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Synthetic Studies on Securitinine and Related Compounds. II.[1] A Synthesis of 10a-Episecuritinine

Zen-ichi Horii, Takeshi Imanishi,
Miyoji Hanaoka, and Chuzo Iwata

Faculty of Pharmaceutical Sciences, Osaka University[2]

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10a-Episecuritinine (II), a diastereoisomer of securitinine (III), was synthesized from 2-hydroxy-2-(4-methoxy-2-piperidyl)cyclohexanone (I) whose stereochemistry was already determined.

In the previous paper,[1] we reported the synthesis and the stereochemistry of 2-hydroxy-2-(4-methoxy-2-piperidyl)cyclohexanone (I). Now we wish to report the synthesis of racemic 10a-episecuritinine (II), a diastereoisomer of an alkaloid securitinine (III),[3] starting from I through the route shown in Chart 1.

The amine (I) was formylated with acetic-formic anhydride[4] at 90° to give the formamide (IV) in 80% yield. Bromination of IV with bromine in 1% ethanol–chloroform

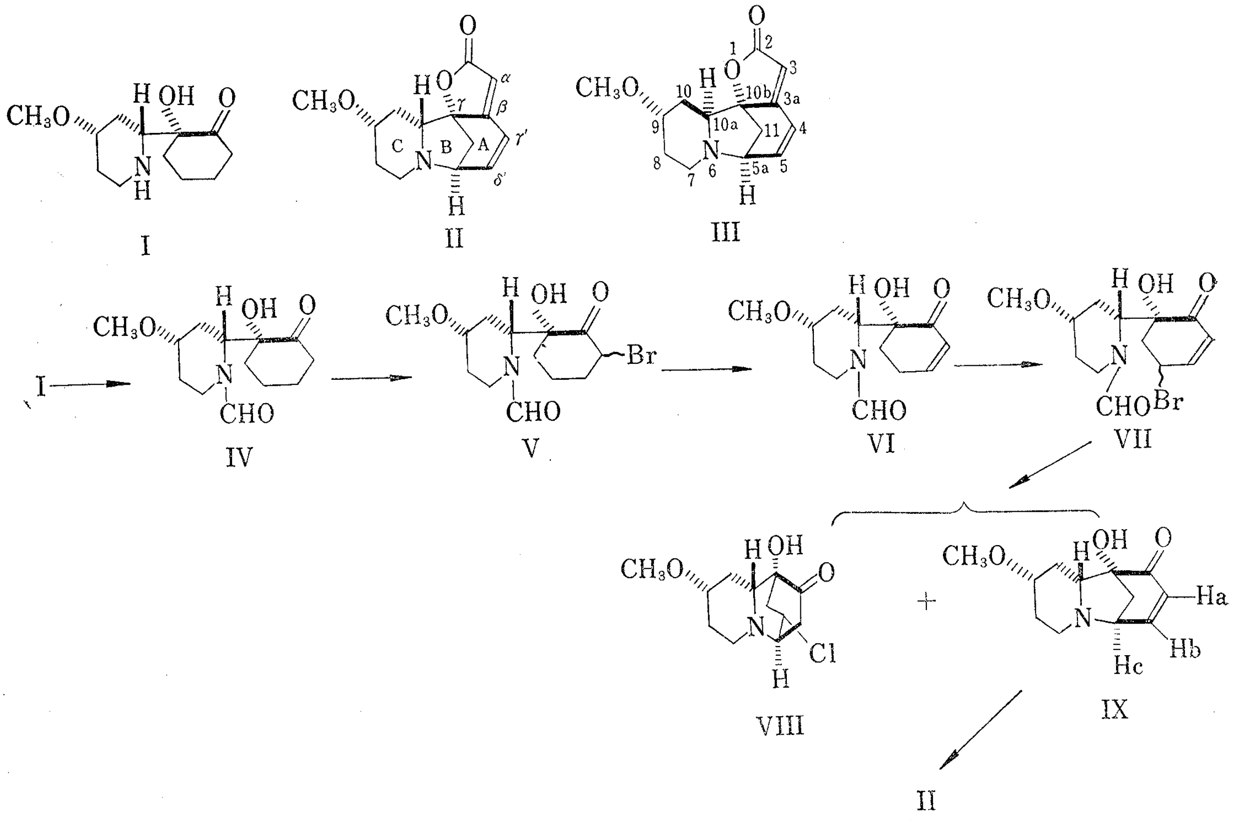

Chart 1

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[1] Part I: Z. Horii, T. Imanishi, T. Tanaka, I. Mori, M. Hanaoka, and C. Iwata, *Chem. Pharm. Bull.* (Tokyo), 20, 1768 (1972).

[2] Location: *6-1-1, Toneyama, Toyonaka, Osaka.*

[3] Z. Horii, M. Ikeda, M. Hanaoka, M. Yamauchi, Y. Tamura, S. Saito, T. Tanaka, K. Kotera, and N. Sugimoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 918 (1966); *idem, ibid.*, **15**, 1633 (1967).

[4] V.C. Mehlenbacher, *Org. Analysis*, **1**, 37 (1953).

solution saturated with dry hydrogen chloride[5] at 50° gave the α-bromo-ketone (V), which was dehydrobrominated by heating with lithium carbonate and lithium bromide in dimethylformamide to give the α,β-unsaturated ketone (VI), mp 89—91°, in overall yield of 47% from IV. The infrared (IR) spectrum of VI shows a band at 1676 cm^{-1} due to an α,β-unsaturated ketone and its nuclear magnetic resonance (NMR) spectrum exhibits two olefinic proton signals at 4.01 and 3.01 τ.

Allylic bromination of VI with N-bromosuccinimide in dry carbon tetrachloride in the presence of benzoyl peroxide gave the bromide (VII) as an isomeric mixture in 70% yield. The bromide (VII) was hydrolyzed with 20% hydrochloric acid at 90°, followed by refluxing with potassium carbonate in wet chloroform to give the isoquinuclidine (VIII) and the desired ketone (IX) in 14% and 12% yields, respectively. The structures of these products were confirmed by the following spectral data.

There is no signal due to olefinic proton in the NMR spectrum of VIII. The IR spectrum of VIII exhibits a ketone absorption band of a bicyclo[2,2,2]octanone system[6] at 1743 cm^{-1} and its mass spectrum has molecular ion peaks at *m/e* 261 and 259 (1: 3), which indicate the presence of one chlorine atom in its molecule. The product (VIII) was assumed to be obtained by Michael addition of the nitrogen to the conjugated system *via* the displacement of bromide by chloride anion. The second product (IX) exhibits a molecular ion peak at *m/e* 223 in its mass spectrum. The IR spectrum of IX shows an α,β-unsaturated ketone absorption band at 1682 cm^{-1} and its NMR spectrum has a doublet of doublets of one proton at 6.15 τ (Hc), a doublet of one proton at 3.82 τ (Ha) and a doublet of doublets of one proton at 3.14 τ (Hb). The ultraviolet (UV) spectrum of IX shows two absorption maxima at 218 mμ due to an α,β-unsaturated ketone and 312 mμ due to a homoconjugation[7] between the nitrogen and the α,β-unsaturated ketone. The latter maximum disappeared by addition of an appropriate amount of hydrochloric acid.

The α,β-unsaturated ketone (IX) was condensed with lithium ethoxyacetylide[8] at −20°, followed by refluxing with 15% sulfuric acid in tetrahydrofuran to give racemic 10a-episecuritinine (II) in overall yield of 27% from IX. The IR spectrum of II shows an α,β-unsaturated γ-lactone absorption band at 1802 and 1754 cm^{-1}, and its NMR spectrum shows a triplet of one proton at 4.40 τ (C_3-H) and multiplets of two protons at 3.84—3.17 τ (C_4-H and C_5-H). The UV spectrum of II shows two absorption maxima at 255 mμ due to an α,β,γ′,δ′-unsaturated γ-lactone and 319 mμ due to a homoconjugation between the nitrogen and the conjugated system. As 10a-episecuritinine (II) was derived using the reactions without any epimerization steps at all asymmetric centers from the amine (I) whose stereochemistry was already known,[1] the stereochemistry of II is shown as depicted.

The longer wave-length maximum of the UV spectrum of II remains unaffected by changing the solvent from ethanol to dioxane, while that of securitinine is solvent-dependent.[3] This phenomenon can be well explained by the relative configuration between C_{10a} and C_{10b} of 10a-episecuritinine.[9]

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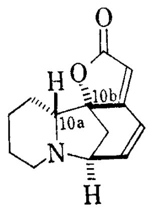
[5] J. Elks, G.H. Phillipps, and W.F. Wall, *J. Chem. Soc.*, **1958**, 4001.

[6] Z. Horii, M. Ito, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1754 (1968); R. Zbinden, and H.K. Hall, *J. Am. Chem. Soc.*, **82**, 1215 (1960); K. Morita, and T. Kobayashi, *J. Org. Chem.*, **31**, 229 (1966); C.B. Page and A.R. Pinder, *J. Chem. Soc.*, **1964**, 4811.

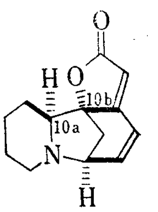
[7] *a*) Z. Horii, M. Ikeda, Y. Tamura, S. Saito, M. Suzuki, and K. Kotera, *Chem. Pharm. Bull.* (Tokyo), **12**, 1118 (1964); *b*) T. Nakano, T.H. Yang, and S. Terao, *J. Org. Chem.*, **29**, 3441 (1964).

[8] J.F. Arens, "Advances in Organic Chemistry: Methods and Results," Vol. II, Interscience, New York, 1960, p. 203.

[9] The corresponding maximum of securinine (**i**) is not dependent on solvent but that of allosecurinine (**ii**), the epimer at C_{10a} of securinine, is solvent-dependent.[7a]



i



ii

Experimental1)

2-(1-Formyl-4-methoxy-2-piperidyl)-2-hydroxycyclohexanone(IV)——A solution of the amine (I, 0.20 g) in acetic-formic anhydride4) (4 ml) was heated at 90° and the reaction mixture was evaporated *in vacuo* at 90°. To the residue were added water and K_2CO_3, and the resulting alkaline mixture was extracted with $CHCl_3$. Evaporation of the dried extract gave an oily residue (0.22 g), which was chromatographed on silica gel (4 g). Elution with EtOH–$CHCl_3$ (1:50 v/v) afforded 180 mg (80%) of the formamide (IV) as a solid, which was recrystallized from *n*-hexane to give colorless cubes, mp 94—95.5°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3303 (OH), 1708 (CO), 1659 (amide). *Anal.* Calcd. for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.32; H, 8.28; N, 5.81. NMR τ: 6.63 (3H, s, -OC$\underline{H}_3$), 5.08 (1H, t, J=5 cps, N-C$\underline{H}$<), 4.51 (1H, s, OH). 1.87 (1H, s, -CHO).

2-Bromo-6-(1-formyl-4-methoxy-2-piperidyl)-6-hydroxycyclohexanone(V)——A solution of the ketone (IV, 305 mg) in $CHCl_3$ (7 ml) and EtOH (0.5 ml) was saturated with dry HCl gas and then to this stirred solution was added a solution of Br_2 (250 mg) in $CHCl_3$ (3 ml) dropwise over a period of 1 hr at 50°. Stirring was continued for another 1 hr at this temperature. After cooling, the reaction mixture was washed with water, satd. $Na_2S_2O_3$, satd. $NaHCO_3$ and water, and dried. Evaporation of the solvent gave 395 mg (87%) of the α-bromo-ketone(V) as a colorless oil, homogeneous on TLC. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3230 (OH), 1729 (CO), 1659 (amide). This crude α-bromo-ketone was used for the next reaction without further purification.

6-(1-Formyl-4-methoxy-2-piperidyl)-6-hydroxy-2-cyclohexenone(VI)——A stirred mixture of the crude bromide (V, 1.0 g), LiBr (1.0 g) and Li_2CO_3 (1.5 g) in dry DMF (20 ml) was heated under N_2 atmosphere at 120° for 5 hr. After cooling, the reaction mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, 10% HCl and water, and dried. Evaporation of the solvent gave an oily residue (0.82 g), which was chromatographed on silica gel (15 g) using $CHCl_3$ as an eluent to afford a solid, which was recrystallized from petr. ether to give 410 mg (54%) of the α,β-unsaturated ketone (VI) as colorless cubes, mp 89—91°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3351 (OH), 1676 (sh) and 1667 (α,β-unsaturated ketone and amide), 1621 (C=C). *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.64; H, 7.59; N, 5.76. NMR τ: 6.51 (3H, s, -OC$\underline{H}_3$), 5.29 (1H, d of d, J=3 and 7.5 cps, N-C$\underline{H}$<), 4.22 (1H, s, OH), 4.01 (1H, d of d, J=3 and 10 cps, -CO-C$\underline{H}$=CH-), 3.01 (1H, m, -CO-CH=C$\underline{H}$-), 1.80 (1H, s, -CHO).

4-Bromo-6-(1-formyl-4-methoxy-2-piperidyl)-6-hydroxy-2-cyclohexenone(VII)——A mixture of the α,β-unsaturated ketone (VI, 0.70 g), NBS (530 mg) and benzoyl peroxide (30 mg) in dry CCl_4 (40 ml) was refluxed for 2.5 hr. After cooling, succinimide was filtered off and the filtrate was washed with water, satd. $NaHCO_3$ and water, and dried. Evaporation of the solvent gave an oily residue (0.81 g), which was chromatographed on silica gel (9 g). Elution with $CHCl_3$ afforded 650 mg (70%) of the bromide (VII) as a colorless viscous oil. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3250 (OH), 1685 (CO), 1660 (amide). NMR τ: 6.52 and 6.49 (3/4H and 9/4H, respectively, each s, -OCH$_3$), 4.02 and 3.68 (3/4H and 1/4H, respectively, each s, OH), 2.8—5.0 (2H, olefinic protons), 1.73 and 1.69 (3/4H and 1/4H, respectively, each s, -CHO). Mass Spectrum *m/e*: 333 and 331 (M$^+$), 252, 142.

Cyclization of VII——A mixture of the bromide (VII, 0.60 g) in 20% HCl (10 ml) was heated at 90° for 4 hr. After cooling, the aqueous layer was washed with $CHCl_3$ and evaporated *in vacuo* to dryness. To this residue was added anhydrous K_2CO_3 (1.5 g), water (0.5 ml) and $CHCl_3$ (60 ml), and then the resulting mixture was refluxed for 4 hr. The reaction mixture was extracted with 10% HCl (10 ml × 2) and the aqueous layer was made alkaline with K_2CO_3 under ice cooling. The $CHCl_3$ extract of the mixture was washed with water and dried. Evaporation of the solvent gave a crude product (380 mg), which was chromatographed on silica gel (5 g). Elution with $CHCl_3$ afforded colorless crystals, which were recrystallized from *n*-hexane to give 66 mg (14%) of the isoquinuclidine(VIII) as colorless needles, mp 132—134°. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3440 (OH), 1737 (CO); $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3335 (OH), 1743 (CO). *Anal.* Calcd. for $C_{12}H_{18}O_3NCl$: C, 55.48; H, 6.90; N, 5.39. Found: C, 55.20; H, 7.09; N, 5.32. NMR τ: 6.60 (3H, s, -OCH$_3$), 6.00 (1H, d of d of d, J=1,6 and 10 cps, >CHCl). Mass Spectrum *m/e*: 261 and 259 (M$^+$), 224. Elution with EtOH–$CHCl_3$ (1:10 v/v) afforded 47 mg (12%) of the α,β-unsaturated ketone(IX) as a colorless viscous oil, which shows one spot on TLC. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3400 (OH), 1682 (α,β-unsaturated ketone). NMR τ: 6.68 (3H, s, -OC$\underline{H}_3$), 6.15 (1H, d of d, J= 5 and 5.5 cps, Hc), 3.82 (1H, d, J=10 cps, Ha), 3.14 (1H, d of d, J=5.5 and 10 cps, Hb). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 218 (4.08), 312 (3.25). Mass Spectrum *m/e*: 223 (M$^+$), 114. The perchlorate of IX, colorless needles, mp 208—210° (from EtOH). *Anal.* Calcd. for $C_{12}H_{18}O_7NCl$: C, 44.52; H, 5.61; N, 4.33. Found: C, 44.33; H, 5.82; N, 4.11.

10a-Episecuritinine(II)——To a stirred solution of CH_3Li (prepared from 0.1 g of Li and 0.5 ml of CH_3I) in dry ether (15 ml) was added dropwise a solution of ethoxyacetylene11) (1.0 g) in dry ether (10 ml) under

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10) All melting points are uncorrected. NMR spectra were taken on Hitachi Perkin-Elmer H-60 type spectrometer at 60Mc in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard. Mass spectra were taken on Hitachi RMU-60 spectrometer. Silica gel (Mallinckrodt) and Kiesel gel PF_{254} (E. Merck) were used for column chromatography and for preparative thin-layer chromatography (TLC), respectively. Organic extracts were dried over anhydrous $MgSO_4$.

11) E.R.H. Jones, G. Eglinton, M.C. Whiting, and B.L. Shaw, *Org. Synth.*, Coll. Vol. IV, 404 (1963).

N_2 atmosphere at −20° over a period of 10 min. A solution of the amine (IX, 45 mg) in dry ether (5 ml) was added to the reaction mixture at −20° over a period of 15 min and then stirring was continued for 2 hr at −20° and for 1 hr at room temperature. To the reaction mixture was added satd. NH_4Cl solution at 0° and the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with brine and dried. The solvent was evaporated *in vacuo,* and to the residue was added THF (3 ml) and 15% H_2SO_4 (0.5 ml). The mixture was refluxed for 15 min. After cooling, the resulting mixture was made alkaline with K_2CO_3 and THF was removed *in vacuo.* The $CHCl_3$ extract of the resudue was washed with water and dried. Evaporation of the solvent gave an oily residue, which was purified by the preparative TLC on silica gel (30 g) using EtOH–$CHCl_3$ (1:20 v/v) as a developing solvent to give 12 mg (27%) of 10a-episecuritinine (II) as a pale-yellow viscous oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 1802 (sh) and 1754 (α,β-unsaturated γ-lactone), 1633 and 850 (C=C). NMR τ: 6.67 (3H, s, -OC$\underline{H}_3$), 6.19 (1H, t, J=4.5 cps, C_{5a}-H), 4.40 (1H, s, C_3-H), 3.84—3.17 (2H, C_4-H and C_5-H). UV $\lambda_{\text{max}}^{\text{EtOH}}$ mμ (log ε): 255 (4.18), 319 (3.22); $\lambda_{\text{max}}^{\text{dioxane}}$ mμ (log ε): 268 (4.10), 324 (3.39). Mass Spectrum *m/e*: 247 (M^+), 216, 134, 114, 106, 82, 78, 56. The picrolonate of II, mp 231—233° (from MeOH). *Anal.* Calcd. for $C_{24}H_{25}O_8N_5$: C, 56.35; H, 4.93; N, 13.69. Found: C, 56.09; H, 5.04; N, 13.65.