1,2,3,5,6,10b-HEXAHYDROPYRROLO[2,1-a]ISOQUINOLINES.
PREPARATION AND STEREOCHEMISTRY OF 3-BENZYL DERIVATIVES

Joan Bosch*, Esther Mestre, Josep Bonjoch, Francisco López, and Ricardo Granados
Department of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona-28, Spain

Abstract - The preparation of cis- and trans-3-benzyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines 1 and 2 and the preferred conformation of the indolizidine ring system of these compounds are reported.

Although benz[a]quinolizidines1 (I, n=2) and related compounds2-6 have been extensively investigated as regards their stereochemistry, comparatively few studies have been made on the indolizidine nucleus of hexahydropyrrolo[2,1-a]isoquinolines (I, n=1).7

On the basis of their spectroscopic data, we discuss the preferred conformation of the indolizidine ring system in the epimeric 3-benzyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines 1 and 2. These compounds were prepared by condensation between mescaline and y-benzyl-y-butyrolactone (X) followed by Bischler-Napieralski cyclization of the resulting N-arylethyl-y-hydroxyamide 4. This approach constitutes the most common synthetic entry to the 1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline ring system.8,9

The required lactone 3 was prepared from allylbenzene, acetic acid, and manganese (III) acetate, according to the method described for the one-step synthesis of y-lactones from olefines, carboxylic acids and higher valent metal carboxylates.10,11
The aminolysis of lactone 3 with mescaline produced γ-hydroxyamide 4, which was characterized by its ir absorptions at 1635 and 3100-3500 cm⁻¹ due to the amide carbonyl group and the OH and NH bonds, respectively. Treatment of 4 with phosphoryl chloride followed by sodium borohydride reduction furnished a diastereomeric mixture of tricyclic amines 1 and 2, which were separated by column chromatography. Alcohol 5, whose structure was confirmed by its conversion into pyrrolidine 6 with thionyl chloride, was isolated as a by-product. Its formation can be attributed to an incomplete cyclization of the nitrilium salt formed as intermediate in the Bischler-Napieralski cyclodehydration, which is reduced during the final sodium borohydride treatment.

The stereochemical assignment of 1 and 2 was effected by their spectroscopic data (ir, ¹H- and ¹³C-nmr), taking into account that 3-substituted hexahydropyrrolo[2,1-a]isoquinolines have two chiral centers and therefore can exist in two possible relative configurations. Each epimer can adopt, respectively, three conformations, readily interconvertible through nitrogen inversion (a→b) and cis-indolizidine ring inversion (b→c).

In the ir spectrum of isomer 1 Bohmann bands at 2740 and 2800 cm⁻¹, characteristic of at least two α C-H bonds trans diaxial to the nitrogen lone pair, were observed. Moreover, in the ¹H-nmr spectrum the angular C₁₀b-H proton resonates at a field higher than δ3.8. These data allow to establish the trans conformation ¹A for the indolizidine ring system. On the contrary, the isomer 2 shows no Bohmann bands and exhibits a ¹H-nmr signal at δ4.55 as a multiplet with W₁/₂=12 Hz, due to the C₁₀b-H methine proton. These observations indicate that this proton is cis to the nitrogen lone pair as well as in a gauche orientation with respect to the C₁-
methylene protons. This implies a cis-fused indolizidine conformation such as \( \zeta \). The different ring fusion of isomers \( \lambda \) and \( \zeta \) was also concluded from their \( ^{13}C \)-nmr spectra. Thus, the shielding of the C-6 benzylic methylene carbon in the cis-fused isomer \( \zeta \) (\( \delta 25.56 \)) relative to the trans-fused isomer \( \lambda \) (\( \delta 29 \)) is analogous to that observed in other fused azacyclic systems having a cis-fusion of type \( \zeta \).\(^{15}\) On the other hand, the chemical shift difference of C10 between isomers \( \lambda \) (\( \delta 62.85 \)) and \( \zeta \) (\( \delta 57.27 \)) is similar to that reported for the angular methine carbon between trans- and cis-fused indolizidine,\(^{16}\) benzo[a]quinolizidine,\(^{17}\) and indolo[2,3-a]quinolizidine\(^{18}\) systems.

**\( ^{13}C \)-Nmr Chemical Shifts\(^a,b\) of Compounds \( \lambda \), \( \zeta \), and \( \zeta' \)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-5</th>
<th>C-6</th>
<th>C-6a</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
<th>C-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>28.88</td>
<td>30.48</td>
<td>64.04</td>
<td>45.86</td>
<td>29.01</td>
<td>130.49</td>
<td>107.44</td>
<td>150.83</td>
<td>140.27</td>
<td>151.88</td>
</tr>
<tr>
<td>( \zeta )</td>
<td>30.42</td>
<td>32.25</td>
<td>63.76</td>
<td>45.09</td>
<td>25.56</td>
<td>130.26</td>
<td>107.00</td>
<td>151.03</td>
<td>140.38</td>
<td>151.58</td>
</tr>
<tr>
<td>( \zeta' )</td>
<td>21.81</td>
<td>30.05</td>
<td>66.34</td>
<td>53.69</td>
<td>34.60</td>
<td>135.23</td>
<td>105.72</td>
<td>152.91</td>
<td>152.91</td>
<td></td>
</tr>
</tbody>
</table>

\( \zeta' \)

- C-10a
- C-10b
- CH2Ar
- C-1'
- C-2'
- C-3'
- C-4'
- C8-OMe
- C9-OMe
- C10-OMe

| \( \lambda \) | 124.85 | 62.85 | 39.55 | 139.72 | 129.12 | 128.27 | 125.99 | 55.92 | 60.52 | 60.69 |
| \( \zeta \) | 125.61 | 57.27 | 41.63 | 140.07 | 129.22 | 128.22 | 125.93 | 55.92 | 60.37 | 60.68 |
| \( \zeta' \) | 105.72 | 55.80 | 39.80 | 138.99 | 128.87 | 127.96 | 125.78 | 55.80 | 60.34 | 55.80 |

a. In ppm relative to TMS. Measured in CDCl3 solution at 50.3 MHz.
b. The assignments are in agreement with off-resonance spectra.
c. For an easier comparison, the numbering of the pyrrolo[2,1-a]isoquinoline system has been maintained.
The modification of the conformational preference of the indolizidine system\textsuperscript{19} in \( \text{C}_6 \) could be accounted for by considering that this isomer has a \textit{trans}-relationship between hydrogens at \( \text{C}_3 \) and \( \text{C}_{10b} \), and that, consequently, in the \textit{trans}-fused conformation \( \text{C}_6 \) the benzyl group adopts an axial orientation.

**EXPERIMENTAL**

\textit{Ir} spectra were taken on a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (cm\textsuperscript{-1}) are listed. Nmr spectra were recorded in CDC\textsubscript{13} with TMS as internal standard (\textsuperscript{1}H-nmr: Perkin-Elmer R-24B; \textsuperscript{13}C-nmr: Varian XL-200). Chemical shifts are reported in ppm downfield (\( \delta \)) from TMS. Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was carried out on SiO\textsubscript{2} (silica gel 60, Merck, 63-200 \( \mu \text{m} \)). TLC was carried out on SiO\textsubscript{2} (silica gel HF\textsubscript{254}, Merck) and the spots were located with uv light or iodoplatinate reagent. The developing solvent was ether/acetone/diethylamine (35:15:2). Microanalyses were performed by the Instituto de Química Bio-Organica, Barcelona.

\( \gamma \)-Benzyl-\( \gamma \)-butyrolactone (\( \delta \)). To a stirred solution of manganous (II) acetate tetrahydrate (67 g, 0.27 mol) in glacial AcOH (380 ml) maintained at 90°C was successively added KMnO\textsubscript{4} (10.1 g, 0.06 mol), acetic anhydride (100 ml), sodium acetate (158 g), and allylbenzene (22.5 g, 0.19 mol). The resulting mixture was refluxed for 6 h, after which it was cooled, diluted with ice-H\textsubscript{2}O, and extracted with ether. The organic extracts were washed with aqueous NaHCO\textsubscript{3}, dried, and evaporated. The residue was distilled to give 5.3 g of unreacted allylbenzene and 11.3 g (44\% based on the unrecovered allylbenzene) of \( \gamma \)-lactone \( \delta \); bp 165-170°C (0.3 mm Hg). An analytical sample was obtained by column chromatography using 1:1 benzene-chloroform as eluent; \textit{ir} (NaCl): 1770 (lactone); nmr (CC\textsubscript{4}): 1.70-2.40 (m,4H,CH\textsubscript{2}), 2.70 and 2.97 (2dd,1H each,J=14 and 6 Hz,CH\textsubscript{2}Ar), 4.50 (q,1H,CH), 7.10 (s,SH,ArH). Anal. Calcd for C\textsubscript{11}H\textsubscript{12}O\textsubscript{2}: C, 74.97; H, 6.86. Found: C, 75.09; H, 6.99.

N-(3,4,5-Trimethoxyphenethyl)-5-phenyl-4-hydropyranamide (\( \mu \)). A mixture of lactone \( \mu \) (7.74 g, 44 mmol) and mescaline\textsuperscript{20} (9.32 g, 44 mmol) was stirred at 110-120°C for 3 h under nitrogen. The resulting mixture was dissolved in CHCl\textsubscript{3} and the solution was successively washed with 1N HCl, aqueous NaHCO\textsubscript{3}, and H\textsubscript{2}O. Evaporation of the solvent followed by crystallization gave 11.8 g (69\%) of hydroxyamide \( \mu \); mp 127-129°C (CHCl\textsubscript{3}-petroleum ether); \textit{ir} (KBr): 3500-3100 (OH), 3340 (NH), 1635 (C=O); nmr: 1.80 (m,3H,OH and 3-CH\textsubscript{2}), 2.15-2.90 (m,8H,CH\textsubscript{2}), 3.45 (m,1H,CHOH), 3.80 (s,9H, OCH\textsubscript{3}), 5.75 (br,1H,NH), 6.35 (s,2H,ArH), 7.20 (s,SH,ArH). Anal. Calcd for C\textsubscript{22}H\textsubscript{23}N\textsubscript{2}O\textsubscript{5}: C, 68.19; H, 7.54; N, 3.61. Found: C, 68.17; H, 7.45; N, 3.34.

(\( 3R\),10b\textsuperscript{S*})- and (\( 3R\),10b\textsuperscript{R*})-3-Benzyl-8,9,10-trimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-d]isoquinoline (\( \lambda \) and \( \mu \)). To a solution of 2 g (5 mmol) of hydroxyamide \( \lambda \) in 50 ml of anhydrous toluene was added 2.5 ml of freshly distilled POCl\textsubscript{3}. After 2 h at reflux under nitrogen, the reaction mixture was evaporated, and CH\textsubscript{3}OH (100 ml) and NaBH\textsubscript{4} (2 g) were added. After being stirred overnight at room temperature, the
solvent was removed and the residue distributed between ether and water. The ethereal solution was extracted with 1 N HCl. The extracts were basified with 5% aqueous NaOH and extracted with ether. The ethereal solution was dried and evaporated to give an oil which was chromatographed. Elution with 1:4 benzene/CHC13 gave 360 mg (30%) of amine 1 which solidified on standing: mp 97-98°C (acetone); ir (KBr): 2740 and 2800 (Bohlmann bands); nmr 1.40-3.45 (m,1ZH), 3.80 (s,9H,0CH3), 6.40 (s, lH,ArH), 7.20 (s,5H,ArH). Anal. Calcd for C22H27N03: C, 74.79; H, 7.69; N, 3.96. Found: C, 75.04; H, 7.90; N, 3.69. Elution with CHC13 gave 340 mg (28%) of amine 2; nmr: 1.30-3.30 (m,1ZH), 3.75 (s,6H,0CH3), 3.80 (s,3H,0CH3), 4.15-4.55 (m,1H,CIOb-H), 6.25 (s, lH,ArH), 7.10 (s,5H,ArH). The oxalate melted at 126-128°C (EtOH). Anal. Calcd for C24H29N07: C, 64.99; H, 6.59; N, 3.15. Found: C, 64.68; H, 6.64; N, 2.87. Finally, on elution with 99:1 CHC13/CH30H, 520 mg (28%) of 1-phenyl-5-(3,4,5-trimethoxyphenethylamino)-2-pentanol (2) were obtained; ir (NaC1): 3100-3600 (OH); nmr: 1.20-2.10 (m,SH), 2.40-3.00 (m,7H), 3.10-3.40 (m,3H), 3.80 (s,9H,0CH3), 6.40 (s,2H,ArH), 7.25 (s,5H,ArH). The oxalate melted at 154-156°C (EtOH). Anal. Calcd for C24H33N08.1/2C2H60: C, 61.71; H, 7.46; N, 2.88. Found: C, 61.65; H, 7.22; N, 2.72.

2-Benzyl-1-(3,4,5-trimethoxyphenethyl)pyrrolidine (6). To a solution of alcohol 7 (797 mg, 2.1 mmol) in anhydrous benzene (12 ml) and pyridine (0.36 ml) was added thionyl chloride (0.2 ml). The mixture was stirred at room temperature for 1 h, poured into water, made alkaline with aqueous NaHC03, and extracted with CH2CI2. The extracts were dried and evaporated to a residue which was chromatographed using 9:1 CHCl3/CH30H as eluent to give 416 mg (53%) of pyrrolidine 6; nmr: 1.6-1.9 (m, 4H), 2.2-3.6 (m,9H), 3.8 (s,9H,0CH3), 6.3 (s,2H,ArH), 7.1 (s,5H,ArH).

REFERENCES AND NOTES


11. For a review on the synthesis of \(\gamma\)-lactones, see: S. Kano, S. Shibuya, and T. Ebata, Heterocycles, 1980, 14, 661.


19. \(\Delta G^\circ\) for the cis \(\rightleftharpoons\) trans indolizidine equilibrium has been determined as -2.4 Kcal/mol: H. S. Aaron and C. P. Ferguson, Tetrahedron Lett., 1968, 6191.


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