Synthesis of some novel bridgehead nitrogen heterocyclic systems containing 1,8-naphthyridine moiety

K Mogilaiah* & G Kankaiah
Department of Chemistry, Kakatiya University, Warangal 506 009, India

Received 20 March 2001; accepted (revised) 10 May 2002

3-Aryl-2-chloro-1,8-naphthyridines 3 on treatment with anthranilic acid, o-phenylenediamine and sodium azide afford quinazolino[3,2-a][1,8]naphthyridin-13-ones 4, benzimidazo[1,2-a][1,8]naphthyridines 5 and tetrazolo[1,5-a][1,8]naphthyridines 6, respectively. The structures of compounds 4-6 have been established by IR, 1H NMR and mass spectral data. The compounds 4 have been evaluated for their antibacterial activity.

Heterocyclic ring fused on substituted 1,8-naphthyridines have become attractive targets in organic synthesis due to their significant biological activities.1,2 Quinazolines,3 benzimidazoles4 and tetrazoles5 are well known for their broad spectrum biological properties. Encouraged by these reports and in continuation of our work on fused 1,8-naphthyridines6-8, we report herein, the synthesis of novel and hitherto unknown bridgehead nitrogen heterocyclic systems viz., quinazolino[3,2-a][1,8]naphthyridin-13-ones 4, benzimidazo [1,2-a][1,8]naphthyridines 5 and tetrazolo[1,5-a][1,8]naphthyridines 6. The synthetic approach is outlined in Scheme I.

2-Amino-3-aryl-1,8-naphthyridines 1, obtained by the condensation of 2-aminonicotinaldehyde with arylacetonitriles, on treatment with HNO2 furnished 3-aryl-2-hydroxy-1,8-naphthyridines 2. Interaction of 2 with POCI3 gave the desired synthons, 3-aryl-2-chloro-1,8-naphthyridines7,8,9 3. The reaction of 3 with an-
thranilic acids in gl. acetic acid under reflux afforded the corresponding quinazolinol[3,2-a][1,8]naphthyridin-13-ones 4. Fusion of o-phenylenediamine with 3 in an oil-bath at 200°C for 2 hr resulted in the formation of benzimidazo[1,2-a][1,8]naphthyridines 5. Treatment of 3 with sodium azide in gl. acetic acid afforded the respective tetr azolo[1,5-a][1,8]naphthyridines 6. The structures of compounds 4-6 have been determined on the basis of their elemental analyses and spectral (IR, ¹H NMR and MS) data (Table I).

**Antibacterial activity**

The compounds 4 were screened for their antibacterial activity against *Escherichia coli* (Gram-negative) and *Bacillus subtilis* (Gram-positive) by filter paper disc technique at 400 and 600 μg/disc concentrations. Standard antibacterial streptomycin was also screened under similar conditions for comparison. The results of the antibacterial screening are given in Table II.

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by precoated TLC plates (E. Merk Kieselgel 60 F254). IR spectra in KBr pellets were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer; ¹H NMR spectra in CDCl₃ on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm); and mass spectra on a Jeol JMS D-300 spectrometer.

### 6-Phenylquinazolinol[3,2-a][1,8]naphthyridin-13-one 4a

A mixture of 3 (Ar = C₆H₅, 0.01 mole) and anthranilic acid (0.01 mole) was refluxed in gl. acetic acid (25 mL) for 3 hr. The reaction mixture was cooled and poured into ice cool water. The solid obtained was filtered, washed with water and recrystallized from ethanol to afford 4a, m.p. 235°C, yield 76%; IR (KBr): 1670 (C=O), 1605 cm⁻¹ (C=N); ¹H NMR (COCl₃): δ 7.74 (m, 2H, C₆H₅, C₉-H), 7.99 (m, 1H, C₈-H), 8.74 (m, 1H, Cl₁-H), 7.21–7.50 (m, 9H, Ar-H); MS: m/z 323 (M⁺, 100%), 295 (34.6), 294 (21.1).
Table II—Antibacterial screening results of the compounds 4a-1

<table>
<thead>
<tr>
<th>Compd</th>
<th>E. coli at</th>
<th>B. subtilis at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 µg/disc</td>
<td>600 µg/disc</td>
</tr>
<tr>
<td>4a</td>
<td>8.0</td>
<td>9.5</td>
</tr>
<tr>
<td>4b</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>4c</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>4d</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td>4e</td>
<td>9.5</td>
<td>10.5</td>
</tr>
<tr>
<td>4f</td>
<td>7.5</td>
<td>8.5</td>
</tr>
<tr>
<td>4g</td>
<td>6.0</td>
<td>7.0</td>
</tr>
<tr>
<td>4h</td>
<td>4.5</td>
<td>6.0</td>
</tr>
<tr>
<td>4i</td>
<td>11.5</td>
<td>12.5</td>
</tr>
<tr>
<td>4j</td>
<td>8.5</td>
<td>9.5</td>
</tr>
<tr>
<td>4k</td>
<td>7.0</td>
<td>8.0</td>
</tr>
<tr>
<td>4l</td>
<td>6.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Strepto-</td>
<td>13.0</td>
<td>15.0</td>
</tr>
<tr>
<td>mycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(13.1), 268 (4.8), 221 (24.8), 206 (3.5), 194 (10.8).

Other compounds in the series were prepared similarly and their characterization data are recorded in Table I.

6-Phenylbenzimidazo[1,2-α][1,8]naphthyridine 6a

A mixture of 3 (Ar = C₆H₅, 0.01 mole) and α-phenylenediamine (0.01 mole) was heated at 200°C in an oil-bath for 2 hr. The solid product obtained was washed with cold methanol and recrystallized from ethanol to furnish 6a, m.p. 192°C; yield 82%; IR (KBr): 3194, 1608, 1605 cm⁻¹ (C = N); ¹H NMR (CDCl₃): δ 8.17 (m, 2H, C₆-H, C₇-H), 7.26 – 7.59 (m, 9H, Ar-H); MS: m/z 295 (M⁺, 100%), 294 (6.7), 268 (3.1), 221 (5.1). Anal. Calc for C₂₄H₁₉N₃: C, 81.86; H, 4.41; N, 14.73. Found: C, 81.52; H, 4.47; N, 14.32%.

Following compounds of the type 5 were also prepared in a similar manner.

5b: (Ar = p-CIC₆H₄): m.p. 205°C; yield 86%; IR (KBr): 1605 cm⁻¹ (C = N). Anal. Calc for C₂₄H₁₉N₃Cl: C, 72.84; H, 3.64; N, 12.75. Found: C, 72.71; H, 3.70; N, 12.86%.

5c: (Ar = p-CH₂OOC₆H₄): m.p. 225°C; yield 84%; IR (KBr): 1610 cm⁻¹ (C = N). Anal. Calc for C₂₄H₁₉N₃O: C, 77.54; H, 4.62; N, 12.92. Found: C, 77.70; H, 4.71; N, 12.83%.

4-Phenyltetrazolo[1,5-α][1,8]naphthyridine 6a

A mixture of 3 (Ar = C₆H₅, 0.01 mole) and sodium azide (0.05 mole) was refluxed in gl. acetic acid (30 mL) for 5 hr, cooled and poured onto crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from ethanol to furnish 6a, m.p. 210°C, yield 75%; IR (KBr): 1615 cm⁻¹ (C = N); ¹H NMR (CDCl₃): δ 8.14 (m, 2H, C₆-H, C₇-H), 8.42 (m, 1H, C₈-H), 9.01 (m, 1H, C₉-H), 7.52 – 7.79 (m, 5H, Ar-H); MS: m/z 247 (M⁺, 14.5%), 221 (12.2), 220 (30.7), 219 (100), 193 (12.3), 192 (24.5), 166 (8.3). Anal. Calc for C₁₄H₉N₅: C, 68.02; H, 3.64; N, 28.34. Found: C, 68.20; H, 3.70; N, 28.48%.

Other members of the series 6 were prepared similarly and their characterization data are as follows:

6b (Ar = p-CIC₆H₄): m.p. 250°C (d), yield 78%; IR (KBr): 1608 cm⁻¹ (C = N). Anal. Calc for C₂₄H₁₉N₃Cl: C, 59.68; H, 2.84; N, 24.87. Found: C, 59.82; H, 2.91; N, 24.95%.

6c (Ar = p-CH₂OOC₆H₄): m.p. 202°C, yield 78%; IR (KBr): 1605 cm⁻¹ (C = N). Anal. Calc for C₂₃H₁₈N₃O: C, 64.98; H, 3.97; N, 25.27. Found: C, 64.82; H, 3.91; N, 25.39%.

Acknowledgement

The authors are thankful to the Head, Department of Chemistry, Kakatiya University, Warangal for providing laboratory facilities. They are also grateful to the Directors, IICT, Hyderabad and CDRI, Lucknow for recording ¹H NMR and mass spectra, respectively.

References