Benzothiazole compounds XXXV. Synthesis of 3-substituted 2-benzylbenzothiazolium salts and their growth-regulating effect on *Triticum aestivum* L.

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Received 18 January 1989

Dedicated to Professor P. Kristian, DrSc., in honour of his 60th birthday

Synthesis of 3-substituted 2-benzylbenzothiazolium salts by the reaction of 2-benzylbenzothiazole with halo derivatives in CH_3CN has been described. Treatment of 2-benzylbenzothiazole with ethyl iodide resulted in an anomalous reaction, giving 3-ethylbenzothiazolium iodide and 1,2-diphenylethane.

Some of the synthesized compounds showed evident or highly significant growth-regulating activity on coleoptiles of *Triticum aestivum* L.

Описано получение солей замещенного в положении 3 2-бензилбензотиазолия путем взаимодействия 2-бензилбензотиазола с галоид--производными в CH_3CN. Реакция 2-бензилбензотиазола с иодистым этилом проходит аномально и ведет к образованию иодида 3-этилбензотиазолия и 1,2-дифенилэтана.

Некоторые из синтезированных соединений проявляли очевидную или высоко значимую активность по регуляции роста колеоптил *Triticum aestivum* L.

In the previous works it was found that some benzothiazole derivatives exhibited growth-regulating effect, dependent on substituents in positions 2 and 3 [1, 2]. The present work is a continuation of study in this field and describes the synthesis of 3-substituted 2-benzylbenzothiazolium salts. Of this type of compounds 2-benzyl-3-methylbenzothiazolium iodide (*I*), 2-benzyl-3-methylbenzothiazolium *p*-toluenesulfonate [3], and 2-benzyl-3-ethylbenzothiazolium iodide (*IV*) [4] have been synthesized so far. The syntheses were carried out in connection with study of their spectra and colouration. It was observed earlier that benzyl group in comparison with other groups brought about, in some cases, a significant increase in stimulation effect on plant growth [5, 6].

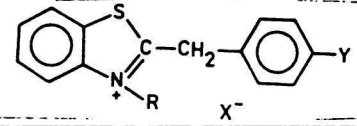
The starting 2-benzylbenzothiazole was prepared from 2-aminothiophenol

and phenylacetic acid in anhydrous 1,2-dichloroethane in the presence of trimethylsilyl polyphosphate [7]. The most suitable medium for preparation of 3-substituted 2-benzylbenzothiazolium salts proved to be anhydrous acetonitrile where relatively pure salts precipitated already in the course of the reaction. It was sufficient to wash these products with anhydrous ether or tetrahydrofuran. In anhydrous dimethylformamide a lot of noticeably coloured oily or pitchy by-products were formed. The methylene group (position 2) in the 2-benzylbenzothiazole molecule makes impossible the conjugation of π-electrons of the C=N bond in the thiazole ring with π-electrons of the aromatic ring of the substituent. Deactivation of nitrogen in the heterocycle does not take place and quaternization reactions proceed relatively easily in spite of sterical hindrance. The corresponding quaternary salts were prepared successfully with a wide range of alkylation agents in relatively good yields (45—79 %).

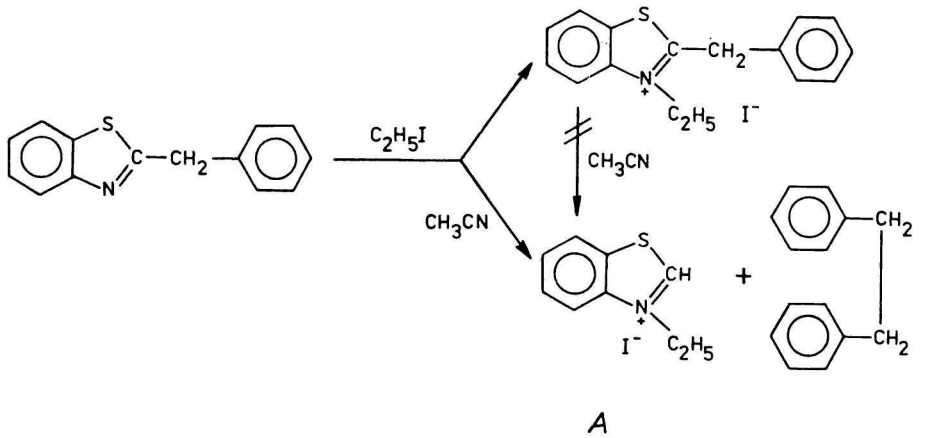
Different reaction course was observed only in treatment of 2-benzylbenzothiazole, 2-(4-nitrophenylmethyl)benzothiazole, and 2-(4-methoxyphenylmethyl)benzothiazole with ethyl iodide. By the described method in CH_3CN after elimination of the benzyl group in position 2, 3-ethylbenzothiazolium iodide was formed. The ^{1}H NMR spectrum of this product showed a triplet at $\delta = 1.1$ ppm ($J = 7$ Hz), a quartet at $\delta = 4.5$ ppm ($J = 7$ Hz), a multiplet at $\delta = 7.5$—7.9 ppm, and a singlet at $\delta = 9.5$ ppm. The ratio of signal intensities was 3 : 2 : 4 : 1. Elemental analysis and melting point were in accordance with the results in [8].

When heating 2-benzylbenzothiazole with ethyl iodide without a solvent, 2-benzyl-3-ethylbenzothiazolium iodide (*IV*) was isolated. The spectrum of this derivative revealed a triplet at $\delta = 1.2$ ppm ($J = 7$ Hz), a singlet at $\delta = 4.4$ ppm, a quartet at $\delta = 4.5$ ppm ($J = 7$ Hz), and a multiplet at $\delta = 7.1$—7.8 ppm. The ratio of signal intensities was 3 : 2 : 2 : 9. The results of analysis and melting point corresponded to the literature data [4]. The reaction course is illustrated in Scheme 1. Heating of ethyl iodide in CH_3CN resulted in elimination of HI which entered the reaction with 2-benzylbenzothiazole under formation of benzothiazole and benzyl iodide. Benzothiazole at the given conditions reacted with ethyl iodide to give 3-ethylbenzothiazolium iodide (*A*, 15 % yield), while benzyl iodide was converted by radical mechanism to 1,2-diphenylethane which was proved in the reaction mixture by gas chromatography. In a control experiment benzyl iodide was heated in CH_3CN at 60 °C and it was found that the amount of 1,2-diphenylethane increased with time. It was found further that 2-benzyl-3-ethylbenzothiazolium iodide on heating in CH_3CN or DMF with or without ethyl iodide was not converted into 3-ethylbenzothiazolium iodide. It means that elimination of C_2H_5I did not take place and consequently, the described reaction could not proceed. The synthesized compounds are presented in Table 1. The compound *IV* was synthesized for biological tests.

Table 1. Characterization of the synthesized compounds



Compound	R	Y	X	Formula	M_r	w_i(calc.)/% / w_i(found)/%					Yield	M.p.
						C	H	N	S	X	%	°C
I	CH_3	H	I	$C_{15}H_{14}INS$	367.28	49.05	3.84	3.82	8.73	34.55	79	219—221
						48.85	3.78	3.75	8.61	34.65		
II	CH_3	OCH_3	I	$C_{16}H_{16}INOS$	397.31	48.37	4.06	3.53	8.07	31.94	51	175—180
						47.86	3.95	3.43	8.00	32.13		
III	CH_3	NO_2	I	$C_{15}H_{13}INO_2S$	412.32	43.70	3.18	6.81	7.78	30.78	67	237—241
						43.75	3.06	6.95	7.78	31.02		
IV	C_2H_5	H	I	$C_{16}H_{16}INS$	381.27	50.40	4.23	3.67	8.41	33.28	62	181—184
						50.19	4.10	3.34	8.27	33.18		
V	C_3H_7	H	I	$C_{17}H_{18}INS$	395.30	51.65	4.59	3.54	8.11	32.10	49	170—174
						51.78	4.60	3.27	8.17	32.29		
VI	$CH_2CH{=}CH_2$	H	I	$C_{17}H_{16}INS$	393.39	51.91	4.10	3.57	8.15	32.26	57	161—164
						51.67	3.99	3.68	8.11	32.08		
VII	C_4H_9	H	I	$C_{18}H_{20}INS$	409.33	52.82	4.92	3.42	7.83	31.00	45	141—144
						52.63	4.93	3.22	7.78	31.32		
VIII	$CH_2C_6H_5$	H	Br	$C_{22}H_{20}BrNS$	410.42	64.38	4.91	3.42	7.81	19.47	59	181—185
						64.26	4.71	3.41	7.70	19.71		
IX	CH_2COOCH_3	H	Br	$C_{17}H_{16}BrNO_2S$	378.36	53.98	4.26	3.70	8.48	21.12	61	172—176
						53.64	4.14	3.95	8.23	21.13		
X	$CH_2COOC_2H_5$	H	Br	$C_{18}H_{18}BrNO_2S$	392.36	53.10	4.62	3.58	8.17	20.37	64	187—191
						54.87	4.59	3.30	7.98	20.63		
XI	$CH_2COOC_3H_7$	H	Br	$C_{19}H_{20}BrNO_2S$	406.34	56.16	4.96	3.45	7.89	19.66	57	200—203
						56.03	4.83	3.44	8.05	19.89		
XII	$CH_2COOC_3H_7$-i	H	Br	$C_{19}H_{20}BrNO_2S$	406.34	56.16	4.96	3.45	7.89	19.66	53	220—223
						55.96	4.95	3.25	7.78	19.83		
XIII	$CH_2COOCH_2C_6H_5$	H	Br	$C_{23}H_{20}BrNO_2S$	454.39	63.63	4.58	3.08	7.06	17.59	63	160—164
						63.42	4.51	3.00	6.95	17.86		



A

Scheme 1

The IR spectra of 2-benzyl-3-alkoxycarbonylmethylbenzothiazolium salts (*IX—XIII*) showed the ν(C=O) band at $\tilde{\nu} = 1745\,\mathrm{cm}^{-1}$, bands belonging to stretching vibrations ν(C=C) and ν(C=N) at $\tilde{\nu} \approx 1505\,\mathrm{cm}^{-1}$ and $\tilde{\nu} \approx 1600\,\mathrm{cm}^{-1}$, and bands belonging to bending vibrations of CH_3 and CH_2 groups at $\tilde{\nu} \approx 1320\,\mathrm{cm}^{-1}$, $\tilde{\nu} \approx 1390\,\mathrm{cm}^{-1}$, and $\tilde{\nu} \approx 1470\,\mathrm{cm}^{-1}$. The bands were of low intensity and their positions were little influenced by change of the substituents in position 3 of the thiazole ring, which made the structural study of benzothiazolium salts by IR spectroscopy difficult. The ^{1}H NMR spectra (Table 2) revealed typical signals of hydrogens of CH_2 or CH_3 groups in positions 2 and 3 of the thiazole ring. The signals of N^+—CH_2 or N^+—CH_3 groups appeared at $\delta = 3.7$—4.5 ppm for alkyls and at $\delta = 5.0$—6.27 ppm for allyl, benzyl, and alkoxycarbonylmethyls. The singlets of CH_2 groups in position 2 were observed in the region of $\delta = 4.0$—4.9 ppm. When the substituents in positions 2 and 3 were the same (*e.g.* in compound *VIII*), the signals for α-hydrogens in position 2 were observed at higher field than for those in position 3.

3-Substituted 2-benzylbenzothiazolium salts represent an interesting group of compounds, mainly from the point of view of study of growth stimulation of the root system of wheat (*Triticum aestivum* L.). Of 13 compounds, 4 (*IV*, *V*, *VI*, *IX*) were shown to be highly active and the activity of *II* and *XIII* was evident (Table 3). The stimulation activity of 2-benzyl-3-methylbenzothiazolium iodide (*I*) was negligible. However, introduction of a methoxy group into *p*-position of the benzyl moiety (*II*) brought about an increase of the activity value. When introducing an NO_2 group into *p*-position of the benzyl moiety (*III*), only inhibitory activity was observed at all concentrations tested (10^{-13}—$10^{-3}\,\mathrm{mol\,dm}^{-3}$). Change of methyl for ethyl group in position 3 (*IV*) brought

Table 2. UV and ^{1}H NMR spectral data of the synthesized benzothiazolium salts

Compound	λ/nm $\log(\varepsilon/(\mathrm{dm^3\,mol^{-1}\,cm^{-1}}))$		δ/ppm
I	245	350	4.5 (s, 3H, N^+—CH_3); 4.9 (s, 2H, CH_2);
	4.369	4.340	7.4—8.2 (m, 9H, H_{arom})
II	245	340	4.19 (s, 3H, N^+—CH_3); 4.6 (s, 2H, Z—CH_2);
	4.421	4.313	3.83 (s, 3H, O—CH_3); 6.9—7.9 (m, 8H, H_{arom})
III	245	490	4.0 (s, 3H, N^+—CH_3); 4.65 (s, 2H, Z—CH_2);
	4.275	4.414	7.2—8.1 (m, 8H, H_{arom})
IV	245	350	4.5 (q, 2H, N^+—CH_2, J = 7 Hz); 1.2 (t, 3H, CH_3, J = 7 Hz);
	4.396	4.369	4.4 (s, 2H, Z—CH_2); 7.1—7.8 (m, 9H, H_{arom})
V	245	350	4.4 (t, 2H, N^+—CH_2, J = 7 Hz); 0.7 (t, 3H, CH_3, J = 9 Hz);
	4.412	4.316	4.45 (s, 2H, Z—CH_2); 1.4—1.8 (m, 2H, CH_2—CH_3); 7.0—7.7 (m, 9H, H_{arom})
VI	245	350	5.0—5.5 (m, 4H, $=CH_2$, N^+—CH_2); 5.85—6.2 (m, 1H, —CH=);
	4.390	4.340	4.4 (s, 2H, Z—CH_2); 7.0—7.7 (m, 9H, H_{arom})
VII	245	350	4.4 (t, 2H, N^+—CH_2, J = 8 Hz); 0.6—1.7 (m, 7H, CH_2—C_3H_7);
	4.374	4.195	4.4 (s, 2H, Z—CH_2); 7.0—7.7 (m, 9H, H_{arom})
VIII	245	300	6.27 (s, 2H, N^+—CH_2); 4.94 (s, 2H, Z—CH_2);
	4.335	4.034	7.4—8.3 (m, 14H, H_{arom})
IX	240	340	5.35 (s, 2H, N^+—CH_2); 3.4 (s, 3H, O—CH_3);
			4.4 (s, 2H, Z—CH_2); 7.0—7.6 (m, 9H, H_{arom})
X	240	340	5.35 (s, 2H, N^+—CH_2); 4.0 (q, 2H, O—CH_2, J = 8 Hz);
	4.131	4.344	1.0 (t, 3H, CH_3, J = 8 Hz); 7.1—7.7 (m, 9H, H_{arom})
XI	240	340	5.4 (s, 2H, N^+—CH_2); 0.65 (t, 3H, CH_3, J = 7 Hz);
	4.163	4.332	1.4—1.8 (m, 2H, CH_2—CH_3); 3.8 (t, 2H, O—CH_2, J = 8 Hz);
			4.4 (s, 2H, Z—CH_2); 7.3—7.8 (m, 9H, H_{arom})
XII	240	340	5.9 (s, 2H, N^+—CH_2); 5.3 (q, 1H, O—CH, J = 8 Hz);
	4.106	4.065	1.43 (d, 6H, CH_3, J = 8 Hz); 4.9 (s, 2H, Z—CH_2); 7.2—7.8 (m, 9H, H_{arom})
XIII	240	340	5.51 (s, 2H, N^+—CH_2); 5.45 (s, 2H, O—CH_2); 4.9 (s, 2H, Z—CH_2); 7.2—8.3 (m, 14H, H_{arom})

Z—CH_2 = ⩾—CH_2.

Table 3

Growth-regulation effects of the synthesized compounds on *Triticum aestivum* L.

Compound	Stimulation			Inhibition		
	$\triangle l$/mm	%	c/(mol dm^{-3})	$-\triangle l$/mm	%	c/(mol dm^{-3})
I	0.28	5.45	10^{-7}	0.86	16.77	10^{-3}
II	0.72*	14.00	10^{-4}	1.60	31.13	10^{-3}
III				2.08	38.52	10^{-3}
IV	0.62**	11.25	10^{-5}	1.87	33.94	10^{-3}
	0.43*	7.80	10^{-4}			
V	0.73**	13.24	10^{-4}	1.74	31.58	10^{-3}
VI	1.06**	20.11	10^{-5}	1.78	33.78	10^{-3}
	1.04*	19.73	10^{-4}			
VII				1.83	34.86	10^{-3}
VIII	0.19	3.70	10^{-5}	1.41	27.49	10^{-3}
IX	1.25**	24.31	10^{-4}	1.86	36.19	10^{-3}
X	0.49	8.37	10^{-5}	2.59	44.28	10^{-3}
XI				2.48	43.29	10^{-3}
XII				2.65	46.25	10^{-3}
XIII	0.57*	11.08	10^{-9}	1.92	37.36	10^{-3}
IAA	5.93	100.33	10^{-5}	2.77	46.72	10^{-3}
2,4-D	2.56	51.09	10^{-5}	2.01	40.12	10^{-3}
CCC				1.75	32.35	10^{-3}

IAA — 2-indolylacetic acid; 2,4-D — 2,4-dichlorophenoxyacetic acid; CCC — 2-chloroethyltrimethylammonium chloride.

* Evident activity. ** Highly-evident activity.

about a substantial increase of stimulation activity. 2-Benzyl-3-ethylbenzothiazolium iodide was shown to be active at $c = 10^{-4}$ mol dm^{-3} and highly active at $c = 10^{-5}$ mol dm^{-3}. The wide range of activity is advantageous in practical applications. 2-Benzyl-3-propylbenzothiazolium iodide (*V*) showed even higher activity, though only at $c = 10^{-4}$ mol dm^{-3}. Lengthening of the alkyl chain in position 3 in 2-benzyl-3-butylbenzothiazolium iodide (*VII*) led to total loss of stimulation activity. The double bond in 2-benzyl-3-allylbenzothiazolium iodide (*VI*), in comparison to *V*, brought about a significant increase of the studied activity, while introduction of benzyl group into positions 2 and 3 (*VIII*) caused almost total loss of stimulation activity.

Of the series of 2-benzyl-3-alkoxycarbonylmethylbenzothiazolium salts, only 2-benzyl-3-methoxycarbonylmethylbenzothiazolium bromide (*IX*) was observed to show a stimulation activity, which represented the highest value (24.31 %) in the whole group. Change of methoxy for ethoxy group (*X*) led to

substantial decrease of stimulation activity (0—15.94 %). With 2-benzyl-3--propoxycarbonylmethylbenzothiazolium bromide (*XI*) and 2-benzyl-3--isopropoxycarbonylmethylbenzothiazolium bromide (*XII*) stimulation activity was not observed at all.

Experimental

Melting points were established on a Kofler block and analytical values of the synthesized compounds are presented in Table 1. IR spectra were measured in nujol with a Specord 75 IR spectrophotometer calibrated with a polystyrene foil. UV spectra were measured in acetonitrile ($c = 5 \times 10^{-5}$ mol dm^{-3}) with a Specord M 40 UV VIS apparatus and ^{1}H NMR spectra with a Tesla 587 (80 MHz) and a Jeol FX-100 (100 MHz) spectrometers. ($^2H_6$)Dimethyl sulfoxide and (^{2}H)trifluoroacetic acid were used as solvents and hexamethyldisiloxane as internal standard. Gas liquid chromatography was performed on a Chrom 4 apparatus using an XE-60 packed column.

Biological tests were carried out according to [9]. 2-Indolylacetic acid (IAA), 2,4-dichlorophenoxyacetic acid (2,4-D), and 2-chloroethyltrimethylammonium chloride (CCC) were used as standards. Laboratory tests were performed at 10^{-13}—10^{-3} mol dm^{-3} concentrations. IAA is highly active only at laboratory conditions when tested in the dark or at red light. At daylight it decomposes and its activity is lower.

2-Benzyl-3-methylbenzothiazolium iodide (I)

2-Benzylbenzothiazole (4.5 g; 0.02 mol) and methyl iodide (6 g; 0.04 mol) were heated in anhydrous acetonitrile (15 cm^3) at 60—70 °C for 5 h. After cooling, the crystals were washed with anhydrous ether or THF.

The compounds *II*, *III*, *V*—*XIII*, and *A* were prepared by similar way.

2-Benzyl-3-ethylbenzothiazolium iodide (IV)

2-Benzylbenzothiazole (4.5 g; 0.02 mol) and ethyl iodide (10 g; 0.06 mol) were heated without any solvent at 60 °C for 6 h. The solid compound was washed with THF several times and dried.

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Translated by A. Kardošová