Synthetic Studies on Securitinine and Related Compounds. II.\(^1\)

A Synthesis of 10a-Episecuritinine

ZEN-ICHI HORII, TAKEHI Imanishi,
MIYOH HANAOKA, and CHUZO IWATA

Faculty of Pharmaceutical Sciences, Osaka University\(^2\)

(Received January 27, 1972)

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

![Chemical structures](chart1.png)

Chart 1

---

2) Location: 6-1-1, Toneyama, Toyonaka, Osaka.
4) V.C. Mehlenbacher, Org. Analysis, 1, 37 (1953).
solution saturated with dry hydrogen chloride 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 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 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 at −20°, followed by refluxing with 15% sulfuric acid in tetrahydrofuran to give racemic 10α-episecuritine (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 (C₃-H) and multiplets of two protons at 3.84—3.17 τ (C₂-H and C₃-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 10α-episecuritine (II) was derived using the reactions without any epimerization steps at all asymmetric centers from the amine (I) whose stereochemistry was already known, 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 securitine is solvent-dependent. This phenomenon can be well explained by the relative configuration between C₁₀α and C₁₀β of 10α-episecuritine.⁹

---

9) The corresponding maximum of securitine (i) is not dependent on solvent but that of alloscururinie (ii), the epimer at C₁₀α of securitine, is solvent-dependent.⁷⁶
Experimental

2-(1-Formyl-4-methoxy-2-piperidyl)-2-hydroxycyclohexanone (IV)—A solution of the amine (I, 0.20 g) in acetic-formic anhydride (4 ml) was heated at 90° and the reaction mixture was evaporated in vacuo at 90°. To the residue were added water and K₂CO₃, and the resulting alkaline mixture was extracted with CHCl₃. Evaporation of the dried extract gave an oily residue (0.22 g), which was chromatographed on silica gel (4 g). Elution with EtOH–CHCl₃ (1:50 v/v) afforded 180 mg (80%) of the formamidine (IV) as a solid, which was recrystallized from n-hexane to give colorless cubes, mp 94—95.5°. IR νmax cm⁻¹: 3303 (OH), 1708 (CO), 1659 (amide). Anal. Calcd. for C₇H₁₆O₃N: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.32; H, 8.28; N, 5.81. NMR: δ: 6.63 (3H, s, -OCH₃), 5.08 (1H, t, J = 5 cps, N-CH₂), 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 CHCl₃ (7 ml) and EtOH (0.5 ml) was saturated with dry HCl gas and then to this stirred solution was added a solution of Br₂ (250 mg) in CHCl₃ (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. Na₂S₂O₅, satd. NaHCO₃ 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 νmax 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 Li₂CO₃ (1.5 g) in dry DMF (20 ml) was heated under N₂ atmosphere at 120° for 5 hr. After cooling, the reaction mixture was poured into ice-water and extracted with CHCl₃. The CHCl₃ 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 CHCl₃ 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 νmax cm⁻¹: 3251 (OH), 1676 (sh) and 1667 (α,β-unsaturated ketone and amide), 1621 (C=C). Anal. Calcd. for C₁₀H₁₂O₃N: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.64; H, 7.59; N, 5.76. NMR: δ: 6.51 (3H, s, -OCH₃), 5.20 (1H, d of d, J = 3 and 7.5 cps, N-CH₂), 4.22 (1H, s, OH), 4.01 (1H, d of d, J = 3 and 10 cps, -OCH₂CH=), 3.01 (1H, m, -CO-CH₂-CH=), 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 CCl₄ (40 ml) was refluxed for 2.5 hr. After cooling, succinimide was filtered off and the filtrate was washed with water, satd. NaHCO₃ 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 CHCl₃ afforded 650 mg (70%) of the bromide (VII) as a colorless viscous oil. IR νmax cm⁻¹: 3250 (OH), 1685 (CO), 1660 (amide). NMR: δ: 6.32 and 6.49 (3/4H and 9/4H, respectively, each s, -OCH₃), 4.02 and 3.68 (3/4H and 1/4H, respectively, each s, OH), 2.8—5.0 (2H, olefinic protons), 1.75 and 1.69 (3/4H and 1/4H, respectively, each s, -CHO). Mass Spectrum m/z: 335 and 331 (M⁺), 352, 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 CHCl₃ and evaporated in vacuo to dryness. To this residue was added anhydrous K₂CO₃ (1.5 g), water (0.5 ml) and CHCl₃ (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 basic with K₂CO₃ under ice cooling. The CHCl₃ 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 CHCl₃ 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 νmax cm⁻¹: 3440 (OH), 1737 (CO); νmax cm⁻¹: 3335 (OH), 1743 (CO). Anal. Calcd. for C₁₄H₁₄O₂NCl: C, 55.48; H, 6.90; N, 5.39. Found: C, 55.20; H, 7.09; N, 5.32. NMR: δ: 6.60 (3H, s, -OCH₃), 6.00 (1H, d of d, J = 1.6 and 10 cps, γ-CHCl). Mass Spectrum m/z: 261 and 259 (M⁺), 224. Elution with EtOH–CHCl₃ (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 νmax cm⁻¹: 3400 (OH), 1682 (α,β-unsaturated ketone). NMR: δ: 6.68 (3H, s, -OCH₃), 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 νmax nm: (log e): 218 (4.08), 312 (3.25). Mass Spectrum m/z: 223 (M⁺), 114. The perchlorate of IX, colorless needles, mp 208—210° (from EtOH). Anal. Calcd. for C₁₁H₁₆O₂NCl: C, 44.52; H, 5.61; N, 4.33. Found: C, 44.33; H, 5.82; N, 4.11.

10a-Epsecucitrinine (II)—To a stirred solution of CH₃Li (prepared from 0.1 g of Li and 0.5 ml of CH₃I) in dry ether (15 ml) was added dropwise a solution of ethoxyacetylethene (10 g) in dry ether (10 ml) under

10) All melting points are uncorrected. NMR spectra were taken on Hitachi Perkin-Elmer H-60 type spectrometer at 60Mc in CDC₁₃ with (CH₃)₄Si as an internal standard. Mass spectra were taken on Hitachi RMU-60 spectrometer. Silica gel (Malinkrodt) and Kiesel gel PF₅₂ (E. Merck) were used for column chromatography and for preparative thin-layer chromatography (TLC), respectively. Organic extracts were dried over anhydrous MgSO₄.

N₂ 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. NH₄Cl 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% H₂SO₄ (0.5 ml). The mixture was refluxed for 15 min. After cooling, the resulting mixture was made alkaline with K₂CO₃ and THF was removed in vacuo. The CHCl₃ extract of the residue 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–CHCl₃ (1:20 v/v) as a developing solvent to give 12 mg (27%) of 10α-episecuritinine (II) as a pale-yellow viscous oil. IR νmax cm⁻¹: 1802 (sh) and 1754 (a,β-unsaturated γ-lactone), 1633 and 850 (C=O). NMR δ: 6.67 (3H, s, -OCH₃), 6.19 (1H, t, J=4.5 cps, C₃-H), 4.40 (1H, s, C₃-H), 3.84—3.17 (2H, C₄-H and C₅-H). UV λmax [μ] (log ε): 255 (4.18), 319 (3.22); λmax [μ] (log ε): 268 (4.10), 324 (3.39). Mass Spectrum m/z: 247 (M⁺), 216, 134, 114, 106, 82, 78, 56. The picrolonate of II, mp 231—233° (from MeOH). Anal. Calcd. for C₂₄H₂₄O₅N₂: C, 56.35; H, 4.93; N, 13.69. Found: C, 56.09; H, 5.04; N, 13.65.