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

P. M. Kochergin, L. A. Reznichenko,
R. N. Gireva, and E. V. Aleksandrova

A series of 1-alkyl(1,2-dialkyl)-substituted 4-nitro-5-hydroxyalkylamino- and 4-hydroxyalkylamino-5-nitro-
imidazoles 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 com-
pounds 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 correspond-
ing 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-hy-
droxy-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-hydroxy-
ethylamino)adenine [8] respectively were obtained in the reaction of 2-nitrochlorobenzene and 8-bromo adenine with 2-
aminoethanol.

*For Communication 96, see [1].
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 nitroaminomidazoles (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 I and 2). In the IR spectra of the nitro compounds there are absorption bands for the NO₂ 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.