Synthesis and pesticidal activity of acyl derivatives of 4-chloro-2-aminobenzothiazole and the products of their reduction

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4-Chloro-2-(acylamino)benzothiazoles were prepared by acylation of 4-chloro-2-aminobenzothiazole with acyl chlorides. The products were reduced by $LiAlH_4$ to afford 4-chloro-2-(alkylamino)- or 4-chloro-2-(aryloxyalkylamino)benzothiazoles, which in the following step undergo again acylation and reduction. The prepared compounds were tested for herbicidal, insecticidal, and fungicidal activity.

The present work was aimed to prepare new compounds possessing potential pesticidal activity. The synthetic goal of the work was to investigate the conditions of acylation and reduction in the case of relatively deactivated system of the heterocyclic amine and to find out the reaction site of the acylation of secondary 4-chloro-2-R-aminobenzothiazole.

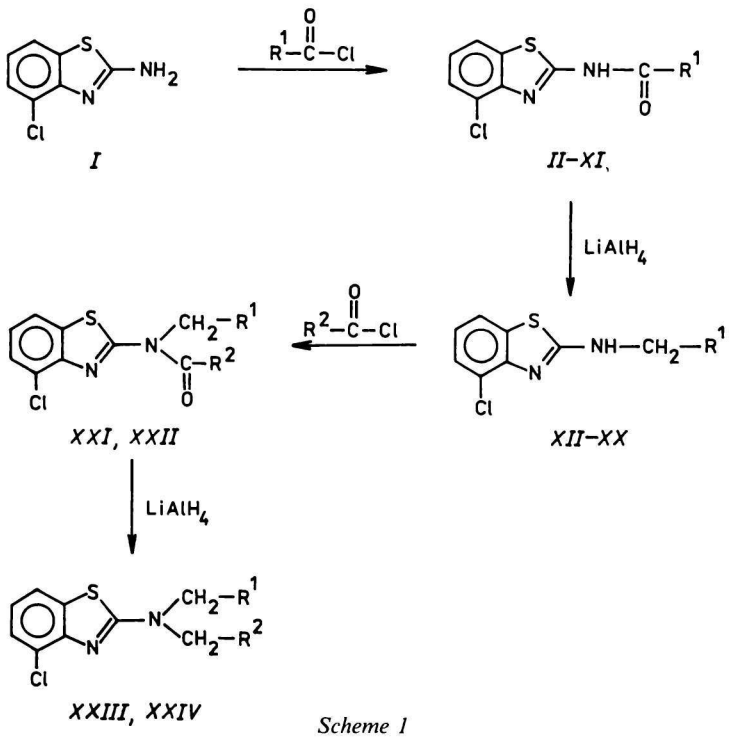
The work is a continuation of our publications devoted to the acylation of benzothiazole derivatives with the aim to investigate their biological activity [1—5] as well as to seek for the possibilities of their synthetic applications [6, 7].

Benzothiazoles are known as biologically active compounds. This is true also in the case of their 2-amino derivatives. *E.g.* 4-chloro-2-imino-3-benzothiazolineacetic acid is used as a growth-regulating agent [8] and both 6-X-2-(aryloxyacetamido)- and 6-X-2-(aryloxyethylamino)benzothiazoles [1] exhibit a herbicidal activity. The activity is influenced by the type of substituent in position 6. 3-Aryloxyacetyl-2-benzothiazolinones [2—4] reach and exceed in their herbicidal and growth-regulating activity the activity of standard 2-methyl-4-chlorophenoxyacetic acid.

4-Chloro-2-aminobenzothiazole belongs to the weak bases and exists in two tautomeric forms as 2-amino and 2-imino compound, which are represented in the reactions by two *N*-donor centres. The alkylations take place in the position 3 giving small yields (7—11%) [9, 10]. Similarly as in the case of other derivatives of 2-aminobenzothiazole the acylation proceeds on the amino group attached in position 2. The present experiments [1, 8—10] demonstrate that 2-alkyl or 2-arylalkyl derivatives of 2-aminobenzothiazole cannot be prepared

by a direct alkylation. One of the possible ways is the reduction of 2-acylamino derivatives of benzothiazole.

The compounds *II*—*XI*, *XXI* and *XXII* (Scheme 1) were prepared by acylation with acyl chlorides in the medium of dimethylformamide or its mixture with other solvents (acetone, benzene, tetrahydrofuran). The presence of DMF in the reaction mixture substantially increases the yields of the reaction products (from 50% to 80—90%). The compounds *XII*—*XX*, *XXIII* and *XXIV* were prepared by reaction with lithium aluminium hydride in the medium of diethyl ether or tetrahydrofuran (Scheme 1).



Scheme 1

The position of the acylation can be deduced from the results of ^{1}H NMR spectral measurements of the reduction products, because the signals of the methylene group protons attached to the NH group in position 2 of benzothiazole skeleton exhibit a multiplicity affected also by the proton of NH group. It can be also concluded from above that 4-chloro-2-(R-amino)benzothiazoles exist prevailingly as amino, but not as imino tautomers. Thus, the signal of the methylene hydrogen of compound *XII* appears as a quintet and that of compound *XIII* as a doublet. In the case of phenylmethylene, phenoxymethylene,

and phenylthiomethylene derivatives (compounds *XIV*—*XX*) the hydrogens of methylene group attached directly to the NH group exhibit in the spectra a quadruplet, which can be well distinguished from the neighbouring methylene group represented by a triplet.

The signal of the amide group proton was not identified in the spectra. The hydrogen signal of the secondary amino group can be observed as a triplet in the region of $\delta = 8.3$—8.7 for compounds measured in deuterated dimethyl sulfoxide. For compounds measured in deuterochloroform the signal of the NH group proton can be found in the region of $\delta = 10.43$—10.75 and in the case of disubstituted compounds *XXI*—*XXIV* it is absent. The position of signals of the methylene protons of acyl group is strongly dependent on the neighbouring atoms. It can be observed as a singlet for compound *IV* at $\delta = 3.80$ and for *X* at $\delta = 3.87$. The phenoxy group shifts the above singlet by $\delta = 1$ to the lower-field region and the 2,4,5-trichlorophenoxy group (compound *IX*) causes an analogical shift to $\delta = 5.10$.

In the region of aromatic protons the signal of one hydrogen can be clearly distinguished as a doublet, shifted mostly to the lower-field region at $\delta = 7.7$. This can be assigned to the proton in the position 7 of benzothiazole skeleton, the electron density of which is decreased by chlorine and sulfur atoms and its signal is splitted by the proton in position 6.

In the IR spectra of 4-chloro-2-(R-amido)benzothiazoles a band corresponding to the stretching vibration of the carbonyl group can be observed in the region of $\tilde{\nu} = 1660$—$1715\ \mathrm{cm}^{-1}$ The bands of carbonyl stretching vibration of amides derived from aryloxyacetic acids are found in the region of higher wavenumbers and also in the case of the acylation of secondary amino groups appear in the close surroundings of $\tilde{\nu} = 1700\ \mathrm{cm}^{-1}$

The compound *XI* exhibits at $\tilde{\nu} = 1788$ and $1719\ \mathrm{cm}^{-1}$ intensive bands of the symmetric and asymmetric stretching vibrations of the imidic dicarbonyl system. The band of the C=O stretching vibration of the amide group occurs as a shoulder at $\tilde{\nu} = 1700\ \mathrm{cm}^{-1}$ The NH stretching vibrations of amides and secondary amines are observed as two bands in the wide region of wavenumbers from 3220 to $3380\ \mathrm{cm}^{-1}$ In comparison with the starting 4-chloro-2-aminobenzothiazole, the ν(NH) bands of which can be found at $\tilde{\nu} = 3465\ \mathrm{cm}^{-1}$ and $3280\ \mathrm{cm}^{-1}$, the prepared compounds exhibit the ν(NH) bands at lower values of wavenumbers almost by $80\ \mathrm{cm}^{-1}$

The investigation of herbicidal activity of the prepared compounds showed that also derivatives containing the same moieties as the active aryloxyacetic acids (*i.e.* 2,4-dichlorophenoxyacetyl, 2,4,5-trichlorophenoxyacetyl, 2-methyl-4-chlorophenoxyacetyl, and 4-chlorophenoxyacetyl) do not exhibit higher herbicidal activity than 50% of that of the standard (2-methyl-4-chlorophenoxy-

Table 1

Characterization of the prepared compounds

Compound	R^1 / R^2	Formula / M_r	w_i(calc.)/% / w_i(found)/% C	H	Cl	N	S	M.p. °C
II	CH_3	$C_9H_7ClN_2OS$	47.69	3.11	15.64	12.36	14.14	295—297
	—	226.7	47.43	3.28	15.39	12.52	13.84	
III	C_6H_5	$C_{14}H_9ClN_2OS$	58.23	3.14	12.28	9.70	11.10	166—168
	—	288.7	58.41	3.36	11.97	9.63	10.79	
IV	$C_6H_5CH_2$	$C_{15}H_{11}ClN_2OS$	59.50	3.66	11.71	9.25	10.59	183—185
	—	302.8	59.77	3.48	12.05	9.38	10.59	
V	$C_6H_5OCH_2$	$C_{15}H_{11}ClN_2O_2S$	56.52	3.48	11.12	8.79	10.06	118—120
	—	318.8	56.59	3.22	11.46	8.90	9.88	
VI	$4\text{-}ClC_6H_4OCH_2$	$C_{15}H_{10}Cl_2N_2O_2S$	51.01	2.85	20.07	7.93	9.08	150—152
	—	353.2	49.79	2.85	20.44	8.21	9.16	
VII	$2\text{-}CH_3\text{-}4\text{-}ClC_6H_3OCH_2$	$C_{16}H_{12}Cl_2N_2O_2S$	52.33	3.29	19.31	7.63	8.73	139—142
	—	367.3	52.16	3.34	19.38	7.62	8.72	
VIII	$2,4\text{-}Cl_2C_6H_3OCH_2$	$C_{15}H_9Cl_3N_2O_2S$	46.47	2.34	27.44	7.23	8.27	205—207
	—	367.7	46.38	2.27	27.50	7.45	8.12	
IX	$2,4,5\text{-}Cl_3C_6H_2OCH_2$	$C_{15}H_8Cl_4N_2O_2S$	42.68	1.91	33.60	6.64	7.60	246—248
	—	422.12	42.89	1.81	33.80	6.62	7.61	
X	$C_6H_5SCH_2$	$C_{15}H_{11}ClN_2OS_2$	53.81	3.31	10.59	8.37	19.15	167—168
	—	334.8	53.57	3.20	10.34	8.44	19.32	
XI	$o\text{-}C_6H_4(CO)_2NCH_2$	$C_{17}H_{10}ClN_3O_3S$	54.92	2.71	9.54	11.30	8.62	322—324
	—	371.8	55.10	2.62	9.64	11.43	8.72	
XII	CH_3	$C_9H_9ClN_2S$	50.82	4.26	16.67	13.17	15.07	124—127
	—	212.7	50.91	4.37	16.80	13.28	15.11	
XIII	C_6H_5	$C_{14}H_{11}ClN_2S$	61.20	4.03	12.90	10.20	11.67	130—132
	—	274.7	61.33	4.09	13.11	10.20	11.56	
XIV	$C_6H_5CH_2$	$C_{15}H_{13}ClN_2S$	62.38	4.54	12.28	9.70	11.10	140—142
	—	288.8	62.33	4.53	12.42	9.71	11.20	

Table 1 (Continued)

Compound	R^1 R^2	Formula M_r	w_i(calc.)/% w_i(found)/%					M.p. °C
			C	H	Cl	N	S	
XV	$C_6H_5OCH_2$	$C_{15}H_{13}ClN_2OS$	59.11	4.30	11.63	9.19	10.52	142—144
	—	304.8	59.07	4.32	11.47	9.14	10.49	
XVI	2-CH_3-4-$ClC_6H_3OCH_2$	$C_{16}H_{14}ClN_2OS$	54.40	3.99	20.07	7.93	9.08	134—136
	—	353.3	54.38	3.86	20.21	7.75	9.04	
XVII	2,4-$Cl_2C_6H_3OCH_2$	$C_{15}H_{11}ClN_2OS$	48.21	2.97	28.46	7.50	8.58	133—135
	—	373.7	48.15	3.12	28.50	7.64	8.57	
XVIII	2,4,5-$Cl_3C_6H_2OCH_2$	$C_{15}H_{10}Cl_4N_2OS$	44.14	2.47	34.75	6.86	7.86	135—138
	—	408.1	44.29	2.68	2..94	6.98	8.22	
XIX	$C_6H_5SCH_2$	$C_{15}H_{13}ClN_2S_2$	53.80	3.31	10.59	8.36	19.15	147—149
	—	334.8	53.67	3.20	10.79	8.34	19.32	
XX	*o*-$C_6H_4(CH_2)_2NCH_2$	$C_{17}H_{16}ClN_3S$	61.90	4.89	10.75	12.74	9.72	134—137
	—	329.8	62.15	4.98	10.62	12.52	9.48	
XXI	CH_3	$C_{18}H_{16}Cl_2N_2O_2S$	54.69	4.07	17.94	7.09	8.11	136—138
	2-CH_3-4-$ClC_6H_3OCH_2$	395.3	54.45	3.98	18.18	7.22	8.11	
XXII	$C_6H_5OCH_2$	$C_{23}H_{18}Cl_2N_2O_3S$	58.35	3.83	14.96	5.92	6.77	137—139
	4-$ClC_6H_4OCH_2$	473.4	58.49	3.68	14.92	6.25	6.42	
XXIII	CH_3	$C_{16}H_{15}ClN_2S$	63.46	4.99	11.70	9.25	10.58	119—123
	C_6H_5	302.8	63.67	5.13	11.32	9.57	10.76	
XXIV	CH_3	$C_{18}H_{18}Cl_2N_2OS$	56.70	4.77	18.51	7.35	8.41	106—108
	2-CH_3-4-$ClC_6H_3OCH_2$	381.3	56.54	4.48	18.49	7.06	8.29	

acetic acid). The acyl derivatives tested for growth-regulating activity were also inactive.

In the case of reduced compounds *XV—XVII*, *XX*, *XXII*, and *XXIII* a 30% gibberellin and auxinoic activity appeared in comparison with standards.

The compounds *IV—VI* exhibited a 50% fungicidal activity against *Tilletia caries*. The remaining compounds inhibited the growth of all used strains with a 25% activity against the standard.

By the insecticidal tests the prepared compounds in amounts of 5000 and 1000 ppm showed an activity from 20 to 44% of the standard against *T. urticae* and *A. fabae* using a contact application. Compounds *XVIII* and *XX* presented a 100% inhibition using an ovicidal test against *T. urticae*.

Experimental

The ^{1}H NMR spectra of saturated solutions of prepared compounds were measured on a Tesla BS 487 instrument (80 MHz). The IR spectra were taken on a Perkin—Elmer 567 spectrophotometer in the region of $\tilde{\nu} = 400$—$4000\ cm^{-1}$ using suspensions in paraffin oil.

The standard herbicidal screening was performed using the following model plants: *Avena sativa, Panicum miliaceum, Fagopyrum vulgare, Lepidum sativum*, and *Sinapis alba*. 2-Methyl-4-chlorophenoxyacetic acid was used as a standard. Doses of 0.50 and $0.25\ g\ m^{-2}$ were employed by preemergent and postemergent application, respectively. The appearance of plants was evaluated after 2 weeks by a scale 0—5, where 0 means undamaged plant and 1—5 corresponds to 20—100% inhibition.

The fungicidal tests were provided according to [11] by *in vitro* method using the following model cultures: *Erysiphe graminis* (on barley), *Phytophtora infestans* (on tomatoes), *Tilletia caries* (soil and agar), *Botritis cinerea* (agar), *Fusarium nivale* (agar), and *Alternaria alternata* (agar). Vitavax, Euparen, Captan, and methyl isothiocyanate were used as standards. The evaluation scale was: 0 — control, 1—4 inhibition of the growth of microorganisms by 25—100%.

The insecticidal tests were performed according to [12] *in vitro* using Fenitrotion as a standard. The compounds were applied in concentrations $c/(mg\ cm^{-3})$: 5, 1, 0.5, and 0.1.

4-Chloro-2-(acylamino)benzothiazoles II—XI and 4-chloro-2-[(R^1-methyl)acylamino]benzothiazoles XXI, XXII

To the compound *I*, *XII* or *XV*, respectively (0.01 mol) dissolved in the mixture of anhydrous tetrahydrofuran ($10\ cm^3$) and dimethylformamide ($4\ cm^3$) acyl chloride (0.0103 mol) was added under stirring. The reaction mixture was stirred for 20 min at room temperature and after cooling down to 0°C anhydrous pyridine or triethylamine

Table 2

^{1}H NMR spectral data of the prepared compounds

Compound	Solvent	δ
II	DMSO	2.10 (s, 3H); 7.04—7.47 (m, 2H); 7.70—7.95 (m, 1H)
III	DMSO	7.13—7.57 (m, 6H); 7.85 (d, 1H, J = 9 Hz); 8.05—8.22 (q, 1H)
IV	DMSO	3.77 (s, 2H); 7.07—7.50 (m, 7H); 7.83 (q, 1H, J = 8 Hz)
V	DMSO	4.87 (s, 2H); 6.77—7.55 (m, 7H); 7.85 (d, 1H, J = 6 Hz)
VI	DMSO	4.87 (s, 2H); 6.77—7.55 (m, 7H); 7.85 (d, 1H, J = 7 Hz)
VII	DMSO	2.20 (s, 3H); 4.90 (s, 2H); 6.75—7.50 (m, 5H); 7.82 (d, 1H, J = 8 Hz)
IX	DMSO	5.10 (s, 2H); 7.12—7.50 (m, 2H); 7.43 (s, 1H); 7.67 (s, 1H); 7.87 (d, 1H, J = 8 Hz)
X	DMSO	3.87 (s, 2H); 6.95—7.47 (m, 7H); 7.77 (d, 1H, J = 8 Hz)
XI	DMSO	4.60 (s, 2H); 7.23—7.52 (s, 3H); 7.85 (s, 4H); 8.27 (s, 1H)
XII	DMSO	1.15—1.40 (t, 3H); 3.00—3.60 (2H, qint); 6.80—7.50 (m, 4H)
XIII	DMSO	4.55 (d, 2H, J = 6 Hz); 6.83—7.40 (m, 7H); 7.55 (d, 1H, J = 6 Hz); 8.71 (t, 1H, J = 6 Hz)
XIV	DMSO	2.80—2.97 (t, 2H); 3.45—3.67 (q, 2H); 6.825—7.30 (m, 2H); 7.25 (s, 5H); 7.55 (d, 1H, J = 8 Hz); 8.35 (t, 1H, J = 6 Hz)
XV	DMSO	3.63—3.85 (q, 2H); 4.05—4.23 (t, 2H); 6.80—7.37 (m, 7H); 7.55 (d, 1H, J = 8 Hz); 8.45 (t, 1H, J = 6 Hz)
XVI	$CDCl_3$	2.10 (s, 3H); 3.70—3.92 (q, 2H); 4.00—4.25 (t, 2H); 6.47—7.50 (m, 6H)
XVII	$CDCl_3$	3.75—4.00 (q, 2H); 4.05—4.30 (t, 2H); 6.75—7.50 (m, 6H)
XVIII	DMSO	3.52—3.84 (q, 2H); 4.00—4.34 (t, 2H); 6.75—7.61 (m, 5H); 8.40 (t, 1H, J = 6 Hz)
XIX	DMSO	3.01—3.31 (t, 2H); 3.32—3.69 (q, 2H); 6.725—7.55 (m, 6H); 7.82—8.21 (s, 1H); 8.37 (t, 1H, J = 6 Hz)
XX	$CDCl_3$	2.72—3.12 (q, 2H); 3.32—3.60 (t, 2H); 3.77 (s, 4H); 6.75—7.40 (m, 8H)
	DMSO	2.70—2.99 (t, 2H); 3.32—3.60 (q, 2H); 3.80 (s, 4H); 6.68—7.25 (m, 2H); 7.02 (s, 4H); 7.47 (d, 1H, J = 8 Hz); 8.22 (t, 1H, J = 6 Hz)
XXI	$CDCl_3$	1.27—1.60 (t, 3H); 2.22 (s, 3H); 4.12—4.45 (q, 2H); 4.95 (s, 2H); 6.50—6.72 (d, 1H); 6.90—7.40 (m, 4H); 7.60 (d, 1H, J = 6 Hz)
XXII	DMSO	4.30—4.75 (m, 4H); 5.40 (s, 2H); 6.75—7.50 (m, 11H); 7.85 (d, 1H, J = 8 Hz)
XXIII	DMSO	1.00—1.25 (t, 3H); 3.07—3.56 (4H, qint); 6.64—7.56 (m, 7H); 7.97—8.30 (d, 1H)
XXIV	DMSO	0.95—1.26 (t, 3H); 2.04 (s, 3H); 3.12—3.44 (q, 2H); 3.56—3.75 (t, 2H); 3.77—3.97 (t, 2H); 6.60—7.25 (m, 4H); 7.30—7.57 (d, 1H); 7.96—8.25 (s, 1H)

(0.0103 mol) was added dropwise. The mixture was stirred for 2 h under reflux, poured into cool water and neutralized by $NaHCO_3$. The eliminated precipitate was sucked off, washed with water and crystallized from ethanol or from a mixture of ethanol—dimethylformamide. The characteristics of prepared compounds are given in Tables 1 and 2.

4-Chloro-2-(R¹-methylamino)benzothiazoles XII—XX and 4-chloro-2-[(R¹-methyl)-(R²-methyl)amino]benzothiazoles XXIII, XXIV

To a solution of 4-chloro-2-(acylamino)benzothiazole or to its 2-(R^1-methyl) derivative (0.005 mol) in tetrahydrofuran the suspension of $LiAlH_4$ (0.2 g) in tetrahydrofuran (10 cm^3) was added by small portions during 10 min under intensive stirring at the temperature of 5 °C. Then the reaction mixture was heated to 25 °C and intensively stirred for 1 h. The solvent was distilled off *in vacuo* and the distillation residue was carefully mixed with crushed ice (50 g). The precipitate was sucked off, washed with water, dried and extracted with ethanol under boiling (3 times of 15 cm^3 solvent). The ethanolic extracts were concentrated to a volume approx. 5 cm^3, from which the crude product precipitated after cooling down and recrystallized from cyclohexane or from a mixture of cyclohexane and benzene. The characteristics of synthesized compounds are given in Tables 1 and 2.

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