Synthesis and biological activity of 6-X-2-(4-R-phenoxyacetylamino)benzothiazole derivatives

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6-X-2-(4-R-Phenoxyacetylamino)benzothiazoles have been prepared by acylation of 6-X-2-aminobenzothiazole with phenoxyethanoyl chloride and 4-chlorophenoxyethanoyl chloride. The prepared amides were reduced with $LiAlH_4$ and the structures of the products were confirmed by means of their IR and NMR spectra. The compounds were tested for herbicidal and antifungal activities; some of them exhibited high herbicidal activity.

6-X-2-(4-R-Феноксиацетиламино)бензотиазолы были получены ацилированием 6-X-2-аминобензотиазолов феноксиэтаноилхлоридом и 4-хлорфеноксиэтаноилхлоридом. Полученные амиды были восстановлены $LiAlH_4$ и структуры продуктов были подтверждены на основании их ИК- и ЯМР-спектров. У соединений была проверена их гербицидная и фунгицидная активности. Некоторые из них проявляли высокую гербицидную активность.

In the present work the preparation of 15 new derivatives of 2-aminobenzothiazole is described. As known from the literature [1, 2] and practice, the benzothiazole ring is involved in several biologically active compounds. For example, Benztiazuron and Metabenztiazuron, derivatives of 2-aminobenzothiazole, are utilized as preemergent herbicides.

2-Aryloxyethanoic acids belong to biologically highly effective compounds. They are herbicides known as growth regulators. Combination of both biologically active systems is of importance for studies of the dependence of biological activity on the structures of both benzothiazole derivatives and aryloxyalkanecarboxylic acids.

2-Aminobenzothiazole occurs in two tautomeric forms [3]. Both forms may enter the acylation reaction. Acylation with aryloxyethanoyl chlorides, reduction of the obtained products with $LiAlH_4$, and proving their structures by means of their

IR and ^{1}H NMR spectra completed the knowledge about acylation of the tautomeric system of 2-aminobenzothiazole.

Quantitative acylation of 2-aminobenzothiazole with aryloxyethanoyl chlorides into the position 2 can be accomplished in pyridine at 0 °C; at 5 °C also the 6-nitro derivative is quantitatively acylated. The reaction is very sensitive to temperature and it is necessary to keep it low, otherwise, the product obtained is nonuniform.

In the IR spectra of the prepared amides (Table 1) bands of medium intensity belonging to stretching vibrations of NH group appeared at $\tilde{\nu} = 3345$—3385 cm^{-1}. As evident from the spectra of the individual derivatives, this band is dependent on the substituent in the position 6. The stretching vibrations of the C=O group were observed as intensive maxima at $\tilde{\nu} = 1680$—1700 cm^{-1}. With the reduced derivatives the $\tilde{\nu}$(NH) were displaced towards lower wavenumbers (region of 3208—3230 cm^{-1}), the absorption bands in the region of the amide carbonyls were absent, however, intensive bands attributable to $\tilde{\nu}$(C=N) of 2-alkylaminobenzothiazole occurred at 1614—1620 cm^{-1}. The observed maxima in the IR spectra were in accordance with the literature data for 2-amino-, 2-acylamino-, and 2-alkylaminobenzothiazoles [4—6].

In the ^{1}H NMR spectra the signals of protons of the O—CH_2—CO— group appeared as singlets in the region of $\delta_r = 4.85$—4.92 ppm. The signals assigned to aromatic protons at $\delta_r = 6.75$—9.00 ppm were multiplets. After reduction, the spectra of 6,7-benzo-2-phenoxyethylaminobenzothiazole exhibited a triplet at $\delta_r = 4.15$ ppm and a doublet at $\delta_r = 3.87$ ppm proving the change in the structure after reduction.

The prepared compounds were tested for antifungal activity according to the method in [7] on the following cultures of dermatophytes: *Trichophyton rubrum, Trichophyton megninii, Trichophyton mentagrophytes, Trichophyton Kaufmann—Wolf, Trichophyton verrucosum, Trichophyton violaceum, Microsporum gypseum, Microsporum cookei,* and *Epidermophyton floccosum.* The compounds *I—XV* up to MIC = 100 μg cm^{-3} have not inhibited the growth of fungi.

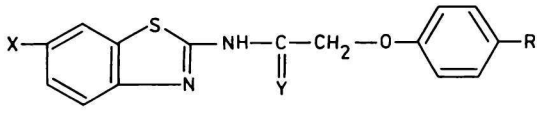
With the compounds *I—V* standard herbicidal tests of the first and second screenings were carried out after the method in [8]. The compounds *I—III* in 1.5 g m^{-2} and 0.5 g m^{-2} doses totally inhibited the growth of *Lepidium sativum* and *Sinapis alba.* The compound *V* was inactive and the compound *IV* totally inhibited the growth only at higher concentrations. Evaluation of herbicidal tests (Table 2) showed that the compounds prepared were less active than the starting aryloxyethanoic acids.

Experimental

Infrared spectra of suspensions in paraffin oil were measured on a Specord 75 IR (Zeiss, Jena) spectrophotometer in the range of $\tilde{\nu} = 400$—4000 cm^{-1}.

Table 1

6-X-2-(4-R-Phenoxyacetylamino)benzothiazoles *I*—*X* and 6-X-2-(4-R-Phenoxyethylamino)benzothiazoles *XI*—*XV*



I—*X* Y = O
XI—*XV* Y = H_2
I—*VII*, *XI*—*XIII* R = Cl
VIII—*X*, *XIV*, *XV* R = H

Compound	X	Formula M_r	w_i(calc.)/% w_i(found)/%					M.p./°C	ν(NH)	ν(CO)	ν(C—O—C)	ν(C=N)
			C	H	N	Cl	S		$\tilde{\nu}$/cm^{-1}			
I	CH_3	$C_{16}H_{13}O_2N_2ClS$	57.74	3.94	8.42	10.65	9.63	202—203	3343	1686	1260	—
		332.8	57.85	3.84	8.13	10.60	9.41					
II	Cl	$C_{15}H_{10}O_2N_2Cl_2S$	51.04	2.85	7.93	20.07	9.08	190	3372	1690	1271	—
		353.2	50.84	2.80	8.08	20.35	9.24					
III	CH_3CONH—	$C_{17}H_{14}O_3N_3ClS$	54.33	3.76	11.18	9.43	8.51	263	3243	1679	1271	—
		375.8	54.65	3.86	11.38	9.62	8.81		3265	1700 sh		
IV	NO_2	$C_{15}H_{10}O_4N_3ClS$	49.53	2.77	11.15	9.74	8.81	208	3278	1686	1271	—
		363.8	49.49	2.61	11.43	9.87	8.89					
V	SCN	$C_{16}H_{10}O_2N_3S_2Cl$	51.13	2.68	11.18	9.43	17.06	241—242	3371	1690	1271	—
		375.8	51.28	2.66	11.36	9.59	17.12					
VI	Br	$C_{15}H_{10}O_2N_2BrClS$	45.31	2.54	7.04	8.91	8.06	185	3372	1690	1271	—
		397.7	45.44	2.56	7.14	8.98	8.16					
VII		$C_{19}H_{13}O_2N_2ClS$	61.87	3.55	7.60	9.61	8.69	197—198	3364	1657	1271	—
		368.0	61.90	3.53	7.67	9.70	8.67					

Table 1 (Continued)

Compound	X	Formula M_r	w_i(calc.)/% w_i(found)/%					M.p./°C	ν(NH)	ν(CO)	ν(C—O—C)	ν(C=N)
			C	H	N	Cl	S		$\tilde{\nu}$/cm^{-1}			
VIII	CH_3	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39	—	10.75	175—176	3378	1690	1271	—
		298.3	64.52	4.81	9.40	—	10.66			1700		
IX	NO_2	$C_{16}H_{11}N_3O_4S$	54.71	3.37	12.76	—	9.73	329	3314	1680	1276	—
		329.3	54.89	3.23	12.95	—	9.69					
X		$C_{19}H_{14}N_2O_2S$	68.32	4.13	8.42	—	9.68	165	3364	1686	1270	—
		334.3	68.51	4.28	8.59	—	9.60					
XI	Br	$C_{15}H_{12}N_2ClOSBr$	46.96	3.15	7.30	9.24	8.35	130—132	3428	—	1275	1620
		383.8	47.08	3.12	7.28	9.46	8.40		3228			
XII	Cl	$C_{15}H_{12}N_2Cl_2OS$	53.11	3.56	8.26	20.90	9.45	174—175	3228	—	1270	1614
		339.2	53.16	3.42	8.20	21.20	9.38					
XIII	CH_3	$C_{16}H_{15}N_2ClOS$	60.28	4.74	8.78	11.12	10.60	142—143	3171	—	1245	—
		318.8	60.34	4.81	8.61	11.11	10.29					
XIV	CH_3	$C_{16}H_{16}N_2OS$	67.58	5.67	9.85	—	11.27	125—126	3208	—	1243	1614
		284.3	67.74	5.63	9.90	—	11.36					
XV		$C_{19}H_{16}N_2OS$	71.23	5.03	8.74	—	10.01	150	3228	—	1230	1624
		320.4	71.41	5.15	8.64	—	10.12					

^{1}H NMR: δ_r/ppm: *IV* 4.925 (2H, s), 6.87—8.36 (10H, m); *VI* 4.875 (2H, s), 6.82—8.25 (8H, m); *VII* 4.900 (2H, s), 6.87—9.00 (8H, m); *VIII* 4.925 (2H, s), 6.80—8.02 (12H, m); *IX* 2.375 (3H, s), 4.850 (2H, s), 6.65—7.75 (8H, m); *X* 4.900 (2H, s), 6.75—9.00 (9H, m); *XV* 3.875 (2H, d), 4.150 (2H, t), 6.75—8.50 (12H, m).

* 2-(4-Chlorophenoxyacetylamino)naphtho[1,2-*d*]thiazole; ** 2-phenoxyacetylaminonaphtho[1,2-*d*]thiazole; *** 2-phenoxyethylaminonaphtho[1,2-*d*]thiazole.

Table 2

Herbicidal activity of the prepared compounds

Plant	Dose/(g m^{-2})	*I*	*II*	*III*	*V*	*VII*
		A/B	A/B	A/B	A/B	A/B
Avena sativa	1.5	2/2	0/2	1/2	0/0	0/0
	0.5	2/2	0/0	0/0	0/0	0/0
Fagopyrum vulgare	1.5	2/5	0/3	2/2	0/0	0/0
	0.5	2/4	0/2	1/2	0/0	0/0
Panicum miliaceum	1.5	5/5	3/4	4/5	0/0	3/4
	0.5	4/4	3/4	4/4	0/0	0/0
Lepidium sativum	1.5	5/5	5/5	5/5	0/0	5/5
	0.5	5/5	5/5	5/5	0/0	0/5
Sinapis alba	1.5	5/5	5/5	5/5	0/0	5/5
	0.5	5/5	5/5	5/5	0/0	4/4
Brassica napus	0.5	3/–	5/–	5/–	—	—

Evaluation: 0 — plants not damaged; 5 — plants perished; — the compound not tested on the respective plant. A — Evaluation after 2 weeks; B — evaluation after 4 weeks.

^{1}H NMR spectra of saturated solutions of the samples in DMSO were measured on a Tesla BS 487 A spectrometer at $\nu = 80$ MHz using tetramethylsilane as standard.

The starting 6-X-2-aminobenzothiazole derivatives were prepared according to [9, 10].

6-X-2-(4-R-Phenoxyacetylamino)benzothiazoles (I—X)

6-X-2-Aminobenzothiazole (5 mmol) was dissolved in pyridine (15 cm^3) and to the cooled solution (0 °C) the solution of aryloxyethanoyl chloride (7 mmol) in tetrahydrofuran (20 cm^3) was added dropwise under stirring. After the addition was completed, the temperature of the reaction mixture was raised to 25 °C (in the case of the 6-NO_2 derivative to 35 °C) and the mixture was stirred for 2 h. Then crushed ice (100 cm^3) was added and the precipitate was sucked, washed with water and the solution of $NaHCO_3$, and recrystallized from acetic acid. Characterization of the prepared compounds is in Table 1.

6-X-2-(4-R-Phenoxyethylamino)benzothiazoles (XI—XV)

To 6-X-2-(4-R-phenoxyacetylamino)benzothiazole (1 mmol) in diethyl ether (25 cm^3) $LiAlH_4$ (0.2 g) in diethyl ether (20 cm^3) was added with stirring at 25 °C and the mixture was refluxed for 2 h. After the reaction was completed, the mixture was poured onto crushed ice and ether was distilled off *in vacuo*. The precipitate was filtered off and boiled with ethanol

3 times. The filtrate was evaporated and after cooling, the precipitate was filtered off and crystallized from the mixture of benzene—ether. Characterization of the prepared compounds is in Table 1.

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