SYNTHESES OF FUNCTIONALIZED *N*-(2-PYRIDYL)-α-AMINO ACIDS AND ESTERS BY RING OPENING OF IMIDAZO[1,2-a]PYRIDINE

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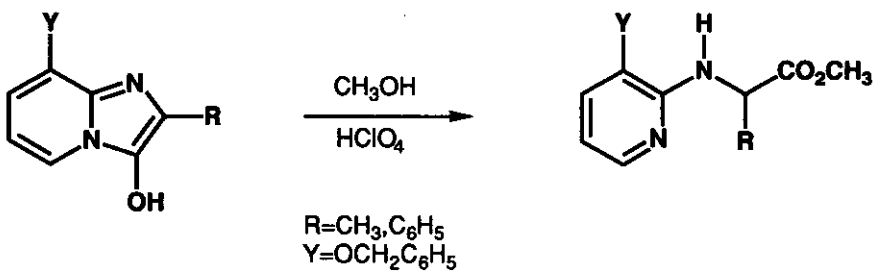
Abstract - This report is devoted to the ring opening of the imidazole nucleus of functionalized imidazo[1,2-a]pyridines, by methanol in strong acid medium ($HClO_4$) leading to esters of *N*-(2-pyridyl)-α-amino acids in which the heterocyclic moiety bears a functional group. Direct obtention of this kind of compounds could be achieved by condensation of glyoxal derivatives with ethers of 2-amino-3-hydroxypyridine or with 2-amino-3(or 5)-nitropyridine in methanolic perchloric acid.

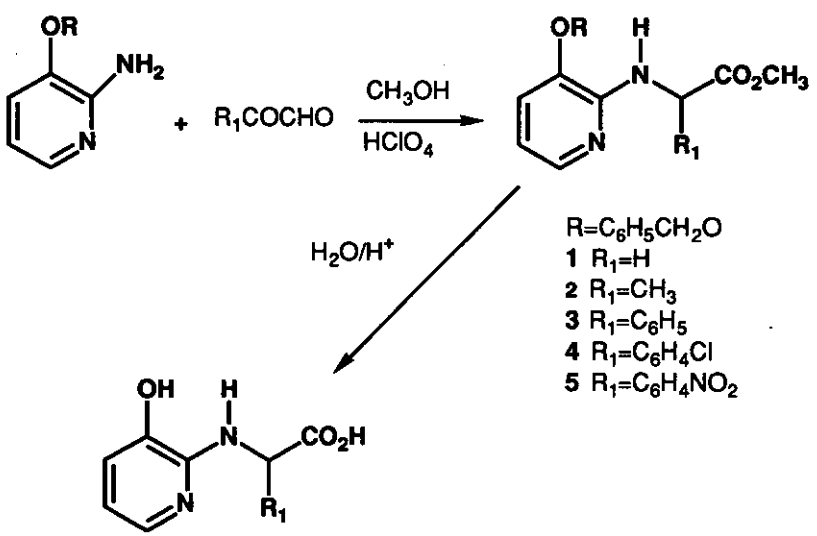
The synthesis of *N*-phenylamino acids derivatives can be performed by reaction of aniline with α-halo esters and α-halo nitriles.[1] Direct arylation of α-amino acid derivatives is only possible with aryl halides substituted by strongly electron-withdrawing groups.[2] Only a limited range of *N*-phenyl derivatives of natural α-amino acids is accessible by these procedures. *N*-Alkyl and *N*-aryl-α-amino acids have been used as starting materials both in drugs[3] and heterocyclic synthesis.[4] In addition, some *N*-arylalanine derivatives such as Ridomil are selective herbicides.[5] The lack of a general methodology for the synthesis of *N*-(2-heteroaryl)-α-amino acids from 2-aminoazines is due to the fact that the direct alkylation of the *N*-endocyclic atom proceeds more rapidly that the desired *N*-exocyclic alkylation.[6] However, efficient general procedures for the synthesis of *N*-(2-heteroaryl)-α-amino acids and their derivatives was described by Alcaide[7] with the one-pot reaction of 2-aminoheterocycles with glyoxals and alcohols in the presence of perchloric acid. Bristow[8] reported the synthesis of *N*-(2-pyridyl)glycine in a moderate yield by

reaction of 2-aminopyridine with formaldehyde, sodium hydrogen sulfite, and sodium cyanide followed by the hydrolysis of the *N*-(2-pyridyl)aminoacetonitrile thus formed. This reaction was used by Goto[9] in the synthesis of *N*-(2-pyrazinyl)glycine and some derivatives in relation with model compounds of the cypridine luciferine. If the method developed by Alcaide was applied with success to pyridine, pyrimidine, and thiazolidine, the substituted compounds have seldom been described. Alcaide reported the synthesis of methyl and chloro substituted *N*-(2-heteroaryl)-α-amino acid esters but no mention of hydroxy or nitro derivatives was made. In order to obtain this kind of compounds, we used two methods. The first one was the ring opening of the imidazole nucleus by methanol in the presence of a strong acid ($HClO_4$) as described by the following scheme:



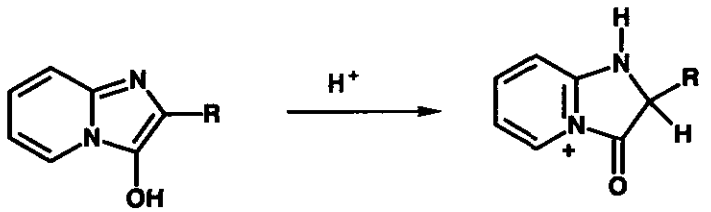
$R=CH_3, C_6H_5$
$Y=OCH_2C_6H_5$

The second method was the application of the procedure described by Alcaide to functionalized pyridines as summarized by the following scheme:

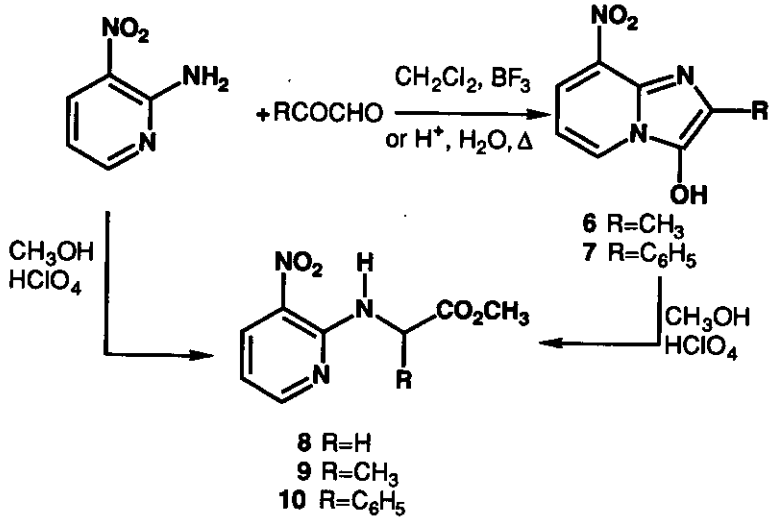


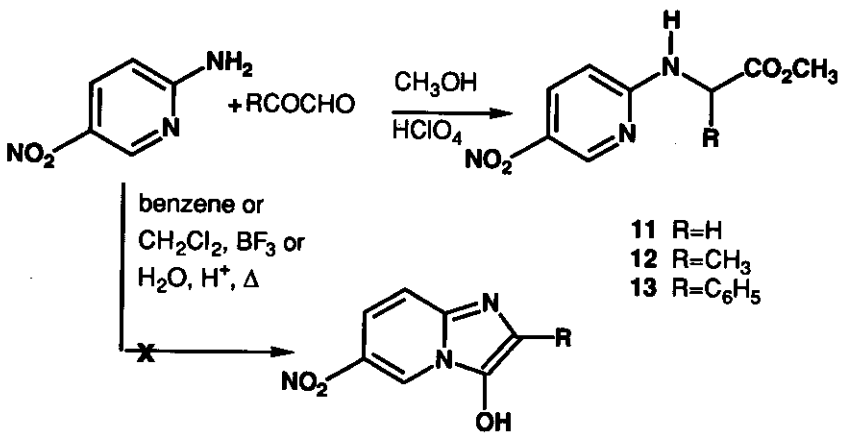
$R=C_6H_5CH_2O$
1 $R_1=H$
2 $R_1=CH_3$
3 $R_1=C_6H_5$
4 $R_1=C_6H_4Cl$
5 $R_1=C_6H_4NO_2$

The reaction of 2-amino-3-hydroxypyridine with glyoxal, methylglyoxal, phenylglyoxal, p-chlorophenylglyoxal, and p-nitrophenylglyoxal in boiling methanol as solvent and in the presence of excess aqueous 60 % perchloric acid gave *N*-(2-pyridyl)-α-amino acid esters (**1-4**), and (**5**) respectively in fair to good yields. One can account for the formation of compounds (1-5) by a reaction pathway analogous to that described by Alcaide which involves the tautomeric oxo form of a protonated 3-hydroxyimidazo[1,2-a]pyridine intermediate.

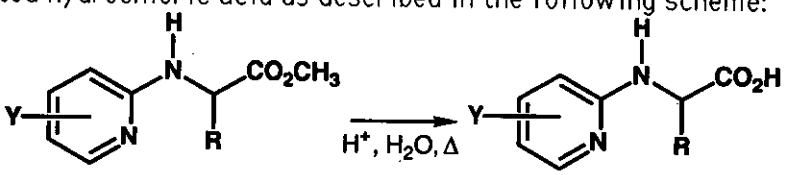


Indeed 2-substituted 8-benzyloxy-3-hydroxyimidazo[1,2-a]pyridines were obtained by condensation of 2-amino-3-benzyloxypyridine with glyoxal derivatives when the reaction was performed either in benzene at room temperature, or in dichloromethane in the presence of $BF_3{\cdot}Et_2O$ complex, or in some cases in hot hydrochloric acid.[10] Similarly 2-methyl-(**6**) or 3-hydroxy-2-phenyl-8-nitroimidazo[1,2-a]pyridine (**7**) obtained by condensation of 2-amino-3-nitropyridine and methylglyoxal or phenylglyoxal gave an analogous reaction and produced on treatment with methanol-$HClO_4$, *N*-(3-nitro-2-pyridyl)-α-amino acid esters (**9**, **10**). These compounds were directly obtained from 2-amino-3-nitropyridine and glyoxal derivatives in a one-pot synthesis with the same reactional medium ($HClO_4$, methanol). In the case of 2-amino-5-nitropyridine, no imidazo[1,2-a]pyridine was obtained on treatment with glyoxal derivatives under the usual above conditions, but with methanol-perchloric acid, *N*-(5-nitro-2-pyridyl)-α-amino acid esters (**11-13**) were produced. These results showed that the nucleophilicity of the endocyclic nitrogen is very sensitive to the nature and the position of the substituent borne by the 2-aminopyridines.





Hydrolysis of the *N*-(2-pyridyl)-α-amino acid esters so obtained was realized in hot concentrated hydrochloric acid as described in the following scheme:

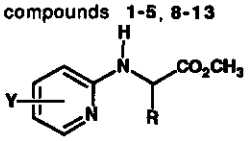


1 Y=3-$C_6H_5CH_2O$, R=H
2 Y=3-$C_6H_5CH_2O$, R=CH_3
12 Y=5-NO_2, R=CH_3
8 Y=3-NO_2, R=H
9 Y=3-NO_2, R=CH_3

14 Y=3-OH, R=H
15 Y=3-OH, R=CH_3
16 Y=5-NO_2, R=CH_3
17 Y=3-NO_2, R=H
18 Y=3-NO_2, R=CH_3

	H_3	H_4	H_5	H_6	NH	CHR	$OCH_2C_6H_5$	$OCH_2C_6H_5$	R	$COOCH_3$	coupling constants (Hz)
1		6.88 dd	6.52 dd	7.70 dd	5.46 br s	4.23	5.05 s	7.43-7.30 m		3.48 s	J6-5=4.8 J6-4=1.1 J5-4=7.6
2		6.89 dd	6.51 dd	7.68 dd	5.39 d	4.78 q	5.07 s	7.43-7.30 m	1.50 d	3.72 s	J6-5=5.1 J6-4=1.3 J4-5=7.8
3		6.89 dd	6.51 dd	7.68 dd	5.81 br d	5.80 d	5.09 s	7.50-7.39 m	7.37-7.28 m	3.71 s	J6-5=5.1 J6-4=1.1 J4-5=7.8
4		6.90 dd	6.51 dd	7.65 dd	5.90 br s	5.78 d	5.10 s	7.31-7.24 m	7.48-7.40 m	3.71 s	J6-5=5.1 J6-4=1.1 J4-5=7.8
5		6.91 dd	6.52 dd	7.65 dd	5.92 br s	5.81 d	5.10 s	7.37-7.24 m	7.48-7.24 m	3.72 s	J6-5=5.1 J6-4=1.0 J4-5=7.8
8		8.40 dd	6.73 dd	8.43 dd	8.48		4.40 s			3.79	J6-4=1.6 J4-5=4.6 J5-6=8.3
9		8.38 dd	6.70 dd	8.43 dd	5.95		4.91 m		1.60 d	3.77	J6-4=1.7 J4-5=4.6 J5-6=8.4
10		8.13 dd	7.44 dd	8.97 d	5.68 d		6.43 d		7.35 m	3.75	J6-4=1.8 J4-5=4.0 J5-6=9.2
11	6.48 d	8.20 dd		9.00 d	5.68 s		4.27 s			3.82 s	J3-4=9.1 J6-4=2.5
12	6.46 d	8.18 dd		8.90 d	5.91 d		4.76 q		1.55 d	3.80	J3-4=9.1 J6-4=2.7
13	6.50 d	8.10 dd		8.90 d	5.69		6.44 d		7.44-7.30 m	3.74 s	J3-4=9.0 J6-4=2.6

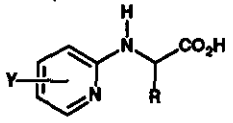
Table 1: ^1H nmr (400 MHz, $CDCl_3$), chemical shifts in ppm downfield to TMS for compounds **1-5, 8-13**



1 R= H , Y=3-$OCH_2C_6H_5$
2 R= CH_3 , Y=3-$OCH_2C_6H_5$
3 R= C_6H_5 , Y=3-$OCH_2C_6H_5$
4 R= C_6H_4Cl , Y=3-$OCH_2C_6H_5$
5 R= $C_6H_4NO_2$, Y=3-$OCH_2C_6H_5$
8 R=H , Y=3-NO_2
9 R=CH_3 , Y=3-NO_2
10 R=C_6H_5 , Y=3-NO_2
11 R=H , Y=5-NO_2
12 R=CH_3 , Y=5-NO_2
13 R=H , Y=5-NO_2

	H3	H5	H4	H6	NH	CH	R	OH	coupling constants (Hz)
14		6.26 dd	6.78 dd	7.37 dd	5.73 s	3.54 s		12.20	J4-5=7.3 J5-6=4.9 J6-4=0.9
15		6.25 dd	6.84 dd	7.39 dd	6.04 s	4.08 q	1.81 d	12.62	J4-5=7.2 J5-6=5.0 J6-4=10.9
16	6.67 d		8.10 dd	8.87 d	3.66 s	4.52 d	1.41 d	12.80	J3-4=8.1 J4-6=4.4
17		8.39 dd	6.69 dd	8.45 dd	8.93 s	3.73 s		12.03	J4-6=9.9 J6-5=3.3 J4-5=7.9
18		8.45 dd	6.83 dd	8.47 dd	8.32 s	4.73 q	1.49 d	12.92	J4-6=1.6 J6-5=4.4 J4-5=8.2

Table 2: ^1H nmr(400 MHz, DMSO-D6), chemical shifts in ppm downfield to TMS

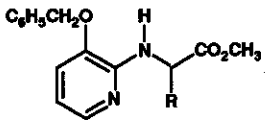


14 R=H , Y=3-OH
15 R=CH_3 , Y=3-OH
16 R=CH_3 , Y=5-NO_2
17 R=H , Y=3-NO_2
18 R=H , Y=5-NO_2

	C2	C3	C4*	C5*	C6	CH	$OCH_2C_6H_5$	OCH_3	COO	$OCH_2C_6H_5$	R
1	149.25	141.67	112.63	115.73	138.80	42.86	70.20	52.02	172.01	i:136.30 m:128.67 p:128.22 o:127.53	
2	148.96	141.51	112.53	115.88	138.84	49.30	70.27	52.13	175.22	i:136.36 m:128.69 p:128.22 o:127.51	18.69
3	148.62	141.55	112.89	116.15	138.98	58.02	70.32	52.45	172.28	i:136.39 m:128.69 p:128.16 o:127.36	i:137.73 m:128.01 p:128.20 o:127.53
4	148.31	141.59	113.44	116.28	138.83	57.38	70.38	52.64	172.41	i:136.28 m:128.73 p:127.39 o:128.24	i:136.42 m:128.91 p:134.03 o:128.86
5	148.19	141.60	113.06	116.34	138.57	57.528	70.42	52.65	172.35	i:136.22 m:128.74 p:28.26 o:127.39	i:136.28 m:128.92 p134.08 o:127.87

* Assignments may be reversed

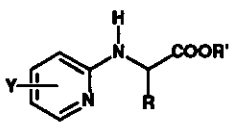
Table 3: ^{13}C nmr (100 MHz, $CDCl_3$), chemical shifts in ppm downfield to TMS



1 R=H
2 R=CH_3
3 R=C_6H_5
4 R=C_6H_4Cl
5 R=$C_6H_4NO_2$

	C2	C3	C4	C5	C6	CH	R=CH_3	R=C_6H_5	COO	OCH_3
8	151.91	128.97	135.24	112.71	155.24	43.00			170.41	52.44
9	151.55	128.62	135.26	112.62	155.31	49.94	18.21		173.62	52.44
10	146.50	132.81	136.78	107.53	159.42	58.52		i:136.21 m:129.11 p:128.60 o:127.41	171.45	53.04
11	160.26	107.52	132.82	136.74	146.64	43.43			170.54	52.64
12	159.99	107.75	132.61	136.52	146.64	50.11	18.30		173.81	52.62
13	159.57	107.62	132.74	136.61	146.53	58.52		i:136.22 m:129.13 p:128.54 o:127.41	171.50	53.01
14	149.93	140.44	116.64	110.81	136.41	45.91			173.31	
15	149.54	140.12	116.82	110.71	136.68	50.92	19.61		177.44	
16	160.71	108.62	134.93	131.82	146.36	52.01	17.31		174.32	
17	151.00	127.11	135.03	111.18	156.43	46.23			170.77	
18	150.94	127.83	135.34	112.77	155.87	49.44	17.75		173.92	

Table 4: ^{13}C nmr (100 MHz), chemical shifts in ppm for compounds **8-13** ($CDCl_3$) and **14-18** (DMSO-D_6)



8 R=H , R'=CH_3 , Y=3-NO_2
9 R=CH_3 , R'=CH_3 , Y=3-NO_2
10 R=C_6H_5 , R'=CH_3 , Y=3-NO_2
11 R=H , R'=CH_3 , Y=5-NO_2
12 R=CH_3 , R'=CH_3 , Y=5-NO_2
13 R=C_6H_5 , R'=CH_3 , Y=5-NO_2
14 R=H,R'=H , Y=3-OH
15 R=CH_3 , R'=H, Y=3-OH
16 R=CH_3 , R'=H , Y=5-NO_2
17 R=H , R'=H , Y=3-NO_2
18 R=CH_3 , R'=H , Y=3-NO_2

The benzyl ether linkage was cleaved under these conditions so that phenols were directly obtained. In the case of phenyl glycinate, important resinification occurred and it was no possible to obtain the desired compounds. Efforts to realize this transformation are undertaken at the present time by a two steps procedure: saponification of the ester group followed by the hydrogenolysis of the benzyl ether linkage in the presence of Pd/C. The assignments of the sructure of these compounds were based mainly on spectroscopic and analytical data.

In conclusion, the present work shows that the Alcaide synthesis of *N*-(2-pyridyl)-α-amino acid esters or acids by ring opening of intermediate 3-hydroxyimidazo-[1,2-a]pyridines could be extended to the synthesis of functionalized derivatives bearing an ether, an hydroxyl or a nitro group on the pyridine ring.

EXPERIMENTAL SECTION

Melting points were determined in capillary tubes on a Buchi SMP 20 apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on Bruker WP60 (60 MHz), Bruker WP80 (80 MHz), and Bruker AM 400WB (400 MHz) spectrometers. The following abbreviations are used: br = broad, d = doublet, dd = double doublet, m = multiplet, q = quadruplet, s = singlet, t = triplet, i = ipso, m = meta, p = para, o = ortho. Chemical shifts were related to tetramethylsilane as an internal standard in DMSO-D_6 (hexadeuteriodimethyl sulfoxide) and $CDCl_3$ (deuteriochloroform). Uv spectra were determined on a Beckman 5270 or Perkin Elmer Lambda 15 spectrophotometer. Mass spectra were measured on a Riber 10-10 apparatus operating with an activation energy of 70 ev or on Kratos Concept II NH spectrometer in a FAB mode (1mA, 7kv, Xe). Combustion analysis for C, H, and N were performed by Service Central de Microanalyse du CNRS.

Methyl *N*-(3-benzyloxy-2-pyridyl)-α-glycinate (1):

To a solution of 2 g (10 mmol) of 2-amino-3-benzyloxypyridine[13] in 3 ml of perchloric acid (65 % aqueous solution), was added in one portion a mixture of 1.93 ml (10 mmol) of an aqueous solution of glyoxal (30 %) and 10 ml of methanol. The mixture

was warmed at reflux for 48 h. After cooling at 0 °C and neutralization by a saturated solution of sodium carbonate, the resulting mixture was extracted by three portions of methylene dichloride. The organic phases were dried on magnesium sulfate, filtered and evaporated under reduced pressure. The oily residual product was chromatographed on a silica gel column with the following eluents: hexane / ethyl acetate (1/1-75 ml) then ethyl acetate (100 ml). The last fractions (homogenous CCM) were dried over magnesium sulfate and evaporated under reduced pressure to give the compound (**1**) as an oily product (50 %, 1.36 g); n_D^{23} 1.5735; ir ν_{max} (liquid film, KBr) cm^{-1}: 3410, 3150 (secondary amine NH), 1745 (ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 272 ($M^{+\cdot}$, 10.32), 213(7.26), 199(22.71), 91(100). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.28. Found: C, 66.65; H, 6.13; N, 9.93.

Methyl *N*-(3-benzyloxy-2-pyridyl)-α-alaninate (2):

a) First method

The preceding procedure was applied to 2-amino-3-benzyloxypyridine (2 g, 10 mmol) and pyruvic aldehyde (1.8 ml of 40 % aqueous solution, 10 mmol) which were warmed in methanolic (10 ml) perchloric acid (3 ml) for 25 h. A similar work-up led after the slow evaporation of the last fractions of elution to a solid which was recrystallized from methanol affording the compound (**2**) as a yellow solid (78 %, 2.23 g): mp 62-64 °C; ir ν_{max} (KBr) cm^{-1}: 3460, 3000 (NH), 1750 (ester CO); ^1H nmr and ^{13}C nmr see theoretical part; ms m/z (rel. int.): 286 ($M^{+\cdot}$, 14.52), 227(18.88), 135(30.42), 91(100). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.78. Found: C, 67.08; H, 6.38; N, 9.65.

b) Second method

To a solution of 1 g (3.54 mmol) of 8-benzyloxy-3-hydroxy-2-methylimidazo [1,2-a]pyridine (**10**) in 10 ml of methanol was added 3 ml of perchloric acid (65 % aqueous solution). The resulting mixture was warmed at reflux for 20 h. After cooling, the mixture was treated with saturated aqueous solution of sodium carbonate and extracted with methylene dichloride. The organic layers were evaporated under

reduced pressure and chromatographed on a silica gel column with the same solvents used in the first method to give after evaporation a crystalline product (0.86 g, 85 %) which presented physicochemical data identical to those described above for the compound (**2**).

Methyl *N*-(3-benzyloxy-2-pyridyl)-α-phenylglycinate (3):

a) First method

According to the procedure described for the compound (1) and starting from 2-amino-3-benzyloxypyridine (2 g, 10 mmol) and phenylglyoxal monohydrate (1.52 g, 10 mmol, time of reflux: 40 h) the compound (**3**) was obtained as a crystalline product (76 % 2.64 g): mp 79-80 °C; ir ν_{max} (KBr) cm^{-1}: 3400, 3000 (NH), 1750 (ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 348 ($M^{+\cdot}$, 21.88), 289(46.70), 197(41.92), 91(100). *Anal.* Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.78; N, 8.04. Found: C, 71.99; H, 5.77; N, 8.10.

b) Second method

According to the procedure described for the compound (**2**) (second method, 30 h) and starting from 8-benzyloxy-3-hydroxy-2-phenylimidazo[1,2-a]pyridine (1.58 g, 5 mmol), the compound (**3**) was obtained as a crystalline product (50 %, 0.87 g). It presented physicochemical data identical to those described above for the compound synthetized by the first method.

Methyl *N*-(3-benzyloxy-2-pyridyl)-α-p-chlorophenylglycinate(4):

According to the procedure described for the compound (1) (first method, reflux time: 45 h) and starting from 2-amino-3-benzyloxypyridine (2 g, 10 mmol) and p-chlorophenylglyoxal (1.68 g, 10 mmol), the compound (**4**) was obtained after the usual treatment as an oily product (56 %, 2.19 g): n_D^{23} 1.5938; ir ν_{max} (KBr) cm^{-1}: 3450, 3050 (NH), 1750 (ester CO); ^1H nmr and ^{13}C nmr see theoretical part; ms m/z (rel. int.): 384 ($M^{+\cdot}$, 10.52), 382(27.79), 325(25.85), 323(75.91), 233(100), 231(58.64), 91(100). *Anal.* Calcd for $C_{21}H_{19}N_2O_3Cl \cdot 0.5\ H_2O$: C, 64.36; H, 5.14; N, 7.14.

Found: C, 64.06; H, 4.93; N, 6.80.

Methyl *N*-(3-benzyloxy-2-pyridyl)-α-p-nitrophenylglycinate (5):

According to the procedure described for the compound (1) (first method, reflux time: 45 h) and starting from 2-amino-3-benzyloxypyridine (2 g, 10 mmol) and p-nitrophenylglyoxal (1.79 g, 10 mmol),[14] the compound (5) was obtained after the usual treatment as a crystalline product (40 %, 1.57 g): mp 144-146 °C; ir ν_{max} (KBr) cm^{-1}: 3450, 3350 (NH), 1745 (ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 393($M^{+\cdot}$, 25.42), 334(82.2), 242(30.27), 91(100). *Anal.* Calcd for $C_{21}H_{19}N_3O_5$: C, 64.11; H, 4.86; N, 10.68. Found: C, 64.08; H, 4.72; N, 10.52.

***N*-(3-Hydroxy-2-pyridyl)-α-glycine(14):**

A solution of compound (1) (1.07 g, 10 mmol) in 5 ml of hydrochloric acid was warmed at reflux for 2 h. After evaporation under reduced pressure, hydrochloride of compound (14) was obtained in a nearly quantitative yield. After neutralization with a hot aqueous solution of sodium carbonate, the resulting mixture was evaporated under reduced pressure. The residue was dissolved in hot ethanol; the mixture was filtered and cooled. After filtration the compound (14) was obtained as a crystalline product (85 %, 1.43 g): mp>230 °C; ir ν_{max} (KBr) cm^{-1}: 3420-2980 (NH, OH); uv λ_{max} (H_2O) nm: 305(log ε 2.73), 244(3); uv λ_{max} (H_2O, HCl) nm: 309(log ε 2.53), 242(2.69); uv λ_{max} (H_2O, NaOH) nm: 305(2.67), 246(2.95); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 168($M^{+\cdot}$, not observed), 150(37.92), 122(41.25), 94(10.42), 66(27.92). *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.66. Found: C, 49.88; H, 4.65; N, 16.34.

***N*-(3-Hydroxy-2-pyridyl)-α-alanine (15):**

According to the procedure described for the compound (14) the compound (15) was obtained after recrystallization from methanol as a crystalline product in a 95 % yield: mp108-110 °C; ir ν_{max} (KBr) cm^{-1}: 3400, 2985(NH, OH); uv λ_{max} (H_2O) nm: 312(log ε 3.73), 243(3.60); uv λ_{max} (H_2O, HCl) nm: 307(log ε 3.96), 240(3.83); uv λ_{max}

(H_2O, NaOH) nm: 310(log ε 3.92), 250(3.91); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 182($M^{+\cdot}$, not observed), 164(27.60), 136(8.46), 107(8.10), 66(18.06). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.57. Found: C, 52.39; H, 5.25; N, 15.15.

Methyl *N*-(5-nitro-2-pyridyl)-α-glycinate (11):

According to the procedure described for the compound (1) and starting from 2-amino-5-nitropyridine (10 mmol, 1.39 g) and glyoxal (1.93 ml of 30 % aqueous solution, reflux time: 48 h), the compound (11) was obtained after recrystallization from methanol as a crystalline product (80 %, 1.69 g): mp 180-182 °C; ir ν_{max} (KBr) cm^{-1}: 3380(NH), 1730(ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 211($M^{+\cdot}$, 11.09), 152(100), 106(62.96), 78(25.16). *Anal.* Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.29; N, 19.89. Found: C, 45.13; H, 4.43; N, 19.60.

Methyl *N*-(5-nitro-2-pyridyl)-α-alaninate (12):

According to the procedure described for the compound (11) and starting from 2-amino-5-nitropyridine (10 mmol, 1.39 g) and pyruvic aldehyde (1.8 ml of 40 % aqueous solution, 10 mmol), the compound (12) was obtained after recrystallization from methanol as a crystalline product (88 %, 1.98 g): mp 115-116 °C; ir ν_{max} (KBr) cm^{-1}: 3370(NH), 1745(ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 225($M^{+\cdot}$, 13.13), 166(100), 119(23.16), 75(83.35). *Anal.* Calcd for $C_9H_{11}N_3O_4$: C, 48.02; H, 4.92; N, 18.65. Found: C, 47.83; H, 4.99; N, 18.06.

Methyl *N*-(5-nitro-2-pyridyl)-α-phenylglycinate (13):

According to the procedure described for the compound (11) and starting from 2-amino-5-nitropyridine (10 mmol, 1.39 g) and phenylglyoxal monohydrate (1.52 g, 10 mmol), the compound (13) was obtained after recrystallization from methanol as a crystalline product (80 %, 2.29 g): mp 135-137 °C; ir ν_{max} (KBr) cm^{-1}: 3400(NH), 1750(ester CO); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 287($M^{+\cdot}$,

7.06), 220(100), 182(28.94), 77(22.26). *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.62. Found: C, 58.52; H, 4.72; N, 14.57.

Methyl *N*-(3-nitro-2-pyridyl)-α-alaninate (8):

According to the procedure described for the compound (11) and starting from 2-amino-3-nitropyridine (1.39 g, 10 mmol) and glyoxal (1.93 ml of 30 % aqueous solution), the compound (**8**) was obtained as a crystalline product after recrystallization from methanol (85 %, 1.79 g): mp 88-90 °C; ir ν_{max} (KBr) cm^{-1}: 3395(NH), 3100-2950(CH), 1750(ester CO); uv λ_{max} (H_2O) nm: 401(log ε 3.14), 258(3.04),219(3.65); uv λ_{max} (H_2O, HCl) nm: 371(log ε 3.52), 266(3.48), 209(4.03); uv λ_{max} (H_2O, NaOH) nm: 414 (log ε 3.78), 264(3.72), 213(4.56); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 211($M^{+\cdot}$, 15.17), 152(100), 105(7.83, 78(26.15). *Anal.* Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.29; N, 19.89. Found: C, 45.53; H, 4.31; N, 19.66.

Methyl *N*-(3-nitro-2-pyridyl)-α-alaninate(9):

According to the procedure described for the compound (1) and starting from 2-amino-3-nitropyridine (1.39 g, 10 mmol) and pyruvic aldehyde (1.8 ml of 40 % aqueous solution, 10 mmol), the compound (**9**) was obtained after recrystallization from methanol as a crystalline product (80 %, 1.8 g): mp 60-62 °C; ir ν_{max} (KBr) cm^{-1}: 3395(NH), 1740(ester CO); uv λ_{max} (H_2O) nm: 381(log ε 3.42), 246(3.15), 204(3.85); uv λ_{max} (H_2O, HCl) nm: 348(log ε 3.82), 250(3.72), 195(4.2); uv λ_{max} (H_2O, NaOH) nm: 97(log ε 3.97), 251(3.84), 202(4.54); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 225($M^{+\cdot}$, 8.44),166(100), 119(74.82), 79(50.68). *Anal.* Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.65. Found: C, 48.09; H, 4.85; N, 18.52.

Methyl *N*-(3-nitro-2-pyridyl)-α-phenylglycinate (10):

According to the procedure described for the compound (1) and starting from 2-amino-3-nitropyridine (1.39 g, 10 mmol) and phenylglyoxal monohydrate (1.52 g, 10 mmol), the compound (**10**) was obtained as a crystalline product after recrystallization from

methanol (82 %, 2.35 g): mp 138-140 °C; ir ν_{max} (KBr) cm^{-1}: 3400(NH), 1745(ester CO); uv λ_{max} (H_2O) nm: 348(log ε 4.37), 221(4.12), 206(4.08); uv$_{max}$ (H_2O, HCl) nm: 317(log ε 4.13), 219(4.29), 206(4.25); uv λ_{max} (H_2O, NaOH) nm: 370(log ε 4.06), 217(4.55); ^1H nmr and ^{13}C nmr see theoretical part; ms m/z (rel. int.): 287($M^{+\cdot}$, 7.25), 228(100), 78(41.82). *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58, 53; H, 4.56; N, 14.62. Found: C, 58.22; H, 4.51; N, 14.58.

***N*-(3-Nitro-2-pyridyl)-α-glycine(17):**

According to the procedure described for the compound (**14**) and starting from **8** (2.11 g, 10 mmol), the compound (**17**) was obtained as a crystalline product after recrystallization from water (80 %, 1.97 g): mp>230 °C; ir ν_{max} (KBr) cm^{-1}: 3550-3530(NH), 3300-3000(OH), 1690(C=O acid); uv λ_{max} (H2O) nm: 486(log ε 3.87), 291(3.79), 233(4.36); uv λ_{max} (H_2O, HCl) nm: 402(log ε 3.22), 265(3.22), 214(3.79); uv λ_{max} (H_2O, NaOH) nm: 414(log ε 3.82), 262(3.72), 212(4.57); ^1H nmr and ^{13}C nmr see theoretical part; ms m/z (rel. int.): 211($M^{+\cdot}$, 6.19), 167(65.55),120(100). *Anal.* Calcd for $C_7H_7N_3O_4$: C, 42.64; H, 3.57; N, 21.31. Found: C, 42.78; H, 3.74; N, 21.92.

***N*-(3-Nitro-2-pyridyl)-α-alanine(18):**

According to the procedure described for the compound (**14**) and starting from **9**(2.5 g, 10 mmol), the compound (**18**) was obtained as a crystalline product after recrystallization from water (78 %, 1.65 g): mp 128-130°C; ir ν_{max} (KBr) cm^{-1}: 3550-3535(NH),3300-2895(OH), 1695(C=O); uv λ_{max} (H_2O) nm: 416(log ε 3.52), 245(3.52), 231(4.04); uv λ_{max} (H_2O, HCl) nm: 359(log ε 3.42), 245(3.52), 209(3.90); uv λ_{max} (H_2O, NaOH) nm: 401(log ε 4.09), 268(3.93), 211(4.59); ^1H nmr and ^{13}C nmr: see theoretical part; ms m/z (rel. int.): 197($M^{+\cdot}$, not observed), 179(21.95), 150(44.12), 123(71.0), 77(48.09), 139(47.44), 93(15.65), 66(100). *Anal.* Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.24; H, 4.34; N, 19.67.

***N*-(5-Nitro-2-pyridyl)-α-alanine (16):**

According to the procedure described for the compound (**14**) and starting from **12**(2.25

g, 10 mmol), the compound (**16**) was obtained as a crystalline product after recrystallization from water (81 %, 1.71 g): mp 166-168 °C; ir ν_{max} (KBr) cm^{-1}: 3300(NH amine), 3100-3000(OH), 1700(C=O); uv λ_{max} (H_2O) nm: 370(log ε 2.92), 232(2.69), 190(3.66); uv λ_{max} (H_2O, HCl) nm: 313(log ε 3.95), 213(3.82), 198(4.47); uv λ_{max} (H_2O, NaOH) nm: 370(log ε 4.5), 211(4.58); ^1H nmr and ^{13}C nmr see theoretical part; ms m/z (rel. int.): 211($M^{+\cdot}$, 8.84), 160(100), 119(62.20), 78(18.29). *Anal.* Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found:C, 45.22; H, 4.13; N, 19.59

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