A Convenient Synthesis of 2,2',6,6'-Tetramethyl-4,4'-bipyridine and Its Oxidation to 2,2',6,6'-Tetracarboxy-4,4'-bipyridine

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By reaction of 2,6-dimethylpyridine (1b) with sodium the tetrahydro-4,4'-bipyridine bis-sodium salt 2b is formed. Of different dehydrogenation reagents tested, only sulfur dioxide affords the title compound 3b, in 49% overall yield. By oxidation of 3b with chromium trioxide, 2,2',6,6'-tetracarboxy-4,4'-bipyridine (3c, 70%) is produced, a valuable precursor for several 2,2',6,6'-tetrasubstituted 4,4'-bipyridines, e.g., the corresponding acid chloride 3d and the carboxylic esters 3e and 3f.

Crown ethers containing a pyridine moiety linked in the 2,6-position have proven to be valuable complexing agents for cations with specific selectivities. Corresponding bis-crown ethers derived from 2,2',6,6'-tetracarboxy-4,4'-bipyridine are reversible redox systems, for which complexation constants for several cations increase dramatically on reduction.

For these new ligands, 2,2',6,6'-tetramethyl-4,4'-bipyridine (3b) serves as an indispensable starting material, for which we herewith describe a convenient synthesis.

The various but tedious laboratory syntheses for 4,4'-bipyridine (3a) have become obsolete, now that 3a is produced on a technical scale as a precursor for herbicides. For substituted derivatives, however, e.g., 2,2',6,6'-tetramethyl-4,4'-bipyridine (3b), one still has to rely on a procedure from 1899 (low yields given), which has been somewhat modified in a patent (no yields given).

All practical methods for the preparation of (tetrasubstituted) bipyridines start with the reductive coupling of the respective pyridines, i.e. of 1a and 1b, with sodium to form the tetrahydro-4,4'-bipyridine intermediates 2a and 2b.

The crucial final step in all these procedures is the formal abstraction of two hydride ions from 2. With most of the oxidizing agents tested, pyridines 1 are recovered as the principal products (probably via reversible single electron-transfer), instead of the expected bipyridines 3. Air oxidation of 2a affords 3a in acceptable yields only under "carefully controlled conditions." In our hands only 1b could be identified when the reduction mixture containing 2b (vide infra) was treated with air. Dehydrogenation of 2b with p-benzoquinone or dibenzoyl...
dimide showed no success either, although the \( N,N' \)-diacetyl derivatives of \( 2a \) are reported to form \( 3a \) in high yield with these reagents.\(^7\)

These difficulties could be overcome when \( 1b \) was reductively dimerized to \( 2b \) in tetrahydrofuran, and the crude \( 2b \) was treated with sulfur dioxide. Thus \( 3b \) was obtained in 49% overall yield.

Sulfur dioxide has occasionally been employed as a dehydrogenating agent for \( 1,4 \)-dihydropyridines\(^8\) and \( N,N' \)-dialkyl-4,4’-tetrahydrobipyridines.\(^9\) Up to now, one can only speculate on the reaction course. Most probably sulfur dioxide is reduced to sulfoxylate anion either by direct hydride ion transfer from \( 2b \) or through intermediates. The sulfoxylate anion is known to disproportionate into thiosulfate so that the overall reaction may be described by the equation:

\[
2b + 2\text{SO}_2 \rightarrow 3b + 2\text{NaHSO}_3 \rightarrow \text{Na}_2\text{S}_2\text{O}_3 + \text{H}_2\text{O}.
\]

Intermediate \( 4 \) is claimed to be the precursor of the corresponding \( N \)-sulfonic acid (no physical or analytic data given), obtained by subsequent treatment with hydrogen peroxide.\(^11\)

Dehydrogenation of 1,4-cyclohexadiene to benzene by \( \text{SO}_2 \) occurs via an ene reaction.\(^12\) If one accepts this reaction as a suitable model for the transformation \( 2b \rightarrow 3b \) the intermediate \( 5 \) should be taken into account.

In 1898 the tetramethyl compound \( 3b \) had been transformed into the tetracarboxylic acid \( 3e \) with \( \text{KMnO}_4 \) in a very tedious and inefficient reaction.\(^9\) Likewise, a low yield (30%) of 2-carboxy-5-nitropyridine was reported for \( \text{KMnO}_4 \) oxidation of 2-methyl-5-nitropyridine; with \( \text{CrO}_3 / \text{H}_2\text{SO}_4 \) this carboxylic acid was obtained in 80% yield.\(^13\) Hence the latter method was applied to the case of \( 3b \), and indeed gave 2,2,6,6-tetraacetyl-4,4’-bipyridine (\( 3e \)) in 70% yield.

Acid \( 3e \) is a valuable starting material for other 2,2,6,6-tetrasubstituted 4,4’-bipyridines,\(^1\) e.g., the acid chloride \( 3d \), and the esters \( 3f \), f, which were prepared by standard methods.\(^1\)

**Table. Physical and Spectroscopic Data of Products \( 3b \) and \( 3e-f \)**

<table>
<thead>
<tr>
<th>Product</th>
<th>mp(^a) (°C)</th>
<th>Molecular Formula(^b) or Lit. mp (°C)</th>
<th>IR (^c) (KBr or ( % ) (cm(^{-1}))</th>
<th>UV (^d) (MeCN)</th>
<th>( 'H-NMR (^e) (60 MHz; \text{CDCl}_3/TMS) )</th>
<th>( ^{13}C-NMR (^f) (22.6 MHz; \text{CDCl}_3/TMS) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 3b )</td>
<td>151 (H(_2)O)</td>
<td>149(^a)</td>
<td>2920, 1600, 1385, 1380, 1255, 860, 725</td>
<td>298 (4.50); 278 (3.76)</td>
<td>2.58 (s, 12H, ( \text{CH}_2 )); 7.10 (s, 4H, 4,4’-bipy-H)</td>
<td>24.59 (q, ( \text{CH}_2 )); 118.08 (d, C-3, 4,4’-bipy); 146.74 (s, C-4, 4,4’-bipy); 158.50 (s, C-2, 4,4’-bipy)</td>
</tr>
<tr>
<td>( 3c )</td>
<td>270 (dec)</td>
<td>( \text{C}_4\text{H}_8\text{N}_2\text{O}_6 ) ( (332.2) )</td>
<td></td>
<td></td>
<td>8.40 (s, 4H, 4,4’-bipy-H)(^a)</td>
<td></td>
</tr>
<tr>
<td>( 3d )</td>
<td>205–206 ( (\text{CH}_2\text{Cl}_2) )</td>
<td>( \text{C}_4\text{H}_6\text{Cl}_2\text{N}_2\text{O}_4 ) ( (405.8) )</td>
<td></td>
<td></td>
<td>221 (4.41); 271 (sh)</td>
<td>8.50 (s, 4,4’-bipy-H)</td>
</tr>
<tr>
<td>( 3e )</td>
<td>248–250 ( (\text{MeOH}) )</td>
<td>( \text{C}_4\text{H}_8\text{N}_2\text{O}_4 ) ( (388.3) )</td>
<td></td>
<td></td>
<td>223 (4.62); 279 (sh)</td>
<td>4.93 (s, 12H, ( \text{CH}_2 )); 8.50 (s, 4H, 4,4’-bipy-H)</td>
</tr>
<tr>
<td>( 3f )</td>
<td>143–145 ( (\text{EtOH}) )</td>
<td>( \text{C}_4\text{H}_8\text{N}_2\text{O}_4 ) ( (443.9) )</td>
<td>216 (4.57); 279 (sh)</td>
<td></td>
<td>1.30 (t, 12H, ( J = 8, \text{CH}_2 )); 4.27 (q, 8H, ( J = 8, \text{CH}_2 )); 8.53 (s, 4H, 4,4’-bipy-H)</td>
<td>13.51 (q, ( \text{CH}_2 )); 61.58 (t, ( \text{CH}_2 )); 124.87 (d, C-3, 4,4’-bipy); 145.59 (s, C-4, 4,4’-bipy); 149.15 (s, C-2, 4,4’-bipy); 163.37 (s, ( \text{CO}_2\text{H} ))</td>
</tr>
</tbody>
</table>

\(^a\) Kofler microscope; corrected.

\(^b\) Satisfactory microanalyses obtained: C ± 0.3, H ± 0.2, N ± 0.2.

\(^c\) Recorded on a Perkin-Elmer 157 G spectrophotometer.

\(^d\) Measured using a Perkin-Elmer 330 UV spectrometer.

\(^e\) Obtained on a Varian T 60 spectrometer.

\(^f\) Recorded on a Bruker WH 90 spectrometer.

\(^d\) In DMSO-\( d_6 \); signals of the four acid protons not visible.
the aqueous phase is extracted 6–8 times with t-BuOMe (20 mL). A yellowish residue is obtained by evaporation of the organic phase. Recrystallization from water gives 3b as a colorless, crystalline solid; yield: 2.25 g (49%).

2,2',6,6'-Tetrachloro-4,4'-bipyridine (3d):
A mixture of 3e (1.40 g, 4.22 mmol), SOCl₂ (0.5 mL) is heated under reflux for 4 h. After removal of excess SOCl₂ by distillation, the residue is recrystallized from CH₂Cl₂ to give 3d as colorless, microcrystalline compound; yield: 20.1 g (96%).

2,2',6,6'-Tetraacetoxycarbonyl-4,4'-bipyridine (3e): 15
A mixture of 3e (1.60 g, 4.82 mmol), abs. MeOH (50 mL), and conc. H₂SO₄ (0.5 mL) is heated under reflux for 4 h. After cooling to room temperature, the product is filtered off and recrystallized from MeOH to give 3e as colorless crystals; yield: 2.09 g (96%).

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(18) By this classical method esters of 2,6-dicarboxy pyridine are obtained quantitatively due to their low solubility in the cold reaction mixture; see: Matsumoto, I., Yoshizawa, J. Japanese Patent 7329794 (1973), Japan. Kokai; C.A. 1973, 79, 31909.