Synthesis and antimicrobial activity of 2-alkylthio-6--salicylideneaminobenzothiazoles

[a]E. SIDÓOVÁ and [b]P. FOLTÍNOVÁ

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

[b]*Institute of Experimental Biology, Faculty of Natural Sciences, Komenský University, 886 04 Bratislava*

Received 9 July 1979

Sixteen 2-alkylthio-6-salicylideneaminobenzothiazoles have been prepared by the reaction of salicylaldehyde with 2-alkylthio-6-aminobenzothiazoles and their structures have been proved by ^{1}H-n.m.r. spectroscopy. The synthesized compounds were tested for antimicrobial activity. The highest fungicidal and fungistatic activities were found with benzyl derivative in 12.5 and 3.1 μg/ml concentrations, respectively against *Trichophyton rubrum.*

Реакцией салицилальдегида с 2-алкилтио-6-аминобензтиазолами было приготовлено 16 2-алкилтио-6-салицилиденаминобензтиазолов и их структура была подтверждена измерением спектров ^{1}H-ЯМР. Вещества были испытаны на их антимикробиальное действие. Наиболее сильное фунгицидное и фунгистатическое действие по отношению к *Trichophyton rubrum* обнаружено в случае бензилового производного при концентрации 12,5 или 3,1 μг/мл.

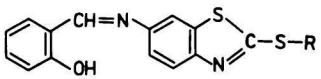
The aim of the synthesis of 2-alkylthio-6-salicylideneaminobenzothiazoles was to prepare antimicrobially active compounds on the basis of active 2-alkylthio-6-aminobenzothiazoles [1—3] and some salicyl derivatives. The compounds presented in Table 1 were synthesized from 2-alkylthio-6-aminobenzothiazoles and salicylaldehyde.

The structures of the synthesized compounds were proved by ^{1}H-n.m.r. spectroscopy. The spectra with all compounds showed the same broad signal at $\delta \sim 13$ p.p.m. belonging to proton of the hydroxyl group, bound by a strong hydrogen bond, a singlet at $\delta = 8.63$ p.p.m. belonging to proton of the azomethine group, and a multiplet of aromatic protons in the region of $\delta = 7.5$—6.7 p.p.m. integrating to 7H. Changes in the ^{1}H-n.m.r. spectra could be observed only in connection with the change of the alkyl group (R) on the basic skeleton [4].

Antibacterial activity of the synthesized compounds was followed on *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa.*

Table 1

2-Alkylthio-6-salicylideneaminobenzothiazoles



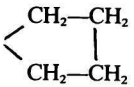
Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
I	CH_3	$C_{15}H_{12}N_2OS_2$	300.40	59.97	4.03	9.33	21.35	76.7	143.5—144.5
				60.27	3.82	9.06	21.08		
II	C_2H_5	$C_{16}H_{14}N_2OS_2$	314.43	61.12	4.49	8.91	20.40	71.5	133—134.5
				60.86	4.53	8.89	20.23		
III	$(CH_2)_2CH_3$	$C_{17}H_{16}N_2OS_2$	328.46	62.17	4.91	8.53	19.52	58.8	92—94.5
				62.03	4.89	8.41	19.47		
IV	$CH(CH_3)_2$	$C_{17}H_{16}N_2OS_2$	328.46	62.17	4.91	8.53	19.52	61.0	92.5—93
				61.87	4.92	8.50	19.47		
V	$CH_2CH=CH_2$	$C_{17}H_{14}N_2OS_2$	326.44	62.55	4.32	8.58	19.64	99.5	110—111.5
				62.37	4.25	8.53	19.54		
VI	$(CH_2)_3CH_3$	$C_{18}H_{18}N_2OS_2$	342.48	63.13	5.30	8.18	18.72	98.5	80.5—82
				62.86	5.28	8.09	18.90		
VII	$CH_2CH(CH_3)_2$	$C_{18}H_{18}N_2OS_2$	342.48	63.13	5.30	8.18	18.72	92.7	83—84.5
				63.02	5.45	8.13	18.54		
VIII	$CH_2(CH_3)C_2H_5$	$C_{18}H_{18}N_2OS_2$	342.48	63.13	5.30	8.18	18.72	60.9	60—62.5
				62.86	5.38	8.08	18.63		
IX		$C_{19}H_{18}N_2OS_2$	354.50	64.38	5.12	7.90	18.09	68.4	81.5—82.5
				64.30	5.11	7.90	17.92		
X	$(CH_2)_5CH_3$	$C_{20}H_{22}N_2OS_2$	370.54	64.83	5.98	7.56	17.31	69.6	77.5—78.5
				64.87	6.24	7.31	17.60		

Table 1 (Continued)

Compound	R	Formula	*M*	Calculated/found				Yield	M.p.
				% C	% H	% N	% S	%	°C
XI	$(CH_2)_6CH_3$	$C_{21}H_{24}N_2OS_2$	384.57	65.59	6.29	7.28	16.68	65.2	85.5—86.5
				65.59	6.36	7.11	16.42		
XII	$(CH_2)_7CH_3$	$C_{22}H_{26}N_2OS_2$	398.59	66.29	6.58	7.03	16.09	91.0	76.5—77.5
				66.40	6.76	7.13	16.88		
XIII	$(CH_2)_8CH_3$	$C_{23}H_{28}N_2OS_2$	412.62	66.95	6.84	6.79	15.54	91.6	79—80
				66.89	7.04	6.78	15.54		
XIV	$(CH_2)_{15}CH_3$	$C_{30}H_{42}N_2OS_2$	510.81	70.54	8.29	5.48	12.55	68.6	91.5—92.5
				70.53	8.59	5.32	12.29		
XV	$CH_2C_6H_5$	$C_{21}H_{16}N_2OS_2$	376.50	66.99	4.28	7.44	17.03	73.7	139.5—141
				66.83	4.19	7.44	17.03		
XVI	CH_2CH_2OH	$C_{16}H_{14}N_2O_2S_2$	330.43	58.16	4.27	8.48	19.41	66.6	131—132.5
				58.14	4.23	8.45	19.34		

The observed activities were lower than that of salicylaldehyde. Except allyl derivative (*V*), which was active against *Staphylococcus aureus* and *Bacillus subtilis* in concentration 200 μg/ml, all compounds were antibacterially active only in concentrations higher than 200 μg/ml.

The antifungal activity (Table 2) of the compounds with alkyls up to C_5 (*I*—*IX*) was the same as that of salicylaldehyde, hydroxyethyl derivative (*XVI*) was against *Microsporum gypseum* more active than salicylaldehyde or salicylic acid, and the compounds with alkyls of C_{6-16} (*X*—*XIV*) were antifungally less active than salicylaldehyde. Benzyl derivative (*XV*) was against *Microsporum gypseum* and *Trichophyton rubrum* more active than both starting compounds [3].

The unfavourable effect of long alkyls on antiprotozoal activity is evident from Table 2. Methyl derivative (*I*) was equally active as salicylaldehyde, allyl (*V*) and

Table 2

Antimicrobial activity of 2-alkylthio-6-salicylideneaminobenzothiazoles

Compound	Fungicidal/fungistatic concentration μg/ml			Lethal concentration μg/ml	
	1	*2*	*3*	*4*	*5*
I	200/50	50/12.5	50/12.5	200	50
II	200/50	50/12.5	50/12.5	200	200
III	200/50	50/12.5	50/12.5	200	200
IV	200/50	50/12.5	50/12.5	200	200
V	200/50	50/12.5	50/12.5	50	50
VI	200/50	50/12.5	50/12.5	200	200
VII	200/50	50/12.5	50/12.5	200	200
VIII	200/50	50/12.5	50/12.5	200	200
IX	200/50	50/12.5	50/12.5	200	200
X	>200/200	50/>12.5	50/>12.5	200	200
XI	>200/200	200/50	200/50	200	>200
XII	>200/200	200/50	200/50	200	>200
XIII	>200/200	>200/>50	200/>50	200	>200
XIV	>200/>200	200/200	>200/200	200	>200
XV	50/12.5	50/12.5	12.5/3.1	200	>200
XVI	50/12.5	50/12.5	50/12.5	50	50
Salicylic acid	200/50	50/12.5	50/12.5	200	>200
Salicylaldehyde	200/50	50/12.5	50/12.5	200	50

Concentrations tested: 200, 50, 12.5, and 3.1 μg/ml.

1. Microsporum gypseum; 2. Epidermophyton floccosum; 3. Trichophyton rubrum; 4. Trichomonas foetus; 5. Euglena gracilis.

hydroxyethyl (*XVI*) derivatives were more active, and the other derivatives were less active than salicylaldehyde.

Of all compounds tested, benzyl derivative (*XV*) was most active fungicidally (12.5 μg/ml) and fungistatically (3.1 μg/ml) against *Trichophyton rubrum.*

Experimental

Physical constants, analytical data, and yields of the synthesized compounds are presented in Table 1. Melting points were determined on a Kofler block. ^{1}H-N.m.r. spectra were measured on a Tesla BS 487 apparatus at 80 MHz and 24°C; concentration 10% solutions in deuteriochloroform. Tetramethylsilane was used as internal standard and chemical shifts were read with the accuracy of ± 0.01 p.p.m.

Antimicrobial activity was followed by the plate diffusion test [5] and antifungal activity by the test tube dilution method [6].

2-Alkylthio-6-salicylideneaminobenzothiazoles (I—XVI)

2-Alkylthio-6-aminobenzothiazole [3] (0.02 mol) was dissolved in necessary amount of ethanol (20—60 ml) at heating. Salicylaldehyde (2.45 g; 0.02 mol) was added to the solution and the reaction mixture was boiled for 2 min and decolourated with charcoal. When the product precipitated from the reaction mixture on heating in crystalline or oily forms, then ethanol was added before decolouration in such amount so that a homogeneous solution was obtained. The yellow crystalline product was washed with ethanol and dried; further purification was not necessary.

Acknowledgements. The authors are grateful to RNDr. E. Solčániová, CSc. and Ing. E. Greiplová and her coworkers (Institute of Chemistry, Komenský University, Bratislava) for the ^{1}H-n.m.r. measurements and for the analyses of the synthesized compounds, respectively.

References

1. Sutoris, V., Blöckinger, G., and Foltínová, P., *Czech. Appl.* 4672 (1974).
2. Sidóová, E. and Odlerová, Ž., *Czech.* 189212 (1978).
3. Sidóová, E., Odlerová, Ž., Volná, F., and Blöckinger, G., *Chem. Zvesti 33,* 830 (1979).
4. Solčániová, E., unpublished results.
5. Foltínová, P. and Blöckinger, G., *Biológia* (Bratislava) *25,* 175 (1970).
6. Foltínová, P., Sutoris, V., Blöckinger, G., and Ebringer, L., *Folia Microbiol.* (Prague) *23,* 225 (1978).

Translated by A. Kardošová