Title: Synthesis of Tris[(2-pyridyl)methyl]amine  June 10, 2003
J. M. McCormick

Statement of Purpose: Tris[(2-pyridyl)methyl]amine, TPA, will be synthesized in order to explore its coordination chemistry with Pb²⁺.

Background:

\[
\text{2-(aminomethyl)pyridine} + 2 \text{2-picolychloride hydrochloride} \xrightarrow{\text{NaOH}} \text{tris[(2-pyridyl)methyl]amine (TPA)}
\]

Physical Properties:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molar Mass (g/mole)</th>
<th>Melting Point (°C)</th>
<th>Density (g/cm³)</th>
<th>Hazards</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-(aminomethyl)pyridine</td>
<td>108.14</td>
<td></td>
<td>1.049</td>
<td>corrosive, irritant, hydroscopic</td>
</tr>
<tr>
<td>2-picolychloride hydrochloride</td>
<td>169.03</td>
<td>125-129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPA</td>
<td>290.36</td>
<td>73-77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>water</td>
<td>18.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sodium hydroxide</td>
<td>40.00</td>
<td></td>
<td></td>
<td>corrosive, toxic</td>
</tr>
<tr>
<td>methylene chloride</td>
<td>84.93</td>
<td></td>
<td></td>
<td>toxic, irritant</td>
</tr>
<tr>
<td>hexane</td>
<td>86.18</td>
<td></td>
<td></td>
<td>flammable, irritant</td>
</tr>
<tr>
<td>sodium sulfate (anhydrous)</td>
<td>142.04</td>
<td></td>
<td></td>
<td>irritant, hygroscopic</td>
</tr>
<tr>
<td>deuterochloroform</td>
<td>120.39</td>
<td></td>
<td></td>
<td>highly toxic, carcinogen</td>
</tr>
</tbody>
</table>
Synthesis of Tris[(2-pyridyl)methyl]amine

Procedural Outline:

- In a 200-mL round bottom flask place 25.6 g (160 mmol) 2-picolyl chloride hydrochloride in 40 mL distilled water.
- Add 8 mL (80 mmol) 2-(aminomethyl)pyridine.
- Slowly add 31.0 mL at a 10 M NaOH solution (aqueous) dropwise over 2 hr.
- Heat flask at 70°C for 30 min.
- Cool red reaction mixture and extract 3 x 150 mL CHCl₃.
- Combine extracts and dry over Na₂SO₄.
- Remove CHCl₃ by rotary evaporation.
- Vacuum distill (200°C, 0.01 mm Hg) to obtain product (yield: 11.3g, 50%).

- Change to 10g in 2 mL H₂O
- Change to 3 mL
- Change to 5.03 mL NaOH in 12 mL H₂O
- Change to 20 min.
- Substitute 1 mL CH₂Cl₂ for CHCl₃ and change to 4 x 50 mL
- Dissolve residue in minimal amount of hot hexane.
- Filter hot solution and let stand (crystals should form).
- Recover crystals by vacuum filtration.
- Recrystallize from hexane.

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Results:
To a solution of 10.11g 2-picolyl chloride hydrochloride (Acror, Lot # A016040301) in 20 mL distilled H2O was added 3.20 mL 2-(aminomethyl)pyridine (Acror, Lot # A013625401) with stirring. To this mixture was added a solution of 5.03g NaOH (Fisher, Lot # 996529 99531 2 lot # 6/19/03) in 12 mL H2O in a slow, dropwise manner using an addition funnel. The addition was regulated so that it took approximately 1.5 hr to add all of the NaOH solution. During the addition the initially yellow reaction mixture turned deep red and droplets of an oily (red?) substance separated. After all of the NaOH solution had been added, the reaction mixture was heated to 70°C and held there for 20 min. The cooled reaction mixture was extracted four times with 50 mL CH2Cl2 (Fisher, Lot # 010927). The combined extracts were dried over Na2SO4 (Aldrich, Lot # 04218 R2) and gravity filtered to remove the Na2SO4. The CH2Cl2 was removed by rotary evaporation to give a red oil that solidified upon standing. The red solid was dissolved in the minimal amount of hot hexane. The yellow solution was decanted from a small amount of a red oil that did not dissolve, and filtered hot. Some oil was accidently poured into the filter paper, but it adhered to the paper and did not pass through. No solids were observed on the filter paper. Upon cooling light-yellow crystals formed from the red-orange solution. These were collected by vacuum filtration and dried briefly in air. Crude product was recrystallized  

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From hot hexane and allowed to air dry over the weekend. Final yield was 2.08 g (24%) of light-yellow crystals. The melting point of the product was determined to be 85°C, sharp (uncorrected) using a Mel-Temp (no serial number evident). NMR spectra of the product were recorded using a Bruker Avance 400 MHz spectrometer (serial # 810406499). All manipulations of the spectra were performed using Bruker XWINNMR version 3.1 running on a Silicon Graphics O2 workstation.

'H NMR of TPA (Jun16-2003, exp0, CDCl3 solvent)

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Current Data Parameters
NAME: JMcMick
LOC: [location] 3

T2 - Processing parameters
SI: 30000
F1: 250000 Hz
DE: 0.30 deg
DG: 1.00 Hz

T1 - Analysis parameters
NAME: JMcMick
LOC: [location] 3

T2 - Processing parameters
SI: 30000
F1: 250000 Hz
DE: 0.30 deg
DG: 1.00 Hz

1H NMR of TPA showing peak positions in Hz. JMcMick June 16, 2003.
**Synthesis of Tri(2-pyridyl)methylamine**

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Multiplicity</th>
<th># 'H</th>
<th>J (Hz)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.89</td>
<td>singlet</td>
<td>2</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>7.14</td>
<td>triplet of doublets</td>
<td>1</td>
<td>1.3, 6.1</td>
<td>D</td>
</tr>
<tr>
<td>7.58</td>
<td>doublet</td>
<td>1</td>
<td>7.8</td>
<td>B</td>
</tr>
<tr>
<td>7.63</td>
<td>triplet of doublets</td>
<td>1</td>
<td>1.8, 7.6</td>
<td>C</td>
</tr>
<tr>
<td>8.15</td>
<td>doublet of quartets</td>
<td>1</td>
<td>0.9, 4.9</td>
<td>E</td>
</tr>
</tbody>
</table>

Peak at 3.89 ppm clearly does not couple to any other 'H, and so must be A, as confirmed by integration. Peak at 8.15 ppm is the most distant of the peaks in the aromatic region, so it is most likely E. The value of J for this resonance and the one at 7.14 ppm suggests the 'H are adjacent to each other. Thus, the 7.14 ppm resonance is assigned as 'H D. The peak at 7.58 ppm is assigned as B as it shows the cleanest splitting (only one strong coupling to C is expected). The peak at 7.63 ppm is coupled to C (J ≈ 1.5 Hz) and B (J ≈ 7.7 Hz), which is consistent with it being 'H C. There appears to be higher order effects present, and perhaps coupling to 15N in 'H E.
**Synthesis of Tris[(2-pyrindyl)methyl]amine**

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.13</td>
<td>A</td>
</tr>
<tr>
<td>122.01</td>
<td>B or C</td>
</tr>
<tr>
<td>122.97</td>
<td>C or D</td>
</tr>
<tr>
<td>136.06</td>
<td>F</td>
</tr>
<tr>
<td>159.25</td>
<td>B</td>
</tr>
</tbody>
</table>

From DEPT-135, peak at 60.13 ppm is negative and must be carbon (A). The peak at 159.25 ppm does not appear in the DEPT, and so is carbon (B). The remaining peaks are the other pyridine carbons. The peaks at ~122 ppm can be accounted for by carbons (C) and (D), as the are expected to be very similar. This leaves the 136.06 ppm peak as arising from carbon (F).
Synthesis of Tris[2-(pyridyl)methyl]amine

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IR Spectrum of TPA (32 scans, 1 cm⁻¹ resolution, background collected before scan, automatic baseline correction and scaling).

The IR spectrum was obtained on a Nicolet 210 FTIR Spectrometer (serial number AAC9100467). Peaks to left of 3000 cm⁻¹ indicate aromatic C-H, and peaks to right of 3000 cm⁻¹ are consistent with aliphatic C-H. Peaks in 1500-1700 cm⁻¹ region could be aromatic C=C. Broad peak at ~3600 cm⁻¹ could be either N-H (unlikely) or an artifact of the background correction (from H₂O).

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Calculations:

\[
\begin{align*}
\text{Volume} & \quad 3.20 \text{ mL} \\
\text{Density} & \quad 1.049 \text{ g/mL} \\
\text{Mass} & \quad 3.36 \text{ g} \\
\text{Molar Mass} & \quad 108.14 \text{ g/mol} \\
\text{Moles} & \quad 0.0310 \text{ mole} \\
\end{align*}
\]

\[
3.20 \text{ mL} \left(\frac{1.049 \text{ g}}{\text{mL}}\right) = 3.36 \text{ g}
\]

\[
3.36 \text{ g} \left(\frac{1 \text{ mole}}{108.14 \text{ g}}\right) = 0.0310 \text{ mole}
\]

\[
10.11 \text{ g} \left(\frac{1 \text{ mole}}{164.03 \text{ g}}\right) = 0.0612 \text{ mole}
\]

\[
0.0612 \text{ mole} \left(\frac{1 \text{ mole TPA}}{2 \text{ mole HCl}}\right) = 0.0306 \text{ mole HCl}
\]

HCl is the limiting reagent.

\[
0.0612 \text{ mole} \left(\frac{1 \text{ mole TPA}}{2 \text{ mole HCl}}\right) \left(\frac{290.36 \text{ g}}{1 \text{ mole TPA}}\right) = 8.98 \text{ g}
\]

\[
\% \text{ yield} = \frac{2.08 \text{ g}}{8.98 \text{ g}} \times 100 = 23.2\%
\]

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Discussion of Conclusions and Error Analysis:
The reported melting point is lower and has a broader range (73-77°C) than what was found (85°C, sharp) using the modified procedure. This indicates higher product purity was obtained with new method. The reported ¹H NMR consists of peaks at 3.9 ppm (singlet) and between 7.1 and 8.5 ppm (multiplets), which matches what was found here (singlet at 3.59 ppm, multiplets at 7.14, 7.58, 7.63 and 8.15 ppm).
The ¹³C NMR has not been reported, but the peaks at 60.13 ppm (C=CH), 127.01 (pyridine C=N), 127.97 (pyridine C=N) 136.06 ppm (pyridine C=H) and 154.25 (pyridine C=O) are consistent with the structure of TPA. The IR spectrum of TPA was not reported, but the presence of aromatic and aliphatic C-H is consistent with TPA. The 1500 - 1700 cm⁻¹ is similar to that of pyridine (Dolphin, D. and Wick, A. "Tabulation of Infrared Spectral Data." Wiley-Interscience; New York, 1977, p. 537). Taken together it appears that the target molecule was synthesized with high purity.

The 24% yield was disappointing, given the reported yield was 51%, albeit for a material of lower purity. The yield could be increased, perhaps, by minimizing the side reaction that leads to the red oil. Whether this a light-induced reaction or a redox reaction with the atmosphere deserves further investigation.

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Synthesis of Tris[2-pyridyl]methy]amine

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The synthetic procedure apparently gives the desired product in high purity, but low yield is a problem. Further investigations on optimizing the reaction conditions is necessary, but for the desired purpose of this synthesis, probably unnecessary.

Summary of Results:

Properties of TPA

Melting Point: 85°C, sharp (uncorrected)
Physical appearance: light yellow crystals

NMR (CDCl₃), all values in ppm

\[ ^1H: 3.89 (s), 2H; 7.14 (m), 1H; 7.58 (m), 1H; 7.63 (m), 1H; 8.15 (m), 1H \]

\[ ^13C: 60.13, 122.01, 122.97, 136.06, 159.25 \]

Yield: 24%