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RESEARCH IN THE IMIDAZOLE SERIES. 96.* REACTION OF 1-METHYL-4-NITRO-5-CHLORIMIDAZOLE WITH PHENOLS, NAPHTHOLS, AND 8-HYDROXYQUINOLINE

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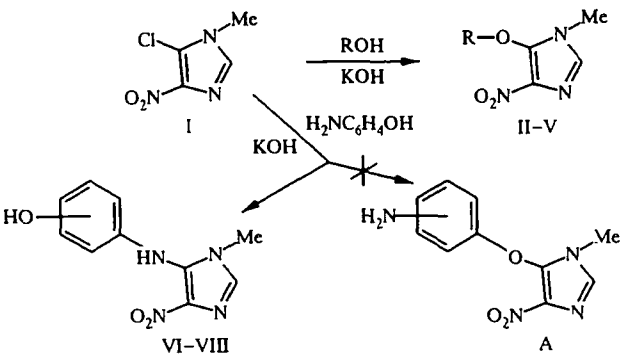
By reactions of 1-methyl-4-nitro-5-chlorimidazole with 4-nitrophenol, α- and β-naphthols, and 8-hydroxyquinoline, a number of 1-methyl-4-nitro-5-aryl(heteryl)oxyimidazoles have been obtained. With aminophenols, under analogous conditions, 1-methyl-4-nitro-5-hydroxyphenylaminoimidazoles have been obtained.

The reactions of 4-nitro-5-haloimidazoles with phenol and its derivatives have received very little attention [2, 3], and its reactions with naphthols and hydroxyquinolines have not been investigated at all.

In connection with a search for biologically active substances, we investigated in more detail the reaction of 1-methyl-4-nitro-5-chlorimidazole (I) with phenol derivatives, and also with α- and β-naphthols and 8-hydroxyquinoline.

In contrast to the procedures described in [2, 3], which give low yields of the synthesized compounds (30-60%), we carried out the reaction of the nitrochlorimidazole I with hydroxy derivatives of benzene, naphthalene, and quinoline in an aqueous solution in the presence of an equimolar quantity of potassium hydroxide to bind the hydrogen chloride that is released. The optimal process temperature is 70-85°C. At higher temperatures, considerable tarring of the reaction mass is observed.

By the interaction of the imidazole I with 4-nitrophenol, α- and β-naphthols, and 8-hydroxyquinoline, we obtained the corresponding 1-methyl-4-nitro-5-aryl(heteryl)oxyimidazoles (II-V).



II R = 4-$O_2NC_6H_4$; III R = 1-naphthyl; IV R = 2-naphthyl; V R = 8-quinolyl

VI 2-OH; VII 3-OH; VIII 4-OH

Aminophenols have two reaction centers; and, in aqueous KOH solution, their reaction with compound I could theoretically lead to the formation of 1-methyl-4-nitro-5-aminophenyloxyimidazoles (structure A) and/or 1-methyl-4-nitro-5-hydroxyphenylaminoimidazoles VI-VIII.

*For Communication 95, see [1].

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TABLE 1. Characteristics and Elemental Analyses of Compounds II-VIII

Compound	Empirical formula	Found, %			Calculated, %			mp, °C (with decomp.)	Yield, %
		C	H	N	C	H	N		
II	$C_{10}H_8N_4O_5$	45,65	3,17	21,24	45,45	3,09	21,21	195...197	75
III	$C_{14}H_{11}N_3O_3$	62,48	4,11	15,67	62,45	4,08	15,61	162,5...163	73
IV	$C_{14}H_{11}N_3O_3$	63,34	4,06	16,16	62,45	4,08	15,61	164,5...165	70
V	$C_{13}H_{10}N_4O_3$	58,01	3,69	20,85	57,77	3,70	20,73	160...162	72
VI	$C_{10}H_{10}N_4O_4$	51,58	4,65	24,20	51,28	4,30	23,90	230...231*	80
VII	$C_{10}H_{10}N_4O_4$	51,33	4,40	24,12	51,28	4,30	23,90	198...200	90
VIII	$C_{10}H_{10}N_4O_4$	51,92	4,31	23,67	51,28	4,30	23,90	195...196	90

*According to [3], mp 222-224°C.

TABLE 2. Spectral Characteristics of Compounds II-VIII

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum* in DMSO-d_6, δ, ppm (singlet)
II	1020 (R-O-R); 1350, 1360, 1510, 1550 (NO_2)	3,70 (3H, N—CH_3), 7,38 (2H, J = 8 Hz, 2,6 Ph), 7,84 (1H, 2-H imidazole), 8,30 (2H, d, J = 10Hz, 3,5-H Ph)
III	1040 (R-O-R); 1360, 1540 (NO_2)	3,55 (3H, N—CH_3), 7,0...8,0 (8H, m, arom)
IV	1040 (R-O-R); 1360, 1510 (NO_2)	3,60 (3H, N—CH_3), 6,7...8,0 (8H, m, arom)
V	1050 (R-O-R); 1370, 1500 (NO_2)	
VI	1620, 3300 (N—H); 1220 (Ph—OH)	3,22 (3H, N—CH_3), 6,7...7,0 (4H, m, Ph), 7,50 (1H, 2-H imidazole), 8,32 (1H, br. s, N—H)
VII	1369, 1580 (NO_2); 1615, 3250 (NH); 1200 (Ph—OH)	3,48 (3H, N—CH_3), 6,40 (3H, m, 4,5,6-H Ph), 7,05 (1H, m, 2-H Ph). 7,65 (1H, 2-H imidazole), 8,90 (1H, br. s, N—H)
VIII	1350, 1550 (NO_2); 1620, 3340 (NH); 1220 (Ph—OH)	3,25 (3H, N—CH_3), 6,75 (2H, J = 10 Hz, 3,5-H Ph), 7,0 (2H, d, J = 10Hz, 2,6-H Ph), 7,44 (1H, 2-H imidazole), 8,79 (1H, br. s, N—H)

*PMR spectrum of compound II was taken in DMF-d_7.

Under the conditions used in this work, the nitrochlorimidazole I reacts with o-, m-, and p-aminophenols to form 4-nitro-5-aminoimidazole derivatives VI-VIII as the sole products. This was also noted in [3] in the example of o-aminophenol. Such behavior of aminophenols in their reactions with the nitrochlorimidazole I is apparently explained by the greater nucleophilicity of the amino group in comparison with the hydroxyl group.

The aminophenols interact analogously with other heteroaromatic [4] and aromatic [5] compounds containing a mobile chlorine atom.

The individuality of the synthesized compounds II-VIII was confirmed by TLC, and structures were confirmed by chemical and physicochemical methods. In the IR spectra of compounds II-V, there are absorption bands in the 1020-1050 cm^{-1} region that are characteristic for the ether bond [6, 7].*

Because of the presence of the phenolic hydroxyl in the structure, compounds VI-VIII are soluble in aqueous caustic solutions, and they give a characteristic color reaction for phenolic hydroxyl with ferric chloride.

In the IR spectra of the 4-nitro-5-arylaminoimidazoles VI-VIII, there are no absorption bands in the 1020-1050 cm^{-1} region, but there are bands of stretching vibrations of the NH group in the 1615-1620 and 3250-3340 cm^{-1} regions, and of the phenolic hydroxyl in the 1200-1220 cm^{-1} region.

The PMR spectra (Table 2) of compounds II-IV and VI-VIII provide further proof of their structures. These spectra contain singlets of protons of the N-CH_3 group in the 3.22-3.70 ppm region and of the proton in position 2 of the imidazole ring (7.44-7.84), and also signals of aromatic protons in the interval 6.40-8.30 ppm. In the PMR spectra of compounds VI-VIII, in contrast to those of II-IV, there are signals from protons of the NH group in the 8.32-8.90 ppm region.

In the mass spectrum of compound VIII, we found a peak of the molecular ion with m/z 234 (100%), corresponding to its molecular weight.

*As in Russian original; no [7] in References section — Translator.

EXPERIMENTAL

The course of the reactions and the individuality of the products were monitored by TLC on Silufol UV-254 plates in systems consisting of n-propanol and acetic acid (3:1), n-propanol and an aqueous ammonia solution (3:1), benzene and dioxane (1:1), or benzene and dioxane (1:10). The IR spectra of the compounds were taken in a UR-2 instrument (KBr tablets). The PMR spectra were obtained in a Tesla BS-497 spectrometer (100 MHz), internal standard HMDS. The mass spectrum of compound VIII was taken in a Varian MAT-112 spectrometer with direct introduction of the sample into the ion source. The ionization chamber temperature was 180°C, the ionizing electron energy 70 eV.

1-Methyl-4-nitro-5-chlorimidazole (I) was obtained by a procedure given in [8].*

1-Methyl-4-nitro-5-aryl(heteryl)oxyimidazoles (II-V). A mixture of 0.01 mole of 4-nitrophenol, α- or β-naphthol, or 8-hydroxyquinoline and 0.01 mole of KOH in 50 ml of water was heated to 40-50°C until the starting materials were completely dissolved (10-15 min). Then, 0.01 mole of compound I was added in portions to the solution. The reaction mixture was stirred 3-4 h at 70-80°C and then cooled; the precipitate was filtered off, washed with water, and dried, obtaining colorless crystalline substances that were soluble in most organic solvents, insoluble in water and in aqueous caustic solutions. The compounds were purified for analysis by crystallization from acetone (II), ethanol (IV), or anhydrous ethanol (III, V).

1-Methyl-4-nitro-5-hydroxyphenylaminoimidazoles (VI-VIII). To a solution of 0.05 mole of aminophenol and 0.05 mole of KOH in 150 ml of water, 0.05 mole of compound I was added. The mixture was heated 2 h at 80-85°C and then cooled; the precipitate was filtered off, washed with water, and dried. Obtained compounds VI-VIII in the form of bright yellow crystalline substances. Compounds VI-VIII dissolve in aqueous caustic solutions with the formation of dark red solutions, from which they are recovered in unchanged form upon acidification. These compounds give a positive reaction with ferric chloride for phenolic hydroxyl. The substances were purified for analysis by crystallization from aqueous acetic acid (VI), ethanol (VII), or water (VIII).

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