StereoSpecific
Cα-HydroxyethylatIOn
Of the Penicillin Nucleus

Sir:
Recent discoveries of potent β-lactam antibiotics possessing a hydroxyethyl moiety instead of the usual amido side chain at Cα have stimulated the interest in synthetic methods for obtaining hydroxyethyl penicillanates.1) Convenient method for the preparation of 6-hydroxyethyl penicillanate by using metal-halogen exchange reaction was reported earlier by Di-Ninno, et al.2) As an extension of their work, we studied the effect of halogen atom size on the stereochemistry of the incoming hydroxyethyl moiety.

Methyl 6-chloro-6-iodo- (1), 6,6-dibromo- (2) and 6,6-diiodo- (3) penicillanate were reacted with methylmagnesium iodide and acetaldehyde followed by protic quenching. (Fig. 1) The products were isolated by column chromatography (benzene - ethyl acetate, 5:1, Rf 0.5~0.55) and their physico-chemical and spectral properties were determined.

4a, 4b,c: IR (NaCl) vmax (cm⁻¹) 3700~3100 (m), 1785 (vs), 1755 (vs); 1H NMR (60 MHz, CDCl₃) δ 1.38 (3/3H, d, J=6 Hz, 8-CH₃), 1.45 (3/3H, d, J=6 Hz, 8-CH₃), 2.90 (1H, m, OH), 4.55 (1H, m, 8-H), 5.52 (1/3H, s, 5-H), 5.78 (2/3H, s, 5-H); Anal Calcd for C₁₁H₁₆NO₄SBr: C 39.06, H 4.77, N 4.14; Found: C 39.08, H 4.78, N 4.16.

5a, 5b,c: IR (NaCl) max(cm⁻¹) 3700~3100 (m), 1780 (vs), 1755 (vs); 1H NMR (60 MHz, CDCl₃) δ 1.25 (3H, d, J=6 Hz, 8-CH₃), 2.50 (1H, m, 8-H), 3.00 (1H, m, 8-H), 5.77 (1H, s, 5-H); Anal Calcd for C₁₁H₁₆NO₄SCl: C 44.88, H 5.48, N 4.77; Found: C 44.86, H 5.48, N 4.75.

6a: IR (NaCl) v max (cm⁻¹) 3600~3200 (m), 1780 (vs), 1750 (vs); 1H NMR (60 MHz, CDCl₃) δ 1.25 (3H, d, J=6 Hz, 8-CH₃), 2.55 (1H, d, J=4 Hz, OH), 3.30 (1H, dd, J₁=6 Hz, J₂=4 Hz, 8-H), 5.77 (1H, s, 5-H); Anal Calcd for C₁₁H₁₆NO₄SBr: C 34.30, H 4.17, N 3.64; Found: C 34.30, H 4.16, N 3.65.

In the metal-halogen exchange reaction, the yield of each isomer was determined by the integration of the H₅ peak in the 1H NMR spectra. The H₅ peak of the 6α-hydroxyethylated product is further down-field than that of the 6β-hydroxyethylated product because the halogen atom and H₅ are in cis stereochemistry.3) Table 1 shows a consistent trend in composition as the reactants vary from 1 to 3, which appears product related to the size of the halogen atoms. Once the anion is formed at Cα, two factors should be important in determining the stereochemistry at Cα of the penicillin nucleus. One is the tendency to attack the less hindered α-face, and the other is the preference for trans stereochemistry between the penicillin ring and the remaining halogen atom, i.e., β-face attack. The β-face attack always yields a single 8R isomer under the above reaction conditions.2) As shown in Table 1, the β-face attack was increased as the size of remaining halogen atom was increased.

Table 1. Isomer distribution in the metal-halogen exchange reaction.*

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product ratio (%)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b, c</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>—</td>
</tr>
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</table>

* The reactants and products are those shown in Fig. 1.

Fig. 1. Hydroxyethylation at Cα of the methyl 6,6-dihalopenicillanates.
In the case of methyl 6,6-diiodopenicillanate (3), only β-face attack was observed yielding a single isomer \((6a)\).

From the results, we can conclude that the size of the remaining halogen atom plays an important role in the determination of the stereochemistry at C₆ of the penicillin nucleus. Therefore, methyl 6,6-diiodopenicillanate \(^{9}\) is superior to other 6,6-dihalo derivatives \(^{5}\) in the stereospecific hydroxyethylation at C₆ of the penicillin nucleus.

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References