NEW AMARYLLIDACEAE ALKALOIDS FROM NARCISSUS PAPYRACEUS
KER-GAWLER

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Abstract. Three new alkaloids, 2-methylpapyramine (1), 2-methylmaritidine (2) and 9-2-demethylhomolycorine N-oxide (3) have been isolated from aerial parts of Narcissus papyraceus Ker-Gawler, together with lycorine, papyramine, pseudolycorine, homolycorine and 9-0-demethylhomolycorine.

Narcissus papyraceus Ker-Gawler (Amaryllidaceae) is a widely distributed plant of the Mediterranean and Macaronesic Region.1 The plant is believed to be toxic for herbivorous mammalians. The toxicity might be related to the alkaloids content which is five times higher in the aerial part than in the bulbs.2 Earlier work on the constituents of the bulbs describes the isolation of nine alkaloids.3 In this paper we report the isolation from aerial parts of N. papyraceus of three new alkaloids: O-methylpapyramine (1), O-methylmaritidine (2) and 9-O-demethylhomolycorine N-oxide (3), together with homolycorine (4) and 9-O-demethylhomolycorine (5), papyramine (6), lycorine (7) and pseudolycorine (8). The last three alkaloids were also present in the bulbs.3

Dried aerial parts of N. papyraceus were extracted with methanol. Acid-base extraction afforded the crude basic material that was chromatographed using basic alumina and EtOAc-ethanol to give alkaloids 1-8.

O-Methylpapyramine (1) was eluted from the column with EtOAc and was purified by column chromatography (EtOAc-hexane 4:1). Its ms was consistent with a molecular formula C_{19}H_{25}NO_{4} (M^+ 331). A base peak at M^+-55 suggested a 5,10b-ethanophenanthridine skeleton without substituent at C-11.4,5 The 1H nmr spectrum revealed the presence of two olefinic and two p-oriented aromatic protons, two O-Me aromatic groups and two O-Me aliphatic groups but no signal due to a N-methyl group. The chemical shift of two methine carbon atoms in the 13C nmr spectrum (δ 72.4 and 96.4 ppm) readily located both aliphatic methoxyl groups at C-3 and C-6. The β configuration at C-3 was deduced from the J_{2,3} = 4.6 Hz and by partial synthesis from papyramine (6), of known configuration. The configuration at C-6 was also β (trans to the ethane bridge) since 2D-NOESY and nOe diff.
experiments exhibited noE between H-6 and H-12 (8%). As expected, acidic hydrolysis of 1 afforded papyramine (6), however no 1 was formed when 6 was treated with MeOH/HCl, excluding the possibility of being an artifact. Preparation of 6-O-acetyl-papyramine was required to achieve the introduction of the O-Me group at C-6, as previously observed for 6-methoxyhuphanidrine.\textsuperscript{6}

![Chemical structures](image)

O-Methylmaritidine (2) was eluted from the column with EtOAc-ethanol (9:9:0.1). Ms fragmentation suggested a 5,10b-ethanophananthidine skeleton. Its $^1$H nmr was positively compared with the reported data for maritidine,\textsuperscript{7,8} although a singlet at $\delta$ 3.82 indicated a 3-methoxy substituent as the main difference. The configuration B at C-3 was set up on the basis of the coupling constants of H-1, H-2 and H-3 ($J_{1,3} = 0$ and $J_{2,3} = 4.8$ Hz) and by comparison with those reported for maritidine and epimaritidine.\textsuperscript{9} Furthermore, the structure of 2 was confirmed by its partial synthesis from papyramine. Reaction of 6 with thionyl chloride followed by lithium aluminium hydride reduction afforded O-methylmaritidine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
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<tbody>
<tr>
<td>1</td>
<td>R = $\beta$-OMe</td>
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<tr>
<td>2</td>
<td>R = H</td>
</tr>
<tr>
<td>3</td>
<td>R = $\alpha$-$\beta$-OH</td>
</tr>
<tr>
<td>4</td>
<td>$R_1 = R_2 = \text{Me}$</td>
</tr>
<tr>
<td>5</td>
<td>$R_1 = R_2 = \text{H}$</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>$R_1 + R_2 = \text{CH}_3$</td>
</tr>
<tr>
<td>8</td>
<td>$R_1 = \text{H}, R_2 = \text{Me}$</td>
</tr>
</tbody>
</table>
The third new compound in *N. papyraceus* was 9-O-demethylhomocorine N-oxide (3) which was eluted with EtOAc-ethanol (10:2). A base peak at m/z 109 suggested a lycorine-type alkaloid. Characteristic of the $^1$H nmr was the presence of one O-Me group and a low field N-Me group in agreement with the N-oxide functionality. The 2D-COSY spectrum located the O-Me group at C-10, as in 9-O-demethylhomolycorine (5). Treatment of 5 with 36% $\text{H}_2\text{O}_2$ gave a single N-oxide which was shown to be identical to 3. The $\alpha$ configuration of the N-oxide group was deduced from the 2D-NOESY spectrum since NOE was observed between H-11 and both N-Me and O-Me (nOe diff. experiments gave a NOE between H-11/N-Me and H-11/O-Me of 2% and 4% respectively). The isolation of 3 confirms the presence of N-oxides among the Amaryllidaceae alkaloids.

Papyramine (6) was the main alkaloid found in this plant. It exist in solution as an equilibrium mixture of epimers at C-6, which was showed to be solvent dependent. The $\alpha/\beta$ ratio was: 3/2 in $\text{CDCl}_3$, 1/1 in DMSO and 2/1 in $\text{CDCl}_3$-TFA. $^1$H and $^{13}$C nmr data for each epimer are given in the experimental part.

Lycorine, homolycorine and 9-O-demethylhomolycorine were fully identified by comparison with authentic samples.

**EXPERIMENTAL**

Melting points were determined in a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Pekin-Elmer Model 241 polarimeter. The uv spectra were recorded in a Hewlett-Packard 8452A spectrophotometer, ir spectra with a Beckman Model Aculab IV spectrophotometer, nmr spectra with a Bruker WP-200 SY instrument in the solvent specified with $\text{Me}_4\text{Si}$ as internal standard, operating at 200 MHz for $^1$H and 50 MHz for $^{13}$C. Mass spectra were recorded on a HP GC/MS 5988A and high resolution mass spectra on a Kratos MS-50 instrument. The absorbent used for column chromatography was basic alumina 60 (Merck 1067) and silica gel 60 (Merck 7734).

**Isolation of alkaloids from *Narcissus papyraceus* Ker-Gawler.** Aerial parts of *N. papyraceus*, collected in Campanillas (Málaga), were dried to 2.75 kg, powdered and extracted in a soxhlet apparatus with MeOH (15 l, 9 days). The extracts were concentrated and the resulting syrup was dissolved in 3% HCl (3 l) and washed with hexane. The aqueous layer was brought up to pH 8 with concentrated NH$_4$OH and extracted with EtOAc. This extract (40 g) was finally chromatographed on basic alumina using EtOAc step gradient (0-100%) with ethanol to give compounds 1-8 in the following order of elution:

O-methylpapyramine (1) (10:0), homolycorine (6) (10:0), O-methylmaritidine (2) (9.9:0.1), lycorine (4) (9.5:0.5), 9-O-demethylhomolycorine (7) (9:1), papyramine (8) (8.5:1.5), 9-O-demethylhomolycorine N-oxide (3) (8:2) and pseudolycorine (5) (7.5:2.5).
(-) O-Methylpapyramine (1): (Yield 0.3 g). Amorphous. [α]D24 + 31° (c 0.1, MeOH). Uv (MeOH) λmax nm (log ε): 206 (4.72); 230(h) (3.98); 286 (3.67). Ir (CHCl3) νmax cm⁻¹: 1610, 1510, 1470, 1410, 1330, 1272, 1250, 1225, 1120. 1H Nmr (CDCl3) δ (ppm): 6.73 (s, H-10); 6.71 (s, H-7); 6.59 (d, H-1, J1,2 = 10 Hz); 5.90 (dd, H-2, J2,1 = 10, J2,3 = 4.6 Hz); 4.43 (s, H-6); 3.79 (s, OMe arom.); 3.77 (s, OMe arom.); 3.75 (m, H-3); 3.52 (s, OMe); 3.47 (dd, H-4a, J4a,4ax = 4.37, J4a,4ax = 13.5 Hz); 3.26 (s, OMe); 3.28 (ddd, H-12, J12,11 = 4.8, J12,11 = 9.7, Jgem = 13.5 Hz); 2.65 (ddd, H-12', J12',11 = 5.7, J12',11 = 8.3, Jgem = 13.5 Hz); 1.85 (m, H-4eq, 2H-11); 1.52 (ddd, H-4ax, J4ax,3 = 4.1, J4ax,4a = 13.5, Jgem = 13.5). 13C Nmr (CDCl3) δ (ppm): 148.2 (C-9); 147.3 (C-8); 138.1 (C-10a); 132.4 (C-1); 125.5 (C-6a); 125.3 (C-2); 112.4 (C-7); 105.0 (C-10); 96.4 (C-6); 72.4 (C-3); 57.1 (C-4a); 56.8 (OMe); 56.0 (OMe); 55.8 (OMe); 48.4 (C-12); 43.7 (C-10b); 41.1 (C-11); 28.5 (C-4). Eims m/z (%): 331 (M+, 50); 300 (40); 276 (100); 245 (60); 214 (20); 201 (10). Hrms: Calcd for C19H25N4O4; 331.1784. Found: 331.1794.

(+)-O-Methylmaritidin (2): (Yield 0.05 g). mp 240-242 °C (crystallized as HCl derivative from MeOH-EtOAc); [α]D23 + 16° (c 0.1, MeOH). Uv (MeOH) λmax nm (log ε): 236 (h) (4.23); 286 (4.30). Ir (KBr) νmax cm⁻¹: 1610, 1600, 1580, 1475, 1440, 1425, 1060. 1H Nmr (CDCl3) δ (ppm): 6.81 (s, H-10), 6.57 (s, H-7), 6.49 (d, H-1, J1,2 = 10.1 Hz), 6.08 (dd, H-2, J1,2 = 10.1, J2,3 = 4.8 Hz), 4.80 (d, H-6, Jgem = 15.8 Hz), 4.25 (d, H-6', Jgem = 15.8 Hz), 4.08 (ddd, H-12, J12,11 = 4.3, J12',11 = 12.0, Jgem = 12.6 Hz), 3.9 (ddd, H-4a, J4a,4ax = 13.5, J4a,4eq = 3.8 Hz), 3.85 (m, H-3), 3.86 (s, OMe), 3.82 (s, OMe), 3.34 (s, OMe), 3.27 (ddd, H-12, J12,11 = 7.1, J12,11 = 8.8, Jgem = 12.6 Hz), 2.95 (ddd, H-4eq, Jgem = 13.6, J4eq,4ax = 3.8, J4eq,4ax = 2 Hz), 2.37 (ddd, H-11, J11,12 = 4.3, J11,12 = 8.8, Jgem = 12.5 Hz), 2.22 (ddd, H-11', J11',12 = 7.1, J11',12 = 12.0, Jgem = 12.5 Hz), 1.73 (ddd, H-4ax, Jgem = 13.5, J4ax,4ax = 13.5, J4ax,4ax = 3.9 Hz). 13C Nmr, (CDCl3) δ (ppm): 149.0 (C-9), 148.9 (C-8), 138.0 (C-10a), 128.2 (C-1), 127.3 (C-2), 116.5 (C-6a), 110.0 (C-7), 106.2 (C-10), 70.7 (C-3), 64.8 (C-4a), 57.1 (C-6), 56.1 (3xOMe), 52.3 (C-12), 44.9 (C-10b), 40.6 (C-11), 25.6 (C-4). Eims m/z (%): 301 (M+, 42), 286 (24), 270 (22), 231 (100), 203 (26). Hrms: Calcd for C19H23N3O4; 301.1671. Found: 301.1663.

(+)-9-O-Demethylhomocorlycine N-oxide (3): (Yield 0.3 g). mp 153-154 °C (from ethanol); [α]D23 + 19° (c 0.1, MeOH). Uv (MeOH) λmax nm (log ε): 230 (4.43), 270 (4.28), 304 (3.9); (MeOH-NaOH): 208 (5.34), 248 (4.57), 274 (h) (4.30), 340 (3.82). Ir (KBr) νmax cm⁻¹: 3180, 1700, 1580, 1480, 1430, 1320, 1300, 1250, 1220, 1200, 1050. 1H Nmr (CDCl3-CD3OD) δ (ppm): 7.44 (s, H-8), 7.24 (s, H-11), 5.76 (br d, H-4, J = 2.2 Hz), 4.83 (m, H-5a), 3.96 (s, OMe), 3.87 (br d, H-11c, J11c,11b = 9.9 Hz), 3.57 (m, 2 H-2), 3.5 (dd, H-11b, J11b,11c = 9.9, J11b,5a = 2.0 Hz), 2.94 (s, N-Me), 2.88 (m, H-3), 2.72 (m, H-3'), 2.46 (m, 2 H-5). 13C Nmr (CDCl3-CD3OD) δ (ppm): 167.1 (C-7), 153.4 (C-10), 147.9 (C-9), 135.6 (C-3a), 134.9 (C-11a), 121.0 (C-4), 117.6 (C-7a), 117.1 (C-8), 112.6 (C-11), 79.3 (C-11c), 78.8 (C-5a), 70.7 (C-2), 56.8 (OMe), 56.2 (N-Me), 37.4 (C-11b), 31.4 (C-5), 26.2 (C-3). Eims m/z (%): 317 (M+ 10), 281 (10), 240 (10), 165 (5), 125 (20), 109 (100), 108 (20).
(-)-Lycorine (7): (Yield 1.3 g). mp 255 °C (from methanol); \([\alpha]_D^{23} = 68^\circ \text{ (c 0.24, EtOH)}\); lit.\(^{12}\) mp 257-258 °C; \([\alpha]_D = 78.5^\circ \text{ (EtOH)}\).

(-)-Pseudolycorine (8): (Yield 0.075 g). mp 236-237 °C (from ethanol); \([\alpha]_D^{22} = 60^\circ \text{ (c 0.04, MeOH)}\); lit.\(^{13}\) mp 237-240 °C.

(+)-Homolycorine (4): (Yield 0.14 g). mp 166-167 °C (ethyl ether); \([\alpha]_D^{23} = 86^\circ \text{ (c 0.1, MeOH)}\); lit.\(^{14}\) mp 175 °C (H\(_2\)O); \([\alpha]_D = 85^\circ \text{ (EtOH)}\).

(+)-9-O-Demethylhomolycorine (5): (Yield 3.5 g). mp 213-214 °C (from EtOAc); \([\alpha]_D^{24} = 111^\circ \text{ (c 0.1, MeOH)}\); lit.\(^{15}\) mp 213-214 °C.

Papyramine (6): (Yield 4.5 g). mp 112 °C (EtOAc - ether). \([\alpha]_D^{22} = 0^\circ \text{ (c 0.25, MeOH)}\). Uv (MeOH) \(\lambda_{\text{max}}\) nm (log \(\varepsilon\)): 206 (4.61), 238 (3.77), 282 (3.82). Ir (KBr) \(v_{\text{max}}\) cm\(^{-1}\): 3040, 3000, 1580, 1490, 1440, 1410, 1380, 1070. Eims m/z (%): 317 (M\(^+\), 60), 286 (20), 268 (10), 262 (100), 247 (40), 219 (10), 203 (20).

\(\alpha\)-Epimer:

\(^1\)H Nmr (CDCl\(_3\)) \(\delta\) (ppm): 6.99 (s, H-7), 6.76 (s, H-10), 6.62 (d, H-1, \(J_{1,2} = 10.0\) Hz), 5.97 (dd, H-2, \(J_{2,1} = 10.0\), \(J_{2,3} = 4.9\) Hz), 5.86 (s, H-6), 3.86 (s, 2 OMe), 3.85 (m, H-3), 3.7 (ddd, H-12, \(J_{12,11} = 4.6\), \(J_{12,11} = 8.2\), \(J_{\text{gem}} = 13.9\) Hz), 3.58 (dd, H-4a, \(J_{4a,4eq} = 4.1\), \(J_{4a,4ax} = 13.5\) Hz), 3.35 (s, OMe), 3.00 (ddd, H-12', \(J_{12',11} = 6.5\), \(J_{12',11} = 8.4\), \(J_{\text{gem}} = 13.8\) Hz), 2.20 (br d, H-4eq, \(J_{\text{gem}} = 13.5\) Hz), 1.96 (m, 2H-11), 1.74 (ddd, H-4ax, \(J_{4ax,4a} = 13.5\), \(J_{\text{gem}} = 13.5\) Hz). \(^{13}\)C Nmr (CDCl\(_3\)) \(\delta\) (ppm): 148.0 (C-9), 147.4 (C-8), 136.1 (C-10a), 132.2 (C-1), 127.0 (C-6a), 125.3 (C-2), 110.6 (C-7), 105.0 (C-10), 86.7 (C-6), 72.1 (C-3), 61.9 (C-4a), 55.8 (OMe), 55.6 (OMe), 44.4 (C-10b), 42.1 (C-12), 41.7 (C-11), 28.4 (C-4).

\(\beta\)-Epimer:

\(^1\)H-Nmr (CDCl\(_3\)) \(\delta\) ppm: 6.85 (s, H-7), 6.8 (s, H-10), 6.64 (d, H-1, \(J_{1,2} = 10\) Hz), 5.97 (dd, H-2, \(J_{2,1} = 10\), \(J_{2,3} = 4.9\) Hz), 5.14 (s, H-6), 3.85 (m, H-4a), 3.86 (s, 2 OMe), 3.82 (m, H-3), 3.36 (m, H-12), 3.31 (s, OMe), 2.82 (ddd, H-12', \(J_{12',11} = 6.5\), \(J_{12',11} = 8.4\), \(J_{\text{gem}} = 13.8\) Hz), 2.05 (m, H-4eq), 1.96 (m, 2H-11), 1.6 (ddd, H-4ax, \(J_{4ax,4a} = 13.8\), \(J_{\text{gem}} = 13.8\) Hz). \(^{13}\)C Nmr (CDCl\(_3\)) \(\delta\) (ppm): 148.3 (C-9), 147.4 (C-8), 137.1 (C-10a), 131.8 (C-1), 125.6 (C-2), 112.0 (C-7), 105.0 (C-10), 88.6 (C-6), 72.1 (C-3), 56.4 (C-4a), 55.8 (OMe), 55.6 (OMe), 47.5 (C-12), 43.8 (C-10b), 40.6 (C-11), 27.8 (C-4).

ACKNOWLEDGEMENTS

This work was supported by the Consejería de Educación y Ciencia de la Junta de Andalucía. We are grateful to the Spanish Ministerio de Educación y Ciencias for a FPI grant to one of us (A.I. García)
REFERENCES


Received, 30th November, 1989