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NEW DERIVATIVES OF 5–CHLORO–1,2–BENZISOTHIAZOLIN–3–ONE

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Abstract: The synthesis of new, biologically active, derivatives of 5–chloro–1,2–benzisothiazolin–3–one is described. 2–(5–Chloro–1,2–benzisothiazolyloxy)propionic acid, 2–(5–chloro–1,2–benzisothiazolyloxy)–butyric acid, (5–chloro–1,2–benzisothiazolin–3–one–2–yl) acetic acid and a mixture of 3–(5–chloro–1,2–benzisothiazolyloxy)propionic acid, as well as esters and amides of these acids were obtained. (5–Chloro–1,2–benzisothiazolin–3–on–2–yl)acetamide in the reaction with formaline and piperidine give *N*–piperidinomethylamide. Its hydrochloride derivative *in vitro* and *in vivo* shows a very high activity against *Trichomonas vaginalis* and *Trichomonas anseris*, as different G–positive and G–negative bacteria *in vitro* tests.

Keywords: 5–chloro–1,2–benzisothiazolin–3–one, –alkanoic acids, –esters, –amides, *N*–piperidinomethylacetamide–, synthesis, antibacterial, trichomonacidal activity.

Continuing the search for new derivatives of the parent heterocyclic system of 1,2–benzisothiazolin–3–one (BIT) with an antimicrobial activity, several new derivatives of 5–chloro–1,2–benzisothiazolin–3–one (5–Cl–BIT) were synthesized. From the already known 1,2–benzisothiazolin–3–ones, the parent 1,2–benzoisothiazolin–3–one (1) and its 5–chloro–(1–9) and 6–chloro– derivatives display a strong antibacterial and antifungial activity. 6–Chloro–1,2–benzisothiazolin–3–one was used as the fungicidal agent (Ticlatone, Landromil).

In the early papers (10, 11) the syntheses of 1,2–benzisothiazolin–3–one derivatives which showed a trichomonacidal activity (aminomethyl and aminoethyl derivatives of BIT–acetic and –propionic acid) were described. In this paper, the synthesis of several new derivatives of 5–chloro–1,2–benzisothiazolin–3–one, which are the microbiocidal agents is presented.

The substrate in the performed reactions was 5–chloro–1,2–benzisothiazolin–3–one, which was synthesized by the previously described method from 5–chloroanthranilic acid (2).

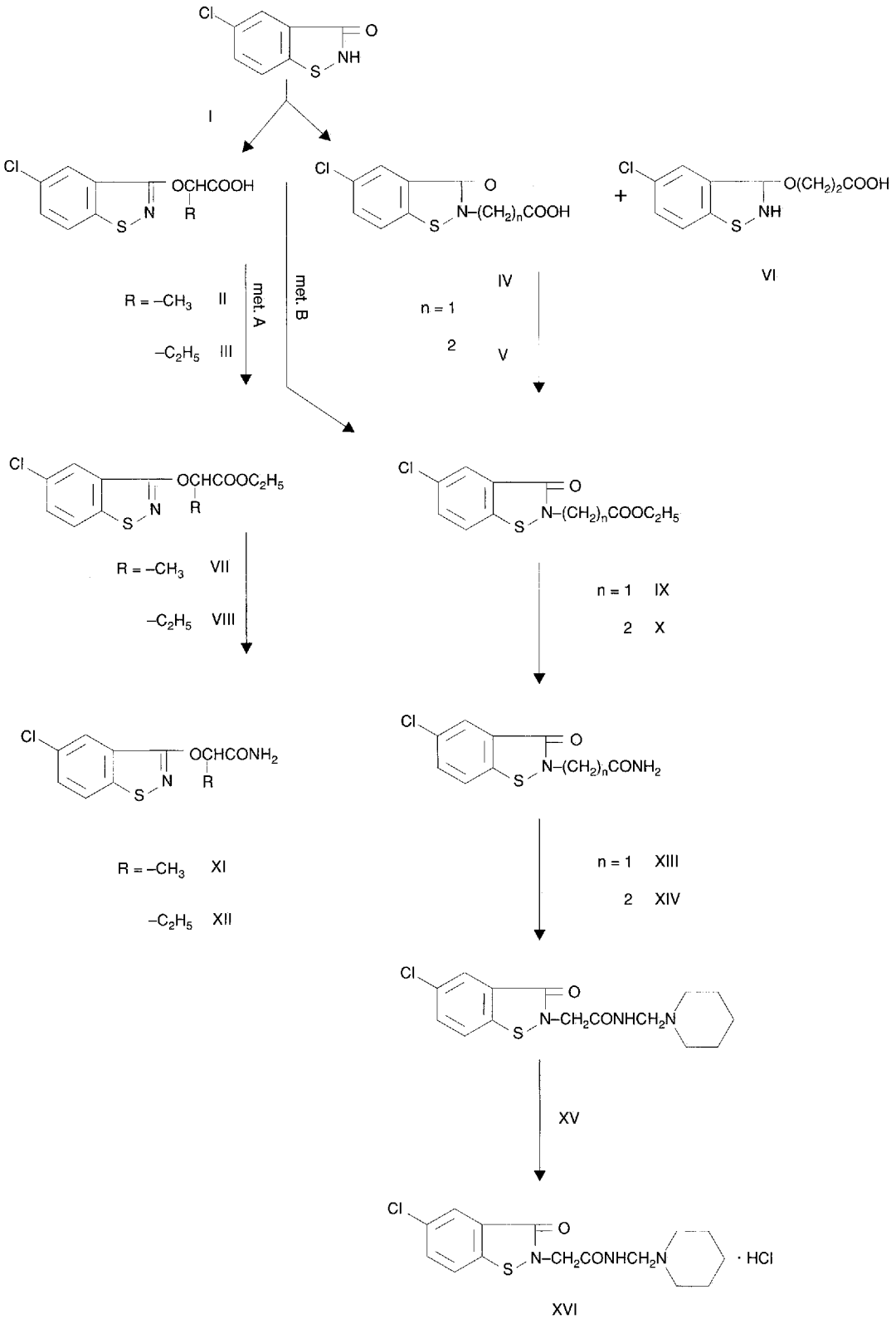
RESULTS AND DISCUSSION

In the reaction of sodium salt of 5–Cl–BIT in boiling dioxane with sodium salt of 2–bromopropionic acid or 2–bromobutyric acid the respective *O*–substituted [**II, III**] derivatives, not previously reported in the literature, were obtained. In the reaction of sodium salt of 5–Cl–BIT with the sodium salt of 3–bromopropionic acid, a mixture of *N*–substituted isomers [**V**] with small admixture of *O*–substituted product [**VI**] was obtained. This mixture was separeted by preparative TLC. However, in the reaction with bromoacetic acid only the *N*–substituted product [**IV**] was obtained.

From these newly obtained acids, by the method described above, the corresponding esters [**VII–X**] and amides [**XI–XIV**] were synthesized. Esters [**VII–X**] were obtained in the reaction carried out in abs. ethanol in the presence of conc. H_2SO_4 (method A). Esters [**IX–X**] were also synthesized by another method (B) in the reaction of 5–Cl-BIT sodium salt with either bromoacetic acid or 3–bromopropionic acid ethyl esters in boiling dioxane. 5–Cl–BIT–acetic acid and its ethyl ester were reported in the literature (12). Two methods of the synthesis of this acid are described. The first is the reaction of 2–chlorothiobenzoylchloride with aminoacetic acid, the second one is the reaction of 5–Cl–BIT sodium salt with ethyl chloroacetate in DMSO. The mixture of *O*– and *N*–substituted esters is formed. After the chromatographic separation, the pure esters hydrolyzed give the respective acids. From esters [**VII–X**], their amides [**XI–XIV**] were obtained in the reaction with 25% NH_4OH. From (5–chloro–1,2–benzisothiazolin–3–one–2–yl) acetamide [**XIII**] its *N*–piperidinomethyl derivative [**XV**] was synthesized, the hydrochloride [**XVI**] of which was supplied for microbiological tests.

The structures of all the new compounds were confirmed with the ^{1}H–NMR, IR and UV spectra, as well as with elemental analyses. The purity of all the compounds was tested by TLC.

In the IR spectra of *N*–substituted compounds two carbonyl bands are present, and in the *O*–substituted products there is only one carbonyl band. Moreover, the *O*–substituted compounds


I
R = –CH3 II
–C2H5 III
met. A
met. B
n = 1 IV
2 V
VI
R = –CH3 VII
–C2H5 VIII
n = 1 IX
2 X
R = –CH3 XI
–C2H5 XII
n = 1 XIII
2 XIV
XV
· HCl
XVI

Scheme 1.

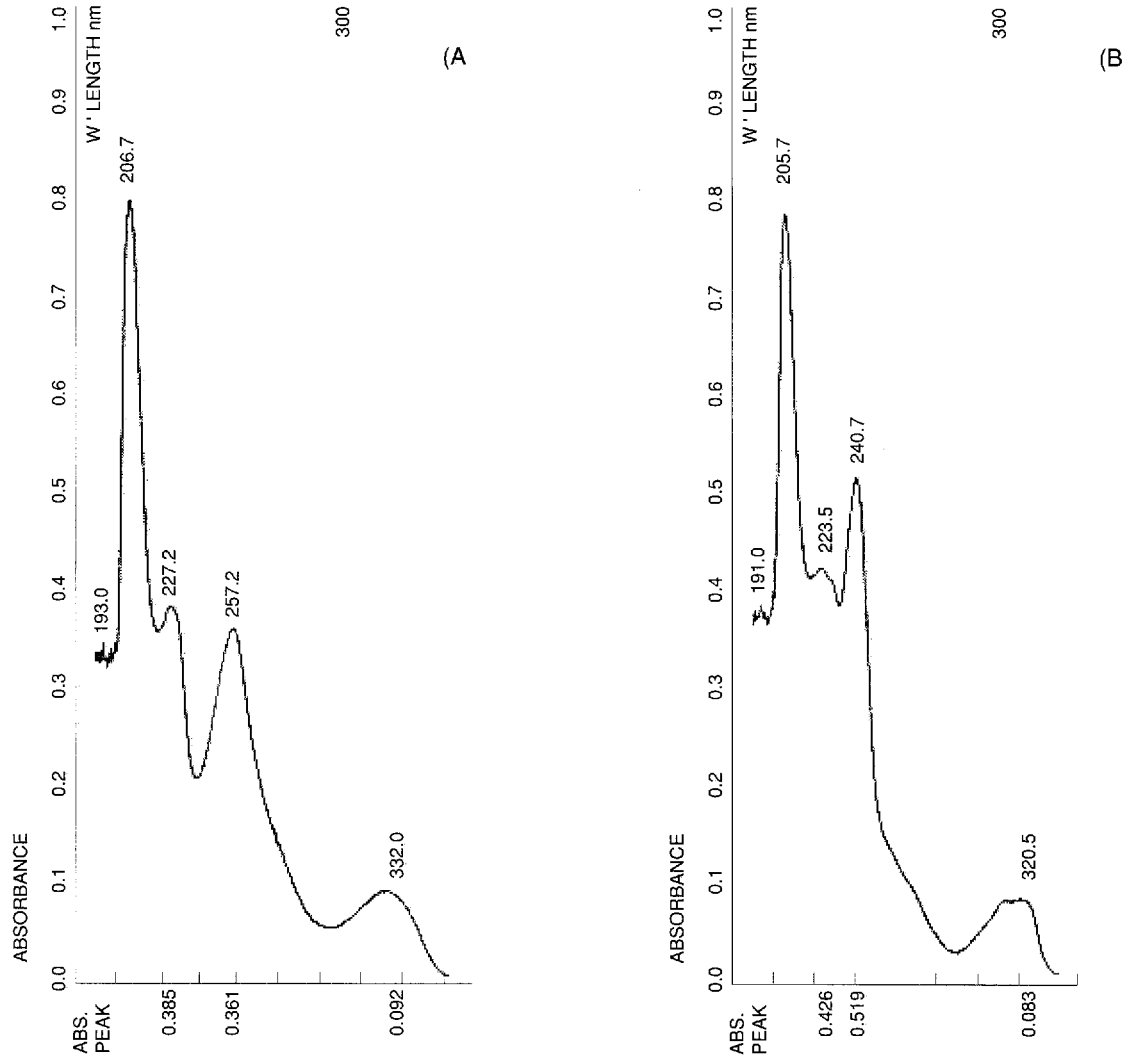


Figure 1. UV absorption spectra of 2–(5–chloro–1,2–benzisothiazolin–3–on–2–yl)propionic acid (A) and 3–(5–chloro–1,2–benzisothiazolyloxy)propionic acid (B), in methanol.

show a characteristic band of moderate average intensity in the range of 1510–1560 cm^{-1} of the isothiazole ring. *N*– and *O*–substituted derivatives of 5–Cl–BIT also differ in the UV spectra. As compared with *N*—isomers, the *O*–substituted compounds (with double bond of the hetercyclic ring) show a hypsochromic displacement and a reduced intensity. Such a behavior not previously reported in the literature is presented in the Figure 1 exemplifying the absorption curve for compounds **[V]** and **[VI]** (the positions of UV maxima and the resprectivites molar absorptivites, ε, for the obtained compounds are given in the Table 1). Also, the TLC data show a difference between *O*– and *N*–isomers; the R_f values for *O*–isomers are higher than those for *N*–substituted compounds.

The hydrochloride of *N*–piperidinomethyl–(5–chloro–1,2–benzisothiazolin–3–on–2–yl)acetamide **[XVI]** showed a very high trichomonacidal activity (against *Trichomonas vaginalis* and *T. anseris*) (tested in the Veterinary Institute in Puławy). *In vitro*, MIC value against *T. vaginalis* 200.31 μg/ml, against T. *anseris* 100.15 μg/ml.

In the *in vivo* tests, 100% of the guinea–pigs

Table 1.

	Formula Molecular mass	M.p. °C Crystall form Solvent	Yield %	R_f	Analyses calc% found%	IR cm^{-1}	λ nm max ε	^{1}H-NMR δ ppm
II	$C_{10}H_8ClNO_3S$ 257.69	187-188 plates 30% ethanol	28	I 0.36	C 46.60 46.46 H 3.13 3.39 Cl 13.76 13.62 N 5.43 5.30 S 12.44 12.31	1700 C=O 1540 ring	206 32000 225 17600 241 22000 312 4000	3H(CH_3)d 1.75; 1H(CH)q 5.53; 3H(Ar)m 7.80; 1H(COOH)s 12.46 (acetone-d_6)
III	$C_{11}H_{10}ClO_3S$ 271.72	191-192 needles 40% ethanol	25	I 0.38	C 48.62 48.64 H 3.71 4.00 Cl 13.05 12.97 N 5.15 5.43 S 11.80 11.76	1685 C=O 1510 ring	206 27200 225 14800 242 18400 313 3200	3H(CH_3)t 1.6; 2H(CH_2)t 2.09; 1H(CH)t 5.31; 3H(Ar)m 7.75; 1H(COOH)s 12.48 (acetone-d_6)
IV	$C_9H_6ClNO_3S$ 229.66	227-229 needles 30% ethanol 227-229 [12]	73	I 0.21		1700 C=O 1590 3-one	207 33400 227 16000 259 14400 332 4000	
V	$C_{10}H_8ClNO_3S$ 257.69	216-218 needles 30% ethanol	60	I 0.32	C 46.60 46.37 H 3.13 3.14 Cl 13.76 13.55 N 5.43 5.15 S 12.44 12.24	1680 C=O 1575 3-one	207 32000 227 15600 257 14400 332 3600	2H(CH_2)t 2.31;2H(CH_2)t 4.05; 3H(Ar)m 7.40; 1H(COOH)s 12.51 (DMSO-d_6)
VI	$C_{10}H_8ClNO_3S$ 257.69	159-163 needles 30% ethanol	3	I 0.48	N 5.43 5.69	1700 C=O 1540 ring	206 31600 224 17000 241 20800 321 3300	
VII	$C_{12}H_{12}ClNO_3S$ 271.74	58 needles	76	II 0.53	C 50.44 50.23 H 4.23 4.50 Cl 12.41 12.42 N 4.90 5.20 S 11.22 11.12	1750 C=O 1540 ring	208 16500 240 19600 311 3200	3H(CH_3)t 1.21; 3H(CH_3)q 1.71; 2H(CH_2)q 4.24, 1H(CH)q 5.46; 3H(Ar) 7.83 (acetone-d_6)
VIII	$C_{11}H_{10}ClN_3S$ 271.72	51-52 needles	84	II 0.54	C 52.08 52.22 H 4.71 4.99 Cl 11.83 11.69 N 4.67 4.83 S 10.70 11.02	1750 C=O 1560 ring	208 18100 240 19500 311 3200	3H(CH_3)t 1.21; 3H(CH_3)q 1.71; 2H(CH_2)q 4.24, 1H(CH)m 5.46; 3H(Ar) 7.83 (acetone-d_6)

Table 1. – cont.

	Formula Molecular mass	M.p. °C Crystall form Solvent	Yield %	R_f	Analyses calc% found%	IR cm^{-1}	λ nm max ε	^{1}H-NMR δ ppm
IX	$C_{13}H_{14}ClNO_3S$ 299.77	109-110 needles abs. ethanol 198-210 [12]	68 A 75 B	II 0.30	C 48.62 48.38 H 3.71 3.69 Cl 13.05 12.98 N 5.15 5.35 S 11.80 11.56	1720 C=O 1640 3-one	210 20000 229 15100 257 11900 331 4000	
X	$C_{12}H_{12}ClNO_3S$ 285.75	83-84 needles cyclohexane	29 A 63 B	II 0.25	C 50.44 50.59 H 4.23 4.30 Cl 12.41 12.25 N 4.90 4.86 S 11.22 10.98	1695 C=O 1620 3-one	210 20000 228 13500 257 11800 330 4000	
XI	$C_{10}H_9ClN_2O_2S$ 256.71	168-169 needles benzene	33	I 0.65	C 46.78 46.52 H 3.54 3.83 Cl 13.81 13.98 N 10.91 10.82 S 12.49 12.74	1540 ring 3240, 2160 NH 1620 C=O	208 11400 240 13400 311 2400	3H(CH_3)d 1.56; 1H(CH)q 5.37; 1H s 7.29; 1H s 7.63 (NH_2), 3H(Ar)m 7.73 (DMSO-d_6)
XII	$C_{11}H_{11}ClN_2O_2S$ 270.74	154 needles benzene	54	I 0.65	C 48.79 48.47 H 4.09 4.34 Cl 13.09 13.88 N 10.35 10.12 S 11.84 12.02	3280 3120 NH 1650 C=O 1530 ring	208 19300 240 18500 311 3900	3H(CH_3)t 0.97; 2H(CH_2)q 1.26; 1H(CH)t 5.16 1H s 7.32, 1H s 7.71 (CH_2); 3H(Ar) m 7.88 (DMSO-d_6)
XIII	$C_9H_7ClN_2O_2S$ 242.68	267-268 needles	87	I 0.48	C 44.54 44.76 H 2.92 2.88 Cl 14.61 14.78 N 11.54 11.26 S 13.21 13.33	3200, 3040 NH 1660 C=O 1620 3-one	210 20400 228 14600 257 11500 331 4200	2H(CH_2)s 4.42; 1H s 7.29, 1H s 7.64 (NH_2) 3H(Ar)m 7.99 (DMSO-d_6)
XIV	$C_{10}H_9ClN_2O_2S$ 229.66	270-272 needles	16	I 0.48	C 46.78 46.93 H 3.54 3.81 Cl 13.81 13.57 N 10.91 11.17 S 12.49 12.33	3240, 3030 NH 1620 C=O 1580 3-one	211 20000 243 10900 256 10500 326 3300	4H(2CH_2)m 2.50; 3H (Ar) m 7.69, 1H s 7.57; 1H s 8.25 (NH_2) (DMSO-d_6)

infected with *T.vaginalis*, recovered completely after 7 days of the application of [**XVI**] in a dose of 300 μg/kg.

This compound shows also an antibacterial activity (tested in the Departament of Pharmaceutical Microbiology, Faculty of Pharmacy, School of Medicine, Lublin).

In vitro it this was tested on 19 different Gram–positive and Gram–negative bacteria. The MIC values varied between 1.95 μg/ml for *Streptococcus pyogenes* and 6.25 μg/ml for *Salmonella enteridis*.

EXPERIMENTAL

Melting points (a Tottoli apparatus, Büchi, Switzerland) are uncorrected. IR spectra were recorded on a Specord 71 spectrophotometer (C. Zeiss, Germany) using the suspensions in nujol. ^{1}H–NMR spectra were measured in the perdeuterated acetone or DMSO solutions on Tesla 567 A spectrometer with TMS as an internal standard. The UV spectra were obtained with a Cecil CE 6000 spectrophotometer (England) in methanolic solutions ($1 \cdot 10^{-6}$ mol·l^{-1}). For TLC, silica gel 40 F_{254} plates (5 x 20 cm; 0.25 mm; Merck) were used; mobile phase: I) – $CHCl_3$–CH_3OH (3:2 v/v); II) – $CHCl_3$; III) – $CHCl_3$–CH_3OH (9:1 v/v) The chromatograms were detected in UV 254 nm. For preparative thin layer chromatography, PSC plates (20 x 20 cm; 2 mm; Merck) were used; mobile phase III) – $CHCl_3$–CH_3OH (9:1 v/v). The separated compounds [**V**] and [**VI**] were isolated from the plates with boiling C_2H_5OH.

The syntheses were performed under the chromatographic control (TLC). All the new compounds [**II–XVI**] were synthesized according to the reaction Scheme 1.

The starting compound, 5–chloro–1,2–benzisothiazolin–3–one [**I**], was obtained with the method previously described (2).

The reaction of 5–chloro–1,2–benzisothiazolin–3––one with bromoalkanoic acids (compounds **II–VI**)

3.7 g (0.02 mol) of compounds **I** was dissolved in 100 ml of hot abs. C_2H_5OH with 0.92 g (0.04 mol) of sodium prior dissolved. Then, C_2H_5OH was distilled off under a reduced pressure, 200 ml of dioxane and, alternatively, 0.02 mol of 2–bromopropionic acid, 2–bromobutyric acid, 3–bromopropionic acid, or bromoacetic acid were added to the residue and heated for 8 h. After cooling, sodium salts of each of the products (with NaBr) were collected by filtration, washed with dioxane, and dried. The precipitates were dissolved in 100 ml of hot H_2O, acidified with 25% HCl, cooled, collected by filtration, washed with cold H_2O. dried, and recrystallized. Compounds **V** and **VI** were separated by the preparative TLC chromatography.

2–(5–Chloro–1,2–benzisothiazolyloxy)propionic acid ethyl ester [**VII**]
2–(5–chloro–1,2–benzisothiazolyloxy)butyric acid ethyl ester [**VIII**]
(5–chloro–1,2–benzisothiazolin–3–one–2–yl)acetic acid ethyl ester [**IX**]
3–(5–chloro–1,2–benzisothiazolin–3–one–2–yl)propionic acid ethyl ester [**X**]

Method A

0.01 mol samples of compounds **II, III, IV** or **V** were refluxed for 8 h in 50 ml of abs. C_2H_5OH with 1 ml of conc. H_2SO_4 added. Then, C_2H_5OH was distilled off under a reduced pressure, 100 ml of cold H_2O was added to the residues and the products were extracted 3 times with 50 ml of ethyl ether. The ether each extracts were washed twice with 50 ml of cold H_2O, and dried over anhydrous Na_2SO_4. For compounds **VII** and **VIII** 50 ml of petroleum ether was added to the ether each extracts, and was left to a slow crystallization at room temperature. The obtained products were collected by filtration and washed with petroleum ether. For compounds **IX** and **X**, after removing of ethyl ether under a reduced pressure, the residue was recrystallized from either C_2H_5OH [**IX**] or cyclohexane [**X**].

Method B

0.02 mol of compound **I** was dissolved in 100 ml of abs. C_2H_5OH with 0.46 g (0.02 mol) sodium prior dissolved. Ethanol was distilled off under a reduced pressure. Then, 100 ml of dioxane and either 0.025 mol of bromoacetic acid ethyl ester or 3–bromopropionic acid ethyl ester was added. The mixture was refluxed for 8 h. After cooling, NaBr was filtered off and washed with dioxane. From the filterate, the solvent was distilled off under a reduced pressure, and an oily resiude was recrystallized from C_2H_5OH [**IX**] or cyclohexane [**X**].

The properties of compounds **IX** and **X** obtained with method A or method B are the same.

2–(5–Chloro–1,2–benzisothiazolyloxy)propionic acid amide [**XI**]
2–(5–chloro–1,2–benzisothiazolyloxy)butyric acid amide [**XII**]
(5–chloro–1,2–benzisothiazolin–3–one–2–yl)–acetamide [**XIII**]

3–(5–chloro–1,2–benzisothiazolin–3–one–2–yl)propionic acid amide [**XIV**]

50 ml of 25% solution of NH_4OH were added to 0.02 mol of esters [**VII–X**] and left at room temperature either for 24 h for compounds **IX** and **X** and 72 h for **VII** and **VIII**. The obtained products were collected by filtration, washed with cold H_2O, dried, and recrystallized.

The analytical data for the new compounds **II–XIX** are given in the Table 1.

N–Piperidinomethylamide of (5–chloro–1,2–benzisothiazolin–3–on–2–yl)acetic acid [**XV**]

5.43 g (0.02 mol) of compound **XIII** was heated for 8 h on a boiling waterbath with 2.13 g (0.025 mol) of piperidine and 3.2 ml of 40% formaline in 250 ml of abs. C_2H_5OH. After cooling, the precipitate was collected by filtration, washed with 20 ml of abs. C_2H_5OH and 50 ml of ethyl ether. The yield 80.0% (5.01 g); needles; m.p. 195–196°C

IR (cm^{-1}): NH 3150; C=O 1650, 1610

^{1}H–NMR (δ, ppm): 1.40, s, 4H, $2CH_2$; 2.52, d, 6H, $3CH_2$; 3.19, d. 2H, CH_2; 4.49, s, 2H, CH_2; 7.89, m, 3H, Ar; 8.44, t, 1H, NH (DMSO–d_6)

Elemental analysis for $C_{15}H_{18}ClN_3O_2S$ (339.84)

	C%	H%	Cl%	N%	S%
calc.:	53.01;	5.34;	10.43;	12.36;	9.43
found:	53.27;	5.52;	10.55;	12.39;	9.37

TLC (mobile phase III) R_f=0.29

N–Piperidinomethylamide of (5–chloro–1,2–benzisothiazolin–3–on–2–yl;)acetic acid, hydrochloride [**XVI**]

3.40 g (0.01 mol) of compound **XV** was suspended in 100 ml of abs. C_2H_5OH, and this solution was saturated with gaseous HCl. The precipitate was collected by filtration and washed with 100 ml of ethyl ether. The yield 90.0% (3.40 g); plates; m.p. 208–209°C.

Elemental analysis for $C_{15}H_{18}ClN_3O_2S \cdot HCl$ (376.30)

	C%	H%	Cl%	N%	S%
calc.:	47.87;	5.09;	18.84;	11.16;	8.52
found:	48.04;	5.33;	19.01;	10.99;	8.37

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