NEW HETEROCYCLIC SYSTEMS: THIOPHEN CONDENSED 1-aza BICYCLO[3.3.1]NONANES

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Abstract - We described the synthesis of new heterocyclic systems by acidic treatment of N-benzyl, N-thenyl or N,N-dithenyl aminocetaldehydes dimethylacetics.

In a previous communication we showed that Ticlopidine (2, \( R = 2-C1-C6H5-CH2 \)) , a new inhibitor of platelets aggregation and antithrombotic agent, could be synthesised according to the following reaction sequence:

Scheme I

This cyclisation process derived from Bobbitt's synthesis of isoquinolines.

N-Alkylation of (1) or (2) with various alkyl halides RX (K2CO3 2eq, KI cat., DMF, 90°) gave the expected tertiary amines (2) or (4). But amines (2 a-c) obtained by alkylation of (1) with the corresponding meta-methoxy substituted benzyl halides, cyclized to benzo(c)thieno[2,3-f] 1-azabicyclo[3.3.1]nonanes (6 a-c)
by treatment in 6N hydrochloric acid at room temperature or, more rapidly, at reflux.

Scheme II

![Scheme II diagram]

On the same conditions, (2,6) obtained by Mannich condensation of guaiacol and (4) with formaldehyde (40% aqueous solution, ethanol, r.t., 69% yield) cyclized into (6,8).

The same new tetracyclic compounds were also prepared from the methoxymethoxytetrahydrothienopyridine(7) as illustrated in the following reaction. (Scheme III).

Scheme III

![Scheme III diagram]

When the intermediates (1,2) or (3) were used as exemplified in scheme IV, the isomeric benzo(c) thieno[3,2-f] 1-azabicyclo[3.3.1] nonane (4) was formed.

Scheme IV

![Scheme IV diagram]
Such a double cyclisation also occurred when the methoxyphenyl ring was replaced by the thiophene nucleus as illustrated in scheme V.

**Scheme V**

![Scheme V diagram]

<table>
<thead>
<tr>
<th>Tetracyclic Compounds</th>
<th>Yield %</th>
<th>mp°C (Solvent)</th>
<th>H-NMR δ (CDCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (+)</td>
<td>69</td>
<td>104-106 (iPr₂O)</td>
<td>6.91 (d, 1H, J=6Hz); 6.70 (d, 1H, J=5Hz); 3.50 (s, 3H); 3.19 (m, 2H)</td>
</tr>
<tr>
<td>66 (-)</td>
<td>39</td>
<td>hydrochloride &gt; 260</td>
<td>6.78 (d, 1H, J=5Hz); 6.53 (d, 1H, J=5Hz); 6.57 (s, 1H); 6.37 (s, 1H); 3.77 (s, 3H); 3.64 (s, 3H); 3.26 (s, 2H)</td>
</tr>
<tr>
<td>66 (-)</td>
<td>67</td>
<td>hydrochloride 245-255</td>
<td>6.87 (d, 1H, J=5Hz); 6.67 (d, 1H, J=5Hz); 6.26 (s, 1H); 4.02 (s, 3H); 3.76 (s, 3H); 3.69 (s, 3H)</td>
</tr>
<tr>
<td>66 (+)</td>
<td>50</td>
<td>hydrochloride &gt; 260</td>
<td>6.98 (d, 1H, J=5Hz); 6.67 (d, 1H, J=5Hz); 6.63 (s, 2H); 3.70 (s, 3H); 3.17 (m, 2H)</td>
</tr>
<tr>
<td>54 (+)</td>
<td>71</td>
<td>74-76 (iPr₂O)</td>
<td>4.40 (d, 1H, J=17Hz); 3.65 (d, 1H, J=17Hz); 3.40 (s, 3H); 4.30 (d, 1H, J=17Hz); 3.60 (d, 1H, J=17Hz); 3.05 (m, 2H)</td>
</tr>
<tr>
<td>66 (-)</td>
<td>66</td>
<td>63-85 (iPr₂O)</td>
<td>6.75 (d, 1H, J=5Hz); 6.45 (d, 1H, J=5Hz); 4.40 (d, 2H, J=17Hz); 3.65 (d, 2H, J=17Hz)</td>
</tr>
<tr>
<td>66 (-)</td>
<td>59</td>
<td>107-109 (iPr₂O)</td>
<td>4.45 (d, 1H, J=17Hz); 3.75 (d, 1H, J=17Hz); 4.55 (d, 1H, J=17Hz); 3.85 (d, 1H, J=17Hz); 3.30 (m, 2H)</td>
</tr>
<tr>
<td>80 (+)</td>
<td>61</td>
<td>145-147 (iPr₂O)</td>
<td>6.95 (d, 1H, J=5Hz); 6.70 (d, 1H, J=5Hz); 4.55 (d, 2H, J=17Hz); 3.80 (d, 2H, J=17Hz); 3.15 (m, 2H)</td>
</tr>
</tbody>
</table>
All these cyclisations were also expected since Bobbitt's work on the formation of dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes (22) from the dibenzylamines (21) in which R was a hydroxy or methoxy substituant (scheme VI).

Recently, Takayama and coll.\(^8\) showed that the cyclisation of (21) analogs could be carried out even in the absence of electron-donating group if the reaction was performed in 70% perchloric acid. Nevertheless, neither with this reagent nor with trifluoromethanesulfonic acid\(^10\), we were able to prepare cyclic analogs of (6,8,9,10) or (14) which did not contain a methoxy or hydroxy groups in the right position.

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