Benzothiazole compounds. XVII. Preparation and biological activity of Mannich bases with 2-benzothiazolinone

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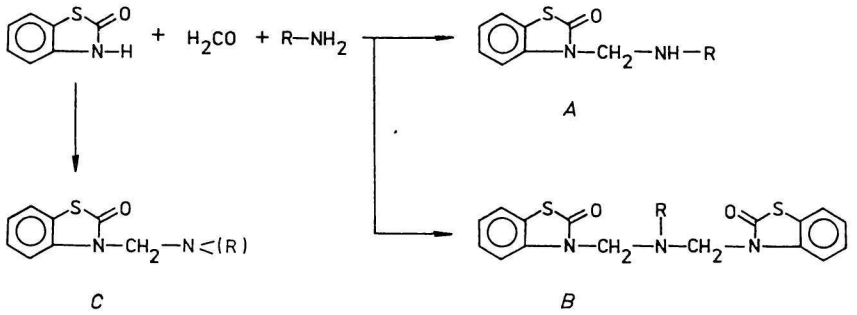
Reaction of 2-benzothiazolinone with formaldehyde and primary amines leads to formation of mono or bis derivatives. Reaction of 2-benzothiazolinone with formaldehyde and secondary amines is also described. Position of the substituents on 2-benzothiazolinone was established by ultraviolet and infrared spectroscopy. It has been found that the prepared compounds are less effective against mycobacteria and viruses than the corresponding derivatives of 2-benzothiazolinethione.

2-Бензтиазолинон реагирует с формальдегидом и первичными аминами с образованием моно- и биспроизводных. Описывается также реакция 2-бензтиазолинона с формальдегидом и вторичными аминами. Положение заместителей на 2-бензтиазолиноне было определено по УФ и ИК спектрам. Было найдено, что приготовленные соединения обладают меньшей эффективностью при воздействии на микобактерии и вирусы, чем соответствующие производные 2-бензтиазолинтиона.

Results of our previous paper dealing with reaction of primary amines with 2-mercaptobenzothiazole (2-MBT) and formaldehyde [1] pointed to a relationship between basicity of amines and formation of mono and bis derivatives. The conclusions of this work[1] were confirmed experimentally in reactions of primary amines of such values of basicity which should lead to formation of mono derivatives [2]. The purpose of the present communication was to find out whether primary amines, depending on their pK_B, react with 2-benzothiazolinone under formation of mono or bis derivatives, or whether the substitution of 2-benzothiazolinone takes place in position 3 as it is in the Mannich reaction with 2-MBT. Knowing the activity of the bases with 2-MBT against mycobacteria [3] and viruses [4] it became possible to examine the effect on biological activity of the replacement of sulfur with oxygen in the respective derivatives.



Scheme 1

Reaction of 2-benzothiazolinone with formaldehyde and primary amines having high pK_B values (Scheme 1) produced mono derivatives of Mannich bases (*A*) similarly as in the reactions with 2-MBT. In consonance with the results of our former work [1], amines having low pK_B values gave bis derivatives (*B*). Reaction yields of mono derivatives (62—86%) were much higher than yields of bis derivatives (20—41%) (Table 1). Bases with secondary amines (*C*) were formed in about the same yields as the bases with 2-MBT (73—80% [5], 98% [6]).

All prepared compounds are white crystalline products well soluble in dimethyl sulfoxide and dimethylformamide, insoluble in water.

In ultraviolet spectra the derivatives of 2-benzothiazolinone exhibit two intense absorption bands, one having maximum in the region 241—244 nm, and the other, a split band, in the region 281.5—289.5 nm (Table 2). In all cases these spectra differ only slightly from the spectrum of unsubstituted 2-benzothiazolinone, which points to the fact that the chromophore in molecules of the measured compounds is the N—(O=C)—S group. This conclusion is also confirmed by comparison of the absorption spectra of 2-MBT derivatives [1] with those of 2-benzothiazolinone derivatives. While the spectra of 2-MBT and 2-benzothiazolinone differ in the position of absorption maxima and the values of molar absorption coefficients, the spectra of 2-MBT derivatives are very similar to the spectrum of the starting compound. These findings represent a clear evidence that the Mannich reaction with 2-benzothiazolinone did not result in a change of the chromophore group and led to 3-substituted products. These facts are reflected in the infrared spectra, in which an absorption band at 1665 cm^{-1}, corresponding to the C=O group, occurs. Based on these results it is clear that, of the two tautomeric forms of 2-benzothiazolinone (OH or NH) [7, 8], only the NH form participates in the reactions.

Antimycobacterial activity of compounds *I*, *III*, *V*, *XI*, *XII*, and 2-benzothiazolinone itself is shown in Table 3. Data on antimycobacterial activity of 2-MBT and compounds *Ia* and *Va* (thioanalogues of *I* and *V*, respectively) are included for a comparison. As may be seen, the replacement of sulfur with oxygen in the molecules of the tested compounds results in a loss of their activity against *M.*

Table 1

Characteristics of synthesized compounds

Compound	R	Formula	*M*	Calculated/found				Yield %	M.p. °C	Type of compound	pK_B 25°C
				% C	% H	% N	% S				
I	C_6H_5	$C_{14}H_{12}N_2OS$	256.2	65.62	4.68	10.93	12.50	76	158—161	*A*	9.42
				65.48	4.72	10.94	12.51				
II	4-CH_3—C_6H_4	$C_{15}H_{14}N_2OS$	270.3	66.64	5.21	10.36	11.86	79	111—114	*A*	8.93
				66.87	5.24	9.99	11.85				
III	C_2H_5	$C_{18}H_{17}N_3O_2S_2$	371.4	58.20	4.60	11.31	17.26	41	150—153	*B*	3.27
				57.92	4.57	11.21	17.30				
IV	CH_2=CH—CH_2	$C_{19}H_{17}N_3O_2S_2$	383.4	59.51	4.46	10.95	16.72	37	117—120	*B*	4.20
				59.66	4.53	10.84	16.74				
V	C_6H_5—CH_2	$C_{23}H_{19}N_3O_2S_2$	433.5	63.72	4.41	9.49	14.79	26	169—172	*B*	4.62
				63.53	4.43	9.58	14.81				
VI	CH_3—O—$(CH_2)_3$	$C_{20}H_{21}N_3O_3S_2$	415.5	57.81	5.08	10.11	15.43	30	106—109	*B*	—
				57.46	5.20	9.84	15.28				
VII	$(CH_3)_2CH$—O—$(CH_2)_3$	$C_{22}H_{25}N_3O_3S_2$	443.5	59.57	5.67	9.47	14.45	20	69—71	*B*	—
				58.97	5.64	9.27	14.14				
VIII	CH_3—$(CH_2)_3$—$CH(C_2H_5)$—CH_2—O—$(CH_2)_3$	$C_{27}H_{35}N_3O_3S_2$	513.6	63.13	6.86	8.18	12.48	22	47—50	*B*	—
				63.28	7.12	8.08	11.98				
IX	$(C_2H_5)_2$	$C_{12}H_{17}N_2OS$	237.3	60.74	7.21	11.18	13.50	77	57—60	*C*	—
				60.79	6.78	11.67	13.72				
X	Pyrrolidino	$C_{12}H_{14}N_2OS$	234.3	60.51	6.01	11.95	13.68	60	44—46	*C*	—
				60.50	6.15	11.65	13.42				
XI	Piperidino	$C_{13}H_{16}N_2OS$	248.3	62.88	6.48	11.28	12.91	86	94—96	*C*	—
				62.62	6.62	11.24	13.04				
XII	Morpholino	$C_{11}H_{14}N_2O_2S$	250.3	57.58	5.63	11.19	12.80	62	84—87	*C*	—
				57.49	5.54	11.08	12.82				

Table 2

Positions and intensities of absorption bands
of 2-benzothiazolinone and Mannich reaction products

Compound	Type of compound	λ_{max}/nm (log a_{max})		
2-Benzothiazolinone		243 (3.792)	281.5 (3.493)	288.5 (3.492)
I	*A*	241 (4.269)	281.5 (3.668)	288.5 (3.678)
III	*B*	243 (3.820)	281.5 (3.525)	288.5 (3.517)
XII	*C*	243 (3.798)	281.5 (3.512)	288.5 (3.494)

Table 3

Antimycobacterial activity MIC in μg/ml of compounds

Compound	*M. tuberculosis* $H_{37}R_v$	*M. kansasii*	*M. avium*	*M. fortuitum*
I	>100	>100	>100	>100
III	100	>100	>100	>100
V	>100	>100	>100	>100
XI	>100	>100	>100	>100
XII	>100	>100	>100	>100
2-Benzothiazolinone	>100	>100	>100	>100
2-MBT	25	50	50	X
Ia	10	25	100	>100
Va	10	25	100	100

X — not tested.

tuberculosis $H_{37}R_V$, *M. kansasii,* and *M. avium.* The corresponding derivatives of 2-benzothiazolinethione and 2-benzothiazolinone are equally ineffective against *M. fortuitum.*

Antiviral activity of the prepared compounds as well as that of 2-benzothiazolinone and 2-MBT is shown in Table 4. The derivatives of 2-benzothiazolinone exhibit against *Vakcinia* virus an activity attaining almost medium degree of selectivity. The compounds are ineffective against viruses *NDV* and *WEE.* The size of the inhibition zone in the case of *Vakcinia* virus is about the same with both 2-benzothiazolinone and 2-MBT. The inhibitory effect of 2-benzothiazolinone on multiplication of *NDV* virus is negligible. A comparison of the antiviral activities of 2-benzothiazolinone derivative *I* and equally substituted derivative of 2-benzothiazolinethione *Ia* shows that the replacement of sulfur with oxygen resulted in a loss of biological activity.

Table 4

Inhibitory effect of compounds on *Vakcinia*, *NDV*, and *WEE* viruses

Compound	Concentration mg/ml of DMSO	Toxicity zone (diameter) mm	Inhibition zone (diameter) mm		
			Vakcinia	*NDV*	*WEE*
I	50	12	0	0	0
II	100	10	29	0	0
III	50	21	27	0	0
IV	10	27	0	0	0
V	100	14	17	0	0
VI	25	23	0	0	0
VII	25	23	0	0	0
VIII	100	22	30	0	0
IX	50	26	35	0	0
X	25	22	0	0	0
XI	25	21	0	0	0
XII	10	11	0	0	0
2-Benzothiazolinone	100	11	33	0	0
2-MBT	5*	9	30	17	0
Ia	100	25	48	0	0

* Concentration in mg/ml of ethanol.

Experimental

Ultraviolet spectra were measured on a SF-8 spectrophotometer (Lomo, Leningrad) in solutions of ethanol (for u.v. spectroscopy, Lachema, Brno). Spectral data are listed in Table 2. Infrared spectra were recorded on a Specord 75 IR instrument in nujol suspensions.

Antimycobacterial activity was tested on strains from the Research Institute of Preventive Medicine, Bratislava. The classical dilution method modified for mycobacteria [9] was used. The obtained results are summarized in Table 3.

Antiviral activity was tested at the Institute of Virology, Slovak Academy of Sciences, Bratislava. Characteristics of the used objects and procedures were described elsewhere [4].

2-Benzothiazolinone derivatives (I—XII)

To amine (0.1 mol) kept at 0—5°C (to aromatic amines at 30—32°C) 30—34% formaldehyde (0.1 mol; 10 ml) was added dropwise under stirring. After dilution with 96% ethanol (100 ml), 2-benzothiazolinone [10] (0.1 mol; 15.1 g) was added by portions. (The mixtures with aromatic amines were refluxed for 5 min.) After 10 min, the solution was cooled to −5°C and the crystalline product was filtered off and washed with ethanol.

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