Synthesis of 2-Acetoxy-3,4,5-trihydro-azepino[2,3-b]indoles and 2-Acetoxy-1-acetylamino-3,4-dihydrocarbazoles

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Z. Naturforsch. 54b, 131–135 (1999); received June 15, 1998

1-Hydroxyimino-1,2,3,4-tetrahydrocarbazoles, 2-Acetoxy-3,4,5-trihydro-azepino[2,3-b]-indoles, 2-Acetoxy-1-acetylamino-3,4-dihydrocarbazoles

An attempt to synthesize aminocarbazoles 2 and its derivatives 3, intened precursors for pyridocarbazoles 4, afforded 2-acetoxy-3,4,5-trihydro-azepino[2,3-b]indoles 6 and 2-acetoxy-1-acetylamino-3,4-dihydrocarbazoles 7.

It is well established that the pyridocarbazole ring is an appropriate skeleton to design DNA intercalating drugs [1]. Some compounds such as ellipticine and olivacine elicit high antitumour properties [1–3]. Since the discovery of the potent activity of 11H-pyrido[2,3-a]carbazoles [1] and 6H-pyrido[3,2-b]carbazoles [3], numerous syntheses have been reported [1, 4, 5]. Indoles [4a–e], but also 3-aminocarbazoles [4h], stilbenes [4e], substituted benzenes [4g] or quinolines [1, 4f] were often used as starting materials. These methods, however, often have low yields due either to the large number of steps [4g] or to the presence of several isomers [4c–d, 4i]. Aminocarbazoles themselves are known for their central nervous system activity paralleling tryptamine types [6]. Hence our present investigation was aimed to derive previously unknown aminocarbazoles 2 and its derivatives 3 from the corresponding 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles 1 in a single step (Scheme 1).

With the above objective in mind, 1-hydroxyimino-1,2,3,4-tetrahydrocarbazole 1a was treated with a mixture of acetic anhydride and anhydrous phosphoric acid for 1.5 h at 80 °C [7, 8]. The reaction mixture yielded a dirty white product which showed two spots on t.l.c. These two products were separated by column chromatography. The fraction eluted with petroleum ether – ethyl acetate in the ratio 95:5 yielded a compound which crystallized in yellow prisms (m.p., 172 °C; yield, 35%). The IR spectrum showed the presence of a $\text{OCOCH}_3$ ($v_{\text{C=O}}$ 1750 cm$^{-1}$) group. But the spectrum lacked the absorption expected of either amide carbonyl or -NH$_2$ group. The $^1$H NMR

\begin{equation}
\text{Scheme 1}
\end{equation}

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The petroleum ether: ethyl acetate (90:10) fraction afforded colourless crystals on crystallization from chloroform (m.p. 152 °C; yield, 30%). Its IR spectrum showed absorption peaks in the amide and ester carbonyl regions. The resonances in the $^1$H NMR spectrum of the compound as singlets at $\delta$ 2.23 and $\delta$ 2.65 further confirm the presence of -NHCOCH$_3$ and -OCOCH$_3$ protons. A two proton multiplet at $\delta$ 2.00–2.12, a five proton aromatic multiplet at $\delta$ 7.30–8.40 and one proton broad singlet at $\delta$ 9.80 have also appeared. The molecular ion peak at $m/e$ 284 (14%) in its mass spectrum and the elemental analysis: C 67.73, H 5.57 and N 9.95 are agreed with the molecular formula C$_{16}$H$_{16}$N$_2$O$_3$. Based on the spectral and analytical data, the structure of the compound was found to be 7a.

A similar series of compounds were realized with 1b, 1c and 1d (Scheme 2 and Table I).

The plausible mechanisms for the formation of products have also been proposed. The acetic anhydride – anhydrous phosphoric acid reaction re-
Table I. Physical and spectral data of new 2-acetoxy-3,4,5-trihydro-azepino[2,3-b]indoles (6) and 2-acetoxy-1-ace-

tylamo-3,4-dihydrocarbazoles (7).

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p./°C</th>
<th>Yield (%)</th>
<th>IR (v)</th>
<th>MS(70 eV)</th>
<th>Molecular formula</th>
<th>Analysis (^a)</th>
<th>(^b)</th>
<th>(^c)</th>
<th>(^d)</th>
<th>(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>171</td>
<td>35</td>
<td>1750</td>
<td>242</td>
<td>C(<em>{2}H</em>{13}N_{2}O_{2}) (242.27)</td>
<td>69.42</td>
<td>69.25</td>
<td>2.08-2.20</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.23 (s, 3H, -OCONH(<em>{2})), 2.84-2.88 (m, 4H, C(</em>{2})-H and C(<em>{2})-H), 7.08-7.62 (m, 4H, C(</em>{2})-H, C(<em>{3})-H, C(</em>{3})-H and C(<em>{3})-H) and 9.20 (b s, 1H, NH, D(</em>{2})O exchangeable)</td>
</tr>
<tr>
<td>7a</td>
<td>152</td>
<td>30</td>
<td>1750</td>
<td>284</td>
<td>C(<em>{16}H</em>{18}N_{3}O_{3}) (284.31)</td>
<td>67.61</td>
<td>67.73</td>
<td>2.00-2.12</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.23 (s, 3H, -OCONH(<em>{2})), 2.65 (s, 3H, -OCONH(</em>{2})), 2.88-2.98 (m, 2H, C(<em>{2})-H and C(</em>{2})-H), 7.30-8.40 (m, 5H, C(<em>{2})-H, C(</em>{3})-H, C(<em>{3})-H and -NHCOCH(</em>{3})) and 9.80 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>6b</td>
<td>204</td>
<td>35</td>
<td>1740</td>
<td>256</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (256.30)</td>
<td>70.31</td>
<td>70.22</td>
<td>1.97-2.09</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.24 (s, 3H, -OCONH(<em>{2})), 2.49 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.86-2.90 (m, 4H, C(</em>{2})-H and C(<em>{2})-H), 7.00-7.41 (m, 3H, C(</em>{3})-H, C(<em>{4})-H and C(</em>{4})-H) and 9.37 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>7b</td>
<td>135</td>
<td>23</td>
<td>1750</td>
<td>298</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (298.34)</td>
<td>68.46</td>
<td>68.20</td>
<td>1.94-2.00</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.23 (s, 3H, -OCONH(<em>{2})), 2.52 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.66 (s, 3H, -OCONH(</em>{2})), 3.02-3.06 (m, 2H, C(<em>{3})-CH(</em>{2})), 7.05-7.81 (m, 4H, C(<em>{2})-H, C(</em>{3})-H and C(<em>{3})-H and -NHCOCH(</em>{3})) and 9.20 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>6c</td>
<td>198</td>
<td>35</td>
<td>1740</td>
<td>256</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (256.30)</td>
<td>70.31</td>
<td>70.45</td>
<td>2.04-2.05</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.23 (s, 3H, -OCONH(<em>{2})), 2.44 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.72-2.87 (m, 4H, C(</em>{3})-CH(<em>{2}) and C(</em>{4})-CH(<em>{2})), 7.10-7.34 (m, 4H, C(</em>{4})-H, C(<em>{3})-H and C(</em>{3})-H) and 8.94 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>7c</td>
<td>165</td>
<td>21</td>
<td>1750</td>
<td>298</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (298.34)</td>
<td>68.46</td>
<td>68.62</td>
<td>2.02-2.10</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.24 (s, 3H, -OCONH(<em>{2})), 2.64 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.65 (s, 3H, -OCONH(</em>{2})), 2.85-2.94 (m, 2H, C(<em>{3})-CH(</em>{2})), 7.19-8.00 (m, 4H, C(<em>{3})-H, C(</em>{4})-H and C(<em>{4})-H and -NHCOCH(</em>{3})) and 9.52 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>6d</td>
<td>220</td>
<td>35</td>
<td>1740</td>
<td>256</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (256.30)</td>
<td>70.31</td>
<td>70.18</td>
<td>2.08-2.12</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.28 (s, 3H, -OCONH(<em>{2})), 2.40 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.76-2.90 (m, 4H, C(</em>{3})-CH(<em>{2}) and C(</em>{4})-CH(<em>{2})), 7.12-7.74 (m, 3H, C(</em>{4})-H, C(<em>{3})-H and C(</em>{3})-H) and 9.18 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
<tr>
<td>7d</td>
<td>178</td>
<td>23</td>
<td>1750</td>
<td>298</td>
<td>C(<em>{17}H</em>{19}N_{2}O_{3}) (298.34)</td>
<td>68.46</td>
<td>68.18</td>
<td>1.98-2.06</td>
<td>(m, 2H, C(<em>{1})-CH(</em>{2}))</td>
<td>2.22 (s, 3H, -OCONH(<em>{2})), 2.55 (s, 3H, C(</em>{2})-CH(<em>{2})), 2.63 (s, 3H, -OCONH(</em>{2})), 2.92-3.12 (m, 2H, C(<em>{3})-CH(</em>{2})), 7.08 (m, 4H, C(<em>{3})-H, C(</em>{4})-H and C(<em>{4})-H and -NHCOCH(</em>{3})) and 9.40 (b s, 1H, NH, D(_{2})O exchangeable)</td>
</tr>
</tbody>
</table>


a Uncorrected, measured using Mettler FP5 apparatus and a Boetius microheating table;

b recorded on a Perkin-Elmer 597 Infrared spectrometer;

c recorded on a Jeol-JMS-D 300 Mass spectrometer;

d satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer Modell 240 CHN analyzers;

e NMR spectra were recorded on Varian AMX400 FT-NMR spectrometer using tetramethylsilane as internal refer­

ence in CDCl\(_{3}\). The chemical shifts are quoted in parts per million (ppm).

Alized with the ketoxime 1 can be mechanistically viewed as proceeding through the Beckmann rearrangement to give the ring enlarged amide followed by a keto-enol tautomeration and O-acytylation to give the product, 2-acetoxy-3,4,5-trihydro-azepino[2,3-b]indole 6 (Scheme 3.1). The conversion 1→7 can be interpreted as occurring via a [3,3] sigmatropic rearrangement of the enamine followed by prototropic shift and acetylation of the resultant α-acetoxy amino compound (Scheme 3.2).
Experimental

Synthesis of 2-acetoxy-3,4,5-trihydro-azepino[2,3-b]indoles and 2-acetoxy-1-acetylamino-3,4-di­hydrocarbazoles by the reaction of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles with acetic anhydride – anhydrous phosphoric acid mixture.

General procedure

1-Hydroxyimino-1,2,3,4-tetrahydrocarbazole (1, 0.005 mol) was added to a solution of acetic anhydride (10.2 g, 0.1 mol) and anhydrous phosphoric acid (9.8 g, 0.1 mol). The mixture was held at 80 °C for 1.5 h and the resulting solution was poured into ice water. The product thus obtained was extracted with chloroform and then washed with water. Evaporation of the solvent yielded the dirty white product which was found to be a mixture of two components. These two products were separated by column chromatography using the following solvent systems.

1. Petroleum ether : ethyl acetate (95:5);

Acknowledgements

We thank CSIR, Ministry of Human Resource Development, Government of India, New Delhi, for the award of Senior Research Fellowship to one of us (K. S.) and RSIC, CDRI, Lucknow and SIF, IISc, Bangalore for providing the spectral and analytical data.