THE REDUCTION OF 4-ACYL-\(\beta\)-LACTAMS WITH SODIUM BOROHYDRIDE: A POSSIBLE DICHOTOMY OF STEREOCHEMICAL PATHWAYS

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Abstract — Stereoechemical result of the sodium borohydride reduction of 4-acyl-\(\beta\)-lactams to 4-(\(\alpha\)-hydroxyalkyl)-\(\beta\)-lactams is reported. The stereoselectivity is accounted for by competition between two possible stereoechemical pathways.

Although several cases of complex metal hydrides reductions of ketonic group in 3-acyl-\(\beta\)-lactams are known,\(^1\) to the best of our knowledge only one case of this type of reaction in 4-acyl-\(\beta\)-lactams has been reported. Thus, Singh and Mehrotra\(^2\) have studied the reduction of 4-benzoyl-\(\beta\)-lactams 1a and 1b with lithium aluminium hydride in ether to give carbinols 2a and 2b for which two or three pairs of diastereoisomers are possible, respectively. However, no stereoechemical conclusions may be deduced from Singh's paper. In our hands, the reaction of 4-benzoyl-\(\beta\)-lactam 1c\(^3\) with lithium aluminium hydride in the conditions reported by these authors gave a complex mixture of products from which we are unable to isolate the corresponding 4-(\(\alpha\)-hydroxybenzyl)-\(\beta\)-lactam 2c.\(^4\) Nevertheless, treatment of compounds 1c-f with sodium borohydride in ethanol\(^5\) afforded 4-(\(\alpha\)-hydroxybenzyl)-\(\beta\)-lactams 2c-f in fairly good yields of isolated products without detection of other by-products. On the other hand, inspection of the crude reaction mixtures (by

\[\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{O} \\
1 & \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{OH} \\
2 & \\
1, 2 & \quad R \\
a & \text{CH(CH}_3\text{)}_2 \\
b & \text{CH(Ph)CH}_3 \\
c & \text{Ph} \\
d & \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \\
e & \text{CH}_3\text{OC}_6\text{H}_4 \\
f & \text{BrCH}_2\text{C}_6\text{H}_4
\end{align*}\]
'H-nmr) indicates that only one racemate has been formed in all cases (Table).

Table. 4-(α-Hydroxybenzyl)-β-lactams 2 prepared

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Yield a (%)</th>
<th>Mp (°C) b (solvent)</th>
<th>Ir (cm⁻¹)b</th>
<th>'H-Nmr (δ, ppm) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>64</td>
<td>179-181 (EtOH)</td>
<td>3400</td>
<td>1750</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.7</td>
<td>5.5</td>
</tr>
<tr>
<td>2d</td>
<td>77</td>
<td>195-197 (MeOH)</td>
<td>3550</td>
<td>1735</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>2e</td>
<td>60</td>
<td>213-215 (MeOH)</td>
<td>3550</td>
<td>1720</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>2f</td>
<td>67</td>
<td>184-188 (EtOH)</td>
<td>3420</td>
<td>1760</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.8</td>
<td>5.3</td>
</tr>
</tbody>
</table>

a) Of pure, isolated products with correct elemental analyses.
b) In KBr pellet.
c) Spectra registered in CDCl₃ solutions at 80 MHz.

A suitable related compound 4 obtained by reduction of 4-acyl-β-lactam 3 (only one racemate was obtained) has been analyzed by X-ray diffraction (Figure 1). The configuration of compound 4 was determined as 4R,4'R-4S,4'S.

In sharp contrast, the reduction of 4-benzoyl-β-lactam 5, in the same experimental conditions to that used for β-lactams 1 and 3, gave 4-(α-hydroxybenzyl)-β-lactam 6 as a mixture of diastereoisomers in the relative proportion 55:45. Attempts of configurational assignment have been performed as follows: the coupling constant J₄-H₄' is greater in the major isomer (10.0 Hz vs. 7.0 Hz).

Conformational analysis of both stereoisomers with the aid of the appropriate stereomodels indicates that the more stable conformer with protons H₄-H₄' in antiperiplanar arrangement must
be more populated in 6β than in 6α (Figure). Thus the major coupling constant corresponds to the 4R,4'S-4S,4'R isomer, 6β. 9

We speculate with two stereochemical pathways to explain the observed results (Figure 2). Reactive conformation 7, like rigid Cram model, 10 could account for the formation of 4R,4'R-4S,4'S diastereoisomers by attack to the less hindered side of the carbonyl group. On the other hand, reactive conformation 8, like antiperiplanar Conforth model, 11 could account for the formation of 4R,4'R-4S,4'S isomers. When R is phenyl or methyl group (β-lactams 1 and 3) steric interaction between R and the R' moiety of the acyl group on the C-4 position destabilizes reactive conformation 7. When R = H both models are possible.

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REFERENCES AND NOTES


5. To a suspension of the 4-benzoyl-ß-lactams (1 mmol) in hot ethanol (60 ml), sodium borohydride (2 mmol) was added portionwise and the reaction mixture was heated at reflux for 20 min. After hydrolysis and filtration, the solid reaction crude was extracted (chloroform), dried (Na2SO4) and the solvent evaporated in vacuo. Finally the solid product obtained was recrystallized from methanol or ethanol.

6. Yield, 52%. mp 132-134°C (methanol). Ir (KBr): 3450 (OH), 1720 (C=O) cm⁻¹. ¹H-nmr (CDCl₃) δ 0.9 (d, 3H, J = 7 Hz, CH₃), 1.3 (s, 3H, CH₃), 1.6 (s, 1H, OH), 3.8 (s, 3H, OCH₃), 4.2 (s, 1H, CH), 7.6-7.7 (m, 14H, arom.).

7. X-Ray analysis has been performed by Dr. A. Monge and Miss V. Pérez-García (Instituto de Química Inorgánica "Elhuyar"). Full data will be published by the authors in due course. We thank this private communication.

8. Overall yield, 58%. Isomer separation was performed by fractional crystallization from ethanol. *Major isomer*, 68%: mp 164-166°C; ir (KBr) 3440 (OH) and 1725 (C=O) cm⁻¹. ¹H-nmr (CDCl₃) δ 2.0 (d, 1H, J = 4 Hz, OH), 3.6 (s, 3H, OCH₃), 4.2-4.2 (dd, 1H, J₁ = 10 Hz, J₂ = 4 Hz, CHOH), 4.9 (d, 1H, J = 10 Hz, H-4), 6.4-7.8 (m, 19H, arom.). *Minor isomer*, 60%: mp 188-190°C; ir (KBr) 3440 (OH) and 1720 (C=O) cm⁻¹. ¹H-nmr (CDCl₃) δ 1.9 (d, 1H, J = 3 Hz, OH); 3.8 (s, 3H, OCH₃), 4.6-4.9 (dd, 1H, J₁ = 7 Hz, J₂ = 3 Hz, CHOH), 5.2 (d, 1H, J = 7 Hz, H-4), 6.6-7.7 (m, 19H, arom.).


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