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# Synthesis and spectroscopic properties of novel polyfunctionally substituted 2,6- and 2,7-naphthyridines

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ABSTRACT

Series of 5,6-dihydro-8-hydroxy-5-oxo-2,6-naphthyridine-7-carboxylic acid derivatives (**2**,**4**) and the isomeric 7,8-dihydro-5-hydroxy-8-oxo-2,7-naphthyridine-6-carboxylic acid derivatives (**3**,**5**) having potential pharmacological activity were synthesized from 3,4-pyridinedicarboxylic acid derivatives. Spectroscopic data (IR, $^{1}$H- and $^{13}$C-NMR, MS) are analyzed and support the enol–lactam structure of compounds **2**–**5** in solution, solid state and gas phase. Results in the different series (2,6- *vs* 2,7- naphthyridines and *N*-unsubstituted lactam *vs* *N*-methyl derivatives) are compared, and common and differential features amongst them are indicated.



## 1. Introduction

Hydroxypyridonecarboxylic acid derivatives containing an aromatic or heteroaromatic fused ring represent a type of polyfunctional compounds which attracted researchers' interest, either by their value as synthetic intermediates [1,2] or to the variety of biological activities they have shown. 2-Quinolinones having immunomodulating and antiangiogenic activity [3], isoquinolinones with antiinflammatory and analgesic activity [2], and different types of naphthyridinones have been described among others. Specially, 1,8-naphthyridine derivatives were the most studied ones, some of which possess interesting biological properties such as antiallergic, gastric antisecretory and herbicide [4]. On the other hand, our group has synthesized a series of hydroxy-1,6- and 1,7-naphthyridinonecarboxylic acid [5,6] derivatives from 2,3-pyridinedicarboxylic acid, under biological evaluation process at present.

Opposite to compounds mentioned above, hydroxy derivatives of 2,6- and 2,7-naphthyridinones have almost not been explored. Gabriel Colman studied the rearrangement of 3,4-pyridinedicarboximidoacetic acid ethyl ester (**1a**) with sodium methoxide and only obtained one of the two possible products which was identified as the 2,7-diazaderivative **3** (X = $CH_3$) (Scheme 1) [7]. Bearing in mind the absence of further studies and the potential importance of the expected compounds, we were interested in making deeper research about them. Accordingly, a series of *N*-substituted 3,4-pyridinedicarboximides **1** (*N*-substituted 1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-diones), were treated with hot alkoxides affording the expected hydroxy derivatives of 2,6- and 2,7-naphthyridinones (**2** and **3**, Scheme 1). Synthesis of *N*-lactam substituted naphthyridinones **4** and **5** employing two synthetic approaches is also presented (Scheme 2).

## 2. Experimental

### 2.1. General data

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer. Deuteriochloroform or DMSO-$d_6$ were used as the solvent, and the standard concentration of the samples for $^{1}$H-NMR was 10 and 25 mg/mL for $^{13}$C-NMR. Chemical shifts are reported in ppm ($\delta$) relative to TMS as an internal standard. Deuterium oxide was employed to confirm exchangeable protons (ex). Splitting multiplicities are reported as singlet (s), broad signal (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Two-dimensional spectra (HMQC, HMBC and ROESY) were recorded with a Bruker AVANCE DRX 300 spectrometer. Electron impact MS were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 70 eV. The IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. TLC analyses were carried out on Silica gel 60 $F_{254}$ using chloroform–methanol (9:1) as solvent. Preparative thin layer separations (PLC) were carried out by centrifugally accelerated, radial chromatography using Chromatotron model 7924T. The rotors were

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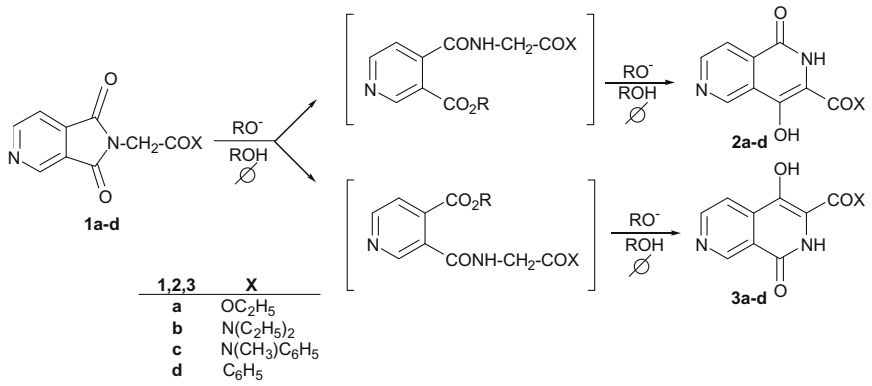
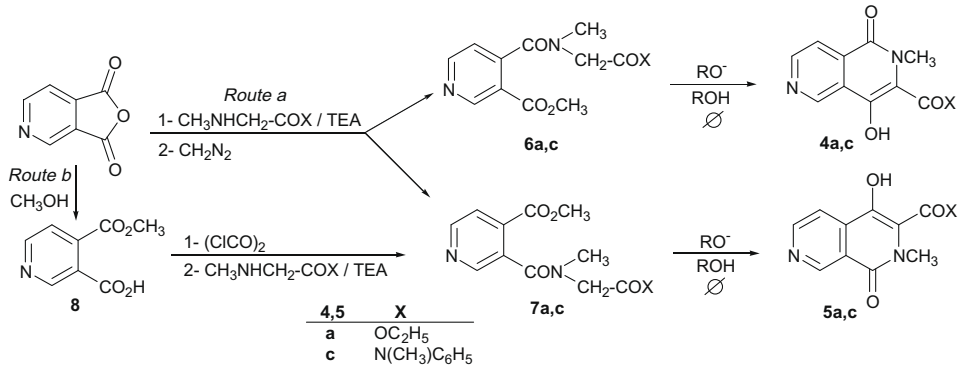



**Scheme 1.** Synthesis of *N*-lactam unsubstituted naphthyridinones **2** and **3**.




**Scheme 2.** Synthesis of *N*-lactam substituted naphthyridinones **4** and **5**.

coated with Silica Gel 60 PF254 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.

### *2.2. 1H-Pyrrolo[3,4-c]pyridine-1,3(2H)-dione-2-acetic acid derivatives (3,4-Pyridinedicarboximidoacetic acid derivatives) (**1a–d**): General procedure*

A mixture of 3,4-pyridinedicarboximide [8] (1 g, 0.007 mol), triethylamine (1.10 g, 0.008 mol), the corresponding halogen derivative (0.008 mol) and dimethylformamide (5 mL) was heated for 2–3 h in an oil bath (80–90 °C) and monitored by TLC. When the reaction was completed, the reaction mixture was poured into ice-water and the resulting solid filtered, washed with water and recrystallized.

#### *2.2.1. 1H-Pyrrolo[3,4-c]pyridine-1,3(2H)-dione-2-acetic acid ethyl ester (**1a**)*

Yield 74%, mp 82–84 °C (2-propanol) (lit. [7] 101 °C). $^1$H NMR ($CDCl_3$): $\delta$ = 9.20 (s, 1H, H-4), 9.11 (d, $^3J_{H6\text{-}H7}$ = 4.5 Hz, 1H, H-6), 7.82 (d, $^3J_{H6\text{-}H7}$ = 4.5 Hz, 1H, H-7), 4.46 (s, 2H, $NCH_2$), 4.24 (q, $^3J_{CH2\text{-}CH3}$ = 7.2 Hz, 2H, $OCH_2$) and 1.29 (t, $^3J_{CH2\text{-}CH3}$ = 7.2 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 166.7, 166.2 and 165.9 (3 CO), 155.8 (C-6), 145.0 (C-4), 139.4 (C-7a), 125.8 (C-3a), 117.1 (C-7), 62.1 ($OCH_2$), 39.1 ($NCH_3$) and 14.0 ($CH_3$). IR (KBr): 3417, 2985, 1783, 1720, 1613 cm$^{-1}$. MS (EI): *m/z* 234 ($M^{+\cdot}$, 8%), 189 (3%), 162 (44%), 161 (100%), 134 (7%), 133 (4%), 106 (7%), 105 (16%), 78 (26%), 77 (15%), 51 (17%), 50 (43%). Analyses (%C,%H,%N) calcd for $C_{11}H_{10}N_2O_4$: 56.41, 4.27, 11.97; found: 56.30, 4.30, 11.92.

#### *2.2.2. N,N-Diethyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione-2-acetamide (**1b**)*

Yield 65%, mp 106–108 °C (2-propanol). $_1$H NMR ($CDCl_3$): $\delta$ = 9.19 (s, 1H, H-4), 9.09 (d, $^3J_{H6\text{-}H7}$ = 4.6 Hz, 1H, H-6), 7.84 (d, $^3J_{H6\text{-}H7}$ = 4.6 Hz, 1H, H-7), 4.52 (s, 2H, $NCH_2$), 3.39 (br q, 4H, $NCH_2$), 1.33 (t, $^3J_{CH2\text{-}CH3}$ = 7.1 Hz, 3H, $CH_3$) and 1.13 (t, $^3J_{CH2\text{-}CH3}$ = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 166.8, 166.5 and 163.8 (3 CO), 155.5 (C-6), 144.8 (C-4), 139.7 (C-7a), 126.1 (C-3a), 117.0 (C-7), 41.3 ($NCH_2$), 40.9 ($NCH_2$), 39.3 ($NCH_2$), 14.1 ($CH_3$) and 12.8 ($CH_3$). IR (KBr): 3442, 2933, 1782, 1721, 1654, 1396 cm$^{-1}$. MS (EI): *m/z* 261 ($M^{+\cdot}$, 16%), 161 (29%), 105 (9%), 100 (86%), 72 (100%), 58 (19%), 50 (26%), 44 (50%). Analyses (%C,%H,%N) calcd for $C_{13}H_{15}N_3O_3$: 59.77, 5.75, 16.09; found: 59.68, 5.80, 16.02.

#### *2.2.3. N-Methyl-N-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione-2-acetamide (**1c**)*

Yield 77%, mp 116–118 °C (2-propanol). $^1$H NMR ($CDCl_3$): $\delta$ = 9.15 (s, 1H, H-4), 9.05 (d, $^3J_{H6\text{-}H7}$ = 4.7 Hz, 1H, H-6), 7.75 (d, $^3J_{H6\text{-}H7}$ = 4.7 Hz, 1H, H-7), 7.50 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 6.7 Hz, 2H, H*m*-$C_6H_5$), 7.42 (t, $^3J_{Hm\text{-}Hp}$ = 6.7 Hz, 1H, H*p*-$C_6H_5$), 7.37 (d, $^3J_{Ho\text{-}Hm}$ = 6.7 Hz, 2H, H*o*-$C_6H_5$), 4.19 (s, 2H, $NCH_2$) and 3.29 (s, 3H, $NCH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 166.7, 166.3 and 165.0 (3 CO), 155.6 (C-6), 144.8 (C-4), 142.0 (*Cipso*-$C_6H_5$), 139.7 (C-7a), 130.3 (C*m*-$C_6H_5$), 128.7 (C*p*-$C_6H_5$), 127.4 (C*o*-$C_6H_5$), 126.0 (C-3a), 116.9 (C-7), 40.0 ($NCH_2$) and 37.7 ($NCH_3$). IR (KBr): 2923, 1722, 1674, 1596, 702 cm$^{-1}$. MS (EI): *m/z* 295 ($M^{+\cdot}$, 63%), 161 (60%), 147 (4%), 134 (100%), 120 (12%), 107 (62%), 106 (64%), 105 (15%), 78 (33%), 77 (63%), 51 (28%), 50 (20%). Analyses (%C,%H,%N) calcd for $C_{16}H_{13}N_3O_3$: 65.08, 4.41, 14.24; found: 64.95, 4.46, 14.18.

*2.2.4. 1H-Pyrrolo[3,4-c]pyridine-1,3(2H)-dione-2-acetophenone (**1d**)*

Yield 57%, mp 155–158 °C (2-propanol). $^1$H NMR ($CDCl_3$): $\delta$ = 9.22 (s, 1H, H-4), 9.12 (d, $^3J_{H6\text{-}H7}$ = 4.9 Hz, 1H, H-6), 8.01 (d, $^3J_{Ho\text{-}Hm}$ = 7.2 Hz, 2H, H*o*-$C_6H_5$), 7.82 (d, $^3J_{H6\text{-}H7}$ = 4.9 Hz, 1H, H-7), 7.65 (t, $^3J_{Hm\text{-}Hp}$ = 7.2 Hz, 1H, H*p*-$C_6H_5$), 7.54 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.2 Hz, 2H, H*m*-$C_6H_5$) and 5.17 (s, 2H, $NCH_2$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 190.2, 166.7 and 166.3 (3 CO), 155.8 (C-6), 145.0 (C-4), 139.5 (C-7a), 134.3 (C*p*-$C_6H_5$), 134.1 (C*ipso*-$C_6H_5$), 129.0 (C*o*-$C_6H_5$), 128.2 (C*m*-$C_6H_5$), 126.0 (C-3a), 117.0 (C-7) and 44.4 ($NCH_2$). IR (KBr): 1779, 1722, 1596, 1219, 772 cm$^{-1}$. MS (EI): *m/z* 266 ($M^{+\cdot}$, 3%), 161 (6%), 106 (13%), 105 (100%), 78 (12%), 77 (56%), 51 (26%), 50 (20%). Analyses (%C,%H,%N) calcd for $C_{15}H_{10}N_2O_3$: 67.67, 3.76, 10.53; found: 67.74, 3.80, 10.48.

*2.3. Reaction of compounds **1a–d** with sodium alkoxides: General procedure*

To a solution of sodium alkoxide prepared from sodium (0.23 g, 0.01 mol) in the corresponding anhydrous alcohol (5 mL, ethanol for compound **1a**, 2-propanol for compounds **1b–d**) heated in an oil bath (90–100 °C), 3,4-pyridinedicarboximides **1** (0.0025 mole) were added all at once as the powder. After 30 min the reaction mixture was poured into ice-acetic acid and extracted with chloroform (3 × 10 mL). The organic layers were pooled, washed with water, dried and evaporated *in vacuo*. The crude products obtained showed two spots by TLC. Separation of the two compounds was achived by centrifugal PLC. The first band eluted gave the 2,6-naphthyridine derivatives **2a-d**. The slower moving band afforded the 2,7-naphthyridine derivatives **3a-d**.

*2.3.1. 5,6-Dihydro-8-hydroxy-5-oxo-2,6-naphthyridine-7-carboxylic acid ethyl ester (**2a**)*

Yield 35%, mp 204–205 °C (dec) (methanol). $^1$H NMR ($CDCl_3$): $\delta$ = 10.49 (br s, ex, 1H, NH), 9.55 (s, 1H, H-1), 9.10 (br s, ex, 1H, OH), 8.94 (d, $^3J_{H3\text{-}H4}$ = 5.2 Hz, 1H, H-3), 8.20 (d, $^3J_{H3\text{-}H4}$ = 5.2 Hz, 1H, H-4), 4.51 (q, $^3J_{CH2\text{-}CH3}$ = 7.3 Hz, 2H, $OCH_2$) and 1.48 (t, $^3J_{CH2\text{-}CH3}$ = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 164.3 (COX), 157.7 (C-5), 154.2 (C-3), 150.4 (C-1), 147.5 (C-8), 134.4 (C-4a), 125.4 (C-8a), 120.0 (C-4), 108.1 (C-7), 63.0 ($OCH_2$) and 14.2 ($CH_3$). IR (KBr): 3390, 1650, 1624, 1585, 1286 cm$^{-1}$. MS (EI): *m/z* 234 ($M^{+\cdot}$, 100%), 206 (38%), 188 (92%), 160 (33%), 133 (83%), 105 (56%), 103 (43%), 78 (39%), 77 (36%), 51 (28%), 50 (33%). Analyses (%C,%H,%N) calcd for $C_{11}H_{10}N_2O_4$: 56.41, 4.27, 11.97; found: 56.32, 4.35, 12.06.

*2.3.2. N,N-Diethyl-5,6-dihydro-8-hydroxy-5-oxo-2,6-naphthyridine-7-carboxamide (**2b**)*

Yield 31%, mp 222–224 °C (2-propanol). $^1$H NMR (DMSO-$d_6$): $\delta$ = 11.56 (br s, ex, 2H, NH and OH), 9.23 (s, 1H, H-1), 8.70 (d, $^3J_{H3\text{-}H4}$ = 5.2 Hz, 1H, H-3), 7.97 (d, $^3J_{H3\text{-}H4}$ = 5.2 Hz, 1H, H-4), 3.40 (q, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 4H, $NCH_2$) and 1.10 (t, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 6H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 161.9 (COX), 158.7 (C-5), 146.7 (C-3), 146.1 (C-1), 130.5 (C-4a), 129.9 (C-8), 128.3 (C-8a), 122.9 (C-7), 119.2 (C-4), 40.1 ($NCH_2$) and 13.4 ($CH_3$). IR (KBr): 2965, 1661, 1602, 1545, 1457 cm$^{-1}$. MS (EI): *m/z* 262 (35%), 261 ($M^{+\cdot}$, 67%), 244 (3%), 189 (7%), 162 (19%), 161 (18%), 134 (11%), 133 (12%), 74 (39%), 73 (22%), 72 (100%), 58 (76%), 44 (28%). Analyses (%C,%H,%N) calcd for $C_{13}H_{15}N_3O_3$: 59.77, 5.75, 16.09; found: 59.65, 5.73, 16.02.

*2.3.3. 5,6-Dihydro-8-hydroxy-N-methyl-5-oxo-N-phenyl-2,6-naphthyridine-7-carboxamide (**2c**)*

Yield 36%, mp 249-251 °C (2-propanol). $^1$H NMR (DMSO-$d_6$): $\delta$ = 11.50 (br s, ex, 1H, NH), 9.19 (br s, ex, 1H, OH), 9.10 (s, 1H, H-1), 8.64 (d, $^3J_{H3\text{-}H4}$ = 5.0 Hz, 1H, H-3), 7.88 (d, $^3J_{H3\text{-}H4}$ = 5.0 Hz, 1H, H-4), 7.35 (d, $^3J_{Ho\text{-}Hm}$ = 6.9 Hz, 2H, H*o*-$C_6H_5$), 7.29 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 6.9 Hz, 2H, H*m*-$C_6H_5$), 7.17 (t, $^3J_{Hm\text{-}Hp}$ = 6.9 Hz, 1H, H*p*-$C_6H_5$) and 3.34 (s, 3H, $NCH_3$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 162.7 (COX), 158.4 (C-5), 147.3 (C-3), 146.5 (C-1), 143.1 (C*ipso*-$C_6H_5$), 130.9 (C-4a), 129.9 (C-8), 129.2 (C*m*-$C_6H_5$), 128.1 (C-8a), 127.6 (C*p*-$C_6H_5$), 126.6 (C*o*-$C_6H_5$), 122.1 (C-7), 119.6 (C-4) and 37.3 ($NCH_3$). IR (KBr): 2923, 1722, 1674, 1596, 702 cm$^{-1}$. MS (EI): *m/z* 295 ($M^{+\cdot}$, 100%), 278 (1%), 189 (3%), 161 (8%), 134 (9%), 107 (76%), 106 (35%), 78 (23%), 77 (51%), 65 (7%), 51 (24%). Analyses (%C,%H,%N) calcd for $C_{16}H_{13}N_3O_3$: 65.08, 4.41, 14.24; found: 65.20, 4.46, 14.17.

*2.3.4. 7-Benzoyl-5,6-dihydro-8-hydroxy-5-oxo-2,6-naphthyridine (**2d**)*

Yield 28%, mp 228–230 °C (dec) (2-propanol). $^1$H NMR (DMSO-$d_6$): $\delta$ = 12.20 and 11.13 (br s, ex, 2H, OH and NH) 9.39 (s, 1H, H-1), 8.86 (d, $^3J_{H3\text{-}H4}$ = 5.0 Hz, 1H, H-3), 8.09 (d, $^3J_{H3\text{-}H4}$ = 5.0 Hz, 1H, H-4), 7.89 (d,$^3J_{Ho\text{-}Hm}$ = 7.1 Hz, 2H, H*o*-$C_6H_5$), 7.67 (t, $^3J_{Hm\text{-}Hp}$ = 7.1 Hz, 1H, H*p*-$C_6H_5$) and 7.55 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.1 Hz, 2H, H*m*-$C_6H_5$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 190.8 (COX), 155.9 (C-5), 150.6 (C-3), 149.1 (C-1), 144.0 (C-8), 136.7 (C*ipso*-$C_6H_5$), 133.3 (C*p*-$C_6H_5$), 131.2 (C-4a), 129.7 (C*o*-$C_6H_5$), 128.9 (C*m*-$C_6H_5$), 126.8 (C-8a), 121.1 (C-7) and 120.7 (C-4). IR (KBr): 1660, 1626, 1600, 1312, 694 cm$^{-1}$. MS (EI): *m/z* 266 ($M^{+\cdot}$, 83%), 248 (4%), 188 (9%), 160 (14%), 133 (13%), 105 (35%), 103 (19%), 78 (23%), 77 (100%), 51 (28%). Analyses (%C,%H,%N) calcd for $C_{15}H_{10}N_2O_3$: 67.67, 3.76, 10.53; found: 67.79, 3.83, 10.46.

*2.3.5. 7,8-Dihydro-5-hydroxy-8-oxo-2,7-naphthyridine-6-carboxylic acid ethyl ester (**3a**)*

Yield 54%, mp 170–171 °C (dec) (methanol). $^1$H NMR ($CDCl_3$): $\delta$ = 10.34 (br s, ex, 1H, NH), 9.67 (s, 1H, H-1), 8.97 (d, $^3J_{H3\text{-}H4}$ = 5.6 Hz, 1H, H-3), 8.87 (br s, ex, 1H, OH), 7.97 (d, $^3J_{H3\text{-}H4}$ = 5.6 Hz, 1H, H-4), 4.51 (q, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 2H, $OCH_2$) and 1.48 (t, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 164.2 (COX), 158.2 (C-8), 152.3 (C-3), 151.2 (C-1), 145.1 (C-5), 137.2 (C-4a), 125.5 (C-8a), 116.1 (C-4), 110.2 (C-6), 63.3 ($OCH_2$) and 14.2 ($CH_3$). IR (KBr): 3394, 1648, 1586, 1271 cm$^{-1}$. MS (EI): *m/z* 234 ($M^{+\cdot}$, 75%), 206 (37%), 188 (100%), 160 (65%), 133 (51%), 105 (15%), 78 (33%), 77 (33%), 51 (55%), 50 (68%). Analyses (%C,%H,%N) calcd for $C_{11}H_{10}N_2O_4$: 56.41, 4.27, 11.97; found: 56.54, 4.31, 11.90.

*2.3.6. N,N-Diethyl-7,8-dihydro-5-hydroxy-8-oxo-2,7-naphthyridine-6-carboxamide (**3b**)*

Yield 50%, mp 215–217 °C (2-propanol). $^1$H NMR (DMSO-$d_6$): $\delta$ = 11.51 (br s, ex, 2H, NH and OH), 9.28 (s, 1H, H-1), 8.79 (d, $^3J_{H3\text{-}H4}$ = 5.5 Hz, 1H, H-3), 7.72 (d, $^3J_{H3\text{-}H4}$ = 5.5 Hz, 1H, H-4), 3.40 (q, $^3J_{CH2\text{-}CH3}$ = 7.2 Hz, 4H, $NCH_2$) and 1.10 (t, $^3J_{CH2\text{-}CH3}$ = 7.2 Hz, 6H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 162.1 (COX), 153.9 (C-8), 151.2 (C-3), 150.6 (C-1), 137.3 (C-5), 136.9 (C-4a), 123.4 (C-8a), 120.1 (C-6), 117.2 (C-4), 42.2 ($NCH_2$) and 13.9 ($CH_3$). IR (KBr): 2970, 1655, 1594, 1479, 1456 cm$^{-1}$. MS (EI): *m/z* 262 (36%), 261 ($M^{+\cdot}$, 54%), 244 (2%), 189 (11%), 188 (14%), 162 (33%), 161 (18%), 134 (11%), 105 (7%), 74 (39%), 73 (18%), 72 (100%), 58 (77%), 44 (26%). Analyses (%C,%H,%N) calcd for $C_{13}H_{15}N_3O_3$: 59.77, 5.75, 16.09; found: 59.85, 5.80, 16.01.

*2.3.7. 7,8-Dihydro-5-hydroxy-N-methyl-8-oxo-N-phenyl-2,7-naphthyridine-6-carboxamide (**3c**)*

Yield 58%, mp 236-238 °C (2-propanol). $^1$H NMR (DMSO-$d_6$): $\delta$ = 11.40 (br s, ex, 1H, NH), 9.19 (s, 1H, H-1), 9.11 (br s, ex, 1H, OH), 8.71 (d, $^3J_{H3\text{-}H4}$ = 5.3 Hz, 1H, H-3), 7.61 (d, $^3J_{H3\text{-}H4}$ = 5.3 Hz, 1H, H-4), 7.35 (d, $^3J_{Ho\text{-}Hm}$ = 7.1 Hz, 2H, H*o*-$C_6H_5$), 7.29 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.1 Hz, 2H, H*m*-$C_6H_5$), 7.17 (t, $^3J_{Hm\text{-}Hp}$ = 7.1 Hz, 1H, H*p*-$C_6H_5$) and 3.34 (s, 3H, $NCH_3$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 162.4 (COX), 151.5 (C-8), 151.3 (C-3), 150.3 (C-1), 143.8 (C*ipso*-$C_6H_5$), 139.0 (C-4a), 131.2 (C-5), 129.3 (C*m*-$C_6H_5$), 127.8

(C*p*-$C_6H_5$), 126.6 (C*o*-$C_6H_5$), 125.4 (C-6), 120.5 (C-8a), 115.7 (C-4) and 39.4 ($NCH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 165.2 (COX), 156.2 (C-8), 151.9 (C-3), 150.7 (C-1), 142.2 (C-5), 141.5 (*Cipso*-$C_6H_5$), 137.9 (C-4a), 131.1 (C*m*-$C_6H_5$), 129.7 (C*p*-$C_6H_5$), 126.2 (C*o*-$C_6H_5$), 125.1 (C-8a), 121.5 (C-4), 112.2 (C-6) and 40.0 ($NCH_3$). IR (KBr): 3419, 1652, 1593, 1495, 699 $cm^{-1}$. MS (EI): *m/z* 295 ($M^{+\cdot}$, 100%), 189 (2%), 161 (9%), 134 (12%), 107 (86%), 106 (41%), 105 (39%), 78 (31%), 77 (79%), 65 (12%), 51 (40%). Analyses (%C,%H,%N) calcd for $C_{16}H_{13}N_3O_3$: 65.08, 4.41, 14.24; found: 65.10, 4.43, 14.30.

### 2.3.8. 6-Benzoyl-7,8-dihydro-5-hydroxy-8-oxo-2,7-naphthyridine (**3d**)

Yield 49%, mp 255–257 °C (dec) (2-propanol). $^1H$ NMR (DMSO-$d_6$): $\delta$ = 11.29 and 9.57 (br s, ex, 2H, OH and NH) 9.41 (s, 1H, H-1), 8.90 (d, $^3J_{H3\text{-}H4}$ = 5.3 Hz, 1H, H-3), 7.90 (d, $^3J_{Ho\text{-}Hm}$ = 7.0 Hz, 2H, Ho-$C_6H_5$), 7.86 (d, $^3J_{H3\text{-}H4}$ = 5.3 Hz, 1H, H-4), 7.70 (t, $^3J_{Hm\text{-}Hp}$ = 7.0 Hz, 1H, H*p*-$C_6H_5$) and 7.57 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.0 Hz, 2H, H*m*-$C_6H_5$). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ = 201.5 (COX), 156.4 (C-8), 151.8 and 151.7 (C-3 and C-1), 139.6 (C-4a), 137.7 (C-5), 136.8 (*Cipso*-$C_6H_5$), 134.2 (C*p*-$C_6H_5$), 130.1 (C*o*-$C_6H_5$), 129.1 (C*m*-$C_6H_5$), 126.1 (C-8a), 122.5 (C-6) and 116.3 (C-4). IR (KBr): 2295, 1645, 1602, 1266, 693 $cm^{-1}$. MS (EI): *m/z* 266 ($M^{+\cdot}$, 100%), 248 (2%), 188 (5%), 160 (10%), 133 (14%), 105 (29%), 77 (78%), 51 (34%). Analyses (%C,%H,%N) calcd for $C_{15}H_{10}N_2O_3$: 67.67, 3.76, 10.53; found: 67.58, 3.80, 10.47.

## 2.4. Synthesis of naphthyridinones **4** and **5:** General procedures

*Route a:* to a solution of 3,4-pyridinedicarboxylic anhydride [9] (0.007 mol) and the appropriate *N*-methylaminoacetic acid derivative hydrochloride (0.008 mol) in chloroform (10 mL) at room temperature, was added dropwise and with stirring triethylamine (0.008 mol) in chloroform (10 mL). After stirring for 1 h the reaction mixture was cooled (ice bath), filtered, and the organic solution concentrated *in vacuo*. The oily residue was dissolved in anhydrous methanol (5 mL) (ice bath) and an ethereal solution of diazomethane was added in small portions until the solution acquired a pale yellow colour. After 2 h at room temperature, the reaction mixture (containing compounds **6** and **7**) was concentrated *in vacuo* and used in the next step without purification.

A mixture of compounds **6** and **7** obtained as above (1.1 g) was dissolved in the appropriate alcohol (5 mL, ethanol for compounds **6a,7a** and 2-propanol for compounds **6c,7c**) and 3 mL of the corresponding 2 M sodium alkoxide was added and heated at reflux for 15 min. The brown–red suspension was poured into ice-acetic acid and extracted three times with chloroform. The organic layers were pooled, washed with water, dried and concentrated *in vacuo*. The crude product showed two spots by TLC (in 9:1 chloroform–methanol). Separation of the two products was accomplished by centrifugal PLC. The first band eluted gave the major product which was recrystallized affording compounds **4a,c**. The slower moving band afforded compounds **5a,c** (35% and 32%, respectively).

*Route b:* a suspensión of the stable hemiester **8** [9] (3.3 g, 0.018 mol) in dry benzene (7 mL) and oxalyl chloride (2.8 g, 0.022 mol) was heated at 40 °C for 3 h. The solvent and excess of oxalyl chloride were removed *in vacuo* and the residual oil was dissolved in dry THF (7 mL). The solution was stirred and treated with the appropriate *N*-methylaminoacetic acid derivative hydrochloride (0.018 mol) and then triethylamine (2.9 g, 0.029 mol) was added dropwise. The reaction mixture was heated at reflux for 1 h, evaporated *in vacuo* and dry benzene (5 mL) was added twice evaporating each time to dryness affording the corresponding compound **7** as oil which was used in the next step without purification.

Compounds **7a,c** (1.1 g) obtained as above were treated with the corresponding sodium alkoxide as was described for route *a* affording compounds **5a,c**.

### 2.4.1. 5,6-Dihydro-8-hydroxy-6-methyl-5-oxo-2,6-naphthyridine-7-carboxylic acid ethyl ester (**4a**)

Yield 49%, mp 104–106 °C (2-propanol). $^1H$ NMR ($CDCl_3$): $\delta$ = 11.21 (br s, ex, 1H, OH), 9.52 (s, 1H, H-1), 8.91 (d, $^3J_{H3\text{-}H4}$ = 5.1 Hz, 1H, H-3), 8.22 (d, $^3J_{H3\text{-}H4}$ = 5.1 Hz, 1H, H-4), 4.51 (q, $^3J_{CH2\text{-}CH3}$ = 7.4 Hz, 2H, $OCH_2$) 3.70 (s, 3H, $NCH_3$), and 1.46 (t, $^3J_{CH2\text{-}CH3}$ = 7.4 Hz, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 166.2 (COX), 159.1 (C-5), 150.4 (C-3), 148.4 (C-8), 147.2 (C-1), 134.4 (C-4a), 124.9 (C-8a), 121.8 (C-7), 120.2 (C-4), 63.0 ($OCH_2$), 36.6 ($NCH_3$) and 14.1 ($CH_3$). IR (KBr): 2985, 1719, 1680, 1577, 1319 $cm^{-1}$. MS (EI): *m/z* 248 ($M^{+\cdot}$, 67%), 220 (1%), 202 (57%), 191 (29%), 175 (34%), 174 (75%), 164 (19%), 150 (11%), 133 (78%), 118 (6%), 105 (79%), 78 (39%), 77 (39%), 50 (100%). Analyses (%C,%H,%N) calcd for $C_{12}H_{12}N_2O_4$: 58.06, 4.84, 11.29; found: 58.22, 4.93, 11.19.

### 2.4.2. 5,6-Dihydro-8-hydroxy-N,6-dimethyl-5-oxo-N-phenyl-2,6-naphthyridine-7-carboxamide (**4c**)

Yield 47%, mp 176–179 °C (2-propanol). NMR spectra of the major diastereomer is detailed. $^1H$ NMR (DMSO-$d_6$): 9.11 (br s, ex, 1H, OH), 9.10 (s, 1H, H-1), 8.63 (d, $^3J_{H3\text{-}H4}$ = 4.9 Hz, 1H, H-3), 7.89 (d, $^3J_{H3\text{-}H4}$ = 4.9 Hz, 1H, H-4), 7.33 (d, $^3J_{Ho\text{-}Hm}$ = 7.0 Hz, 2H, H*o*-$C_6H_5$), 7.23 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.0 Hz, 2H, H*m*-$C_6H_5$), 7.15 (t, $^3J_{Hm\text{-}Hp}$ = 7.0 Hz, 1H, H*p*-$C_6H_5$), 3.50 (s, 3H, $NCH_3$) and 3.45 (s, 3H, $NCH_3$). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ = 161.8 (COX), 158.3 (C-5), 146.6 (C-3), 145.3 (C-1), 141.6 (*Cipso*-$C_6H_5$), 129.2 (C-4a), 128.5 (C*m*-$C_6H_5$), 128.3 (C-8), 127.3 (C*p*-$C_6H_5$), 125.4 (C-8a), 125.2 (C*o*-$C_6H_5$), 125.0 (C-7), 118.8 (C-4) 36.1 ($NCH_3$) and 32.7 ($NCH_3$). IR (KBr): 3059, 1655, 1622, 1586, 1495, 696 $cm^{-1}$. MS (EI): *m/z* 309 ($M^{+\cdot}$, 24%), 175 (5%), 134 (60%), 107 (100%), 79 (13%), 77 (59%), 65 (11%), 51 (5%), 50 (22%), 42 (39%). Analyses (%C,%H,%N) calcd for $C_{17}H_{15}N_3O_3$: 66.02, 4.85, 13.59; found: 66.12, 4.79, 13.68.

### 2.4.3. 7,8-Dihydro-5-hydroxy-7-methyl-8-oxo-2,7-naphthyridine-6-carboxylic acid ethyl ester (**5a**)

Yield 68%, mp 90–92 °C (2-propanol). $^1H$ NMR ($CDCl_3$): $\delta$ = 10.90 (br s, ex, 1H, OH), 9.66 (s, 1H, H-1), 8.91 (d, $^3J_{H3\text{-}H4}$ = 5.8 Hz, 1H, H-3), 7.91 (d, $^3J_{H3\text{-}H4}$ = 5.8 Hz, 1H, H-4), 4.50 (q, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 2H, $OCH_2$), 3.67 (s, 3H, $NCH_3$) and 1.45 (t, $^3J_{CH2\text{-}CH3}$ = 7.0 Hz, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 166.1 (COX), 159.6 (C-8), 151.6 and 151.3 (C-3 and C-1), 146.8 (C-5), 135.9 (C-4a), 122.0 (C-8a), 115.9 (C-4), 115.3 (C-6), 63.2 ($OCH_2$), 36.1 ($NCH_3$) and 14.0 ($CH_3$). IR (KBr): 2984, 1728, 1682, 1590, 1318 $cm^{-1}$. MS (EI): *m/z* 248 ($M^{+\cdot}$, 73%), 220 (1%), 202 (72%), 175 (33%), 174 (95%), 134 (23%), 133 (95%), 105 (94%), 78 (40%), 77 (42%), 51 (46%), 50 (64%), 42 (100%). Analyses (%C,%H,%N) calcd for $C_{12}H_{12}N_2O_4$: 58.06, 4.84, 11.29; found: 58.08, 4.92, 11.20.

### 2.4.4. 7,8-Dihydro-5-hydroxy-N,7-dimethyl-8-oxo-N-phenyl-2,7-naphthyridine-6-carboxamide (**5c**)

Yield 71%, mp 157–158 °C (2-propanol). NMR spectra of the major diastereomer is detailed. $^1H$ NMR (DMSO-$d_6$): $\delta$ = 10.05 (br s, ex, 1H, OH), 9.28 (s, 1H, H-1), 8.70 (d, $^3J_{H3\text{-}H4}$ = 5.4 Hz, 1H, H-3), 7.60 (d, $^3J_{H3\text{-}H4}$ = 5.4 Hz, 1H, H-4), 7.34 (d, $^3J_{Ho\text{-}Hm}$ = 7.3 Hz, 2H, H*o*-$C_6H_5$), 7.24 (t, $^3J_{Hm\text{-}Hp}$ = $^3J_{Hm\text{-}Ho}$ = 7.3 Hz, 2H, H*m*-$C_6H_5$), 7.18 (t, $^3J_{Hm\text{-}Hp}$ = 7.1 Hz, 1H, H*p*-$C_6H_5$), 3.52 (s, 3H, $NCH_3$) and 3.41 (s, 3H, $NCH_3$). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ = 161.5 (COX), 158.3 (C-8), 150.7 and 150.3 (C-3 and C-1), 141.2 (*Cipso*-$C_6H_5$), 137.5 (C-4a), 129.3 (C-5), 129.0 (C*m*-$C_6H_5$), 128.5 (C*p*-$C_6H_5$), 127.9 (C*o*-$C_6H_5$), 125.8 and 125.6 (C-6 and C-8a), 114.8 (C-4), 36.5 ($NCH_3$) and 32.8 ($NCH_3$). IR (KBr): 3057, 1652, 1618, 1592, 1495, 702 $cm^{-1}$. MS (EI): *m/z* 309 ($M^{+\cdot}$, 22%), 202 (1%), 175 (3%), 134 (40%), 107 (100%), 105 (23%), 77 (67%), 65 (11%), 51 (33%), 50 (29%), 42 (39%). Analyses

(%C,%H,%N) calcd for $C_{17}H_{15}N_3O_3$: 66.02, 4.85, 13.59; found: 66.12, 4.83, 13.65.

## 3. Results and discussion

### 3.1. Synthesis

Reaction of compounds **1a–d** with hot alkoxides under different conditions led in all cases to two main compounds ferric chloride positive. These compounds were isolated by chromatographic methods, and were identified (see below) as the corresponding 5,6-dihydro-8-hydroxy-5-oxo-2,6-naphthyridine-7-carboxylic acid derivatives (**2a–d**) and 7,8-dihydro-5-hydroxy-8-oxo-2,7-naphthyridine-6-carboxylic acid derivatives (**3a–d**) (Scheme 1). Such result is in agreement with the general accepted mechanism (a ring opening-ring closing rearrangement) [10]. In all cases, 2,7-naphthyridine **3** was mainly obtained as the result of alkoxide attack on the most reactive carbonyl group (4 respect to pyridine nitrogen).

*N*-Methylnaphthyridinones **4** and **5** were obtained through synthetic strategies employing 3,4-pyridinedicarboxylic anhydride as starting material, and involved synthesis and ring closing of *N,N*-disubstituted amide esters (**6** and **7**, respectively) (Scheme 2). Route ***a*** involves 3,4-pyridinedicarboxylic anhydride aminolysis with methylaminoacetic acid derivatives and further methylation with diazomethane, leading to a mixture of the amide esters **6** and **7**. Treatment of reaction products with hot alkoxides leads to a mixture of naphthyridinones **4a,c** (main products) and **5a,c.** Such result is in agreement with regioselective cleavage of the anhydride leading preferably to esters **6**. Route ***b*** employs the stable hemiester **8** [9] as intermediate, which becomes compounds **7** by amidation with methylaminoacetic acid derivatives *vía* acid halide. Subsequent cyclization with alkoxides lead to naphthyridinones **5a,c**.

### 3.2. Spectroscopic properties of hydroxynaphthyridinones 2–5

The polyfunctional features of the synthesized naphthyridines, and the possibility of protrotopic equilibria derived from them (lactam–lactim and keto–enol) determinate the possibility of several structures for those compounds. However, positive ferric chloride test, the presence of signals assigned to enol protons in $^1$H-NMR spectra, IR bands between 1640 and 1665 cm$^{-1}$ (assigned to a lactam carbonyl), and the absence of signals over 170 ppm in $^{13}$C-NMR spectra account for the enol–lactam structure of compounds **2–5**. Structures and assignment of NMR spectra were confirmed by bidimensional heteronuclear correlation spectra (HMQC, HMBC) and ROESY for compounds **2c** and **3c**. The main correlations observed which account for proposed structures are shown in Figs. 1 and 2.

Chemical shifts in NMR spectra are strongly conditioned by mesomeric effects. $^1$H-NMR spectra show the three pyridine protons sharply differentiated with their expected chemical shifts and multiplicity, appearing H-1 at 9.50–9.67, H-3 at 8.63–8.97 and H-4 at 7.60–8.22 ppm. However, 2,6-naphthyridines **2** and **4** present greater chemical shifts for H-4 but lower chemical shifts for H-1 and H-3, *vs* the corresponding protons in the 2,7-naphthyridines **3** and **5**. These results may be a consequence of the presence of lactam carbonyl through the contribution of mesomeric structures **A** (for 2,6-naphthyridines) and **A′** and **B′** (for 2,7-naphthyridines) (Fig. 3).

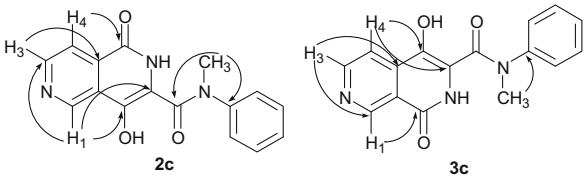



**Fig. 1.** Main correlations observed in the HMBC spectra.

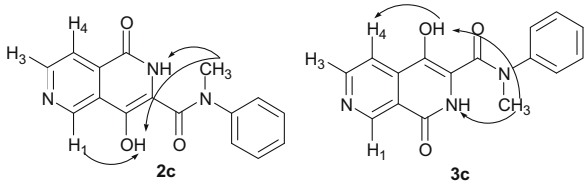



**Fig. 2.** Main correlations observed in the ROESY spectra.

In the case of pyridine carbons, chemical shifts are also mainly influenced by the presence of the heterocyclic nitrogen, C-1 and C-3 appearing as the most deshielded, and C-4 and C-8a as the most shielded. However, the influence of the lactam moiety on pyridine nucleus allows us again to distinguish the 2,6- from 2,7-naphthyridine series. Thus, the contribution of electronic effects through structures **A**,**B** determines that in compounds **2,4** C-4 and C-8a appear more deshielded than in compounds **3,5**. Likewise, contribution of electronic effects through structures **A′**–**C′** determines the greatest chemical shifts for C-1, C-3 and C-4a in the 2,7- *vs* 2,6-series.

Enol carbon appears in a variable range (128.3–148.4 ppm), mainly depending on the nature of X group (being more deshielded in esters and ketones than in amides) and on the nature of the solvent (see below). Instead, it does not vary substantially with the series (2,6- or 2,7-) and with *N*-methylation. Chemical shifts of the other alkene carbon (C-7 for 2,6- series and C-6 for 2,7-series) and the lactam carbonyl ($\delta$ 108.1–125.6 and $\delta$ 151.5–159.6 ppm, respectively) were within the range of related compounds [6,11].

Chemical equivalence of both ethyl groups in the $^1$H and $^{13}$C-NMR of compounds **2b** and **3b**, as well as the absence of diastereomeric carboxamides for compounds **2c** and **3c** indicate that the CO-N bond enjoy free rotation at room temperature. This facts are in line with a resonance assisted hydrogen bonding effect (RAHB) [6,12] where the stabilized keto–enol system involves the extranuclear amide carbonyl leading to an important

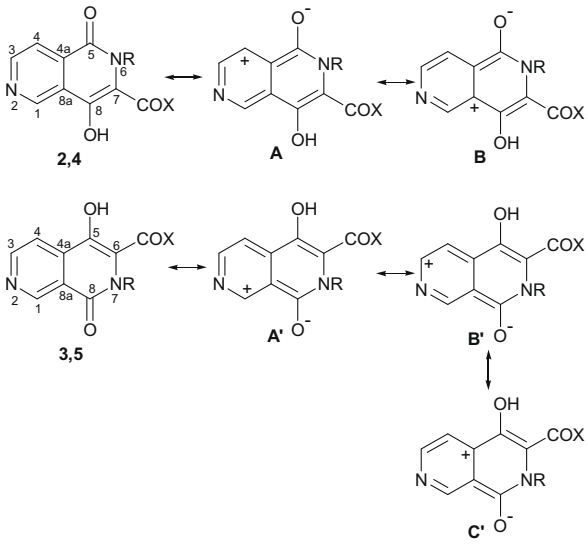



**Fig. 3.** Mesomeric structures of naphthyridinones **2–5** showing the influence of lactam carbonyl.

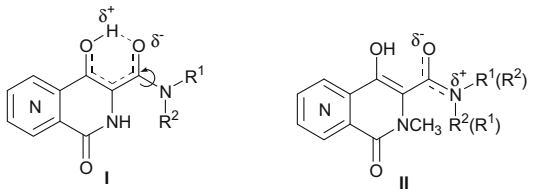


**Fig. 4.** Structures showing electron delocalization in naphthyridinecarboxamides.

single-bond character of the amide CO-N bond (Fig. 4, Structure **I**). On the contrary, NMR spectra of compounds **4c** and **5c** show the existence of diastereomeric carboxamides. This fact is explained as the result of lactam *N*-substitution steric effect which inhibits the keto–enol system planarity [13] and hence the RAHB effect, thus favoring delocalization typical of amides, and leading to a partial double bond character of amide CO–N bond (Fig. 4, Structure **II**).

Solvent influence was evaluated by comparison of spectra of amide **3c** in deuteriochloroform and in DMSO-$d_6$. Substantial variation is only observed in carbons of the lactam moiety. A paramagnetic shift for enol carbon (C-8) and a diamagnetic shift of the other alkene carbon (C-7) is observed specially in deuteriocloroform. Such behavior is similar to that observed in other enol compounds with intramolecular hydrogen bond [11].

Infrared spectra of compounds **2–5** in solid state (potassium bromide) show absorption bands which do not allow us to differentiate series 2,6- from 2,7-naphthyridines. Importance of lactam nitrogen *N*-methylation is observed in the ester carbonyl stretching. This band appears in compounds **2a** and **3a** at *ca.* 1650 $cm^{-1}$ compatible with a structure similar to **I** (Fig. 4), having an intramolecular hydrogen bond. Instead, in *N*-methyl derivatives **4a** and **5a** the ester carbonyl absorption occurs at *ca.* 1710 $cm^{-1}$, in the range of the frequency of benzoic and α,β-unsaturated esters [14], probably as the result of *N*-lactam substitution which inhibits the planarity of the keto–enol system as was indicated above.

The electron impact mass spectra of naphthyridines **2–5** show molecular ions with variable abundance, being most intense in *N*-lactam unsubstituted compounds (base ions for compounds **2a,c** and **3c,d**). Related to them, M+1 ions resulting from ion-molecule reactions are important, specially in *N,N*-diethylamides (**2b** and **3b**), with a relative abundance of 52% and 67% of the parent ion, respectively.

In general, spectra of isomeric 2,6- and 2,7-naphthyridinones are similar, not presenting features which allow us to distinguish them by this method. Instead, fragmentation pattern shows differences according to the function derived from carboxyl group, and in minor proportion to the presence of methyl group on the lactam nitrogen.

Main fragmentation pathways begin with lateral chain degradation and support the enol structure of compounds **2–5** in gas phase (Scheme 3). Thus in esters, the dominant route involves CO-OR cleavage with enol hydrogen transfer to the OR group (*ortho* effect) and subsequent heterolytic cleavage affording $[M\text{-}ROH]^{+\cdot}$ ions (Route ***a***) and fragments derived from them. Instead, in amides homolytic cleavage leads to odd electron ions $[HNRR']^{+\cdot}$ (base ion for compounds **4c** and **5c**) (Route ***b***), thus reflecting the strong tendency of carboxamide nitrogen to originate ions with charge retention. Although in *N,N*-diethyl amides **2b** and **3b** such odd electron ion ($[NHEt_2]^{+\cdot}$) appears with low abundance, ions arising from their further fragmentation are observed (*m/z* 58, $[NHEt_2\text{-}Me]^+$, >70%); therefore this route cannot be discarded in such compounds.

Other pathway (Route ***c***) involves an α-cleavage leading to carboxamide ion $[CONRR']^{+\cdot}$ Fragmentation continues with the loss of CO originating $[NRR']^+$, base ion for compounds **2b** and **3b.**

Esters **2a** and **3a** present important peak at *m/z* 206 resulting from McLafferty rearrangement of the molecular ion. Instead, the corresponding peak (at *m/z* 220) appears with very low intensity in the spectra of the *N*-methyl derivatives **4a** and **5a**.

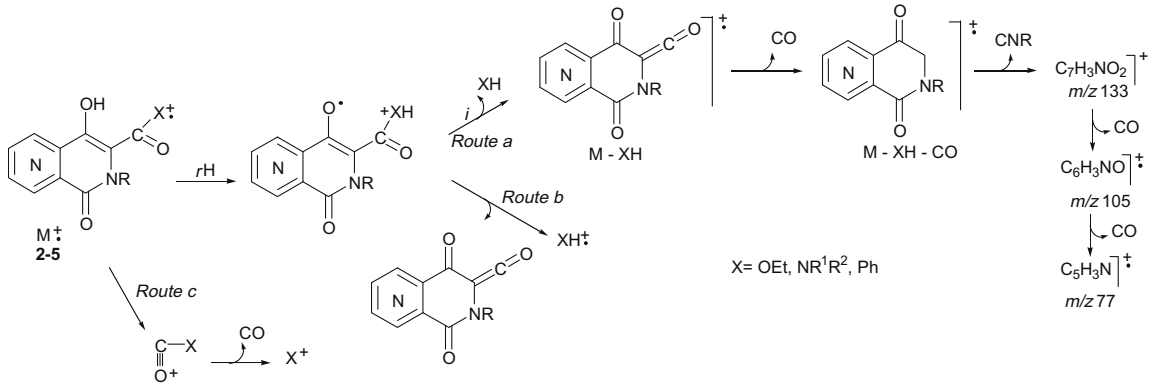
Spectra of ketones **2d** and **3d** present, besides the expected ions *m/z* 105 $[COPh]^+$ and 77 $[Ph]^+$ resulting from α-cleavage, ions at *m/z* 188, 160 and 133 which composition corresponds to fragments originated by route ***a***. This type of fragmentation, uncommon in ketones, may be explained by an enol hydrogen transfer to C-phenyl, followed by heterolytic cleavage and benzene liberation. Opposite to the other compounds, ketones **2d** and **3d** present characteristic low intensity peaks resulting from the loss of water.

Others less important fragmentation routes, which begin with the loss of X, OH and R-NCO from the molecular ion, are observed in some cases.

## 4. Conclusions

Series of novel selectively substituted 2,6- and 2,7-naphthyridinones were obtained employing different methods that involve the synthesis of the lactam ring from pyridine derivatives. Thus, 5,6-dihydro-8-hydroxy-5-oxo-2,6-naphthyridine-7-carboxylic acid derivatives (**2**) and the isomeric 7,8-dihydro-5-hydroxy-8-oxo-2,7-naphthyridine-6-carboxylic acid derivatives (**3**) were obtained by alkoxide induced rearrangement of 3,4-pyridinedicarboximidoacetic acid derivatives (**1**). Analogous compounds substituted on the lactam nitrogen (**4** and **5**) were obtained employing two approaches that involve the synthesis and ring closing of *N,N*-disubstituted amide esters **6** and **7** obtained from 3,4-pyridinedicarboxylic anhydride.

Spectroscopic properties (IR, $^1H$ and $^{13}C$ NMR and MS) of compounds were analyzed and the proposed structures confirmed. $^1H$ and $^{13}C$ chemical shifts are strongly conditionated by mesomeric




**Scheme 3.** Mass spectra fragmentation pathways of naphthyridinones **2–5** under EI conditions.

effects and allow to distinguish the 2,6- from 2,7-series. Differences amongst *N*-lactam unsubstituted naphthyridines (**2** and **3**) and the corresponding *N*-methyl derivatives (**4** and **5**) are also observed. The first group show a resonance-assisted hydrogen bonding effect (RAHB) where the stabilized keto–enol system involves the extranuclear carbonyl (Structure **I**). Instead, the lactam *N*-substitution probably inhibits the keto–enol system planarity and the RAHB effect, leading to a partial double bond character of amide CO–N bond in amides **4c** and **5c** (Structure **II**), and a higher frequency of the ester carbonyl stretching in the IR spectra of compounds **4a** and **5a**. Main fragmentation pathways observed in the mass spectra begin with lateral chain degradation and support the enol structure of compounds **2**–**5** in gas phase.

The presented methods were appropriate for the obtention of polyfunctional naphthyridinones **2–5**, a practically unexplored kind of compounds until the present.

## Acknowledgment

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