DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 2-HYDROXY- AND 2-DIETHYLAMINO-ETHYLAMIDES OF 1-ALKYL(1,2-DIALKYL)-4-AMINOIMIDAZOLYL-5-CARBOXYLIC ACIDS

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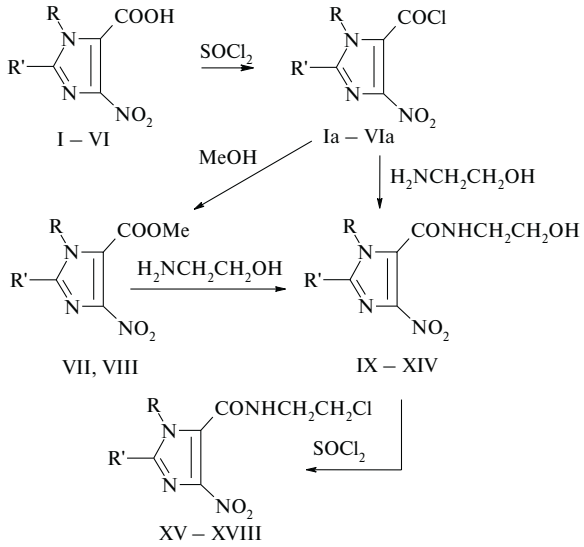
In continuation of the search for new biologically active compounds begun in [1, 2], we have synthesized a series of 2-hydroxy- and 2-diethylaminoethylamides of 1-alkyl-(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acids.

The initial 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5-carboxylic acids (I – VI) were synthesized from 4-nitro-5-chloro(bromo)imidazoles [3, 4] by hydrolysis of the intermediate 4-nitro-5-cyanoimidazoles [5, 6] using a method described in [7, 8]. Acids I – VI were converted into the corresponding chloroanhydrides (Ia – VIa) by heating with thionyl chloride as described in [8]. Compounds Ia – VIa were brought into reactions with methanol or aminoethanol to obtain methyl esters of 1-methyl(1-isobutyl-2-isopropyl)-4-nitroimidazolyl-5-carboxylic acids (VII, VIII) and 2-hydroxyethylamides of 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5-carboxylic acids (IX – XIV).

It was established that reactions of the chloroanhydrides of acids Ia – VIa with aminoethanol proceed unambiguously at the amino group, leading to the formation of 2-hydroxyethylamides of imidazolecarboxylic acids IX – XIV.

The purity of compounds IX – XIV was checked by TLC. The proposed structures were confirmed by the counter synthesis of amides IX and XIII from esters VII and VIII, by the conversion of compounds IX – XIV into 2-chloroethylamides of 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5-carboxylic acids (XV – XVIII) under the action of thionyl chloride, and by the spectral characteristics of compounds IX – XVIII (Table 1).



The IR spectra of amides IX – XIV exhibit absorption bands due to CO groups (at 1640 – 1680 cm^{-1}), NH groups (3250 – 3340 cm^{-1}), OH groups (3410 – 3450 cm^{-1}), and NO_2 groups (1340 – 1380 and 1510 – 1550 cm^{-1}). The spectra of compounds XV – XVII contain, in contrast to those of the initial 2-hydroxyethylamides, no absorption bands due to OH groups.

The ^1H NMR spectra of amides IX – XI and XIII display, in addition to signals from protons of the alkyl groups in positions 1 and 1,2 of the imidazole nucleus, triplets from protons of the NH and OH groups (8.82 – 9.18 and 4.65 – 4.70 ppm, respectively). The mass spectra of amides IX – XIV and the chlorine-containing derivatives XV and XVII contain peaks with m/z corresponding to the masses of the molecular ions.

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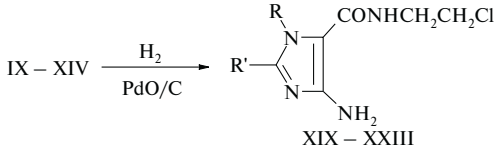
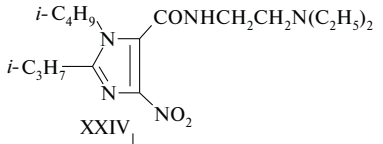
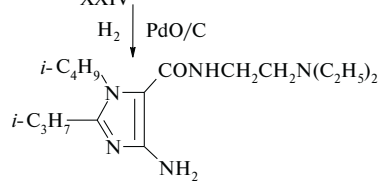
In the final stage of synthesis, we performed catalytic hydrogenation of 2-hydroxyethylamides of 4-nitroimidazolyl-5-carboxylic acids IX – XI and XIII to the corresponding 2-hydroxyethylamides of 1-alkyl(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acids (XIX – XXIII). These reactions readily proceed at room temperature in the presence of a catalyst (5% palladium oxide on carbon); the process is conducted in a lower alcohol medium with hydrogen at atmospheric pressure. Hydrogenation of the amino acid XXIV under analogous conditions led to the corresponding 2-diethylaminoethylamide XXV.



XIX – XXIII



XXIV



XXV

The proposed structures of compounds XIX – XXIII and XXV were confirmed by the data of IR, UV, ^{1}H NMR, and mass spectroscopy. The mass spectra contain peaks with *m/z* corresponding to the masses of the molecular ions (Table 2). The mass spectrum of 2-diethylaminoethylamide XXV, similar to that of the initial nitro compound XXIV, contains a peak with *m/z* = 86 corresponding to the $CH_2N(C_2H_5)_2$ fragment.

The IR spectra of compounds XIX – XXIII and XXV, in contrast to the spectra of the initial nitro compounds IX – XIV and XXIV, contain no absorption bands of the NO_2 group; instead, bands of NH_2 groups are observed in the region of 3350 – 3450 cm^{-1}. The ^{1}H NMR spectrum of aminoamide XX displays signals of protons from the two methyl groups at 2.42 ppm (C–CH_3) and 3.86 ppm (N–CH_3), the NH_2 group (at 5.1 ppm), the CH_2 – CH_2 group (3.6 ppm), and an NH or OH group (7.3 ppm). The UV spectra of amino compounds XIX, XXI, and XXIII in ethanol solutions are characterized by maximum absorption at 272 – 274 nm (log ε = 3.94 – 4.01).

EXPERIMENTAL PART

The IR spectra were measured on a UR-20 spectrophotometer (Germany). The mass spectra were obtained with a Varian MAT-12 spectrometer equipped with a system of direct sample injection into an ion source. The ^{1}H NMR spectra were recorded on a Tesla BS-497 instrument operated at a working frequency of 100 MHz, using HMDS as the internal standard. The UV spectra were recorded with an M-40 spectrophotometer. TLC was performed on Silufol UV-254 plates developed by exposure to iodine vapor or UV light. The data of elemental analyses for compounds X – XIV, XIX – XXVI (C, H, N) and XV – XVIII (C, H, N, Cl) agree with the values calculated by the empirical formulas.

Acids I – VI were synthesized as described in [7, 8] and converted into the corresponding chloroanhydrides (Ia – VIa) by treatment with thionyl chloride according to [8]. These chloroanhydrides were brought into reactions with methanol and freshly distilled aminoethanol. The yields of esters VII, VIII and amides IX – XIV were calculated with

TABLE 1. Yields and Characteristics of Nitro Compounds IX – XXVI

Compound	Empirical formula	R	R^1	M.p., °C	M$^+$	IR spectrum (KBr disks): ν_{max}, cm^{-1}				Yield, %
						CO	NO_2	NH	OH	
IX	$C_7H_9N_3O_5$	CH_3	H	149 – 151*	214	1660	1350, 1550	3290	3450	76 – 89
X	$C_8H_{12}N_4O_4$	CH_3	CH_3	174 – 176	228	1655		3280	3440	62
XI	$C_{11}H_{18}N_4O_4$	C_3H_7	C_2H_5	165 – 166	270	1680		3280		58
XII	$C_{13}H_{22}N_4O_4$	C_4H_9	C_3H_7	129 – 130	298	1680		3280		75
XIII	$C_{13}H_{22}N_4O_4$	*i*-C_4H_9	*i*-C_3H_7	168 – 169	298	1650		3340	3410	80 – 85
XIV	$C_{15}H_{26}N_4O_4$	C_5H_{11}	C_4H_9	75 – 77	326	1680	1340, 1510	3250		70
XV	$C_7H_9ClN_4O_3$	CH_3	H	154 – 155	232	1680	1350, 1510	3260		92
XVI	$C_8H_{11}ClN_4O_3$	CH_3	CH_3	151 – 154		1650	1380, 1510	3320		73
XVII	$C_{13}H_{22}ClN_4O_3$	C_4H_9	C_3H_7	112 – 113	316	1680		3280		97
XVIII	$C_{13}H_{22}ClN_4O_3$	*i*-C_4H_9	*i*-C_3H_7	143 – 144		1640		3320		83
XXIV	$C_{17}H_{31}N_5O_3$	*i*-C_4H_9	*i*-C_3H_7	77 – 79	353	1650		3290		61
XXVI	$C_6H_6N_4O_2$			139 – 140**			1380, 1520		2240 (CN)	74

* Reported m.p., 148 – 149°C [5].
** In [9] compound XXVI was obtained in the form of an oil.

TABLE 2. Yields and Characteristics of Nitro Compounds XIX – XXIII and XXV

Compound	Empirical formula	M.p., °C	M^+	IR spectrum*: ν_{max}, cm^{-1}				UV spectrum (in ethanol): λ_{max}, nm (log ε)	Yield, %	R	R′
				CO	NH	NH_2	OH				
XIX	$C_7H_{12}N_4O_2$	119 – 120**	184	1610	3350,	3450		374(4.01)	92	CH_3	H
XX	$C_8H_{14}N_4O_2$	172 – 174	198	1660	3260,	3400,	3445		60	CH_3	CH_3
XXI	$C_{11}H_{20}N_4O_2 \cdot HCl$	113 – 115	240	1660	3210,	3300,	3320	374(3.98)	85	C_3H_7	C_2H_5
XXII	$C_{13}H_{24}N_4O_2$	94 – 96	268	1650	3200,	3320,	3420	373(3.95)	78	i-C_4H_9	i-C_3H_7
XXIII	$C_{15}H_{28}N_4O_2$	97 – 98	296	1620	3200,	3320,	3380	372(3.94)	67	C_5H_{11}	C_4H_9
XXV	$C_{17}H_{33}N_5O$	124 – 125	323	1650	3200,	3320,	3420		84	i-C_4H_9	i-C_3H_7

* Compound XIX measured in nujol mull; other compounds, in KBr disks.
** In [7] compound XIX was obtained in the form of an oil.

respect to the initial acids I – VI. Methyl esters VII and VIII were obtained from acids I and V as described in [8].

2-Hydroxyethylamides of 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5-carboxylic acids (IX – XIV). Method A. To 1-methyl-4-nitroimidazolyl-5-carboxylic acid chloroanhydride (Ia), prepared from 3.4 g (0.02 mole) of acid I and dissolved in 50 ml of anhydrous benzene, was added dropwise with stirring and cooling 7.3 g (0.06 mole) of aminoethanol. The mixture was stirred for 2 h at 20 – 22°C and allowed to stand for 10 – 12 h. Then benzene and residual aminoethanol were distilled off in vacuum, the residue was washed with diluted hydrochloric acid, and the precipitate was filtered, washed with water, and dried to obtain 3.3 g (76%) of compound IX. A similar procedure was used to obtain compounds XI – XIV.

Method B. A mixture of 5.5 g (0.022 mole) of technical-purity chloroanhydride IIa and 3.3 ml (0.05 mole) of aminoethanol was stirred for 30 min at 50 – 55°C, boiled for 2 h, and cooled. The precipitate was separated by filtration, washed with benzene and water, and dried to obtain 3.9 g of compound X.

Method C. A mixture of 1.85 g (0.01 mole) of ester VII and 1.5 ml (0.02 mole) of aminoethanol in 20 ml of methanol was boiled for 4 h, cooled, and poured into water. The precipitate was separated by filtration, washed with water, and dried to obtain 1.9 g (89%) of compound IX. A mixture of this product with compound IX obtained by method A showed no depression in the melting temperature. The IR spectra of these substances were identical as well.

The same method was used to obtain amide XIII (yield, 85%) from ester VIII; the product was also identical to the substance synthesized by method A.

The general properties of compounds IX – XIV are as follows: pale-yellow crystalline substances, insoluble in water and soluble in organic solvents; do not form hydrochlorides and picrates. Prior to analyses, these substances were additionally purified by recrystallization from methanol.

2-Chloroethylamides of 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5-carboxylic acids (XV – XVIII). To a suspension of 0.01 mole of the initial compound (IX, X, XII, XIII) in 30 – 40 ml of anhydrous benzene were added dropwise 0.05 mole of thionyl chloride and 2 drops of DMF. The mixture was stirred for 4 h at 65 – 70°C and cooled. The precipitate was separated by filtration, washed with benzene, and dried to obtain the target compound (XV – XVIII). The products appear as pale-yellow crystalline substances soluble in organic solvents and insoluble in water; do not form hydrochlorides and picrates. Prior to analyses, these substances were additionally purified by crystallization from methanol (XV, XVIII), dioxane (XVI), and aqueous acetone (XVII).

2-Hydroxyethylamides of 1-alkyl(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acids (XIX – XXIII). A solution of 0.02 mole of the initial compound (IX – XIV) in 130 – 150 ml of methanol was hydrogenated in the presence of 1.0 – 1.5 g of a 5% carbon-supported palladium oxide catalyst until hydrogen absorption ceased (1.5 – 2 h). Then the catalyst was separated by filtration and washed with metha-

TABLE 3. Parameters of the ^1H NMR Spectra of Compounds IX – XI, XIII, XV – XVIII, and XX

Compound	Chemical shift δ, ppm*
IX	3.68 (s, 3H, N–CH), 4.70 (t, 1H, J 6 Hz, O-H), 7.79 (s, 1H, 2-H), 888 (t, 1H, J 6 Hz, N–H)
X	2.38 (s, 3H, C–CH_3), 3.4 (m, 4H, CH_2-CH_2), 3.64 (s, 3H, N–CH_3)
XI	4.65 (bs, 1H, O–H), 8.82 (bs, 1H, N–H)
XIII	0.85 (d, 6H, J 7 Hz, C^2-CH(CH_3)$_2$), 1,3 (d, 6H, J 7 Hz, CH(CH_3)$_2$), 4.05 (d, 2H, J 6 Hz, CH_2-CH)
XV	3.7 (m, 7H, N–CH_3 + CH_2CH_2), 7.81 (s, 1H, C_2-H), 9.18 (bs, 1H, N–H)
XVI	2.42 (s, 3H, C–CH_3), 3.59 (s, 3H, N–CH_3)
XVII	1.0 (m, 7H, C–C_3H_7), 3.78 (m, 4H, N–CH_2CH_2), 4.11 (t, 2H, J 6 Hz, N–CH_2), 13.0 (bs, 1H, N–H)
XVIII	0.85 (d, 6H, J 6 Hz, C-(CH_3)$_2$)
XX	2.42 (s, 3H, C–CH_3), 3.86 (s, 3H, N–CH_3), 3.6 (m, 4H, CH_2CH_2), 7.3 (bs, 1H, NH or OH), 5.1 (bs, 2H, NH_2)

* ^1H NMR spectra of samples dissolved in DMSO-d_6 (IX, X, XX), DMF-d_7 (XI, XV), $CDCl_3$ (XII, XIII, XVII, XVIII), CF_3COOD (XVI).

nol (2 × 10 ml). The solvent was distilled off in vacuum. The oily residue was mixed with 5 – 6 ml of ether and triturated. The crystalline precipitate was separated by filtration, washed with ether, and dried to obtain the target compound (XIX, XX, XXII, XXIII). Base XXI, which did not crystallize, was converted into hydrochloride by treatment with an ethanol solution of hydrogen chloride, followed by precipitation with ether.

The products appeared as colorless crystalline substances (except for compound XXI) insoluble in water and soluble in organic solvents and aqueous mineral acid solutions. Prior to analyses, these substances were additionally purified by crystallization from methanol.

2-Diethylaminoethylamide of 1-isobutyl-2-isopropyl-4-nitroimidazolyl-5-carboxylic acid (XXIV). Compound XXIV was obtained from acid V by a procedure analogous to that used for the synthesis of amide IX (Method A), using freshly distilled 2-diethylaminoethylamine. Prior to analyses, the product was additionally purified by crystallization from aqueous methanol.

2-Diethylaminoethylamide of 1-isobutyl-2-isopropyl-4-aminoimidazolyl-5-carboxylic acid (XXV). Compound XXV was obtained by hydrogenating amide XXIV according to a method used for the synthesis of compounds XIX – XXIII. Prior to analyses, the product was additionally purified by crystallization from aqueous methanol.

1,2-Dimethyl-4-nitro-5-cyanoimidazole (XXVI). To a solution of 11.0 g (0.05 mole) of 1,2-dimethyl-4-nitro-5-bromoimidazole [4] in 100 ml of anhydrous ethanol were added 4.9 g (0.1 mole) of finely triturated sodium cyanide and 0.75 g (0.005 mole) of sodium iodide and the mixture was boiled for 6 h. The precipitate of inorganic salts was separated by filtration. The filtrate was distilled in vacuum to remove ethanol. The residue was treated with 10 ml of water. The precipitate was separated by filtration, washed with water, and dried to obtain 6.14 g of a substance with m.p. 139 – 140°C (from anhydrous ethanol); in [9], this product was obtained in the form of oil.

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