Synthesis of 5-Hydroxy-2-oxotetrahydropyrroles

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The versatility of the title compounds as starting materials for the synthesis of naturally occurring substances is well documented\(^1\),\(^2\),\(^3\). The methods available for their preparation are as follows:

1. Selective reduction of cyclic imides by means of NaBH\(_4\) or NaBH\(_4\)-H\(^2\) or diisobutylaluminum hydride (DIBAH)\(^4\), which is almost invariably accompanied by over-reduction products;

(b) osmium tetroxide-catalyzed sodium metaperiodate\(^a\) cleavage of 4-pentenoic acid amides, utilized in the synthesis of isologistrobine\(^5\).

The latter process seems to be of general applicability, but separation of the \(\alpha\)-carbinol-lactams from the formaldehyde which is also formed can present problems.

We would like to report here a procedure, based on the latter method, which allows the clean, high-yield preparation of 5-hydroxy-2-oxotetrahydropyrroles by oxidation of the amides of cis- or trans-4-octen-1,8-dioic acids (1) and (2), both of which are easily prepared\(^5\).

\[
\begin{align*}
1 & & & 2 \\
\text{H} & \text{C} & \text{H} & \text{C} & \text{H} \\
\text{H} & \text{(CH}_2)_2 & \text{COOH} & \text{H} & \text{C} \\
\text{H} & \text{(CH}_2)_2 & \text{COOH} & \text{H} & \text{C} \\
\end{align*}
\]

Reaction of the corresponding acid chlorides with suitable amines in the presence of triethylamine in chloroform produces excellent yields of the amides 3a-g and 4a-g, listed in Table 1. When these compounds were treated with Lenniez-Johnson reagent \(^6\), good yields of practically pure 5-hydroxy-2-oxotetrahydropyrroles 5a-g were obtained, as summarized in Table 2.

\[
\begin{align*}
3a-g & & & 5a-g \\
\text{H} & \text{C} & \text{H} & \text{(CH}_2)_2 & \text{CO-NH-R} \\
\text{H} & \text{(CH}_2)_2 & \text{CO-NH-R} & \text{R-NH-CO-(CH}_2)_2 \\
\text{H} & \text{(CH}_2)_2 & \text{CO-NH-R} & \text{H} & \text{C} \\
\end{align*}
\]

The \(^1\)H-N.M.R. spectra of products 5b, 5d, and 5e, registered immediately after their isolation, indicate that they can exist to some extent (10–50%) in the open form, whose existence has not been observed previously\(^4\). On being allowed to stand at room temperature the cyclization proceeds to completion within a few hours.
Table 1. cis- and trans-4-Octen-1,8-dioic Acid Amides 3a-g and 4a-g

<table>
<thead>
<tr>
<th>R</th>
<th>Yield [%] of 3</th>
<th>Yield [%] of 4</th>
<th>m.p. (solvent)</th>
<th>Molecular formula*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>77</td>
<td>85</td>
<td>159-160° (dec) (C$_2$H$_5$OH)</td>
<td>C$<em>8$H$</em>{12}$N$_2$O$_2$ (170.2)</td>
</tr>
<tr>
<td>b</td>
<td>87</td>
<td>93</td>
<td>89-91° (ether)</td>
<td>131° (1:1 C$_2$H$_5$OH/H$_2$O)</td>
</tr>
<tr>
<td>c</td>
<td>96</td>
<td>98</td>
<td>125° (1:1 C$_2$H$_5$OH/H$_2$O)</td>
<td>193° (C$_2$H$_5$OH)</td>
</tr>
<tr>
<td>d</td>
<td>100</td>
<td>100</td>
<td>188-189° (C$_2$H$_5$OH)</td>
<td>219-220° (C$_2$H$_5$OH)</td>
</tr>
<tr>
<td>e</td>
<td>93</td>
<td>98</td>
<td>143° (2:3 C$_2$H$_5$OH/H$_2$O)</td>
<td>155° (C$_2$H$_5$OH)</td>
</tr>
<tr>
<td>f</td>
<td>91</td>
<td>94</td>
<td>132-133° (4:1 C$_2$H$_5$OH/H$_2$O)</td>
<td>189-190° (9:1 C$_2$H$_5$OH/H$_2$O)</td>
</tr>
<tr>
<td>g</td>
<td>98</td>
<td>100</td>
<td>166° (C$_2$H$_5$OH)</td>
<td>228-229° (dioxan)</td>
</tr>
</tbody>
</table>

* All products gave satisfactory microanalyzes (C ±0.3, H ±0.2, N ±0.2) and I.R. and N.M.R. spectra consistent with the assigned structures; microanalyses were performed by the Microanalytical Laboratories of the Institute of Pharmaceutical Chemistry of the University of Padova.

b Obtained with R-(+) -phenylethylamine.

c [x]$_D^{25}$: +60° (c 1, C$_3$H$_5$OH).

d [x]$_D^{25}$: +129° (c 1, C$_3$H$_5$OH).

Table 2. 5-Hydroxy-2-oxotetrahydroxyprolines 5a-g

<table>
<thead>
<tr>
<th>Prod.</th>
<th>Yield [%]</th>
<th>m.p. (Lit. m.p.)</th>
<th>Molecular formula*</th>
<th>I.R. (CHCl$<em>3$) $\nu</em>{max}$ [cm$^{-1}$]</th>
<th>$^1$H-N.M.R. (CDCl$_3$) δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>72</td>
<td>98-99° (98-99°)</td>
<td>C$<em>6$H$</em>{10}$NO$_2$ (101.1)</td>
<td>3420, 3250, 1680</td>
<td>4.9 (m, 1H); 5.3 (broad s, 1H); 8.3 (broad s, 1H)</td>
</tr>
<tr>
<td>5b</td>
<td>81</td>
<td>53-55°</td>
<td>C$<em>6$H$</em>{10}$NO$_2$ (171.2)</td>
<td>3300, 1660</td>
<td>0.92 (d, 6H, J = 6 Hz); 4.65 (d, 1H, J = 7 Hz); 5.2 (m, 1H)</td>
</tr>
<tr>
<td>5c</td>
<td>87</td>
<td>118-119° (120-125°)</td>
<td>C$<em>6$H$</em>{12}$NO$_2$ (205.2)</td>
<td>3320, 1670</td>
<td>1.7-2.7 (m, 4H); 2.85 (t, 2H, J = 8 Hz); 3.37 (dt, 1H, J = 14 Hz, 8 Hz); 3.7 (dt, 1H, J = 14 Hz, 7 Hz); 4.55 (s, 1H); 4.95 (s, 1H); 7.25 (s, 5H)</td>
</tr>
<tr>
<td>5d</td>
<td>92</td>
<td>116° (116°)</td>
<td>C$<em>6$H$</em>{12}$NO$_2$ (183.2)</td>
<td>3300, 1660</td>
<td>3.66 (m, 1H), 5.13 (broad s, 1H); 5.3 (m, 1H)</td>
</tr>
<tr>
<td>5e</td>
<td>80</td>
<td>90-100°</td>
<td>C$<em>6$H$</em>{12}$NO$_2$ (205.2)</td>
<td>3300, 1670</td>
<td>1.65 (d, 3H, J = 7 Hz); 3.93 (broad s, 1H); 4.93 (m, 1H); 5.33 (q, 1H, J = 7 Hz); 7.3 (m, 5H)</td>
</tr>
<tr>
<td>5f</td>
<td>87</td>
<td>112-113° (116-119°)</td>
<td>C$<em>6$H$</em>{12}$NO$_2$ (177.2)</td>
<td>3320, 1680</td>
<td>1.8-2.7 (m, 4H); 4.63 (d, 1H); 5.45 (m, 1H); 7.3 (m, 5H)</td>
</tr>
<tr>
<td>5g</td>
<td>95</td>
<td>131-135° (132-135°)</td>
<td>C$<em>6$H$</em>{12}$NO$_2$ (207.2)</td>
<td>3350, 1680</td>
<td>1.8-2.7 (m, 4H); 3.8 (s, 3H); 4.2 (d, 1H); 5.5 (m, 1H); 6.8-7.5 (m, 4H)</td>
</tr>
</tbody>
</table>

* All compounds gave satisfactory microanalyses (C ±0.2, H ±0.2, N ±0.2).

Applications of suitable 5-hydroxy-2-oxotetrahydroxyprolines obtained in this way to the synthesis of 11-deoxy-8-azaprostaglandin is under investigation.

cis- and trans-4-Octen-1,8-dioic Acid Amides 3a-g and 4a-g: General Procedure:
A solution of the acid 1 or 2 (4g, 0.023 mol), freshly distilled thionyl chloride (15 ml) in benzene (25 ml) containing a few drops of dimethylformamide is heated at 60° for 5 h. The mixture is then evaporated in vacuo, and the last traces of thionyl chloride are eliminated at reduced pressure by codistillation three times with 15 ml portions of benzene. The chlorides of the acids 1 and 2, so obtained, are used without further purification.

A solution of the chloride (0.023 mol) in dry chloroform (20 ml) is added dropwise to an ice-cooled stirred solution of the respective amine (0.046 mol) and triethylamine (0.06 mol) in chloroform (25 ml). Stirring is continued for 6 h at room temperature. The mixture is then diluted with water (50 ml) and the organic extract washed with 2 normal hydrochloric acid (50 ml), then with 5% aqueous sodium hydrogen carbonate, dried (MgSO$_4$) and the solvent removed. The residue is recrystallized from a suitable solvent (see Table 1).

5-Hydroxy-2-oxotetrahydroxyprolines: General Procedure:
To a stirred solution of the amide (0.004 mol) in dioxane (40 ml; distilled from LiAlH$_4$) and water (13 ml) is added a small crystal (0.001 g) of osmium tetroxide. When the solution has turned
brownish 1 (~ 10 min), sodium metaperiodate (2.06 g, 0.0092 mol), is added at 25-26°. When the reaction is complete (the progress is monitored by T.L.C. on silica gel with chloroform-ether/methanol 3:2:0.1 as eluent), the precipitated solid is filtered and the filtrate evaporated in vacuo at 1 torr. The residue is dissolved in chloroform (50 ml), dried (MgSO4), and evaporated to leave a residue, which is crystallized from a suitable solvent (see Table 2).

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5 E. Winterfeldt, Synthesis 1975, 617.