Studies on Seven-Membered Heterocycles. XXXI.1) Synthesis of 1,4-Oxazepinones and 1,4-Diazepinones from 2-Pyridones and Their Conversion into Fully Unsaturated 1,4-Oxazepines and 1,4-Diazepines

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Thermolysis of the 6-aza-3-oxatricyclo[3.2.0.0^2,4]heptan-7-ones (8 and 21) and 3,6-diazatricyclo[3.2.0.0^2,4]heptan-7-ones (9 and 22), prepared from the corresponding 2-pyridones (5) via the 2-azaazabicyclo[2.2.0]hex-5-en-3-ones (7 and 18), resulted in valence isomerization with ring opening to give the novel 1,4-oxazepin-5-ones (10a–e and 15a–c) and 1,4-diazepin-5-ones (11a–e and 16a–c), respectively. Treatment of the N-unsubstituted compounds 15 and 16 with triethylammonium tetrafluoroborate afforded the fully unsaturated 1,4-oxazepines (23a–c) and 1H-1,4-diazepines (24a–c), respectively.

Keywords 2-pyridone; 1,4-oxazepin-5-one; 1,4-diazepin-5-one; 1,4-oxazepine; 1,4-diazepine; 6-aza-3-oxatricyclo[3.2.0.0^2,4]-heptan-7-one; 3,6-diazatricyclo[3.2.0.0^2,4]heptan-7-one; thermal valence isomerization; ring expansion

gave the key tricyclic oxirane compounds 8a–e, 6-aza-3-oxatricyclo[3.2.0.0^2,4]heptan-7-ones, in ca. 95% yields, the aziridine compounds 9a–e, 3,6-diazatricyclo[3.2.0.0^2,4]-heptan-7-ones, were prepared in ca. 40% yields by the reaction of 7 with ethoxycarbonylnitrene generated from N-ethoxycarbonyl-p-nitrobenzenesulfonylhydroxylamine by treatment with benzyltritylimmonium bromide and sodium hydrogencarbonate,13 when the N-protecting methoxymethyl (MOM) group is absent in the bicyclic compounds 7, the yields of either the oxirane or aziridine compounds are very low (10–15%).

The structures of the tricyclic compounds 8 and 9 were characterized on the basis of their spectral data, particularly by proton nuclear magnetic resonance (1H-NMR) spectral comparison with the already reported compounds 11 and 3,7 of which the stereochemistry, however, has not been examined in detail. In the 1H-NMR spectrum of 8b, a nuclear Overhauser effect (NOE) enhancement (15–20%) was observed only between the 2-Me (δ 1.63) and the 4-H (δ 4.23) signals; indicating that 8b is the anti-stereocluster shown in Fig. 1 and not the syn-structure, and consequently, all of the tricyclic compounds reported are considered to have similar stereocounters.

Heating the tricyclic compounds 8a–d and 9a–e in dichlorobenzene at 150°C until almost all of the starting compounds had been consumed (for 4–6 h) resulted in valence isomerization with ring opening to give the novel 1,4-oxazepin-5-ones (10a–d) and 1,4-diazepin-5-ones (11a–e), respectively, in 70–90% yields. In the case of the oxirane compound 8e (R^4 = Me), thermolysis at 150°C for 5 h gave only the 5-hydroxy-2-pyridone derivative 12e in 85% yield and no oxazepinone (10e), whereas at 120°C for 2 h resulted in the formation of 10e in 40% yield, together with 12e (ca. 20%) and the starting 8e (35%), showing that 10e may readily undergo thermal rearrangement to give 12e. Therefore, the thermal behavior of the diheteroepinones 10 and 11 was examined. The oxazepinones (10a,b,e) were heated in dichlorobenzene at 165°C in a sealed tube for 10 h to result in rearrangement giving the expected 5-hydroxy-2-pyridones (12) in moderate yields, probably by the path involving the azirinonorcaradiene intermediates, as shown in Chart 2. The electron-donating 3-Me group (R^4) in 10e may assist the formation of the norcaradiene intermediate, and thus 10e might readily be converted to 12e at lower temperature. On the contrary, even when the diazepinones...
(11a,b) were heated at 200°C for 10 h, no reaction occurred. An analogous difference in thermolitic behavior between oxepines and aepines has been observed for a variety of heteroepines.2,7)

Hydrolysis of the N-methoxyethyl(MOM)-diheptetepinones (10a and 11a) with hydrogen chloride in acetone gave the N-hydroxymethyl compounds 13a and 14a in 47% and 35% yields, respectively. In the infrared (IR) spectra of 13a and 14a, the amide carbonyl absorption bands appeared at lower wave-lengths (13a: 1650 cm⁻¹; 14a: 1652 cm⁻¹) than those of the MOM compounds 10a and 11a (1670 cm⁻¹): indicating that the carbonyl oxygen is hydrogen bonded with the OH hydrogen atom.

Treatment of 13a and 14a with ammonia in ether resulted in dehydroxymethylation to afford the desired N-unsubstituted parent 1,4-oxazepin-5-one (15a) and 1H-1,4-diazepin-5-one (16a), respectively, in ca. 50% yields. The N-unsubstituted compounds 15 and 16 could also be prepared by the following different route, shown in Chart 3.

The 2-aza-3-oxobicyclo[2.2.0]hex-5-enes (17a—c), prepared from the corresponding N-unsubstituted 2-pyridones (5) by irradiation, were treated with tert-butyldimethylsilyl...
in dimethylformamide to give the N-TBDMs derivatives 18 in ca. 90% yields. Treatment of 18a–c with m-CPBA afforded the oxirane compounds 19 in 95–97% yields and treatment with ethoxy carbonylnitrene generated by the method described for 9 gave the aziridine compounds 20 in ca. 50% yields. The protecting TBDMS group in 19 and 20 could be readily removed only by passage through a short alumina column using ether–methanol (50:1) as an eluent, giving rise to the N-unsubstituted lactam compounds 21 and 22, respectively, in quantitative yields. These compounds (21 and 22) were also obtained directly from the N-unsubstituted bicyclic compounds 17 by treatment with m-CPBA or ethoxy carbonylnitrene, but in very low yields (10–20%). Heating the tricyclic rings 21 and 22 also resulted in ring opening to give the 1,4-oxazepine-5-ones (15a–c) and 1H-1,4-diazepin-5-ones (16a–c), respectively, in ca. 90% yields.

The structures of the new diheteroepinones were elucidated from their spectral data and the results of the following chemical studies. For example, the IR spectra of 15a and 16a showed a strong absorption band at 1670 cm⁻¹ due to the conjugated amide carbonyl group. The ¹H-NMR of 15a and 16a showed two AB pairs of doublets at δ 5.52 and 4.99 (J = 6 Hz) for 15a, 5.58 and 5.18 (J = 8 Hz) for 16a assignable to 2-H and 3-H, and at δ 4.80 and 6.26 (J = 7.5 Hz) for 15a, 4.92 and 6.98 (J = 10 Hz) for 16a due to 6-H and 7-H, respectively, in addition to the signal at δ 7.5 (NH).

In order to convert the diheteroepinones into fully unsaturated diheteroepines, 15 and 16 were treated with TBDMS chloride in the presence of diethylamine or with n-butyl lithium followed by methyl iodide, but only decomposition occurred, and the expected O-silylation or O-methylation products could not be obtained. However, treatment of 15 and 16 with triethylsiloxonium tetrafluoroborate in dichloromethane resulted in O-ethylation predominantly to give the desired fully unsaturated 5-ethoxy-1,4-oxazepines (23a–c) and 5-ethoxy-1H-1,4-diazepines (24a–c), respectively, in 75–90% yields. As was expected, the 1,4-oxazepines (23) having an anti-aromatic ring system with π electrons are relatively unstable and susceptible to decomposition in a silica gel or alumina column, whereas the 1,4-diazepines (24) stabilized by the electron-withdrawing ethoxy carbonyl group on the nitrogen atom are stable and can be purified by chromatography, by analogy with 1,3-diheteroepines[2,4,5] 1,4-diheteroepines[2,9] and 1-acylazepines[2].

The structures of the diheteroepines 23 and 24 were characterized on the basis of the spectral data and the result of the following thermolysis. For example, in the ¹H-NMR spectra of 23a and 24a, signals due to four ring protons lie in the olefinic range (δ 5.1–5.9 for 23a; δ 5.1–6.6 for 24a) as two pairs of doublets. Heating the oxazepine (23a) at 45°C for 1 h in benzene gave 2-ethoxy-5-hydroxy pyridine (26) in 60% yield, presumably via the aza-norcaradiene.

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>2-H</th>
<th>3-H</th>
<th>6-H</th>
<th>7-H</th>
<th>Me</th>
<th>CH₃O-CH₂-NH</th>
<th>CH₃-CH₂-O₂C-</th>
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<tr>
<td>10a</td>
<td>5.67 (d)</td>
<td>5.15 (d)</td>
<td>4.94 (d)</td>
<td>6.33 (d)</td>
<td>—</td>
<td>3.30 4.73</td>
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<td>5.80 (d)</td>
<td>5.30 (d)</td>
<td>5.06 (q)</td>
<td>—</td>
<td>1.86 (d)</td>
<td>3.32 4.82</td>
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<tr>
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<td>J₂,3 = 6, J₆,₇ = 0.8</td>
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<td>5.26 (q)</td>
<td>5.10 (d)</td>
<td>6.54 (d)</td>
<td>1.80 (d)</td>
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<td>J₂,3 = 5, J₆,₇ = 0.8</td>
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<td>5.45 (d)</td>
<td>—</td>
<td>6.57 (q)</td>
<td>1.78 (d)</td>
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<tr>
<td>10e</td>
<td>6.06 (q)</td>
<td>5.27 (d)</td>
<td>6.73 (d)</td>
<td>1.83 (d)</td>
<td>—</td>
<td>3.34 4.99</td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>J₂,3 = 5, J₆,₇ = 7</td>
<td>J₂,3 = 5, J₆,₇ = 7</td>
<td></td>
<td>5.38 (d)</td>
<td>5.08 (d)</td>
<td>7.01 (d)</td>
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<td>J₂,3 = 6, J₆,₇ = 10</td>
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<td>5.74 (d)</td>
<td>5.45 (q)</td>
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<td>2.14 (d)</td>
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<td>J₂,3 = 7, J₆,₇ = 1</td>
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<td>5.56 (d)</td>
<td>—</td>
<td>6.90 (q)</td>
<td>1.91 (d)</td>
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<td>J₂,3 = 7, J₆,₇ = 1</td>
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<td>5.26 (d)</td>
<td>—</td>
<td>7.09 (d)</td>
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<tr>
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<td>5.52 (d)</td>
<td>4.99 (dd)</td>
<td>4.80 (dd)</td>
<td>6.26 (d)</td>
<td>—</td>
<td>7.5 (br)</td>
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<td>J₂,3 = 6, J₆,₇ = 7.5</td>
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<td>4.90 (m)</td>
<td>—</td>
<td>1.82 (d)</td>
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<td>5.08 (d)</td>
<td>—</td>
<td>5.01 (m)</td>
<td>4.88 (dd)</td>
<td>6.37 (d)</td>
<td>1.71 (d)</td>
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<td>J₂,3 = 6, J₆,₇ = 6, J₆,₇ = 2.5, J₆,₇ = 7.5</td>
<td>J₂,3 = 5, J₆,₇ = 2.5</td>
<td>6.98 (d)</td>
<td>—</td>
<td>7.4 (br)</td>
<td>1.32 4.27</td>
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<tr>
<td>16b</td>
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<td>J₂,3 = 5, J₆,₇ = 2</td>
<td>5.93 (d)</td>
<td>4.92 (dd)</td>
<td>—</td>
<td>2.16 (s)</td>
<td>8.6 (br)</td>
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<td>J₂,3 = 5, J₆,₇ = 2</td>
<td>5.68 (m)</td>
<td>4.50 (dd)</td>
<td>7.02 (d)</td>
<td>2.00 (d)</td>
<td>8.2 (br)</td>
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(CDC₃), J = Hz.
intermediate 25. Similarly, thermolysis of 24a afforded 2-ethoxy-5-ethoxy carbamylaminopyridine (27) in 78% yield, though somewhat more drastic conditions (heating in dichlorobenzene at 180°C for 12 h) were required.

These thermal behaviors are similar to those observed for 5-phenyl-1,4-diheterocycles. 7 In both cases (23a and 24a), the formation of other possible rearrangement products (28) was not observed, probably because the electron-donating ethoxy group favors the C4–X bond cleavage to give predominantly 26 and 27, as shown in the structure 25, and therefore, the C3–X bond cleavage products 28 are not formed.

In conclusion, the present results provide the first examples of 1,4-diheterocinones as well as a new route to fully unsaturated 1,4-oxazepines and 1,4-diazepinones.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Jasco FT/IR-410 spectrometer and mass spectra (MS) were measured with a JEOL DX-300 instrument. 1H-NMR spectra were recorded on a JEOL JNM-MH100 or GSX-400 spectrometer in CDCl3, using tetramethylsilane as an internal standard unless otherwise stated; spectral assignments were confirmed by spin-decoupling experiments and, in the case of NH protons, by exchange with D2O. Microanalyses were performed in the Microanalytical Laboratory of this Faculty by Mrs. R. Igarashi. Photolyses were carried out under a nitrogen atmosphere in an immersion apparatus equipped with a 400 W high-pressure Hg lamp, which was cooled internally with running water.

1-Methylthioethyl-2-pyridones (6a–e): General Procedure: A solution of chloromethyl methyl ether (1.2 mol eq) in CH2Cl2 (10 ml) was added with stirring to a solution of 2-pyridone (5a–e, 15.4 g, 10 g) in CH2Cl2 (150 ml). The reaction solution was stirred for 24 h at room temperature and then diluted with CH2Cl2 (200 ml). The mixture was successively washed with saturated NaHCO3 and saturated NaCl, dried over MgSO4, and evaporated in vacuo. The residue was chromatographed on silica gel using ether–hexane (1:2) as an eluent to give 6 as a colorless oil.

1-Methylthioethyl-2-pyridone (6a): Yield, bp 102–103.5°C (2.5 mmHg). IR (KBr): 1660 (C = O) cm–1. 1H-NMR δ: 3.39 and 5.35 (3H, s and 2H, s, CH2OH), 6.30 (1H, m, 5-H), 6.50 (1H, m, 6-H), 7.40 (1H, d, 3-H), 7.50 (1H, m, 6-H), 7.13 (1H, s), 1.55 (1H, s), 3.15 (2H, s, J = 7 Hz), 7.93 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C6H10N2O: 159.0637. Found: 159.0637.

1-Methylthioethyl-2-pyridone (6b): Yield, bp 70–71°C (3.5 mmHg). IR (KBr): 1672 (C = O) cm–1. 1H-NMR δ: 3.38 and 5.30 (3H, s and 2H, s, CH2OH), 2.19 (3H, s, CH3), 6.06 (1H, d, 5-H), 6.35 (1H, d, 3-H), 3.50 (2H, s, J = 7 Hz), 7.13 (1H, s), 1.50 (1H, s), 7.96 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C8H14N2O: 173.0706. Found: 173.0706.

1-Methylthioethyl-2-pyridone (6c): Yield, bp 111–113°C (3 mmHg). IR (KBr): 1674 (C = O) cm–1. 1H-NMR δ: 3.40 and 5.31 (3H, s and 2H, s, CH2OH), 2.08 (3H, brs, s-Me), 5.64 (1H, d, 4-H), 7.18 (1H, br dd, 6-H), 7.26 (1H, dd, 4-H), 7.09 (1H, s), 2.18 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C8H14N2O: 173.0706. Found: 173.0706.

1-Methylthioethyl-3-pyridone (6d): Yield, bp 115–118°C (3.5 mmHg). IR (KBr): 1662 (C = O) cm–1. 1H-NMR δ: 3.43 and 5.38 (3H, s and 2H, s, CH2OH), 2.16 (3H, brs, s-Me), 6.20 (1H, d, 5-H), 7.28 (1H, m, 4-H), 7.36 (1H, dd, 6-H), 7.17 (1H, s), 1.57 (1H, s), 7.94 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C8H14N2O: 173.0706.

1-Methylthioethyl-4-pyridone (6e): Yield, bp 112–114°C (3.5 mmHg). IR (KBr): 1664 (C = O) cm–1. 1H-NMR δ: 3.33 and 5.43 (3H, s and 2H, s, CH2OH), 2.38 (3H, s, Me), 6.59 (1H, d, 5-H), 7.62 (1H, s), 7.15 (1H, d, 4-H), 7.97 (1H, s). High-resolution MS m/z: M+ Calc. for C8H14N2O: 173.0706.

1-Methylthioethyl-2-azabicyclo[2.2.2]hex-5-en-3-ones (7a–e): General Procedure: A solution of 2-pyridone (6a–e, 1–2 g) in benzene (300 ml) was irradiated; this photolysis was followed in terms of the disappearance of the spot of the starting 6 on silica gel thin-layer chromatography (TLC) and was complete in 20–40 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel using ether–hexane (1:2) as an eluent to give 7 as a colorless viscous oil.

1-Methylthioethyl-2-azabicyclo[2.2.2]hex-5-en-3-one (7a): Yield, bp 71°C. IR (neat): 1755 (C = O), 1558 (C = C) cm–1. 1H-NMR δ: 3.28 and 4.54 (3H, s and 2H, d, J = 11 Hz, CH2OCH2), 4.27 (1H, m, 4-H), 4.47 (1H, dd, 1-H), 6.65 (1H, m, 5-H), 6.72 (1H, dd, 6-H), 7.32 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C13H14N2O: 193.0637. Found: 193.0621.

1-Methylthioethyl-2-azabicyclo[2.2.2]hex-5-en-3-one (7b): Yield, bp 76°C. IR (neat): 1750 (C = O), 1624 (C = C) cm–1. 1H-NMR δ: 3.32 and 4.53 (3H, s and 2H, s, CH2OH), 1.90 (3H, m, 5-Me), 4.06 (1H, m, 4-H), 4.23 (1H, m, 1-H), 6.23 (1H, m, 6-H), 7.32 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C12H14N2O: 185.0706. Found: 185.0739.

1-Methylthioethyl-2-azabicyclo[2.2.2]hex-5-en-3-one (7c): Yield, bp 75°C. IR (neat): 1756 (C = O), 1624 (C = C) cm–1. 1H-NMR δ: 3.39 and 4.53 (3H, s and 2H, d, J = 11 Hz, CH2OCH2), 1.86 (3H, s, 5-Me), 3.97 (1H, m, 4-H), 4.23 (1H, m, 1-H), 6.16 (1H, m, 5-H), 7.32 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C12H15N2O: 188.0816. Found: 188.0816.

1-Methylthioethyl-2-azabicyclo[2.2.2]hex-5-en-3-one (7d): Yield, bp 75°C. IR (neat): 1760 (C = O), 1624 (C = C) cm–1. 1H-NMR δ: 3.32 and 4.53 (3H, s and 2H, d, J = 11 Hz, CH2OCH2), 1.86 (3H, s, 5-Me), 3.97 (1H, m, 4-H), 4.23 (1H, m, 1-H), 6.16 (1H, m, 5-H), 7.32 (2H, s, J = 7 Hz). High-resolution MS m/z: M+ Calc. for C12H15N2O: 188.0816.
to a solution of a bicyclic compound (7a–e, ca. 1 g) in CH₂Cl₂ (100 mL). N-Ethoxycarbonyl-N-nitrobenzenesulfonfluorohydrazone (1.5 mol eq) was added in small portions over a 0.5 h period to the above mixture with vigorous stirring in an ice bath. The reaction mixture was stirred for a further 5 h at room temperature and diluted with CH₂Cl₂ (100 mL). The organic layer was separated, washed with saturated NaCl solution, dried, and evaporated in vacuo. The residue was chromatographed on silica gel using ether–hexane (1:2–1:1) as an eluent to give 9a as a colorless viscous oil.

3-Ethoxycarbonyl-6-methoxyethyl-3,6-diaza-tricyclo[3.2.0.0²⁶]heptan-7-one (9a): 35% yield. IR (neat): 1770 and 1726 (C=O) cm⁻¹. ¹H-NMR: δ 1.29 and 4.19 (1H, t and 2H, q, CO₂Et), 3.32 and 4.57 (3H, s, and 3H, q, CH₃OEt), 1.55 (3H, d, 4-H), 3.59 (1H, dd, 4-H), 3.74 (2H, m, 2-H, and 5-H). 1H, (2H, d, 1-H), J₁₂ = 3.5Hz, J₃₅ = 1.8Hz, J₁₂,J₃₅ = 3.7Hz. High-resolution MS m/z: M⁺ Caled for C₇H₁₂N₂O₃ 226.0954. Found: 226.0959.

3-Ethoxycarbonyl-6-methoxyethyl-2-methyl-3,6-diaza-tricyclo[3.2.0.0²⁶]heptan-7-one (9b): 40% yield. IR (neat): 1788 and 1720 (C=O) cm⁻¹. ¹H-NMR: δ 1.29 and 4.09 (1H, t and 2H, q, CO₂Et), 3.72 and 4.49 (3H, s, and 2H, d, J = 11.5Hz, CH₂OH, 1.55 (3H, s, 2-Me), 3.52 (1H, d, 4-H), 3.66 (1H, dd, 5-H), 3.96 (1H, d, 1-H), J₁₂ = 1.8Hz, J₃₅ = 3.5Hz. High-resolution MS m/z: M⁺ Caled for C₇H₁₄N₂O₃ 240.1100. Found: 240.1125.

3-Ethoxycarbonyl-6-methoxyethyl-4-methyl-3,6-diaza-tricyclo[3.2.0.0²⁶]heptan-7-one (9c): 39% yield. IR (neat): 1774 and 1726 (C=O) cm⁻¹. ¹H-NMR: δ 1.29 and 4.20 (1H, t and 2H, q, CO₂Et), 3.35 and 4.60 (3H, s, and 2H, s, CH₂OEt), 1.61 (3H, s, 4-Me), 3.48 (1H, d, 2-H), 3.69 (1H, d, 5-H), 4.12 (1H, dd, 1-H), J₁₂ = 3.5Hz, J₃₅ = 1.8Hz. High-resolution MS m/z: M⁺ Caled for C₇H₁₄N₂O₃ 240.1100. Found: 240.1094.

3-Ethoxycarbonyl-6-methoxyethyl-1-methyl-3,6-diaza-tricyclo[3.2.0.0²⁶]heptan-7-one (9d): 40% yield. IR (neat): 1768 and 1726 (C=O) cm⁻¹. ¹H-NMR: δ 1.29 and 4.16 (1H, t and 2H, q, CO₂Et), 3.33 and 4.53 (3H, s, and 2H, d, J = 11.5Hz, CH₂OH), 1.37 (3H, s, 1-Me), 3.56 (1H, dd, 4-H), 3.68 (1H, d, 3-H), 3.95 (1H, d, 5-H), J₁₂ = 2Hz, J₃₅ = 3.5Hz. High-resolution MS m/z: M⁺ Caled for C₇H₁₄N₂O₃ 240.1100. Found: 240.1096.

3-Ethoxycarbonyl-6-methoxyethyl-5-methyl-3,6-diaza-tricyclo[3.2.0.0²⁶]heptan-7-one (9e): 34% yield. IR (neat): 1766 and 1724 (C=O) cm⁻¹. ¹H-NMR: δ 1.26 and 4.18 (1H, t and 2H, q, CO₂Et), 3.35 and 4.55 (3H, s, and 2H, d, J = 12Hz, CH₂OH), 1.43 (3H, s, 5-Me), 3.22 (1H, d, 1-H), 3.55 (1H, d, 4-H), 3.75 (1H, dd, 2-H), J₁₂ = 3.5Hz, J₃₅ = 2Hz. High-resolution MS m/z: M⁺ Caled for C₇H₁₄N₂O₃ 240.1100. Found: 240.1108.

**Thermolysis of 8a–d: Formation of 4-Methoxymethyl-1,4-oxazepin-5-ones (10a–d)**

A solution of a triecyclic compound (8a–d, ca. 0.5 g) in dichlorobenzene (3–5 mL) was heated at 150°C. The reaction was followed in terms of the disappearance of the spot of the starting 8 in thin layer chromatography (TLC) and was completed in 4–6 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel using ether–hexane (1:2) as an eluent to give 10a as a yellow viscous oil. ¹H-NMR spectral data of 10a–d are collected in Table I.

4-Methoxymethyl-1,4-oxazepin-5-one (10a): 72% yield. IR (neat): 1670 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₀H₁₁N₄O₂ 169.0739. Found: 169.0722.

4-Methoxymethyl-2,4-oxazepin-5-one (10b): 70% yield. IR (neat): 1671 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₀H₁₁N₄O₂ 169.0739.

4-Methoxymethyl-2,5-oxazepin-5-one (10c): 75% yield. IR (neat): 1660 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₀H₁₁N₄O₂ 169.0739.

4-Methoxymethyl-5,6-oxazepin-5-one (10d): 85% yield. IR (neat): 1690 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₀H₁₁N₄O₂ 169.0739.

**Thermolysis of 11a, b**

A solution of 11 (ca. 50 mg) in dichlorobenzene was heated at 200°C for 10 h in a sealed tube and worked up as described for the thermolysis of 10a–d to give 11a as a white solid. ¹H-NMR spectral data of 11a, b are given in Table II.

4-Hydroxy-1-methoxymethyl-1,4-oxazepin-5-one (11a): A mixture of 10a (200 mg), acetone (4 mL), and 0.5 mL HCl (4 mL) was stirred for 4 h at room temperature and then diluted with CH₂Cl₂ (100 mL). The organic layer was separated, washed with water, dried, and evaporated in vacuo. The residue was chromatographed on silica gel using ether–hexane (1:2) as an eluent to give 11a as a white solid, 41% yield, mp 70.5–71.5°C, yellow plates (from i-PrEt). IR (KBr): 3350 (OH), 1650 (C=O) cm⁻¹. ¹H-NMR δ: 3.95 and 4.80 (1H, t and 2H, d, J = 8Hz, HOCH₂), 5.00 (1H, d, 6-H), 3.52 (1H, d, 3-H), 5.72 (1H, d, 2-H), 6.40 (1H, d, 7-H). J₁₂,J₃₅ = 6Hz, J₃₅,J₃₅ = 8Hz. Anal. Caled for C₇H₁₀N₂O₃ C: 51.06; H: 5.00; N: 9.93. Found: C: 51.13; H: 4.91; N: 9.92.

4-Hydroxy-1-methoxymethyl-1,4-oxazepin-5-one (11b): 41% yield, mp 71°C, yellow oily viscous oil. IR (neat): 1731 and 1665 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₀H₁₁N₄O₃ 170.0410. Found: 170.0413.
t, and 2H, d, J = 8 Hz, HOCH₂CH₂, 4.27 (1H, d, J = 4 Hz), 5.06 (1H, d, 3H), 5.45 (1H, d, 2H), 7.00 (1H, d, 7H), Jₑ₈ = 8 Hz, J₈₉ = 10 Hz. High-resolution MS m/z: M⁺ Caled for C₁₅H₂₁N₅O₅: 212.0797. Found: 212.0809.

1.4-Oxazepine-5(15a) Ammonia (0.1 g, 4 ml) was added dropwise over a 5 min period to a solution of 15a (56 mg) in ether (10 ml) with stirring. The reaction mixture was diluted with CH₂Cl₂ (50 ml) and the orange mixture was washed with water, dried, and evaporated in vacuo. The residue was chromatographed on silica gel using ether-hexane (1:4) as an eluent to give 15a: 18.5 mg, 42% yield, yellow viscous oil (solidified below 20 °C). IR (neat): 3200 (NH), 1670 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₃H₁₉N₅O₅: 211.10320. Found: 211.10326. 1H-NMR spectral data are collected in Table I.

1.6-Benzoxazepine-5(16a) Compound 14a (60 mg) was treated with aqueous ammonia and worked up as described for 15a to give 16a: 23 mg, 45% yield, mp 69–70 °C, yellow prisms (from benzene-IEP). IR (KBr): 3200 (NH), 1744 and 1674 (C=O) cm⁻¹. High-resolution MS m/z: M⁺ Caled for C₁₆H₁₈N₅O₅: 282.0691. Found: 282.0692. 1H-NMR spectral data are collected in Table I.

2-Azabicyclo[2.2.2]octane-5(3)-one (17a) The pyridones (5a–e, 1–2 g) were irradiated and worked up as described for 7 to give 17a–e.

2-Azabicyclo[2.2.2]octane-5(3)-one (17a): 42% yield, mp 65–66 °C (lit. 1.175 mp 65.5–66.5 °C), colorless prisms (from benzene-IEP).

5-Methyl-2-azabicyclo[2.2.2]octane-5(3)-one (17b): 65% yield, mp 55–56 °C (lit. 1.201 mp 56 °C), white crystals (from ethanol). IR (KBr): 3262 (NH), 1734 (C=O) cm⁻¹. 1H-NMR δ: 1.91 (3H, m, 5-Me), 4.05 (1H, m, 4-H), 4.26 (1H, m, 1-H), 6.19 (1H, m, 6-H), 6.5 (1H, br, NH), J₈₉ = 2.2 Hz, J₈₉₁₄ = 0.8 Hz, J₆₉₈₉ = 1.2 Hz, J₆₉₈₉ = 0.8 Hz, J₉₆₉₈₉ = 1.6 Hz. Anal. Caled for C₉H₁₀N₅O₅: 66.03; H₆.74; N₇.67. Found: C, 64.5; H, 6.45; N, 12.63.

2-Azabicyclo[2.2.2]octane-5(3)-one (17c): 36% yield, mp 48–49 °C, colorless prisms (from benzene-IEP). MS m/z: 109 (M⁺). IR (KBr): 3232 (NH), 1734 (C=O) cm⁻¹. 1H-NMR δ: 1.81 (3H, m, 6-Me), 3.98 (1H, m, 4-H), 4.21 (1H, m, 1-H), 6.21 (1H, m, 5-H), 6.5 (1H, br, NH), J₈₉ = 2.2 Hz, J₈₉₁₄ = 2.8 Hz, J₈₉₁₈ = 0.5 Hz, J₆₉₈₉ = 0.7 Hz, J₆₉₈₉ = 1.5 Hz, J₆₉₈₉₁₄ = 1.6 Hz. Anal. Caled for C₉H₁₀N₅O₅: 66.03; H₆.74; N₇.67. Found: C, 65.79; H, 6.48; N, 12.64.

2-(tert-Butylmethylidene)-2-azabicyclo[2.2.2]octane-5(3)-one (18a–e) General Procedure: tert-Butylmethylidene chloride (1.2 mol eq) and triethylamine (1.2 mol eq) were successively added to a solution of a bicyclic compound (17a–c, 1–2 g) in dimethylformamide (10–20 ml) with stirring in an ice bath. The reaction mixture was further stirred for 2 h at room temperature and then extracted with ether. The extract was washed with saturated NaCl, dried, and evaporated in vacuo. The residue was chromatographed on silica gel using ether-hexane (1:5) as an eluent to give 18 as a colorless viscous oil.

2-(tert-Butylmethylidene)-2-azabicyclo[2.2.2]octane-5(3)-one (18a): 90% yield. IR (neat): 1736 (C=O), 1556 (C=O) cm⁻¹. 1H-NMR δ: 0.18 and 0.22 (each 3H, t, Si-Me), 0.95 (3H, m, 4-H), 2.45 (1H, d, J = 3 Hz), 6.42 (1H, m, 5-H), 6.54 (1H, dd, 4-H), J₈₉ = 2 Hz, J₈₉₁₄ = 0.8 Hz, J₆₉₈₉ = 1.2 Hz, J₆₉₈₉ = 2.5 Hz. High-resolution MS m/z: M⁺ Caled for C₁₃H₁₉N₅O₅: 211.10326. Found: 211.10326.

2-(tert-Butylmethylidene)-2-azabicyclo[2.2.2]octane-5(3)-one (18b): 88% yield. IR (neat): 1737 (C=O), 1620 (C=O) cm⁻¹. 1H-NMR δ: 0.18 and 0.22 (each 3H, t, Si-Me), 0.94 (9H, s, tert-Bu), 1.90 (1H, m, 5-Me), 4.05 (1H, m, 4-H), 4.16 (1H, m, 1-H), 6.16 (1H, m, 6-H), J₈₉ = 2 Hz, J₈₉₁₄ = 0.8 Hz, J₆₉₈₉ = 0.8 Hz, J₆₉₈₉₁₄ = 1.2 Hz, J₆₉₈₉₁₄ = 1.6 Hz. High-resolution MS m/z: M⁺ Caled for C₁₅H₂₁N₅O₅: 223.1392. Found: 223.1402.

2-(tert-Butylmethylidene)-6-methyl-2-azabicyclo[2.2.2]octane-5(3)-one (18c): 85% yield. IR (neat): 1736 (C=O), 1630 (C=O) cm⁻¹. 1H-NMR δ: 0.12 and 0.17 (each 3H, s, Si-Me), 0.90 (9H, s, tert-Bu), 1.75 (1H, m, 6-Me), 3.88 (1H, m, 4-H), 4.07 (1H, m, 1-H), 6.13 (1H, m, 5-H), J₈₉ = 2 Hz, J₈₉₁₄ = 0.5 Hz, J₆₉₈₉ = 0.7 Hz, J₆₉₈₉₁₄ = 1.5 Hz, J₆₉₈₉₁₄ = 1.6 Hz. High-resolution MS m/z: M⁺ Caled for C₁₅H₂₁N₅O₅: 223.1392. Found: 223.1408.

6-(tert-Butylmethylidene)-6-methyl-2-azabicyclo[2.2.2]octane-5(3)-one (18d): 85% yield. IR (neat): 1736 (C=O), 1630 (C=O) cm⁻¹. 1H-NMR δ: 0.25 and 0.30 (each 3H, s, Si-Me), 0.99 (9H, s, tert-Bu), 3.76 (1H, dd, 4-H), 3.95 (1H, dd, 1-H), 4.10 (1H, dd, 4-H), 4.19 (1H, dd, 2-H), J₈₉ = 3.5 Hz, J₈₉₁₄ = 1.8 Hz, J₆₉₈₉₁₄ = 2 Hz, J₆₉₈₉₁₄ = 4 Hz. High-resolution MS m/z: M⁺ Caled for C₁₅H₂₁N₅O₅: 225.1185. Found: 225.1174.
1. 5-Etheroxy-4-ethylcarboxy-1,3-dihydroxy-4-diazepine (24b): 88% yield, yellow viscous oil (solidified at below 25°C). IR (neat): 722 (C=O), 1668 (C=O) cm⁻¹. 1H-NMR δ: 1.28 and 1.30 (each 3H, t, OCH₂CH₃), 4.12 and 4.20 (each 2H, q, OCH₂), 2.20 (3H, s, -Me), 5.48 (1H, s, -6H), 5.66 (1H, d, 2H), 6.20 (1H, d, 3H), J₆₋₇ = 5Hz. High-resolution MS m/z: M⁺ Caled for C₂₂H₂₄N₄O₂: 324.161. Found: 324.1180.

2. 5-Ethoxy-4-ethylcarboxy-1,3-dihydroxy-4-diazepine (24c): 80% yield, yellow viscous oil. IR (neat): 1720 (C=O), 1648 (C=O) cm⁻¹. 1H-NMR δ: 1.28 and 1.30 (each 3H, t, OCH₂CH₃), 4.12 and 4.19 (each 2H, q, OCH₂), 1.97 (1H, d, 2Me), 5.42 (1H, d, 6H), 6.10 (1H, q, 3H), 6.93 (1H, d, 7H), J₆₋₇ = 1.5Hz, J₇₋₈ = 9Hz. High-resolution MS m/z: M⁺ Caled for C₂₀H₂₂N₄O₂: 293.1563. Found: 293.1452.

Thermolysis of 23a
A solution of 23a (50 mg) in toluene (3 ml) was heated at 45°C for 1h and then evaporated in vacuo. The residue was chromatographed on silica gel using ether–hexane (1:1) as an eluent to give 2-ethoxy-5-hydroxyxypyrrolo[2,3-c]pyridine (26): 30 mg, 60% yield, mp 56–57°C, colorless prisms (from ether–hexane). MS m/z: 210 (M⁺). IR (KBr): 3322 (1698) (C=O) cm⁻¹. 1H-NMR δ: 1.30 and 1.38 (each 3H, t, OCH₂CH₃), 4.22 and 4.30 (each 2H, q, OCH₂), 6.68 (1H, d, 3H), 7.76 (1H, d, 4H), 8.02 (1H, d, 6H), 7.47 (1H, d, 6H), J₆₋₇ = 9Hz, J₇₋₈ = 2Hz. High-resolution MS m/z: M⁺ Caled for C₁₆H₁₈N₂O₂: 249.1208. Found: 249.1158.

Thermolysis of 24a
A solution of 24a (50 mg) in dichlorobenzene (2 ml) was heated at ca. 180°C for 12h in a sealed tube and then chromatographed on silica gel using ether–hexane (1:1) as an eluent to give 2-ethoxy-5-(2-hydroxyacetyl)amino)pyridine (27): 39 mg, 78% yield, mp 94–95°C, colorless prisms (from EtOAc). MS m/z: 210 (M⁺). IR (KBr): 3322 (1698) (C=O) cm⁻¹. 1H-NMR δ: 1.30 and 1.38 (each 3H, t, OCH₂CH₃), 4.22 and 4.30 (each 2H, q, OCH₂), 6.68 (1H, d, 3H), 7.76 (1H, d, 4H), 8.02 (1H, d, 6H), 7.47 (1H, d, 6H), J₆₋₇ = 9Hz, J₇₋₈ = 2Hz. High-resolution MS m/z: M⁺ Caled for C₁₆H₁₈N₂O₂: 249.1208. Found: 249.1158.

References and Notes


12) A part of this work has been reported in a preliminary communication: J. Kurita, Y. Yoneda, N. Nakasawa, and T.


