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

[a]E. SIDÓOVÁ, [b]Ž. ODLEROVÁ, 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*

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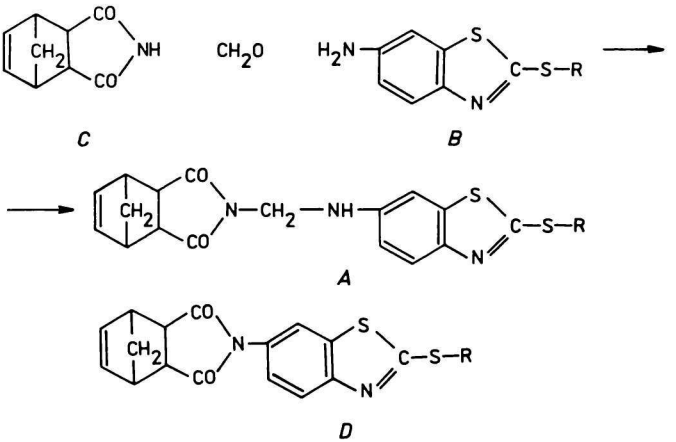
Mannich compounds on the basis of bicyclo[2.2.1]hept-5-en-2,3-dicarboximide and 2-alkylthio-6-aminobenzothiazoles were synthesized and tested for antimycobacterial activity against tuberculosis mycobacteria and for antiviral activity. The antimycobacterial activity of the synthesized compounds was evidently lower than that of the starting 2-alkylthio-6-aminobenzothiazoles and 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)benzothiazoles.

Были синтезированы соединения Манниха из бицикло[2.2.1]гепт-5-эн-2,3-дикарбоксимида и 2-алкилтио-6-аминобензтиазолов. Вещества были испытаны на антивирусное и антимикобактериальное действие по отношению к туберкулезным микобактериям. Последнее явно слабее, чем у исходных 2-алкилтио-6-аминобензтиазолов и также у 2-алкилтио-6-(бицикло[2.2.1]гепт-5-эн-2,3-дикарбоксимидо)бензтиазолов.

2-Alkylthio-6-aminobenzothiazoles (*B*) as well as the structurally very similar 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)benzothiazoles (*D*) are active against tuberculosis mycobacteria [1, 2] (Scheme 1).

The aim of the present work was to find out the effect of the —CH_2—NH— group incorporated between the imide nitrogen and the benzothiazole skeleton of the compound *D* on antimicrobial activity. On this purpose we prepared 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximidomethylamino)benzothiazoles (*A*) by the reaction of 2-alkylthio-6-aminobenzothiazoles (*B*) [1] with bicyclo[2.2.1]hept-5-en-2,3-dicarboximide (*C*) [3] in the presence of formaldehyde similarly as *Schindlbauer* and *Marini* [4] performed the aminomethylation of succinimide, maleinimide, and phthalimide with aromatic amines.



Scheme 1

By the above-mentioned reaction we obtained monoderivatives of primary amines, which was in agreement with the results of aminomethylations described in [5, 6].

The antimycobacterial activity of the prepared compounds was lower than that of *B* and *D*. The 3-cyclohexenyl derivative *XII* alone was active in minimal inhibition concentration (MIC) 50 μg/ml against *M. tuberculosis* $H_{37}R_v$ and *M. kansasii*, however, this activity was lower than that of the generally used antituberculotics (Isoniazid, Ethionamide). It is noticeable that in the series *D* the 3-cyclohexenyl derivative was inactive while the *n*-hexyl derivative was highly active [2]. The MIC of the compounds *III* and *VIII* against *M. tuberculosis* $H_{37}R_v$ was 100 μg/ml while the other derivatives were active only in higher concentrations.

The compounds *II*, *IX*, and *XV* were tested also for antiviral activity and were found to be inactive. On the other hand, other Mannich compounds on the basis of 2-alkylthio-6-aminobenzothiazoles, where 2-mercaptobenzothiazole was the H-active component in the Mannich synthesis, were antivirally active [7].

It can be concluded that the structural change against 2-alkylthio-6-aminobenzothiazoles (*B*) and 2-alkylthio-6-)bicyclo[2.2.1]hept-5-en-2,3-dicarboximido)benzothiazoles (*D*) did not prove good from the view-point of antimycobacterial activity. From the view-point of antiviral activity, bicyclo[2.2.1]hept-5-en-2,3-dicarboximide — the H-active component of the Mannich compounds on the basis of 2-alkylthio-6-aminobenzothiazoles — was found to be less advantageous than 2-mercaptobenzothiazole.

Experimental

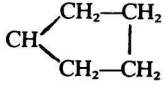
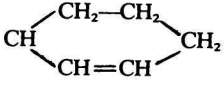
Physical constants, analytical data, and yields of the synthesized compounds are given in Table 1. Melting points were determined on a Kofler block.

Table 1

Characterization of 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximidomethylamino)benzothiazoles

Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
I	CH_3	$C_{18}H_{17}N_3O_2S_2$	371.48	58.20	4.61	11.31	17.26	67.6	180.5—181.5
				58.19	4.68	11.19	17.23		
II	CH_2CH_3	$C_{19}H_{19}N_3O_2S_2$	385.51	59.20	4.97	10.90	16.63	77.0	152.5—154
				58.86	4.99	10.73	16.67		
III	$CH_2CH_2CH_3$	$C_{20}H_{21}N_3O_2S_2$	399.54	60.12	5.30	10.52	16.05	71.7	132 —134
				60.15	5.33	10.38	16.03		
IV	$CH(CH_3)_2$	$C_{20}H_{21}N_3O_2S_2$	399.54	60.12	5.30	10.52	16.05	68.3	134.5—136.5
				60.13	5.28	10.41	16.01		
V	$CH_2CH=CH_2$	$C_{20}H_{19}N_3O_2S_2$	397.52	60.43	4.82	10.57	16.13	53.0	145.5—146
				60.40	4.92	10.39	16.14		
VI	$(CH_2)_3CH_3$	$C_{21}H_{23}N_3O_2S_2$	413.56	60.99	5.61	10.16	15.51	74.2	128 —129
				61.27	5.77	10.10	15.28		
VII	$CH_2CH(CH_3)_2$	$C_{21}H_{23}N_3O_2S_2$	413.56	60.99	5.61	10.16	15.51	49.2	153.5—155
				61.14	5.62	10.10	15.58		
VIII	$CH(CH_3)CH_2CH_3$	$C_{21}H_{23}N_3O_2S_2$	413.56	60.99	5.61	10.16	15.51	76.4	114.5—116.5
				60.68	5.81	10.08	15.77		
IX	$(CH_2)_4CH_3$	$C_{22}H_{25}N_3O_2S_2$	427.59	61.80	5.89	9.83	15.00	68.0	112 —113.5
				61.73	5.92	9.78	15.22		

Table 1 (Continued)

Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C
				% C	% H	% N	% S		
X		$C_{22}H_{23}N_3O_2S_2$	425.57	62.09 62.11	5.45 5.55	9.87 9.81	15.07 15.26	99.5	143 —144.5
XI	$(CH_2)_5CH_3$	$C_{23}H_{27}N_3O_2S_2$	441.62	62.55 62.39	6.16 6.30	9.52 9.38	14.52 14.64	53.0	111.5—113.5
XII		$C_{23}H_{23}N_3O_2S_2$	437.59	63.13 63.12	5.30 5.21	9.60 9.53	14.65 14.63	46.6	151 —153
XIII	$(CH_2)_6CH_3$	$C_{24}H_{29}N_3O_2S_2$	455.65	63.27 63.37	6.42 6.44	9.22 9.27	14.07 14.36	82.7	112.5—114
XIV	$(CH_2)_8CH_3$	$C_{26}H_{33}N_3O_2S_2$	483.70	64.56 64.83	6.88 7.11	8.69 8.49	13.26 13.59	64.1	107.5—109.5
XV	$CH_2C_6H_5$	$C_{24}H_{21}N_3O_2S_2$	447.58	64.40 64.68	4.51 4.66	9.39 9.29	14.33 14.38	59.6	171.5—173
XVI	CH_2CH_2OH	$C_{19}H_{19}N_3O_3S_2$	401.51	56.84 56.53	4.77 4.99	10.47 10.46	15.97 16.16	56.7	157.5—159

Antimycobacterial activity was followed in a liquid Šula medium by the dilution test [8] using dimethyl sulfoxide as solvent. The resulting concentration of the compounds in the medium was 1, 5, 10, 25, 50, and 100 μg/ml. *Mycobacterium (M.) tuberculosis* $H_{37}R_v$ (sensitive to antituberculotics) from the collection of the Research Institute of Preventive Medicine, Centre of Epidemiology and Microbiology, and *M. kansasii* (photochromogenic atypical mycobacterium) from the collection of Dr. E. H. Runyon (Salt Lake City, Utah, USA) were used for tests. The activity of the compounds was compared with that of isonicotinohydrazide (Isoniazid, Jenapharm, GDR) and 2-ethylisonicotinothioamide (Ethionamide, Trécator, Teraplix, Paris).

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

To bicyclo[2.2.1]hept-5-en-2,3-dicarboximide (0.03 mol) [3] dissolved in ethanol (50 ml), 36—38% formaldehyde (0.03 mol) was added and the reaction mixture was boiled. After total dissolution of the imide, 2-alkylthio-6-aminobenzothiazole (0.03 mol) dissolved in ethanol (20 to 100 ml) was added dropwise under reflux. After 10 min reflux water was added till a slight turbidity was observable. The reaction mixture was then boiled and decolourized with charcoal. White crystalline 2-alkylthio-6-(bicyclo[2.2.1]hept-5-en-2,3-dicarboximidomethylamino)benzothiazoles precipitated from the solution after cooling. The obtained products were purified by crystallization from the mixture of ethanol—water in the ratio of 2 : 1 to 10 : 1 using charcoal.

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