REGULAR PAPER

Mass Spectra of Stereoisomers of Indolizidin-8-ol Derivatives

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The mass spectra of indolizidin-8-ol derivatives (1~6) were measured by electron impact ionization.

The characteristic fragment ions were observed in the mass spectra of the indolizidin-8-ol derivatives at m/z 154, m/z 140, m/z 136, m/z 110, m/z 97, m/z 96, m/z 84, m/z 70, m/z 69, and m/z 55.

The peak intensities at M⁺⁺ and m/z 154 in the mass spectra at 70 eV of the epimers of indolizidin-8-ol derivatives show little difference, but careful examination of the spectra at 70 eV and 20 eV enables distinction between two epimers. The difference between alkyl and phenyl substituents can be recognized by the peak intensities at m/z 154, m/z 140, and m/z 136.

Introduction

In connection with the synthetic study of amino alcohols with analgesic activity, indolizidin-8-ol derivatives (1~6) involving two epimers were synthesized (Fig. 1). The mass spectrometry of these compounds has not been examined yet. We were especially interested in examining whether the stereochemistry of epimeric pairs of indolizidin-8-ols could be distinguished from their mass spectra.

In previous papers,1,2) we reported the mass spectra (MS) of indolizidine and quinolizidine derivatives for which it is possible to distinguish between the epimers. This paper deals with the results of mass spectral fragmentation patterns concerning these stereoisomers. The observed decompositions were characterized by cleavage of a bond beta to the nitrogen in accordance with the well known fission pattern of tertiary amines,3) which lead to loss of an alkyl group.

The MS of stereoisomeric pairs of indolizidin-8-ols were found to differ in a systematic way which could be used to make stereochemical assignments.

Results and Discussion

Mass spectral data at 70 and 20 eV for the indolizidin-8-ol derivatives (1~6) are shown in Tables 1 and 2, and for 4 the MS are shown in Fig. 2. The fragmentations are shown in Scheme 1. The elemental compositions of the fragment ions were established by high resolution measurement.

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Table 1. The Important Peaks and Their Relative Intensities (%) in the Mass Spectra of Indolizidin-8-ol Derivatives at 70 eV

<table>
<thead>
<tr>
<th>Compd.</th>
<th>m/z</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>M+*</td>
</tr>
<tr>
<td>1: ax-OH</td>
<td>15.1</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>13.0</td>
</tr>
<tr>
<td>2: ax-OH</td>
<td>9.9</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>8.4</td>
</tr>
<tr>
<td>3: ax-OH</td>
<td>7.2</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>6.6</td>
</tr>
<tr>
<td>4: ax-OH</td>
<td>6.4</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>5.7</td>
</tr>
<tr>
<td>5: ax-OH</td>
<td>5.3</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>4.7</td>
</tr>
<tr>
<td>6: ax-OH</td>
<td>6.4</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Table 2. The Important Peaks and Their Relative Intensities (%) in the Mass Spectra of Indolizidin-8-ol Derivatives at 20 eV

<table>
<thead>
<tr>
<th>Compd.</th>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M+*</td>
</tr>
<tr>
<td>1: ax-OH</td>
<td>17.7</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>13.3</td>
</tr>
<tr>
<td>2: ax-OH</td>
<td>14.7</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>12.2</td>
</tr>
<tr>
<td>3: ax-OH</td>
<td>14.1</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>11.2</td>
</tr>
<tr>
<td>4: ax-OH</td>
<td>12.3</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>10.8</td>
</tr>
<tr>
<td>5: ax-OH</td>
<td>11.2</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>9.5</td>
</tr>
<tr>
<td>6: ax-OH</td>
<td>9.5</td>
</tr>
<tr>
<td>eq.-OH</td>
<td>4.7</td>
</tr>
</tbody>
</table>

The fragmentation patterns in electron ionization MS were classified into indolizidine ring fragmentations and loss of the alkyl radical from the alkyl group.

Molecular ion

The molecular ions of epimer A (equatorial: R, axial: OH) in the MS of 1~6 showed greater intensity than those of epimer B (equatorial: OH, axial: R). The results are explained by the fact that the hydroxyl group has less bulk than the alkyl and phenyl groups.4)~8)

m/z 154 and 140 ions

The ions at m/z 154 and 140 were observed in the MS of alkyl derivatives 1~5, but these peaks were not observed in phenyl derivative 6. Therefore, the alkyl derivatives can be distinguished from the
Scheme 1. Fragmentation pathways of indole.

Red in all of the MS except 6 and 6.

m/z 97

m/z 69

m/z 136

m/z 154

m/z 140

Fig. 2. MS of 8-butylnicotinilidin-8-ols.

Mass spectra of stereoisomers of indolin-8-ol derivatives.
**m/z 97 and 96 ions**

The ion at m/z 97 was observed in strong intensity. Particularly in the phenyl derivative 6 the ion showed the base peak or similar. The strong intensity of this ion was based on the influence of the beta-cleavage of a nitrogen atom and the stability of the neutral fragment molecule (1-substituted-1-hydroxyethylene) which arose by decomposition. When the substituent is a phenyl group, the fragment molecule has a very stable structure by the conjugation of the phenyl group and the ethylene group. From the reason, it is considered that the formation of the ion at m/z 97 is promoted.

The ion at m/z 97 further loses a hydrogen atom to give the ion at m/z 96, which is stabilized by the conjugated double bond. Moreover, the ion at m/z 97 loses an ethylene molecule to give the ion at m/z 69.

**m/z 84 ion**

The ion at m/z 84 was observed as the base peak in the MS of all compounds except epimer A of the phenyl derivative. The elemental composition is C_5H_9N. The ion seems to be formed by fragmentation pathways with a hydrogen migration from the molecular ion by the mechanism similar to that of formation of the ion at m/z 98 in mass spectra of 1-hydroxyquinolizidine.\(^9\)

**m/z 70 and 69 ions**

These ions were observed in the moderate intensities. The formations of the two ions were triggered by cleavage of bond of a beta-position of a nitrogen atom. The formation of the ion at m/z 70 was accompanied by a hydrogen migration. It seems that the origin of the hydrogen atom is a hydrogen atom of the hydroxyl group, on the basis of experimental results using the deuterium analog of the hydroxyl group.

The ion at m/z 69 was formed from the molecular ion by a mechanism similar to that of the formation of the ion at m/z 83 in 1-hydroxyquinolizidine.\(^9\)

**Conclusion**

Electron ionization MS of 8-substituted-indolizidin-8-ols were measured.

The orientations of the alkyl substituents in the 8-substituted-indolizidin-8-ols could be estimated by comparison of the peak intensities at m/z 154 and M^+^+. The distinction of alkyl derivatives from phenyl derivatives is possible by observing the peak intensities at m/z 154, m/z 140, and m/z 97. Moreover, these compounds show common ions at m/z 97, m/z 84, and m/z 70, accompanied by rearrangement of a hydrogen.

**Experimental**

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected.

Low and high resolution MS were obtained using a Hitachi RMU-7MG double-focusing mass spectrometer. All compounds were introduced via a direct inlet system at appropriate temperatures. The ion accelerating voltage was 3.2 kV. The ionizing energies were 70 and 20 eV. The total ion current was 80 μA. The ion source temperature was 180°C. Carbon-13 nuclear magnetic resonance (\(^{13}\)C-NMR) spectra were recorded on a JEOL FX-200 spectrometer with tetramethylsilane as an internal standard. All compounds used in this work were prepared according to the procedures described below. The purities of the compounds were checked.
using a gas chromatograph-mass spectrometer. The stereochemistry of the hydroxyl group at the 8-position in epimers was determined by $^{13}$C-NMR spectra.

**General procedures for the synthesis of the 1-substituted-indolizidin-8-ols (1~6)**

A solution of the crude indolizidin-8-one\(^{10}\) (0.05 mol) in 20 ml of dry ether was added dropwise with stirring to a solution of freshly prepared alkyl lithium or phenyllithium (0.10 mol) in dry ether in an ice bath. After the addition, the mixture was stirred overnight at 20°C. The reaction mixture was poured into ice-water. The ethereal layer was separated from the aqueous layer. The aqueous layer was then extracted with ether. The combined organic portions were washed with 5% HCl. The HCl layer was made alkaline with 10% NaOH and extracted with CHCl\(_3\). The CHCl\(_3\) layer was washed with H\(_2\)O, dried over Na\(_2\)SO\(_4\), and evaporated to afford a crude amino alcohol, which was purified by distillation. Each epimer was separated by thin-layer chromatography on alumina (Merck, Aluminiumoxid 60 PF\(_{254}\)) and column chromatography (Merck, Aluminiumoxid 90).

**Compound 1 Epimer A:** Colorless oil, Yield 39%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 71.5 (C\(_8\)); 
**Epimer B:** Colorless oil, Yield 10%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 72.8 (C\(_8\)).

**Compound 2 Epimer A:** Colorless oil, Yield 17%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 70.8 (C\(_8\)); 
**Epimer B:** Colorless needles, mp 67~68°C. Yield 21%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 73.5 (C\(_8\)).

**Compound 3 Epimer A:** Colorless oil, Yield 42%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 70.8 (C\(_8\)); 
**Epimer B:** Colorless needles, mp 72~73°C. Yield 29%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 73.7 (C\(_8\)).

**Compound 4 Epimer A:** Colorless oil, Yield 45%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 70.8 (C\(_8\)); 
**Epimer B:** Colorless needles, mp 86~87°C. Yield 38%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 73.7 (C\(_8\)).

**Compound 5 Epimer A:** Colorless oil, Yield 41%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 70.8 (C\(_8\)); 
**Epimer B:** Colorless needles, mp 69~70°C. Yield 20%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 73.7 (C\(_8\)).

**Compound 6 Epimer A:** Colorless oil, Yield 54%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 71.6 (C\(_8\)); 
**Epimer B:** Colorless needles, mp 83~84°C. Yield 35%, $^{13}$C-NMR (CDCl\(_3\)) $\delta$: 73.8 (C\(_8\)).

**References**


**Keywords**

Amino alcohol
Indolizidin-8-ol
Epimer
Mass spectrum
Stereoisomer