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IMPROVED SYNTHESIS OF *N*-SUBSTITUTED 2,3-PYRIDINE-DICARBOXIMIDES WITH MICROWAVE IRRADIATION

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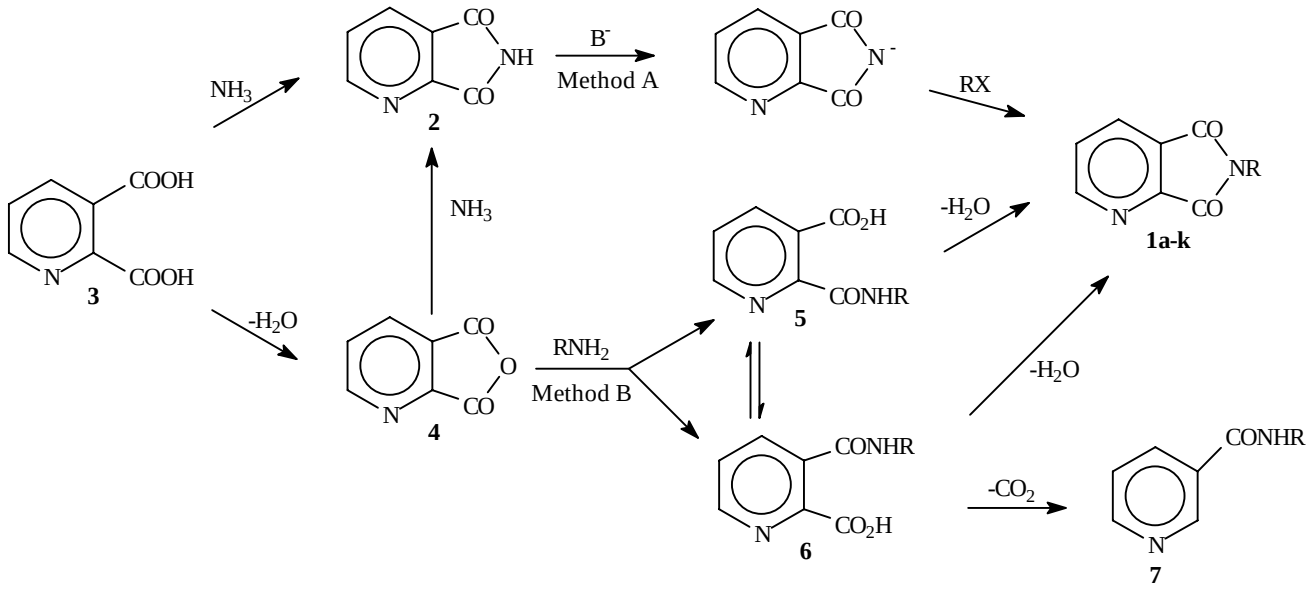
Abstract- The microwave-induced synthesis of *N*-substituted 2,3-pyridinedicarboximides (**1**) by means of two different approaches is presented. One involves direct *N*-alkylation of quinolinimide (**2**) (Method A) and the other, dehydrative condensation of quinolinic anhydride (**4**) and amines (Method B). Reactions resulted highly accelerated, with improved yields in relation to those obtained by conventional heating. The scope and limitations of each method and its variants are discussed.

INTRODUCTION

In the course of our research related to the synthesis of 1,6- and 1,7-naphthyridines we needed to employ quinolinimidoacetic acid derivatives as precursors.[1] This fact lead us to explore synthetic methods to obtain *N*-substituted 2,3-pyridinedicarboximides (N-substituted quinolinimides) (**1**) in general. There are two main synthetic approaches to obtain such compounds, which are general synthetic methods of cyclic imides,[2,3] and are commonly limited by their low yields, by-product formation and harsh reaction conditions.

The first method involves *N*-alkylation of quinolinimide (**2**) which is obtained from quinolinic acid (**3**) or its corresponding anhydride (**4**), (Method A, Scheme), and its application is limited by the nature of the alkylating agent.

Scheme



The second method involves dehydrative condensation of the quinolinic anhydride (**4**) and the corresponding amine (Method B). Reaction takes place through initial aminolysis with formation of two intermediates (quinolinamic acids **5** and **6**) with different yields. Subsequent heating of the mixture, usually in acidic media, gives the corresponding *N*-substituted imide (**1)** by dehydration of the most abundant[4] or both intermediates.[5] Low yields are often observed due to the formation of stable nicotinamides (**7**)[6] resulting from thermal decarboxylation of the by-product **6** and the **5**→**6** isomerization produced through hydrolysis of the corresponding quinolinimide (**1**).[4,7]

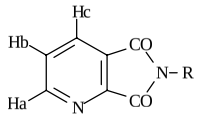
Our attempts to employ the above methods for the synthesis of quinolinimidoacetic acid derivatives were in general unsatisfactory. This fact led us to undertake the optimization of these methods taking advantage of the rapid heating capability of microwave irradiation.[11] Thus, a series of *N*-substituted quinolinimides (**1a-k**) with aryl, heteroaryl, alkyl, aralkyl and functionalized alkyl groups, depicted in Table 1, were synthesized.

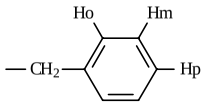
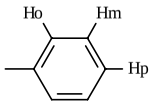
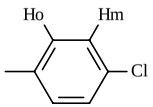
RESULTS AND DISCUSSION

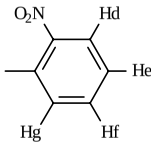
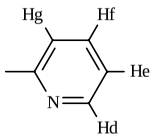
Synthesis of *N*-substituted quinolinimides (1) by *N*-alkylation of quinolinimide (2) (Method A)

Employment of this method led us to the necessity of improve the synthesis of the unsubstituted quinolinimide (**2**). With these aim, quinolinic acid (**3**) or its anhydride (**4**) were treated with aqueous

Table 1
N-Substituted Quinolinimides (**1a-k**)



Compd	R	mp (°C)	Analysis (Calcd/Found) %C	%H	%N	MS m/z (%)	δ (ppm)	Mult.	^{1}H-RMN (CCl_3D) Assign.	J (Hz)
1a	CH_3	123 [a] (ethanol)	59.26 59.32	3.73 3.77	17.28 17.21	162 (100) ($M^{+\bullet}$)	8.96 8.17 7.62 3.26	dd dd dd s	Ha Hc Hb CH_3	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.6; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.6; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9
1b	$CH(CH_3)_2$	126 [b]	63.15 63.20	5.30 5.24	14.73 14.68	190 (55.22) ($M^{+\bullet}$) 175 (100) [c]	8.95 8.13 7.60 4.60 1.51	dd dd dd m d	Ha Hc Hb CH CH_3	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.6; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.6; J_{Hb-Ha}:4.9; J_{CH-CH3}:6.9; J_{CH3-CH}:6.9
1c	$C(CH_3)_3$	102 [d]	64.69 64.62	5.92 5.95	13.72 13.75	204 (43.08) ($M^{+\bullet}$) 149 (100) [e]	8.93 8.09 7.57 1.72	dd dd dd s	Ha Hc Hb CH_3	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9
1d		162 [f] (ethanol)	70.58 70.50	4.23 4.29	11.76 11.69	238 (63.36) ($M^{+\bullet}$) 79 (100)	8.95 8.15 7.60 7.46 7.33 4.91	dd dd dd dd m s	Ha Hc Hb Ho Hm, Hp CH_2	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9; J_{Ho-Hm}:7.8; J_{Ho-Hp}:1.7
1e		205 [g] (ethanol)	69.64 69.57	3.60 3.65	12.49 12.58	224 (100) ($M^{+\bullet}$)	9.06 8.29 7.71 7.50	dd dd dd m	Ha Hc Hb Ho, Hm, Hp	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9
1f		203 (2-propanol)	60.37 60.32	2.73 2.78	10.83 10.92	258 (100) ($M^{+\bullet}$)	9.06 8.28 7.71 7.50 7.43	dd dd dd d d	Ha Hc Hb Ho Hm	J_{Ha-Hb}:5.0; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.7; J_{Hb-Ha}:5.0; J_{Ho-Hm}:7.0; J_{Hm-Ho}:7.0

1g		147 (ethanol)	58.00 58.03	2.62 2.67	15.61 15.56	269 (5.48) ($M^{+\bullet}$) 223 (100) [h]	9.08 8.30 8.24 7.82 7.73 7.67 7.55	dd dd dd ddd dd ddd dd	Ha Hc Hd Hf Hb He Hg	J_{Ha-Hb}:5.0; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.6; J_{Hc-Ha}:1.5; J_{Hd-He}:8.2; J_{Hd-Hf}:1.5; J_{Hf-He}:7.6; J_{Hf-Hg}:7.9; J_{Hf-Hd}:1.5; J_{Hb-Hc}:7.6; J_{Hb-Ha}:5.0; J_{He-Hd}:8.2; J_{He-Hf}:7.6; J_{He-Hg}:1.5; J_{Hg-Hf}:7.9; J_{Hg-He}:1.5
1h		192 (ethanol)	64.00 64.04	3.13 3.18	18.66 18.70	225 (51.71) ($M^{+\bullet}$) 77 (100) [i]	9.08 8.70 8.31 7.93 7.72 7.48 7.41	dd d dd dt dd d dd	Ha Hd Hc Hf Hb Hg He	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hd-He}:3.8; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hf-Hg}:7.8; J_{Hf-He}:7.8; J_{Hf-Hd}:1.9; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9; J_{Hg-Hf}:7.8; J_{He-Hf}:7.8; J_{He-Hd}:3.8
1i	$CH_2CO_2CH_3$	102 [j] (methanol)	54.55 54.34	3.66 3.82	12.72 12.60	220 (9.02) ($M^{+\bullet}$) 161 (100) [k]	9.00 8.70 7.65 4.50 3.80	dd dd dd s s	Ha Hc Hb CH_2 CH_3	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.6; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.6; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9
1j	$CH_2CO_2C_2H_5$	121 [l] (2-propanol)	56.41 56.45	4.30 4.37	11.96 11.90	234 (2.52) ($M^{+\bullet}$) 161 (100) [m]	9.01 8.70 7.65 4.50 4.20 1.30	dd dd dd s c t	Ha Hc Hb NCH_2 OCH_2 CH_3	J_{Ha-Hb}:4.9; J_{Ha-Hc}:1.5; J_{Hc-Hb}:7.7; J_{Hc-Ha}:1.5; J_{Hb-Hc}:7.7; J_{Hb-Ha}:4.9; $J_{CH2-CH3}$:7.2; $J_{CH3-CH2}$:7.2
1k	$CH_2CON(C_2H_5)_2$	142 (2-propanol)	59.76 59.81	5.79 5.84	16.08 16.03	295 (28.47) ($M^{+\bullet}$) 134 (100) [n]	8.97 8.17 7.61 4.54 3.39 1.31 1.11	dd dd dd s m t t	Ha Hc Hb NCH_2 CH_2CH_3 CH_3 CH_3	J_{Ha-Hb}:5.0; J_{Ha-Hc}:1.4; J_{Hc-Hb}:7.6; J_{Hc-Ha}:1.4; J_{Hb-Hc}:7.6; J_{Hb-Ha}:5.0; $J_{CH2-CH3}$:7.0; $J_{CH3-CH2}$:7.0

[a] lit.,[16] mp 121-123°C. [b] Hamprecht *et al.*[17] reported mp 102-104°C but structure was not confirmed by spectroscopic methods. [c] $M^{+\bullet}$ - CH_3. [d] Hamprecht *et al.*[17] reported mp 58-60°C but structure was not confirmed by spectroscopic methods. [e] It corresponds to the protonated quinolinimide. It results from the loss of the chain with double hydrogen transfer. [f] lit.,[18] mp 164°C. [g] lit.,[15] mp 210°C. [h] $M^{+\bullet}$- NO_2. [i] $C_5NH_3^{+\bullet}$. [j] lit.,[1] mp 102°C. [k] $M^{+\bullet}$ - CO_2CH_3 [l] lit.,[1] mp 121°C. [m] $M^{+\bullet}$- COC_2H_5 [n] $M^{+\bullet}$ - $CON(CH_3)C_6H_5$ - CNH.

ammonia or with a reagent capable of generate ammonia (urea, acetamide, ammonium carbonate) in absence of solvent, and exposed to microwave irradiation as source of heating.. The best yields (75%) were obtained from the acid and 28% aqueous ammonia under a power of 600 W for 8 min. These results surpassed those obtained by Keana *et al*.[12] employing acetamide and acetic anhydride in a 2.5 h reaction.

N-Alkylation was simply achieved by microwave irradiation of a mixture of quinolinimide (**2**), triethylamine and the corresponding alkyl halide in dry DMF. The method represents a typical example of the Microwave Oven-induced Reaction Enhancement (MORE) chemistry developed by Bose[13] and throws good results for the substitution of quinolinimide hydrogen by alkyl (even secondary), aralkyl and functionalized alkyl groups. Optimized data and yields are given in Table 2. Employment of microwaves results in highly accelerated reactions and with better yields comparing to the results of reaction with conventional heating (see Entries 6 and 7 for **1d**, Entries 17 and 18 for **1i** and Entries 21 and 22 for **1k**).

Synthesis of *N*-substituted quinolinimides (1) by dehydrative condensation of quinolinic anhydride (4) and amines (Method B)

Two different methodologies were used. When the amine is employed as hydrochloride (essential in the case of glicine esters), a one pot reaction in DMF without isolating quinolinamic acids (**5** and **6**) was used (Method B1, Table 2). Thus, a mixture of quinolinic anhydride (**4)**, the amine salt, triethylamine and molecular sieves 4Å in DMF is submitted to microwave irradiation. Although one advantage of the use of DMF as solvent is its capability to retain water formed in the reaction, thus avoiding the need for a water separator,[13] in our case employment of molecular sieves improves the results.

In those cases in which the amine could be used directly as free base, it is convenient to isolate intermediate acids (**5** and **6**) generated from **4** employing a solvent with low polarity such as carbon tetrachloride, benzene, *n*-hexane or cyclohexane.[14] Filtration, washing with the same solvent to eliminate amine excess and further microwave promoted cyclization in acetic anhydride lead in short times to imides (**1**) as the major products, with good yields and high purity (Method B2, Table 2). Amounts of nicotinamide as secondary product do not exceed 5% and in some cases non or only traces of such by-product are observed.

The importance of performing cyclization of quinolinamic acids (**5** and **6**) in acetic anhydride as well as the use of microwaves as thermal source become evident in all its magnitude in the attainment of

Table 2
Synthesis of *N*-Substituted Quinolinimides (**1a-k**)

Entry	Compd	Method A		Method B_1		Method B_2		
		Conditions [a,b]	Yields [c] (%)	Conditions [a,b]	Yields [c] (%)	Solvent [d]	Conditions [a,b]	Yields [c] (%)
1	**1a**	400 w; 4 min	79	800 w; 6 min	51			
2	**1b**	800 w; 4 min	85			C_6H_{14}	600 w; 2 min	79
3	**1c**					C_6H_{12}	700 w; 1.30 min	51
4	**1c**					C_6H_{12}	[e]	0[f]
5	**1c**					C_6H_{12}	reflux; 30 min	[g]
6	**1d**	400 w; 6 min	89			CCl_4	600 w; 1.30 min	95
7	**1d**	180°C; 2 h	12			CCl_4	[h]	75 [i]
8	**1e**					C_6H_6	600 w; 2 min	86
9	**1e**					C_6H_6	[j]	55 [k]
10	**1e**					C_6H_6	200°C; 2 h	12[l]
11	**1f**					C_6H_6	600 w; 2 min	95
12	**1g**					C_6H_{12}	600 w; 1.30 min	53
13	**1g**					C_6H_{12}	[e]	5 [m]
14	**1g**					C_6H_{12}	reflux; 30 min	[g]
15	**1h**					C_6H_6	600 w; 1.30 min	40
16	**1h**					C_6H_6	[n]	[o]
17	**1i**	300 w; 3 min	89	400 w; 2 min	80			
18	**1i**	140°C; 44 h	20	140°C; 2 h	20			
19	**1j**	300 w; 3 min	82	400 w; 2 min	80			
20	**1j**	140°C; 40 h	29					
21	**1k**	300 w; 7 min	70	400 w; 6 min	68			
22	**1k**	140°C; 48 h	15	150°C; 2 h	16			

[a] Power (watts) or temperature. [b] Complete disappearance of starting materials was monitored by TLC. [c] Yields based on isolation of chromatographically homogeneous products. [d] Solvent in which the quinolinamic acid mixture (**5**+**6**) was isolated. [e] 900 w, 10 min in acetic acid. [f] 30% of nicotinamide (**7c**) was isolated. [g] Intractable mixture. [h] 800 w, 4 min in acetic acid. [i] 15% of nicotinamide (**7d**) was isolated. [j] 900 w, 3 min in acetic acid. [k] 10% of nicotinamide (**7e**) and 10% of quinolinic acid dianilide[19] was isolated. [l] 45% of nicotinamide (**7e**) was isolated from a complex mixture of products. [m] 30% of nicotinamide (**7g**) was isolated. [n] 800 w, 6 min in acetic acid. [o] A mixture of *ca.* 8% of imide (**1h**) and 30% of nicotinamide (**7h**) was obtained (estimated yields based on the area of ^{1}H-NMR signals).

compounds (**1c,g**), which with conventional heating lead to complex mixtures of compounds with nicotinamide (**7**) as the main product (Table 2, see Entries 3-5 for **1c** and Entries 12-14 for **1g**).

Reaction of **4** with amines employing reagents which were adsorbed on silicagel and using microwave irradiation as in precedent cases shows disadvantages over the previous methodologies and amounts of nicotinamides (**7**) obtained with this technique are higher.

EXPERIMENTAL

Reactions were performed using an unmodified house microwave oven and conventional glass apparatus (unsealed). Melting points were determined with a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker MSL spectrometer with deuteriochloroform as the solvent. Chemical shift values are reported in ppm (δ) relative to TMS as internal standard. J values are given in Hertz (Hz). MS (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 70 eV. TLC analyses were carried out on aluminum sheets silica gel 60 F_{254} using a benzene-methanol mixture (9:1) as solvent. Column chromatographies were performed on silica gel 60 (230-400 mesh) with tipically 30-50 g of stationary phase *per gram* substance. Reagents, solvents and starting material were purchased from standard sources and purified according to literature procedures.

Synthesis of quinolinimide (2)

A mixture of quinolinic acid (**3**) (1 g, 6 mmol) and 28% aqueous ammonia (10 mL) was irradiated at 600 W for 8 min. The resulting suspension was cooled and triturated in ice-water affording quinolinimide (**2**), which was filtered off, dried and recrystallized from ethanol (75%); mp 234°C (lit.,[12] mp 230-231°C).

Synthesis of *N*-substituted quinolinimides (1a-k)

Method A

A mixture of quinolinimide (**2**) (150 mg,1 mmol), the appropriate alkyl halide (1 mmol) and triethylamine (0.28 mL, 2 mmol) in dry DMF (2 mL) was exposed to microwave irradiation. When the reaction was completed the resulting solution was poured into ice-water affording a solid which was filtered off, washed with water, dried and recrystallized.With this procedure were prepared compounds (**1a**), (**1b**), (**1d**), and (**1i-1k**). Melting points, analyses and spectroscopic data are given in Table 1. Power, times and yields are depicted in Table 2.

Method B1

A mixture of quinolinic anhydride (**4**) (150 mg, 1 mmol), the appropriate amine hydrochloride (1 mmol), and triethylamine (0.56 mL, 4 mmol) in dry DMF (2 mL) and 4Å molecular sieves (100 mg) (previously

activated 24 h at 150°C in a vacuum stove) was exposed to microwave irradiation. The resulting suspension was poured into ice-water and the solid was filtered off, washed, dried and recrystallized. With this procedure were prepared compounds (**1a**), (**1i**), (**1j)** and (**1k**). Melting points, analyses and spectroscopic data are given in Table 1. Power, times and yields are depicted in Table 2.

Method B2

To a stirred suspension of quinolinic anhydride (**4**) (150 mg, 1 mmol) in a low polarity solvent (3 mL), the appropriate amine (1 mmol) was added. The resulting solid was filtered off and washed with the solvent. The dried product was triturated with acetic anhydride (2 mL) and the mixture was exposed to microwave irradiation. The resulting solution was cooled affording a solid which was filtered, dried and recrystallized. With this procedure were prepared compounds (**1b**-**1h**). Melting points, analyses and spectroscopic data are given in Table 1. Power, times, organic solvents and yields are depicted in Table 2.
When cyclizations were carried out in acetic acid, lower yields of compounds (**1)** and substantial amounts of nicotinamides (**7**) were obtained (Entries 4, 7, 9, 13 and 16).
By TLC it was determined that the product isolated from reaction of **4** with amines before irradiation is in all cases a mixture of two compounds of low Rf, which cannot be isolated by chromatographic methods. Treatment of the crude product with polar solvents (water, acetone or methanol) selectively solubilizes the compound of lowest Rf (**6**) (minor product) and allows isolation of the compound of highest Rf, which resulted the most abundant quinolinamic acid (**5**). In this way, compounds (**5d**) and (**5e)** were isolated as a solid.

2-(*N*-Benzylcarbamoyl)pyridine-3-carboxylic acid (5d)

mp 136-7°C (lit.,[18] 137°C); ^{1}H NMR: δ 13 (br s, OH), 9.30 (br s, NH), 8.93 (dd, J_3=8.1 Hz, J_4=1.8 Hz, pyridine Hγ), 8.69 (dd, J_3=4.6 Hz, J_4=1.8 Hz, pyridine Hα), 7.67 (dd, J_3=8.1 Hz, J_3= 4.6 Hz, pyridine Hβ), 7.38 (m, C_6H_5), 4.72 (d, J_3=6.0 Hz, CH_2).

2-(*N*-Phenylcarbamoyl)pyridine-3-carboxylic acid (5e)

mp 134-5°C (lit.,[15] 138-9°C); ^{1}H NMR: δ 13 (br s, OH), 10.88 (br s, NH), 8.96 (dd, J_3=8.2 Hz, J_4=1.8 Hz, pyridine Hγ), 8.80 (dd, J_3=4.6 Hz, J_4=1.8 Hz, pyridine Hα), 7,74 (dd, J_3=8.2 Hz, J_3=4.6 Hz, pyridine H β), 7.72 (d, J_3=6.5 Hz, C_6H_5, *ortho* H), 7.45 (dd, J_3=7.4 Hz, J_3=6.5 Hz, C_6H_5, *meta* H), 7.27 (t, J_3=7.4 Hz, C_6H_5, *para* H).

3-(*N*-Benzylcarbamoyl)pyridine-2-carboxylic acid (**6d**)

^{1}H NMR (assigned signals from the NMR spectrum of a crude mixture of compounds (**5d)** and (**6d**): δ 13 (br s, OH), 8.88 (dd, , J_3=4.6 Hz, J_4=1.5 Hz, pyridine Hα), 8.60 (br s, NH), 8.25 (dd, J_3=7.7 Hz, J_4=1.5 Hz, pyridine Hγ), 7.65 (dd, J_3=7.7 Hz, J_3=4.6 Hz, pyridine Hβ), 7.35 (m, C_6H_5), 4.66 (d, J_3=5.1 Hz, CH_2). From the area of the signals corresponding to benzylic methylene and to the pyridine Hγ, it can be inferred that **5d**/**6d** ratio is 72/28.

ACKNOWELDGEMENTS

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6. Yields of nicotinamides (**7**) are in certain cases so high that reaction between quinolinic anhydride (**4**) and anilines in acetic acid has been proposed as a method for the synthesis of *N*-arylnicotinamides.[4]
7. A related antecedent is found in the transformation of 2-(*N*,*N*-diethylcarbamoyl)pyridine-3-carboxylic acid (main product of aminolysis of quinolinic anhydride (**4**) with diethylamine) in *N*,*N*-diethylnicotinamide.[8] Authors also justify that transformation as a consequence of an isomerization previous to decarboxylation. However, in this case the isomerization mechanism must be different from that proposed by Harrington,[4] since *N*,*N*-disubstitution of amide prevents imide formation. Authors suggest in this case an isomerization resulting from intramolecular acidolysis of the amide, similar to that proposed by Kenyon[9] and Norula[10] for the interconversion of quinolinic acid hemiesters.
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