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5. Zen-ichi Horii, Miyoji Hanaoka, Masazumi Ikeda, Yasuhiko Yamawaki, Yasumitsu Tamura,*1 Seiichi Saito, Noboru Shigematsu, and Keiji Kotera*2 : Hofmann Degradations of Tetrahydrosecurinine and Tetrahydrosecurininol. Stereochemistry at C-3a of Tetrahydrosecurinine.*3

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In an early stage of the structural studies of securinine, an alkaloid of *Securinega suffruticosa* REHD., Hofmann degradations of tetrahydrosecurinine (II)[1] and tetrahydrosecurininol (III)[2] have been carried out, but structures of the degradation products left unassigned. The recent establishment[1~5] of the structure of securinine (I) prompted us to investigate these products, since it would afford a further support for the structure of the alkaloid. The present paper describes the Hofmann degradations of II and III, and the synthetic proofs for structures of the products. The result also leads to estabiishment of the configuration at C_{3a} of tetrahydrosecurinine as shown in structure (II).

Refluxing tetrahydrosecurinine (II) with methyl iodide in acetone or benzene formed a normal methiodide (IV). While, when the reaction was carried out in methanol a different methiodide resulted, whose infrared spectrum lacked a lactone carbonyl band, but instead showed bands at 3268 and 1736 cm^{-1}, ascribed to a hydroxyl and an ester carbonyl, respectively. Therefore, we assigned a structure (V) to this methiodide. Both methiodides (IV and V) were treated with silver oxide or with basic ion-exchange resin.[6] The methiodide (V) gave a normal methohydroxide, whereas the methiodide (IV) gave the betaine (VI),[7] whose structure was assigned on the basis of its infrared spectrum : a carboxylate anion band at 1580 cm^{-1} instead of a lactone carbonyl band. Pyrolysis of the betaine (VI) or the methohydroxide from V at 240~250° effected a Hofmann degradation to give, after fractional distillation, two oily bases, VII as a low boiling fraction and VIII as a high boiling fraction, in each case.

The presence of the hydroxyl group in VIII was indicated from its infrared spectrum and by formation of the acetyl derivative. Dehydration of VIII by heating with 85% phosphoric acid, followed by hydrogenation over platinum oxide, gave the same amine (IX) as was obtained by hydrogenation of VII over platinum oxide. This structural correlation shows that both compounds (VII) and (VIII) were formed by cleavage of the same C-N bond in tetrahydrosecurinine (II).

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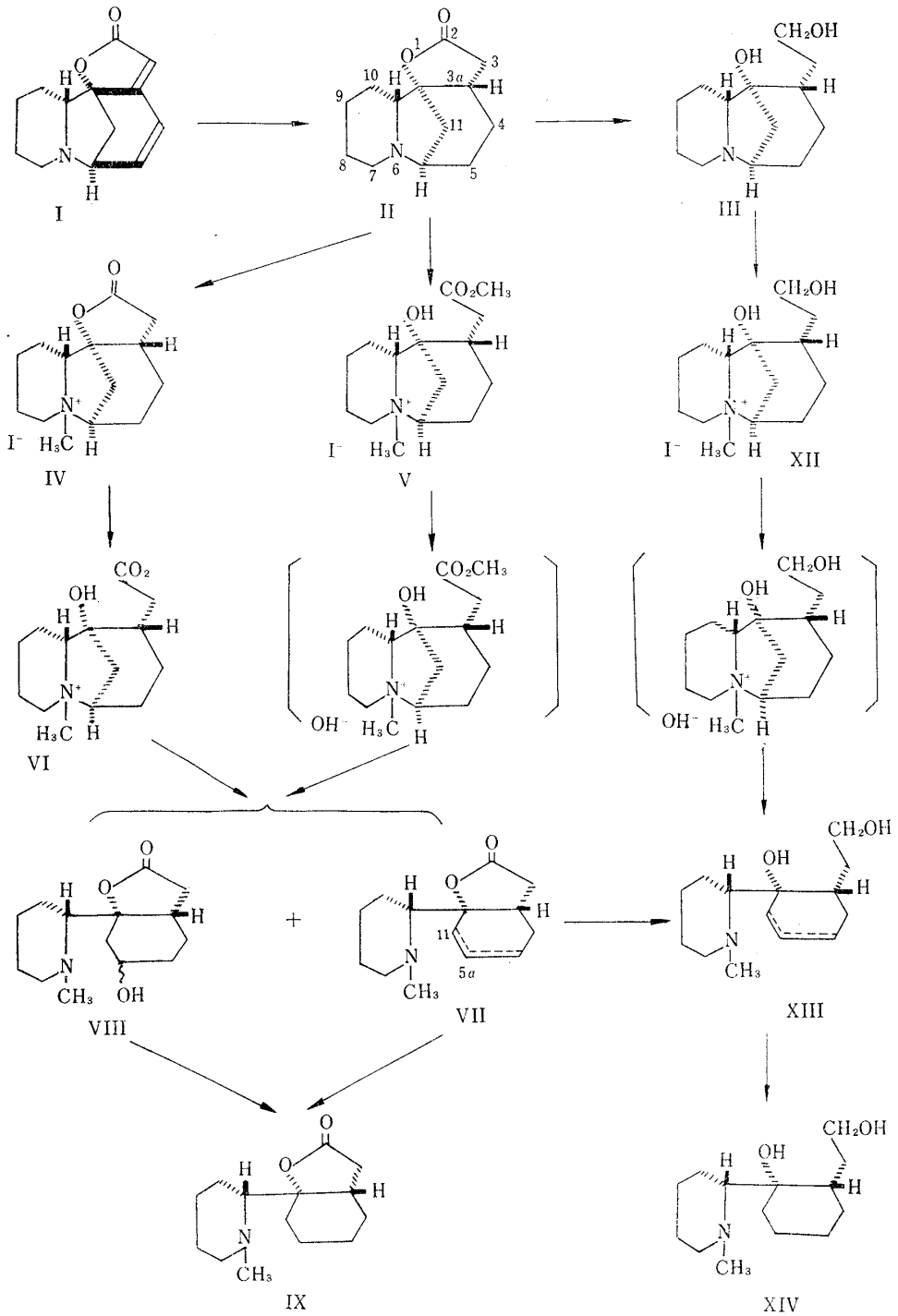

Chart 1.

Theoretically, ring cleavage during the Hofmann degradation of Ⅱ could occur at N-C_{5a}, N-C_7 or N-C_{10a}, with the possibility of giving three isomers. Of these, the possibility that the cleavage might occur at N-C_7 was excluded from lack of a characteristic terminal methylene band in the infrared spectrum of Ⅶ. However, a choice from the rest two possibilities was difficult without further informations. The synthesis of racemic Ⅸ by the series of reactions shown in Chart 2 provided an unequivocal proof for the structure of Ⅸ, and consequently those of Ⅶ and Ⅷ.

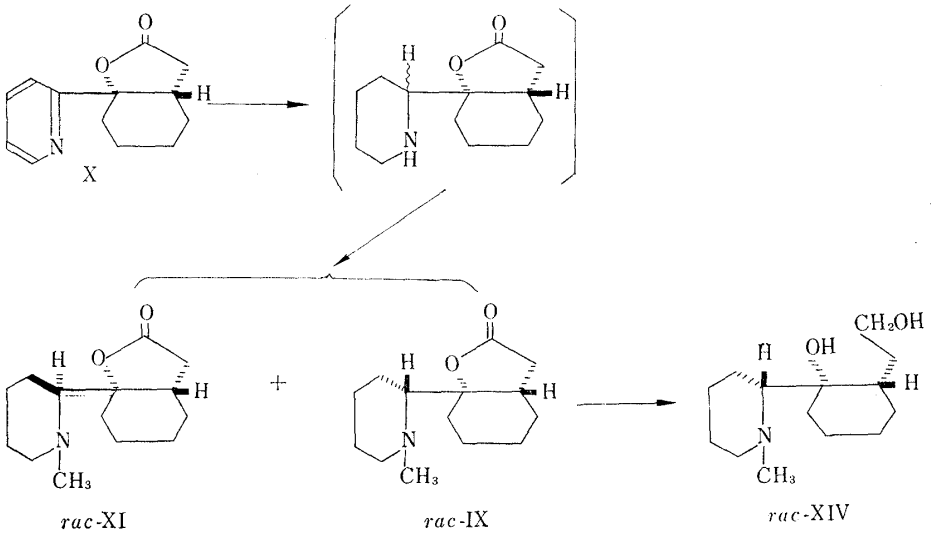

Chart 2.

Hydrogenation of *cis*-2-hydroxy-2-(2-pyridyl)cyclohexaneacetic acid lactone (X)[8] over platinum oxide in acetic acid, followed by reductive methylation employing formalin and 10% palladium on charcoal, gave an oily mixture of the amino-lactones (*rac*-IX and *rac*-XI). Gas chromatography of this mixture indeed revealed two components. Treatment of the mixture with perchloric acid gave a crystalline perchlorate of *rac*-IX, m.p. 234~235° (decomp.), which showed the same infrared spectrum as that of the perchlorate of IX obtained by the degradation of tetrahydrosecurinine (II). The free base (*rac*-IX) showed the same retention time in gas chromatography, the same Rf-value in thin-layer chromatography and the same infrared spectrum in chloroform as those of IX. The establishment of structure (IX) would also lead to structures (VII)*4 and (VIII) as depicted.

The mother liquor separated from the crystalline perchlorate gave an alternative base (*rac*-XI),*5 characterized as a picrate, m.p. 196~197.5°, which was depressed on admixture with the picrate of *rac*-IX, m.p. 200~201°.

The Hofmann degradation of tetrahydrosecurininol (III)[2] was also carried out. Pyrolysis of the methohydroxide of tetrahydrosecurininol (III) at 150~180° gave only a normal methine base (XIII), which was identified with the lithium aluminum hydride reduction product of VII. Hydrogenation of XIII over platinum oxide yielded the dihydro derivative (XIV), which showed the same infrared spectrum in chloroform as that of *rac*-XIV, obtained by lithium aluminum hydride reduction of *rac*-IX.

Now, the establishment of the structures of IX and XIV, obtained *via* the Hofmann degredation of tetrahydrosecurinine (II) and tetrahydrosecurininol (III), respectively, proves unequivocally that II has a *cis*-fused lactone ring in its molecule. Since the stereochemistry of three asymmetric centers, C_{5a}, C_{10a}, and C_{10b}, is apparent from the stereochemistry (I) of securinine established already,[1~5] the configuration at C_{3a}, accordingly, the full stereochemistry of tetrahydrosecurinine are represented by structure (II).

*4 A double bond is assumed to locate between C_{5a} and C_{11}, because the NMR spectrum of VII in $CDCl_3$ at 60 Mc.p.s. with tetramethylsilane as an internal reference shows only two protons at 7.7~7.9 τ, ascribed to the allylic methylene protons.

*5 Compounds *rac*-IX and *rac*-XI showed similar but different IR spectra in $CHCl_3$, and were shown to be separable by thin-layer chromatography and gas chromatography.

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Experimental*6

Reaction of Tetrahydrosecurinine (II) with Methyl Iodide——a) Tetrahydrosecurinine[1] (II, 2.5 g.) was refluxed with a large excess of MeI in Me_2CO (70 ml.) or benzene (70 ml.) for 3 hr. The precipitate was collected and recrystallized from MeOH to afford tetrahydrosecurinine methiodide (IV, 3.0 g. (82%)) as white crystals, m.p. 260~262° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1773 (γ-lactone). *Anal.* Calcd. for $C_{14}H_{22}O_2NI$: C, 46.29; H, 6.10; N, 3.86. Found: C, 46.31; H, 5.73; N, 3.84.

b) Tetrahydrosecurinine (II, 1.0 g.) was refluxed with a large excess of MeI in MeOH (10 ml.) for 2 hr. The solvent was evaporated and the residue was recrystallized from iso-PrOH to afford methyl tetrahydrosecurininate methiodide (V, 1.46 g. (82%)) as white crystals, m.p. 193~195°. IR ν_{max}^{Nujol} cm^{-1}: 3268 (OH), 1736 (ester). *Anal.* Calcd. for $C_{15}H_{26}O_3NI$: C, 45.57; H, 6.63; N, 3.54. Found: C, 45.36; H, 6.40; N, 3.63.

The Betaine (VI) derived from Tetrahydrosecurinine Methiodide (IV)——The methiodide (IV, 3.0 g.) was treated with Ag_2O or basic ion-exchange resin (Amberlite IRA-400-OH). Evaporation of the aqueous solution obtained and recrystallization of the residue from EtOH-H_2O gave the betaine (VI, 2.1 g. (89%)) as white crystals, m.p. 228~229° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3100~3400 (OH), 1580 (carboxylate anion). *Anal.* Calcd. for $C_{14}H_{23}O_3N \cdot 2H_2O$: C, 58.11; H, 9.41; N, 4.84. Found: C, 58.05; H, 9.10; N, 4.92.

Des-N-methyltetrahydrosecurinine A (VII) and Des-N-methyltetrahydrosecurinine B (VIII)——a) From the betaine (VI): The betaine (VI, 2.1 g.) was fused at 240~250° (bath temperature)/5 mm. Hg for 10 min. After cooling, H_2O (5 ml.) was added and the mixture was extracted with Et_2O. The dried Et_2O extract was evaporated and the residue was distilled to afford two oily fractions; $b.p_{0.05}$ 140~160° (bath temperature), 1.1 g. (64%) and $b.p_{0.05}$ 160~180° (bath temperature), 0.4 g. (21%). The perchlorate of the low boiling fraction (VII) was recystallized from MeOH-H_2O as colorless cubics, m.p. 235~236° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1792 (γ-lactone), 1653 (double bond). $[\alpha]_D^{20}$ +78.5° (c=0.043). *Anal.* Calcd. for $C_{14}H_{22}O_6NCl$: C, 50.07; H, 6.60; N, 4.17. Found: C, 49.49; H, 6.24; N, 4.27.

The high boiling fraction was chromatographed on silica gel with $CHCl_3$-MeOH (9:1) as eluent to remove VII contaminated and converted to the perchlorate of VIII, which was recrystallized from MeOH-H_2O as colorless crystals, m.p. 254~256° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3509 (OH), 1789 (γ-lactone). $[\alpha]_D^{20}$ +41.5° (c=0.08). *Anal.* Calcd. for $C_{14}H_{23}O_7NCl$: C, 47.53; H, 6.84; N, 3.96. Found: C, 47.79; H, 6.66; N, 3.97.

Heating the betaine (VI, 1.4 g.) at 240~250° (bath temperature) at atmospheric pressure gave VII (360 mg.) and VIII (760 mg.).

b) From methyl Tetrahydrosecurininate methiodide (V): The methiodide (V, 600 mg.) was treated with Ag_2O and the methohydroxide obtained was fused at 245~250° (bath temperature). Treatment of the reaction mixture as described above gave VII (160 mg.) and VIII (80 mg.). The perchlorates, m.p. 230~231° (decomp.) and m.p. 249~250° (decomp.), of VII and VIII, were identical in mixed melting points and IR spectra with VII and VIII obtained in (a).

The Acetate of Des-N-methyltetrahydrosecurinine B (VIII)——A mixture of the perchlorate (100 mg.) of VIII, Ac_2O (0.8 ml.) and dry pyridine (0.5 ml.) was refluxed for 1 hr. and poured into ice-H_2O, made alkaline with conc. K_2CO_3 solution and extracted with Et_2O. The dried extract was evaporated and the residue (100 mg.) was converted to the perchlorate of the acetate, which was recrystallized from MeOH-Et_2O, m.p. 207~209°. IR ν_{max}^{Nujol} cm^{-1}: 1790 (γ-lactone), 1722 (ester). *Anal.* Calcd. for $C_{16}H_{25}O_8NCl$: C, 48.55; H, 6.62; N, 3.54. Found: C, 48.73; H, 6.59; N, 3.43.

Dihydro-des-N-methyltetrahydrosecurinine A (IX)——a) From des-N-methyltetrahydrosecurinine A (VII): Compound (VII, 1.1 g.) was hydrogenated in MeOH (20 ml.) over PtO_2 (250 mg.) at atmospheric pressure and room temperature. The catalyst was filtered off. The filtrate was evaporated and the residue was distilled to afford IX (1.0 g. (90%)), $b.p_5$ 167~172° (bath temperature). The perchlorate was recrystallized from MeOH as colorless needles, m.p. 253° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1786 (γ-lactone). $[\alpha]_D^{20}$ +41.5° (c=0.07). *Anal.* Calcd. for $C_{14}H_{24}O_7NCl$: C, 49.77; H, 7.16; N, 4.14. Found: C, 49.90; H, 7.11; N, 4.32.

b) From des-N-methyltetrahydrosecurinine B (VIII): A mixture of the perchlorate (60 mg.) of VIII, which was shown to be completely without contamination by VII by GLC and TLC,*7 and 85% H_3PO_4 (0.5 ml.) was heated at 160~180° for 2 hr. The reaction mixture was cooled, made alkaline with conc. K_2CO_3

*6 Melting points and boiling points are uncorrected. Extracts were dried over anhyd. Na_2SO_4. Specific rotations were measured with Yanagimoto photomagnetic direct reading polarimeter model OR-20, using 10 cm. cell and 66% EtOH. Analyses of gas-liquid chromatography (GLC) were conducted with Shimadzu gas chromatography GC-1B equipped with a hydrogen flame ionization detector, employing SE-30 column (column temperature 175°).

*7 Thin-layer chromatography (TLC) was carried out with cyclohexane-$CHCl_3$-Et_2NH (7:2:1) as the solvent on Wakogel B-5 (silica gel, Wako Pure Chem. Ind. Ltd.).

solution and extracted with Et_2O. The dried Et_2O extract was evaporated and the residue (20 ml.) was hydrogenated over PtO_2 (25 mg.) in MeOH (10 ml.) at atmospheric pressure and room temperature. The catalyst was filtered off. The filtrate was evaporated and the residue was purified by chromatography on silica gel with $CHCl_3$–MeOH (9:1) as eluent to give an oil, which was identical in TLC*7 (Rf=0.72) and GLC with IX obtained from VII. The perchlorate was recrystallized once from MeOH, m.p. 251~252° (decomp.), and was identified in mixed melting point and IR spectrum with the perchlorate of IX obtained in (a).

Des-N-methyltetrahydrosecurininol (XIII)——a) From tetrahydrosecurininol (III): The methiodide[2] (XII, 3.0 g.) of tetrahydrosecurininol was treated with Ag_2O. The aqueous solution obtained was evaporated to dryness to afford the methohydroxide as white needles. This methohydroxide was fused at 150~180° (bath temperature)/20 mm. Hg for 30 min. Treatment of the residue as described for VII and VIII gave XIII (1.6 g. (82%)), b.$p_{0.1}$ 139~141°. The hydrochloride was recrystallized from MeOH–Et_2O, m.p. 226~228°. IR ν_{max}^{Nujol} cm^{-1}: 1656 (double bond). $[\alpha]_D^{20}$ −30.7° (c=0.06). *Anal.* Calcd. for $C_{14}H_{26}O_2NCl$: C, 60.96; H, 9.50; N, 5.08. Found: C, 61.12; H, 9.15; N, 5.09.

b) From des-N-methyltetrahydrosecurinine A (VII): To a suspension of $LiAlH_4$ (0.2 g.) in anhyd. Et_2O (20 ml.), an Et_2O solution (20 ml.) of VII recovered from the perchlorate (0.3 g.) was added dropwise, and mixture was refluxed for 6 hr. The reaction mixture was decomposed with 10% NaOH solution and the resulting solid was filtered off and washed several times with Et_2O. The filtrate and washings were dried and evaporated. The distillation of the residue gave an oil (XIII), b.$p_{0.4}$ 170° (bath temperature), which was converted to the hydrochloride (0.2 g.), m.p. 215~217°. This hydrochloride was identical in mixed melting point and IR spectrum (Nujol) with the hydrochloride of XIII obtained in (a).

Dihydro-des-N-methyltetrahydrosecurininol (XIV)——Compound (XIII, 1.5 g.) was hydrogenated over PtO_2 (30 mg.) in EtOH (20 ml.) at atmospheric pressure and room temperature. After an uptake of 1 molar equivalent of H_2, the catalyst was filtered off and the filtrate was evaporated. Recrystallization of the residue from petr. benzin gave XIV as white crystals, m.p. 122~123°. $[\alpha]_D^{20}$ +6° (c=0.03). *Anal.* Calcd. for $C_{14}H_{27}O_2N$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.50; H, 11.32; N, 5.57.

Refluxing XIV (0.95 g.) with MeI (2 ml.) in Me_2CO (8 ml.) for 4 hr., evaporation of the solvent from the reaction mixture and recrystallization of the residue from Me_2CO gave the methiodide (1.2 g. (79%)) as colorless plates, m.p. 214~215°. *Anal.* Calcd. for $C_{15}H_{30}O_2NI$: C, 47.00; H, 7.89; N, 3.65. Found: C, 46.73; H, 7.81; N, 3.60.

***cis*-2-Hydroxy-2-(N-methyl-2-piperidyl)cyclohexaneacetic Acid Lactone (*rac*-IX and *rac*-XI)**——*cis*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic acid lactone[8] (X, 1.2 g.) was hydrogenated over PtO_2 (100 mg.) in glac. AcOH (15 ml.) at atmospheric pressure and room temperature. After cessation of H_2 uptake (8 hr.), the catalyst was filtered off and the filtrate was evaporated at reduced pressure. The residue was made alkaline with conc. K_2CO_3 solution and extracted with Et_2O. Evaporation of the dried Et_2O extract gave a viscous oil (1.2 g.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1754 (γ-lactone).

A solution of the crude oil (1.2 g.) obtained above and 37% HCHO (2 ml.) in MeOH (20 ml.) was hydrogenated over Pd-C (10%; 200 mg.) at atmospheric pressure and room temperature. After cessation of H_2 uptake (ca. 100 ml.; 10 hr.), the catalyst was filtered off and the solvent and excess HCHO were evaporated. To the residue was added Ac_2O (5 ml.), and the mixture was heated for 2 hr. on a water bath. Excess Ac_2O was evaporated under reduced pressure and the residue was made alkaline with conc. K_2CO_3 solution and extracted with Et_2O layer was extracted with 10% HCl. The HCl extract was washed with Et_2O, made alkaline with conc. K_2CO_3 solution, reextracted with Et_2O and dried. The dried Et_2O extract was evaporated and distillation of the residue gave a viscous oil, b.$p_{0.3}$ 165~170°. This oil showed two spots (Rf=0.88 and 0.81) on TLC.*8 The addition of the perchloric acid to the Et_2O solution of this oil gave precipitates. Recrystallization of the precipitates from MeOH afforded the perchlorate of *rac*-IX, 234~235° (decomp.), which showed an identical IR spectrum (Nujol) with that of the perchlorate of IX. IR ν_{max}^{KBr} cm^{-1}: 1786 (γ-lactone). *Anal.* Calcd. for $C_{14}H_{24}O_6NCl$: C, 49.77; H, 7.16; N, 4.14. Found: C, 49.90; H, 7.15; N, 4.25.

The free base (*rac*-IX) recovered from the perchlorate was shown to be homogeneous by TLC*8 and GLC, and identical in IR spectrum ($CHCl_3$), TLC*8 Rf value and GLC retention time with the degradation product (IX). The picrate of *rac*-IX was prepared from the free base recovered from the perchlorate of *rac*-IX and recrystallized from EtOH as yellow prisms, m.p. 200~201°. *Anal.* Calcd. for $C_{20}H_{26}O_9N_4$: C, 51.50; H, 5.62; N, 12.01. Found: C, 51.65; H, 5.61; N, 11.93.

The Et_2O mother liquor, which was separated from the perchlorate of *rac*-IX, was made alkaline with conc. K_2CO_3 solution and extracted with Et_2O. Evaporation of the dried extract gave an oil (*rac*-XI), which was shown to be homogeneous by TLC*8 (Rf=0.89), but showed a different IR spectrum ($CHCl_3$) and TLC*8 Rf value from those of *rac*-IX. The picrate of *rac*-XI was recrystallized from EtOH, m.p. 196~197.5° (depressed to 180~183° on admixture with the picrate of *rac*-IX). *Anal.* Calcd. for $C_{20}H_{26}O_9N_4$: C, 51.50; H, 5.62; N, 12.01. Found: C, 51.37; H, 5.58; N, 11.95.

*8 TLC was carried out with $CHCl_3$–pyridine (9:1) as the solvent on Wakogel B-5.

Both picrates of *rac*-IX and *rac*-XI were not identical in IR spectra (Nujol).

1-(2-Hydroxyethyl)-2-(N-methyl-2-piperidyl)cyclohexanol (*rac*-XIV)——The reduction of the lactone (*rac*-IX, 0.5 g.) with $LiAlH_4$ (0.5 g.) in anhyd. Et_2O (50 ml.) was carried out as described for the reduction of VII. Distillation gave *rac*-XIV (0.4 g.) as a viscous oil, b.p_5 160° (bath temperature). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3333, 3106 (OH). This compound showed an identical IR spectrum ($CHCl_3$) and TLC*9 Rf value with those of the degradation product (XIV). The methiodide was recrystallized from EtOH, m.p. 187~188°. *Anal.* Calcd. for $C_{15}H_{30}O_2NI$: C, 47.00; H, 7.89; N, 3.65. Found: C, 46.94; H, 7.92; N, 3.75.

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Summary

The Hofmann degradations of tetrahydrosecurinine (II) and tetrahydrosecurininol (III) resulted in N-C_{5a} ring opening. The former gave two products, a normal methine base (VII) and an abnormal product (VIII), and the latter gave a normal methine base (XIII) alone. These products, (VII), (VIII), and (XIII), were interrelated as follows. Dehydration of VIII followed by hydrogenation gave an amino-lactone (IX), which was also prepared from VII by hydrogenation. On the other hand, lithium aluminum hydride reduction of VII gave XIII, which was converted to an amino-diol (XIV) by hydrogenation. The syntheses of the racemates of IX and XIV provided the proofs for their structures. The result establishes the configuration at C_{3a} of II.

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*9 TLC was carried out with $CHCl_3$–pyridine (9:1) as the solvent on Aluminum oxide G (Merck Co. Ltd.).