# 1,6- and 1,7-Naphthyridines **III**. $^{13}$C-NMR Analysis of Some Hydroxy Derivatives



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The $^{13}$C-NMR spectra of some 1,6-naphthyridines **2** and 1,7-naphthyridines **3**, as well as those of *N*-methyl derivatives **4** and **5**, were recorded and analyzed. Results in dimethyl-$d_6$ sulfoxide and deuteriochloroform provide useful data on intra and intermolecular hydrogen bonds.

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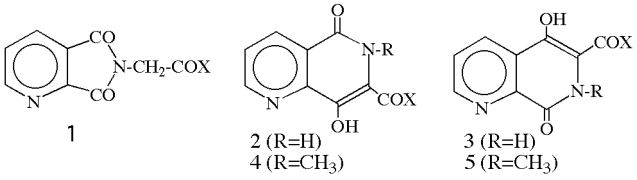
## Introduction.

In previous work, we studied the alkoxide-catalyzed rearrangement of quinolinimidoacetic acid derivatives **1**, that leads to the formation of two isomeric compounds, 7-substituted 8-hydroxy-1,6-naphthyridin-5(6*H*)ones **2** and 6-substituted 5-hydroxy-1,7-naphthyridin-8(7*H*)ones **3** (Scheme I) [1], which were separated by chromatographic methods. Structural assignment of these compounds was carried out by comparison of $^1$H-NMR spectra with those of model compounds (nicotinamide and picolinamide). On the basis of these studies, for low R*f* compounds the structure of 1,6-naphthyridines **2** and for high R*f* compounds that of 1,7-naphthyridines **3** were assigned [2].

In the present work the above assignment was confirmed by means of 1D nOe difference experiments and the $^{13}$C-NMR spectra of compounds **2** and **3** were analyzed with particular attention to the relationships between structure and spectroscopic behavior. Besides, spectra of the corresponding *N*-methyl derivatives **4** and **5** (Scheme I) obtained from acyclic precursors [3], as well as those of quinolinimides **1**, were also studied**.**

Scheme I

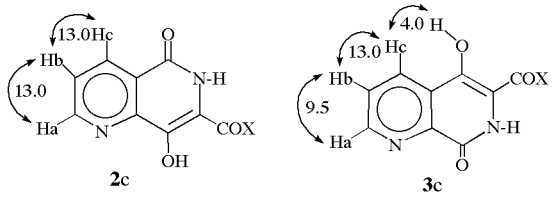



| Compound | X |
|---|---|
| **1a-5a** | $OCH_3$ |
| **1b-5b** | $OC_2H_5$ |
| **1c-5c** | $OCH(CH_3)_2$ |
| **1d, 2d, 4d** | $C_6H_5$ |
| **2e-5e** | $OCH_2CH(CH_3)_2$ |
| **2f-5f** | $OCH_2CH_2CH_3$ |

## Unequivocal Structure Assignment of Compounds **2** and **3**.

The results obtained by means of 1D nOe difference experiments in dimethyl-$d_6$ sulfoxide (DMSO-$d_6$) allowed unambiguous assignment of isomers **2** and **3** that confirmed both the proposed structures and the assignment of the pyridine hydrogens carried out previously [1]. Thus, using isopropyl esters **2c** and **3c** as models, in the compound of higher R*f* a positive nOe is observed between the enol hydroxyl and the Hc of the pyridine nucleus (Scheme II), evidencing that it is actually 1,7-naphthyridine **3c** [4].

Scheme II




## $^{13}$C-NMR Analysis of Compounds **1-5**.

Spectral assignments of compounds **1-5** were made taking account the analysis of signal multiplicity and coupling constant values and by comparison with data from the literature [7-9].

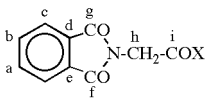
Chemical shift values of the carbon atoms belonging to compounds **1-5** are listed in Tables I-III and were determined throughout using DMSO-$d_6$ as solvent. In cases of suitable solubility, deuteriochloroform was also used to observe solvent influence.

Chemical shifts of quinolinimides **1** (Table I) were found to be within the expected range for such structures and failed to show substantial differences when varying the solvent.

The enol structure of compounds **2-5** (Tables II and III) was corroborated by a signal at δ 134.3-143.9 and another at 109.5-122.1, attributable to Cg and Ch respectively, both within the range of structurally related compounds [10]. Such values vary mainly with amide *N*-methylation as well as with solvent change (see below) [12]. Likewise, Cf chemical shifts (δ 156.9-159.5) were within the range of the amide carbonyl belonging to related isoquinolones [10] and failed to show substantial variations either with the series (1,6- vs. 1,7-) or with *N*-methylation.

Table I

$^{13}$C Chemical Shift Assignments of Quinolinimides **1** [a]

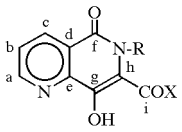


| Comp. Nº | solvent | Ca | Cb | Cc | Cd | Ce | Cf and Cg | Ch | Ci | Others |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $Cl_3CD$ | 155.5 | 127.6 | 131.5 | 127.3 | 151.6 | 165.4, 165.3 | 38.8 | 167.3 | 52.8 ($CH_3$) |
| **1a** | DMSO-$d_6$ | 155.3 | 128.2 | 131.7 | 127.0 | 151.1 | 165.4, 165.3 | 38.9 | 167.7 | 52.9 ($CH_3$) |
| **1b** | DMSO-$d_6$ | 155.3 | 128.1 | 131.7 | 127.0 | 151.1 | 165.4, 165.3 | 39.1 | 167.2 | 59.5 ($CH_2$), 13.9 ($CH_3$) |
| **1c** | DMSO-$d_6$ | 155.3 | 128.1 | 131.6 | 127.0 | 151.1 | 165.4, 165.3 | 39.3 | 166.7 | 68.9 (CH), 21.3 ($CH_3$) |
| **1d** | DMSO-$d_6$ | 155.2 | 128.1 | 131.6 | 127.2 | 155.6 | 165.8, 165.7 | 44.4 | 190.8 | 134.6, 129.0, 128.6, 127.9 ($C_6H_5$) |

[a] 5,7 Dihydro-5,7-dioxo-6-pyrrolo[3,4-b]pyridine-6-acetic acid derivatives.

Table II

$^{13}$C Chemical Shift Assignments of 1,6-Naphthyridines **2** and **4**



| Comp. Nº | | Ca | Cb | Cc | Cd | Ce | Cf | Cg | Ch | Ci | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | DMSO-$d_6$ | 154.3 | 125.2 | 136.1 | 124.9 | 147.1 | 158.0 | 143.2 | 113.0 | 165.0 | 52.8 ($CH_3$) |
| **2b** | DMSO-$d_6$ | 154.1 | 124.8 | 135.9 | 124.7 | 146.9 | 158.0 | 143.2 | 112.3 | 162.9 | 62.1 ($CH_2$), 13.9 ($CH_3$) |
| **2c** [a] | DMSO-$d_6$ | 154.1 | 124.8 | 135.9 | 124.7 | 146.8 | 158.0 | 143.2 | 112.3 | 162.9 | 69.9 (CH), 21.5 ($CH_3$) |
| **2d** | DMSO-$d_6$ | 153.9 | 124.3 | 136.2 | 123.7 | 147.6 | 158.7 | 138.4 | 121.5 | 189.4 | 137.4, 133.2, 129.5 y 128.4 ($C_6H_5$) |
| **4a** | DMSO-$d_6$ | 153.8 | 124.0 | 136.4 | 121.6 | 146.5 | 158.4 | 134.3 | 121.1 | 162.7 | 53.2 ($OCH_3$), 33.0 ($NCH_3$) |
| **4a** | $Cl_3CD$ | 153.7 | 124.6 | 136.9 | 123.3 | 145.7 | 159.5 | 142.0 | 117.4 | 164.4 | 53.1 ($OCH_3$), 34.8 ($NCH_3$) |
| **4b** [b] | DMSO-$d_6$ | 153.9 | 123.9 | 136.4 | 121.7 | 146.6 | 158.5 | 135.5 | 121.3 | 162.4 | 61.1 ($OCH_2$), 32.9 ($NCH_3$), 13.9 ($CH_2CH_3$), |
| **4b** | $Cl_3CD$ | 153.8 | 124.5 | 136.9 | 123.4 | 145.8 | 159.6 | 142.3 | 117.6 | 164.1 | 62.7 ($OCH_2$), 34.8 ($NCH_3$), 14.1 ($CH_2CH_3$), |
| **4e** | DMSO-$d_6$ | 154.1 | 124.1 | 136.5 | 121.8 | 146.5 | 158.1 | 135.5 | 121.0 | 162.5 | 71.4 ($OCH_2$), 33.2 ($NCH_3$), 27.2 (CH), 19.0 ($CHCH_3$) |
| **4e** | $Cl_3CD$ | 153.9 | 124.7 | 136.9 | 123.5 | 145.8 | 159.2 | 143.1 | 117.2 | 164.6 | 72.9 ($OCH_2$), 35.3 ($NCH_3$), 27.7 (CH), 19.2 ($CHCH_3$) |
| **4f** | DMSO-$d_6$ | 153.9 | 123.9 | 136.5 | 121.7 | 146.6 | 158.5 | 135.5 | 121.2 | 162.4 | 67.5 ($OCH_2$), 33.0 ($NCH_3$), 21.4 ($CH_2CH_3$), 10.4 ($CH_2CH_3$) |

[a] $^1J_{Ca\text{-}H}$=180.6 Hz, $^3J_{Ca\text{-}Hc}$=8.6 Hz, $^2J_{Ca\text{-}Hb}$=3.6 Hz, $^1J_{Cb\text{-}H}$=168.7 Hz, $^2J_{Cb\text{-}Ha}$=8.9 Hz, $^1J_{Cc\text{-}H}$=168.2 Hz, $^3J_{Cc\text{-}Ha}$=6.3 Hz, $^3J_{Cd\text{-}Hb}$=6.4 Hz, $^3J_{Ce\text{-}Ha}$ =11.24 Hz, $^3J_{Ce\text{-}Hc}$=4.7 Hz, $^3J_{Ci\text{-}H}$=4.5 Hz. [b] Signals were unequivocally assigned by HMQC and HMBC spectra (Table IV, Figure 1).

Scheme III

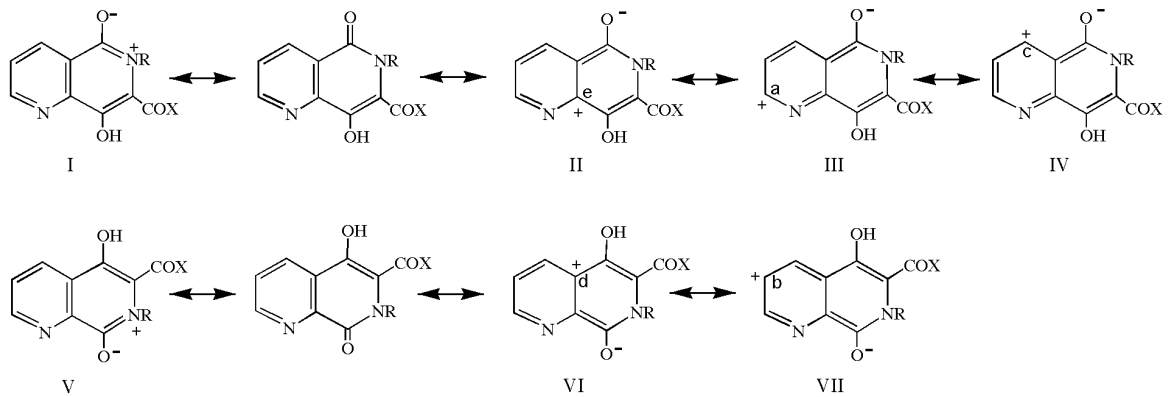
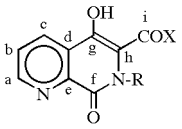


Table III

$^{13}$C Chemical Shift Assignments of 1,7-Naphthyridines **3** and **5**




| Comp. Nº | | Ca | Cb | Cc | Cd | Ce | Cf | Cg | Ch | Ci | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | DMSO-$d_6$ | 152.3 | 127.1 | 131.9 | 128.0 | 144.1 | 157.2 | 143.0 | 109.7 | 164.6 | 52.9 ($CH_3$) |
| **3b** | DMSO-$d_6$ | 152.2 | 127.0 | 131.8 | 127.8 | 144.1 | 157.1 | 143.2 | 109.6 | 164.4 | 62.1 ($CH_2$), 13.9 ($CH_3$) |
| **3c** [a] | DMSO-$d_6$ | 152.2 | 127.0 | 131.7 | 127.8 | 144.2 | 157.2 | 143.4 | 109.5 | 164.1 | 70.5 (CH), 21.4 ($CH_3$) |
| **3d** | DMSO-$d_6$ | 151.8 | 126.7 | 132.0 | 129.3 | 142.6 | 156.9 | 140.7 | 122.1 | 191.6 | 137.1, 133.4, 129.9, 128.5 ($C_6H_5$) |
| **5a** | DMSO-$d_6$ | 152.2 | 127.8 | 132.1 | 129.7 | 142.6 | 159.0 | 136.1 | 120.8 | 164.3 | 53.4 ($OCH_3$), 34.8 ($NCH_3$) |
| **5a** | $Cl_3CD$ | 153.3 | 126.8 | 132.3 | 126.8 | 147.8 | 159.5 | 143.9 | 112.4 | 166.9 | 53.5 ($OCH_3$), 36.9 ($NCH_3$) |
| **5b** [b] [c] | DMSO-$d_6$ | 152.1 | 127.6 | 132.2 | 129.5 | 142.4 | 158.9 | 136.0 | 121.0 | 163.8 | 63.1 ($OCH_2$), 34.8 ($NCH_3$), 14.7 ($CH_2CH_3$) |
| **5b** | $Cl_3CD$ | 153.1 | 126.5 | 132.3 | 126.6 | 147.6 | 159.5 | 143.8 | 112.6 | 166.4 | 63.0 ($OCH_2$), 36.9 ($NCH_3$), 14.1 ($CH_2CH_3$) |
| **5f** | DMSO-$d_6$ | 151.2 | 126.8 | 131.4 | 128.7 | 141.5 | 158.1 | 135.5 | 120.3 | 163.1 | 67.6 ($OCH_2$), 34.0 ($NCH_3$), 21.3 ($OCH_2CH_2$), 10.4 ($CH_2CH_3$) |
| **5f** | $Cl_3CD$ | 153.1 | 126.4 | 132.2 | 126.6 | 147.7 | 159.4 | 143.8 | 112.5 | 166.6 | 68.6 ($OCH_2$), 36.9 ($NCH_3$), 21.7 ($OCH_2CH_2$), 10.5 ($CH_2CH_3$) |

[a] $^1J_{Ca-H}$=184.8 Hz, $^3J_{Ca-Hc}$=8.19 Hz, $^2J_{Ca-Hb}$=3.5 Hz, $^1J_{Cb-H}$=167.9 Hz, $^2J_{Cb-Ha}$=8.9 Hz, $^1J_{Cc-H}$=169.5 Hz, $^3J_{Cc-Ha}$=4.2 Hz, $^3J_{Cd-Hb}$=6.6 Hz, $^3J_{Ce-Ha}$= 12.35 Hz, $^3J_{Ce-Hc}$=4.5 Hz, $^3J_{Ci-H}$=4.0 Hz. [b] Signals were unequivocally assigned by HMQC and HMBC spectra (Table V, Figure 2). [c] $^1J_{Ca-H}$=183.1 Hz, $^3J_{Ca-Hc}$=6.8 Hz, $^2J_{Ca-Hb}$=3.4 Hz, $^1J_{Cb-H}$=166.2 Hz, $^2J_{Cb-Ha}$=9.0 Hz, $^1J_{Cc-H}$=169.5 Hz, $^3J_{Cc-Ha}$=5.7 Hz, $^3J_{Cd-Hb}$=5.6 Hz, $^3J_{Ce-Ha}$=12.5 Hz, $^3J_{Ce-Hc}$=4.4 Hz, $^3J_{Ci-H}$=4.9 Hz.

In the case of the pyridine carbon atoms, chemical shifts are mainly influenced by the presence of the heterocyclic nitrogen, Ca and Ce appearing as the most deshielded, Cb and Cd as the most shielded and Cc with intermediate values.

The influence of the lactame moiety on the pyridine nucleus was observed when comparing the 1,6- with the 1,7-naphthyridine series. Thus, the contribution of electronic effects (Scheme III) through structures II, III and IV determines that in compounds **2** and **4** the Ca,c,e appear more deshielded than in compounds **3** and **5**. Likewise, the contribution of structures VI and VII leads to greater chemical shifts of the Cb,d in the 1,7- vs. 1,6- series. These results show that the secondary carbon pattern (Ca,b,c) is similar to that of the corresponding hydrogen atoms, as was also explained on the basis of electronic effects alone [1,3].

Previous $^{13}$C chemical shift assignments were corroborated by two dimensional spectra of heteronuclear correlation (HMQC, HMBC) of compounds **4b** and **5b**. Single bond and long-range correlations are presented in Tables IV and V respectively. Contour plots of the HMBC spectra are shown in Figures I and II. Observed three bond correlation for Cf-Hc confirms the 1,6-naphthyridine structure

Table IV

HMQC Single-bond and HMBC Long-range Proton-carbon Correlations of Compound **4b**

| Carbon δ(ppm) | Proton single bond coupling δ(ppm) | Proton three bond coupling δ(ppm) | Proton two bond coupling δ(ppm) |
|---|---|---|---|
| Ci-163.2 | _ | $OCH_2$ - 4.41 | _ |
| Cf-159.3 | _ | $NCH_3$ -3.42, Hc- 8.61[a] | _ |
| Ca-154.7 | Ha-9.05 | Hc- 8.61 | Hb-7.71 |
| Ce-147.4 | _ | Ha-9.05, Hc- 8.61 | _ |
| Cc-137.2 | Hc- 8.61 | Ha-9.05 | _ |
| Cg-136.3 | _ | _ | _ |
| Cb-124.7 | Hb-7.71 | _ | Ha-9.05 |
| Cd-122.6 | _ | Hb-7.71 | _ |
| Ch-122.2 | _ | $NCH_3$ -3.42 | _ |
| $OCH_2$-62.1 | $CH_2$ - 4.41 | _ | $CH_2CH_3$ -1.35 |
| $NCH_3$-33.7 | $NCH_3$ -3.42 | _ | _ |
| $CH_2CH_3$-14.8 | $CH_2CH_3$ -1.35 | _ | $CH_2$ - 4.41 |

[a] Confirms the 1,6-naphthyridine structure for compound **4b**.

Table V

HMQC Single-bond and HMBC Long-range Proton-carbon Correlations of Compound **5b**

| Carbon δ(ppm) | Proton single bond coupling δ(ppm) | Proton three bond coupling δ(ppm) | Proton two bond coupling δ(ppm) | Proton four bond coupling δ(ppm) |
|---|---|---|---|---|
| Ci-163.8 | _ | $OCH_2$ - 4.42 | _ | _ |
| Cf-158.9 | _ | $NCH_3$ -3.48 | _ | Hc- 8.39 [a] |
| Ca-152.1 | Ha-8.93 | Hc- 8.39 | Hb-7.83 | _ |
| Ce-142.4 | _ | Ha-8.93, Hc– 8.39 | _ | _ |
| Cg-136.0 | _ | Hc- 8.39 [a] | _ | _ |
| Cc-132.2 | Hc- 8.39 | Ha-8.93 | _ | _ |
| Cd-129.5 | _ | Hb-7.83 | _ | _ |
| Cb-127.6 | Hb-7.83 | _ | Ha-8.93 | _ |
| Ch-121.0 | _ | $NCH_3$ -3.48 | _ | _ |
| $OCH_2$-63.1 | $CH_2$ - 4.42 | _ | $CH_2CH_3$ -1.36 | _ |
| $NCH_3$-34.8 | $NCH_3$ -3.48 | _ | _ | _ |
| $CH_2CH_3$-14.7 | $CH_2CH_3$ -1.36 | _ | $CH_2$ - 4.41 | _ |

[a] Confirms the 1,7-naphthyridine structure for compound **5b**.

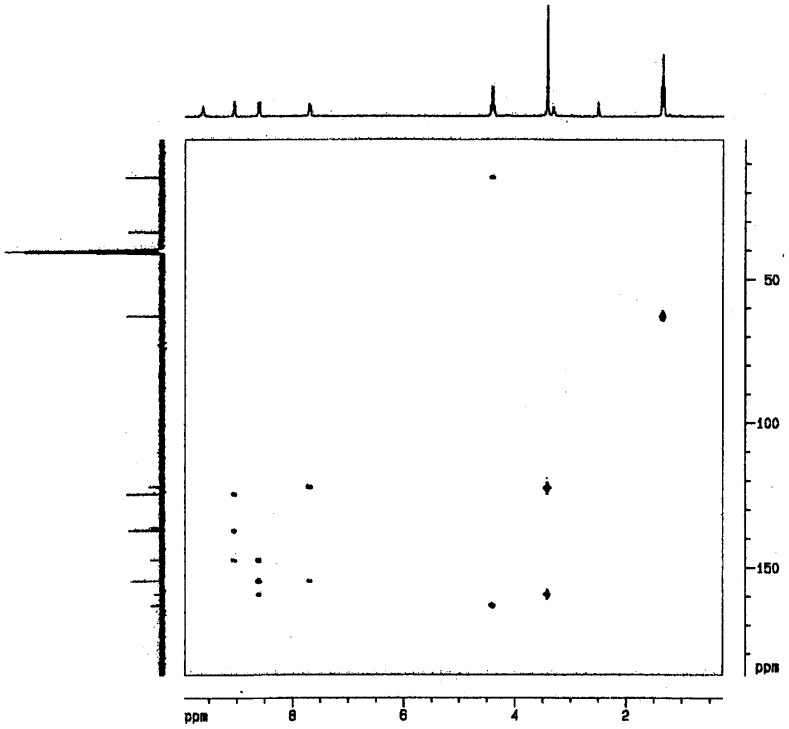
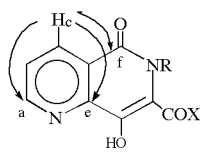



Figure I. Contour plot of the 300 MHz HMBC spectrum of compound **4b**.

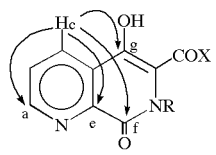
for compound **4b**. The Cf-Hc four bond and Cg-Hc three bond correlations confirm the 1,7-naphthyridine structure of compound **5b** (Scheme IV).

The comparison of the chemical shifts displayed by the pyridine carbons in naphthyridines **2** and **3** with regard to the corresponding quinolinimides **1** (Δδ) discloses that variations follow a similar pattern (Table VI). In particular Cc shifts afford a useful diagnostic tool to assign the structure of isomeric naphthyridines **2** and **3.** This is due to the fact that such carbon resonances appear in a relatively signal-free region of the spectrum and undergo a marked paramagnetic shift (4.2-4.6) in the 1,6- series, whereas

Scheme IV




**4b**




**5b**

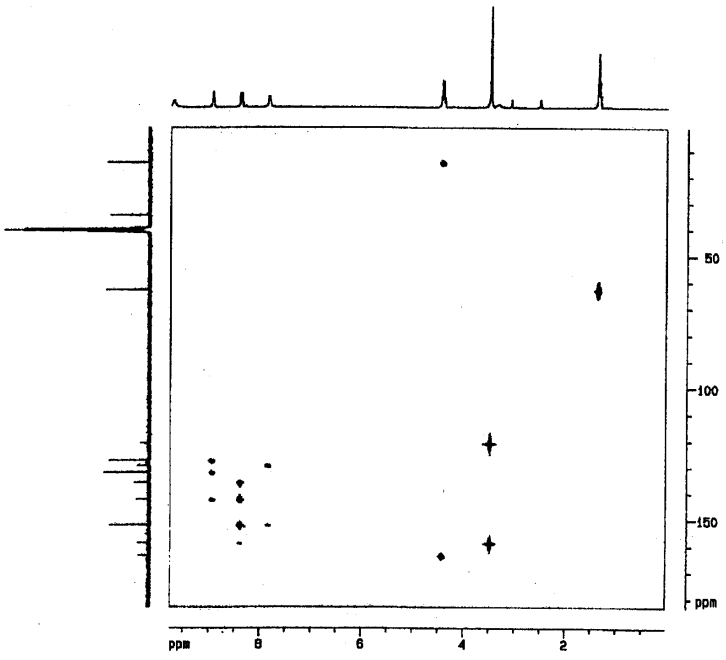



Figure II. Contour plot of the 300 MHz HMBC Spectrum of compound **5b**.

there is only a slight effect in the case of 1,7-naphthyridines (0.1-0.4).

Influence of the Solvent.

In order to observe the influence of the solvent on chemical shifts, spectra of several naphthyridines **4** and **5** were compared in DMSO-$d_6$ and deuteriochloroform [12]. Following solvent change, chemical shifts of the carbons belonging to the lactame moiety underwent marked modifications, except for Cf. Cg,h,i variations may be related to the possibility of hydrogen bond formation. Thus, in spectra of compounds **4** and **5** in deuteriochloroform**,** a solvent in which they may be stabilized by formation of chelated conjugate structures ($A_1 \leftrightarrow A_2$, Scheme V) [13], Cg and Ci appeared more deshielded than in DMSO-$d_6$, in which solvated structure B is the most likely (Scheme V) [4]. As in other compounds with an intramolecular hydrogen bond, a diamagnetic shift of the α–carbon with respect to the carbonyl group (Ch) is observed [19].

Scheme V

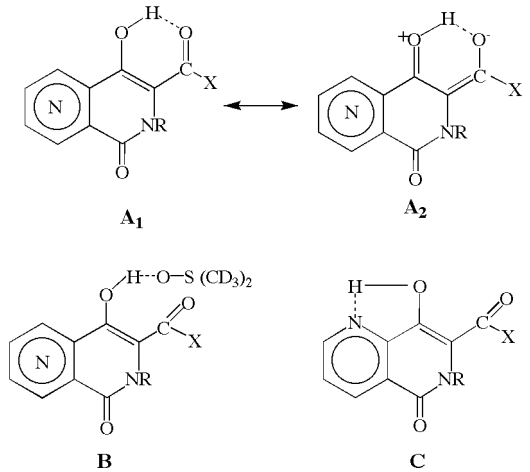



Table VI

Relative $^{13}$C Chemical Schifts of Compounds **2** and **3** *vs* those of Compounds **1** (Δδ)

| Δδ (ppm) | Ca | Cb | Cc | Cd | Ce |
|---|---|---|---|---|---|
| **Δ2a-1a** | -1.0 | -3.0 | +4.4 | -2.1 | -4.0 |
| **Δ2b-1b** | -1.2 | -3.3 | +4.2 | -2.3 | -4.2 |
| **Δ2c-1c** | -1.2 | -3.3 | +4.3 | -2.3 | -4.3 |
| **Δ2d-1d** | -1.3 | -3.8 | +4.6 | -3.5 | -8.0 |
| **Δ3a-1a** | -3.0 | -1.1 | +0.2 | +1.0 | -7.0 |
| **Δ3b-1b** | -3.1 | -1.1 | +0.1 | +0.8 | -7.0 |
| **Δ3c-1c** | -3.1 | -1.1 | +0.1 | +0.8 | -6.9 |
| **Δ3d-1d** | -3.4 | -1.4 | +0.4 | +2.1 | -13.0 |

With regard to the chemical shifts of the ester carbonyl (Ci), in deuteriochloroform a slightly greater shielding was observed in 1,6-naphthyridines **4** vs. 1,7-naphthyridines **5**. Besides possible electronic effects, this finding may be partly attributed to a smaller contribution of structure A owing to the possibility of hydrogen bond with the pyridine nitrogen (C, Scheme V), as was observed in the solid state [3,20]. The disappearance of intramolecular hydrogen bonds in DMSO-$d_6$ (B, Scheme V) determines that

Cg,h,i chemical shifts are similar in 1,6- and 1,7- naphthyridines.

## EXPERIMENTAL

The $^{13}C$ NMR spectra were recorded on a Bruker MSL-300 spectrometer. The standard concentration of the samples was 20mg/mL. Chemical shifts are given in ppm downfield from tetramethylsilane. The nOe difference experiments were performed on a Bruker MSL-300 spectrometer at 300.1 MHz. They were carried out by presaturation of the signal and substraction of the FID of the control spectrum from the FID on irradiation. The nOe difference spectra were recorded for saturation time of 2 seconds and irradiation power levels between 30 and 36 dB below 2W depending on the selectivity required. Two-dimensional spectra (HMQC and HMBC) were recorded with a Bruker AVANCE DRX 300 spectrometer.

Literature procedures were followed in the preparation of compounds **1-5** [1,3]. Purity was ascertained by tlc experiments on aluminium sheets Silica gel 60 $F_{254}$ using five different solvent mixtures.

Acknowledgement.

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## REFERENCES AND NOTES

[1] M. M. Blanco, M. G. Lorenzo, I. A. Perillo and C. B. Schapira. *J. Heterocyclic Chem.*, **33**, 361 (1996).

[2] R*f*: ratio front in tlc experiments on Silica gel using chloroform-methanol (9:1) as the solvent.

[3] M. M. Blanco, I. A. Perillo and C. B. Schapira, *J. Heterocyclic Chem.*, **36**, 979 (1999).

[4] The presence of an intramolecular hydrogen bonding between the enol hydrogen and ester carbonyl, as is evident in 1,7-naphthyridines [3] would avoid this correlation. However, it is well accepted the breaking of such bonds in DMSO-$d_6$ solutions as well as the presence of intermolecular hydrogen bond between the hydroxyl and the solvent [5,6] (structure B, Scheme V).

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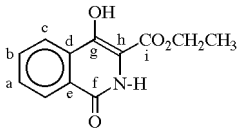
[10] The 4-hydroxy-1(2*H*)isoquinolone-3-carboxylic acid ethyl ester (**6**) [11] was taken as reference. The $^{13}C$ unequivocal assignments (HMQC and HMBC) are presented below.




**6**

$^{13}C$-NMR (DMSO-$d_6$): δ 164.8 (Ci), 158.2 (Cf), 144.8 (Cg), 132.8 (Cb), 130.8 (Cd), 130.6 (Ca), 129.0 (Ce), 127.3 (Cj), 123.1 (Cc), 108.3 (Ch), 62.1 ($CH_2$) and 13.9 ($CH_3$).

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[12] The solvent influence on the $^{13}C$ chemical shifts of compounds **2** and **3** could not be study because their slight solubility in deuteriochloroform.

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[20] Structures A and C (Scheme V) as well as mesomeric structures I and V (Scheme III) that contribute to lactame nucleus aromaticity, are responsible for enol stability.