Synthesis and biological activity of 2-alkylthio--6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)-benzothiazoles

[a]E. SIDÓOVÁ, [b]Ž. ODLEROVÁ, [c]A. PERJÉSSY, and [c]G. BLÖCKINGER

[a]*Institute of Chemistry, Komenský University, 816 50 Bratislava*

[b]*Research Institute of Preventive Medicine, Centre of Epidemiology and Microbiology, 809 58 Bratislava*

[c]*Department of Organic Chemistry, Faculty of Natural Sciences, Komenský University, 816 31 Bratislava*

Received 13 February 1979

6-(Bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)-2-benzothiazolinethione and its *S*-alkyl (C_{1-16}) derivatives were synthesized and tested for insecticidal, fungicidal, herbicidal, and antimycobacterial activities. High fungicidal activity was found against *Phytophthora infestans* on tomatoes. The antimycobacterial activity against *Mycobacterium avium* was found to be most significant.

Синтезирован 6-(бицикло[2.2.1]гепт-5-ен-2,3-дикарбоксимидо)-2-бензотиазолинтион и его *S*-алкил (C_{1-16}) производные. Соединения были испытаны на их инсектицидную, фунгицидную, гербицидную и антимикобактериальную активности. Было найдено сильное фунгицидное действие на *Phytophthora infestans* на томатах. Самым значительным оказалось антимикобактериальное действие на *Mycobacterium avium*.

The knowledge on the biological activity of bicyclo[2.2.1]hept-5-en-2,3-dicarboximides [1—3] and 2-alkylthio-6-aminobenzothiazoles [4—6] iniciated the synthesis of 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)benzothiazoles. The aim of the present work was to investigate the possibility of synthesis of new biologically active compounds from the above-mentioned two structural elements.

The synthesis of the compounds presented in Table 1 was carried out in two ways according to Scheme 1.

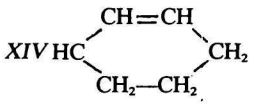
The first procedure was more advantageous because it started from one intermediate (*I*) and available alkyl halides. The second procedure required the preparation of the individual 2-alkylthio-5-aminobenzothiazoles, the isolation of which, in some cases, was relatively difficult due to their lower melting points (the derivatives with the alkyl chain of C_5).

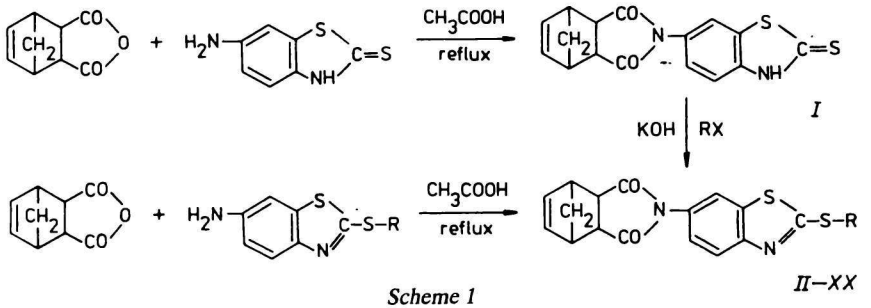
Table 1

2-Alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)benzothiazoles

Compound	R	Formula	*M*	Calculated/found				Procedure	Yield %	M.p. °C
				% C	% H	% N	% S			
II	CH_3	$C_{17}H_{14}N_2O_2S_2$	342.43	59.62	4.12	8.18	18.73	*A*	76.6	187—188.5
				59.55	4.22	8.48	18.72			
III	C_2H_5	$C_{18}H_{16}N_2O_2S_2$	356.45	60.65	4.52	7.86	17.99	*A*	56.3	155—157
				60.64	4.77	8.03	17.74			
IV	$(CH_2)_2CH_3$	$C_{19}H_{18}N_2O_2S_2$	370.48	61.59	4.90	7.56	17.31	*A*	54.2	153—155
				61.53	4.86	7.35	17.02			
V	$CH(CH_3)_2$	$C_{19}H_{18}N_2O_2S_2$	370.48	61.59	4.90	7.56	17.31	*A*	72.7	203—205
				61.67	4.96	7.59	17.37			
VI	$CH_2CH=CH_2$	$C_{19}H_{16}N_2O_2S_2$	368.46	61.93	4.38	7.60	17.40	*A*	90.1	170—171
				62.05	4.44	7.33	17.30			
VII	$(CH_2)_3CH_3$	$C_{20}H_{20}N_2O_2S_2$	384.50	62.47	5.24	7.29	16.68	*A*	60.5	100—102
				62.64	5.23	7.55	16.75			
VIII	$CH_2CH(CH_3)_2$	$C_{20}H_{20}N_2O_2S_2$	384.50	62.47	5.24	7.29	16.68	*A*	63.4	148.5—150.5
				62.50	5.26	7.26	16.88			
IX	$CH(CH_3)C_2H_5$	$C_{20}H_{20}N_2O_2S_2$	384.50	62.47	5.24	7.29	16.68	*A*	66.3	181.5—183.5
				62.65	5.33	7.17	16.56			
X	$(CH_2)_4CH_3$	$C_{21}H_{22}N_2O_2S_2$	398.55	63.29	5.56	7.03	16.09	*A*	50.4	110—112
				63.32	5.66	7.04	16.35			
XI	$CH_2CH_2CH(CH_3)_2$	$C_{21}H_{22}N_2O_2S_2$	398.55	63.29	5.56	7.03	16.09	*B*	58.5	107.5—109.5
				63.00	5.54	6.93	16.34			
XII	$CH(CH_2)_4$	$C_{21}H_{20}N_2O_2S_2$	396.53	63.61	5.08	7.06	16.17	*B*	73.2	184—185.5
				63.34	5.07	6.90	16.47			
XIII	$(CH_2)_5CH_3$	$C_{22}H_{24}N_2O_2S_2$	412.56	64.04	5.87	6.79	15.54	*A*	58.6	83—85
				64.32	5.73	6.67	15.48	*B*	72.5	

Table 1 (Continued)

Compound	R	Formula	*M*	Calculated/found				Procedure	Yield %	M.p. °C
				% C	% H	% N	% S			
XIV		$C_{22}H_{20}N_2O_2S_2$	408.54	64.68 64.48	4.93 5.07	6.86 6.75	15.70 15.71	*B*	46.8	172.5—174.5
XV	$(CH_2)_6CH_3$	$C_{23}H_{26}N_2O_2S_2$	426.58	64.76 64.74	6.14 6.12	6.57 6.42	15.27 15.11	*A*	75.4	81.5—83.5
XVI	$(CH_2)_7CH_3$	$C_{24}H_{28}N_2O_2S_2$	440.61	65.42 65.53	6.41 6.32	6.36 6.23	14.55 14.57	*A*	94.2	76.5—78
XVII	$(CH_2)_8CH_3$	$C_{25}H_{30}N_2O_2S_2$	454.66	66.04 66.32	6.65 6.65	6.16 6.04	14.10 14.11	*B*	49.6	88.5—90.5
XVIII	$(CH_2)_{15}CH_3$	$C_{32}H_{44}N_2O_2S_2$	552.85	69.52 69.66	8.02 8.21	5.07 4.91	11.60 11.61	*A*	43.4	72—74
XIX	$CH_2C_6H_5$	$C_{23}H_{18}N_2O_2S_2$	418.52	66.00 66.08	4.33 4.53	6.69 6.99	15.32 15.23	*A*	90.4	171.5—173
XX	CH_2CH_2OH	$C_{18}H_{16}N_2O_3S_2$	372.45	58.04 57.90	4.33 4.28	7.52 7.60	17.22 17.14	*A*	68.8	152—154



Scheme 1

In concentrated acetic acid at reflux temperature the primarily formed monoamides of bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid decompose under the formation of the corresponding imides [7, 8].

When the obtained products were decolourized with charcoal at elevated temperature, however, under b.p. of the solvent, white or only slightly yellowish crystalline compounds, stable for several years at laboratory conditions, were obtained.

From the i.r. spectra it can be assumed that the compound *I*, like 2-mercaptobenzothiazole, appears in the basic state in the tautomeric imino form. A weak band at 3400 cm^{-1} belonging to the N—H stretching vibration and a band of medium intensity at 1320 cm^{-1} belonging to the C=S vibration were observed in the spectra. Both these bands were absent in the spectra of the alkylation products *II*—*XX*. A very weak absorption band at 1630 cm^{-1} attributed to the stretching C=N vibration was practically overlapped by the absorption of the C=C bonds. In the spectrum of the compound *I* an intensive band, observed approximately at 1716 cm^{-1}, was split into a doublet as a consequence of coupling of two C=O bond

Table 2

Insecticidal activity of some synthesized compounds

Compound	*Musca domestica*	*Tetranychus urticae*		*Aphis fabae*	
	c	c	o	c	s
II	0	0.5	2	0.5	0
IV	1.7	0.5	4.5	1	0
V	0	0.5	0.5	3.5	0
VI	0	0	0.5	1.5	0
IX	0	—	0	1.5	0
XVI	0.5	1.5	0.5	2	0

Scale of valuation: 0—10; — not tested.
c — contact activity; o — ovicidal activity; s — systemic activity.

Chem. zvesti 34 (2) 269—277 (1980)

Table 3

Fungicidal activity of some synthesized compounds

Compound	*EP*, cucumbers (S) 300 µg/ml		*PI*, tomatoes (S) 300 µg/ml	*PI*, tomato leaves		*EG*, barley	
	s	w	w	5000 µg/ml	1000 µg/ml	1000 µg/ml	400 µg/ml
I	3	3	4	2	2	0	0
II	3	2	4	xxxx	xxx	3.5 xx	3 x
III	3	3	4	4	3	0	0.5
IV	3	2.6	4	xxx	xxx	2.5	1
V	2.2	3	4	xxxx	xxx	3.5xx	2.5
VI	3	1.5	4	4 x	2.5	0	0
VII	3	3	4	3.5 x	1.5	1	0
VIII	3	3	4	xxxx	xxx	3 x	1.5
IX	3	3	4	4	3	0	0.5
X	3	3	4	3.5	4	0.5	0
XIII	1.6	3	4	2.5	2.5	0.5	0.5
XV	3	3	4	3	1	0	0
XVI	3	2.2	4	2.5	2	0	0
XIX	—	—	4	4	2.5	0	0

Scale of valuation: 0—4; x — phytotoxicity; — not tested.

EP — Erysiphe polyphaga; PI — Phytophthora infestans; EG — Erysiphe graminis.

S — systemic activity; s — spray; w — watering.

vibrations in the imide cycle. The wavenumbers and intensities of these absorption bands were with the alkyl derivatives *II*—*XX* practically unchanged.

The compounds *I*—*X*, *XIII*, *XV*, *XVI*, and *XIX* were tested for insecticidal, herbicidal, and fungicidal activities in the first screening. The insecticidal activity of the synthesized compounds was low (Table 2). The highest value was obtained in ovicidal activity on *Tetranychus urticae* with the *n*-propyl derivative (*IV*) against the standard Akarithion. The synthesized compounds were herbicidally inactive.

The fungicidal activities of the compounds considerably changed in dependence on the test objects from zero to the highest values and were affected by the mode of application, concentration, and in most cases also by the substituent on sulfur in the position 2 (Table 3). The synthesized compounds were most active against *Phytophthora infestans* on tomatoes; the systemic activity with all tested com-

Table 4

Antimycobacterial activity MIC in μg/ml of the synthesized compounds and standards

Compound	*M. tuberculosis* $H_{37}R_v$	*M. kansasii*	*M. avium*	*M. fortuitum*
I	>100	>100	—	—
II	100 (50)	>100	—	—
III	>100	>100	—	—
IV	>100	>100	—	—
V	>100	>100	—	—
VI	>100	>100	—	—
VII	100 (25)	100 (50)	>100	>100
VIII	50	50	25	25
IX	100	>100	—	—
X	10	>100	1	>100
XI	10	50	>100	>100
XII	>100	>100	—	—
XIII	10	25 (10)	1	>100
XIV	>100	>100	—	—
XV	10	25 (10)	>100	>100
XVI	10	25 (10)	>100	>100
XVII	10	>100	>100	>100
XVIII	>100	>100	>100	>100
XIX	>100	>100	>100	>100
XX	>100	>100	—	—
2-Mercapto-benzothiazole	25 (10)	100	100 (50)	100
Isoniazid	1	10	10	50
Ethionamide	1	10	25	50

Partial inhibition concentration is given in parentheses.
— not tested.

pounds was awarded with maximum 4 points. In the greenhouse experiment on tomato leaves the obtained values (against the standard Dithiane M-45) depended significantly on the alkyl bound on sulfur in the position 2. The derivatives *II*, *IV*, *V*, and *VIII* were found to be significantly phytotoxic. The highest fungicidal activity was obtained with ethyl (*III*), *sec*-butyl (*IX*), and *n*-amyl (*X*) derivatives.

The tests for antimycobacterial activity showed that the derivatives with straight or branched alkyl chains of C_5 to C_9 were most active against *Mycobacterium (M.) tuberculosis* $H_{37}R_v$. The compound with extremely long alkyl chain (C_{16}) was inactive similarly as the cycloalkyl or cycloalkenyl derivatives.

n-Hexyl (*XIII*), *n*-heptyl (*XV*), and *n*-octyl (*XVI*) derivatives showed good activities against *M. kansasii*, while the *n*-nonyl derivative (*XVII*) was inactive. The derivatives with branched alkyl chain were less active against *M. kansasii* and those with cycloalkyl chain were inactive (Table 4).

The activity of *n*-amyl (*X*) and *n*-hexyl (*XIII*) derivatives (1 μg/ml) against *M. avium* was most significant. The obtained values were 10 times higher than those obtained with Isoniazid (isonicotinohydrazide) and 25 times higher than those obtained with Ethionamide (2-ethylthioisonicotinamide). These two compounds were found to be the best derivatives from the whole series [7]. Their activities, however, decreased in the course of further incubation to maximum concentration of 5 μg/ml for *M. avium* and 25 μg/ml for *M. tuberculosis* $H_{37}R_v$. This fact gave evidence about the bacteriostatical activity of the *n*-amyl (*X*) and *n*-hexyl (*XIII*) derivatives with the possibility of regeneration of the sublethally damaged mycobacterial cells under a certain concentration of the compound. At the interpretation of the results of antimycobacterial activity the generation time of the individual species of mycobacteria was taken into consideration.

Experimental

Physical constants, analytical data, and yields of the synthesized compounds are presented in Table 1. All melting points were determined on a Kofler block. The i.r. spectra in the range 900—3600 cm^{-1} were taken with a Zeiss UR-20 spectrophotometer. Chloroform solutions of compounds (0.2 M) were measured in cells of 0.1 mm thickness.

The antimycobacterial activity against tuberculosis mycobacteria was followed in a liquid Šula medium by the dilution test according to the method described in [9]. Dimethyl sulfoxide was used as solvent. The resulting concentrations of the compounds in the medium were 0.5, 1, 5, 10, 25, 50, and 100 μg/ml. The following microorganisms were used as test objects: *M. tuberculosis* $H_{37}R_v$ (sensitive to antituberculotics) and *M. avium* from the collection of the Research Institute of Preventive Medicine, Centre of Epidemiology and Microbiology, Bratislava, *M. kansasii PKG* (photochromogenic atypical mycobacterium) from the collection of Dr. E. H. Runyon (Salt Lake City, Utah, USA), and *M. fortuitum* from the collection of Professor Hauduroy (Lausanne). The activities of compounds were compared with those of 2-mercaptobenzothiazole [10], isonicotinohydrazide (Isoniazid,

Jenapharm, GDR), and 2-ethylthioisonicotinamide (Ethionamide, Trécator, Teraplix, Paris).

The compounds *I—X*, *XIII*, *XV*, *XVI*, and *XIX* were tested for pesticidal activity by standard methods used at the Research Institute of Agrochemical Technology, Bratislava. They were tested for insecticidal activity on *Musca domestica* and *Calandra granaria* (standard Malathion), *Aphis fabae* (standard Fosfotion), and for acaricidal activity on *Tetranychus urticae* (standard Akarithion). The herbicidal activity was followed by the method of preemergence (10 and 5 kg/ha) and postemergence (5 and 1 kg/ha) application, respectively, on oat *(Avena sativa)*, buckwheat *(Polygonum vulgare)*, mustard *(Sinapis alba)*, millet *(Panicum miliaceum)*, and cardemine *(Lepidium)*. Systemic fungicidal activity was followed against *Phytophthora infestans* (standard Novozir N; 50%) on tomatoes and *Erysiphe polyphaga* on cucumbers; as tan on *Tillecia tritici* (standard Vitavax), *Fusarium nivale* (standard Methylene dirhodanide), *Sclerotinia fructicola, Alternaria species*, and *Cladosporium cucumericum* (standard Kaptan), *Phytophthora infestans* on tomato leaves (standard Dithiane M-45), and on *Erysiphe graminis* (standard Karathane).

6-(Bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)-2-benzothiazolinethione (I) [8]

Bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid anhydride (8.2 g; 0.05 mol) was dissolved in glacial acetic acid (150 ml). 6-Amino-2-benzothiazolinethione [11] (9.1 g; 0.05 mol) was added to the solution and the reaction mixture was refluxed for 30 min. During heating a yellowish crystalline product precipitated from the reaction mixture in 92.7% yield.

The compound was recrystallized from the mixture of ethanol—water. After addition of charcoal, the solution was thoroughly stirred for 5 min and filtered without further heating; m.p. 214—216°C.

For $C_{16}H_{12}N_2O_2S_2$ (328.30) calculated: 58.51% C, 3.69% H, 8.53% N, 19.53% S; found: 58.32% C, 3.80% H, 8.52% N, 19.23% S.

2-Alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)-benzothiazoles (II—XX) [7]

The used procedures for the preparation of the individual compounds and their characterization are presented in Table 1. The *n*-hexyl derivative (*XIII*) was synthesized after both procedures; the mixed melting point showed no depression.

All compounds were purified by crystallization from the mixture of ethanol—water in the ratio of 2 : 1 to 10 : 1; the solution was not heated after the addition of charcoal.

Procedure A

6-(Bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)-2-benzothiazolinethione (*I*) (6.6 g; 0.02 mol) was dissolved in the solution of potassium hydroxide (1.4 g; 0.025 mol) in the mixture of ethanol (100 ml) and water (50 ml). The appropriate alkyl halide (0.025 mol) was added to the reaction mixture which was then refluxed for 10 min. Then charcoal was

added and after 5 min the solution was filtered. The filtrate was evaporated under reduced pressure without heating. White crystalline products were obtained.

Alkyl iodides were used in the syntheses except for the preparation of the compounds *VI* and *XIV* (bromides) and *XIX* (chloride). At the preparation of *n*-hexadecyl derivative (*XVIII*) the reaction time was 2 h.

Procedure B

Bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid anhydride (3.3 g; 0.02 mol) was dissolved at heating in glacial acetic acid (50 ml). The appropriate 2-alkylthio-6-aminobenzothiazole [6] (0.02 mol) was added to the solution and the mixture was refluxed for 30 min. Then a few ml of water were added in order to reduce the solubility of impurities and the solution was decolourized with charcoal without further heating. After filtration the oily product was precipitated with ice (300 g) and after several hours became a crystalline compound.

Acknowledgements. The authors thank Ing. J. Synak, CSc. and his coworkers (Research Institute of Agrochemical Technology, Bratislava) for the pesticidal tests and Ing. E. Greiplová and her coworkers (Institute of Chemistry, Komenský University, Bratislava) for the analysis of the synthesized compounds.

References

1. Furdík, M. and Sidóová, E., *Acta Fac. Rerum Natur. Univ. Comenianae (Chimia) 9*, 255 (1965).
2. Furdík, M., Sidóová, E., and Priehradný, S., *Acta Fac. Rerum Natur. Univ. Comenianae (Chimia) 12*, 253 (1968).
3. Sidóová, E., *Acta Fac. Rerum Natur. Univ. Comenianae (Chimia) 16*, 49 (1971).
4. Sutoris, V., Blöckinger, G., and Foltínová, P., *Czech. Appl.* 4672 (1974).
5. Sidóová, E. and Odlerová, Ž., *Czech.* 189212 (1978).
6. Sidóová, E., Odlerová, Ž., Volná, F., and Blöckinger, G., *Chem. Zvesti 33*, 830 (1979).
7. Sidóová, E. and Odlerová, Ž., *Czech.* 195149 (1979).
8. Sidóová, E., *Czech.* 195150 (1979).
9. Odlerová, Ž., Medvecký, R., and Hammelová, E., *Stud. Pneumol. Phtiseol. Czechoslov. 36*, 507 (1976).
10. Blöckinger, G. and Sutoris, V., *Czech.* 143604 (1971).
11. Blöckinger, G. and Sutoris, V., *Czech.* 168746 (1975).

Translated by A. Kardošová