Studies on 1-Alkyl-2(1H)-pyridone Derivatives. XXX.¹
Reactions of 1-Alkyl-2(1H)-pyridones with Fumaric Acid Monomethyl Ester and Acrylic Acid

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Studies aimed at the synthesis of 6-azabicyclo[3.2.1]octane derivatives from 1-alkyl-2(1H)-pyridones (Ia—d) were carried out. Reactions of Ia—d with fumaric acid monomethyl ester and acrylic acid gave 6-alkyl-8-endo-methoxycarbonyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acids (VIIa—d) and 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acids (Xa—d), respectively.

Keywords—1-alkyl-2(1H)-pyridone; fumaric acid monomethyl ester; acrylic acid; 6-azabicyclo[3.2.1]octane; 6-alkyl-8-endo-methoxycarbonyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid; 6-alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid

Diels–Alder adducts of 1-substituted-2-pyridones are interesting as possible synthetic intermediates² of iboga alkaloids. Our previous work³ in this series has shown that the reactions of 1-methyl-2(1H)-pyridone (Ia) with dimethyl fumarate (II) and fumaric acid (III) gave dimethyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5-endo-6-exo-dicarboxylate (IV) and 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-endo-dicarboxylic acid (Va) (which would be formed by transformation from the Diels–Alder adduct), respectively, as shown in Chart 1. These results prompted us to examine the reactions of 1-substituted-2-pyridone with dienophiles having a carboxyl group in the expectation that they might give 6-azabicyclo[3.2.1]octene derivatives. This expectation was realized, and the results are reported in the present paper (Chart 2).

![Chart 1]

(Chart 1)
Reactions of 1-Benzyl-2(1H)-pyridone with Fumaric Acid Monomethyl Ester and Acrylic Acid

The reaction of 1-benzyl-2(1H)-pyridone (Ib) with fumaric acid monomethyl ester (VI) was carried out at 150-160 °C for 7 d to produce 6-benzyl-8-endo-methoxycarbonyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid (VIIb), as shown in Table I. The structure of VIIb was confirmed in the following way. The elemental analysis and the spectral examinations indicated that VIIb was a 6-azabicyclo[3.2.1]octane derivative formed from the adduct of Ib and VI. Hydrolysis of VIIb gave 6-benzyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2,8-endo-dicarboxylic acid (Vb)4) (Chart 3). Next, the location of the methoxycarbonyl group was determined by inspection of the infrared (IR) spectra of VIIb and the diester (VIII). Esterification of VIIb with MeOH and SOCl₂ afforded dimethyl 6-benzyl-7-oxo-6-azabicyclo [3.2.1]oct-2-ene-2,8-dicarboxylate (VIII), the IR spectrum of which showed absorptions due to ester carbonyl (8-position) at 1724 cm⁻¹ and ester conjugated with a double bond (2-position) at 1716 cm⁻¹. Based on a comparison of the IR spectrum of VIIb with that of VIII, the carbonyl absorptions at 1725 and 1710 cm⁻¹ in the IR spectrum of VIIb could be assigned to an ester and a carboxyl group conjugated with a double bond, respectively. Consequently, it was proved that the methoxycarbonyl group was at the 8-position in VIIb.

Heating of Ib and acrylic acid (IX) at 150—160 °C for 7 d afforded 6-benzyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid (Xb), as shown in Table I. Confirmation of its structure was provided by the elemental analysis and spectral examinations. The IR spectrum of Xb exhibited absorptions due to lactam carbonyl at 1645 cm⁻¹ and a carboxyl group conjugated with a double bond at 1705 cm⁻¹. The proton nuclear magnetic resonance (¹H-NMR) spectrum of Xb in pyridine-d₅ showed the signals due to one proton at δ 7.00 and two protons at δ 1.95—2.35, which could be assigned to the C₃-proton at the double bond conjugated with the carboxyl group and methylene at the 4-position, respectively. Moreover, the ¹H-NMR spectral characteristics of Xb were quite similar to those of Vb and VIIb.

The mechanism of the formation of Xb was investigated as follows. 2-Benzyl-2-azabicyclo[2.2.2]oct-7-ene-5-exo-carboxylic acid (XI)² was suggested as a possible intermediate in a speculative mechanism for the synthesis of the 6-azabicyclo[3.2.1]octene system.

\[
\begin{align*}
& \text{N} \quad \text{O} \\
& \text{H} \quad \text{COOH}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & : \text{Me} \\
\text{R}^2 & : \text{R}^1 = \text{C}_2\text{H}_5\text{CH}_2
\end{align*}
\]

Chart 2

\[
\begin{align*}
& \text{N} \quad \text{O} \\
& \text{H} \quad \text{COOH}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & : \text{Me} \\
\text{R}^2 & : \text{R}^1 = \text{C}_2\text{H}_5\text{CH}_2
\end{align*}
\]

Chart 3
reported in our previous paper,\textsuperscript{3)} as shown in Chart 4. Heating of XI at 150—160 °C for 48 h gave Xb in 66.7% yield, whereas methyl 2-benzyl-2-azabicyclo[2.2.2]oct-7-ene-5-exo-carboxylate\textsuperscript{2)} was recovered in 60% yield under the same reaction conditions. The above results offer a chemical basis for the mechanism and provide the location of the methoxycarbonyl group in VIIb, as shown in Chart 4.

\textbf{Reactions of 1-Alkyl-2(1H)-pyridones with VI and IX}

The reactions of 1-alkyl-2(1H)-pyridones (Ia, c, d) with VI and IX gave VIIa, c, d and Xa, c, d, respectively, as shown in Table I. These structures were confirmed by the elemental analyses and spectral examinations. Furthermore, VIIa, c, d were hydrolyzed to give the corresponding dicarboxylic acids (Va, c, d) (Chart 3), which were identical with the corresponding authentic samples.\textsuperscript{3,4)}

<table>
<thead>
<tr>
<th>Starting material I</th>
<th>R\textsuperscript{1}</th>
<th>Dienophile (VI or IX) R\textsuperscript{2}</th>
<th>Product (VII or X) Yield (%)</th>
<th>Recovery of I (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>COOMe</td>
<td>20.8</td>
<td>40.4</td>
</tr>
<tr>
<td>a</td>
<td>Me</td>
<td>H</td>
<td>15.2</td>
<td>48.3</td>
</tr>
<tr>
<td>b</td>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}</td>
<td>COOMe</td>
<td>22</td>
<td>56.9</td>
</tr>
<tr>
<td>b</td>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}</td>
<td>H</td>
<td>21.8</td>
<td>56.8</td>
</tr>
<tr>
<td>c</td>
<td>Et</td>
<td>COOMe</td>
<td>9.4</td>
<td>58.5</td>
</tr>
<tr>
<td>c</td>
<td>Et</td>
<td>H</td>
<td>9.9</td>
<td>56.7</td>
</tr>
<tr>
<td>d</td>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}</td>
<td>COOMe</td>
<td>14.3</td>
<td>64.7</td>
</tr>
<tr>
<td>d</td>
<td>C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}</td>
<td>H</td>
<td>30.1</td>
<td>52</td>
</tr>
</tbody>
</table>

\textbf{Experimental}

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-430 spectrophotometer. Mass spectra (MS) were taken on a Hitachi RMU-6MG spectrometer. \textsuperscript{1}H-NMR spectra were taken at 60 MHz with tetramethylsilane (TMS) as an internal standard on
a JEOL JNM-PX-60 spectrometer, in C6D6-N unless otherwise noted. The chemical shifts are expressed as ppm downfield from TMS. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad and Ar = aromatic. The unit (Hz) of coupling constants (J Hz) is omitted.

**General Procedure for the Preparation of 6-Alkyl-8-endo-methoxycarbonyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic Acids (VIIa—d)** — A mixture of a 1-alkyl-2(1H)-pyridone (Ia—d, 30 mmol) and fumaric acid monomethyl ester (VI, 15 mmol) was heated in a sealed tube at 150—160 °C (an oil bath) for 7 d. The reaction mixture was washed with hot isopropyl ether. The resulting residue was dissolved in CHCl3 and the solution was washed with 10% HCl. The fraction eluted with CHCl3-MeOH (50:1) was evaporated to give VIIa—d (Table I).

6-Benzy1-8-endo-methoxycarbonyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic Acid (VIIb): Colorless prisms, mp 194—196 °C (EtOH). Anal. Calcd for C15H15NO3: C, 70.02; H, 5.88; N, 5.41. Found: C, 69.87; H, 5.86; N, 5.35. MS m/z: 239 (M+). IR νmax cm⁻¹: 1742 (COOMe), 1708 (COOH), 1660 (NC=O). ^1H-NMR δ: 2.43 (1H, br d, J = 20, C4-Hendo), 2.63 (1H, br d, J = 20, C4-Hexo), 3.34—3.77 (1H, m, C8-H), 3.53 (3H, s, COOMe), 3.80—4.07 (2H, m, C1-H, C5-H), 4.37 (1H, d, J = 18, C4-Hendo), 4.35. MS m/z: 315 (M+). IR νmax cm⁻¹: 1735 (COOMe), 1705 (COOH), 1658 (NC=O), 742, 698 (δCH). ^1H-NMR δ: 2.40 (1H, br d, J = 20, C4-Hendo), 2.50—3.20 (3H, m, C4-Hexo, N-CH-C2-H), 3.20—4.15 (4H, m, C1-H, C4-Hendo), C4-Hendo, C4-Hexo, C3-H, N-CH3, C4-Hendo, C3-H, 3.53 (3H, s, COOME), 4.33 (1H, d, J = 5, C4-Hendo), 7.10 (1H, s, C2-Hendo), 7.10 (1H, s, Ar-H).

**Preparation of Va—d by Hydrolysis of VIIa—d** — A mixture of VIIa—d (1 mmol), 10% KOH (3 ml) and MeOH (3 ml) was stirred at room temperature for 24 h. The reaction mixture was acidified with 10% HCl (3 ml). The resulting solid was collected and recrystallized from EtOH to give Va—d (Chart 3) in 63.8, 73.8, 68.5 and 73.1% yields, respectively. The products (Va—d) were identified by comparison with the corresponding authentic samples.

**Preparation of VIII—Compound VIIb (0.32 g) was added to an ice-cooled mixture of SOCl2 (0.32 g) and MeOH (3 ml), and the mixture was stirred to completion at room temperature. The reaction mixture was poured into ice-water and made basic with NaHCO3, and the basic mixture was extracted with benzene. The benzene extract was evaporated to give a solid, which was recrystallized from benzene to afford dimethyl 6-benzy1-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (VIII, 0.26 g), mp 86—87 °C, in 77.8% yields as colorless prisms. Anal. Calcd for C18H19N05: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.67; H, 5.81; N, 4.14. MS m/z: 329 (M+). IR νmax cm⁻¹: 1735 (COOMe), 1705 (COOH), 1658 (NC=O), 742, 698 (δCH). ^1H-NMR δ: 2.40 (1H, br d, J = 20, C4-Hendo), 2.50—3.20 (3H, m, C2-Hexo, N-CH3—C2-H), 3.20—4.15 (4H, m, C1-H, C4-Hendo), C4-Hendo, C4-Hexo, C3-H, N-CH3, C4-Hendo, C3-H, 3.53 (3H, s, COOME), 4.33 (1H, d, J = 5, C4-Hendo), 7.10 (1H, s, C2-Hendo), 7.10 (5H, s, Ar-H).

**General Procedure for the Preparation of 6-Alkyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic Acids (Xa—d)** — A mixture of a 1-alkyl-2(1H)-pyridone (Ia—d, 30 mmol) and acrylic acid (IX, 15 mmol) was heated in a sealed tube (copper) at 150—160 °C (an oil bath) for 7 d. The reaction mixture was washed with hot isopropyl ether. The resulting residue was dissolved in CHCl3 and the CHCl3 solution was washed with 10% HCl. The CHCl3 layer was dried over MgSO4 and evaporated. The resulting solid was recrystallized from EtOH to give Xa, mp 171—172 °C, as colorless prisms. Anal. Calcd for C17H15NO3: C, 70.02; H, 5.88; N, 5.41. Found: C, 69.72; H, 5.86; N, 5.31. MS m/z: 257 (M+). IR νmax cm⁻¹: 1705 (COOH), 1645 (NC=O), 732, 700 (δCH). ^1H-NMR δ: 1.60 (1H, d, J = 11, C4-Hendo), 1.95—2.35 (3H, m, C4-Hexo), 3.60 (1H, m, C2-Hendo), 3.97 (1H, d, J = 5, C4-Hendo), 4.23 (1H, d, J = 15,
N–CH–C₆H₅), 4.80 (1H, d, J = 15, N–CH–C₆H₅), 7.00 (1H, m, C₃-H), 7.23 (5H, s, Ar-H).

6-Ethyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic Acid (Xc): The reaction mixture was worked up as described for Xa, to give Xc, mp 182–183°C (EtOH), as colorless prisms. Anal. Calcd for C₁₀H₁₃NO₃: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.36; H, 6.58; N, 7.12. MS m/z: 195 (M⁺). IR νmax cm⁻¹: 1710 (COOH), 1640 (NC = O).

¹H-NMR δ: 1.03 (3H, t, J = 7, CH₂-CH₃), 1.65 (1H, d, J = 12, C₈-Hendo), 1.95–2.50 (3H, m, C₄-H ~ 2, C₈-Hexo), 2.80–3.65 (2H, m, CH₂-CH₃), 3.70 (1H, m, C₅-H), 3.87 (1H, d, J = 5, C₁-H), 7.03 (1H, d, J = 5, C₁-H), 7.03 (1H, m, C₃-H).

7-Oxo-6-phenethyl-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic Acid (Xd): The reaction mixture was worked up as described for Xb, to give Xd, mp 197–198°C (EtOH), as colorless prisms. Anal. Calcd for C₁₆H₁₇NO₃: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.57; H, 6.39; N, 5.33. MS m/z: 271 (M⁺). IR νmax cm⁻¹: 1718 (COOH), 1645 (NC = O), 740, 704 (δCH). ¹H-NMR δ: 1.60 (1H, d, J = 11, C₈-Hendo), 1.93–2.45 (3H, m, C₄-H × 2, C₈-Hexo), 2.70–3.17 (2H, m, N–CH–CH₂–C₆H₅), 3.43–4.05 (3H, m, C₅-H, N–CH₂–CH–C₆H₅), 3.85 (1H, d, J = 6, C₁-H), 7.03 (1H, m, C₃-H), 7.25 (5H, s, Ar-H).

Preparation of Xb by Heating of XI—2-Benzyl-2-azabicyclo[2.2.2]oct-7-ene-5-exo-carboxylic acid (XL²¹ 0.03 g) was heated at 150–160°C (an oil bath) for 2 d in a sealed tube. The resulting solid was recrystallized from EtOH to give Xb (0.02 g) in 66.7% yield.

References