Wallach, J, Kavanagh, PV, Mclaughlin, G, Morris, N, Power, JD, Elliott, SP, Mercier, MS, Lodge, D, Morris, H, Dempster, NM and Brandt, SD

Preparation and characterization of the 'research chemical' diphenidine, its pyrrolidine analogue, and their 2,2-diphenylethyl isomers

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Article

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Preparation and characterization of the ‘research chemical’ diphenidine, its pyrrolidine analogue, and their 2,2-diphenylethyl isomers


Correspondence to: Simon D. Brandt, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK. E-Mail: s.brandt@ljmu.ac.uk

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15) HPLC-DAD traces for synthesized diphenidine isomers (1) and (2) and comparison with a diphenidine sample obtained from an online test purchase
1) Representative photograph of a diphenidine product obtained online

Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum BX FTIR model using a Pike MIRacle ATR system. Data were acquired with the Spectrum v5.01 software (scan range 4000-400 cm\(^{-1}\), resolution 4 cm\(^{-1}\), 16 scans).

Note: CAS number refers to the hydrochloride salt of diphenidine.
2) ATR-IR and NMR data of 1,2-diphenylethylamine HCl & 2,2-diphenylethylamine HCl

NMR 1,2-diphenylethanamine base (m.p. HCl salt 252.5-254.0 °C):

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.11 (10H, m, Ar-H), 4.19 (1H, dd, $J = 8.8$, 4.9 Hz, C$_1$H), 3.01 (1H, dd, $J = 13.3$, 4.9 Hz, C$_2$H), 2.83 (1H, dd, $J = 13.3$, 8.8 Hz, C$_3$H), 1.4 (2H, s, NH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.64 (quat. Ar-C), 139.09 (quat. Ar-C), 129.34 (Ar-CH), 128.39 (Ar-CH), 127.04 (Ar-CH), 126.42 (Ar-CH), 126.35 (Ar-CH), 57.55 (C$_1$H), 46.59 (C$_2$H).

NMR 2,2-diphenylethylamine base (m.p. HCl salt > 260 °C):

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.14 (10H, m, Ar-H), 3.98 (1H, t, $J = 7.6$ Hz, C$_1$H), 3.31 (2H, d, $J = 7.6$ Hz, C$_2$H), 1.45 (2H, s, NH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.69 (2 x quat. Ar-C), 128.61 (4 x Ar-CH), 128.08 (4 x Ar-CH), 126.52 (2 x Ar-CH), 55.02 (C$_1$H$_2$), 47.01 (C$_2$H).
3) ATR-IR of 1-(1,2-diphenylethyl)piperidine (1,2-DEP, diphenidine) (1) and 1-(2,2-diphenylethyl)piperidine (2,2-DEP, diphenidine isomer) (2)
4) ATR-IR of 1-(1,2-diphenylethyl)pyrrolidine (1,2-DEPy) (3) and 1-(2,2-diphenylethyl)pyrrolidine (2,2-DEPy) (4)
5) ATR-IR of two diphenidine samples obtained online
6) GC-MS and EI ion trap MS spectra of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine HCl
7) ESI-triple quadrupole tandem mass spectra of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine HCl

Cone 14V
MRM COLLISION 28V 49 (0.825) Cn (Cen,2, 80.00, Ht); Cm (2:59), 1.05e7

Cone 16V
MRM COLLISION 28V 9 (0.151) Cn (Cen,2, 80.00, Ht); Cm (2:60), 1.62e5
8) LC-ESI-MS/MS chromatograms of 1,2-diphenylethanamine HCl & 2,2-
diphenylethanamine HCl

Selected ion transitions:

- m/z 198 > 72 (48 eV)
- m/z 198 > 103 (35 eV)
- m/z 198 > 166 (28 eV)
- m/z 198 > 181 (20 eV)
9) LC-ESI-MS/MS chromatograms 1-(1,2-diphenylethyl)pyrrolidine (1,2-DEPy) (3) and 1-(2,2-diphenylethyl)pyrrolidine (2,2-DEPy) (4)

Selected ion transitions:

\[ m/z \ 252 > 72 \ (48 \text{ eV}) \]
\[ m/z \ 252 > 103 \ (35 \text{ eV}) \]
\[ m/z \ 252 > 166 \ (28 \text{ eV}) \]
\[ m/z \ 252 > 181 \ (20 \text{ eV}) \]
10) GC-EI-MS traces of (1) – (4) and two diphenidine samples obtained online
11) LC-ESI-MS/MS traces of synthesized (1) and (2) and two diphenidine samples obtained online

Selected ion transitions:

- $m/z$ 266 > 72 (48 eV)
- $m/z$ 266 > 103 (35 eV)
- $m/z$ 266 > 166 (28 eV)
- $m/z$ 266 > 181 (20 eV)
12) ESI-triple quadrupole tandem mass spectra of two diphenidine samples obtained online
13) $^1$H and $^{13}$C NMR of diphenidine free base

![1.2-DEP (diphenidine) structure]

$^{13}$C NMR (100 MHz, CDCl$_3$, free base) δ 139.98 (quat. Ar-C), 139.44 (quat. Ar-C), 129.35 (2 × Ar-CH), 128.89 (2 × Ar-CH), 127.81 (2 × Ar-CH), 127.62 (2 × Ar-CH), 126.77 (Ar-CH), 125.89 (Ar-CH), 72.32 (CH, C$_3$), 51.40 (2 × CH$_3$, C$_{2}$), 39.18 (CH$_2$, C$_{2}$), 20.37 (2 × CH$_3$, C$_{2}$), 24.56 (CH$_2$, C$_{2}$).

$^1$H NMR (400 MHz, CDCl$_3$, free base) δ 7.37–7.03 (8H, m, Ar-H), 7.04–6.95 (2H, m, Ar-H), 3.58 (1H, dd, J = 9.4, 5.2 Hz, C$_2$H), 3.30 (1H, dd, J = 13.3, 5.2 Hz, C$_2$H), 2.99 (1H, dd, J = 13.4, 9.4 Hz, C$_2$H), 2.55–2.20 (4H, m, 2 × C$_2$H$_2$), 1.64–1.45 (4H, m, 2 × C$_2$H$_2$), 1.36 (2H, quintet, J = 5.9 Hz, C$_2$H$_2$).
14) Assigned $^{13}$C and $^1$H aliphatic and chemical shifts in ppm for compounds (1) – (4) and (1) HCl.

<table>
<thead>
<tr>
<th>$^{13}$C Shift</th>
<th>1,2-DEP HCl (1)</th>
<th>1,2-DEP (1)</th>
<th>2,2-DEP (2)</th>
<th>1,2-DEPy (3)</th>
<th>2,2-DEPy (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;</td>
<td>72.90</td>
<td>72.32</td>
<td>64.53</td>
<td>73.31</td>
<td>61.74</td>
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<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>36.75</td>
<td>39.18</td>
<td>48.89</td>
<td>42.96</td>
<td>50.87</td>
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<tr>
<td>C&lt;sub&gt;α&lt;/sub&gt;</td>
<td>53.39</td>
<td>51.40</td>
<td>54.85</td>
<td>53.0</td>
<td>54.55</td>
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<tr>
<td>Cβ</td>
<td>22.71</td>
<td>26.37</td>
<td>25.99</td>
<td>23.35</td>
<td>23.50</td>
</tr>
<tr>
<td>Cγ</td>
<td>22.24</td>
<td>24.66</td>
<td>24.43</td>
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</table>

Assigned $^{13}$C aliphatic chemical shifts in ppm for compounds (1) – (4) and (1) HCl.

<table>
<thead>
<tr>
<th>$^1$H Shift</th>
<th>1,2-DEP HCl (1)</th>
<th>1,2-DEP (1)</th>
<th>2,2-DEP (2)</th>
<th>1,2-DEPy (3)</th>
<th>2,2-DEPy (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;</td>
<td>4.23 d (11.6, 1H)</td>
<td>3.58, dd (9.4, 5.2, 1H)</td>
<td>2.93, d (7.3, 2H)</td>
<td>3.30, dd (9.9, 4.3, 1H)</td>
<td>3.14, d (7.4, 2H)</td>
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<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>4.04 dd (12.8, 3.1, 1H)</td>
<td>3.30, dd (13.3, 5.2, 1H)</td>
<td>4.21, t (7.3, 1H)</td>
<td>3.36, dd (13.3, 4.3, 1H)</td>
<td>4.22, t (7.1, 1H)</td>
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<tr>
<td></td>
<td>3.46 t (12.2, 1H)</td>
<td>2.99, dd (13.4, 9.4, 1H)</td>
<td>2.96, dd (13.3, 9.9, 1H)</td>
<td></td>
<td></td>
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<tr>
<td>C&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3.64 d (10.3, 1H)</td>
<td>2.55-2.29, m (4H)</td>
<td>2.39, t (5.4, 4H)</td>
<td>2.64, m (2H)</td>
<td>2.51, t (6.1, 4H)</td>
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<tr>
<td></td>
<td>3.54 d (11.6, 1H)</td>
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<td>2.45, m (2H)</td>
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<tr>
<td></td>
<td>2.68-2.39 m (2H)</td>
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</tr>
<tr>
<td>Cβ</td>
<td>2.68-2.39 m (1H)</td>
<td>1.64-1.45, m (4H)</td>
<td>1.46, quint (5.5, 4H)</td>
<td>1.77, quint (3.3, 4H)</td>
<td>1.72, quint (3.1, 4H)</td>
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<td></td>
<td>1.93-1.76 m (3H)</td>
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<tr>
<td>Cγ</td>
<td>2.31 q (13.2, 12.2, 1H)</td>
<td>1.36, quint (5.9, 2H)</td>
<td>1.37, quint (5.4, 2H)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.27 q (13.4, 12.4, 1H)</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Assigned $^1$H aliphatic chemical shifts in ppm for compounds (1) – (4) and (1) HCl. m = multiplet; d = doublet; t = triplet; q = quartet; quint = quintet.
15) HPLC-DAD traces for synthesized diphenidine isomers (1) and (2) and comparison with a diphenidine sample obtained from an online test purchase. Note: The overlapping UV maxima for traces (a) and (c) were 257 and 267 nm, respectively.