Chemistry of Heterocyclic Compounds, Vol.35, No. 2, 1999

ALKYLATION OF 2-ACETYLAMINO-5-(BENZIMIDAZOL-2-YL)THIAZOLE DERIVATIVES

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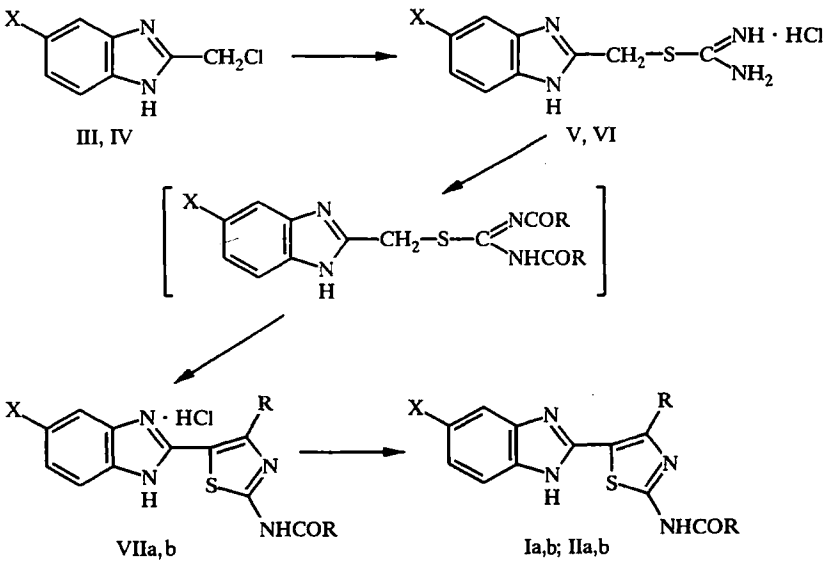
Alkylation of 2-acetylamino-5-(benzimidazol-2-yl)thiazole derivatives has been studied. In the system DMSO—KOH powder methylation of the amide-group nitrogen atom takes place mainly, while in the acetone-concentrated aqueous KOH system, the pyrrole nitrogen atom in the imidazole ring is preferentially methylated.

Basicity and nucleophilicity are the key concepts in describing the chemical properties of nitrogen-containing compounds. We have previously described [1] the synthesis of derivatives of 2-acylamino-5-(benzimidazol-2-yl)thiazoles (Ia, b and IIa, b) from 2-chloromethylbenzimidazole III and its 5-nitroderivative IV by the acylation of the corresponding thiuronium salts V and VI followed by intramolecular cyclization of the intermediate diacetylthioureas, which results in the target products. The latter contain four nitrogen atoms, which in principle can show basic behavior (coordinate protons) and nucleophilic behavior (coordinate electrophilic groups):



Ia,b, III, V, VIIa,b X = H; IIa,b, IV, VI X = NO_2; Ia, IIa, VIIa, VIIa R = Me; Ib, IIb, VIIb R = Et

Proton coordination (at least in the crystalline state) has been unambiguously determined by X-ray structure study of 2-acetylamino-5-(2-benzimidazolyl)-4-methylthiazole hydrochloride (VIIa), which is an intermediate product in the synthesis of thiazole Ia previously described [1].

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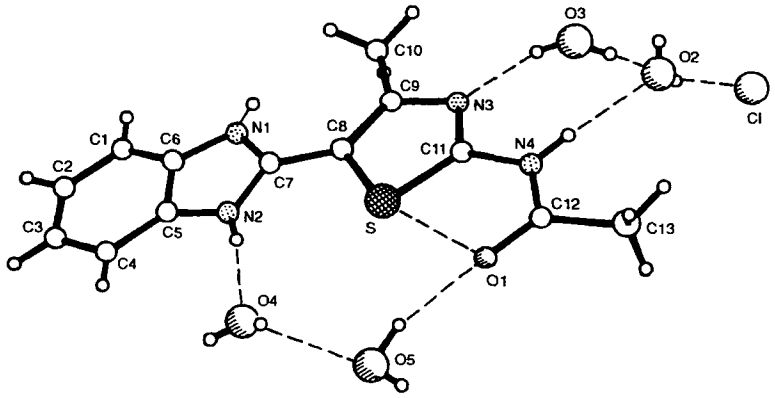


Fig. 1. Projection of three-dimensional of 2-acetylamino-5-(benzimidazol-2-yl)-4-methylthiazole VIIa hydrochloride cation.

A single crystal of VIIa hydrochloride was made by repeated crystallization from aqueous alcohol. Figure 1 shows the spatial projection of the cation of that compound, together with its environment in the crystal (water molecules and chlorine anion) and the numbering of the atoms. Tables 3-5* give the atomic coordinates, interatomic distances in A and the values of certain of the bond and torsion angles in the VIa hydrochloride cation.

Figure 1 shows that the proton is coordinated by nitrogen atom of the imidazole ring. Protonation substantially alters the interatomic distances in the imidazole moiety of VIIa hydrochloride by comparison with those in the free base Ia. The lengths of the $N_{(1)}$—$C_{(7)}$ and $N_{(2)}$—$C_{(7)}$ bonds equalize to 1,345(4) and 1,334(5) Å, in contrast to the molecule of 2-acetyl-5-benzimidazol-2-yl)-4-methylthiazole, in which the lengths of the $N_{(1)}$—$C_{(7)}$ and $N_{(2)}$—$C_{(7)}$ bonds are 1,323(3) and 1,374(3) Å respectively [1]. The lengths of the $N_{(1)}$—$H_{(1N)}$ and $N_{(2)}$—$H_{(2N)}$ bonds when compared with that of the $N_{(2)}$—$H_{(2N)}$ bond in the free base, which is 0,93(3) Å [1], also become equalized and amount to 0.852 (3) and 0.773 (5) Å.

The electron-density shift from the thiazole ring to the electron-deficient benzimidazolonium hydrochloride VIIa cation, which leads to the following changes by comparison with the structure of Ia [1].

The length of the $C_{(7)}$—$C_{(8)}$ bond between the heterocycles is reduced from 1.456 (3) to 1.443 (3) Å. The cation of 2-acetyl-5-(benzimidazol-2-yl)-4-methylthiazole hydrochloride on the whole is more nearly planar. The thiazole ring is turned on the $C_{(7)}$—$C_{(8)}$ bond through 2.9° with respect to the plane of the imidazole ring (torsion angle is 10.8° for the free base Ia) [1]. The amide moiety is planar, as in the free base Ia (the torsion on the $N_{(4)}$—$C_{(12)}$ bond is 0.6°), and it is twisted through 1.9° on the $C_{(11)}$—$N_{(4)}$ bond relative to the plane of the thiazole ring. The carbonyl moiety of the amide group is in the s-*cis* conformation in relation to the thiazole ring, S...O interatomic distance 2.671 Å, as in the molecule acetylaminothiazole Ia [1]; this is much less than the sum of the effective van der Waals radii of the oxygen and sulfur atoms (1.40 and 1.85 Å respectively [2]).

Compounds Ia, b are interesting objects for alkylation because the molecules contain different types of nitrogen atoms: two pyridine ones, a pyrrole one, and an amide one. The pyridine nitrogen atoms have [3] high nucleophilicity and can be alkylated directly by alkyl halides or dialkyl sulfates. However, we have been unable to choose a suitable solvent in which one could perform such an alkylation of 2-acetylamino-5-(benzimidazol-2-yl)-4-methylthiazole Ia with a reasonably good yield for any distinct product. In polar aprotic solvent in the presence of strong bases (in the systems DMSO—KOH and acetone—KOH), as considered by the authors of [3, 4, 5], alkylation occurs in a different way: KOH acts not so much as an agent that binds the hydrogen halide released but rather as a deprotonating agent: it detaches a proton from the pyrrole or amide nitrogen atoms, which increases the nucleophilic activity of the latter considerably. We have studied the alkylation of compounds Ia, b and IIa, b by methyl iodide in these systems with various reagent ratios.

* The VIIa single crystal showed a fairly complicated system of intermolecular hydrogen bonds involving the participation of four water molecules, organic cation, and chlorine anion, which will form the subject of a special paper.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Yield, %
		C	H	N	O	S				
VIIa	$C_{13}H_{12}N_4OS \cdot HCl \cdot 4H_2O$	41,01 / 40,99	5,67 / 5,69	14,75 / 14,71	21,15 / 21,00	8,56 / 8,42	344...345	318 (4,32)	1680	71
VIIb	$C_{15}H_{16}N_4OS \cdot HCl \cdot 4H_2O$	44,25 / 44,06	6,35 / 6,16	13,76 / 13,70	19,28 / 19,56	7,91 / 7,84	296...298	317 (4,51)	1640, 3200, 3280	75
VIIIa	$C_{14}H_{14}N_4OS$	58,57 / 58,72	4,99 / 4,93	19,77 / 19,57	5,72 / 5,59	10,95 / 11,19	296...298	321 (4,24)	1660	85
VIIIb	$C_{16}H_{18}N_4OS$	61,07 / 61,12	5,82 / 5,77	17,93 / 17,82	5,13 / 5,09	10,05 / 10,20	218...220	317 (4,33)	1600	52
IXa	$C_{14}H_{14}N_4OS$	58,63 / 58,72	5,07 / 4,93	19,73 / 19,57	5,40 / 5,59	11,17 / 11,19	138...140	298 (4,14)	1680	70
IXb	$C_{16}H_{18}N_4OS$	61,25 / 61,12	5,71 / 5,77	17,75 / 17,82	5,08 / 5,09	10,21 / 10,20	125...127	291 (4,08)	1660	46
Xa	$C_{11}H_{10}N_4S \cdot HCl \cdot H_2O$	46,47 / 46,40	4,58 / 4,60	19,51 / 19,67	5,66 / 5,62	11,11 / 11,16	360	320 (3,88)	—	76
Xb	$C_{12}H_{12}N_4S \cdot HCl \cdot H_2O$	48,18 / 48,24	4,15 / 4,05	18,83 / 18,75	5,51 / 5,35	10,67 / 10,73	295 (dec.)	323 (4,48)	—	85
XIIa	$C_{12}H_{13}N_4S$	58,86 / 58,99	5,77 / 5,78	22,91 / 22,93	—	12,46 / 12,30	195...197	309 (4,19)	—	82
XIIb	$C_{13}H_{14}N_4S$	60,38 / 60,44	5,48 / 5,46	21,69 / 21,68	—	12,45 / 12,42	231...232	299 (4,16)	—	78
XIIIa	$C_{15}H_{16}N_4OS$	60,01 / 59,98	5,41 / 5,37	18,72 / 18,65	5,31 / 5,33	10,55 / 10,67	240...241	298 (4,42)	1680	86
XIIIb	$C_{17}H_{20}N_4OS$	62,30 / 62,16	6,03 / 6,14	17,11 / 17,06	4,88 / 4,87	9,68 / 9,77	112...122	280 (4,43)	1660	74
XIV	$C_{16}H_{19}N_4OS$	43,43 / 43,45	4,35 / 4,32	12,53 / 12,67	3,67 / 3,61	7,33 / 7,25	314...315	309 (4,45)	1665	82
XVa*	$C_{15}H_{15}N_5O_3S$	52,33	4,47	20,34	13,74	9,12	—	250 (4,23)	1650	81
XVIa	$C_{15}H_{15}N_5O_3S$	52,16	4,38	20,28	13,89	9,29		299 (4,21) 327 (4,25)		
XVb*	$C_{17}H_{19}N_5O_3S$	54,72	5,05	18,91	12,64	8,68	—	250 (4,21)	1660	77
XVIb	$C_{17}H_{19}N_5O_3S$	54,68	5,13	18,75	12,85	8,59		299 (4,20) 325 (4,13)		

* Data given for an isomer mixture.

TABLE 2. PMR Spectral Characteristics of Synthesized Compounds

Compound	Chemical shifts, δ, ppm, PPM, SSCC (*J*, Hz)				
	4-R	COR	N_{Het}—CH_3 (3H, s)	CON—CH_3 (3H, s)	H_{arom}
VIIa	2,70 (3H, s)	2,30 (3H, s)	—	—	7,4...8,0 (4H, sym. m, AA'BB')
VIIb	3,03 (3H, t); 1,25 (2H, q) J = 7,2	2,62 (3H, t); 1,17 (2H, q) J = 7,2	—	—	7,4...8,0 (4H, sym. m, AA'BB')
VIIIa	2,70 (3H, s)	2,42 (3H, s)	3,77	—	7,4...8,0 (4H, sym. m, AA'BB')
VIIIb	1,18 (3H, t); 2,75 (2H, q) J = 7,2	1,30 (3H, t); 3,05 (2H, q) J = 7,2	3,75	—	7,4...8,0 (4H, sym. m, AA'BB')
IXa	2,47 (3H, s)	2,40 (3H, s)	—	4,13	7,4...8,0 (4H, asym. m, ABCD)
IXb	1,17 (3H, t); 2,80 (2H, q) J = 7,2	1,20 (3H, t); 2,62 (2H, q) J = 7,2	—	4,10	7,5...8,0 (4H, asym. m, ABCD)
Xa	2,63 (3H, s)	—	—	—	7,4...8,0 (4H, sym. m, AA'BB')
Xb	1,27 (3H, t); 2,80 (2H, q) J = 7,2	—	—	—	7,4...8,0 (4H, sym. m, AA'BB')
XIIa	2,45 (3H, s)	—	—	4,17	7,4...8,0 (4H, asym. m, ABCD)
XIIb	1,21 (3H, t); 2,75 (2H, q) J = 7,2	—	—	4,13	7,4...8,0 (4H, asym. m, ABCD)
XIIIa	2,47 (3H, s)	2,40 (3H, s)	3,73	4,10	7,4...8,0 (4H, asym. m, ABCD)
XIIIb	1,21 (3H, t); 2,77 (2H, q) J = 7,2	1,15 (3H, t); 2,68 (2H, q) J = 7,2	3,73	4,08	7,4...8,0 (4H, asym. m, ABCD)
XIV	2,43 (3H, s)	2,33 (3H, s)	3,75	3,95	7,4...8,0 (4H, sym. m, AA'BB')
XVa	2,52 (3H, s)	2,45 (3H, s)	3,75	4,18	8,82 (H_A); 8,45 (H_B); 8,02 (H_C) J_{AB} = 2,5; J_{AB} = 9,0
XVIa	2,52 (3H, s)	2,45 (3H, s)	3,75	4,25	8,79 (H_A); 8,42 (H_B); 8,03 (H_C) J_{AB} = 2,5; J_{AB} = 9,0
XVb	1,23 (3H, t); 2,73 (2H, q) J = 7,2	1,17 (3H, t); 2,00 (2H, q) J = 7,2	3,72	3,87	8,78 (H_A); 8,37 (H_B); 8,03 (H_C) J_{AB} = 2,5; J_{AB} = 9,0
XVIb	1,23 (3H, t); 2,73 (2H, q) J = 7,2	1,17 (3H, t); 2,00 (2H, q) J = 7,2	3,72	3,93	8,70 (H_A); 8,37 (H_B); 8,08 (H_C) J_{AB} = 2,2; J_{AB} = 9,0

TABLE 3. Atomic Coordinates ($\times 10^4$) for the Cation of 2-Acetylamino-5-(benzimidazol-2-yl)-4-methylthiazole* VIIa

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
S	7652 (1)	4124 (1)	6276 (1)	$C_{(2)}$	6678 (11)	8481 (5)	840 (7)
$O_{(1)}$	7794 (4)	3191 (2)	8977 (3)	$C_{(3)}$	6554 (11)	8785 (5)	2128 (8)
Cl	6208 (8)	-1239 (4)	6975 (5)	$C_{(4)}$	6710 (10)	8090 (5)	3376 (7)
$O_{(2)}$	580 (3)	-1400 (3)	7084 (2)	$C_{(5)}$	7010 (9)	7067 (5)	3283 (6)
$O_{(3)}$	7555 (9)	716 (4)	4240 (6)	$C_{(6)}$	7146 (5)	6767 (2)	1996 (3)
$O_{(4)}$	6830 (9)	6478 (4)	7109 (5)	$C_{(7)}$	7500 (4)	5391 (2)	3683 (3)
$O_{(5)}$	6981 (6)	5098 (2)	9680 (3)	$C_{(8)}$	7771 (4)	4350 (2)	4443 (3)
$N_{(1)}$	7454 (4)	5710 (2)	2280 (3)	$C_{(9)}$	8144 (5)	3449 (2)	3970 (3)
$N_{(2)}$	7242 (4)	6192 (2)	4321 (3)	$C_{(10)}$	8403 (6)	3296 (3)	2470 (4)
$N_{(3)}$	8300 (5)	2590 (2)	5023 (3)	$C_{(11)}$	8083 (4)	2844 (2)	6265 (3)
$N_{(4)}$	8198 (8)	2106 (4)	7480 (5)	$C_{(12)}$	8040 (5)	2311 (2)	8795 (3)
$C_{(1)}$	6964 (10)	7470 (5)	742 (7)	$C_{(13)}$	8176 (6)	1402 (3)	9984 (4)

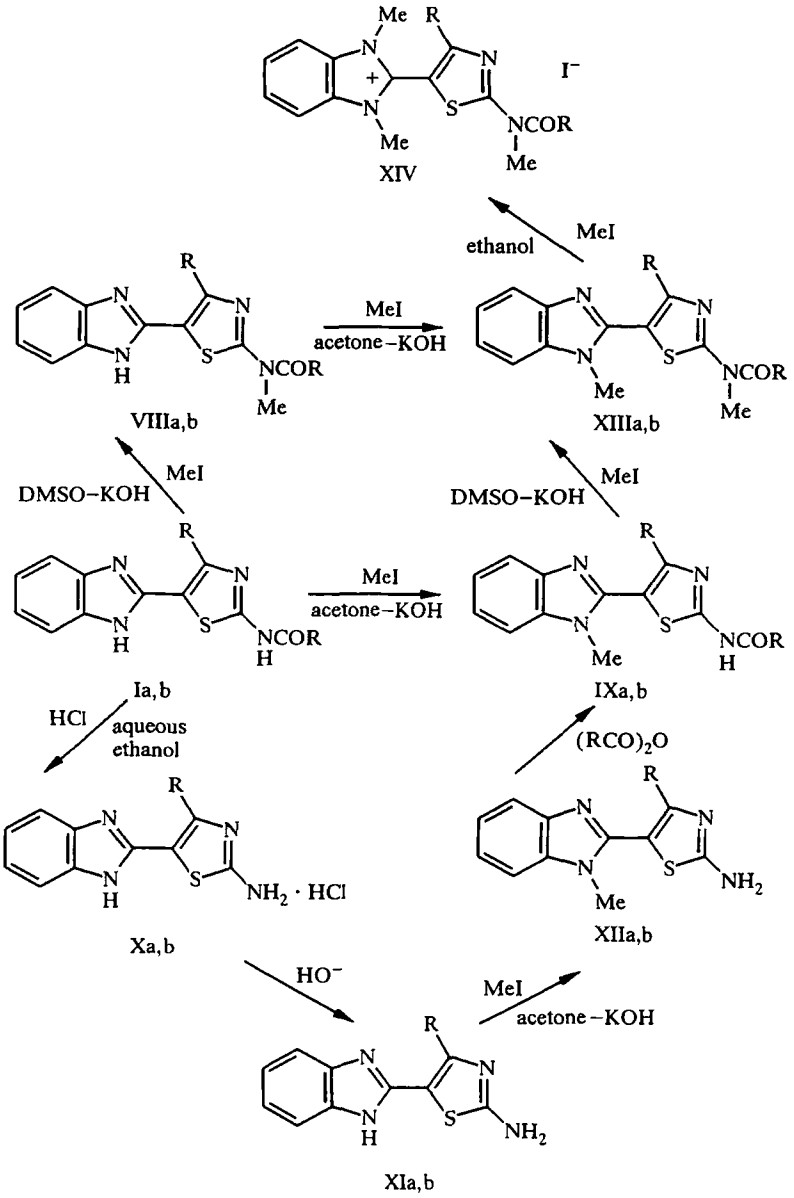
* The coordinates of the hydrogen atoms and the values of the temperature factors are available from the authors.

TABLE 4. Some Bond Lengths in the VIIa Hydrochloride Cation

Bond	Bond length, Å	Bond	Bond length, Å
$C_{(1)}$—$C_{(2)}$	1,371 (10)	$C_{(7)}$—$C_{(8)}$	1,443 (4)
$C_{(2)}$—$C_{(3)}$	1,385 (11)	$C_{(8)}$—$C_{(9)}$	1,367 (5)
$C_{(3)}$—$C_{(4)}$	1,375 (9)	$C_{(9)}$—$C_{(10)}$	1,500 (5)
$C_{(4)}$—$C_{(5)}$	1,387 (9)	S—$C_{(8)}$	1,736 (3)
$C_{(5)}$—$C_{(6)}$	1,381 (7)	S—$C_{(11)}$	1,713 (3)
$C_{(1)}$—$C_{(6)}$	1,387 (9)	$N_{(3)}$—$C_{(9)}$	1,377 (4)
$N_{(1)}$—$C_{(6)}$	1,385 (4)	$N_{(3)}$—$C_{(11)}$	1,306 (5)
$N_{(2)}$—$C_{(5)}$	1,389 (6)	$N_{(4)}$—$C_{(11)}$	1,380 (5)
$N_{(1)}$—$C_{(7)}$	1,345 (4)	$N_{(4)}$—$C_{(12)}$	1,351 (6)
$N_{(2)}$—$C_{(7)}$	1,334 (5)	$N_{(4)}$—$H_{(4N)}$	0,82 (3)
$N_{(1)}$—$H_{(1N)}$	0,85 (3)	$O_{(1)}$—$C_{(12)}$	1,222 (4)
$N_{(2)}$—$H_{(2N)}$	0,77 (5)	$C_{(12)}$—$C_{(13)}$	1,499 (4)

TABLE 5. Some Bond Angles (θ, deg) and Torsion Angles (ψ, deg) in VIIa Hydrochloride Cation

Angle	θ	Angle	θ
$C_{(1)}$—$C_{(2)}$—$C_{(3)}$	121,7 (0,6)	S—$C_{(8)}$—$C_{(9)}$	110,3 (0,2)
$C_{(2)}$—$C_{(3)}$—$C_{(4)}$	121,9 (0,6)	$C_{(8)}$—S—$C_{(11)}$	88,4 (0,1)
$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	116,7 (0,6)	$N_{(3)}$—$C_{(9)}$—$C_{(8)}$	114,6 (0,3)
$C_{(4)}$—$C_{(5)}$—$C_{(6)}$	121,3 (0,6)	$N_{(3)}$—$C_{(9)}$—$C_{(10)}$	117,4 (0,3)
$C_{(5)}$—$C_{(6)}$—$C_{(1)}$	121,7 (0,6)	$C_{(9)}$—$N_{(3)}$—$C_{(11)}$	110,5 (0,3)
$C_{(6)}$—$C_{(1)}$—$C_{(2)}$	116,7 (0,6)	S—$C_{(11)}$—$N_{(3)}$	116,2 (0,2)
$N_{(1)}$—$C_{(6)}$—$C_{(5)}$	106,4 (0,3)	$N_{(3)}$—$C_{(11)}$—$N_{(4)}$	120,7 (0,3)
$N_{(2)}$—$C_{(5)}$—$C_{(6)}$	107,7 (0,5)	$C_{(11)}$—$N_{(4)}$—$C_{(12)}$	124,0 (0,4)
$C_{(5)}$—$N_{(2)}$—$C_{(7)}$	107,6 (0,4)	$C_{(11)}$—$N_{(4)}$—$H_{(4N)}$	115,5 (1,8)
$N_{(1)}$—$C_{(7)}$—$N_{(2)}$	110,0 (0,3)	$O_{(1)}$—$C_{(12)}$—$N_{(4)}$	120,8 (0,3)
$C_{(6)}$—$N_{(1)}$—$C_{(7)}$	108,3 (0,3)	$N_{(4)}$—$C_{(12)}$—$C_{(13)}$	116,0 (0,3)
$C_{(7)}$—$N_{(1)}$—$H_{(1N)}$	128,0 (1,5)	Angle	ψ
$C_{(7)}$—$N_{(2)}$—$H_{(2N)}$	131,8 (3,5)		
$N_{(2)}$—$C_{(7)}$—$C_{(8)}$	122,9 (0,3)	S—$C_{(8)}$—$C_{(7)}$—$N_{(2)}$	2,9
$C_{(7)}$—$C_{(8)}$—$C_{(9)}$	131,0 (0,3)	$C_{(12)}$—$N_{(4)}$—$C_{(11)}$—S	-1,9
		$O_{(1)}$—$C_{(12)}$—$N_{(4)}$—$C_{(11)}$	-0,6

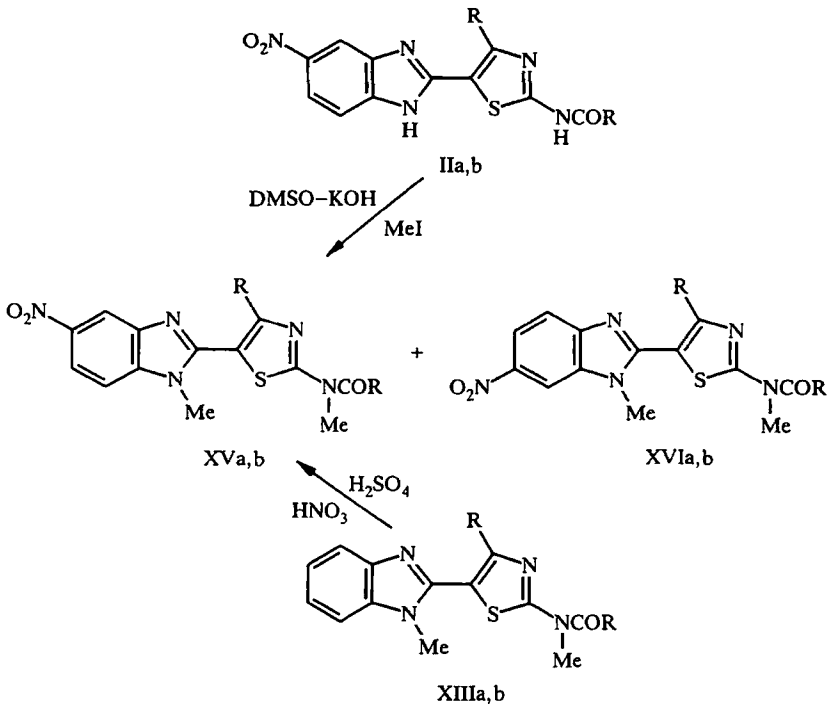


Ia, VIIIa — XIIIa, XIV R = Me; Ib, VIIIb — XIIIb R = Et

With a 1:1 ratio for Ia, b:CH_3I, in the DMSO—KOH system the products from monomethylation on nitrogen atom of the amide group (VIIIa, b) were obtained, whose PMR spectra contained a new singlet from the methyl protons at 3.77 ppm. The signals from the protons in the acyl and alkyl groups (RCO and R) were hardly displaced at all by comparison with those for the analogous protons in the initial substances Ia, b [1]. The aromatic protons in the benzene ring correspond to a symmetrical multiplet with a AA'BB' spin system (Table 2).

Monomethylation of compounds Ia, b in the acetone-KOH system gave products from methylation of the imidazole nitrogen atom (IXa, b). PMR spectra of these products have a proton singlet from the methyl group introduced in the region of 4.10-4.13 ppm, together with signals from the alkyl group R in position 4 in the thiazole ring, which are displaced to the strong-field side, and also signals from the protons of the benzene ring, which form an unsymmetrical multiplet of ABCD spin system.

Acid hydrolysis of amides Ia, b in an aqueous alcohol medium gave the corresponding amines, which were isolated as the hydrochlorides (Xa, b). Treatment of the latter with aqueous ammonia gave the bases (XIa, b). When compounds XIa, b were methylated in the two-phase system acetone-concentrated aqueous KOH, similarly to 2-aminobenzimidazole [6] the products of alkylation of the imidazole nitrogen atom (XIIa, b) were formed. In



IIa, XIIIa, XVa, XVIa R = Me; IIb, XIIIb, XVb, XVIb R = Et

the PMR spectra of these compounds the protons of the NCH_3 group resonate in the region of 4.13-4.17 ppm, while the aromatic protons in the benzene ring correspond to an unsymmetrical multiplet of ABCD spin system (Table 2).

Further acylation of amines XIIa, b with carboxylic acid anhydrides led to the amides IXa, b, which were obtained, as stated above, on monomethylation of compounds Ia, b in the acetone—KOH system.

Amines VIIIa, b and IXa, b reacted with excess of methyl iodide in the DMSO—KOH and in the acetone-KOH system to give products of the methylation of both of the NH groups: compounds XIIIa, b. In their PMR spectra (Table 2) two signals from the NCH_3 group protons and an unsymmetrical multiplet from the benzene ring protons are observed.

When compound XIIIa was treated with excess of methyl iodide in ethanol in the absence of bases, the salt-type product XIV was formed, whose PMR spectrum contained two singlets from the NCH_3 groups whose intensity ratio was 2:1, the weak-field signal being the stronger one. Occurence in the PMR spectrum of a symmetrical multiplet of the benzene-ring aromatic proton spin system AA'BB', allows to consider that excess methylation takes place on the pyridine nitrogen atom of the imidazole ring, not the thiazole one.

The structural differences between compounds VIII and IX make themselves felt also in the UV spectra. Long-wave absorption band for the products from N-monomethylation of the imidazole moiety of amides IXa, b (Table 1), shifted hypsochromically in comparison with the band in the unmethylated benzimidazolylthiazoles Ia, b, with λ_{max} = 317-318 nm [1]. The absorption bands almost coincide for the products from amide monomethylation of VIIIa, b and for the unmethylated compounds Ia, b.

When the nitroderivatives IIa, b react with methyl iodide in a ratio 1:1 in the DMSO—KOH and acetone-KOH systems, we proved unable to isolate individual monoalkylation products. Alkylation in excess CH_3I in the DMSO—KOH system leads to methylation of nitrogen atoms in the imidazole ring and amide group, but on account of the lack of symmetry in the nitrobenzimidazole moiety of the molecule, mixture of 5- and 6-nitrobenzimidazoles (XV and XVI) is formed. The XVa:XVIa isomer ratio determined from the PMR spectra was 3:1, while the XVb:XVIb isomer ratio was 55:45.

The same mixture of isomers XV and XVI was also formed on nitrating compounds XIIIa, b with mixture of nitric and sulfuric acids. The ratio of them in these cases was close to 1:1.

The synthesized alkyl derivatives are crystalline and mostly high-melting substances soluble in polar solvents but not soluble in water (Table 1).

In our case, alkylation with equimolar amount of CH_3I was always accompanied by formation of dialkylation products (5-10%), which were removed by recrystallization, so the yields of monomethylation products did not exceed 85%.

EXPERIMENTAL

The electronic absorption spectra were recorded on a Specord M-40 spectrophotometer in ethanol, while the IR spectra were recorded on a Specord instrument in vaseline oil. The PMR spectra were recorded on Tesla BS-467 instrument (60 MHz), internal standard HMDS. Single crystal of VIIa hydrochloride hydrate was grown by repeated crystallization from aqueous alcohol. The X-ray structure study was performed using CAD-4 automatic diffractometer. The calculations were performed by a direct method in an anisotropic approximation (isotropic for the hydrogen atoms) to $R = 0.030$ and $R_w = 0.034$*.

2-Acetylamino-5-(benzimidazol-2-yl)-4-methylthiazole (Ia), 5-(Benzimidazol-2-yl)-4-ethyl-2-propionyl-aminothiazole (Ib) and the corresponding hydrochlorides VIIa, b were synthesized as previously described [1].

2-Acetylamino-4-methyl-5-[5(6)-nitrobenzimidazol-2-yl]thiazole (IIa) and 4-Ethyl-5-[5(6)-nitrobenzimidazol-2-yl]-2-propionylaminothiazole (IIb) were prepared by nitrating of compounds IIa, b by a standard method [6] and by cyclization *via* the thiuronium salt VI [1].

2-(N-Acetyl-N-methyl)amino-5-(benzimidazol-2-yl)-4-methylthiazole (VIIIa). To solution of 2.5 g (7 mmol) of compound Ia in 20 ml of DMSO we added 0.78 g (14 mmol) of finely powdered KOH and 1.61 g (8 mmol) of CH_3I. The reaction mass was stirred at room temperature for 3 h and poured into 100 ml of water. The precipitate was filtered off and recrystallized from ethanol.

Similarly, from compound Ib **5-(benzimidazol-2-yl)-2-(N-propionyl-N-methyl)amino-4-ethylthiazole (VIIIb)** was obtained.

2-Acetylamino-4-methyl-5-(1-methylbenzimidazol-2-yl)thiazole (IXa). A. To solution of 1.2 g (5 mmol) of compound Ia in 20 ml of acetone we added 10 ml of 50% aqueous solution of KOH, and with vigorous stirring at a temperature of 5-10°C we added by drops 0.85 g (6 mmol) of CH_3I. The reaction mass was stirred for 20-30 min, and the organic layer was separated, while the aqueous one was extracted with acetone (2 × 15 ml). The combined acetone extracts were evaporated to dryness, and the product IXa was recrystallized from ethanol.

Similarly, from compound Ib **4-ethyl-5-(1-methylbenzimidazol-2-yl)-2-propionylaminothiazole (IXb)** was obtained, from compound XIa **2-amino-4-methyl-5-(1-methylbenzimidazol-2-yl)thiazole (XIIa)** was obtained, and from compound XIb **2-amino-4-ethyl-5-(1-methylbenzimidazol-2-yl)thiazole (XIIb)** was obtained.

B. Solution of 1 g (4 mmol) of amine XIIa in 10 ml of acetic anhydride was boiled for 10-15 min, and the excess anhydride was hydrolyzed with 10 ml of water. The precipitate formed on cooling of product IXa was recrystallized from ethanol.

Similarly, amide IXb from amine XIIb and propionic anhydride was obtained.

Monohydrate of 2-Amino-5-(benzimidazol-2-yl)-4-methylthiazole Hydrochloride (Xa). Solution of 8.5 g (22 mmol) of compound Ia in mixture of 50 ml of ethanol and 20 ml of 20% aqueous solution of HCl was boiled for 5 h and then cooled. The precipitate of product Xa was filtered off and recrystallized from aqueous ethanol.

Similarly, from compound Ib **monohydrate of 2-amino-5-(benzimidazol-2-yl)-4-ethylthiazole hydrochloride (Xb)** was obtained.

2-(N-Acetyl-N-methyl)amino-4-methyl-5-(1-methylbenzimidazol-2-yl)thiazole (XIIIa). To solution of 2.5 g (6.6 mmol) of compound IXa in 20 ml of DMSO we added 0.78 g (14 mmol) of finely ground KOH and 1.42 g (10 mmol) of CH_3I, with stirring at room temperature for 2 h and the addition of a further 0.4 g (7 mmol) and 1.42 g (10 mmol) of CH_3I. The obtained mixture was stirred for 3 h, poured into 100 ml of water, precipitate filtered off, recrystallized from ethanol.

Similarly, **4-methyl-5-(1-methylbenzimidazol-2-yl)-2-(N-propionyl-N-methyl)aminothiazole (XIIIb)** from compound IXb was obtained.

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* The crystal structure of VIIa hydrochloride hydrate will be the subject of a special paper.

2-[N-Acetyl-N-methyl)amino-4-methylthiazol-5-yl]-1,3-dimethylbenzimidazolium Iodide (XIV). To solution of 1.5 g (5 mmol) of compound VIa in 30 ml of ethanol we added 2.1 g (15 mmol) of CH_3I. The solution was boiled for 5 h, cooled, and diluted with 50 ml of ether. The precipitate of product XIV was washed with ether and dried in air.

2-(N-Acetyl-N-methyl)amino-4-methyl-5-(1-methyl-5-nitrobenzimidazol-2-yl)thiazole (XVa) and 2-(N-Acetyl-N-methyl)amino-4-methyl-5-(1-methyl-6-nitrobenzimidazol-2-yl)thiazole (XVIa). A. To solution of 2.18 g (5 mmol) of compound IIa in 25 ml of DMSO we added 0.87 g (15.6 mmol) of finely ground KOH and 1.1 g (7.6 mmol) of CH_3I and stirred the mixture for 3 h. The mixture was then diluted with water (100 ml), and the precipitate was separated and recrystallized from ethanol.

B. To solution of 2.18 g (5 mmol) of compound XIIIa in 4 ml of concentrated sulfuric acid at 10-15°C we added dropwise nitrating mixture, which consisted of 0.8 ml of HNO_3 (ρ= 1.4 g/cm^3) and 1.2 ml of concentrated H_2SO_4. The reaction mass was allowed to stand at room temperature for 20-30 min and then poured onto 30 g of crushed ice. The residue was recrystallized from ethanol.

Similarly, from compounds IIb and XIIIb mixture of **4-ethyl-5-(1-methyl-5-nitrobenzimidazol-2-yl)-2-(N-propionyl-N-methyl)aminothiazole (XVb)** and **4-ethyl-5-(1-methyl-6-nitrobenzimidazol-2-yl)-2-(N-propionyl-N-methyl)aminothiazole (XVIb)** was obtained.

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