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Intramolecular Cyclization of 6-Hydroxy-6-(2-piperidyl)-2-cyclohexene-$\Delta^{1,\alpha}$-acetic Acid γ-Lactone, a Degradation Product of Securinine

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The amino-lactone (VII), a degradation product of securinine, cyclized on heating into the isoquinuclidine (VIII). The Hofmann-Löffler reaction of amino-ketone (XVIII) afforded the α-ketol (*rac*-X), identical with X derived from VIII.

It has been reported the degradation product (III) of allosecurinine (I) cyclized on heating to give the isoquinuclidine derivative (V),[2] while the lactone (VI), derived from securinine (II), gave under the same condition only the conjugated lactone (VII).[3] The cyclization of III was assumed[2] that the lone pair of nitrogen attacked to the conjugated lactone (IV) as the Michael type condensation *via* the isomerization of the double bond. If this assumption of cyclization path-way would be true, the amino-lactone (VII) might also cyclize under the more drastic condition.

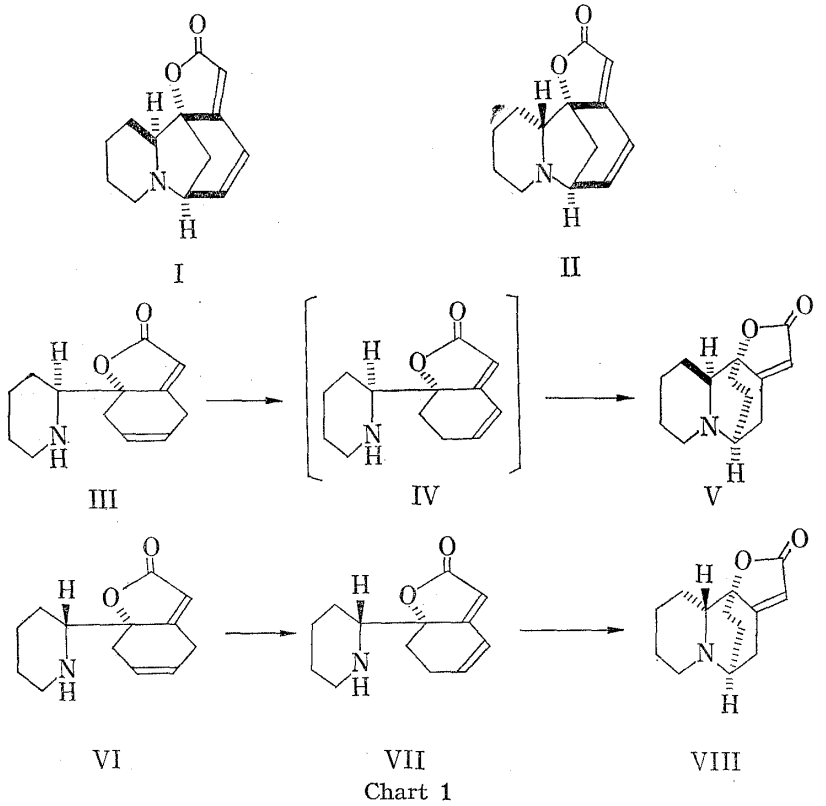

Chart 1

1) Location: *Toneyama, Toyonaka, Osaka*
2) Z. Horii, Y. Yamawaki, Y. Tamura, S. Saito, H. Yoshikawa, and K. Kotera, *Chem. Pharm. Bull.* (Tokyo), 13, 1311 (1965).
3) S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, and Y. Tamura, *Tetrahedron*, 19, 2085 (1963).

Repeated heating of VII at 180—190° under reduced pressure afforded the desired cyclization product (VIII) in 13% yield with the recovery of the starting material in 50% yield. In agreement with the structure (VIII), the product exhibited absorptions at 2821, 2721, 2681 (*trans*-quinolizidine band), 1794, 1735 and 1644 cm^{-1} in the infrared spectrum and at 215 mμ in the ultraviolet spectrum, characteristic to an α,β-unsaturated γ-lactone grouping with a hydrogen at α-position. The absorption of NH band in the infrared spectrum of VII disappeared in that of VIII. In the nuclear magnetic resonance spectrum one olefinic proton appeared as a triplet at 4.40 τ with coupling constant (J=2.0 cps). These data are exactly similar to those of V.[2,4] Thus the formation of VIII from VII supports the interpretation of the cyclization process of II, described in a previous paper.[2]

In order to obtain a further confirmation of the structure (VIII), the isoquinuclidine (VIII) was transformed into the α-ketol (X) as follows; lithium aluminum hydride reduction of VIII followed by ozonolysis gave X. The same reaction sequences of dihydroallosecurinine (XI) and the isoquinuclidine (V) afforded α-ketols, (XII) and (XIII), respectively. The infrared spectrum data of α-ketols (X, XII and XIII) as well as IX,[5] derived from dihydrosecurinine, are shown in Table I.

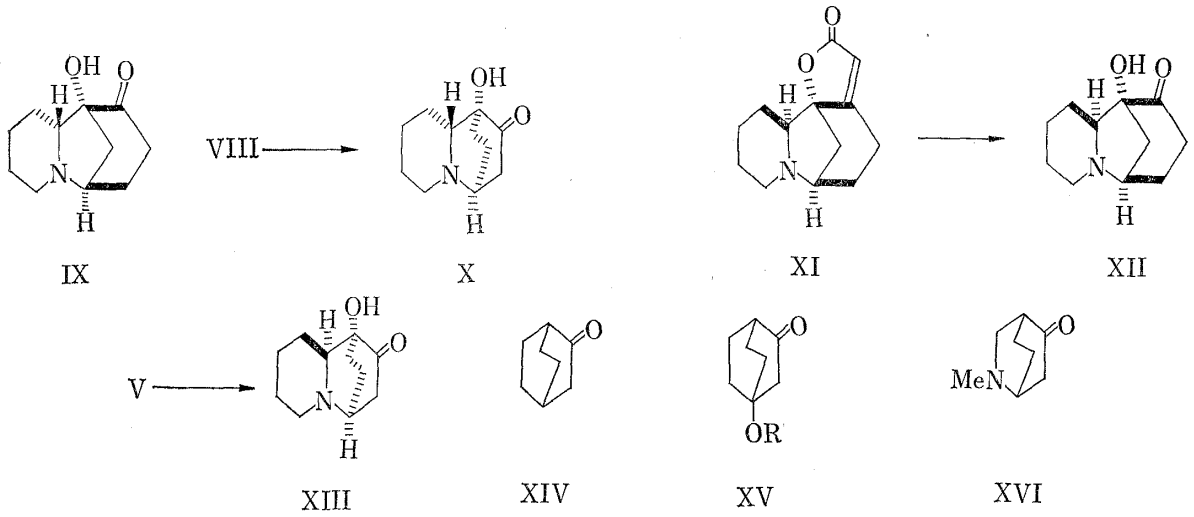

Chart 2

Table I. The Infrared Spectra of α-Ketols (IX, X, XII, XIII) and Ketones (XIV, XV, XVI) (cm^{-1})

Compound	C=O	Compound	C=O
IX	1709[a], 1724[b]	XIV[6]	1730[c]
X	1733[a], 1742[b]	XV[7]	1729[a]
XII	1698[a], 1718[b]	XVI[8]	1742[c]
XIII	1730[a], 1741[b]		

a) Measured in carbon tetrachloride.
b) the perchlorate: Measured in KBr disk.
c) Measured in liquid film.

As seen in Table I, the carbonyl absorption bands of X and XIII appeared at higher wave number near 1730 cm^{-1} than those of IX and XII, and are very similar to those of

4) IR: 2770, 2703, 2632, 1815, 1733, 1642 cm^{-1}; UV: 215 mμ; NMR: 4.4τ.
5) *a*) I. Satoda, M. Murayama, T. Tsuji, and E. Yoshii, *Tetrahedron Letters*, **1962**, 1199; *b*) Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, and K. Kotera, *Tetrahedron*, **19**, 2101 (1963).

bicyclo[2,2,2]octanone systems (XIV, XV and XVI).[6-8] These data indicate the α-ketols (X and XIII) possess azabicyclo[2,2,2]octanone ring system, and therefore the structures of V and VIII are shown as depicted.

In continuation of synthetic works on Securinega alkaloids, Hofmann-Löffler reaction was applied to the amino-ketone (XVIII) as one of the synthetic methods of decahyd o-6,10-methanopyrido[1,2*a*]azepin system, commonly appeared in Securinega alkaloids.

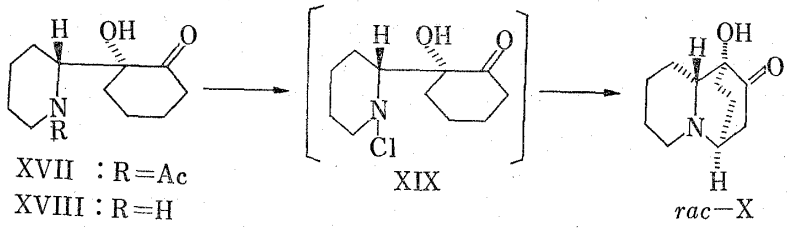

Chart 3

Hydrolysis of 2-(1-acetyl-2-piperidyl)-2-hydroxycyclohexanone (XVII)[9] with 10% hydrochloric acid gave the amino-ketone (XVIII), which was readily converted into the N-chloroamine (XIX) with 10% aqueous sodium hypochlorite in methylene chloride. Irradiation of ultraviolet light on XIX in trifluoroacetic acid until a negative chloroamine test was obtained (45 minutes), followed by refluxing with potassium carbonate in methanol and subsequent chromatography on silica gel afforded the α-ketol (*rac*-X) though in poor yield with recovery of the starting material (XVIII). The product showed absorptions at 3416, 2757, 2707, 2681, 1733 cm^{-1} in the infrared spectrum, and was shown to be identical with the α-ketol (X) by comparison of their infrared spectra in carbon tetrachloride and thin-layer chromatographical behaviour.

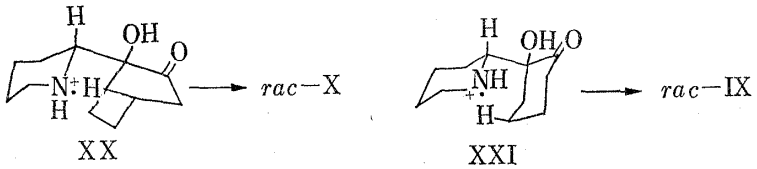

Chart 4

In Hofmann-Löffler reaction[10] hydrogen abstraction tends to proceed in a linear fashion, namely, the N-H-C angle of intermediate amminium radical is 180°. On inspection with Dreiding model, the angle of the intermediate (XX) into *rac*-X is almost linear, however, that of the intermediate (XXI) into *rac*-IX is not linear. In this reaction of XVIII, no formation of the desired *rac*-IX as the product might be depended on this factor. The low yield of *rac*-X would be probably explained by the fact that the reaction must pass through an unstable boat conformation of cyclohexanone ring as the intermediate (XX).

Experimental

mp and bp are uncorrected. The extracts were dried over anhydrous Na_2SO_4 unless otherwise specified.

Cyclization of the Lactone (VII)——Compound (VII,[3] 3.0 g) was heated at 180—190° under reduced pressure (1—2 mmHg)for 1.5 hr and distilled at 160—170° (bath temperature)/0.3 mmHg to give a yellow oil.

6) R. Zbinden and H.K. Hall, *J. Am. Chem. Soc.*, **82**, 1215 (1960).
7) K. Morita and T. Kobayashi, *J. Org. Chem.*, **31**, 229 (1966).
8) C.B. Page and A.R. Pinder, *J. Chem. Soc.*, **1964**, 4811.
9) Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai, and N. Sugimoto, *Tetrahedron*, **23**, 1165 (1967).
10) M.E. Wolff, *Chem. Revs.*, **63**, 55 (1963).

The same procedure was repeated to the distillate twice to give a yellow oil (2.5 g) containing some crystals, which was chromatographed on Al_2O_3 (50 g). Elution with benzene gave crystals, which was recrystallized from *n*-hexane to yield the isoquinuclidine (VIII, 0.5 g (13%)) as colorless needles, mp 84.5—85°. IR ν_{max}^{KBr} cm^{-1}: 2821, 2721, 2681 (*trans*-quinolizidine), 1794, 1735 (conjugated γ-lactone), 1644 (double bond). UV λ_{max}^{EtOH} mμ (log ε): 215 (4.21). NMR τ: 4.40 (1H, triplet, J=2.0 cps,=CH). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.05; H, 7.73; N, 6.34. Elution with $CHCl_3$ gave a yellow oil (1.5 g), which was identical with the starting material (VII).

The α-Ketol (X)——A solution of VIII (230 mg) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (200 mg) in anhydrous ether (8 ml). After the reaction mixture was refluxed under stirring for 5 hr, excess hydride was decomposed with water (1 ml) and 5% aqueous NaOH solution (5 ml). The inorganic material precipitated was filtered off and washed with ether. The filtrate and washings were dried and evaporated to give a colorless viscous oil (230 mg). Ozone was passed through a solution of the above oil in 5% HCl (4 ml) at 0° for 5 hr. The solution was warmed on a water bath for 50 min to decompose the ozonide, washed with $CHCl_3$, made alkaline with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried extract and distillation of the residue gave the α-ketol (X, 92 mg (41.5%)) as colorless crystals, bp 130—140° (0.1 mmHg) (bath temperature). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3416 (hydroxyl), 2757, 2707, 2681 (*trans*-quinolizidine), 1733 (ketone). The perchlorate was recrystallized from EtOH–ether as colorless needles, mp 178—180°. IR ν_{max}^{KBr} cm^{-1}: 3390, 3289 (hydroxyl), 1742 (ketone). *Anal.* Calcd. for $C_{11}H_{18}O_6NCl$: C, 44.67; H, 6.13; N, 4.73. Found: C, 44.63; H, 6.02; N, 4.79.

The α-Ketol (XII)——Dihydroallosecurinine[2] (XI, 500 mg) was treated according to the method described for X to give the α-ketol (XII, 350 mg (79%)) as a colorless viscous oil, bp 110—120° (0.35 mmHg) (bath temperature), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3405 (hydroxyl), 2754, 2703 (*trans*-quinolizidine), 1698 (ketone). The perchlorate was recrystallized from MeOH as colorless needles, mp 189—190.5°. IR ν_{max}^{KBr} cm^{-1}: 3407 (hydroxyl), 1718 (ketone). *Anal.* Calcd. for $C_{11}H_{18}O_6NCl$: C, 44.67; H, 6.13; N, 4.73. Found: C, 44.92; H, 6.15; N, 4.75.

The α-Ketol (XIII)——The isoquinuclidine[2] (V, 740 mg) was treated according to the method described for X to give the α-ketol (XIII, 400 mg (61%)) as a colorless viscous oil, bp 120—130° (0.35 mmHg) (bath temperature). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3428 (hydroxyl), 2767, 2705, 2642 (*trans*-quinolizidine), 1730 (ketone). The perchlorate was recrystallized from MeOH as colorless needles, mp 198—199°. IR ν_{max}^{KBr} cm^{-1}: 3431, 3317 (hydroxyl), 1741 (ketone). *Anal.* Calcd. for $C_{11}H_{18}O_6NCl$: C, 44.67; H, 6.13; N, 4.73. Found: C, 44.61; H, 6.03; N, 4.74.

2-Hydroxy-2-(2-piperidyl)cyclohexanone (XVIII)——Compound (XVII,[9] 200 mg) was heated with 10% HCl (20 ml) on water bath under stirring for 4 hr. The reaction mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried extract and recrystallization of the residue from *n*-hexane gave the amino-ketone (XVIII, 120 mg (73%)) as colorless needles, mp 88—89°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3472 (hydroxyl), 3322 (amine), 1706 (ketone). *Anal.* Calcd. for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.00; H, 9.36; N, 7.10.

The Hofmann-Löffler Reaction of the Amino-ketone (XVIII)——A solution of XVIII (1.2 g) in CH_2Cl_2 (80 ml), which was washed with saturated aqueous $NaHCO_3$ solution and distilled, was stirred at room temperature for 0.5 hr with 10% aqueous sodium hypochlorite (25 ml). The aqueous layer was removed and the organic layer was again stirred with fresh hypochlorite solution for 0.5 hr. The same procedure was repeated twice. Combined aqueous layers were extracted with CH_2Cl_2 (25 ml) twice. The organic layer and extract were combined, washed with water (25 ml), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give the N-chloroamine (XIX, 1.1 g) as pale yellow crystals. The purity of XIX was checked by titration with KI–$Na_2S_2O_3$ to be above 95%. Powdered N-chloroamine was added slowly to the stirred freshly distilled CF_3COOH (45 ml) below 0°. The resulting solution was transferred to a quarz flask equipped with Teflon covered magnetic stirring bar. The stirred reaction mixture was exposed to the ultraviolet light[11] in a stream of N_2. A few drops of the reaction mixture were removed and treated with KI reagent to follow the course of the reaction. After a negative test was obtained (45 min), the reaction mixture was evaporated *in vacuo* in a stream of N_2 at room temperature. The residue was refluxed with K_2CO_3 (2.0 g) in MeOH (25 ml) for 1.5 hr. The reaction mixture was evaporated, diluted with ice-water, saturated with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with cold 5% HCl. The aqueous acid layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried extract gave a brown viscous oil (790 mg), which was chromatographed on silica gel (5.0 g) using $CHCl_3$ as solvent. The first fraction (250 mg), showed weak *trans*-quinolizidine band, was again chromatographed on silica gel to give crystals. Distillation of this elute gave the racemic α-ketol (*rac*-X, 10 mg (1.2% based on consumed XVIII)) as colorless crystals, bp 130—140° (0.1 mmHg) (bath temperature). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3416 (hydroxyl), 2757, 2707, 2681 (*trans*-quinolizidine), 1733 (ketone). This compound was identical with X in infrared spectrum in CCl_4 and *Rf* value of thin-layer chromatography on Al_2O_3 (E. Merk) with $CHCl_3$–AcOEt (5:1) as the solvent. The second fraction (350 mg) was identical with XVIII.

11) Irradiation was conducted with Eikosha Halōs 150-watt lamp type PIH-100.