THIURONIUM SALTS IN THE SYNTHESIS OF THIAZOLE DERIVATIVES. SYNTHESIS OF BENZIMIDAZOLYLTHIAZOLES. MOLECULAR AND CRYSTAL STRUCTURE OF 2-ACETYLAMINO-5-(2-BENZIMIDAZOLYL)-4-METHYLTHIAZOLE

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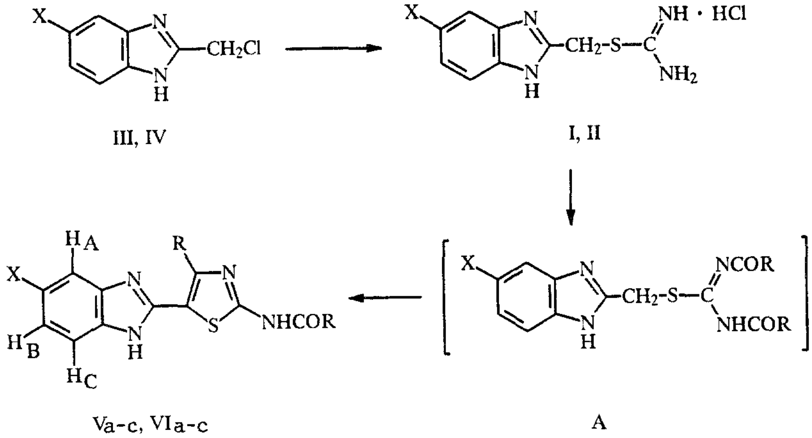
5-(2-Benzimidazolyl)thiazoles were obtained by the reaction of benzimidazolylmethylthiuronium salts with carboxylic acid anhydrides. The three-dimensional structure of 2-acetylamino-5-(2-benzimidazolyl)-4-methylthiazole monohydrate was investigated by x-ray diffraction analysis (XDA).

Benzimidazole derivatives are widely used in medicine [1] and agriculture [2]. In particular, 4-(2-benzimidazolyl)thiazole ("thiabendazole") is used in agriculture as a systemic fungicide and seed disinfectant [3, 4]. It seemed of interest to obtain and investigate the properties of isomeric analogs of "thiabendazole" — 5-(2-benzimidazolyl)thiazole derivatives. Several 5-(2-benzimidazolyl)thiazoles, which are formed in the reaction of 2-chloromethylbenzimidazole and adducts of thiocyanates with amidines, were described in [5]. In the present research, to obtain new 5-(2-benzimidazolyl)thiazole derivatives we used our previously discovered method for the formation of a thiazole ring [6-8], which includes the synthesis of the corresponding thiuronium salts I and II and their subsequent acylation.



I, III, Va-c X=H; II, IV, VIa-c X=NO₂; Va, VIaR=H; Vb, VIbR=Me; Vc, VIc R=Et

Thiuronium salts I and II are obtained by the reaction of equimolar amounts of 2-chloromethylbenzimidazoles III and IV and thiourea in ethanol. The IR spectra of salts I and II contain a characteristic intense band at 1640-1670 cm^{-1} — an overtone of the stretching vibrations of the NH bonds in the amidine fragment of the molecule. The PMR spectra contain a singlet of the protons of the CH_2—S group at 4.22-4.24 ppm (Table 1).

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)				
				CH$_2$ (s, 2H)	4—R, s	RCO, s	benzene ring protons	
I	188...189	258 (3,81) sh 279 (3,90)	1640 3280	4,22			7,4...8,0 (sym.m AAB'B')	75
II	185...186	243 (4,27) 312 (3,94)	1660 3320	4,24			8,65 (H$_A$); 8,33 (H$_B$); 7,95 (H$_C$); J_{AB}=2,5; J_{BC}=9,0	87
Va*	335...337	333 (4,47)	1660 3280 3500		8,27 (1H)	8,65 (1H)	7,17...7,71 (sym.m AA'BB')	80
Vb	344...345	318 (4,32)	1680 3280		2,70 (3H)	2,30 (3H)	7,4...8,0 (sym.m AA'BB')	71
Vc	297...298	317 (4,51)	1640 3280		1,17 (t, 3H) 2,62 (q., 2H) J=7,2	1,25 (t,3H) 3,03 (q, 2H) J=7,2	7,4...8,0 (sym.m AA'BB')	75
VIa*	346...347	259 (4,20) 351 (4,69)	1640 3200		8,32 (1H)	8,68 (1H)	8,47 (H$_A$); 8,17 (H$_B$); 7,7 (H$_C$); J_{AB}=2; J_{BC}=9,0	86
VIb	333...335	240 (4,07) sh 330 (4,36) 351 (4,36)	1650 3200 3400		2,70 (3H)	2,30 (3H)	8,63 (H$_A$); 8,35 (H$_B$); 7,98 (H$_C$); J_{AB}=2,5; J_{BC}=9,0	77
VIc	291...292	252 (4,29) 320 (4,29) 358 (4,31)	1680 3300		1,18 (t, 3H) 2,63 (q., 2H) J=7,2	1,23 (t, 3H) 2,73 (q., 2H) J=7,2	8,62 (H$_A$); 8,32 (H$_B$); 7,97 (H$_C$) J_{AB}=2,5; J_{BC}=9,0	82

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*The PMR spectra were obtained from solutions in d$_6$-DMSO.

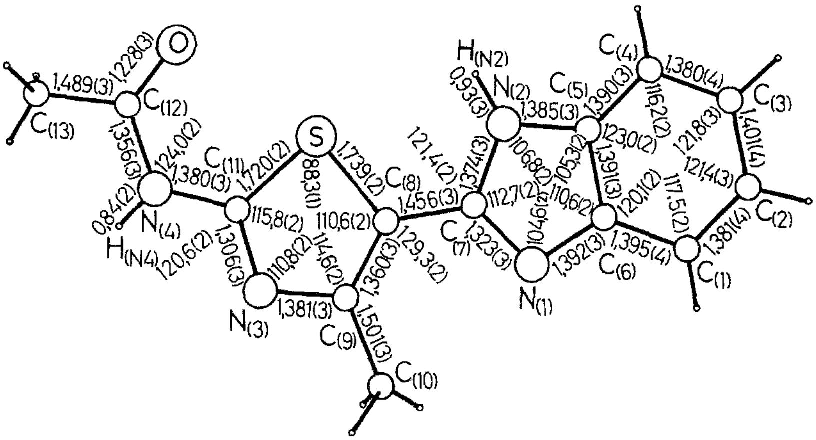

Fig. 1. Projection of the three-dimensional model of the VII molecule, numbering of the atoms, distances between the atoms (Å), and some bond angles (deg).

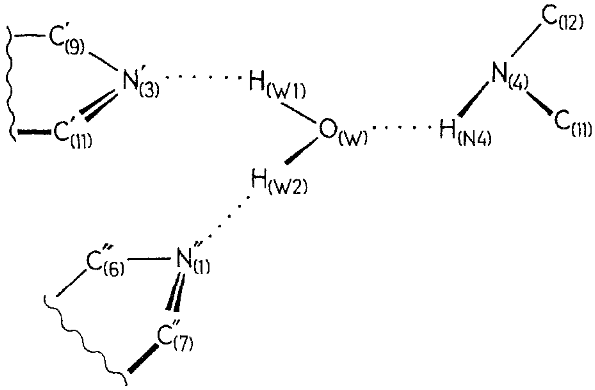

Fig. 2. Coordination of the water molecule in the crystal of the VII molecule.

The reaction of salts I and II with an excess amount of the corresponding anhydride leads to benzimidazolylthiazoles V and VI. Acetic and propionic anhydrides, as well as formyl acetate, which is formed in situ by mixing equimolar amounts of formic acid and acetic anhydride, were used in the reaction with the salts. Thiazoles Va-c and VIb were isolated from the reaction mixtures in the form of crystal hydrates, the compositions of which were established by elementary analysis and differential thermal analysis (DTA). Compounds V are colorless high-melting substances, while thiazoles VI are yellow high-melting substances. The IR spectra of thiazoles V and VI contain characteristic absorption bands of amido groups; the PMR spectra contain signals of R and RCO groups and, in the weak-field region, sets of signals corresponding to aromatic protons (see Table 1).

In accordance with [8, 9], it may be assumed that the conversion of thiuronium salts I and II to thiazoles V and VI proceeds through intermediate diacylthioureas A. Carrying out the reaction of salts I and II with the anhydrides at reduced temperatures (0-5°C) did not make it possible to isolate intermediate diacyl derivatives.

The results of x-ray diffraction analysis (XDA) for 2-acetylamino-5-(2-benzimidazolyl)-4-methylthiazole monohydrate (VII), which was obtained by repeated crystallization from aqueous alcohol solutions of Vb, are presented below. The three-dimensional projection of the VII molecule, the numbering of the atoms, the interatomic distances in angstroms, and some of the bond angles are presented in Fig. 1. The coordinates of the atoms of the VII molecule and the crystallization H_2O are presented in Table 2.

The benzene ring of the VII molecule is planar, and the $C_{(3)}$ (−0.0038 Å) and $C_{(4)}$ (0.0041 Å) atoms have the maximum deviation from the mean-square plane. The mean-square plane of the imidazole ring deviates only slightly (0.6°)

TABLE 2. Coordinates of the Atoms ($\cdot 10^4$) of 2-Acetylamino-5-(2-benzimidazolyl)-4-methylthiazole Monohydrate* (VII) (in angstroms)

Atom	x	y	z	Atom	x	y	z
S	4474(1)	1556(1)	226(1)	C(6)	1295(3)	1079(1)	-4948(3)
O	6042(2)	2170(1)	2762(2)	$C_{(7)}$	2599(3)	1134(1)	-2516(3)
$O_{(W)}$	6791(2)	287(1)	5431(3)	$C_{(8)}$	3355(3)	1002(1)	-835(3)
$N_{(1)}$	1832(2)	742(1)	-3522(2)	$C_{(9)}$	3250(3)	498(1)	177(3)
$N_{(2)}$	2601(3)	1707(1)	-3208(3)	$C_{(10)}$	2312(3)	-66(1)	-197(3)
$N_{(3)}$	4044(2)	535(1)	1767(3)	$C_{(11)}$	4707(3)	1064(1)	1959(3)
$N_{(4)}$	5563(3)	1201(1)	3462(2)	$C_{(12)}$	6186(3)	1753(1)	3813(3)
$C_{(1)}$	418(3)	894(1)	-6414(3)	$C_{(13)}$	7026(4)	1818(1)	5532(3)
$C_{(2)}$	59(3)	1324(1)	-7667(4)	$H_{(N2)}$	3012(30)	2056(11)	-2697(37)
$C_{(3)}$	547(4)	1925(1)	-7474(4)	$H_{(N4)}$	5855(28)	911(11)	4085(31)
$C_{(4)}$	1423(3)	2115(1)	-6036(3)	$H_{(W1)}$	6277(28)	88(11)	6222(31)
$C_{(5)}$	1771(3)	1678(1)	-4783(3)	$H_{(W2)}$	7297(29)	22(11)	4685(31)

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*The coordinates of the hydrogen atoms and the temperature factors can be obtained from the authors.

from the plane of the benzene ring. The thiazole ring is also planar [the $C_{(11)}$ (−0.0071 Å) and $N_{(3)}$ (0.0076 Å) atoms have the maximum deviation from its mean-square plane] and is turned around the $C_{(7)}$—$C_{(8)}$ bond by 9.2° relative to the plane of the imidazole ring.

In the crystal the VII molecules are connected by a system of hydrogen bonds directly with one another and through the water molecule. Each H_2O molecule in the crystal is connected by three hydrogen bonds with three different centers of three VII molecules (Fig. 2). The parameters of the hydrogen bonds are as follows: the $H_{(W1)}\ldots N'_{(3)}$ and $O_{(W)}\ldots N'_{(3)}$ interatomic distances and angle $N'_{(3)}\ldots H_{(W1)}$—$O_{(W)}$ are, respectively, 2.075 Å, 2.886 Å, and 156.8°; the $H_{(W2)}\ldots N''_{(1)}$ and $O_{(W)}\ldots N'_{(1)}$ distances and angle $N''_{(1)}\ldots H_{(W2)}$—$O_{(W)}$ are, respectively, 2.045 Å, 2.940 Å, and 163.7°; the $H_{(N4)}\ldots O_{(W)}$ and $O_{(W)}\ldots N_{(4)}$ distances and angle $O_{(W)}\ldots H_{(N4)}$—$N_{(4)}$ are, respectively, 1.891 Å, 2.722 Å, and 172.5°.

In addition, in the crystal the hydrogen atoms of the imidazole ring are connected by intermolecular hydrogen bonds with the oxygen atoms of the amido group. For example, the $H_{(N2)}\ldots O'$ bond has the following parameters: the $H_{(N2)}\ldots O'$ and $O'\ldots N_{(2)}$ interatomic distances and angles $N_{(2)}$—$H_{(N2)}\ldots O'$ and $C'_{(12)}$—$O'\ldots H_{(N2)}$ are, respectively, 1.911 Å, 2.830 Å, 165.8°, and 138.6°.

Thus benzimidazolylmethylthiuronium salts, like furfurylthiuronium salts with acceptor substituents in the furan ring [8], form thiazole derivatives with carboxylic acid anhydrides.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in ethanol were recorded with a Specord M-40 spectrophotometer. The IR spectra of suspensions in mineral oil were obtained with a Specord IR-75 spectrometer. The PMR spectra of solutions in CF_3COOH—$(CD_3)_2CO$ (1:2) were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The derivatographic studies were carried out with the apparatus of the Paulik—Paulik—Erdei system; the sample weights ranged from 80 to 100 mg, and the temperature-rise rate was 5°C/min.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

The crystals for XDA were obtained by crystallization of Vb from an aqueous alcohol solution. The pale-pink crystals with the composition $C_{13}H_{14}N_4O_2S$ were monoclinic and had the following unit-cell parameters: $a = 8.367(1)$, b = 22.170(6), c = 7.596(1) Å, $\gamma = 90.15(1)°$, V = 1409.0(4) $Å^3$, space group $P2_{1/B}$ (Z = 4). The experimental data were obtained with a CAD_4 automatic diffractometer (graphite monochromator, Mo K_α emission, $\theta/2\theta$ scanning up to $2\theta_{max} = 50°$). A total of 1936 reflections with $I > 3\sigma(1)$ was obtained. The structure was decoded by the direct method by means of the complex of SHELXTL programs [10] with a NOVA-3 computer and was refined within the anisotropic (isotropic for the hydrogen atoms) approximation up to divergence factors R = 0.039 and $R_W = 0.043$.

S-(2-Benzimidazolyl)methylthiuronium Chloride (I, $C_9H_{11}ClN_4S$). A 4.5-g (27 mmole) sample of III was added to a hot solution of 2.1 g (27 mmole) of thiourea in 25 ml of ethanol, and the mixture was allowed to stand at 20°C for 2-3 h. The precipitate was removed by filtration and washed with ether.

S-[5(6)-Nitro-2-benzimidazolyl]methylthiuronium chloride (II, $C_9H_{10}ClN_5O_2S$) was similarly obtained.

5-(2-Benzimidazolyl)-2-formylaminothiazole Tetrahydrate (Va, $C_{11}H_8N_4OS\cdot4H_2O$). A 4.8-g (0.02 mole) sample of salt I was added to a mixture of 10 ml of formic acid and 25 ml of acetic anhydride, and the suspension was stirred at 20°C for 20-30 min, after which the precipitate was removed by filtration. The filtrate was neutralized with 10% NaOH solution to pH 6 and cooled, and the precipitate was removed by filtration. The precipitates were combined and recrystallized from DMF—water (4:1).

5-[5(6)-Nitro-2-benzimidazolyl]-2-formylaminothiazole (VIa, $C_{11}H_7N_5O_3S$) was similarly obtained.

2-Acetylamino-5-(2-benzimidazolyl)-4-methylthiazole Hydrochloride Tetrahydrate (Vb, $C_{13}H_{12}N_4OS\cdot HCl\cdot4H_2O$). A mixture of 7.3 g (0.03 mole) of salt I, 2.5 g (0.03 mole) of sodium acetate, 50 ml of acetic anhydride, and 50 ml of water was stirred at 20°C for 15-20 min, after which it was placed in a refrigerator for 1-2 h. The precipitate was removed by filtration, washed with water, and recrystallized from 50% ethanol.

5-(2-Benzimidazolyl)-2-propionylamino-4-ethylthiazole hydrochloride tetrahydrate (Vc, $C_{15}H_{16}N_4OS\cdot HCl\cdot H_2O$), 2-acetylamino-4-methyl-5-[5(6)-nitro-2-benzimidazolyl]thiazole hydrochloride tetrahydrate (VIb, $C_{13}H_{11}N_5O_3S\cdot HCl\cdot H_2O$), and 5-[5(6)-nitro-2-benzimidazolyl]-2-propionylamino-4-ethylthiazole (VIc, $C_{15}H_{15}N_5O_3S$) were similarly obtained.

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