Synthesis and antimicrobial properties of 2-(2,4-dinitrophenylthio)benzimidazole derivatives

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Properties and reactions of 2-(2,4-dinitrophenylthio)benzimidazole with mineral acids as well as alkylating and acylating reagents are described. Antifungal and antimycobacterial tests with the prepared compounds are presented.

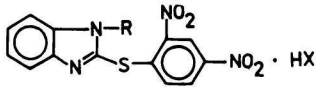
В статье описываются свойства и реакции 2-(2,4-динитрофенилтио)бензимидазола с минеральными кислотами, а также с алкилирующими и ацилирующими реактивами. Одновременно приводятся антифунгильные и антимикобактериальные проверки полученных соединений.

Preparation of 2-(2,4-dinitrophenylthio)benzimidazole (*I*) by the reaction of 2-mercaptobenzimidazole with 2,4-dinitrochlorobenzene in alkali media has been described by three authors [1—3]. They reported for the compound *I* very different melting points, 122°C [3], 181°C [2], and 233°C [1]. *Pianka* in [1] also drew attention to this discrepancy. With regard to such different melting points we assumed that there was not only one compound involved and attempted to prepare and identify these compounds. Reproducing the experiments from [1—3], we prepared and identified the individual products by elemental analysis as follows. The compound with m.p. 233°C corresponded to 2-(2,4-dinitrophenylthio)benzimidazole (*I*). The compound *II* with m.p. 183°C contained 1/2 molecule of HCl, and the compound *III* with m.p. 122°C contained 1 molecule of H_2O. By heating the compounds *II* and *III* at 90—100°C for 1/2 h the compound *I* was obtained.

The reaction of 2-mercaptobenzimidazole with 2,4-dinitrochlorobenzene in benzene under reflux in the absence of base resulted in 2-(2,4-dinitrophenylthio)benzimidazolium chloride (compound *IV*, Table 1), the 2,4-dinitrophenyl group being located on sulfur. We carried out several experiments in order to substitute 2-mercaptobenzimidazole in the position 1 by 2,4-dinitrophenyl group varying the reaction temperatures from 30 to 150°C either in the presence of base

Table 1

Analytical data of the prepared compounds



Compound	R	HX	Formula M_r	Calculated/found % C	% H	% N	% S	% X	M.p. °C	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	$\nu_{arom}(C=C)$
I	H	—	$C_{13}H_8N_4O_4S$	49.136	2.55	17.77	10.13	—	233	1516	1330	1590
			316.3	49.16	2.60	17.91	10.31					
II	H	1/2HCl	$C_{26}H_{17}N_8O_8ClS_2$	46.70	2.56	16.75	9.59	5.30	184	1510	1330	1587
			668.6	46.80	2.66	16.72	9.35	5.10		1530		
III	H	H_2O	$C_{13}H_{10}N_4O_5S$	46.70	3.01	16.76	9.59	—	122	1518	1335	1595
			334.3	46.42	2.87	16.72	9.60					
IV	H	HCl	$C_{13}H_9N_4O_4SCl$	44.26	2.57	15.88	9.08	10.05	206—208	1520		
			352.7	44.46	2.73	15.64	8.86	10.16		1560	1350	1609
V	H	HI	$C_{13}H_9N_4O_4SI$	35.29	2.04	12.40	7.21	28.56	196—198	—	—	—
			444.2	34.88	2.27	12.29	7.19	28.30				
VI	H	HBr	$C_{13}H_9BrN_4O_4S$	39.31	2.28	14.10	8.07	20.11	226	—	—	—
			397.2	38.94	2.01	14.32	8.42	20.45				
VII	H	H_2SO_4	$C_{13}H_{10}N_4O_8S_2$	37.38	2.43	13.52	15.47	—	209—211	1520	1335	1595
			414.3	37.91	2.18	13.22	15.83					
VIII	CH_3	—	$C_{14}H_{10}O_4N_4S$	50.91	3.02	16.96	9.71	—	199—200	1514	1328	1590
			330.2	50.69	2.75	16.87	9.54					
IX	C_2H_5	—	$C_{15}H_{12}N_4O_4S$	52.33	3.48	16.27	9.31	—	162—163	1514	1328	1590
			344.2									

Table 1 (Continued)

Compound	R	HX	Formula M_r	Calculated/found					M.p. °C	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	$\nu_{arom}(C=C)$
				% C	% H	% N	% S	% X				
X	n-C_3H_7	—	$C_{16}H_{14}N_4O_4S$	53.63	3.90	15.63	8.95	—	148	1514	1330	1590
			358.2	53.48	3.61	15.82	8.36					
XI	n-C_4H_9	—	$C_{17}H_{16}N_4O_4S$	54.84	4.29	15.05	8.61	—	136—138	1510	1330	1586
			372.2	54.56	4.16	14.98	8.29			1518		
XII	Benzyl	—	$C_{20}H_{14}N_4O_4S$	59.12	3.44	13.78	7.89	—	232—234	1518	1335	1588
			406.3	59.05	3.16	13.51	7.59					
XIII	Benzoyl	—	$C_{20}H_{12}N_4O_5S$	57.15	2.85	13.33	7.62	—	171—173	1507	1335	1590 C=O
			420.3	57.14	2.63	13.24	7.31			1521		1688
XIV	$C_6H_5SO_2$	—	$C_{19}H_{12}N_4O_6S_2$	50.00	2.65	12.27	14.05	—	186—188	1514	1328*	1157**
			456.4	49.81	2.96	12.54	13.80					1586
XV	4-$CH_3C_6H_5SO_2$	—	$C_{20}H_{14}N_4O_6S_2$	51.05	2.99	11.90	13.63	—	160—162	1514	1342*	1149**
			470.4	51.32	2.81	11.77	13.69					1595

* Intensive band for $\nu_{as}(SO_2)$ and $\nu_s(NO_2)$.

** Intensive band for $\nu_s(SO_2)$.

(pyridine, CH_3COOK, K_2CO_3) or without it. *N*-Isomer of the compound *I* has not been formed.

We have found that 2-(2,4-dinitrophenylthio)benzimidazole in ether (benzene) afforded with mineral acids stable salts which could be purified by crystallization. These salts displayed different antimicrobial activities (Tables 2 and 3).

We have found further that 2-(2,4-dinitrophenylthio)benzimidazole can be easily alkylated or acylated into the position 1 (compounds *VIII—XV*, Table 1). In the literature neither the i.r. nor the ^{1}H-n.m.r. spectra of the compounds *I—III* have been reported. The compounds *IV—XV* are new. The ^{1}H-n.m.r. spectra of the compounds *I—III* have not revealed any evident difference. We failed to record the signal of the proton on heterocyclic nitrogen. The signals of aromatic protons of the synthesized compounds formed multiplets in the region 7.42—7.85 p.p.m. Ref. [4] gives for benzimidazole the value 7.22 p.p.m. The signals of protons of 2,4-dinitrophenyl group have the following values of chemical shifts and interaction constants: 8.82 p.p.m. (2 Hz) doublet; 8.27 p.p.m. (9 Hz) quartet; 7.10 p.p.m. (9 Hz) doublet.

The ^{1}H-n.m.r. spectra proved unambiguously the substitution in the position 1. With the compounds *VIII* and *IX* the signals of protons of the methyl and ethyl groups were recorded.

The aromatic protons of benzimidazole group in the compounds *VIII* and *IX* have the same positions of chemical shifts, they form 2 multiplets at 7.85 and 7.42 p.p.m. The signals of chemical shifts and the interaction constants of protons

Table 2

Antimycobacterial activity (MIC in μg/cm^3) of the prepared compounds

Compound	*M. tuberculosis* $H_{37}R_v$	*M. kansasii*	*M. avium*	*M. fortuitum*
I	10	25	25	25
II	10	25	25	25
III	25	25	50	50
IV	10	25	50	100
V	25	25	100	100
VII	10	25	25	25
VIII	5	25	50	25
IX	5	10	50	10
XI	5	100	100	100
XII	100	100	100	100
XIII	10	25	25	25
Isonicotinohydrazide	1	10	10	50
2-Ethylthioisonicotinamide	1	10	25	50
2-Mercaptobenzothiazole	10	50	25	25

Table 3

Antifungal activity (MIC in μg/cm³) against dermatophytes

Compound	*Trichophyton*						*Microsporum*		*Epidermophyton*
	rubrum	*megninii*	*mentagrophytes*	KAUFMANN—WOLF	*verrucosum*	*violaceum*	*gypseum*	*cookei*	*floccosum*
I	100	100	100	100	100	100	100	100	100
II	25	50	50	50	10	25	25	25	50
IV	25	5	10	5	5	10	10	25	5
a	500	500	500	500	500	500	500	500	500
b	75	100	75	75	75	100	100	100	75
c	100	100	100	100	—	100	100	100	100

MIC of the compounds *III* and *V—XII* corresponds to the values of the compound *I*.
a) Myco Polycid; *b*) 2-mercaptobenzothiazole; *c*) Haloprogin.

of 2,4-dinitrophenylthio group in the compound *VIII* have the following values: 9.10 p.p.m. (2 Hz) doublet; 8.17 p.p.m. (9 Hz) quartet; 7.05 p.p.m. (9 Hz) doublet; CH_3 groups: 3.87 p.p.m. singlet; in the compound *IX*: 9.05 p.p.m. (2 Hz) doublet; 8.15 p.p.m. (9 Hz) quartet; 7.07 p.p.m. (9 Hz) doublet; CH_3- 1.37 p.p.m. (6 Hz) triplet; $-CH_2-$ 4.37 p.p.m. (6 Hz) quartet.

The infrared spectra of the prepared compounds showed intensive absorption bands of symmetric and asymmetric vibrations of NO_2 group in the region of 1310—1345 and 1510—1550 cm^{-1}. The bands of symmetric stretching vibration of NO_2 group were more intensive. The absorption bands with the compounds *II—VII* were wider and more complex.

The prepared compounds were tested for tuberculostatic and antifungal activities. The active compounds against mycobacteria are presented in Table 2. Their activities against atypical mycobacteria [5, 6] under the conditions of tests were almost as high as MIC of antituberculostatics. The compounds *I*, *II*, *VII*, *IX*, and *XIII* were more active than 2-mercaptobenzothiazole [7].

Against dermatophytes the compound *IV* was proved to be most active; its activity was comparable to that of the used antifungal preparations [5]. The starting compound and those substituted on nitrogen were practically inactive (Table 3).

Experimental

Infrared spectra of the prepared compound were measured as suspensions in Nujol on a Specord spectrophotometer in the region of 400—4000 cm^{-1}.

^{1}H-N.m.r. spectra of the prepared compounds (10% solutions in DMSO) were recorded on a Tesla BS 487 A spectrophotometer at working frequency 80 MHz using tetramethylsilane as standard.

The method used for antimycobacterial tests has been described in [7] and for antifungal tests in [8, 9].

The compounds *I—III* were prepared after [1—3].

2-(2,4-Dinitrophenylthio)benzimidazolium chloride

The mixture of 2-mercaptobenzimidazole (3 g; 0.02 mol) and 2,4-dinitrochlorobenzene (4 g; 0.02 mol) in dry benzene (40 cm^3) was refluxed for 1 h. After cooling, crystalline precipitate was formed which on crystallization from benzene, toluene, *etc.* had the melting point 206—207°C.

Salts of 2-(2,4-dinitrophenylthio)benzimidazole (IV—VII)

The mixture of 2-(2,4-dinitrophenylthio)benzimidazole (3.1 g; 0.01 mol), mineral acid (0.03 mol), and ether (60 cm^3) was refluxed under stirring for 30 min. The precipitate, formed after cooling, was crystallized from ethanol.

1-Alkyl-2-(2,4-dinitrophenylthio)benzimidazole (VIII—XV)

To 0.01 M solution of sodium methoxide (40 cm^3) in methanol 2-(2,4-dinitrophenylthio)benzimidazole (0.01 mol) was added in small portions under stirring at 25°C for 20 min. The temperature of the reaction mixture increased gradually to 50°C, then the alkylation or acylation reagent (0.011 mol) was added under vigorous stirring. After 1 h the mixture was cooled and poured onto ice. The formed compound was crystallized from chloroform or ethanol.

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