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

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


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Contents

1) Representative photograph of a diphenidine product obtained online

2) ATR-IR and NMR data of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine HCl

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 E1 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

8) LC-ESI-MS/MS chromatograms of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine HCl

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)

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

12) ESI-triple quadrupole tandem mass spectra of two diphenidine samples obtained online

13) 1H and 13C NMR of diphenidine free base and hydrochloride salt

14) Assigned 13C and 1H aliphatic and chemical shifts in ppm for compounds (1) – (4) and (1) HCl

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

Note: CAS number refers to the hydrochloride salt of diphenidine

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).
2) ATR-IR and NMR data of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine 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$_2$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 (CH$_2$).

NMR 2,2-diphenylethanamine 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$_2$H), 1.45 (2H, s, NH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.69 (2 x quat. Ar-C), 139.09 (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-diphenylethylamine HCl & 2,2-diphenylethanamine HCl
7) ESI-triple quadrupole tandem mass spectra of 1,2-diphenylethanamine HCl & 2,2-diphenylethanamine HCl
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:

\[ m/z \ 252 \to 72 \ (48 \text{ eV}) \]
\[ m/z \ 252 \to 103 \ (35 \text{ eV}) \]
\[ m/z \ 252 \to 166 \ (28 \text{ eV}) \]
\[ m/z \ 252 \to 181 \ (20 \text{ eV}) \]
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

![Diagram of 1,2-DEP (diphenidine)](1)

$^{13}$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$_2$), 125.89 (Ar-CH$_2$), 122.32 (CH, C$_2$), 51.40 (2 × CH$_3$, C$_3$), 39.18 (CH$_2$, C$_4$), 26.37 (2 × CH$_3$, C$_5$), 24.66 (CH$_3$, C$_6$).

$^1$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$_2$), 3.30 (1H, dd, J = 13.3, 5.2 Hz, C$_2$H$_2$), 2.99 (1H, dd, J = 13.4, 9.4 Hz, C$_2$H$_2$), 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>
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</thead>
<tbody>
<tr>
<td>C$_1$</td>
<td>72.90</td>
<td>72.32</td>
<td>64.53</td>
<td>73.31</td>
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<tr>
<td>C$_2$</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$_\alpha$</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>C$_\alpha$</td>
<td>48.81</td>
<td></td>
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</tr>
<tr>
<td>C$_\beta$</td>
<td>22.71</td>
<td>26.37</td>
<td>25.99</td>
<td>23.35</td>
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<td></td>
<td>22.65</td>
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<tr>
<td>C$_\gamma$</td>
<td>22.24</td>
<td>24.66</td>
<td>24.43</td>
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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$_1$</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>
</tr>
<tr>
<td>C$_2$</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>
</tr>
<tr>
<td></td>
<td>3.46 t (12.2, 1H)</td>
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</tr>
<tr>
<td>C$_\alpha$</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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<tr>
<td></td>
<td>2.68-2.39 m (2H)</td>
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<tr>
<td>C$_\beta$</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>1.93-1.76 m (3H)</td>
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<tr>
<td>C$_\gamma$</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>
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<tr>
<td></td>
<td>1.27 q (13.4, 12.4, 1H)</td>
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</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.