Synthetic Studies on Securinine and Related Compounds. I.
Stereochemistries of the Catalytic Hydrogenation Products
of 6-(4-Methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol

Zen-ichi Horii, Takeshi Imanishi, Tetsuaki Tanaka, Ikuko Mori,
Miyoji Hanaoka, and Chuzo Iwata

(Received January 24, 1972)

The catalytic hydrogenation of 6-(4-Methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol
(V) gave VIa as a major product and VIb as a minor product. Their stereocchemistries
were determined by the nuclear magnetic resonance spectra of their oxathiazolidine
derivatives (XIIIa and XIIIb, respectively).

Securinine, a minor alkaloid isolated from the roots of Securinega suffruticosa Rend.
grown in Hou-lung (Formosa), was assigned to have the structure as 9α-methoxyalloscururine
(I) by our group.8 On the other hand, Parello, et al.4 isolated a new alkaloid phyllantine
from Phyllanthus discoides Mueell. Arg. and assigned the structure as 9β-methoxysecururine
(II), a diastereoisomer of secururine. We have investigated the synthetic studies on secururine
and related compounds.

The present paper describes the stereocchemistries of the catalytic hydrogenation products
of 6-(4-methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (V), which would serve a useful
intermediate9 for syntheses of secururine and related compounds.

Condensation of 2-bromo-4-methoxypyridine (III)6 with 1,4-dioxaspiro[4,5]decan-6-one
(IV)7 in dry ether in the presence of n-butyl lithium at −20° gave 6-(4-methoxy-2-pyridyl)-
1,4-dioxaspiro[4,5]decan-6-ol (V) in 60—70% yield. In general, pyridine derivatives are
reduced to the corresponding piperidines by means of catalytic hydrogenation over platinum

---

1) Part of this work was reported at the 91th, Annual Meeting of Pharmaceutical Sociey of Japan, Fukuoka,
   April 1971.
2) Location: 6-1-1, Toneyama, Toyonaka, Osaka.
   1117.
5) Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Koteru, H. Yoshikawa,
oxide or sodium-alcohol reduction.\textsuperscript{8}) Though 4-methoxypyridine can not be reduced to 4-methoxypiperidine under these conditions, it can be reduced by means of catalytic hydrogenation over ruthenium dioxide.\textsuperscript{9}) But hydrogenation of V over ruthenium dioxide was unsuccessful. Recently, there are a few reports that rhodium catalysts are excellent for hydrogenations of pyridines.\textsuperscript{10}) Hydrogenation of V in ethanol in the presence of 5\% rhodium on alumina proceeded slowly to give three products; VIa (51\%), VIb (19\%), and VII (trace). The product (VII) was derived to the amino-ketone (VIII) by hydrolysis, which was identical with an authentic sample.\textsuperscript{5}) The major product (VIa), colorless needles, mp 143—144°, possesses a molecular formula C\textsubscript{14}H\textsubscript{20}O\textsubscript{4}N and the minor product (VIb), colorless plates, mp 82—84°, also possesses the same molecular formula as VIa. These products, VIa and VIb, are diastereoisomeric with each other having the structure (A), as they have analogous fragmentation patterns in their mass spectra.

The piperidine compound (A) have four diastereoisomers theoretically as shown in Chart 2; both B and C are cis-2,4-disubstituted piperidines, and both D and E are trans-2,4-disub-

---


\textsuperscript{9} K. Stach, M. Thiel, and F. Bichelhaupt, \textit{Monatsh.}, 93, 1090 (1962).

stituted piperidines. In order to determine the stereochemistries of VIa and VIb, initially we tried to determine the relative configuration between the methoxyl group at C₄' and the cyclohexane ring at C₆' in these compounds. After acetylations of the products (VIa and VIb) with acetic anhydride, the amides (IXa and IXb, respectively) were dehydrated with thionyl chloride-pyridine to give the same product (X), in which the position of double bond was assigned to locate at endo-position by the following spectral data. The nuclear magnetic resonance (NMR) spectrum of X shows one olefinic proton signal at 3.35r and its ultraviolet (UV) spectrum shows the absorption maximum at 237 mc due to a 2-substituted 2-cyclohexenone system.¹¹ These results show that VIa and VIb have the same configurations of C₄' and C₆'. Since catalytic hydrogenations of disubstituted pyridine derivatives give cis-disubstituted piperidines as major products,¹² it could be concluded that these compounds (VIa and VIb) are cis-2,4-disubstituted piperidines (B and C, or vice versa).

In order to determine the relative configuration of C₄' and C₆, it is desired to fix the C₄'-C₆ bond. Recently, Deyrup and Moyer¹³ reported that 2-oxo-1,2,3-oxathiazolidines were formed by the reactions of β-amino-alcohols with thionyl chloride in the presence of tertiary amines. Accordingly, the β-amino-alcohols (VIa, b and their hydrolyzed derivatives, XIa, b) were converted to the 2-oxo-1,2,3-oxathiazolidines (XIIa, b, and XIIIa, b, respectively) by the treatment of thionyl chloride in pyridine. Their physical data are summarized in Table I. The NMR spectrum of XIIIb exhibits one proton signal at 6.05 r, which was assigned to C₄'-H. On the other hand, the NMR spectra of XIIa, XIIb, and XIIIa exhibit no corresponding signal at the lower field than 6.3 r. In NMR spectra of alkyl substituted 2-oxo-1,2,3-oxathiazolidines, it was reported that the protons at C₄ appeared in 6.3–7.3 r region.¹³ In XIIIb the proton at C₄' is coplanar with the carbonyl group at C₁, thus induc-

Table I. The Physical Data of the 2-Oxo-1,2,3-oxathiazolidines

<table>
<thead>
<tr>
<th>Compound</th>
<th>XIIa</th>
<th>XIIb</th>
<th>XIIIa</th>
<th>XIIIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>mp (°C)</td>
<td>95–96</td>
<td>117–118</td>
<td>129–131</td>
<td>75–76</td>
</tr>
<tr>
<td>IR (KBr; cm⁻¹) CO</td>
<td></td>
<td></td>
<td>1725</td>
<td>1732</td>
</tr>
<tr>
<td>SO</td>
<td>1180</td>
<td>1170</td>
<td>1180</td>
<td>1188</td>
</tr>
<tr>
<td>NMR (CDCl₃; τ) -OCH₃</td>
<td>6.60</td>
<td>6.61</td>
<td>6.66</td>
<td>6.63</td>
</tr>
<tr>
<td>C₄⁻ -H</td>
<td></td>
<td></td>
<td>6.05</td>
<td></td>
</tr>
<tr>
<td>Mass spectrum (m/z)</td>
<td>317 (M⁺)</td>
<td>317 (M⁺)</td>
<td>273 (M⁺)</td>
<td>273 (M⁺)</td>
</tr>
</tbody>
</table>

ing shift of the signal to lower field and in XIIIa, on the contrary, the proton at C₄⁻ is too far from the carbonyl group to be affected by the above interaction as shown in Chart 5. Thus it could be concluded that VIa has the structure (B) and VIb has the structure (C).

The fact that the catalytic hydrogenation of V gave VIa as a major product and VIb as a minor product is explained as follows; VIa was predominantly obtained by the cis attack of hydrogen from the less hindered side (α-side) and VIb was obtained by the cis attack of hydrogen from the hindered side (β-side) in the hydrogen bonded conformation (V') as shown in Chart 6.

![Chart 5](image)

![Chart 6](image)

In order to examine the influence of C₄⁻-substituents on the hydrogenation of V, the ketal (V) was converted to the diol (XV) via the ketone (XIV). The catalytic hydrogenation of XV under similar conditions to those employed for V gave the piperidine (XVI) as a diastereoisomeric mixture in quantitative yield. Jones oxidation of XVI, followed by chromatographic separation gave XIa and XIb in 38% and 21% yields, respectively and no other isomer was obtained. These compounds (XIa and XIb) were identical with the samples prepared by hydrolyses of VIa and VIb, respectively.

![Chart 7](image)

Further work on the syntheses of securitinine and its stereoisomers via these hydrogenated products (VIa and VIb) is in progress.

Experimental

6-(4-Methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (V) — To a stirred solution of n-BuLi (prepared from 3.0 g of n-BuBr and 0.30 g of Li) in dry ether was added a solution of 2-bromo-4-methoxyppyridine (1.1, 0.8 g in dry ether (10 ml) dropwise over a period of 15 min at –20°, and then to the reaction mixture was added a solution of 1,4-dioxaspiro[4.5]decan-6-one (IV, 3.1 g) in dry ether (10 ml) over a period of 15 min. After stirring for 9 hr at this temperature, the reaction mixture was added satd. NH₄Cl solution at 0°. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were washed with brine, dried and evaporated. Distillation of the residue gave 3.5 g (65%) of V as a pale yellow viscous oil, bp 160–170° (0.001 mmHg), which was solidified on standing and recrystallized from n-hexane to give colorless plates, mp 57.5–59°. IR ν<sub>max</sub> cm<sup>-1</sup>: 3289 (OH), 1600 and 1567 (pyridine ring). Anal. Calcd. for C₉H₈O₂N: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.38; H, 7.11; N, 5.64. NMR τ: 6.25 (4H, m, -OC₆H₄CH₂O), 6.15 (3H, s, -OCH₃), 3.25 (1H, d, J = 2.5 and 5.5 cps, pyridine ring proton), 2.91 (1H, d, J = 2.5 cps, pyridine ring proton), 1.62 (1H, d, J = 5.5 cps, pyridine ring proton).

Catalytic Hydrogenation of V — The pyridine (V, 10.0 g) was hydrogenated in EtOH (100 ml) over 5% Rh-Al₂O₃ (15 g) at 100° and 140 atm for 32 hr. After the catalyst was filtered off, the filtrate was evaporated to dryness. The solid residue was extracted with boiling n-hexane. The solvent was evaporated and the residue was recrystallized from n-hexane twice to give 5.2 g (51%) of VIA as colorless needles, mp 143–144°. IR ν<sub>max</sub> cm<sup>-1</sup>: 3333, 3125 (OH, NH). Anal. Calcd. for C₁₀H₁₄O₂N: C, 61.96; H, 9.29; N, 5.16. Found: C, 62.07; H, 9.17; N, 5.23. NMR τ: 6.02 (4H, m, -OC₆H₄CH₂O), 6.64 (3H, s, -OCH₃). Mass Spectrum m/e: 271 (M⁺), 114. The mother liquor was evaporated and recrystallization of the residue from petr. ether gave 2.0 g (19%) of VIB as colorless plates, mp 82–84°. IR ν<sub>max</sub> cm<sup>-1</sup>: 3330, 3122 (OH, NH). Anal. Calcd. for C₁₀H₁₄O₂N: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.97; H, 9.32; N, 5.56. NMR τ: 5.98 (4H, s, -OC₆H₄CH₂O), 6.61 (3H, s, -OCH₃). Mass Spectrum m/e: 271 (M⁺), 114. Hydrolysis of the n-hexane insoluble residue with 15% HCl at 90° for 3 hr, followed by chromatographic separation gave a small amount of VIII as colorless crystals, mp 89–90°, identical with an authentic sample<sup>9</sup> in comparison with IR, TLC and mp.

2-(1-Acetyl-4-methoxy-2-piperidyl)-2-cyclohexanone(X) —a From VIA: A solution of the amine (VIA, 0.40 g) in Ac₂O (10 ml) was heated at 90° and the reaction mixture was evaporated in vacuo at 90°. To the residue was added water and K₂CO₃ and the resulting alkaline solution was extracted with CHCl₃. Evaporation of the dried extract gave an oily residue (0.58 g), which was chromatographed on silica gel (10 g). Elution with CHCl₃ afforded 0.40 g of the amide (IXa) as a colorless viscous oil, which was homogeneous on TLC. IR ν<sub>max</sub> cm<sup>-1</sup>: 3280 (OH), 1621 (amide). To a stirred solution of thionyl chloride (1.5 ml) in dry pyridine (10 ml) was added a solution of the amide (IXa, 0.40 g) in dry pyridine (5 ml) dropwise over a period of 25 min under ice-water cooling. After stirring for 2 hr under cooling and for 1.5 hr at room temperature, the reaction mixture was poured into ice-water and extracted with CHCl₃. The extract was washed with water, 10% HCl and water, and dried. Evaporation of the solvent gave a brown oily residue (275 mg), which was chromatographed on silica gel (4 g). Elution with CHCl₃ and then with EtO–CHCl₃ (1:100 v/v) afforded 170 mg (40%) of the α,β-unsaturated ketone(X) as a colorless oil, homogeneous on TLC. IR ν<sub>max</sub> cm<sup>-1</sup>: 1665 (α,β-unsaturated ketone), 1628 (amide). Mass Spectrum m/e: 251 (M⁺), 208, 176. NMR τ: 7.98 (3H, s, -NCOCH₃), 6.81 (3H, s, -OCH₃), 5.10 (1H, m, N-CH₃), 3.36 (1H, m, -OCH₃). UV λ<sub>max</sub> m̄<sub>u</sub> (log e) : 237 (4.10). The semicarbazone of X, mp 175° (from AcOEt). Anal. Calcd. for C₁₀H₁₄O₂N₂: (1/2 H₂O): C, 54.76; H, 7.94; N, 17.82. Found: C, 57.04; H, 8.13; N, 17.43.

b) From VIB: A solution of the amine (VIB, 0.21 g) in Ac₂O (10 ml) was treated by the same manner as described above. Chromatography of the crude product gave 195 mg of the amide (IXb) as a colorless viscous oil, IR ν<sub>max</sub> cm<sup>-1</sup>: 3280 (OH), 1620 (amide). To a stirred solution of the amide (IXb, 105 mg) in dry pyridine (4.5 ml) was added thionyl chloride (0.1 ml) under ice-water cooling. Stirring was continued for 6 hr under cooling and the reaction mixture was treated by the same manner as described above. The crude product was subjected to preparative thin-layer chromatography on silica gel (30 g) using 5% MeOH–ether as a developing solvent to give 48 mg (47%) of the α,β-unsaturated ketone(X) as a colorless oil, which was identical with the sample obtained from VIA in comparison with IR, TLC, UV and mass spectrum.

2-(4-Methoxy-2-piperidyl)-2-hydroxycyclohexanone(XIa) —A solution of the ketal (VIA, 3.4 g) in 20% HCl (30 ml) was heated at 90° for 4 hr. After neutralization with aqueous NaOH the resulting mixture was extracted with CHCl₃. The CHCl₃ extract was washed with water and dried. Evaporation of

<sup>15</sup> All melting points and boiling point are uncorrected. NMR spectra were taken on Hitachi Perkin-Elmer R-60 type spectrometer at 60 Mc in CDCl₃ with (CH₃)₄Si as an internal standard. Mass spectra were taken on Hitachi RMU-60 spectrometer. Silica gel (Mallinckrodt) and Kiesel gel PF₅₄ (Merck) were used for column chromatographies and preparative thin-layer chromatography (TLC), respectively. Organic extracts were dried over anhydrous MgSO₄.

<sup>16</sup> R.G. Jones and H. Gilman, Org. Reactions, 6, 352 (1951).
the solvent gave 2.5 g (90%) of the ketone(XIA) which was recrystallized from n-hexane to give colorless leaflets, mp 114°-115°. IR ν_max cm⁻¹: 3300, 3215 (OH, NH), 1701 (CO). Anal. Calcd. for C₂₅H₄₀O₅N: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.71; H, 9.29; N, 6.27. NMR r: 6.68 (3H, s, -OCH₃).

2-(4-Methoxy-2-piperidyl)-2-hydroxycyclohexanone(XIB) — A solution of the ketone(VIB, 1.0 g) in 20% HCl (15 ml) was treated by the same manner as for XIA. The crude product (820 mg) was chromatographed on silica gel (10 g) using CHCl₃ as a eluent to afford 650 mg (79%) of the ketone(XIB) as a viscous colorless oil. IR r_max cm⁻¹: 3380, 3340 (OH, NH), 1703 (CO). The picromonate of XIB, mp 190° (from EtOH). Anal. Calcd. for C₂₃H₂₄O₅Na: C, 53.76; H, 5.95; N, 14.25. Found: C, 53.91; H, 5.99; N, 13.76.

2-Oxo-1,2,3-oxathiazolines — a) XIIA: To a stirred solution of thionyl chloride (1.0 ml) in dry pyridine (4 ml) was added a solution of the β-aminoalcohol (Vla, 0.30 g) in dry pyridine (4 ml) dropwise under ice-water cooling. After stirring for 5 hr under cooling, the reaction mixture was poured into ice-water. The resulting mixture was extracted with CHCl₃ (20 ml x 3) and the combined CHCl₃ extracts were washed with water, 10% HCl and water. Evaporation of the dried extract gave an oily residue (315 mg), which was chromatographed on silica gel (5 g). Elution with CHCl₃ afforded a solid, which was recrystallized from n-hexane to give 230 mg (66%) of XIIA as colorless needles, mp 95°-96°. IR ν_max cm⁻¹: 1180 (SO). Anal. Calcd. for C₃H₄O₅NS: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.19; H, 7.11; N, 4.38. Mass Spectrum m/e: 317 (M⁺), 161, 114. NMR r: 6.3-5.7 (4H, m, -OCH₂CH₂O⁻), 6.60 (3H, s, -OCH₃).

b) XIIIB: The β-aminoalcohol (VIB, 0.30 ml) was treated according to the method in the reaction of Vla with thionyl chloride-pyridine to give 214 mg (61%) of the 2-oxo-1,2,3-oxathiazolines(XIIIB) as colorless plates, mp 117°-118°. IR ν_max cm⁻¹: 1170 (SO). Anal. Calcd. for C₃H₄O₅NS: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.84; H, 7.33; N, 4.40. Mass Spectrum m/e: 317 (M⁺), 161, 114. NMR r: 6.15-5.90 (4H, m, -OCH₂CH₂O⁻), 6.60 (3H, s, -OCH₃).

c) XIIIA: The β-aminoalcohol (XIA, 420 mg) was treated according to the method in the reaction of Vla with thionyl chloride-pyridine to give 350 mg (69%) of the 2-oxo-1,2,3-oxathiazolines(XIIIA) as colorless fine needles, mp 129°-131°. IR ν_max cm⁻¹: 1725 (CO), 1180 (SO). Anal. Calcd. for C₃H₄O₅NS: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.65; H, 6.92; N, 5.30. NMR r: 6.66 (3H, s, -OCH₃). Mass Spectrum m/e: 273 (M⁺), 161, 114.

d) XIIIB: The β-aminoalcohol (XIB, 310 mg) was treated according to the method in the reaction of Vla with thionyl chloride-pyridine to give 210 mg (55%) of the 2-oxo-1,2,3-oxathiazolines(XIIIB) as colorless needles, mp 75°-76°. IR ν_max cm⁻¹: 1712 (CO), 1188 (SO). Anal. Calcd. for C₃H₄O₅NS: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.68; H, 6.96; N, 4.99. NMR r: 6.65 (3H, s, -OCH₃), 6.05 (1H, d of d, f = 4 and 13 cps, C₃H⁻). Mass Spectrum m/e: 273 (M⁺), 161, 114.

2-(4-Methyl-2-pyridyl)-2-hydroxycyclohexanone(XIV) — A solution of the ketone (V, 0.50 g) in 10% HCl (10 ml) was heated at 60° for 4 hr. After cooling, the reaction mixture was made alkaline with aqueous NaOH under cooling. The resulting mixture was extracted with CHCl₃ and the CHCl₃ extract was washed with water and dried. Evaporation of the solvent gave an oily residue (475 mg), which was chromatographed on silica gel. Elution with CHCl₃ afforded 358 mg (91%) of the ketone(XIV) as a solid, which was recrystallized from petr. ether to give colorless prisms, mp 84°-85°. IR ν_max cm⁻¹: 1710 (CO), 1600 and 1570 (pyridine ring). Anal. Calcd. for C₂₃H₂₄O₅N: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.20; H, 7.02; N, 6.45. Mass Spectrum m/e: 426 (M⁺), 314, 270, 134, 120, 106, 92 (XIV). To a stirred solution of the ketone(XIV, 175 mg) in MeOH (10 ml) was added NaBH₄ (25 mg) portionwise and stirring was continued for 1.5 hr at room temperature. After addition of water (20 ml), the resulting mixture was extracted with CHCl₃. Evaporation of the dried extract gave 169 mg (96%) of the diol (XV) as a solid, which was recrystallized from n-hexane to give colorless plates, mp 90°-91°. IR ν_max cm⁻¹: 3225 (OH, NH). Anal. Calcd. for C₂₅H₁₇O₅N: C, 64.55; H, 7.48; N, 6.27. Found: C, 64.81; H, 7.55; N, 6.14.

1-(4-Methoxy-2-piperidyl)cyclohexane-1,2-diol(XVI) — The pyridine (XV, 1.03 g) was hydrogenated in 5% Rh-Al₂O₃ (1.5 g) at 80° and 100 atm for 9 hr. The catalyst was filtered off and the filtrate was concentrated to dryness in vacuo to give 1.12 g (quantitative yield) of the piperidine (XVI) as a solid, which was used for the next step without further purification. A sample for analysis was obtained by recrystallization from n-hexane-C₂H₅OH, mp 150°-152°, as colorless crystals. IR ν_max cm⁻¹: 3225 (OH, NH). Anal. Calcd. for C₂₅H₁₇O₅N: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.95; H, 9.97; N, 6.09.

Oxidation of XVI with Jones Reagent — To a stirred solution of the diol (XVI, 720 mg) in purified acetone (15 ml) was added dropwise 2 ml of standard chromic acid reagent¹⁰ under ice-water cooling. After 30 min, MeOH was added to the reaction mixture to decompose excess oxidant and the mixture was diluted with water, made alkaline with K₂CO₃ and extracted with CHCl₃. The extract was washed with water and dried. Evaporation of the solvent gave an oily residue (190 mg), which was chromatographed on silica gel (10 g). Elution with 3% EtOH-CHCl₃ afforded 150 mg (21%) of the ketone(XIB) as a colorless oil. Elution with 5% EtOH-CHCl₃ afforded 280 mg (38%) of the ketone(XIA) as a solid, which was recrystallized from n-hexane to give colorless leaflets, mp 114°-115°. The products (XIA and XIIB) were identical with the samples obtained from Vla and VIB, respectively, in comparison with TLC, IR and mp.