DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 2-HYDROXYETHYL AND 2-CHLOROETHYL ESTERS OF 1-ALKYL(1,2-DIALKYL)-4-AMINOIMIDAZOLYL-5-CARBOXYLIC ACIDS

L. A. Reznichenko,¹ E. V. Aleksandrova,² and P. M. Kochergin³

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 34, No. 7, pp. 31 - 33, July, 2000.

Original article submitted November 22, 1999.

The esters of 1-alkyl(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acids belong to the group of insufficiently studied compounds [1, 2]. In the search for new biologically active substances, it was of interest to synthesize and characterize some of the 4-aminoimidazolyl-5-carboxylic acid esters containing 2-hydroxyethyl and 2-chloroethyl groups in the ester chains.

The initial (1-methyl)- and (1-isobutyl-2-isopropyl)-4nitroimidazolyl-5-carboxylic acids (I, II) were obtained using well-known methods [1, 3, 4] and converted into the corresponding chloroanhydrides (III, IV) as described in [4], which were used without additional purification in the esterification reactions with ethylene glycol and ethylene chlorohydrin.



I, III, V, VII: R = Me, R' = H; II, IV, VI, VIII: $R = Me_2CHCH_2$, $R' = Me_2CH$. It was established that the reaction pathways of chloroanhydrides III and IV with ethylene glycol are rather ambiguous, leading to mixtures of 1-alkyl(1,2-dialkyl)-4-nit-roimidazolyl-5-carboxylic acid 2-hydroxyethyl esters (V, VI) with the corresponding diimidazolyl glycol esters (VII, VIII). We succeeded in separating these products by means of fractional crystallization from lower alcohols. The maximum yields of esters V and VI (60 and 90%, respectively) were obtained using 5 mole of ethylene glycol per mole of chloroanhydride III or IV.

The reactions of chloroanhydrides III and IV with ethylene chlorohydrin proceed by a unique pathway, leading to the corresponding chloroethyl esters of (1-methyl)- and (1-isobutyl-2-isopropyl)-4-nitroimidazolyl-5-carboxylic acids (IX, X) with a yield of 85%. Alternatively, the same 2-chloroethyl esters IX and X (yield of 77 and 57%) were obtained by reactions of 2-hydroxyethyl esters V, VI with thionyl chloride.



The hydrogenation of methyl and ethyl esters of (1-methyl)- and (1-isobutyl-2-isopropyl)-4-nitroimidazolyl-5-carboxylic acids in the presence of various catalysts (carbon-supported palladium chloride, Raney nickel, etc.) was originally described by Mann and Porter [1]. We established that hydrogenation of 4-nitroimidazolyl-5-carboxylic acid esters (VI, IX, X) to the corresponding amines (XI – XIII) is most readily performed with hydrogen at atmospheric pressure and room temperature in a lower alcohol medium in the

¹ Pharmaceutical Chemistry Research Institute, Novokuznetsk, Russia.

² State Medical University, Zaporozh'e, Ukraine.

³ Center for Drug Chemistry–All-Russia Research Institute of Pharmaceutical Chemistry, Moscow, Russia.

369

presence of a catalyst (5% palladium oxide supported on carbon). The yield of 1-alkyl(1,2-dialkyl)-4-nitroimidazolyl-5carboxylic acid esters was 50 - 90%; compound XIII was also obtained at a 80% yield using a reaction of ester XI with thionyl chloride in benzene.



XI, XIII: $R = Me_2CHCH_2$, $R' = Me_2CH$; XII: R = Me, R' = H.

The purity of the previously unreported compounds (V - XIII) was checked by TLC. The proposed structures and compositions were confirmed by the results of elemental analyses, by the data of IR, ¹H NMR, and mass-spectrometric measurements, and by the counter synthesis of compounds IX, X, and XIII.

The IR spectrum of 1,2-diimidazolyl glycol VIII (in contrast to the spectrum of ester VI) contains no absorption bands due to OH groups in the region of 3450 cm^{-1} , while the mass spectrum of the former compound displays a peak due to the molecular ion with m/z = 536.

EXPERIMENTAL PART

The IR spectra were recorded on a UR-20 spectrophotometer (Germany) using samples pelletized with KBr. The mass spectra were obtained with a Varian MAT-112 spectrometer with direct sample injection into the ion source, operated at an ionization chamber temperature of 180°C and an ionizing electron beam energy of 70 eV. The melting temperatures were determined using a heating table of the Boetius type.

The course of the reactions was monitored and the reaction product purity was checked by TLC on Silufol UV-254 plates eluted in the benzene – dioxane mixtures 1 : 1 (system 1) and 1 : 10 (system 2). The spots were visualized by exposure to iodine vapor or under UV illumination.

The results of elemental analyses for the previously unreported compounds V - VIII, XI (C, H, N) and IX, X, XII, XIII (C, H, N, Cl) agree with the data calculated using their empirical formulas. The yields and physicochemical characteristics of compounds V - XIII are presented in Table 1.

The initial (1-methyl)- and (1-isobutyl-2-isopropyl)-4-nitroimidazolyl-5-carboxylic acids (I, II) were obtained as described in [3, 4]. The acids were converted into the corresponding chloroanhydrides (III, IV) by treating with thionyl chloride in anhydrous benzene [4]. Upon evaporation of the residual benzene and excess thionyl chloride in vacuum, the technical-purity chloroanhydrides III and IV were used in esterification reactions with ethylene glycol and ethylene chlorohydrin. The yields of compounds V - X were calculated with respect to the initial acids I and II.

1-Methyl-4-nitroimidazolyl-5-carboxylic acid 2-hydroxyethyl ester (V). To unpurified chloroanhydride III, obtained from 3.4 g (0.02 mole) of acid I, was added 6.3 g (0.1 mole) of ethylene glycol. The mixture was heated to 80 – 90°C, kept until obtaining a transparent solution, cooled, and diluted with 30 ml of water. The precipitated viscous deposit exhibited slow crystallization in the course of trituration. The deposit was separated by filtration, washed with water, and dried to obtain 4.0 g of a substance melting at $56-69^{\circ}$ C. TLC in system 1 showed this substance to be a mixture of two compounds. Double (the first stage with charcoal) crystallization from a 60% aqueous isopropanol solution yielded 2.6 g (60%) of pure ester V; m.p., $60 - 62^{\circ}$ C; R_s 0.47. Upon evaporating isopropanol from the mother liquor, the residue was washed with ether and recrystallized from a 60% aqueous isoropanol solution to obtain 0.4 g (10%) of a product melting at $75 - 78^{\circ}$ C, identified as compound VII; R_e, 0.75.

1-Isobutyl-2-isopropyl-4-nitroimidazolyl-5-carboxylic acid 2-hydroxyethyl ester (VI). Compound VI was obtained by a method analogous to that employed for the synthesis of compound V, proceeding from chloroanhydride IV, prepared using 2.5 g (0.01 mole) of acid II, and 3 ml (0.05 mole) of ethylene glycol. The yield of technical-purity compound VI is 2.78 g (by TLC data, the product contains a certain amount of compound VIII). Recrystallization from an aqueous methanol solution yields pure compound VI; m.p., $103 - 104^{\circ}$ C; R_{p} 0.75 (system 2).

1,2-Di(1-methyl-4-nitroimidazolyl-5-carboxy)ethylene glycol (VII). Compound VII was obtained by a method analogous to that employed for the synthesis of compound V, proceeding from equimolar amounts (0.01 mole) of chloroanhydride III and ethylene glycol; yield, 0.65 g (20%); m.p., $75 - 78^{\circ}$ C (60% aqueous isopropanol); R_{p} 0.75 (system 1). A mixture of this product with compound VI obtained as described above shows no evidence of depression in the melting temperature; the IR spectra of compounds VI and VII are identical.

1,2-Di(1-isobutyl-2-isopropyl-4-nitroimidazolyl-5-car boxylic acid 2-hydroxyethyl ester (VIII). Compound VIII was obtained by a method analogous to that employed for the synthesis of compound VII, proceeding from chloroanhydride IV, prepared using 1.0 g (4 mmole) of acid II, and 0.25 g (4 mmole) of ethylene glycol. TLC of the technical-purity compound VIII shows that the product represents a mixture of compounds VI and VIII in approximately equal amounts. The mixture was separated by means of fractional crystallization from isopropanol. The yield of pure compound VIII, 0.5 g (24%); R_p 0.89 (system 2).

5					1						
Com- pound	Empirical formula	R	R′	M.p., °C	M^+	IR spectrum: v, cm ^{-1}					Viald 0/
						С-О-С	NO_2	СО	OH	NH_2	1 ICIU, 70
V	$C_7H_9N_3O_5$	CH ₃	Н	60 - 62		1120	1330, 1520	1740	3400	_	60
VI	$C_{13}H_{21}N_3O_5$	i-C ₄ H ₉	i-C ₃ H ₇	103 - 104	299	1080	1350, 1520	1740	3450	-	93
						1140					
VII	$C_{12}H_{12}N_6O_8$	CH_3	Н	75 - 78		1105	1340, 1500	1740	-	_	10 - 20
VIII	$C_{24}H_{36}N_6O_8$	i-C ₄ H ₉	i-C ₃ H ₇	175 - 177	536	1010	1310, 1510	1790	—	—	24
IX	C7H8ClN3O4	CH_3	Н	76 - 78	233	1105	1320, 1510	1750	—	—	77 - 85
Х	$C_{13}H_{20}ClN_3O_4$	i-C ₄ H ₉	i-C ₃ H ₇	55 - 57		1110	1330, 1510	1750	-	_	57 - 86
XI	$C_{13}H_{23}N_3O_3$	i-C ₄ H ₉	i-C ₃ H ₇	103 - 104	269	_	—	1680	3430	3320	50
XII	$C_7H_{10}ClN_3O_2$	CH_3	Н	109 - 111	203	_	—	1690	—	3310,	87
										3380	
XIII	$C_{13}H_{22}ClN_3O_2$	i-C ₄ H ₉	i-C ₃ H ₇	153 - 154	287	-	—	1680	-	3160,	80 - 90
										3280,	
										3460	

TABLE 1. Yields and Physicochemical Characteristics of Compounds V - XIII

1-Alkyl(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acid 2-chloroethyl esters (IX, X).

M e t h o d A. To technical-purity chloroanhydride III, prepared using 2.0 g (0.012 mole) of acid I, was added 1.5 ml (0.02 mole) of ethylene chlorohydrin. The mixture was heated for 5 min at $90 - 100^{\circ}$ C, cooled, and diluted with 20 ml of water. The precipitate was separated by filtration, washed with water, and dried to obtain 2.3 g (85%) of compound IX. An analogous procedure (proceeding from acid II via chloroanhydride IV) was used to obtain ester X at an 86% yield.

M e t h o d B. A mixture of 2.15 g (0.01 mole) of ester V and 5 ml of thionyl chloride was heated for 30 min at $50 - 60^{\circ}$ C. Upon evaporation of the residual benzene and excess thionyl chloride, the residue was washed with water and dried to obtain 1.8 g (77%) of ester IX; m.p., $76 - 78^{\circ}$ C (aqueous methanol). A mixture of this product with the sample obtained by method A shows no evidence of depression in the melting temperature; the IR spectra of the two samples of compound IX are identical. An analogous procedure (proceeding from ester VI and thionyl chloride) was used to obtain ester X at a 57% yield (the reaction is conducted at room temperature).

4-Nitroimidazolyl-5-carboxylic acid esters V - X appear as pale-yellow crystalline substances insoluble in water and soluble in most organic solvents. Esters V - X are uncapable of forming hydrochlorides and picrates.

1-Alkyl(1,2-dialkyl)-4-aminoimidazolyl-5-carboxylic acid esters (XI – XIII).

M e t h o d A. To a solution of 0.01 mole of initial nitro compound VI, IX, or X in 50 ml of methanol was added 1.0 g of 5% palladium oxide supported on carbon and the mixture was hydrogenated with hydrogen at atmospheric pressure and room temperature until gas absorption ceased. Then the catalyst was separated by filtration and washed on the filter with methanol (2×8 ml). The filtrate was evaporated in vacuum. The residue was washed with water and dried to obtain amino compounds XI – XIII.

M e t h o d B. A mixture of 2.7 g (0.01 mole) of amino compound XI and 5 ml (0.07 mole of thionyl chloride was boiled for 10 min, cooled, and poured into 50 ml of water with stirring. The residue was separated by filtration, washed with water, and dried to obtain 2.3 g (80%) of compound XIII. A mixture of this product with the sample obtained by method A shows no evidence of depression in the melting temperature; the IR spectra of the two samples of compound XIII are identical.

The amino compounds XI – XIII appear as colorless crystalline substances insoluble in water and soluble in organic solvents and in mineral acid solutions. For analytical purposes, the products were purified by recrystallization from aqueous methanol (compound XI), methanol (XII), and aqueous 2-propanol (XIII).

REFERENCES

- 1. F. G. Mann and J. V. G. Porter, J. Chem. Soc., 751 760 (1945).
- R. N. Gireva, G. A. Aleshina, L. A. Reznichenko, and P. M. Kochergin, *Khim.-Farm. Zh.*, 8(11), 25 – 29 (1974).
- J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, 7, 713-719 (1924).
- R. N. Gireva, G. A. Aleshina, L. A. Reznichenko, and P. M. Kochergin, *Khim.-Farm. Zh.*, 8(10), 24 – 29 (1974).