M. Mercedes Blanco, Celia B. Schapira, Gustavo Levin and Isabel A. Perillo*

Department of Organic Chemistry, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956 (1113), Buenos Aires, Argentina, e-mail: iperillo@ffyb.uba.ar

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Dedicated to the memory of Dr. Samuel Lamdan

A series of 8-hydroxy-1,6-naphthyridin-5(6*H*)-one-7-carboxamides **1** and the isomeric 5-hydroxy-1,7-naphthyridin-8(7*H*)-one-6-carboxamides **2** were synthesized. *N*-Lactam unsubstituted compounds **1a-c** and **2a,b** were obtained by alkoxide-induced rearrangement of the corresponding quinolinimidoacetamides **3**. Compounds **1e,f** and **2e,f** were synthesized by heterocyclization of the corresponding quinolinamic esters **6** and **7**. Spectroscopic properties (uv, ir, ^{1}H and ^{13}C nmr and ms) were analyzed and the proposed structures confirmed.

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Introduction.

In previous papers we have reported our findings on the synthesis and spectroscopic properties of 8-hydroxy-1,6-naphthyridin-5(6*H*)-one-7-carboxylic acid alkyl esters and the isomeric 5-hydroxy-1,7-naphthyridin-8(7*H*)-one-6-carboxylic acid alkyl esters [1-3]. Due to our interest in this type of compounds [4], we have now extended our studies in order to obtain the corresponding carboxamides **1** and **2**. These amides belong to a type of compounds (hydroxypyridonecarboxamides containing an aromatic or heteroaromatic fused ring) which display interesting biological properties including antiinflammatory [6], herbicide [7], gastric antisecretory [8-10] and antiallergic activity [10].

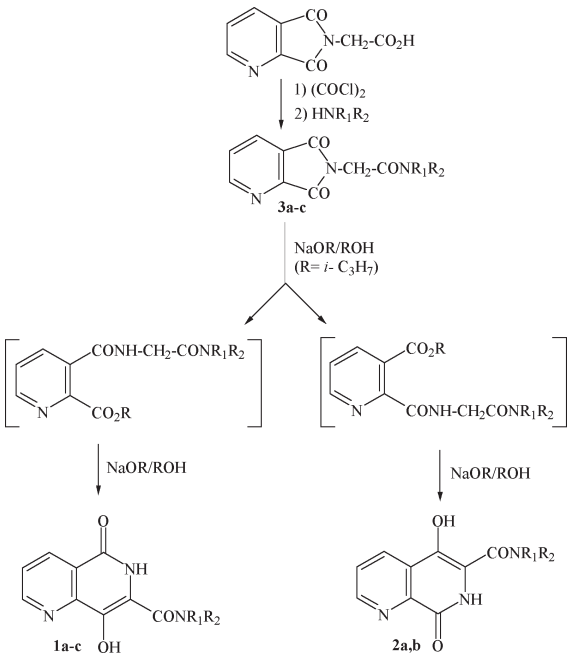
Initially, aminolysis of the corresponding esters seemed to be the most direct route for the synthesis of these amides. However, under diverse conditions, the reaction fails to occur or a complex mixture of unidentified products was obtained.

These results led us to outline a strategy that involved similar methods to that used in the synthesis of the related naphthyridine esters [1,2] which allowed naphthyridinecarboxamides **1** and **2** to be obtained.

Results and Discussion.

N-Lactam unsubstituted naphthyridines (**1a-c** and **2a,b**) were obtained by alkoxide induced rearrangement of the corresponding 5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamides **3** (quinolinimidoacetamides) which were synthesized from quinolinimidoacetic acid *via* acyl chloride and further aminolysis (Scheme I). Thus, the reaction of imides **3a,b** with sodium isopropoxide in anhydrous 2-propanol gave a mixture of two products with predominance of the one having the lower R*f* value (tlc, 9:1 chloroform-methanol). Both gave positive reaction with ferric chloride and were isolated by chromatographic methods. The low R*f* compounds proved to be the 1,6-naphthyridines **1a,b** (30–35% yield) and those of high R*f* the 1,7-naphthyridines **2a,b** (16–25% yield).

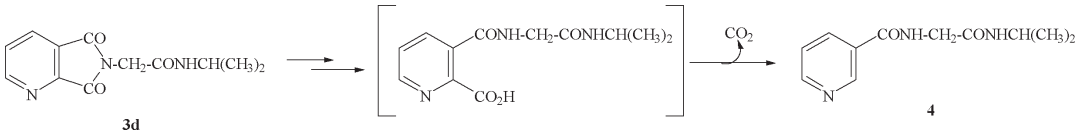
Scheme 1



Comp.	R_1	R_2
1a, 2a	CH_3	C_6H_5
1b, 2b	C_2H_5	C_2H_5
1c, 2c	H	C_6H_5

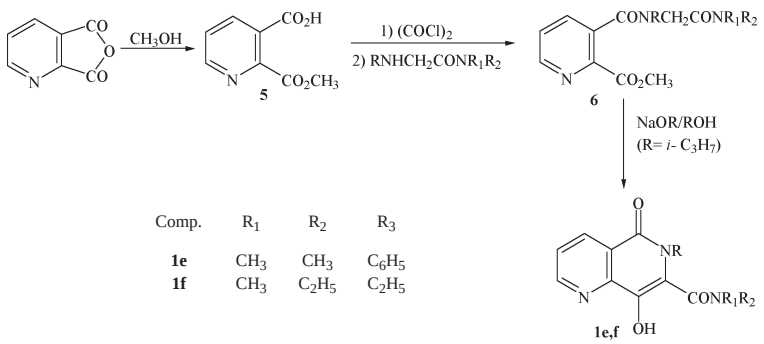
In the case of *N*-monosubstituted quinolinimidoacetamides results were hardly satisfactory. Reactions took place leading to considerable amounts of low R*f* by-products that showed acidic features [11]. Thus, the reaction of *N*-phenylquinolinimidoacetamide (**3c**) with sodium isopropoxide gave 19% of **1c** and only traces of a product that seems to be **2c** by tlc. Instead, reaction of *N*-isopropylquinolinimidoacetamide (**3d**) gave *N*-(isopropylcarbamoylmethyl)-3-pyridinecarboxamide (**4**), which could have originated from alfa-decarboxylation of one of the reaction by-products [14] (Scheme II).

Scheme II



N-Lactam substituted naphthyridines (**1e,f** and **2e,f**) were synthesized by two different routes which involved the synthesis and ring closure of quinolinamic acid alkyl esters. Route *a* starts from the stable hemiester **5** and leads to intermediate esters **6** which were cyclized to the 1,6-naphthyridines **1e,f** with sodium isopropoxide (Scheme III).

Scheme III



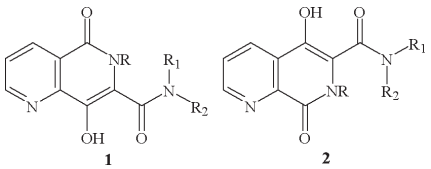
Comp.	R_1	R_2	R_3
1e	CH_3	CH_3	C_6H_5
1f	CH_3	C_2H_5	C_2H_5

Route *b* involves the preparation of the intermediate quinolinamic acid alkyl esters **6** and **7** by aminolysis of quinolinic anhydride with the corresponding aminoacetamide and further esterification with diazomethane. Treatment of the reaction mixture with sodium isopropoxide led to a mixture of 1,7-naphthyridines **2e,f** as the major and 1,6-naphthyridines **1e,f** as the minor product (Scheme IV).

Spectroscopic Features of 1,6- and 1,7-Naphthyridines (**1** and **2**).

On the basis of literature data, the positive ferric chloride test [15], the presence in the ^{1}H nmr spectra of signals attributed to the enol protons, the presence of bands in the 1640-1665 range in the ir spectra and the absence of signals over 165 ppm in the ^{13}C nmr spectra support the enol-lactam structure for compounds **1** and **2**.

Spectral assignments of ^{1}H nmr (Tables I and II) and ^{13}C nmr spectra (Table III) [16] were made on the basis of signal multiplicity, coupling constant values, attached proton test (APT) in certain cases, and by comparison with data of related compounds [1-3].

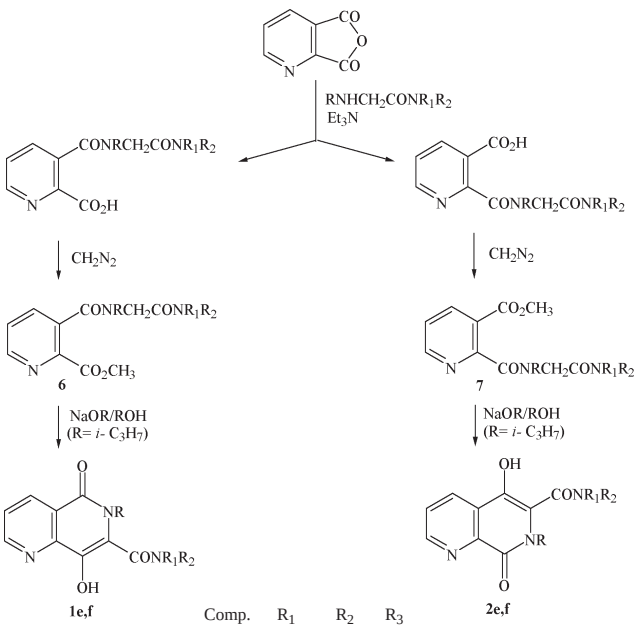


1 **2**

^{1}H Nmr spectra of compounds **1** and **2** showed broad signals between 11.42-8.94 ppm assigned to NH and OH hydrogens, and between 7.52–9.03 ppm those corresponding to the three pyridine hydrogen atoms.

^{13}C Nmr spectra showed nine signals besides those

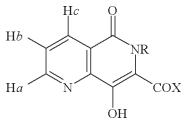
Scheme IV



Comp.	R_1	R_2	R_3
1e, 2e	CH_3	CH_3	C_6H_5
1f, 2f	CH_3	C_2H_5	C_2H_5

belonging to the substituents. Two of them, which appeared between 157.9 and 164.5 ppm, were assigned to carbonyl carbons *Ci(i')* and *Ch(h')*. APT spectra displayed

Table I
8-Hydroxy-1,6-naphthyridin-5(6*H*)-one-7-carboxamides **1a-c,e,f**



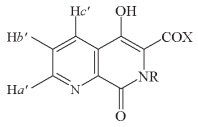
Compd.	Mp	Yield	Formula	Analyses (Calcd./Found)			IR	UV			^{1}H-NMR [a]		
Nº	(ºC)	(%)		%C	%H	%N	ν (cm^{-1})	0.1*N* HCl λ max.(nm)	methanol λ max.(nm)	0.1*N* NaOH λ max.(nm)	δ (ppm)	Multiplicity	Assignment
1a	230	35	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23	3465	328	355	366	11.21	bs	OH/NH [c]
	[b]			65.13	4.48	14.19	3080	256	252	262	8.94	bs	OH/NH [c]
							2980	213	214	223	8.91	d [d]	H*a*
							1680				8.43	d [d]	H*c*
							1650				7.54	dd [d]	H*b*
							1600				7.35	d [d]	C_6H_5, *ortho* H
							1550				7.28	t [d]	C_6H_5, *meta* H
							1450				7.17	t [d]	C_6H_5, *para* H
											3.35	s	NCH_3
1b	194	30	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.08	3340	327	350	358	11.39	bs	OH/NH [c]
	[b]			59.79	5.83	16.12	3016	260	249	262	9.02	bs	OH/NH [c]
							2980	221	220	229	8.99	dd [e]	H*a*
							1665				8.53	dd [e]	H*c*
							1652				7.62	dd [e]	H*b*
							1605				3.32	q [e]	NCH_2
							1550				1.12	t [e]	CH_3
							1450						
1c	272	19	$C_{15}H_{11}N_3O_3$	64.05	3.94	14.94	3450	326	356	360	10.54	bs	OH/NH [c]
[f]	[b]			63.99	3.98	14.87	2990	255	252	260	9.03	d [g]	H*a*
							1660	216	214	224	8.57	d [g]	H*c*
							1650				7.85	dd [g]	H*b*
							1600				7.74	d [g]	C_6H_5, *ortho* H
							1560				7.40	t [g]	C_6H_5, *meta* H
											7.17	t [g]	C_6H_5, *para* H
1e	[h]	49	$C_{17}H_{15}N_3O_3$	66.01	4.89	13.58	3390	328	359	361	8.77	dd [j]	H*a*
	[i]			66.07	4.93	13.53	1673	257	253	263	8.59	dd [j]	H*c*
							1650	222	228	226	7.52	dd [j]	H*b*
							1628	215	216	224	7.44-7.15	m	C_6H_5
							1590				3.63	s	NCH_3
											3.54	s	NCH_3
1f	91	33	$C_{14}H_{17}N_3O_3$	61.08	6.22	15.26	3411	325	350	359	9.24	bs	OH [l]
[k]	[b]	[i]		61.15	6.27	15.20	1662	256	256	260	9.01	dd [m]	H*a*
							1654	220	225	222	8.58	dd [m]	H*c*
							1623	214	215	219	7.63	dd [m]	H*b*
							1584				3.58 and 3.41	m	NCH_2
							1473				3.34	s	NCH_3
											3.30 and 3.26	m	NCH_2
											1.17	t [m]	CH_3
											1.09	t [m]	CH_3

[a] Spectra of compounds **1a-c,f** were performed in DMSO-d_6; spectra of compound **1e** was performed in CCl_3D; [b] Recrystallized from 2-propanol; [c] Exchangeable, the assignment could not be confirmed; [d] $^3J_{Ha\text{-}Hb}$: 4.2 Hz, $^3J_{Hb\text{-}Hc}$: 7.6 Hz, $^3J_{Ho\text{-}Hm}$: 7.5 Hz, $^3J_{Hm\text{-}Hp}$: 7.5 Hz. [e] $^3J_{Ha\text{-}Hb}$: 4.6 Hz, $^4J_{Ha\text{-}Hc}$: 1.6 Hz, $^3J_{Hb\text{-}Hc}$: 8.0 Hz, $^3J_{CH2\text{-}CH3}$: 6.9 Hz; [f] Two dastereomers were observed in the nmr spectra, signals of the major product are indicated; [g] $^3J_{Ha\text{-}Hb}$: 4.4 Hz, $^3J_{Hb\text{-}Hc}$: 7.8 Hz, $^3J_{Ho\text{-}Hm}$: 7.9 Hz, $^3J_{Hm\text{-}Hp}$: 7.9 Hz; [h] The compound was isolated as an oil; [i] Yield starting from the hemiester **5** (route *a*); [j] $^3J_{Ha\text{-}Hb}$: 4.6 Hz, $^4J_{Ha\text{-}Hc}$: 1.8 Hz, $^3J_{Hb\text{-}Hc}$: 8.1 Hz; [k] Assignments in the nmr spectra were confirmed by HMQC and HMBC; [l] Exchangeable; [m] $^3J_{Ha\text{-}Hb}$: 4.6 Hz, $^4J_{Ha\text{-}Hc}$: 1.8 Hz, $^3J_{Hb\text{-}Hc}$: 8.1 Hz, $^3J_{CH3\text{-}CH2}$: 6.9 Hz, $^3J_{CH3\text{-}CH2}$: 7.2 Hz.

three signals of the highest intensity with the same phase, that were assigned to pyridine carbons *Ca(a')* (153.6–149.3), *Cb(b')* (122.7–126.6 ppm) and *Cc(c')* (129.9–137.3 ppm). The four remaining carbons could be identified on the basis of the full-coupled spectra of compounds **1e** and **2e**. Such spectra showed two singlets at *ca.* 131 and 120 ppm and another two signals with long-range correlations (139.9–147.4 ppm, dd, $^3J_{C\text{-}H}$ ~ 12 Hz, $^3J_{CH}$ ~ 5 Hz and 120.4–128.9 ppm, d, $^3J_{C\text{-}H}$ ~ 6 Hz). Singlets were assigned to *Cf(f')* and *Cg(g')* in agreement with literature

Table II

5-Hydroxy-1,7-naphthyridin-8(7*H*)-one-6-carboxamides **2a,b,e,f**



Compd.	Mp	Yield	Formula	Analyses (Calcd./Found)			IR	UV			^{1}H-NMR [a]		
Nº	(ºC)	(%)		%C	%H	%N	ν (cm^{-1})	0.1*N* HCl λ max.(nm)	methanol λ max.(nm)	0.1*N* NaOH λ max.(nm)	δ (ppm)	Multiplicity	Assignment
2a	180	25	$C_{16}H_{13}N_3O_3$	65.08	4.44	14.23	3447	333	325	367	11.32	bs	OH/NH [c]
	[b]			65.01	4.49	14.17	3030	260	252	261	9.04	bs	OH/NH [c]
							2944	225	229	227	8.72	d [d]	H*a′*
							1652				8.14	d [d]	H*c′*
							1634				7.65	dd [d]	H*b′*
							1601				7.34	d [d]	C_6H_5, *ortho* H
							1547				7.25	t [d]	C_6H_5, *meta* H
											7.13	t [d]	C_6H_5, *para* H
											3.28	s	NCH_3
2b	189	16	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.08	3400	322	321	358	11.42	bs	OH/NH [c]
	[b]			59.83	5.84	16.02	3064	257	270	263	9.01	bs	OH/NH [c]
							2930	223	252	225	8.82	d [e]	H*a′*
							1658		225		8.30	d [e]	H*c′*
							1608				7.76	dd [e]	H*b′*
							1590				3.35	q [e]	NCH_2
											1.12	t [e]	CH_3
2e	104	32	$C_{17}H_{15}N_3O_3$	66.01	4.89	13.58	3470	331	326	362	9.21	bs	OH [j]
[f] [g]	[b]	[h]		66.09	4.93	13.51	2962	256	250	258	8.75	dd [i]	H*a′*
							1640	220	226	218	8.17	dd [i]	H*c′*
							1633	213	219		7.68	dd [i]	H*b′*
							1580				7.35	d [i]	C_6H_5, *ortho* H
							1323				7.24	t [i]	C_6H_5, *meta* H
											7.15	t [i]	C_6H_5, *para* H
											3.51	s	NCH_3
											3.35	s	NCH_3
2f	[k]	32	$C_{14}H_{17}N_3O_3$	61.08	6.22	15.26	3470	331	326	362	8.94	bs	OH [j]
		[h]		61.14	6.26	15.22	2962	256	250	258	8.83	bs [l]	H*a′*
							1640	220	226	226	7.86	bs [l]	H*c′*
							1633	213	219	218	7.63	bs [l]	H*b′*
							1580				3.75-3.55	m	NCH_2
							1323				3.48	s	NCH_3
											1.45-1.01	m	CH_3

[a] Spectra of compounds **2a,b,e** were performed in DMSO-d_6; spectra compound **2f** was performed in CCl_3D; [b] Recrystallized from 2-propanol; [c] Exchangeable, the assignment could not be confirmed; [d] $^3J_{Ha\text{-}Hb}$: 4.6 Hz, $^3J_{Hb\text{-}Hc}$: 8.2 Hz, $^3J_{Ho\text{-}Hm}$: 7.7 Hz, $^3J_{Hm\text{-}Hp}$: 7.7 Hz. [e] $^3J_{Ha\text{-}Hb}$: 4.3 Hz, $^3J_{Hb\text{-}Hc}$: 8.2 Hz, $^3J_{CH2\text{-}CH3}$: 7.1 Hz; [f] Two diastereomers were observed in the nmr spectra; signals of the major product are indicated; [g] Assignments in the nmr spectra were confirmed by HMQC and HMBC; [h] Total yield starting from quinolinic anhydride (Route *b*); [i] $^3J_{Ha\text{-}Hb}$: 4.1 Hz, $^4J_{Ha\text{-}Hc}$: 1.5 Hz, $^3J_{Hb\text{-}Hc}$: 8.2 Hz, $^3J_{Ho\text{-}Hm}$: 7.3 Hz, $^3J_{Hm\text{-}Hp}$: 7.3 Hz; [j] Exchangeable; [k] The compound was isolated as an oil; [l] Broad multiplets typical of coalescent signals.

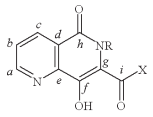
data in related benzothiazines and isoquinolones [17]. The double doublet, which displayed a large J ^{13}C-^{1}H characteristic of the ^{13}C-^{1}H three bond coupling through nitrogen [18], was assigned to *Ce(e')* and the doublet to *Cd(d')*.

Previous assignments were unequivocally confirmed by two dimensional heteronuclear correlation spectra (HMQC and HMBC) of compounds **1f** and **2e.** The observed one (or more) bond correlations are indicated in Tables IV and V. The three-bond correlation for *Ch-Hc* supports the 1,6–naphthyridine structure of compound **1f**, while the three-bond correlation *Cf′– Hc′* confirms the 1,7-naphthyridine structure of compound **2e**.

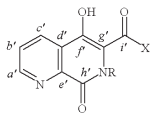
In *N*,*N*-disubstituted carboxamides the partial double bond character of amide CO-N bond, which arises from the contribution of a polar resonance structure along with the normal covalent one, would lead to the nonequivalence of the two substituents when R_1=R_2 as well as to the presence of diastereomeric amides when $R_1 \neq R_2$ [19] (**A**). However, chemical equivalence of both ethyl groups in the ^{1}H nmr spectra of compounds **1b** and **2b** as well as the

TABLE III

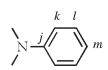
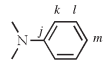
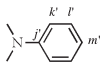
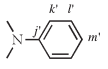
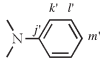
^{13}C-NMR Spectra of 1,6- and 1,7-Naphthyridines **1a,e,f** and **2a,b,e,f** [a]



1

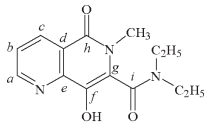


2

Compd.	Solvent	R	X	δ (ppm)									Others
				C*a*/C*a′*	C*b*/C*b′*	C*c*/C*c′*	C*d*/C*d′*	C*e*/C*e′*	C*f*/C*f′*	C*g*/C*g′*	C*h*/C*h′*	C*i*/C*i′*	δ (ppm) and assignment
1a [b]	DMSO-d_6	H		153.6	122.7	135.8	121.4	147.4	131.8	121.3	158.7	162.4	142.6 (C*j*), 128.7 (C*l*), 127.2 (C*m*), 126.2 (C*k*), 36.6 (NCH_3)
1e [c]	CCl_3D	CH_3		153.0	122.9	136.9	123.3	145.2	132.0	120.9	159.4	162.1	142.1 (C*j*), 129.1 (C*l*), 128.0 (C*m*), 125.7 (C*k*), 37.1 (NCH_3), 33.1 (NCH_3)
1f	CCl_3D	CH_3	$N(C_2H_5)_2$	153.1	123.1	137.3	124.8	145.6	132.0	121.1	159.7	161.7	43.1 (NCH_2), 39.4 (NCH_2), 32.5 (NCH_3), 14.1 (CH_3), 12.5 (CH_3)
1f [d]	DMSO-d_6	CH_3	$N(C_2H_5)_2$	153.6	124.9	136.2	120.4	146.7	132.0	124.5	158.9	161.6	42.5 (NCH_2), 38.6 (NCH_2), 31.9 (NCH_3), 13.8 (CH_3), 12.4 (CH_3)
2a [e]	DMSO-d_6	H		149.4	126.3*	130.7	128.9	141.0	130.1	121.1	157.9	162.3	142.6 (C*j′*), 128.6 (C*l′*), 127.0* (C*m′*), 126.1 (C*k′*), 36.8 (NCH_3)
2b	DMSO-d_6	H	$N(C_2H_5)_2$	149.3	126.6	130.9	126.7	141.3	131.2	120.3	158.7	162.0	41.3 (NCH_2), 13.5 (CH_3)
2e [f]	CCl_3D	CH_3		150.6	126.3	130.4	125.1	140.5	131.2	123.7	158.7	164.5	142.4 (C*j′*), 129.3 (C*l′*), 128.4 (C*m′*), 125.3 (C*k′*), 36.9 (NCH_3), 33.8 (NCH_3)
2e [f] [g] [d]	DMSO-d_6	CH_3		149.7	125.9	130.8	126.5	139.9	126.9	125.0	157.8	161.9	142.2 (C*j′*), 128.9 (C*l′*), 127.7 (C*m′*), 125.7 (C*k′*), 36.5 (NCH_3), 33.2 (NCH_3)
2f	CCl_3D	CH_3	$N(C_2H_5)_2$	150.8	126.6	129.9	128.9	140.6	130.4	123.5	158.9	164.0	41.7 (NCH_2) [h], 33.1 (NCH_3), 13.1 (CH_3)

[a] Insolubility of compounds **1b,c** don't allow the nmr spectra to be performed; [b] APT spectrum display with the same phase the signals assigned to C*a*, C*b*, C*c*, C*k*, C*l*, C*m* and CH_3; [c] $^1J_{Ca\text{-}H}$= 181.4 Hz, $^3J_{Ca\text{-}Hc}$= 8.5 Hz, $^1J_{Cb\text{-}H}$= 168.7 Hz, $^2J_{Cb\text{-}Ha}$= 8.7 Hz, $^1J_{Cc\text{-}H}$= 169.0 Hz, $^3J_{Cc\text{-}Ha}$= 6.3 Hz, $^3J_{Cd\text{-}Hb}$= 6.5 Hz, $^3J_{Ce\text{-}Ha}$= 11.9 Hz, $^3J_{Ce\text{-}H}$= 4.8 Hz, $^3J_{Cj\text{-}H}$= 7.8 Hz, $^1J_{Ck\text{-}H}$= 161.6 Hz, $^3J_{Ck\text{-}H}$= 7.3 Hz, $^1J_{Cl\text{-}H}$= 163.6 Hz, $^3J_{Cl\text{-}H}$= 7.6 Hz, $^1J_{Cm\text{-}H}$= 161.9 Hz, $^3J_{Cm\text{-}H}$= 7.9 Hz, $^1J_{NCH3}$= 143.0 Hz, $^1J_{NCH3}$= 141.9 Hz; [d] Assignments were confirmed by HMQC and HMBC; [e] APT spectrum display with the same phase the signals assigned to C*a′*, C*b′*, C*c′*, C*k′*, C*l′*, C*m′* and CH_3; [f] Two diastereomers were observed; signals of the major product are indicated; [g] $^1J_{Ca'\text{-}H}$= 183.2 Hz, $^3J_{Ca'\text{-}Hc'}$= 6.9 Hz, $^1J_{Cb'\text{-}H}$= 168.1 Hz, $^2J_{Cb'\text{-}Ha'}$= 9.0 Hz, $^1J_{Cc'\text{-}H}$= 167.6 Hz, $^3J_{Cc'\text{-}Ha'}$= 6.0 Hz, $^3J_{Cd'\text{-}Hb'}$= 5.9 Hz, $^3J_{Ce'\text{-}Ha'}$= 12.4 Hz, $^3J_{Ce'\text{-}H}$= 5.0 Hz, $^3J_{Cj\text{-}H}$= 8.0 Hz, $^1J_{Ck'\text{-}H}$= 162.0 Hz, $^3J_{Ck'\text{-}H}$= 7.3 Hz, $^1J_{Cl'\text{-}H}$= 162.9 Hz, $^3J_{Cl'\text{-}H}$= 7.4 Hz, $^1J_{Cm'\text{-}H}$= 162.1 Hz, $^3J_{Cm'\text{-}H}$= 7.7 Hz, $^1J_{NCH3}$= 142.2 Hz, $^1J_{NCH3}$= 141.6 Hz; [h] Broad signal; * Exchangeab

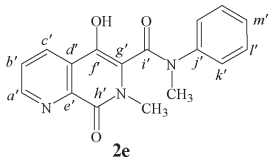
Table IV
HMQC Single-bond and HMBC Long-range Proton-carbon Correlations of Compound **1f**



1f

Carbon δ(ppm)	Proton single-bond coupling δ(ppm)	Proton three bond coupling δ(ppm)	Proton two bond coupling δ(ppm)
C*i* (161.6)	–	NCH_2 (3.58, 3.41, 3.30 and 3.26)	–
C*h* (158.9)	–	NCH_3 (3.34), H*c* (8.58)	–
C*a* (153.6)	H*a* (9.01)	H*c* (8.58)	H*b* (7.63)
C*e* (146.7)	–	H*a* (9.01), H*c* (8.58)	–
C*c* (136.2)	H*c* (8.58)	H*a* (9.01)	–
C*f* (132.0)	–	–	–
C*g* (124.5)	–	NCH_3 (3.34)	–
C*b* (122.9)	H*b* (7.63)	–	H*a* (9.01)
C*d* (120.4)	–	H*b* (7.63)	–
NCH_2 (42.5)	CH_2 (3.30 and 3.26)	–	CH_2CH_3 (1.09)
NCH_2 (38.6)	CH_2 (3.58 and 3.41)	–	CH_2CH_3 (1.17)
NCH_3 (31.9)	NCH_3 (3.34)	–	–
CH_2CH_3 (13.8)	CH_2CH_3 (1.09)	–	CH_2 (3.30 and 3.26)
CH_2CH_3 (12.4)	CH_2CH_3 (1.17)	–	CH_2 (3.58 and 3.41)

Table V
HMQC Single-bond and HMBC Long-range Proton-carbon Correlations of Compound **2e**

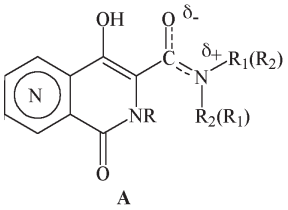


2e

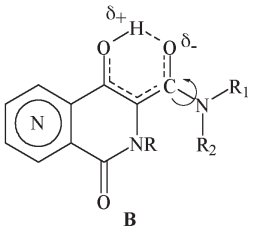
Carbon δ(ppm)	Proton single-bond coupling δ(ppm)	Proton three bond coupling δ(ppm)	Proton two bond coupling δ(ppm)
C*i'* (161.9)	–	NCH_3 (3.35)	–
C*h'* (157.8)	–	NCH_3 (3.51)	–
C*a'* (149.7)	H*a'* (8.75)	H*c'* (8.17)	H*b'* (7.68)
C*j'* (142.2)	–	NCH_3 (3.35), H*l'* (7.24)	–
C*e'* (139.9)	–	H*a'* (8.75), H*c'* (8.17)	–
C*c'* (130.8)	H*c'* (8.17)	H*a'* (8.75)	–
C*l'* (128.9)	H*l'* (7.24)	–	–
C*m'* (127.7)	H*m'* (7.15)	H*k'* (7.35)	–
C*f'* (126.9)	–	H*c'* (8.17)	–
C*d'* (126.5)	–	H*b'* (7.68)	–
C*b'* (125.9)	H*b'* (7.68)	–	H*a'* (8.75)
C*k'* (125.7)	H*k'* (7.35)	H*m'* (7.15)	–
C*g'* (125.0)	–	NCH_3 (3.51)	–
NCH_3 (36.5)	NCH_3 (3.35)	–	–
NCH_3 (32.2)	NCH_3 (3.51)	–	–

absence of diastereomeric carboxamides **1a** and **2a** indicate that the CO-N bond enjoy free rotation at room temperature. These facts are in line with a resonance-assisted hydrogen bonding effect (RAHB) [20] where the stabilized keto-enol system involves the amide carbonyl leading to an important single-bond character of the amide CO-N bond (**B**) [21]. With regard to the spectra of naphthyridine **1c** (R_1=H, R_2=C_6H_5), signals are in agreement with the presence of two diastereomeric amides [22]. Stability of both species could be related to the strong intermolecular association of *N*-monosubstituted amides, in which rotation rate may involve breaking and making of hydrogen bonds [19a].

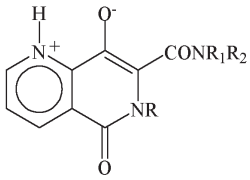
Lactam *N*-substitution inhibits planarity of the keto-enol system [23] leading to the existence of diastereomeric carboxamides in compound **2e** and to the chemical nonequiv-



A



B

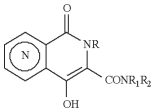


C

the ^{13}C nmr spectrum of compound **1f** exhibited two signals for methylene carbons (38.6 and 42.5 ppm) as well as for methyl carbons (12.4 and 13.8 ppm), indicating the partial double bond character of the amide CO-N bond. Accordingly, in the ^{1}H nmr spectra methyl groups are anisochronous appearing as two triplets at 1.17 and 1.09 ppm. In addition, in the HMQC and HMBC spectra in DMSO-*d6*, methylene hydrogens appeared as four signals at 3.58 and 3.41 ppm, (those linked to the more shielded carbon) and at 3.30 and 3.26 ppm (those linked to the more deshielded carbon). Diastereotopicity of methylene hydrogens could be associated to the presence of a chiral axis [24] arising from a restricted rotation around the naphthyridine-CONH bond, which lead to the presence of atropisomers [25].

Table VI

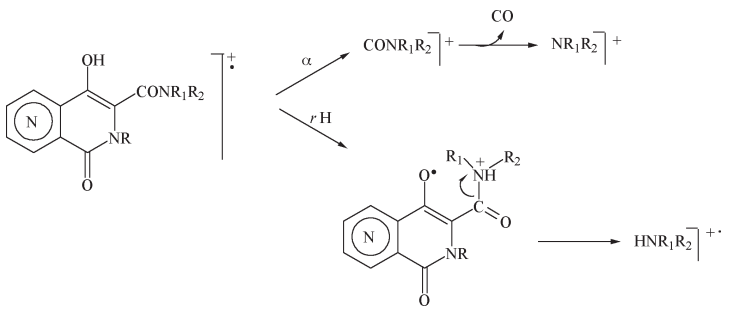
Select Fragments in the EI Mass Spectra of Compounds **1** and **2**



Ion	**1a** R= H R_1= CH_3 R_2= C_6H_5 m/z (%)	**1b** R= H R_1= C_2H_5 R_2= C_2H_5 m/z (%)	**1c** R= H R_1= C_6H_5 R_2= H m/z (%)	**1e** R= CH_3 R_1= CH_3 R_2= C_6H_5 m/z (%)	**1f** R= CH_3 R_1= C_2H_5 R_2= C_2H_5 m/z (%)	**2a** R= H R_1= CH_3 R_2= C_6H_5 m/z (%)	**2b** R= H R_1= C_2H_5 R_2= C_2H_5 m/z (%)	**2e** R= CH_3 R_1= CH_3 R_2= C_6H_5 m/z (%)	**2f** R= CH_3 R_1= C_2H_5 R_2= C_2H_5 m/z (%)
$M^{+\cdot}$	295 (22.2)	261 (3.4)	281 (58.6)	309 (7.6)	275 (20.4)	295 (6.2)	261 (4.6)	309 (5.9)	275 (17.2)
$[M+1]^+$	296 (10.7)	262 (0.6)	282 (13.6)	310 (0.9)	276 (4.9)	296 (1.5)	262 (3.3)	310 (2.3)	276 (11.9)
$[CONR_1R_2]^+$	134 (22.9)	100 (18.2)	120 (-)	134 (100.0)	100 (1.8)	134 (10.5)	100 (34.1)	134 (72.3)	100 (17.2)
$[NR_1R_2]^+$	106 (27.8)	72 (100.0)	92 (-)	106 (68.6)	72 (100.0)	106 (61.0)	72 (100.0)	106 (60.4)	72 (100.0)
$[HNR_1R_2]^{+\cdot}$	107 (100.0)	73 (6.5)	93 (100.0)	107 (55.2)	73 (8.6)	107 (100.0)	73 (7.0)	107 (100.0)	73 (5.6)
$[M\text{-}NR_1R_2]^+$	189 (2.8)	189 (1.7)	189 (4.1)	203 (1.7)	203 (8.9)	189 (2.2)	189 (2.9)	203 (1.3)	203 (2.9)
$[M\text{-}NR_1R_2\text{-}CO]^+$	161 (3.9)	161 (1.5)	161 (2.5)	175 (4.7)	175 (12.7)	161 (4.8)	161 (5.5)	175 (2.9)	175 (4.4)
$[M\text{-}NR_1R_2\text{-}2CO]^+$	133 (2.3)	133 (1.9)	133 (2.1)	147 (5.6)	147 (3.1)	133 (4.9)	133 (3.7)	147 (1.3)	147 (3.0)
$[M\text{-}OH)]^{+\cdot}$	278 (13.0)	244 (-)	264 (1.9)	292 (10.1)	258 (1.4)	278 (6.6)	244 (-)	292 (2.8)	258 (-)
Others	162 (20.7)	162 (10.1)			176 (61.2)	162 (15.6)	162 (18.4)		176 (35.2)
[a]	149 (15.8)	78 (12.5)			58 [b] (25.9)	79 (23.9)	78 (20.6)		58 [b] (20.9)
		58 [b] (16.9)				78 (33.7)	58 [b] (18.0)		
		44 [c] (40.3)				77 (40.3)	51 (14.4)		
						51 (35.6)	44 [c] (59.5)		

[a] Peaks greater than 10% are included. [b] Corresponds to $[HNR_1R_2\text{-}CH_3]^+$. [c] Corresponds to $[NR_1R_2\text{-}C_2H_4]^+$.

Scheme V



thyridines **2**, 1,6-naphthyridines **1** in methanol present a predominance of the zwitterion structure **C** as shown by the striking similarity with those spectra measured in basic medium (enolate anion) and a significant difference with spectra taken in acidic solution (Tables I and II).

Ms showed mainly fragments with charge retention on the nitrogen moiety: $[CONR1R2]^+$, $[NR1R2]^+$ and $[HNR1R2]^+$– (Table VI, Scheme V). In particular, the presence of amine radical-ions resulting from intramolecular hydrogen transfer to the amide nitrogen and further homolytic cleavage, supports the enol structure in the gas phase.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker MSL 300 MHz. Chemical shifts are quoted in parts per million (δ) downfield from an internal TMS reference. The presence of exchangeable protons was confirmed by use of deuterium oxide. Proton signals are quoted as: s (singlet), bs (broad signal), d (doublet), dd (doublet of doublet), t (triplet), dt (doublet of triplet), q (quartet) and m (multiplet). Two-dimensional spectra (HMQC and HMBC) were recorded with a Bruker AVANCE DRX 300 spectrometer.

Ms (electron impact) were performed on a MS Shimadzu QP-1000 instrument at 20 eV. The ir spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer and samples were run as potassium bromide pellets. The uv spectra were recorded on a Jasco 7850 UV-VIS spectrophotometer. Analytical tlc was carried out on aluminum sheets Silica Gel 60 F_{254}. Preparative thin layer separations (plc) were carried out by centrifugally accelerated, radial chromatography using Chromatotron model 7924T. The rotors were coated with Silica Gel 60 PF_{254} and the layer thickness was 2 mm. Chloroform and increasing percentages of methanol were used as eluent. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures. Experiments performed with toxic or severely irritant substances were carried out in an efficient fume cupboard.

5*H*-Pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamides (Quinolinimidoacetamides) (**3**).

General Procedure.

A mixture of quinolinimidoacetic acid [29] (2.06 g, 10 mmoles) in dry benzene (10 mL) and oxalyl chloride (1.39 g, 11 mmoles) (**caution**) was heated at 40º for 5 hours. The reaction mixture was concentrated *in vacuo* and the resulting oil washed twice with dry benzene and concentrated, affording quinolinimidoacetyl chloride (85%) which was used in the next step without purification.

To a mixture of methylene chloride (10 mL), 20% sodium hydroxide (20 mL) and the appropriate amine (4.5 mmoles), a solution of 1 g (4.5 mmoles) of quinolinimidoacetyl chloride in methylene chloride (10 mL) was added dropwise, the temperature being maintained at –15º during the addition. The suspension was stirred at room temperature for 1 hour and the aqueous layer was separated and extracted with methylene chloride (2 x 5 mL). The organic layers were pooled, washed with 5% aqueous acetic acid and water until neutral pH, dried (sodium sulfate) and evaporated *in vacuo*. The resulting oil was triturated with ice-ethanol affording compounds **3a-d**.

N-Methyl-*N*-phenyl-5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamide (**3a**).

This compound was obtained in 60% yield; mp 152 °C (2-propanol); ir: 3061, 2943, 1741, 1734, 1674, 1593, 1384 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.96 (dd, 1H, H2, J = 4.9, 1.4 Hz), 8.16 (dd, 1H, H4, J = 7.6, 1.4 Hz), 7.60 (dd, 1H, H3, J = 7.6, 4.9 Hz), 7.40-7.60 (m, 5H, C_6H_5), 4.24 (s, 2H, CH_2CO), 3.35 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 165.9 and 165.8 (C5 and C7), 165.1 ($CONR_1R_2$), 155.2 (C2), 151.8 (C7a), 142.1 (C_6H_5, *ipso* carbon), 131.3 (C4), 130.2 (C_6H_5, *meta* carbon), 128.7 (C_6H_5, *para* carbon), 127.5 (C_6H_5, *ortho* carbon), 127.4 (C4a), 127.3 (C3), 40.0 (CH_2), 37.7 (NCH_3); ms: m/z 295 (28.5 %) ($M^{+\cdot}$).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.14; H, 4.47; N, 14.17.

N,*N*-Diethyl-5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamide (**3b**).

This compound was obtained in 52% yield; mp 142 °C (2-propanol); lit. [14] mp 142 °C; ir: 3095, 2997, 1783, 1728, 1659, 1593, 1471,1395 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 166.0 and 165.9 (C5 and C7), 163.9 ($CONR_1R_2$), 155.2 (C2), 151.8 (C7a), 131.3 (C4), 127.5 (C4a), 127.3 (C3), 39.2 (CH_2CO), 41.3 and 40.8 (CH_2CH_3), 12.8 (CH_3); ms: m/z 261 (9.5 %) ($M^{+\cdot}$).

N-Phenyl-5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamide (**3c**).

This compound was obtained in 50% yield; mp 215 °C (2-propanol); ir: 3420, 1752, 1735, 1648, 1605, 1598, 1485 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.01 (dd, 1H, H2, J = 4.5, 1.4 Hz), 8.22 (dd, 1H, H4, J = 6.7, 1.4 Hz), 7.63 (dd, 1H, H3, J = 6.7, 4.5 Hz), 7.55 (bs, 1H, NH) 7.49 (d, 2H, C_6H_5, *ortho* hydrogen, J = 7.8 Hz), 7.31 (dd, 2H, C_6H_5, *meta* hydrogen, J = 7.8, 7.4 Hz), 7.13 (t, 1H, C_6H_5, *para* hydrogen, J = 7.4 Hz), 4.59 (s, 2H, CH_2CO); ^{13}C nmr: δ (deuteriochloroform) 165.8 and 165.6 (C5 and C7), 163.1 ($CONR_1R_2$), 155.5 (C2), 151.6 (C7a), 137.0 (C_6H_5, *ipso* carbon), 131.6 (C4), 129.1 (C_6H_5, *meta* carbon), 127.6 (C3), 127.4 (C4a), 124.8 (C_6H_5, *para* carbon), 119.9 (C_6H_5, *ortho* carbon), 41.6 (CH_2); ms: m/z 281 (29.7 %) ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.00; H, 3.98; N, 14.99.

N-Isopropyl-5*H*-pyrrolo[3,4-*b*]-pyridine-5,7-(6*H*)-dione-6-acetamide (**3d**).

This compound was obtained in 49% yield; mp 209 °C (2-propanol); ir: 3428, 3060, 1778, 1732, 1645, 1595, 1476, 1382 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.00 (dd, 1H, H2, J = 4.7, 1.3 Hz), 8.20 (dd, 1H, H4, J = 7.7, 1.3 Hz), 7.64 (dd, 1H, H3, J = 7.7, 4.7 Hz), 6.50 (bs, 1H, NH), 4.80 (m, 1H, CH, J = 6.7 Hz), 4.36 (s, 2H, CH_2CO), 1.18 (d, 6H, CH_3, J = 6.7 Hz); ^{13}C nmr: δ (deuteriochloroform) 165.9 and 165.6 (C5 and C7), 164.3 ($CONR_1R_2$), 155.4 (C2), 151.7 (C7a), 131.5 (C4), 127.5 (C3), 127.4 (C4a), 42.2 (CH), 40.9 (CH_2), 22.6 (CH_3); ms: m/z 247 (1.0 %) ($M^{+\cdot}$).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99.

Found: C, 58.23; H, 5.34; N, 17.05.

Reaction of Compounds **3** with Sodium Alkoxides.

General Procedure.

To a solution of sodium isopropoxide prepared from sodium (0.23 g, 0.01 mol) in anhydrous 2-propanol (5 mL) heated in an oil bath (90-100 ºC), quinolinimidoacetamides **3** (2.5 mmoles) were added all at once in powder form. After 30 minutes the reaction mixture was poured into ice-acetic acid and extracted with chloroform (3 x 10 mL). The organic layers were pooled, washed with water, dried and evaporated *in vacuo*. The crude products obtained from **3a-c** showed two spots by tlc. Separation of the two compounds was achived by centrifugal plc. The first eluted band gave the 1,7-naphthyridine derivatives **2a,b** and only traces of compound **2c** were detected. The slower moving band afforded the 1,6-naphthyridine derivatives **1a-c**. Yields, recrystallization solvents, melting points, analyses and spectroscopic data of the compounds are given in Tables I, II, III and VI. When sodium methoxide in methanol or tert-butoxide in tert-butanol was used to promote the rearrangement yields were lower in all cases.

The crude product obtained from reaction of compound **3d** with alkoxides showed only one spot by tlc which was isolated and identified as *N*-(*N*-isopropylcarbamoyl-methyl)-3-pyridinecarboxamide (60% yield;); mp 179-182 °C (ethanol-water); ^{1}H nmr (deuteriochloroform): δ 9.05 (d, 1H, H-2), 8.73 (dd, 1H, H-6), 8.15 (dd, 1H, H-4), 7.38 (dd, 1H, H-5), 7.30 (bs, 1H, NH), 5.95 (d, 1H, NH), 4.35-4.17 (m, 1H, CH), 4.13 (d, 2H, NCH_2) and 1.24 (d, 6H, CH_3); ms: m/z 222 ($MH^{+\cdot}$) (100%).

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.75; H, 6.88; N, 18.92.

Synthesis and Cyclization of Quinolinamic Acid Methyl Esters **6** and **7**.

General Procedures.

Route *a*.

A suspension of 2,3-pyridinedicarboxylic acid 2-methyl ester **5** (0.85 g, 5 mmoles), prepared following Kenyon and Thaker´s procedure [30], in dry benzene (5 mL) and oxalyl chloride (0.75 g, 6 mmoles) was stirred at 40º for 3 hours. The solvent and excess of oxalyl chloride were removed *in vacuo*. The residual oil was dissolved in dry chloroform (5 mL). Solution was stirred and treated with the appropriate aminoacetamide hydrochloride (5 mmoles) and then a solution of triethylamine (0.81 g, 8 mmoles) in dry chloroform (10 mL) was added dropwise. The reaction mixture was refluxed for 1 hour, cooled and filtered. Solution was concentrated *in vacuo* and dry benzene (5 mL) added twice evaporating each time to dryness affording the corresponding 2-methoxycarbonyl-*N*-(carbamoylmethyl)-*N*-methyl-3-pyridinecarboxamide **6** as an oil that was used in the next step without purification.

Cyclization of quinolinamic acid methyl esters **6** was performed by treating crude products (1.1 g) dissolved in boiling 2-propanol (3 mL) with 2 M sodium isopropoxide (3 mL) and refluxed for 30 minutes. The red-yellow syrup was poured into ice-acetic acid and extracted with chloroform (4 x 5 mL). After washing with water the organic layer was dried, concentrated in vacuo and purified by centrifugal plc affording 6,7-disubstituted 8-hydroxy-1,6-naphthyridines **1e** and **1f**. Yields, melting points, recrystallization solvents, analyses and spectroscopic data of the compounds are given in Tables I, III, and VI.

An analytical sample of **6** (X=N(CH_3)C_6H_5, R=CH_3) was isolated as an oil (81% yield) and purified by centrifugal plc; ^{1}H nmr (deuteriochloroform): δ 8.69 (dd, 1H, H-6), 7.89 (dd, 1H, H-4), 7.50 (dd, 1H, H-5),7.39 (m, 5H, C_6H_5), 3.96 (s, 3H, OCH_3), 3.52 (s, 2H, NCH_2), 3.26 (s, 3H, NCH_3) and 3.20 (s, 3H, NCH_3); ms: m/z 341 (27.0%) ($M^{+\cdot}$), 105 (100%).

Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.25; H, 5.66; N, 12.26.

Route *b*.

To a mixture of quinolinic anhydride (5 mmoles), the appropriate aminoacetamide hydrochloride (6 mmoles) and dry tetrahydrofuran (10 mL) in an ice bath, triethylamine (0.81 g, 8 mmoles) in tetrahydrofuran (10 mL) was added dropwise and with stirring. After stirring for 1 hour at room temperature, the reaction mixture was cooled (ice bath) filtered and the organic solution concentrated in vacuo. The pasty solid was dissolved in anhydrous methanol (5 mL) and an ethereal solution of diazomethane (**caution**) was added in small portions until the solution acquires a pale yellow colour. After 24 hours at room temperature, the reaction mixture was concentrated *in vacuo* affording a mixture of compounds **6** and 3-methoxycarbonyl-N-(carbamoylmethyl)-N-methyl-2-pyridinecarboxamides **7** which was used in the next step without purification.

A crude mixture of esters **6** and **7** obtained as above was treated with sodium isopropoxide as was described for route a affording a mixture of 6,7-disustituted 5-hydroxy-1,7-naphthyridines **2e,f** as the major product together with little amounts of the corresponding 6,7-disubstituted 8-hydroxy-1,6-naphthyridines **1e,f**. Yields, melting points, recrystallization solvents, analyses and spectroscopic data of the compounds are given in Tables I, II, III and VI.

An analytical sample of compound **7** (X=N(CH_3)C_6H_5, R=CH_3) was obtained from the reaction of quinolinic anhydride with *N*-methyl-*N*-phenyl-2-(methylamino)acetamide and further reaction with diazomethane. The crude reaction product showed two spots by tlc. Separation was accomplished by centrifugal plc. The first band eluted afforded compound 7 (X=N(CH_3)C_6H_5, R=CH_3) (70%) as an oil; ^{1}H nmr (deuteriochloroform): δ 8.78 (dd, 1H, H-6), 8.29 (dd, 1H, H-4), 7.45 (dd, 1H, H-5),7.43 (m, 5H, C_6H_5), 3.84 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2), 3.25 (s, 3H, NCH_3) y 3.19 (s, 3H, NCH_3); ms: m/z 341 (35.78%) ($M^{+\cdot}$), 77 (100%).

Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.39; H, 5.56; N, 12.36.

The second band eluted (20% yield) was identified as compound **6** (X=N(CH_3)C_6H_5, R=CH_3).

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