medium of anhydrous acetonitrile or nitromethane to give yields of 45—76 %.

The synthesized compounds (Table 1) were tested for growth-regulating activity on *Triticum aestivum* L. The activity of compounds was substantially lower in comparison with 3-substituted 2-benzylbenzothiazolium salts [1], which means that the absence of methylene group or the prolongation by a further methylene group has a negative influence on the growth-regulating activity. A highly-noticeable activity was found only in the case of 2-[2-(4-nitrophenyl)ethyl]-3-methylbenzothiazolium iodide (*VIII*). The change of the iodide anion in compound *I* for a perchlorate (*II*) or a tetrafluoroborate anion (*III*) caused a decrease of activity (Table 3).

Experimental

The melting points determined on a Kofler block and the elemental analyses of synthesized compounds are given in Table 1.

The UV spectra of compounds were taken on a Specord M-40 UV/VIS instrument (Zeiss, Jena) in acetonitrile solution ($c = 5 \times 10^{-5}$ mol dm^{-3}). The ^{1}H NMR spectra were measured on a Tesla BS 587 (80 MHz) and a Jeol FX-100 (100 MHz) spectrometer. For measurement of ^{13}C NMR spectra a Varian VXR (75 MHz) instrument was used. The compounds were measured in hexadeuterodimethyl sulfoxide and trifluorodeuteroacetic acid using hexamethyldisiloxane as an internal standard.

The growth-regulating tests were aimed at the prolongative growth of primary roots of wheat (*Triticum aestivum* L.) according to a common method [6].

Table 3

Growth-regulating activity of the synthesized compounds tested on *Triticum aestivum* L.

Compound	Stimulation			Inhibition		
	$+\Delta l$/mm	$+\Delta l$/%	c/(mol dm^{-3})	$-\Delta l$/mm	$-\Delta l$/%	c/(mol dm^{-3})
I	0.37	7.64	10^{-9}	1.64	33.09	10^{-3}
II				1.95	34.04	10^{-3}
III	0.22	3.83	10^{-5}	2.52	43.98	10^{-3}
IV	0.23	4.25	10^{-5}	1.93	35.74	10^{-3}
V	0.33	6.26	10^{-7}	2.33	44.22	10^{-3}
VI	0.26	4.81	10^{-5}	0.97	17.97	10^{-3}
VII	0.33	5.75	10^{-5}	2.44	42.59	10^{-3}
VIII	0.70[d]	13.61	10^{-4}	1.25	24.32	10^{-3}
IX	0.21	3.81	10^{-4}	1.71	31.04	10^{-3}
X	0.46	8.76	10^{-5}	1.98	37.72	10^{-3}
XI	0.36	6.15	10^{-5}	2.46	42.06	10^{-3}
XII	0.21	3.88	10^{-9}	2.12	39.26	10^{-3}
XIII	0.47	8.95	10^{-4}	2.01	38.29	10^{-3}
XIV	0.15	2.84	10^{-5}	1.98	35.58	10^{-3}
XV	0.48	8.71	10^{-5}	2.24	40.66	10^{-3}
XVI	0.52	9.53	10^{-4}	2.45	44.47	10^{-3}
XVII	0.16	2.73	10^{-5}	2.68	45.82	10^{-3}
IAA[a]	5.93	100.33	10^{-5}	2.77	46.72	10^{-3}
2,4-D[b]	2.56	51.09	10^{-5}	2.01	40.12	10^{-3}
CCC[c]				1.75	32.35	10^{-3}

a) 2-Indolylacetic acid; *b*) 2,4-dichlorophenoxyacetic acid; *c*) (2-chloroethyl)trimethylammonium chloride. *d*) High-noticeable activity.

2-Phenyl- and 2-(2-phenylethyl)benzothiazoles

Hexamethyldisiloxane (48.7 g; 0.3 mol) and P_2O_5 (28.4 g; 0.2 mol) in anhydrous 1,2-dichloroethane (150 cm^3) were heated at boiling temperature till the solution became clear. To the originated trimethylsilyl ester of polyphosphoric acid a solution of 2-aminothiophenol (12.5 g; 0.1 mol) and benzoic acid (12.2 g; 0.1 mol) in anhydrous 1,2-dichloroethane (40 cm^3) was added dropwise under boiling and stirring. After 3 h the reaction mixture was cooled to room temperature and slowly, under stirring poured into an ice-solution of KOH (28 g; 0.5 mol) in water (1000 cm^3). The mixture was stirred for 30 min and the separated aqueous layer was extracted with 1,2-dichloroethane or chloroform. The fused organic portions after drying were distilled off and the residue was crystallized from ethanol. Yield of 2-phenylbenzothiazole was 75 %, m.p. = 112—114 °C was identical with that obtained at using of polyphosphoric acid [7].

2-(2-Phenylethyl)benzothiazole was prepared from 3-phenylpropanoic acid by an analogous procedure. Yield = 68 %, m.p. = 59—61 °C (ether—petroleum ether, $\varphi_r = 1:1$). For $C_{15}H_{14}NS$ ($M_r = 240.34$) w_i(calc.): 75.06 % C, 5.87 % H, 5.83 % N; w_i(found): 74.84 % C, 5.97 % H, 5.64 % N.

2-Phenyl-3-alkylbenzothiazolium iodide I and IV

2-Phenylbenzothiazole (2.1 g; 0.01 mol) and methyl iodide (7 g; 0.05 mol) in anhydrous dimethylformamide (15 cm^3) was heated for 24 h at 60—70 °C. The crystalline part of 2-phenyl-3-methylbenzothiazolium iodide (*I*) was washed with acetone and crystallized from methanol.

In the analogical way 2-phenyl-3-ethylbenzothiazolium iodide (*IV*) was prepared.

2-Phenyl-3-methylbenzothiazolium salts II and III

To compound *I* (3.5 g; 0.01 mol) dissolved in warm water (10 cm^3) $NaClO_4$ or $NaBF_4$ (0.02 mol) was added and heated for 30 min at boiling temperature. After cooling the precipitate of appropriate perchlorate (*II*) or tetrafluoroborate (*III*) was crystallized from methanol.

2-Phenyl-3-allylbenzothiazolium triiodide (V)

2-Phenylbenzothiazole (4.2 g; 0.02 mol) and allyl iodide (10 g; 0.06 mol) in anhydrous dimethylformamide (20 cm^3) were heated for 40 h at 75 °C. After cooling to room temperature anhydrous ether (50 cm^3) cooled to -5 °C was added. To the oily layer dissolved in anhydrous methanol (15 cm^3) charcoal was added and heated to boiling temperature. After filtering off ether (10 cm^3) was added and the mixture was crystallized under cooling.

3-Substituted 2-(2-phenylethyl)benzothiazolium salts VI—XVII

2-(2-Phenylethyl)benzothiazole (2.3 g; 0.01 mol) and methyl iodide (2.8 g; 0.02 mol) in anhydrous acetonitrile or nitromethane (15 cm^3) were heated for 5 h at 60—70 °C. The isolated crystalline portion of 2-(2-phenylethyl)-3-methylbenzothiazolium iodide (*VI*) was washed with ether or THF.

Analogously the compounds *VII—XVII* were prepared.

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