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4. Zen-ichi Horii, Yasuhiko Yamawaki, Miyoji Hanaoka, Yasumitsu Tamura,*1 Seiichi Saito, and Hiroshi Yoshikawa*2 : Synthesis and Stereochemistry in B/C Ring Juncture of Lactam-carbinol A, a Degradation Product of Securinine.

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Lactam-carbinols A (I) and B (II) are reductive degradation products of the alkaloid securinine (III), and are important in giving, on lithium aluminum hydride reduction, quinolizidines A (IV) and B (V), respectively, which have played important roles in elucidation of the stereochemistry of the alkaloid.[1,2] Lactam-carbinol B (II) and quinolizidine B (V) were synthesized in the racemic forms *via* ethyl *cis*-2-hydroxy-2-(2-pyridyl)cyclohexaneacetate (VI) and shown to be identical with the degradation products.[1] However, the assignment for structure (VI) was not fully discussed. We have now found that condensation of the epoxide from 1-(2-pyridyl)cyclohexene with diethyl malonate, followed by hydrolysis, gives *trans*-2-hydroxy-2-(2-pyridyl)cyclohexaneacetic acid (VIII), which is led to racemic I by hydrogenation, and that VIII is shown to be an isomer of the hydrolysis product (X) of VI. The present paper describes the syntheses and the stereochemistry of VIII and X, and the synthetic proof for the structure of lactam-carbinol A (I). The results confirm unequivocally the stereochemistries in B/C ring junctures of I and II as well as IV and V.

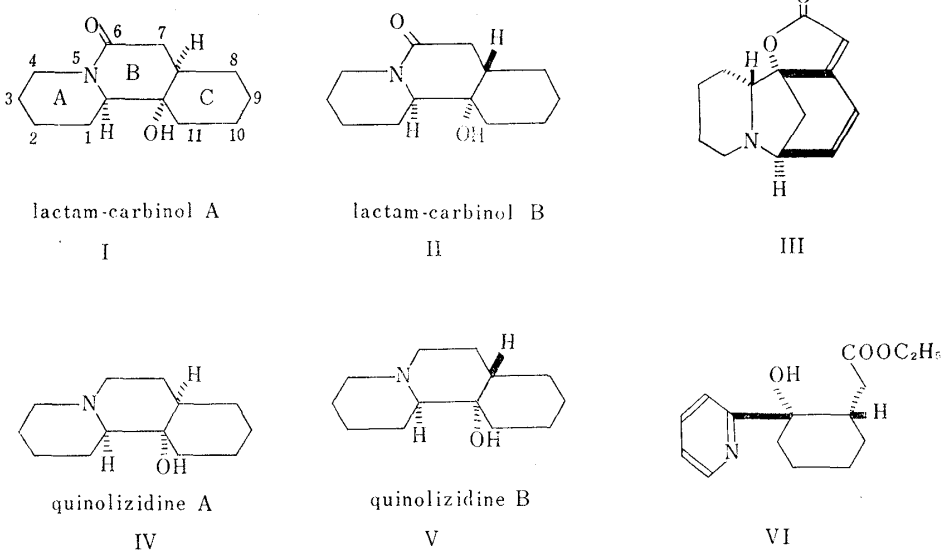

Chart 1.

Epoxidation of 1-(2-pyridyl)cyclohexene[3] with perbenzoic acid in chloroform and condensation of the resulted epoxide with diethyl malonate in ethanol in the presence of sodium ethoxide by refluxing for 24 hours gave the lactone (VII). Hydrolysis of VII

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1) S. Saito, K. Kodera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura : Tetrahedron, **19**, 2085 (1963).
2) Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, K. Kotera : Tetrahedron, **19**, 2101 (1963).
3) H. L. Lochte, P. F. Kruse, Jr., E. N. Wheeler : J. Am. Chem. Soc., **75**, 4477 (1953).

with hydrochloric acid gave the hydrochloride, m.p. 200° (decomp.), of the hydroxy acid (Ⅷ). Hydrogenation of the hydrochloride of Ⅷ over platinum oxide gave racemic I, which shows the same infrared spectrum in chloroform with that of lactam-carbinol A (I) derived from securinine.

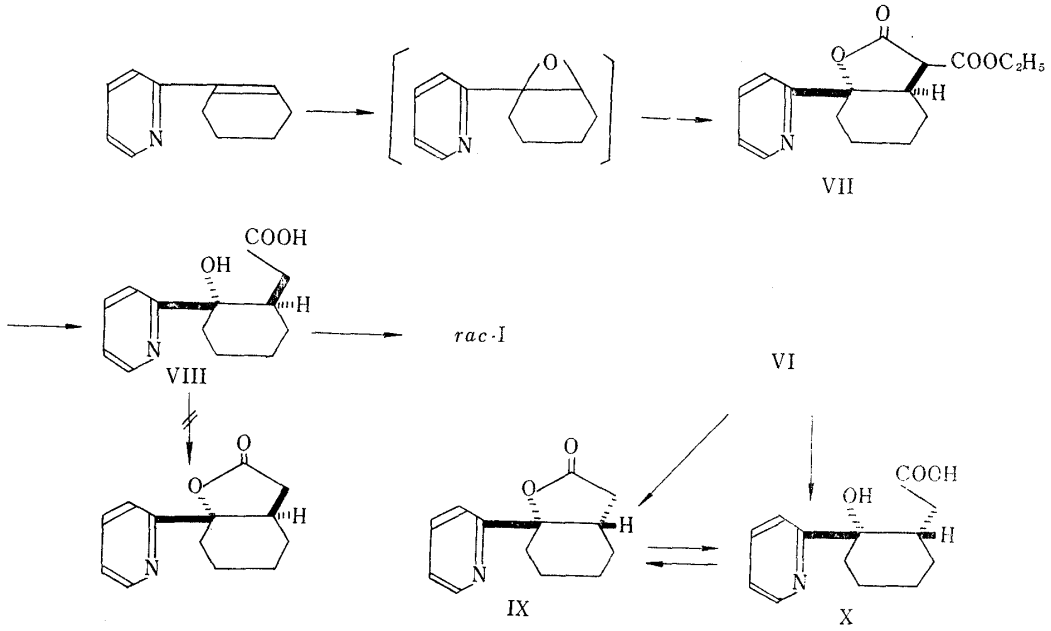

Chart 2.

That the hydroxyl and acetic acid substituents in Ⅷ have the *trans* relationship is suggested first from stereochemical consideration of the reaction employed for Ⅶ: it has been pointed out[4,5] that an attack of a nucleophilic reagent towards the epoxide under basic condition takes place at a carbon bearing less substituents of the epoxide and from back side of the oxygen. Preparation of the corresponding *cis* isomer (X) and comparison of chemical features of both isomers (Ⅷ) and (X) supported this stereochemical assignment.

In the previous paper,[1] we prepared Ⅵ by the condensation of 2-pyridyllithium and ethyl 2-oxocyclohexaneacetate and assigned its configuration from the stereochemical consideration of the reaction. When treated with boiling conc. hydrochloric acid, Ⅵ was easily converted to the lactone (Ⅸ). Hydrolysis of Ⅵ or Ⅸ with 10% sodium hydroxide solution in aqueous ethanol, followed by acidification with dil. hydrochloric acid and then evaporation to dryness under reduced pressure, gave the hydrochloride, m.p. 185° (decomp.), of X, which was shown not to be identical with the hydrochloride of Ⅷ by comparison of their melting points and infrared spectra (Fig. 1). The hydroxy acid (X) was lactonized by heating with 10% hydrochloric acid, while the hydroxy acid (Ⅷ) could not be lactonized on the same condition or even by heating with conc. hydrochloric acid for longer period. These facts prove the configurational assignment of Ⅷ and X as indicated.

The lacton (Ⅸ) was also synthesized by the following alternative route. Hydrolysis of the ketal[6] (Ⅺ) with dil. hydrochloric acid, followed by condensation of the resulted hydroxy-ketone with ethoxyacetylenyllithium[7] in anhydrous ether at −30°, gave the

4) M. S. Newman, C. A. Vander Werf: J. Am. Chem. Soc., **67**, 233 (1945).
5) W.Reeve, S. Sadle: *Ibid.*, **72**, 1251 (1950); C. L. Browne, R. E. Lutz: J. Org. Chem., **17**, 1187 (1952).
6) Z. Horii, M. Hanaoka, Y. Tamura, S. Saito, N. Sugimoto: Chem. & Ind. (London), **1964**, 664.
7) E. R. H. Jones, G. Eglinton, M. C. Whiting, B. L. Shaw: Org. Syntheses, **34**, 46 (1954); J. F. Arens: "Advances in Organic Chemistry," Vol. Ⅱ, 203 (1960), Interscience Publishers, Inc., N. Y.

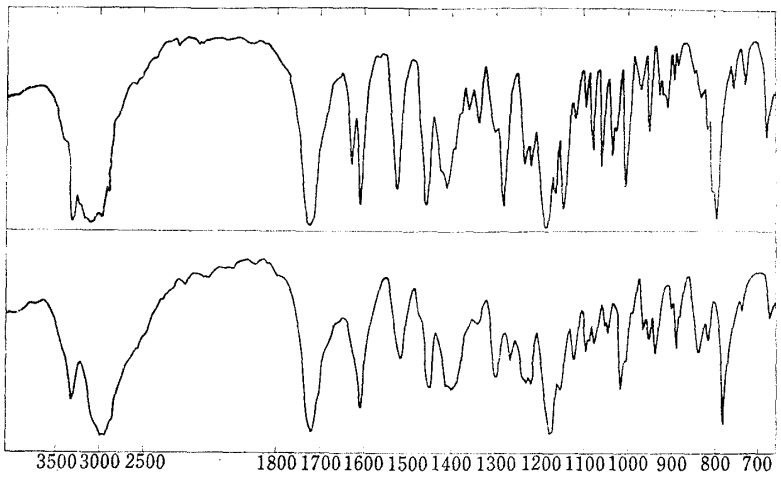

Fig. 1. Infrared Spectra of the Hydrochloride of *trans*- and *cis*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid (Ⅷ and Ⅹ) in Potassium Bromide

diol (Ⅻ). Hydrolysis of Ⅻ by refluxing with dil. sulfuric acid in tetrahydrofuran gave the hydroxy-lactone (ⅩⅢ) and the unsaturated lactone (XIV). Hydrogenation of XIV over platinum oxide gave the lactone (Ⅸ). From analogy to the stereochemical attitudes of such compounds as 2-hydroxy-$\Delta^{1,\alpha}$-cyclohexaneacetic acid lactone[4] (XV) and 3,3*a*,4,5,6,7-hexahydro-3*a*-(3,4-methylenedioxyphenyl)-2*H*-indole[8] (XVI) towards hydrogenation, XIV would be expected to give the *cis* lactone (Ⅸ).

The establishment of the configuration of Ⅷ leads to the unequivocal confirmation of the constitutions and the stereochemistries in B/C ring junctures of Ⅰ and, accordingly, Ⅳ. Similarly, Ⅸ provides a further support to the stereochemistries in B/C ring

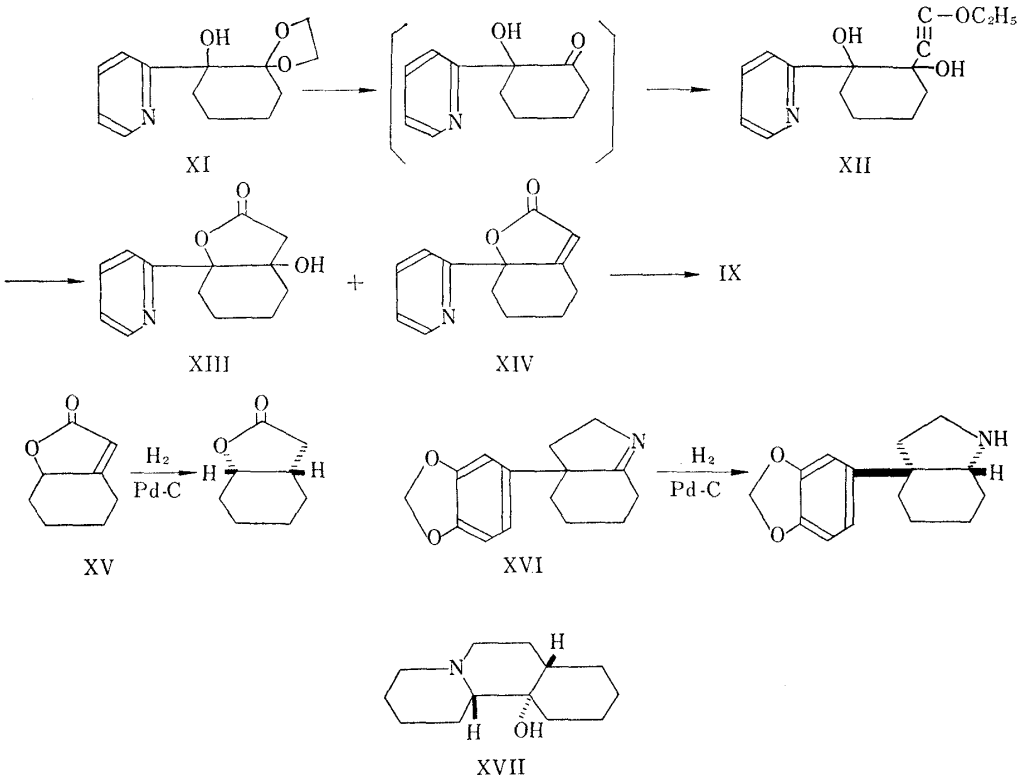

Chart 3.

8) P. F. Hight, W. C. Wildman : J. Org. Chem., **25**, 287 (1960).

junctures of II and V as well as the third quinolizidine (XVII), obtained from VI in the previous paper.[1]

Experimental*3

***trans*-α-Ethoxycarbonyl-2-hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid Lactone (VII)**——A solution of perbenzoic acid (prepared[9] from benzoyl peroxide (50 g.)) in $CHCl_3$ (300 ml.) was added to an ice-cooled solution of 1-(2-pyridyl)cyclohexene[3] (13.5 g.) in $CHCl_3$ (30 ml.). The mixture was allowed to stand at room temperature for 6 days. In order to remove benzoic acid produced and excess perbenzoic acid, the reaction mixture was washed several times with 7.5% NaOH and once with H_2O. Evaporation of the dried solution and distillation of the residue gave the epoxide (4.3 g.), as a colorless oil, b.p_4 97~99°.

To a stirred solution of EtONa in abs. EtOH (prepared from Na (0.8 g.) and abs. EtOH (30 ml.)), a solution of diethyl malonate (5.0 g.) in abs. EtOH (10 ml.) and then a solution of the epoxide (4.3 g.) obtained above in abs. EtOH (10 ml.) were added dropwise in a stream of N_2. The mixture was refluxed for 24 hr. with stirring. The solvent was distilled off from the reaction mixture, the residue was dissolved in H_2O, extracted with $CHCl_3$ and dried. The $CHCl_3$ extract was evaporated and the residue was chromatographed on silica gel. The eluate with benzene-$CHCl_3$ (9:1) gave crystals, which was recrystallized from ligroin to give the lactone (VII, 0.5 g.) as colorless prisms, m.p. 80.5~81.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1779 (γ-lactone), 1730 (ester), 1595, 1575 (pyridine). *Anal.* Calcd. for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.52; H, 6.63; N, 4.94.

***trans*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid (VIII)**——A solution (VII, 100 mg.) in 10% HCl (10 ml.) was refluxed for 2 hr. After cooling, the reaction mixture was washed with $CHCl_3$ and evaporated to dryness under reduced pressure to give a crystalline product (95 mg.). Recrystallization of the product from EtOH-AcOEt gave the hydrochloride of VIII as colorless needles, m.p. 200° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3289 (OH), 1709 (COOH), 1623, 1600 (pyridinium salt). *Anal.* Calcd. for $C_{13}H_{18}O_3NCl$: C, 57.46; H, 6.68; N, 5.15. Found: C, 57.47; H, 6.75; N, 4.93.

***rac*-Lactam-carbinol A (I)**——The hydrochloride (130 mg.) of VIII was hydrogenated in EtOH (30 ml.) over PtO_2 (25 mg.) at atmospheric pressure and room temperature. After 3 molar equivalents of H_2 was uptaken, the catalyst was filtered off. The filtrate was evaporated, and the residue was dissolved in H_2O (10 ml.), neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with satd. NaCl solution, dried and evaporated to give a crystalline product (100 mg.), which was chromatographed on silica gel with $CHCl_3$ as eluent. The first eluted crystals was recrystallized from AcOEt to give *rac*-lactam-carbinol A (I, 50 mg.) as colorless crystals, m.p. 182.5~184°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571, 3413 (OH), 1626 (lactam). *Anal.* Calcd. for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.89; H, 9.66; N, 6.16. This compound was shown to be homogeneous by GLC and identical in GLC retention time and IR spectrum ($CHCl_3$) with lactam-carbinol A (I) derived from securinine. The second eluted white crystals (40 mg.) was shown, by thin-layer chromatography (Wakogel B-5, $CHCl_3$), to be a mixture of I and the compound which was not characterized.

***cis*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid Lactone (IX)**——a) From ethyl *cis*-2-hydroxy-2-(2-pyridyl)cyclohexaneacetate[1] (VI): The ester (VI, 2.0 g.) was refluxed with conc. HCl (20 ml.) for 4 hr. The cooled reaction mixture was made alkaline with K_2CO_3 solution and extracted with Et_2O. Evaporation of the dried extract and distillation of the residue gave the lactone (IX, 1.0 g.) as a yellowish orange viscous oil, b.$p_{0.6}$ 128~130°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1772 (γ-lactone). This compound was proved to be homogeneous by GLC. The picrate was recrystallized from iso-PrOH as yellow needles, m.p. 166~168°. *Anal.* Calcd. for $C_{19}H_{18}O_9N_4$: C, 51.12; H, 4.06; N, 12.55. Found: C, 51.12; H, 4.07; N, 12.64.

b) From 2-hydroxy-2-(2-pyridyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic acid lactone (XIV): The unsaturated lactone (XIV, 50 mg.) described later was hydrogenated in EtOH (10 ml.) over PtO_2 (20 mg.) at atmospheric pressure and room temperature. After 1 molar equivalent of H_2 was uptaken, the catalyst was filtered off. Evaporation of the filtrate and distillation of the residue gave a pale yellow viscous oil (45 mg.), b.p_2 160° (bath temperature), which showed an identical GLC retention time with that of IX obtained in (a). The picrate was recrystallized from iso-PrOH as yellow needles, m.p. 164~167°. This compound was identical in IR spectrum and mixed melting point with the picrate of IX obtained in (a).

***cis*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid (X)**——a) From the lactone (IX): A mixture of the lactone (IX, 1.0 g.), 10% NaOH (10 ml.) and EtOH (5 ml.) was refluxed for 5 hr. EtOH was evaporated, the residual aqueous solution was washed with Et_2O, acidified with dil. HCl, washed again with Et_2O, made alkaline with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ extract gave an

*3 Melting points and boiling points are uncorrected. Extracts were dried over anhyd. Na_2SO_4. 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°).

9) G. Braun: Org. Syntheses, Coll. Vol. I, 431 (1941).

oil (20 mg.), which was identical in IR spectrum ($CHCl_3$) with the starting material (IX). The alkaline aqueous layer was acidified with dil. HCl, evaporated to dryness under reduced pressure, and the residue was extracted with abs. EtOH. The EtOH extract was evaporated to give an oil (200 mg.), which solidified on cooling. Recrystallization from EtOH–AcOEt gave the hydrochloride (120 mg.) of X as colorless crystals, m.p. 185° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3344 (OH), 1712 (COOH), 1605 (pyridinium salt). *Anal.* Calcd. for $C_{13}H_{18}O_3NCl$: C, 57.46; H, 6.68; N, 5.15. Found: C, 56.98; H, 6.79; N, 5.24.

b) From the ester (VI): A mixture of the ester (VI, 0.5 g.), 10% NaOH (5 ml.) and EtOH (2.5 ml.) was refluxed for 5 hr. The reaction mixture was treated as described in (a) to give the hydrochloride (70 mg.) of X. This compound was identical in melting point and IR spectrum with an authentic sample of the hydrochloride obtained in (a).

Lactonization of *cis*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid (X)——A solution of the hydrochloride (70 mg.) of X in 10% HCl (10 ml.) was refluxed for 1 hr. After cooling, the reaction mixture was washed with Et_2O, made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with satd. NaCl solution, dried and evaporated to give an oil (30 mg.), which was identical in IR spectrum with the lactone (IX) obtained above.

Attempts to Lactonization of *trans*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic Acid (VIII)——a) A solution of the hydrochloride (100 mg.) of VIII in 10% HCl (10 ml.) was refluxed for 1~2 hr. After cooling, the reaction mixture was treated as described above. Evaporation of the dried $CHCl_3$ extract gave nothing. The alkaline aqueous layer was acidified with dil. HCl and evaporated to dryness under reduced pressure. The residue was extracted with abs. EtOH. Evaporation of the EtOH extract and recrystallization of the residue from EtOH–AcOEt gave the starting material quantitatively.

b) A solution of the hydrochloride (90 mg.) of VIII in conc. HCl (4 ml.) was refluxed for 4 hr. When the reaction mixture was treated as described in (a), the starting material (60 mg.) was recovered unchanged.

1-Ethoxyacetylenyl-2-(2-pyridyl)-1,2-cyclohexanediol (XII)——2-Hydroxy-2-(2-pyridyl)cyclohexanone ketal[5] (XI, 1.0 g.) was heated with 10% HCl (20 ml.) on a water bath. After cooling, the reaction mixture was made alkaline with conc. NaOH, saturated with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried extract and distillation of the residue gave the ketone (0.6 g.), $b.p_{3\sim4}$ 140° (bath temperature) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1704 (ketone), 1586, 1571 (pyridine)].

To a stirred solution of MeLi in abs. Et_2O (prepared from Li (0.25 g.) and MeI (3.0 g.) in abs. Et_2O (15 ml.)), a solution of ethoxyacetylene (1.25 g.) in abs. Et_2O (10 ml.) was added dropwise at −15° in a stream of N_2. The mixture was stirred for an additional 15 min. To the mixture, a solution of the ketone (0.6 g.), prepared above, in abs. Et_2O (10 ml.) was added during 30 min. at −30°. After the addition was complete, stirring was continued for 1 hr. at −30° and for 3 hr. at room temperature. To decompose the complex produced, satd. NH_4Cl solution was added. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was dried and evaporated. Recrystallization of the residue from ligroin gave the diol (XII) as reddish brown needles, m.p. 96~97.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3497, 3195 (OH), 2242 (C≡C), 1597, 1572 (pyridine). *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.96; H, 7.31; N, 5.36.

1,2-Dihydroxy-2-(2-pyridyl)cyclohexaneacetic Acid Lactone (XIII) and 2-Hydroxy-2-(2-pyridyl)-$\Delta^{1,\prime\prime}$-cyclohexaneacetic Acid Lactone (XIV)——The diol (XII, 500 mg.) was refluxed with 15% H_2SO_4 (1.8 ml.) in tetrahydrofuran (10 ml.) for 30 min. The solvent was evaporated, and the residue was made alkaline with conc. K_2CO_3 solution and extracted with $CHCl_3$. Evaporation of the dried extract and chromatography of the residue (650 mg.) on silica gel with $CHCl_3$ as eluent gave two fractions. The first fraction was recrystallized from ligroin to give the hydroxy-lactone (XIII, 180 mg.) as white crystals, m.p. 114.5~115.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3185~3268 (OH), 1779 (γ-lactone), 1597, 1577 (pyridine). *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.94; H, 6.54; N, 5.76.

The second fraction gave the unsaturated lactone (XIV) as a pale yellow oil (130 mg.), $b.p_2$ 150° (bath temperature), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1744 (γ-lactone), 1644 (C=C), 1597, 1576 (pyridine). The picrate was recrystallized from iso-PrOH as yellow crystals, m.p. 133.5~135°. *Anal.* Calcd. for $C_{19}H_{16}O_9N_4 \cdot \frac{1}{2}H_2O$: C, 50.33; H, 3.78; N, 12.36. Found: C, 50.12; H, 4.02; N, 12.30.

Summary

cis- and *trans*-2-Hydroxy-2-(2-pyridyl)cyclohexaneacetic acid, (X) and (VIII), were synthesized and their stereochemistries discussed. The latter (VIII) was converted into racemic lactam-carbinol A (I), which showed the same infrared spectrum in chloroform as that of natural lactam-carbinol A obtained by degradation of securinine. The present work proved unequivocally the stereochemistries in B/C ring junctures of lactam-carbinols A (I) and B (II), and quinolizidines A (IV) and B (V), degradation products of securinine.

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