SYNTHESIS OF N-ALKYL- AND N-(β-HYDROXYALKYL)-2-(ACYLMETHYLTHIO)BENZIMIDAZOLES AND THEIR PROPERTIES

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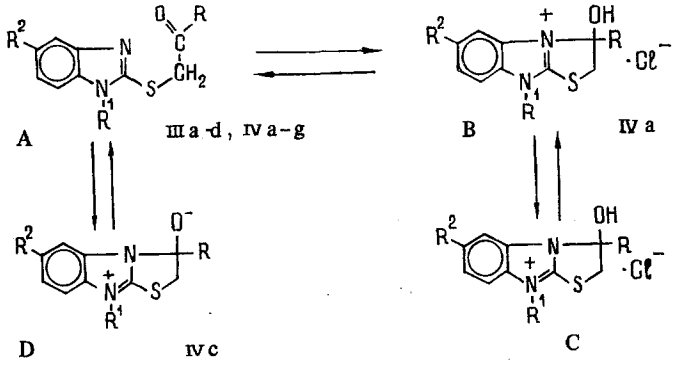
N-alkyl- and N-(β-hydroxyalkyl)-2-(acylmethylthio)benzimidazoles have been obtained by the reaction of N-alkyl- and N-(β-hydroxyalkyl)benzimidazoline-2-thiones with α-haloketones. The structures of the substances synthesized have been confirmed by IR, PMR, and mass spectra. The biological properties of the compounds obtained have been studied.

Natural and synthetic derivatives of benzimidazole have found practical use in medicine as analgesics, anthelminthics, bactericides, and other medicinal agents [1]. In the N-substituted benzimidazoline-2-thione series, the most studied compounds are the 2-alkylthio ethers, which possess neurotropic activity [2].

The aim of our work was to synthesize and study the biological properties of 1-methyl-2-(acylmethylthio)benzimidazoles (IIIa–d) and 1-(β-hydroxyethyl)-2-(acylmethylthio)-5-nitrobenzimidazoles (IVa–g) obtained by the reaction of 1-methylbenzimidazoline-2-thione (I) and of 1-(β-hydroxyethyl)-5-nitrobenzimidazoline-2-thione (II), respectively, with α-halo ketones in methanol (or ethanol).

We have previously shown the existence of ring-chain tautomerism in the structurally close 2-(acylmethylthio)benzimidazoles [3], and therefore the aim of the investigation also included an evaluation of the possibility of the existence of ring isomers at different pH values for the substances synthesized (III and IV) containing substituents at the N^1 nitrogen atom.



R = Alk, Ar, Het; $R^1 = CH_3, C_2H_4OH$; $R^2 = H, NO_2$

Analysis of the IR, PMR, and mass spectra showed that the molecules of compound (III) and (IV), both in the free (regardless of the pH of the medium) state and in the excited state exist exclusively in the open-chain tautomeric form A. Thus, in the IR spectra of the compounds synthesized we detected strong absorption bands of a CO group in the 1736–1660 cm^{-1} region and of OH groups in the 3500–3210 cm^{-1} region, assigned to ν_{OH} in the substituent R^1 (IVa–g).

In the PMR spectrum, this hypothesis is confirmed by the presence of signals with δ 4.40 ppm (for (IVa)) and 5.10 ppm (IVc), characterizing the SCH_2 group in the noncyclic form [4].

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TABLE 1. PMR Spectra of Compounds (IVa and c)

Compound	Chemical shifts, δ, ppm							Spin–spin coupling constants, J, Hz	
	R	OCH_2	NCH_2	SCH_2	H^7	H^6	H^4	H^7, H^6	H^6, H^4
IVa	2,26 s	3,70 t	4,26 t	4,40 s	7,62 7,73	8,00 8,02 8,09 8,11	8,26 8,30	8,8	2,2
IVc	7,68 m	3,72 t	4,28 t	5,10 s	7,59 7,58	7,98 8,00 8,06 8,08	8,21 8,23	8 0	2,2

The distributions of the integral intensities of the signals are, respectively, 3:2:2:2:3 (IVa) and 5:2:2:2:3 (IVc). The H^7 and H^6 aromatic protons of the benzimidazole moiety of the molecule are readily identified (AB system), which permits the position of the NO group in compounds (IVa–c) to be checked.

However, the presence of an OH group in the substituent R^1 led to some indeterminacy in the evaluation of the results of IR and PMR spectroscopy. In this case, the results of the mass-spectrometric investigations are unambiguous. The initial processes of the breakdown of the molecular ion ($M^{\cdot+}$) observed in the mass spectrum, which are connected with the splitting off of the particles $COCH_3$ and CH_2COCH_3 (IVa) or COC_6H_5 and $CH_2COC_6H_5$ (IVc) can be explained exclusively by the chain (open) form of A [5]. Otherwise, fragmentation processes accompanied by the detachment of the particles R and OH (or RH and H_2O) from the tetrahedral carbon atom in the molecule, leading to fragmentary ions with completely aromatic structures should be predominant (forms B–D) [6, 7]. In the case of a cyclic form $M^{+\cdot}$ the process $M^{+\cdot} \xrightarrow{-CH_2S} (M - CH_2S)^+$ takes place [8]. In the mass spectra obtained, no fragmentary ions showing the realization of processes typical for the cyclic forms (B–D) were observed.

The formation of ions with m/z 280 and 252 shows the presence of acetyl and benzoyl groupings in the molecules of (IVa) and (IVc), respectively. The elimination of the particle CH_2COR is connected with the realization of usual β decomposition relative to the hetaryl moiety of the molecule and once more confirms the reality of the existence of only one tautomeric form, A. The mutual arrangement of the substituents in positions 1 and 2 of the benzimidazole molecule is shown in the appearance of an "ortho effect." The following processes are recorded in the mass spectra:

$$1)\ M^{+\cdot} \xrightarrow{-SCH_2COR} (M-SCH_2COR)^+,$$

$$2)\ (M-RCO)^+ \xrightarrow{-CH_2CH_2O} m/z\ 208,$$

$$3)\ (M-CH_2COR)^+ \xrightarrow{-CHO} m/z\ 209\ [9].$$

Mass spectra, m/z (intensity given in % of the maximum ion peak; the peaks of ions with intensities ≥10% are given):

IVa: 42 (11,8), 43 (90,5), 45 (13,8), 75 (10,0), 76 (13,8), 90 (16,3), 117 (11,6), 118 (15,0), 130 (10,7), 134 (10,0), 161 (10,1), 162 (25,0), 163 (25,0), 176 (30,0), 177 (10,0), 190 (10,7), 192 (12,5), 206 (21,2), 208 (26,2), 209 (100,0), 210 (27,5), 211 (10,6), 236 (25,0), 238 (20,0), 252 (75,0), 254 (10,0), 280 (18,8) 295 (50,0), 296 (11,0). $W_\mu = 4,7$.

IVc: 45 (18,7), 50 (10,9), 51 (33,5), 63 (11,8), 65 (20,0), 75 (10,5), 76 (17,0), 77 (43,5), 78 (23,5), 91 (39,2), 93 (30,0), 105 (52,0), 106 (39,2), 118 (16,2), 130 (10,0), 134 (14,8), 162 (23,1), 163 (10,1), 206 (10,4), 208 (10,0), 209 (14,4), 238 (13,9), 252 (100,0), 315 (17,4), 357 (26,1). $W_\mu = 2,6$

The results of microbiological and pharmacological trials show that compound (IV) possesses a weak antifungal activity and a weak radioprotective effective, while (IVd) has a very slight muscle-relaxant action. The remaining compounds exhibited no appreciable activity.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	R	R^1	R^2	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				R_f^*	IR spectrum, cm^{-1}	
						C	H	N	S		C	H	N	S		ν_{CO}	ν_{OH}
IIIa	4-BrC_6H_4	CH_3	H	86	136—137	50,6	4,4	7,4	8,5	$C_{16}H_{13}BrN_2OS \cdot H_2O$	50,7	4,0	7,4	8,4	0,89	1690	—
b	4-$O_2NC_6H_4$	CH_3	H	92	155—156	58,4	4,2	12,6	9,4	$C_{16}H_{13}N_3O_3S$	58,7	4,0	12,8	9,8	0,65	1692	—
c	4-$CH_3OC_6H_4$	CH_3	H	91	123—125	65,3	5,1	9,3	10,0	$C_{17}H_{16}N_2O_2S$	65,3	5,2	9,0	10,3	0,60	1690	—
d	α-C_4H_3S	CH_3	H	57	133—134	58,5	4,4	9,5	22,2	$C_{14}H_{12}N_2OS_2$	58,3	4,2	9,7	22,2	0,56	1681	—
IVa	CH_3	C_2H_4OH	NO_2	90	164—165	43,3	4,8	12,3	10,0	$C_{12}H_{13}N_3O_4S \cdot HCl$	43,4	4,3	12,7	9,7	0,65	1739	3450
b	$C(CH_3)_3$	C_2H_4OH	NO_2	80	145—146	53,4	6,1	12,8	10,0	$C_{15}H_{19}N_3O_4S$	53,4	5,7	12,5	9,5	0,66	1710	3450
c	C_6H_5	C_2H_4OH	NO_2	91	204—205	57,2	4,4	11,3	9,1	$C_{17}H_{15}N_3O_4S$	57,1	4,2	11,8	9,0	0,45	1680	3400
d	4-BrC_6H_4	C_2H_4OH	NO_2	99	210—211	47,2	3,2	9,9	7,1	$C_{17}H_{14}BrN_3O_4S$	46,8	3,2	9,6	7,3	0,45	1684	3400
e	3,4-$(HO)_2C_6H_3$	C_2H_4OH	NO_2	97	204—205	51,9	4,2	10,7	8,1	$C_{17}H_{15}N_3O_6S$	52,4	3,9	10,8	8,2	0,33	1662	3500
f	4-$CH_3C_6H_4$	C_2H_4OH	NO_2	87	219—220	58,4	4,5	11,4	8,9	$C_{18}H_{17}N_3O_4S$	58,2	4,6	11,3	8,6	0,46	1678	3210
g	α-C_4H_3S	C_2H_4OH	NO_2	81	163—164	49,4	3,7	11,5	17,4	$C_{15}H_{13}N_3O_4S_2$	49,6	3,6	11,5	17,6	0,41	1660	3470

*Systems for chromatography: chloroform—acetone (7:3) (IVa); chloroform—acetone (8:2) (IVb); benzene—acetone (8:2) (IIa-d, IVc, d, e, g); benzene—acetone—methanol (8:1:1) (IVe); revealing agent: iodine vapor.

EXPERIMENTAL

IR spectra were taken on a UR-10 spectrophotomer in KBr tablets, PMR spectra on a XL-100 spectrometer at 25°C in DMSO-d_6 with HMDS as internal standard (δ scale), and mass spectra were recorded on a MAT-311 instrument under standard conditions: ionizing voltage 70 V, cathodic emission current 300 μA, accelerating voltage 3 kV, temperature of the source 150°C.

The individuality of the compounds obtained was checked by TLC on Silufol UV-254 plates (Table 2).

2-(4'-Bromophenacylthio)-1-methylbenzimidazole Monohydrate (IIIa). A solution of 1.64 g of 1-methylbenzimidazoline-2-thione (I) in a mixture of 0.56 g of KOH, 5 ml of water and 30–40 ml of methanol (ethanol) was treated with 0.01 mole of p-bromophenacyl bromide, and the reaction mixture was heated at 60–65°C until the pH had fallen to 7, and it was then cooled, and the precipitate was filtered off.

1-Methyl-2-(4'-nitrophenacylthio)benzimidazole (IIb), 2-(4'-methoxyphenacylthio)-1-methylbenzimidazole (IIIc), and 2-(acetothienylthio)-1-methylbenzimidazole (IIId) were obtained under similar conditions.

2-(Acetonylthio)-1-(β-hydroxyethyl)-5-nitrobenzimidazole Hydrochloride (IVa). A mixture of 2.39 g of 1-(β-hydroxyethyl)-5-nitrobenzimidazoline-2-thione (II) and 0.01 mole of chloroacetone in 30 ml of methanol (ethanol) was boiled for 2 h, and was cooled, the solvent was distilled off in vacuum to dryness, and the residue was washed with ether.

1-(β-Hydroxyethyl)-5-nitro-2-(pinacolinylthio)benzimidazole (IVb). This was obtained by boiling compound (II) and bromopinacolone in 50 ml of ethanol for 3 hours. After cooling, the reaction mixture was poured into water, the mixture was neutralized with aqueous ammonia, and the precipitate was filtered off.

1-(β-Hydroxyethyl)-5-nitro-2-(phenacylthio)benzimidazole (IVc); 2-(4'-bromophenacylthio)-1-(β-hydroxyethyl)-5-nitrobenzimidazole (IVd); 2-(3',4'-dihydroxyphenacylthio)-1-(β-hydroxyethyl)-5-nitrobenzimidazole (IVe); 1-(β-hydroxyethyl)-2-(4'-methylphenacylthio)-5-nitrobenzimidazole (IVf); and 2-(acetothienylthio)-1-(β-hydroxyethyl)-5-nitrobenzimidazole (IVg) were obtained in a similar manner to compound (IVb).

The constants and yields of the substances synthesized were given in Table 2.

Properties of the substances obtained: colorless, light yellow (IVb, d), yellow (IIIb, IVa, c, e, f), or light brown (III, IVg) crystalline substances. For analysis they were purified by crystallization from methanol (IIIa, c, d, IVa, b, g) or DMFA (IIb, IVc, d, e, f).

SUMMARY

1-Methyl-2-(acylmethylthio)benzimidazoles and 1-(β-hydroxyethyl)-2-(acylmethylthio)-5-nitrobenzimidazoles have been synthesized and their physicochemical properties and biological activities have been studied.

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