PYRROLO[1,2-α]THIENO[3,2-β][1,4]DIAZEPINES:
NEW 4H AND 4H-5,6-DIHYDRO DERIVATIVES

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Abstract-Synthesis of 4H and 4H-5,6-dihydro pyrrolo[1,2-α]thieno-
[3,2-β][1,4]diazepines from 3-[2-(1-pyrrolyl)thienyl]benzylamine is
described.

In the course of our work on the synthesis of pyrrolothienodiazepines (PTD), we have recently published a
three step synthesis of 4-phenyl-6-hydroxy-6H-PTD derivatives (2) from 2-aminothienyl-3-carbonitrile via 2-
(1-pyrrolyl) thien-3-ylphenylethyleneimine (1).

We describe herein the synthesis of some 4H-PTD and 4H-5,6-dihydro PTD (5, 7-8), from 3-[2-(1-
pyrrolyl)thienyl]benzylamine (3). The latter was obtained in quantitative yield by hydrogenation of the imine (1)
with sodium borohydride in refluxing methanol. Then, the treatment of 3 with acetic anhydride in acetic acid or
with chloroacetyl chloride or ethyl oxalyl chloride in THF gave the corresponding amides (4a-c). Cyclization of
the diazepine ring was then achieved by refluxing phosphoryl chloride to lead 4H-PTD (5a-c). The unsubstituted
4H-PTD (5d) on the 6 position was obtained by treatment of a solution of ethyl diazepinecarboxylate (5c) with
aqueous 2N sodium hydroxide. The reaction did not allow the isolation of the carboxylic acid which was
decarboxylated in the conditions of this reaction.

On the other hand, treatment of the benzylamine (3) with benzaldehyde substituted or not gave the Schiff bases
(6a-e). The ring closure of these latter into 4H-5,6-dihydro PTD.HCl (7a-e) was realized in mild conditions.
The best results were obtained when an isopropanolic solution of 6a-e was treated with 10 equivalents of 12N
hydrochloric acid at room temperature to permit the precipitation of the diazepinium chlorides (7a-e) in about
60% yield. Further, when an ethanolic solution of 3 was treated with 20 equivalents of acetone in presence of
aqueous hydrochloric acid (20 equivalents) at reflux, it gave the dimethyl-4H-5,6-dihydro PTD (8).
Table 1 Spectroscopic and microanalytical data of compounds (3-8)

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>mp or bp(°C) (Solv of cryst)</th>
<th>IR(KBr) ν&lt;sub&gt;max&lt;/sub&gt;(cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H Nmr (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ ppm/TMS J (Hz)</th>
<th>Molecular Formula</th>
<th>Elemental analysis Calcd (%)(Found)</th>
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<tbody>
<tr>
<td>3</td>
<td>90</td>
<td>200/5 mmHg</td>
<td>3350/3280 (NH&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>7.28 (m, H&lt;sup&gt;+&lt;/sup&gt;-Phenyl) 7.06 (d, J=5 86, H-5) 7.00 (d, J=5 86, H-4) 6.79 (s, H-2'5') 6.29 (s, H-3'4') 5.09 (s, CH) 1.80 (s, NH&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>C&lt;sub&gt;15&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;S</td>
<td>C 70 83 5 H 55 N 11 01</td>
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<tr>
<td>4a</td>
<td>95</td>
<td>138 (ether) 1640 (CO)</td>
<td>3220 (NH) 1640 (CO)</td>
<td>8.81 (d, J=8 30, NH) 7.41 (d, J=5 86, H-5) 7.27 (m, H-3'4'5'') 7.09 (d, J=7 33, H-2'6'6) 7.00 (d, J=5 86, H-4) 6.93 (s, H-2'5') 6.25 (s, H-3'4') 6.05 (d, J=8 30, CH) 1.90 (s, CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>C 68 89 5 H 44 9 N 45</td>
</tr>
<tr>
<td>4b</td>
<td>77</td>
<td>50 (ether) 1640 (CO)</td>
<td>3210 (NH) 1640 (CO)</td>
<td>9.19 (d, J=8 30, NH) 7.44 (d, J=5 86, H-5) 7.32 (m, H-3'4'5'') 7.12 (d, J=7 33, H-2'6'6') 7.00 (d, J=5 86, H-4) 6.92 (s, H-2'5') 6.26 (s, H-3'4') 5.99 (d, J=8 30, CH) 4.13 (s, CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;OClS</td>
<td>C 61 72 4 H 57 9 N 8 47</td>
</tr>
<tr>
<td>4c</td>
<td>74</td>
<td>130 (ether) 1670 (CO)</td>
<td>3260 (NH) 1730 (CO) 1670 (CO)</td>
<td>9.82 (d, J=8 30, NH) 7.44 (d, J=5 86, H-5) 7.30 (m, H-3'4'5'') 7.17 (m, H-2'6'6') 7.17 (m, H-4) 6.91 (s, H-2'5') 6.25 (s, H-3'4') 6.07 (d, J=8 30, CH) 4.24 (q, J=6 84, CH&lt;sub&gt;2&lt;/sub&gt;) 1.27 (t, J=6 84 CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S</td>
<td>C 64 39 5 H 12 7 N 90</td>
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<tr>
<td>5a</td>
<td>53</td>
<td>200/1 mmHg 1620 (C=N)</td>
<td>7.58 (d, J=7 81, H-2'6') 7.46 (s, H-9) 7.37 (m, H-3'4'5'') 7.13 (d, J=5 37, H-2) 6.89 (d, J=3 91, H-7) 6.46 (t, J=3 91, H-8) 6.13 (d, J=5 37 H-3) 5.23 (s, CH) 2.33 (s, CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;S</td>
<td>C 73 35 5 H 07 10 05</td>
<td></td>
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<tr>
<td>5b</td>
<td>40</td>
<td>200/1 mmHg 1600 (C=N)</td>
<td>7.60 (d, J=6 83, H-2'6') 7.41 (m, H-3'4'5'') 7.39 (s, H-9) 7.20 (d, J=5 37 H-2) 6.95 (d, J=3 91 H-7)</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CIS</td>
<td>C 65 28 4 H 16 8 N 96</td>
<td></td>
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</tbody>
</table>
$\begin{align*}
5c & \quad 40 \quad 205/1 \text{ mmHg} \quad 1720 (C=O) \quad 1600 (C=N) \\
& \quad \begin{array}{l}
6.51 (t, J=3.91, H-8) \\
6.15 (d, J=5.37, H-3) \\
5.35 (s, CH) \\
4.84 (d, J=12.21, CH_2) \\
4.51 (d, J=12.21, CH_2)
\end{array} \\
& \quad \begin{array}{l}
7.57 (d, J=6.83, H-2') \\
7.43 (m, H-3') \\
7.41 (s, H-9) \\
7.34 (d, J=5.37, H-2) \\
6.95 (d, J=3.91, H-7) \\
6.52 (t, J=3.91, H-8) \\
6.19 (d, J=5.37, H-3) \\
5.49 (s, CH) \\
4.84 (q, J=6.84, CH_2) \\
2.87 (t, J=6.84, CH_3)
\end{array} \\
& \quad \begin{array}{l}
C_{19}H_{16}N_2O_2S \\
67.85 \ 4.76 \ 8.33 \\
(67.75 \ 4.70 \ 8.25)
\end{array}
\end{align*}$

$\begin{align*}
5d & \quad 50 \quad 202/1 \text{ mmHg} \quad 1600 (C=N) \\
& \quad \begin{array}{l}
7.43 (m, H^-\text{Phenyl-H-2, H-6}) \\
7.18 (m, H-9) \\
6.87 (d, J=5.86, H-3) \\
6.35 (d, J=3.91, H-8) \\
6.17 (t, J=3.91, H-7) \\
4.58 (s, H-4)
\end{array} \\
& \quad \begin{array}{l}
C_{16}H_{12}N_2S \\
72.72 \ 4.54 \ 10.60 \\
(72.75 \ 4.50 \ 10.55)
\end{array}
\end{align*}$

$\begin{align*}
6a & \quad 74 \quad 138 \quad (\text{isopropanol}) \quad 1665 (C=N) \\
& \quad \begin{array}{l}
8.31 (s, CH) \\
7.79 (d, J=5.37, H-2''6'') \\
7.43 (m, H-3''4''5'') \\
7.42 (d, J=5.86, H-5) \\
7.29 (s, H^-\text{Phenyl}) \\
7.10 (d, J=5.86, H-4) \\
6.93 (s, H-2'5') \\
6.27 (s, H-3'4') \\
5.49 (s, CH)
\end{array} \\
& \quad \begin{array}{l}
C_{22}H_{18}N_2S \\
77.16 \ 5.30 \ 8.18 \\
(77.01 \ 5.27 \ 8.21)
\end{array}
\end{align*}$

$\begin{align*}
6b & \quad 57 \quad 140 \quad (\text{isopropanol}) \quad 1630 (C=N) \\
& \quad \begin{array}{l}
8.32 (s, CH) \\
7.82 (d, J=5.37, H-3''5'') \\
7.52 (d, J=5.37, H-2''6'') \\
7.43 (d, J=5.86, H-5) \\
7.27 (s, H^-\text{Phenyl}) \\
7.10 (d, J=5.86, H-4) \\
6.94 (s, H-2'5') \\
6.28 (s, H-3'4') \\
5.50 (s, CH)
\end{array} \\
& \quad \begin{array}{l}
C_{22}H_{17}N_2ClS \\
70.11 \ 4.55 \ 8.17 \\
(70.37 \ 4.25 \ 8.20)
\end{array}
\end{align*}$

$\begin{align*}
6c & \quad 72 \quad 180 \quad (\text{isopropanol}) \quad 1620 (C=N) \\
& \quad \begin{array}{l}
8.47 (s, CH) \\
8.30 (d, J=5.37, H-2''6'') \\
8.05 (d, J=5.37, H-3''5'') \\
7.45 (d, J=5.86, H-5) \\
7.29 (s, H^-\text{Phenyl}) \\
7.11 (d, J=5.86, H-4) \\
6.95 (s, H-2'5') \\
6.28 (s, H-3'4') \\
5.58 (s, CH)
\end{array} \\
& \quad \begin{array}{l}
C_{22}H_{17}N_2O_2S \\
68.2 \ 4.42 \ 10.85 \\
(68.77 \ 4.35 \ 10.62)
\end{array}
\end{align*}$

$\begin{align*}
6d & \quad 75 \quad 94 \quad (\text{isopropanol}) \quad 1710 (C=N) \\
& \quad \begin{array}{l}
8.57 (s, CH) \\
8.07 (d, J=8.79, H-5'') \\
7.68 (s, H-3'') \\
7.50 (d, J=8.79, H-6'') \\
7.42 (d, J=5.86, H-5) \\
7.30 (s, H^-\text{Phenyl}) \\
7.04 (d, J=5.86, H-4)
\end{array} \\
& \quad \begin{array}{l}
C_{22}H_{16}N_2Cl_2S \\
64.24 \ 3.92 \ 6.81 \\
(64.30 \ 3.94 \ 6.78)
\end{array}
\end{align*}$
<table>
<thead>
<tr>
<th>Compound</th>
<th>Mass</th>
<th>Peaks</th>
<th>Solvent</th>
<th>Chemical Shifts</th>
<th>Formula</th>
<th>Molecular Weight</th>
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<tr>
<td>6e</td>
<td>84</td>
<td>95</td>
<td>isopropanol</td>
<td>1680 (C=N)</td>
<td>8.56 (s, CH)</td>
<td>C$<em>{22}$H$</em>{16}$N$_3$O$_2$CIS</td>
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<td>8.17 (s, H-3&quot;)</td>
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<td>8.05 (d, J= 8.79, H-5&quot;)</td>
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<td>7.88 (d, J= 8.79, H-6&quot;)</td>
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<td>7.43 (d, J=5 86, H-5)</td>
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<td>7.28 (s, H-&quot;Phenyl&quot;)</td>
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<td>7.04 (d, J=5 86, H-4)</td>
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<td>6.99 (s, H-2&quot;)</td>
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<td>6.28 (s, H-3&quot;)</td>
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<td>5.56 (s, CH)</td>
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<td>7a</td>
<td>54</td>
<td>228</td>
<td>isopropanol</td>
<td>2900/2480 (NH$_2^+$)</td>
<td>10.78 (m, NH$_2^+$)</td>
<td>C$<em>{22}$H$</em>{19}$N$_2$CIS</td>
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<td>10.51 (m, NH$_2$)</td>
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<td>7.46 (m, H-Phenyl&quot;, H-Phenyl&quot;)</td>
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<td>7.38 (s, H-9)</td>
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<td>7.29 (d, J= 5.86, H-2)</td>
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<td>6.41 (d, J=5.86, H-3)</td>
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<td>6.34 (t, J=3 42, H-8)</td>
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<td>5.91 (s, H-7)</td>
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<td>5.54 (m, H-4)</td>
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<td>5.37 (m, H-6)</td>
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<td>7b</td>
<td>51</td>
<td>229</td>
<td>methanol</td>
<td>2900/2500 (NH$_2^+$)</td>
<td>10.83 (m, NH$_2^+$)</td>
<td>C$<em>{22}$H$</em>{18}$N$_2$Cl$_2$S</td>
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<td>10.63 (m, NH$_2$)</td>
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<td>7.69 (m, H-3&quot;5&quot; and H-2'6')</td>
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<td>7.52 (m, H-2&quot;6&quot; and H-3'4'5&quot;)</td>
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<td>7.36 (s, H-9)</td>
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<td>7.34 (d, J= 5.86, H-2)</td>
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<td>6.42 (d, J=5.86, H-3)</td>
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<td>6.35 (s, H-8)</td>
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<td>5.96 (s, H-7)</td>
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<td>5.41 (m, H-4)</td>
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<td>5.66 (m, H-6)</td>
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<td>7c</td>
<td>62</td>
<td>244</td>
<td>methanol</td>
<td>3000/2400 (NH$_2^+$)</td>
<td>11.04 (m, NH$_2^+$)</td>
<td>C$<em>{22}$H$</em>{18}$N$_3$O$_2$CIS</td>
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<td>8.31 (d, J= 8.3, H-3&quot;5&quot;)</td>
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<td>7.98 (d, J= 8.3, H-2'6')</td>
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<td>7.70 (d, J= 8.79, H-2'6')</td>
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<td>7.44 (m, H-3'4'5')</td>
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<td>7.44 (s, H-9)</td>
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<td>7.33 (d, J= 5.86, H-2)</td>
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<td>6.42 (d, J=5.86, H-3)</td>
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<td>6.35 (s, H-8)</td>
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<td>5.91 (s, H-7)</td>
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<td>5.42 (m, H-4)</td>
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<td>5.81 (m, H-6)</td>
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<td>7d</td>
<td>72</td>
<td>195</td>
<td>ethanol</td>
<td>3040/2580 (NH$_2^+$)</td>
<td>10.95 (m, NH$_2^+$)</td>
<td>C$<em>{22}$H$</em>{17}$N$_2$Cl$_3$S</td>
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<td>8.13 (d, J= 8.30, H-5&quot;)</td>
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<td>7.72 (m, H-3&quot;6&quot; and H-2'6')</td>
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<td>7.48 (m, H-3'4'5', H-2, H-9)</td>
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<td>6.53 (d, J=5 86, H-3)</td>
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<td>6.30 (s, H-8)</td>
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<td>5.66 (s, H-7, H-6)</td>
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<td>5.56 (s, H-4)</td>
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</table>
EXPERIMENTAL

All melting points were measured using a Kofler bank apparatus and were uncorrected. Infrared spectra were recorded on a Philips PU 9716 spectrophotometer. $^1$H Nmr spectra were taken on a JEOL JNM-FX 200 in DMSO-d$_6$ solution using TMS as an internal standard.

3-[2-(1-pyrrolyl)]thienyl]benzylamine (3)
To a solution of phenyl-3-[2-(1-pyrrolyl)]thienyl]methyleneimine (1) (2 g, 7.93 mmol) in methanol (100 ml), was added NaBH$_4$ (1.2 g, 31 mmol, 4 equivalents) by small portions. The mixture was heated under reflux for 3 h and the methanol was evaporated in vacuo. The residue was cooled, triturated with water and extracted with ether. The organic layer was dried (MgSO$_4$) and the ether was evaporated in vacuo to give 3 (1.81 g, 90%)

N-benzyl-3-[2-(1-pyrrolyl)]thienyl]acetamide (4a)
The benzylamine (3) (2 g, 7.87 mmol) in a mixture of acetic acid (5 ml, 0.087 mol) and acetic anhydride (5 ml, 0.053 mol) was stirred at room temperature for 6 h. The reaction mixture was then poured on ice and the precipitate was filtered, washed with petroleum ether, dried and recrystallized from ether to give 4a (2.21 g, 95%).

General procedure for the synthesis of amides (4b-c)
The benzylamine (3) (2 g, 7.87 mmol) in THF (30 ml) solution was treated with an excess of triethylamine (14.17 mmol, 1.43 g, 1.8 equivalents) and the corresponding acid chlorides (11.08 mmol, 1.5 equivalents). The reaction mixture was stirred at room temperature for 3 h. Then, it was poured on water, stirred for 2 h and extracted with ether. The organic layer was washed with saturated NaHCO$_3$, dried (MgSO$_4$) and the ether was evaporated in vacuo to give 4b (2 g, 77%), 4c (2.06 g, 74%).
General procedure for the synthesis of 4H-PTD (5a-c)
To the amides (4a) (1 g, 3.37 mmol) or (4b) (1 g, 3.02 mmol) or (4c) (1 g, 2.82 mmol) was added phosphoryl chloride (20 ml, 0.2 mol) and the mixture was heated at reflux for 30 min (4a), 10 min (4b) or 60 min (4c). Then the excess of POC\textsubscript{3} was evaporated in vacuo. After cooling, the residue was triturated with 6N NaOH and extracted with ethyl acetate. The organic layer was washed with water, and with saturated NaHCO\textsubscript{3}, dried (MgSO\textsubscript{4}) and the ethyl acetate was evaporated in vacuo to give 5a (0.5 g, 53%), 5b (0.32 g, 40%), 5c (0.38 g, 40%).

4-Phenyl-4H-pyrrolo[1,2-α]thieno[3,2-f][1,4]diazepine (5d)
5c (1 g, 2.97 mmol) in 10 ml of 6N sodium hydroxide (60 mmol) was heated at reflux for 1 h. Then, water was added and the mixture was extracted with ether. The organic layer was dried (MgSO\textsubscript{4}) and the ether was evaporated in vacuo to give 5d (0.39 g, 50%).

General procedure for the synthesis of Schiff bases (6a-e)
To benzylamine (3) (1 g, 3.93 mmol) in ethanol (25 ml) was added the corresponding aromatic aldehyde (3.93 mmol, 1 equivalent). The mixture was heated at reflux for 30 min. After cooling, the precipitate was filtered, washed with ether and recrystallized to give 6a (1 g, 74%), 6b (0.84 g, 57%), 6c (1.09 g, 72%), 6d (1.21 g, 75%), 6e (1.40 g, 84%).

General procedure for the synthesis of 4H-5,6-dihydro-PTD (7a-e)
To N-arylidene-3-[2-(1-pyrrolyl)thienyl]benzylamine (2.25 mmol) in 2-propanol (15 ml), was added dropwise aqueous 12N hydrochloric acid (1 ml, 0.012 mol). The mixture was stirred at room temperature for 2 h. The precipitate was filtered, washed with anhydrous ether and recrystallized to give 7a (0.46 g, 54%), 7b (0.49 g, 51%), 7c (0.59 g, 62%), 7d (0.72 g, 72%), 7e (0.76 g, 74%).

6-Dimethyl-4-phenyl-5,6-dihydro-4H-pyrrolo[1,2-α]thieno[3,2-f][1,4]diazepinium hydrochloride (8)
To benzylamine (3) (1 g, 3.93 mmol) in ethanol (25 ml) was added acetone (5.9 ml, 0.078 mol) and 12N hydrochloric acid (2.5 ml, 0.078 mol). The mixture was heated at reflux for 10 min and the mixture was concentrated to half volume. After cooling, the precipitate was filtered, washed with anhydrous ether and recrystallized to give 8 (0.6 g, 46%).
REFERENCES


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