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ON THE REACTION OF 2-PHENYLAMINOTHIAZOLINE WITH α-HALOGENOKETONES

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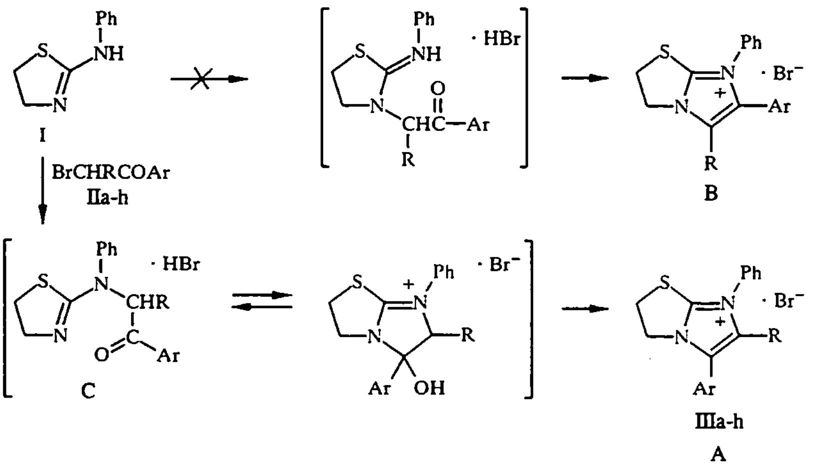
It was established that the alkylation of 2-phenylaminothiazoline with substituted phenacyl bromides proceeds at the exocyclic nitrogen atom with the formation of 5-aryl-7-phenyl-2,3-dihydroimidazo[2,1-b]thiazolium bromides. In order to confirm the structure of the last, the reductive desulfurization of one of them (Ar = p-chlorophenyl) was accomplished using Raney nickel. It was shown that dequaternization of the resulting 1-phenyl-3-ethyl-4-(p-chlorophenyl)imidazolium bromide to 1-phenyl-4-(p-chlorophenyl)imidazole, identical to the sample obtained by direct synthesis, thereby occurs.

In the continuation of investigations into the synthesis and properties of condensed imidazoles with an angular nitrogen atom [1-4], we studied the reaction of 2-phenylaminothiazoline (I) with primary and secondary α-halogenoketones of the aromatic series (IIa-h). Theoretically, such a reaction can proceed at two nucleophilic centers — the exocyclic or the ring nitrogen atoms — with the final formation, i.e., after cyclization, of 5-aryl-7-phenyl- or 6-aryl-7-phenyl-2,3-dihydroimidazo[2,1-b]thiazolium bromides (structures A and B) correspondingly.

It was shown in the work [5] that 2-arylaminothiazolines are only alkylated by alkyl halides at the exocyclic nitrogen atom. Consequently, the products of the reaction of compounds (I) and (IIa-h) should be 2-phenyl-2-acylarylaminothiazoline hydrobromides (structure C), the dehydration of which is accompanied by the formation of the corresponding 5-aryl-7-phenyl-2,3-dihydroimidazo[2,1-b]thiazolium bromides.



II, III a Ar = C_6H_5; b Ar = C_6H_4F-4; c Ar = C_6H_4Cl-4; d Ar = $C_6H_4CH_3$-4; e Ar = $C_6H_4OCH_3$-4; f Ar = C_6H_4Br-4; g Ar = $C_6H_3(OCH_3)_2$-3',4', R = H; h Ar = C_6H_4Cl-4', R = CH_3

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TABLE 1. Characteristics of Compounds (IIIa-h)

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
IIIa	$C_{17}H_{15}BrN_2S$	7,5 7,8	9,1 8,9	261...262	65
IIIb	$C_{17}H_{14}FBrN_2S$	7,3 7,4	8,7 8,5	276...277	75
IIIc	$C_{17}H_{14}ClBrN_2S$	7,2 7,0	8,3 8,1	279...280	81
IIId	$C_{18}H_{17}BrN_2S$	7,6 7,5	8,2 8,6	266...267	60
IIIe	$C_{18}H_{17}BrN_2OS$	7,3 7,2	8,2 8,2	258...259	58
IIIf	$C_{17}H_{14}Br_2N_2S$	6,6 6,4	7,2 7,3	280...281	80
IIIg	$C_{19}H_{19}BrN_2O_2S$	6,9 6,7	7,7 7,6	234...235	79
IIIh	$C_{18}H_{16}ClBrN_2S$	7,1 6,9	7,8 7,85	273...274	48

TABLE 2. PMR and IR Spectral Data of the Compounds (IIIa-h)

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, ppm			
		2- and 3-CH_2, tt	6-CH s	H_{Ar}	other protons
IIIa	1610	4,32, 4,83	8,46	7,57...7,77 m	—
IIIb	1608	4,32, 4,8	8,47	7,40...7,85 m	—
IIIc	1612	4,34, 4,8		7,48...7,71 m	—
IIId	1608	4,31, 4,8	8,39	7,40 d, 7,62 d, 7,71 s	2,40 s (CH_3)
IIIe	1610	4,31, 4,79	8,35	7,14 d, 7,67 d, 7,70 s	3,84 s (OCH_3)
IIIf	1610	4,32, 4,82	8,51	7,65...7,84 m	
IIIg	1610	4,34, 4,8		7,21...7,68 m	4,04 s (OCH_3), 4,05 s OCH_3)
IIIh	1608	4,24, 4,66		7,59...7,70 m	2,18 s (CH_3)

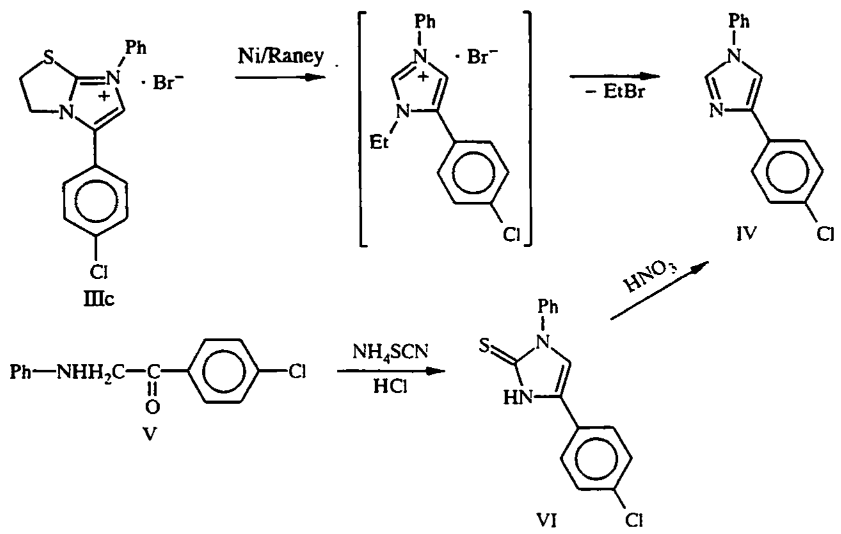
It was established that the boiling of equimolar amounts of the initial substances in propan-2-ol results in the formation of the salts (IIIa-h) in one stage. This is indicated by their data for the elemental analysis and PMR and IR spectra. Intermediate compounds could not thereby be isolated.

Analogous cases are known in the literature. For example, the reaction of thiourea, 2-amino-4,5,6,7-tetrahydrobenzothiazole, or 2-aminonaphtho[1,2-d]thiazole with α-halogenoketones results in the immediate formation of derivatives of 2-aminothiazole, imidazo[2,1-b]-5,6,7,8-tetrahydrobenzothiazole, or naphtho[1,2-d]thiazolo[3,2-a]imidazole [3, 4, 6].

The IR spectra of compounds (IIIa-h) lack bands of the stretching vibrations of the CO group, and have characteristic absorption bands of the CN group in the region of 1608-1612 cm^{-1}.

The PMR spectra registered the signals of protons of the methylene groups at the positions 2 and 3 of the imidazo[2,1-b]thiazole system in the form of two triplets at 4.31-4.83 ppm, the proton of the methine group at the position 6 in the form of a singlet at 8.35-8.51 ppm, as well as the aromatic protons of the aryl and phenyl substituents at the positions 5 and 7 correspondingly (see Table 2).

In order to prove the structure of the synthesized salts (IIIa-h), we accomplished the reductive desulfurization of the product (IIIc) with Raney nickel. This reaction led to the isolation and identification of 1-phenyl-4-(p-chlorophenyl)imidazole (IV), the formation of which is explained by the instability of the intermediate 1-phenyl-3-ethyl-4-(p-chlorophenyl)imidazolium bromide [7]. The structure of compound (IV) was confirmed by the data of elemental analysis, PMR spectra, and direct synthesis. Thus, the heating of the aqueous suspension of N-(p-chlorophenacyl)aniline (V), synthesized from aniline and p-chlorophenacyl bromide, with ammonium thiocyanate in HCl [8] led to the isolation of 1-phenyl-4-(p-chlorophenyl)imidazoline-2-thione (VI), converted by HNO_3 to compound (IV) [9].



The characteristics of the compounds synthesized are presented in Tables 1 and 2.

EXPERIMENTAL

The IR spectra of the samples synthesized were taken on the UR-20 instrument in tablets of KBr. The PMR spectra were recorded on the Bruker-200 instrument (200 MHz); the solvent was DMSO-D_6 or trifluoroacetic acid [for the compounds (IIIc, g)], and the internal standard was TMS (the δ-scale).

The initial 2-phenylaminothiazoline was synthesized from phenyl isothiocyanate and monoethanolamine according to the method of the work [10].

5-Aryl-7-phenyl-2,3-dihydroimidazo[2,1-b]thiazolium Bromides (IIIa-h). To the solution of 1.78 g (0.01 mole) of 2-phenylaminothiazoline in 15-20 ml of propan-2-ol is added 0.01 mole of the corresponding substituted phenacyl bromide. The reaction mixture is boiled for 8-10 h and cooled. The residue of the product is filtered off, washed with ether, dried, and crystallized from isopropanol in the case of (IIIe,h), or the mixture of isopropanol—methanol in the case of (IIIa-d, f, g).

1-Phenyl-4-(p-chlorophenyl)imidazole Hydrobromide (IV). **A.** The mixture of 5-(p-chlorophenyl)-7-phenyl-2,3-dihydroimidazo[2,1-b]thiazolium bromide (IIIc) (2.3 g, 0.006 mole) and 30 g of the freshly prepared paste of Raney nickel in 30 ml of propan-2-ol is boiled for 7 h. The reaction mixture is filtered, and the filtrate is evaporated and cooled prior to the addition of 2-3 drops of 48% HBr. The residue of the product is filtered off. The yield is 0.7 g (~35%). The mp is 221-222°C (from propan-2-ol). The mp of the base obtained by the usual route is 127-128°C.

B. a) **N-(p-Chlorophenacyl)aniline (V).** To the solution of 9.34 g (0.04 mole) of p-chlorophenacyl bromide in 35 ml of methanol are added 3.63 ml of freshly distilled aniline, and the reaction mixture is held for 24 h at 18-20°C. The residue of the product is filtered off. The yield is 5 g (~50%). The mp is 91-92°C (from heptane). The IR spectrum is as follows: 1698 cm^{-1} (CO) and 3298 cm^{-1} (NH). Found, %: N 5.7. $C_{14}H_{21}ClNO$. Calculated, %: N 5.7.

b) **1-Phenyl-4-(p-chlorophenyl)imidazoline-2-thione (VI).** The suspension of 2.46 g (0.01 mole) of compound (V), 1.14 g (0.015 mole) of ammonium thiocyanate, and 1 ml of 36% HCl in 20 ml of water is evaporated to dryness in a porcelain dish on a water bath. The dry residue is suspended in water, filtered, washed with water until a negative reaction for the thiocyanate ion is obtained, and dried. The yield of the product (VI) is 2.1 g (73%). The mp is 249-250°C (from CH_3COOH). The PMR spectrum (δ, ppm) is as follows: 8.51 ppm (1H, s, CH), 6.95-7.69 ppm (9H, m, H_{arom}), and 13.12 ppm (1H, s, NH). Found, %: N 9.7 and S 11.1. $C_{15}H_{11}ClN_2S$. Calculated, %: N 9.8 and S 11.2. The IR spectrum is as follows: 3020 cm^{-1} (NH) and 1602 cm^{-1} (C═N).

c) **1-Phenyl-4-(p-chlorophenyl)imidazole (IV).** Compound (VI) (1.8 g) is boiled in 25 ml of 15% HNO_3 for 30 min. The reaction mixture is cooled and neutralized firstly with NaOH and then with the saturated solution of $NaHCO_3$ to pH 7. The product is filtered off, washed with water, and dried. The yield is 1.5 g (~98%). The mp is 127-128°C. The hydrobromide of (IV) is obtained by the usual route. The mp is 221-222°C. The mixed test with the sample obtained by the method A does not give a depression of the melting temperature. The PMR spectrum (δ, ppm) is as follows: 8.77 ppm (1H, s, 2-H), 9.61 ppm (1H, s, 5-H), 7.85 and 7.90 ppm (2H and 2H, 2 d, H_{Ar}), and 7.54-7.71 ppm (5H, m, H_{Ph}). Found, %: N 11.1. $C_{15}H_{11}ClN_2$. Calculated, %: N 11.0.

REFERENCES

1. A. M. Demchenko, V. A. Chumakov, K. G. Nazarenko, A. N. Krasovskii, V. V. Pirozhenko, and M. O. Lozinskii, Khim. Geterotsikl. Soedin., No. 5, 644 (1995).
2. N. P. Grin', A. I. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 9, 1271 (1972).
3. A. N. Krasovskii, N. P. Grin', P. M. Kochergin, and I. I. Soroka, Farmatsiya, No. 2, 26 (1975).
4. O. M. Krasovskii, É. I. Bogatirfova, and P. M. Kochergin, Farmats. Zh., No. 5, 83 (1997).
5. Elderfield, Heterocyclic Compounds [Russian translation], Vol. 5, Izd-vo Inostr. Lit, Moscow (1961).
6. R. Kh. Uili, D. K. England, and L. K. Berl, Organic Reactions [Russian translation], Collection 6, IL, Moscow (1953), p. 301.
7. K. Hofmann, Imidazole and Its Derivatives. Part I, J. Wiley and Sons, New York (1953), p. 447.
8. A. N. Krasovskii, N. V. Ponomarev, V. E. Yavorovskaya, and A. N. Evstratov, XV Ukr. Rep. Conf. on Organic Chemistry, Uzhgorod (1986), p. 370.
9. C. C. Porretta, F. Cerreto, and R. Floravanti, Farmaco Ed. Sci., **43**, No. 1, 15 (1988).
10. H. Najer and R. Gindicelli, Bull. Soc. Chim. France, No. 5, 960 (1960).