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INVESTIGATIONS IN THE IMIDAZOLE SERIES 97.* SYNTHESIS AND SOME TRANSFORMATIONS OF 5-NITRO-5-HYDROXYALKYLAMINO- AND 4-HYDROXY-ALKYLAMINO-5-NITROIMIDAZOLES

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A series of 1-alkyl(1,2-dialkyl)-substituted 4-nitro-5-hydroxyalkylamino- and 4-hydroxyalkylamino-5-nitroimidazoles were obtained by the reaction of 1-alkyl(1,2-dialkyl)-substituted 4-nitro-5-chloro(bromo)imidazoles with amino alcohols. Their reactions with thionyl chloride and carboxylic acid halides and their catalytic hydrogenation were studied.

The reaction of nitrohalogenoimidazoles with amino alcohols has been insufficiently investigated, while the chemical characteristics of the two described compounds have not been investigated [2]. In the search for biologically active compounds we studied the reaction of 1-alkyl(1,2-dialkyl)-4-nitro-5-chloro(bromo)imidazoles (I-VII) and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitroimidazoles (VIII, IX) with lower amino alcohols (2-aminoethanol and 3-aminopropanol) in greater detail. The reaction takes place readily in isobutanol or in an excess of the amino alcohol itself at 70-100°C and leads to the corresponding substituted 4-nitro-5-aminoimidazoles (X-XXI) and 4-amino-5-nitroimidazoles (XXII-XXIV) with satisfactory and high yields (65-95%).

On heating in n-butanol (110-117°C), as described in [2], appreciable resinification of the reaction mixture is observed, and the yields of the targeted compounds are reduced to 55-60%.

Theoretically the nucleophilic substitution of 4-nitro-5-halogenoimidazoles (I-VII) and 4 halogeno-5-nitroimidazoles (VIII, IX) with such bifunctional compounds as α- and β-amino alcohols can take place in two directions. The reaction involving the amino group leads to the formation of derivatives of nitroaminoimidazoles (X-XXI) and (XXII-XXIV), while the reaction through the hydroxyl group leads to derivatives of 4-nitro-5-hydroxyimidazoles (structure A) and their 4-hydroxy-5-nitro isomers.

The ethers of 4-nitro-5-hydroxyimidazoles are formed during the reaction of 4-nitro-5-halogenoimidazoles with hydroxyl-containing compounds in the presence of alkaline agents [1-4], although with aminophenols under similar conditions 4-nitro-5-hydroxyphenylaminoimidazoles are obtained [1, 5]. Under our selected experimental conditions it was not possible to identify ethers with structure A. The selectivity of the reaction of nitrohalogenoimidazoles with amino alcohols is probably explained by the higher nucleophilicity of the amino group in the molecule of the amino alcohol, as also in the case of aminophenols [1]. Such a reaction of nitrohalogenoimidazoles with amino alcohols is not exceptional. It was shown in a number of papers that aromatic and heterocyclic compounds containing a mobile halogen atom enter into nucleophilic substitution with amino alcohols through the amino group. Thus, 2-hydroxyethylaminonitrobenzene [6, 7] and 8-(2-hydroxyethylamino)adenine [8] respectively were obtained in the reaction of 2-nitrochlorobenzene and 8-bromoadenine with 2-aminoethanol.

*For Communication 96, see [1].

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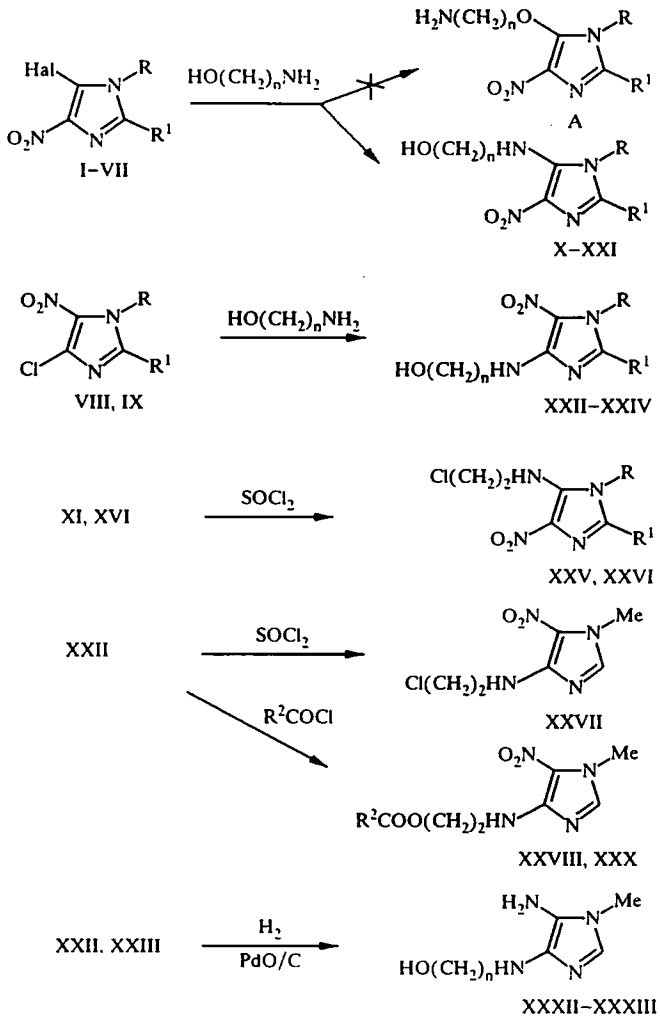

I, III—VI Hal = Cl; II, VII Hal = Br; I, II, X, XI, XVII, XVIII, XVIIIa, XXII, XXIII, XXV R = Me; III, XII, XIX R = Et; IV, XV, XXIV R = Pr; V, XVI, XXVI R = Bu; VI, XIII, XX R = *i*-Bu; VII, XIV, XXI R = $PhCH_2$; I, VIII, X, XVII, XXII, XXIII R^1 = H; II, III, XI, XII, XIV, XVIII, XIX, XXI, XXV R^1 = Me; IV, XV, XXIV R^1 = Et; V, XVI, XXVI R = Pr; VI, XIII, XX R^1 = *i*-Pr; XXVIII R^2 = Me; XXIX R^2 = Pr; XXX R^2 = $CHBrCH_3$; XXXI R^2 = Bu; X—XVI, XXII, XXXII n = 2; XVII—XXI, XXIII, XXIV, XXXIII n = 3

The structure of compounds (X-XXIV) was confirmed by the data from the IR, PMR, and mass spectra and also by certain chemical reactions. Thus, treatment of the hydroxy compounds (XI, XVI, XXII) with thionyl chloride in benzene gave the products from substitution of the hydroxyl group by a chlorine atom, i.e., the 2-chloroethylaminoimidazoles (XXV-XXVII). This rules out the structure of the initial compounds as derivatives of structure A.

The acylation of 1-methyl-4-(2-hydroxyethylmethylamino)-5-nitroimidazole (XXII) by carboxylic acid chlorides in benzene leads to the corresponding esters (XXVIII-XXXI) and not the alternative amides of the initial acids.

Of particular interest are the derivatives of 4,5-diaminoimidazole [9-12]. In order to obtain them we studied the hydrogenation of the nitroaminoimidazoles (XXII) and (XXIII). The reaction takes place readily at atmospheric pressure and room temperature in the presence of palladium oxide on charcoal as catalyst. The obtained derivatives of 4,5-diaminoimidazole (XXXII) and (XXXIII) are extremely labile compounds that readily resinify in air. It was possible to isolate and characterize them in the form of picrates.

The structure of compounds (X-XXXIII) was confirmed by the data from elemental analysis and by spectral methods (Tables 1 and 2). In the IR spectra of the nitro compounds there are absorption bands for the NO_2 group in the region of 1345-1430 and 1530-1570 cm^{-1}. The amino alcohols (X, XI, XV-XVIII, XXII-XXIV) are characterized by the presence of bands for the stretching vibrations of the NH group in the region of 1620-1660 and 3250-3400 cm^{-1} and of the OH group in the region of 3440-3460 cm^{-1}. In the IR spectra of the O-acyl derivatives of the amino alcohols (XXVIII-XXXI) the band of the hydroxyl group disappears, and a distinct band for the ester CO group in the region of 1740-1760 cm^{-1} appears in its place.

TABLE 1. Characteristics of Compounds (X-XXXIII)

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl		
X	$C_6H_{10}N_4O_3$	38.99 38,70	5.54 5,37	30.24 30,10		151...152	87
XI	$C_7H_{12}N_4O_3$					176...177*	95
XII	$C_8H_{14}N_4O_3$	44.68 44,85	6.74 6,58	26.42 26,15		145...146	80
XIII	$C_{12}H_{22}N_4O_3$	52.99 53,32	8.19 8,20	20.42 20,72		116...118	72
XIV	$C_{13}H_{16}N_4O_3$	56.67 56,61	5.99 5,84	20.63 20,73		164...166	76
XV	$C_{10}H_{18}N_4O_3$	49.63 49,58	7.58 7,48	23.32 23,14		110...112	93
XVI	$C_{12}H_{22}N_4O_3$	53.38 53,32	8.56 8,20	20.98 20,72		180...182	85
XVII	$C_7H_{12}N_4O_3$	41.48 42,00	5.86 6,00	27.71 28,00		137...138	94
XVIII	$C_8H_{14}N_4O_3$	44.90 44,85	6.79 6,54	26.07 26,16		135...136	91
XVIIIa†	$C_8H_{14}N_4O_3 \cdot 2H_2O$	39.00 38,40	6.87 7,20	22.39 22,40		91...92	
XIX	$C_9H_{16}N_4O_3$	47.13 47,36	7.24 7,06	24.80 24,55		112...113	65
XX	$C_{13}H_{24}N_4O_3$	54.75 54,91	8.61 8,51	19.69 19,70		127...128	70
XXI	$C_{14}H_{18}N_4O_3$	58.10 57,92	5.93 6,25	19.40 19,30		165...166	67
XXII	$C_6H_{10}N_4O_3$	38.19 38,70	5.53 5,37	29.84 30,10		142...144	95
XXIII	$C_7H_{12}N_4O_3$	42.04 42,00	6.07 6,00	27.55 28,00		110...111	78
XXIV	$C_{11}H_{20}N_4O_3$	51.86 51,56	7.62 7,80	21.75 21,87		93...95	80
XXV	$C_7H_{11}N_4O_2 \cdot HCl$	32.97 32,94	4.99 4,70	21.76 21,96	27.52 27,83	144...145	93
XXVI	$C_{12}H_{21}ClN_4O_2 \cdot HCl$	44.06 44,31	6.68 6,77	16.88 17,23	22.31 21,84	123...124	95
XXVII	$C_6H_9ClN_4O_2$	35.48 35,22	4.58 4,40	27.30 27,40	17.39 17,41	182...184	93
XXVIII	$C_8H_{12}N_4O_4 \cdot HCl$	36.20 36,29	4.90 4,91	21.25 21,17	13.40 13,42	146...148	84
XXIX	$C_{10}H_{16}N_4O_4 \cdot HCl$	41.28 41,02	5.86 5,81	19.21 19,11	12.03 12,03	137...138	84
XXX	$C_9H_{13}BrN_4O_4 \cdot HCl$‡	29.87 30,21	4.11 4,39	15.91 15,66	9.93 9,93	137...139	72
XXXI	$C_{11}H_{18}N_4O_4 \cdot HCl$	43.15 43,06	6.12 6,19	18.74 18,27	11.77 11,58	137...138	75
XXXII	$C_6H_{12}N_4O \cdot 2C_6H_3N_3O_7$	34.44 35,17	3.12 2,89	22.30 22,44		149...150	25
XXXIII	$C_7H_{14}N_4O \cdot C_6H_3N_3O_7$	39.12 39,09	4.15 4,26	24.19 24,56		152...153	30

*According to [2], mp 176-177°C.

†Dihydrate compound (XVIII).

‡Br. found, 22.4%. Calculated 22.35%.

The mass spectra of compounds (X, XI, XV, XVI, XXII, XXIII) contain molecular ion peaks (M^+) corresponding to their molecular masses.

The PMR spectra of 1-methyl-4-nitro-5-(2-hydroxyethylamino)imidazole (X) and its 5-nitro isomer (XXII) contain singlets for the three protons of the N—CH_3 group in the region of 3.68-3.93 ppm and the proton at position 2 of the imidazole ring in the region of 7.30-7.93 ppm, triplets for the NH and OH groups at 7.75-7.8 and 4.8-5.0 ppm respectively, and multiplets for the four protons of the CH_2—CH_2 group in the region of 3.55 ppm. The signal for the protons of the N—CH_3 group of compound (XXII) is shifted downfield somewhat (3.93 ppm) compared with the signal for the protons of the same group in the 4-nitro isomer (X) (3.68 ppm).

TABLE 2. The IR Spectra (cm^{-1}) and the Molecular Ion Peaks (M^+) of Compounds (X, XI, XV-XVIII, XXII-XXXI)

Compound	NO_2	NH	OH (CO)	M^+
X	1420, 1570	1640, 3250	3450	186
XI	1330, 1530	1650, 3240	3455	200
XV	1430, 1540	1650, 3250	3450	242
XVI	1430, 1550	1640, 3255	3450	270
XVII	1350, 1550	1660, 3400	3450	
XVIII	1350, 1560	1620, 3310	3440	
XXII	1370, 1550	1635, 3250	3450	186
XXIII	1350, 1540	1640, 3400	3450	200
XXIV	1345, 1550	1640, 3305	3460	
XXV	1350, 1560	1660, 3250		
XXVI	1345, 1550	1660, 3280		
XXVII	1360, 1570	1660, 3400		
XXVIII	1350, 1550	1650, 3340	(1750)	
XXIX	1350, 1550	1650, 3350	(1760)	
XXX	1360, 1560	1640, 3360	(1760)	
XXXI	1350, 1540	1620, 3340	(1740)	

EXPERIMENTAL

The reactions and the individuality of the products were monitored by TLC on Silufol UV-254 plates. The IR spectra of the compounds were obtained on a UR-20 instrument in tablets with potassium bromide. The PMR spectra were recorded on a Tesla BS-497 spectrometer at 100 MHz with HMDS as internal standard. The mass spectra were obtained on a Varian MAT-112 spectrometer with direct injection into the ion source. The temperature of the ionization chamber was 180°C, and the energy of the ionizing electrons was 70 eV.

1-Methyl-, 1-ethyl-2-methyl-, 1-propyl-2-ethyl-, 1-butyl-2-propyl-, and 1-isobutyl-2-isopropyl-4-nitro-5-chloroimidazoles (I, III-VI) were obtained by the method proposed in [13], 1,2-dimethyl-4-nitro-5-bromoimidazole (II) by the method in [14], and 1-methyl- and 1-propyl-2-ethyl-4-chloro-5-nitroimidazoles (VIII, IX) by the method in [15].

1-Benzyl-2-methyl-4-nitro-5-bromoimidazole (VII). The compound was obtained from 2-methyl-4(5)-nitro-5(4)-bromoimidazole [14] and benzyl chloride under the conditions for the synthesis of 1-acylmethyl-2-methyl-4-nitro-5-bromoimidazoles [16, 17]. The yield was 70%; mp 156-158°C (from ethanol). Found %: Br 27.03. $C_{11}H_{10}BrN_3O_2$. Calculated %: Br 26.99.

The 2-aminoethanol and 3-aminopropanol were freshly distilled.

1-Alkyl(1,2-dialkyl)-4-nitro-5-(hydroxyalkylamino)imidazoles (X-XXI). A. A mixture of 0.05 mole of the nitrohalogenoimidazole (I, II, IV, V) and 0.25 mole of aminoethanol in 60-70 ml of isobutanol was heated at 90-100°C for 3-4 h and cooled to 0-5°C. The precipitate that separated was filtered off, washed with water, and dried, and compounds (X, XI) were obtained.

For the isolation of compounds (XV, XVI), formed from (IV) and (V) respectively, the solvent was distilled under vacuum, and 5 ml of water was added to the residue. The precipitate was rubbed, filtered off, washed with water, and dried.

B. A mixture of 0.1 mole of the nitrohalogenoimidazole (I) or (II) and 0.5 mole of 3-aminopropanol in 70-80 ml of isobutanol was heated at 40-50°C until the initial substances had dissolved. The heat was then removed, since the reaction proceeds with spontaneous heating. The temperature of the reaction mixture (90-100°C) was maintained by cooling the flask periodically with water. After 2 h the reaction mixture was cooled to 15-20°C, and the residue was filtered off, washed with water, and dried. Compounds (XVII, XVIII) were obtained.

C. A mixture of 0.01 mole of the nitrohalogenoimidazole (III, VI, VII) and 0.05 mole of the amino alcohol was stirred at 70-80°C for 2 h, and 5-7 ml of ethanol was added. The precipitate was filtered off, washed with water, and dried. Compounds (XII-XIV, XX, XXI) were obtained. For the isolation of compound (XIX) the excess of the aminopropanol was distilled under vacuum, and the residue was treated as described above.

Compounds (X-XXI) are bright-yellow crystalline substances poorly soluble in lower alcohols and acetone. For analysis the compounds were recrystallized from ethanol (X, XI, XVI) or anhydrous ethanol (XII-XIV, XVII-XXI). During

the recrystallization of compound (XVIII) from aqueous ethanol its dihydrate was isolated. The latter lost its water of crystallization at 80-90°C. The R_f values of the compounds in the 1:1 benzene—dioxane system were: (XIII) 0.62; (XIV) 0.15; (XIX) 0.41; (XX) 0.72; (XXI) 0.13.

PMR spectrum of compound (X) (DMSO-d_6), ppm: 3.55 (4H, m, N—CH_2—CH_2); 3.68 (3H, s, N—CH_3); 5.0 (1H, t, J = 8 Hz, O—H); 7.30 (1H, s, C_2—H); 7.8 (1H, bs, N—H).

1-Alkyl(1,2-dialkyl)-4-(hydroxyalkylamino)-5-nitroimidazoles (XXII-XXIV). A mixture of 0.1 mole of the nitrochloroimidazole (VIII, IX) and 0.5 mole of the amino alcohol in 40-50 ml of isobutanol was heated at 60-70°C for 15-20 min until the initial substances had dissolved. The reaction then proceeded with spontaneous heating. The reaction mixture was kept at 90-100°C for 2 h and treated as described for the isolation of compounds (XVII, XVIII), and compounds (XXII-XXIV) were obtained. For analysis they were purified by crystallization from anhydrous ethanol. PMR spectrum of compound (XXII) (DMSO-d_6), ppm: 3.55 (4H, m, N—CH_2—CH_2); 3.93 (3H, s, N—CH_3); 4.8 (1H, m, O—H); 7.55 (1H, bs, N—H); 7.75 (1H, s, C_2—H).

Hydrochlorides of 1,2-Dialkyl-4-nitro-5-(2-chloroethylamino)imidazoles (XXV, XXVI). To a suspension of 0.01 mole of the compound (XI, XVI) in 10 ml of anhydrous benzene we added a solution of 3 ml (0.03 mole) of thionyl chloride in 10 ml of benzene. The mixture was heated at 50-60°C for 3-4 h until the bright-yellow color of the initial substance had disappeared and was then cooled. The precipitate that separated was filtered off, washed with benzene, and dried. Compounds (XXV, XXVI) are greenish crystalline substances poorly soluble in lower alcohols and acetone, insoluble in nonpolar organic solvents and soluble in DMFA and DMSO. For analysis the compounds were recrystallized from anhydrous ethanol.

1-Methyl-4-(2-chloroethylamino)-5-nitroimidazole (XXVII). The compound was obtained from compound (XXII) by analogy with the synthesis of compounds (XXV, XXVI) with the exception that the intermediate hydrochloride of compound (XXVII) was dissolved in water and neutralized with sodium bicarbonate, and the precipitate was filtered off, washed with water, and dried. For analysis the imidazole (XXVII) was purified by crystallization from anhydrous ethanol.

Hydrochlorides of 1-Methyl-4-(2-acyloxyethylamino)-5-nitroimidazoles (XXVIII-XXXI). To a suspension of 0.1 mole of compound (XXII) in 100 ml of anhydrous benzene with stirring we added 0.2 mole of freshly distilled carboxylic acid chloride (acetic, butyric, α-bromopropionic, or valeric). The mixture was boiled for 6-8 h and cooled. The precipitate was filtered off, washed with benzene, and dried. Compounds (XXVIII-XXXI) were obtained in the form of colorless or slightly greenish crystalline substances soluble in lower alcohols, acetone, and DMFA and insoluble in nonpolar solvents. For analysis the compounds were purified by crystallization from acetone.

Dipicrate of 1-Methyl-4-(2-hydroxyethylamino)-5-aminoimidazole (XXXII). A solution of 1.86 g (0.01 mole) of the compound in 50 ml of anhydrous ethanol was hydrogenated in the presence of 1.0 g of 5% palladium oxide on charcoal at atmospheric pressure and room temperature until the absorption of hydrogen had ceased. The catalyst was then filtered off, and the filtrate was divided into two parts. To one of them we added a saturated alcohol solution of picric acid. The yellow precipitate of the dipicrate (XXXII) was filtered off, washed with ethanol, and crystallized from ethanol. The other portion of the filtrate was evaporated to dryness under vacuum; here the base (XXXII) soon resinified. Resinification also occurs when an alcohol solution of hydrogen chloride is added to the filtrate.

Picrate of 1-Methyl-4-(3-hydroxypropylamino)-5-aminoimidazole (XXXIII). The compound was obtained by the hydrogenation of compound by analogy with the synthesis of compound (XXXII). For analysis the compound was recrystallized from water. The free base of (XXXIII) soon resinifies.

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