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IMIDAZO[2,1-b]THIAZOLIUM SALTS BASED ON 2-PHENYLAMINO-4-METHYLTHIAZOLE

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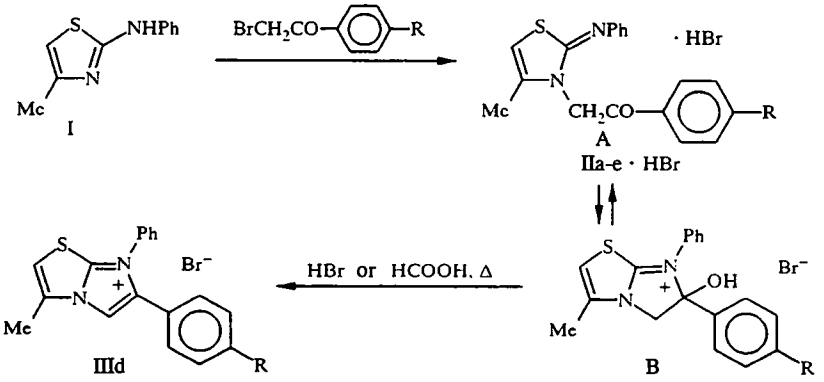
Alkylation of 2-phenylamino-4-methylthiazole with substituted phenacyl bromides led to the synthesis of hydrobromides of 2-phenylimino-3-(p-R-phenacyl)-4-methylthiazoles. It was shown that, depending on the conditions of the cyclization of the last, 3-methyl-6-aryl-7-phenyl- or 3-methyl-5-aroyl-6-alkyl-7-phenyl-imidazo[2,1-b]thiazolium bromides can be synthesized. The spectral characteristics of the compounds synthesized were studied.

Among derivatives of imidazo[2,1-b]thiazole are found compounds possessing antiinflammatory [1-3], analgesic [4], hypoglycemic [5], antihistamine [6], as well as immune-promoting [7] action. One of the main methods for the synthesis of derivatives of the given heterocyclic system is based on the reaction of 2-aminothiazoles with different halogenoketones [6, 8, 9].

In the continuation of investigations [10] into the properties of N-substituted heterocyclic amidines, the reaction of 2-phenylamino-4-methylthiazole (I) with substituted phenacyl bromides led to the synthesis of intermediate compounds — 2-phenylimino-3-acylaryl-4-methylthiazoline hydrobromides (IIa-e), which can exist in the two tautomeric forms A and B [11].

Analysis of the data of PMR and IR spectra (see Tables 1 and 2) indicates unambiguously that the compounds (IIa-e) occur in the open tautomeric form A in contrast to quaternary imidazo[1,2-a]pyridinium salts [10].



In fact, the protons of the methylene group of the phenacyl substituent in the PMR spectra of the hydrobromides of compounds (IIa-e) appear as a singlet in the region of 5.93-6.06 ppm, whereas the characteristic signals of the AB-system could be expected when the structure B is realized owing to the presence of an asymmetric center. Moreover, the IR spectra contain characteristic bands of stretching vibrations of the CO group in the region of 1680-1705 cm^{-1}, which confirms the structure A.

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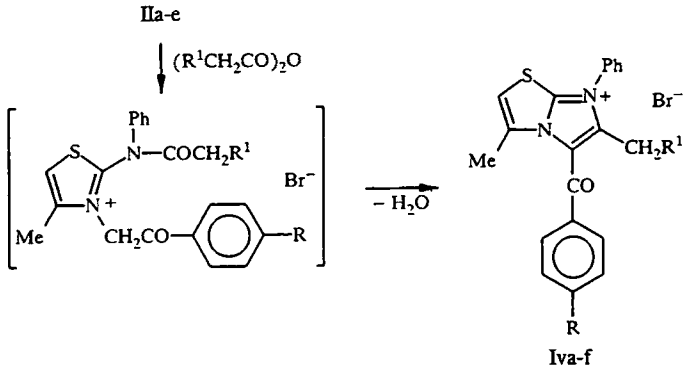
TABLE 1. Characteristics of the Compounds (IIa-e), (IIId), and (IVa-f)

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, cm^{-1}	Yield, %
		N	S			
IIa	$C_{18}H_{16}N_2OS$			143...144	1705, 1625	
IIa·HBr	$C_{18}H_{16}N_2OS \cdot HBr$	6,88 7,20	7,86 8,23	198...199		40
IIb·HBr	$C_{18}H_{15}FN_2OS \cdot HBr$	6,59 6,88	7,53 7,86	211...212		50
IIc·HBr	$C_{18}H_{15}ClN_2OS \cdot HBr$	6,35 6,61	7,25 7,56	214...215	1700, 1600	48
IId·HBr	$C_{19}H_{18}N_2OS \cdot HBr$	6,65 6,95	7,62 7,94	215...216	1700, 1610	39
IIe·HBr	$C_{19}H_{18}N_2O_2S \cdot HBr$	6,45 6,68	7,36 7,64	201...202	1680, 1610	53
IIId	$C_{19}H_{17}BrN_2S$	6,95 7,27	7,94 8,31	255...256	1618	60
IVa	$C_{20}H_{17}BrN_2OS$	6,50 6,78	7,42 7,75	289...290	1658, 1600	85
IVb	$C_{20}H_{16}BrFN_2OS$	6,24 6,50	7,13 7,42	253...254		89
IVc	$C_{20}H_{16}BrClN_2OS$	6,02 6,26	6,87 7,15	276...277	1660, 1590	80
IVd	$C_{21}H_{19}BrN_2OS$	6,29 6,56	7,19 7,49	274...275	1650, 1605	83
IVe	$C_{21}H_{19}BrN_2O_2S$	6,07 6,32	6,94 7,22	239...240	1650, 1610	80
IVf	$C_{22}H_{21}BrN_2OS$	6,10 6,35	6,97 7,26	242...243	1660, 1615	56

The cyclization reaction of compounds (IIa-e) was studied using different dehydrating agents. It was established that the heating of compound (IId) with 48% HBr or 100% HCOOH results in the formation of the salt (IIId); the identity of the samples was shown by the PMR and IR spectral data presented in Tables 1 and 2, as well as the absence of a depression of the melting temperature in the mixed test. The structure of the salt (IIId) was confirmed as 3-methyl-6-(p-tolyl)-7-phenylimidazo[2,1-b]thiazolium bromide by the presence of the singlet signal of the proton at the position 5 in the PMR spectrum at 8.81 ppm.



IVa-e $R^1 = H$, f $R = R^1 = Me$

Treatment of the compounds (IIa-e) with acetic anhydride or propionic anhydride [for (IId)] led to the isolation of 3-methyl-5-(p-R-benzoyl)-6-alkyl-7-phenylimidazo[2,1-b]thiazolium bromides (IVa-f). The structure of compounds (IVa-f) was confirmed by IR and PMR spectral data (see Tables 1 and 3). Thus, the IR spectra contain characteristic bands of stretching vibrations of the CO group in the region of 1650-1700 cm^{-1}. The PMR spectra register the singlet signals of protons of the methyl group at the position 6 in the region of 2.04-2.07 ppm (IVa-e) or the ethyl group at 0.74 ppm (t, CH_3) and 2.49 ppm (q, CH_2) (IVf).

TABLE 2. PMR Spectral Data of Compounds (IIa-e)

Compound	CH_3	CH_2 S	5-H	H_{arom}
IIa	2,04 d*	5,48	5,95 q*	6,83...8,18 m
IIa·HBr	2,22 s	6,04	6,86 s	7,39...8,16 m
IIb·HBr	2,23 s	6,06	6,88 s	7,39...8,23 m
IIc·HBr	2,20 d	6,03	6,86 s	7,75 d, 8,14 d, 7,38...7,58 m
IId·HBr†	2,20 d	6,01	6,83 s	7,38 d, 8,03 d, 7,48 m
IIe·HBr†	2,19 d	5,93	6,78 s	7,17 d, 8,10 d, 7,24...7,56 m

*J = 1.2 Hz

†The signal of the protons R = Me has the form of a singlet at 2.43 ppm [(IId)·HBr, R = Me] and 3.89 ppm [(IIe)·HBr, R = OMe].

TABLE 3. PMR Spectral Data of the Compounds (IIId) and (IVa-f)

Compound	6-CH_3 S	3-CH_3	2-H	H_{arom}
IIId*	—	2,63 d	†	7,15 d, 7,25 d, 7,62 m, 8,79 s
IVa	2,04	2,42 s	7,64 s	7,68...8,13 m
IVb	2,05	2,42 d	†	7,42...8,23 m
IVc	2,06	2,43 s	7,64 s	7,74...8,16 m
IVd*	2,05	2,39 s	7,65 s	7,49 d, 8,04 d, 7,75...7,90 m
IVe*	2,07	2,38 s	7,62 q	7,19 d, 8,11 d, 7,71...7,83 m
IVf*	‡	2,31 d	7,60 d	7,49 d, 8,03 d, 7,69...7,95 m

*The signal of the protons R = Me has the form of a singlet at 2.31 ppm for (IIId) (R = Me), 2.46 ppm for (IVd) (R = Me), 3.92 ppm for (IVe) (R = OMe), and 2.46 ppm for (IVf) (R = Me).

†The signal is superimposed by the H_{arom} signals.

‡6-CH_2CH_3: 0.74 ppm (t, CH_3) and 2.49 ppm (q, CH_2).

It was noted that the treatment of compounds (IIa-e) with concentrated acetic acid does not lead to their cyclization, similarly described in the work [9].

EXPERIMENTAL

The IR spectra were taken on the UR-20 instrument using tablets of KBr. The PMR spectra were recorded on the Bruker-200 instrument (200 MHz) in the solution of DMSO-D_6; the internal standard was TMS.

The initial 2-phenylamino-4-methylthiazole was obtained by the method of the work [11].

2-Phenylimino-3-(p-R-phenacyl)-4-methylthiazole Hydrobromides [(IIa-e)·HBr]. To the solution of 1.9 g (0.01 mole) of 2-phenylamino-4-methylthiazole in 20 ml of propan-2-ol is added 0.01 mole of the corresponding substituted phenacyl bromide, and the mixture is boiled for 1 h. The solvent is evaporated in vacuo. The oily residue is triturated with acetone. The residue of the product (II)·HBr is filtered off and crystallized from the mixture of methanol—propan-2-ol.

3-Methyl-6-(p-tolyl)-7-phenylimidazo[2,1-b]thiazolium Bromide (IIId). A. The hydrobromide (IId) (1.4 g) is boiled for 10 h in 10 ml of 48% HBr. The solvent is evaporated *in vacuo*, and the oily residue is triturated with acetone. The residue of the bromide (IIId) is filtered off. The yield is 0.8 g. Crystallization is performed from propan-2-ol.

B. The hydrobromide (IId) (2 g) is boiled in 15 ml of 100% HCOOH for 3 h. The solvent is evaporated *in vacuo*. The residue is treated as in the experiment A. The yield is 1.4 g.

6-Alkyl-5-aroyl-3-methyl-7-phenylimidazo[2,1-b]thiazolium Bromides (IVa-f). The salts (IIa-e) (0.01 mole) are boiled for 1 h in 20 ml of acetic anhydride or propionic anhydride [for (IId)]. The solvent is evaporated *in vacuo*, and the oily residue is triturated with acetone. The residue of the bromide (IV) is filtered off. Crystallization is performed from propan-2-ol.

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