Bis[1H-imidazol-4(5)-yl]alkanes and 1,2,9,10- and 1,2,11,12-Tetraaminoalkane Tetrahydrochlorides

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Received 22 August 1996; revised 21 October 1996

Bis[1H-imidazol-4(5)-yl]alkanes (n = 4–8) have been prepared by modified Bredereck cyclization of α,ω-dibromomethylalkanediones in formamide at 180°C. They undergo ring-cleavage acylation with methyl chloroformate to a mixture of N-formylated bis(medi-carbamates). Subsequent removal of formyl groups, reduction with palladium on charcoal and hydrolysis afford α,β,ω-1,ω-tetraamino-alkane tetrahydrochlorides.

Several aspects of interest are focused on the synthesis of bis(imidazolyl)alkanes. Two or three imidazole rings of histidine in a variety of biological molecules bind metal ions or protons, so that bis(imidazolyl)alkanes serve as models for binding sites of copper1 and zinc2 in active centres of enzymes. Bis[1H-imidazol-4(5)-yl]alkanes bound to acridine have RNA cleaving properties.3 Pt(II) bis(imidazolyl) complexes have been shown to interact with nucleic acids and to exhibit cytostatic activity.4

An aliphatic (CH2)n or an aromatic bridge can link two imidazole rings between positions 1,1',2,2',6 or 4,4'(5,5'). The latter are similar to naturally occurring 4(5)-substituted imidazoles like histidine and histamine but, with the exception of analogs containing heteroatoms in the linking chain,7 they are the most difficult to synthesize.

Bis(imidazolyl)alkanes are also starting materials for the synthesis of tetraamines. Such α,β,ω-1,ω-tetraaminoalkanes may act as ligands for the preparation of bis[platinum(II)] complexes which are able to undergo intra- and inter-strand interactions with DNA.3

Drey and Fruton5 have prepared bis[1H-imidazol-4(5)-yl]methane (2, n = 1) using the amino acid function of histidine to build the second imidazole ring. Simple systems of imidazole rings with one substituent in position 4(5) are easily obtained by Bredereck cyclization of α-acetoxy or α-halogenomethyl ketones with formamide.10 Schubert et al.11 have prepared homologs (n = 5–8) starting from α,ω-dibromoalkanediones, via α,ω-diaminoalkanediones which were cyclized with NH2SCN to bis[2-sulfanylimidazol-4(5)-yl]alkanes and subsequently reduced to the desired compounds in 3% overall yield.11 Another synthesis involved cyclization of α,ω-dichloroalkanediones with formamidine acetate in liquid ammonia as a solvent12 affording 20–36% yields of bis(imidazolyl)alkanes which were isolated as 1,1'-triphenylmethyl derivatives. Sorrell and Allen13 obtained N-substituted bis(imidazolyl)alkanes from N-substituted α-aminoalkanes with formamide in good yields by reaction of α,ω-dibromo-

Scheme

\[
\begin{array}{cccc}
1-6 & n & R_1, R_2 = \text{H or CH}_3 \\
1 & 4 & \\
2 & 5 & \\
3 & 6 & \\
4 & 7 & \\
5 & 8 & \\
\end{array}
\]
methylalkanediones with formamide at 180°C (Scheme). The \( z, \omega \)-diaminomethyl- and/or \( z, \omega \)-N-formylamidomethylnalkanediones, formed in the first steps, have more chance under diluted reaction conditions to undergo the required cyclization than side reactions (double ammonia alkylations, aldol condensations, dihydropyrazine formation) which occur when the previously dissolved substrate in high concentration is subjected to gradual heating. Another problem lies in the isolation of the free bis(imidazolyl)alkanes. Unlike 1-substituted imidazoles, which are easily extracted from aqueous solutions of formamide, the polar bis(imidazolyl)alkanes require removal of solvent in vacuo, neutralization with \( \text{Na}_2\text{CO}_3 \) and a prolonged time of extraction into chloroform. This method is also limited to systems in which the two \( \alpha \)-bromomethyl ketone units in the molecule are separated from each other by a \( (\text{CH}_2)_n \) chain of at least four carbon atoms, affording 20–30% yields for \( n = 4.5 \); 40% for \( n = 7 \) and 50–60% for \( n = 6.8 \). The cleanest cyclization is that of 2c and 2e affording light yellow crystalline products after extraction. Compounds 2a, 2b, 2d require chromatographic purification prior to recrystallization from water.

Bis(imidazoles) 2e and 2e, the compounds with the highest yields, were submitted to Bamberger ring-cleavage acylation under Schotten–Baumann conditions, using methyl chloroformate as acylating reagent. A mixture of \( N\)-formylated open chain tetra-\( N\)-methylcarbonyl dienes 3 (methyloloxycarbonyl = Moe) was obtained in 60–70% yield (Scheme) which shows in the \( \text{H}^1 \) NMR spectra two HCO protons at \( \delta = 9.1 \) and 9.2, and in the IR spectra a very broad \( \text{N}-\text{diacetyl} \) CO absorption at 1640–1740 cm\(^{-1}\). Bulky reagents such as benzylic chloro- or di-\( \text{tert-} \)butyldicarbonate, efficient in the acylation of 4(5)-substituted imidazoles, failed to give good yields in the acylation of 2 because of steric hindrance. The formyl groups are removed by methanalysis. The resulting compound 4 exhibit in the IR spectrum the C=CNHCO\(_2\text{Me}\) absorption at 1704 cm\(^{-1}\) whereas the reduced 5 (10% Pd/C) show the carbamate band at 1685 cm\(^{-1}\). Hydrolysis of 5 with HCl-acetic acid mixture gives the tetraamine tetrachlorides 6.

In conclusion, bis[1H-imidazol-4(5)-yl]alkanes can be prepared by the Bredereck method. They undergo characteristic ring-cleavage acylation to give finally primary tetraamines of two vicinal diamine units, each at the end of the aliphatic chain.

Solvents of analytical grade and 10%Pd on charcoal were purchased from Merck. \( \text{H}^1 \) and \( \text{C}^{13} \)NMR spectra were recorded on a Jeol EX-400 and a Jeol GSX-270 spectrometer and are given with respect to TMS as internal standard. IR spectra were measured on a Nicolet 520 FT-IR spectrometer. MS spectra were recorded on a Finnigan MAT 93Q (EI) instrument. Flash chromatography was carried out on silica gel (Merck, 70–230 mesh). TLC was performed on Merck 60F<sub>254</sub> plates using UV, 1\( \lambda \) or 10% ethanolic solution of phosphotungstic acid for visualization. Melting points were recorded on a Büchi apparatus. C, H, N analyses were performed by the Microanalytical Laboratory of our Institute. Satisfactory microanalyses were obtained for all new compounds: C ± 0.44, H ± 0.33, N ± 0.42 (Exceptions: 6e, C = 0.55; 4e, H = 0.5; 4e, N = 0.57; 6c, N = 0.65).

### Table 1. \( \text{C}^{13} \) NMR Data for Bis[1H-imidazol-4(5)-yl]alkanes 2

<table>
<thead>
<tr>
<th>Product</th>
<th>( \text{C}^{13} ) NMR (MeOD/TMS), ( \delta )</th>
<th>( \text{H}^{1} ) NMR (MeOD/TMS), ( \delta ) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-2,2' C-4,4' C-5,5' C-6,6' others</td>
<td>H-2,2' H-5,5' H-6,6' others</td>
</tr>
<tr>
<td>2a</td>
<td>138.07 135.76 118.41 30.16 27.21</td>
<td>7.53 6.74 2.56 (6.6) 1.66</td>
</tr>
<tr>
<td>2b</td>
<td>138.04 135.63 118.37 30.33 29.69 27.29</td>
<td>7.53 6.73 2.57 (7.6) 1.65 1.38</td>
</tr>
<tr>
<td>2c</td>
<td>138.01 135.55 118.34 30.51 30.03 27.32</td>
<td>7.52 6.71 2.55 (7.3) 1.62 1.36</td>
</tr>
<tr>
<td>2d</td>
<td>138.36 135.97 118.76 30.87 30.56 30.48 27.67</td>
<td>7.56 6.75 2.58 (7.6) 1.37</td>
</tr>
<tr>
<td>2e</td>
<td>138.54 136.12 118.93 31.06 30.93 30.76 27.86</td>
<td>7.50 6.70 2.48 (7.6) 1.54 1.27</td>
</tr>
</tbody>
</table>

### Table 2. \( \text{C}^{13} \)NMR Data for Ring Opened Compounds 4, 5 and 6

<table>
<thead>
<tr>
<th>Product</th>
<th>C-1,1' C-2,2' C-3,3' C-4,4' C-5,5' C-6,6' CO(_2\text{CH}_3)</th>
<th>CO(_2\text{CH}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4e(^b)</td>
<td>106.29 118.25 31.55 27.97</td>
<td>27.10 154.26 154.03 51.60 51.87</td>
</tr>
<tr>
<td>4e(^b)</td>
<td>106.32 118.28 31.60 28.76</td>
<td>28.25 27.23 154.31 154.08 51.64 51.91</td>
</tr>
<tr>
<td>5e(^b)</td>
<td>44.46 50.75 31.50 28.86</td>
<td>25.38 156.53 51.19 51.31</td>
</tr>
<tr>
<td>5e(^b)</td>
<td>44.58 50.86 31.61 29.06</td>
<td>29.02 25.51 157.19 156.75 51.29 51.43</td>
</tr>
<tr>
<td>6e(^c)</td>
<td>42.06 50.78 31.39 29.47</td>
<td>25.49</td>
</tr>
<tr>
<td>6e(^d)</td>
<td>40.38 48.45 29.59 27.80</td>
<td>27.77 23.60</td>
</tr>
</tbody>
</table>

\(^a\) Recorded in MeOD/TMS.
\(^b\) Recorded in DMSO-\( d_6 \)/TMS.
\(^c\) Recorded in MeOD/TMS.
\(^d\) Recorded in D\(_2\)O/MeOD.
Bis(1H-imidazol-4(5)-yl)alkanes 2a–e; General Procedure:
A 250-mL 3-necked flask with an attached air-cooled condenser and a thermometer was charged with formamide (175 mL), which was purged with nitrogen. N,N-dimethylformamide (9.2 mL) and dichloromethane (9.2 mL) were added to the flask. The mixture was stirred until the solution was homogeneous. The solution was then heated to 80 °C for 2 h. The mixture was then filtered, and the filtrate was concentrated to a small volume. The residue was dissolved in chloroform (50 mL) and washed with water (10 mL). The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was recrystallized from ethanol to give 2a

2a: yield: 0.57 g (24%); mp 189–191 °C; colorless crystals (EtOH).
EIMS: m/z (%) = 191 (M+1+, 19.5), 190 (M+1, 8.4), 96 (IMch2Ch2+1+, 100), 95 (IMch2Ch2+1, 96), 82 (IMch2+1, 15.8), 81 (IMch2+, 20.4), 68 (IM+1, 3.8).

2b: yield: 0.84 g (35%); mp 138–140 °C; colorless crystals (H2O) (Lit.11 mp 138–139.8 °C).
EIMS: m/z (%) = 205 (M+1+, 21.6), 204 (M+, 34.6), 123 (M–IMch2+1, 9), 96 (IMch2+1, 4), 82 (IMch2+1, 100), 81 (IMch2+, 31.3).

2c: yield: 1.58 g (58%); mp 135–137 °C; colorless crystals (H2O/EtOH) (Lit.11 mp 143–144 °C).

EIMS: m/z (%) = 219 (M+1+, 19.4), 137 (M–IMch2+1, 22.0), 96 (IMch2+1, 100), 82 (IMch2+1, 16.8), 81 (IMch2+, 44.8), 68 (IM+1, 4.3).

2d: yield: 1.1 g (38%); mp 133–135 °C; colorless crystals (H2O) (Lit.11 mp 135–136 °C).
EIMS: m/z (%) = 234 (M+1+, 5.5), 232 (M+, 8.0), 151 (M–IMch2+1, 100), 96 (IMch2+1, 4), 82 (IMch2+1, 24.1), 81 (IMch2+, 29.2), 68 (IM+1, 2.0).

2e: yield: 1.6 g (52%); mp 153–155 °C; colorless crystals (H2O/EtOH) (Lit.11 mp 150–152 °C).
EIMS: m/z (%) = 247 (M+1+, 9.1), 246 (M+, 15.5), 165 (M–IMch2+1, 100), 96 (IMch2+1, 4), 82 (IMch2+1, 54.4), 81 (IMch2+, 49.9), 68 (IM+1, 3.0).

N1,N2,N3,N4,N5,N6-Tetra-Moc-1,2,9,10-tetraimidocinoda-1,9-diene (4c); Typical Procedure:
Solutions of methyl chloromiformate (4.7 g, 0.05 mol) in EtOAc (40 mL) and NaHCO3 (2.0 g, 0.05 mol) in water (50 mL) were simultaneously added to two separate dropping funnels into a suspension of 3e (1.1 g, 5 mmol) in a mixture of EtOAc (40 mL) and H2O (10 mL) which was kept in an ice-bath. The mixture was stirred for 1 h at 0 °C and then filtered. At this stage several drops of TLC (different possible intermediates were observed). The H2O layer was removed, the reaction mixture was cooled again, new portions of methyl chloromiformate (4.7 g, 0.05 mol) in EtOAc (10 mL) and NaHCO3 (2.0 g, 0.05 mol) in H2O (50 mL) were added. The mixture was stirred overnight at r.t. After one more addition of the above mixture, the mixture was then concentrated to a small volume. The residue was dissolved in EtOAc (50 mL) and washed with water (10 mL). The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was recrystallized from ethanol (2 × 5 mL) and extracted with Et2O (2 × 20 mL) and dried, yield: 365 mg (82%).

IR (Nujol): ν = 1585, 1567, 1520 cm-1 (NH).

1H NMR (CDCl3 + D2O): δ (J, Hz) = 1.46 (m, 8H, CH2), 1.80 (m, 4H, CH3), 3.32 (d, 4H, J = 5.8, CH2N), 3.62 (q, 2H, J = 6.3, CHN).

1,2,11-Ditetraimidocinoda Tetrahydrodiluride (6e): Compound 5e (200 mg, 0.43 mmol) was hydrolyzed as above affording 6e, yield: 135 mg (83%).

IR (Nujol): ν = 1585, 1567, 1520 cm-1 (NH).

1H NMR (CDCl3 + D2O): δ (J, Hz) = 1.46–1.6 (m, 12H, CH2), 1.7–1.8 (m, 4H, CH3), 3.45 (m, 4H, CH2N), 3.65 (m, 2H, CHN).

Support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We wish to thank Dr. Werner Spähli, Institut für Organische Chemie der Universität München, for recording the mass spectra.