Chem. Pharm. Bull.
35(12)4990—4992(1987)

The Synthesis of Lupin Alkaloids. II.[1] A Formal Synthesis of (±)-Sparteine

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(Received June 9, 1987)

2-Hydroxy-3-(2′-piperidyl)quinolizidine (**5**), an intermediate for the synthesis of (±)-leontiformidine (**1a**), was converted into (±)-sparteine (**7**) by a three-step procedure of oxidation, Mannich reaction and deoxygenation.

Keywords——lupin alkaloid; leontiformidine; sparteine; 8-oxosparteine; 2-hydroxyleontiformidine; 2-oxoleontiformidine; 3-(2′-piperidyl)quinolizidine; stereo-structure; Jones-oxidation

In the preceding paper,[1] we reported the total synthesis of two lupin alkaloids, leontiformidine (**1a**) and leontiformine (**1b**), using the 1,3-dipolar cycloaddition reaction of the enone (**2**) with 1-piperine 1-oxide (nitrone **3**) as a key reaction, as shown in Chart 1. Leontiformidine (**1a**) has a 3-(2′-piperidyl)quinolizidine structure, and another lupin alkaloid, sparteine (**7**), has a similar structure in which the C-1 and N-1′ positions are combined with a methylene group. Therefore, it seemed likely that 2-hydroxyleontiformidine (**5**), an intermediate for the preparation of **1a**, could be converted into **7** by a three-step procedure of oxidation, Mannich reaction and deoxygenation. This paper deals with the chemistry leading to (±)-**7** from **5**.

Chromic acid is generally used in the oxidation of amino alcohols to amino-carbonyl compounds. However, in the oxidation of **5**, epimerization at the C-3 must be considered, because the C-3 of **8** becomes an active methine carbon owing to the effect of the produced carbonyl group, and the 2-piperidyl group should take the thermodynamically stable equatorial form. To avoid epimerization at C-3 of **8**, various oxidations without the use of chromic acid were attempted. Under non-acidic conditions, Oppenauer oxidation and Moffatt oxidation did not occur, and the starting material was recovered. Swern oxidation gave a complicated mixture. Mild conditions using pyridinium chlorochromate (PCC) gave unsatisfactory results. Finally, Jones oxidation afforded **8** in 96% yield.

In order to confirm the stereochemistry of the product **8**, obtained under rather strongly acidic conditions, the reductive removal of the carbonyl oxygen was carried out. Wolff–Kishner reaction of **8** did not proceed, but the tosylhydrazone of **8** was reduced with $LiAlH_4$ to give **1a**, whose spectral data were identical with those of an authentic sample. Consequently, it was found that the stereo-structure at C-3 of **8** did not change during Jones oxidation.

Next, the Mannich reaction of **8** with HCHO was carried out. Under acidic conditions with HCl, the reaction did not occur. At pH 7—8 adjusted with AcOH, 8-oxo-sparteine (**9**) was obtained in 38% yield. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) data of **9** were consistent with those of Bohlmann and Zeisberg.[2] Since **9** has already been converted to (±)-**7** by van Tamelen and Foltz,[3] this synthesis constitutes a formal synthesis of (±)-sparteine.

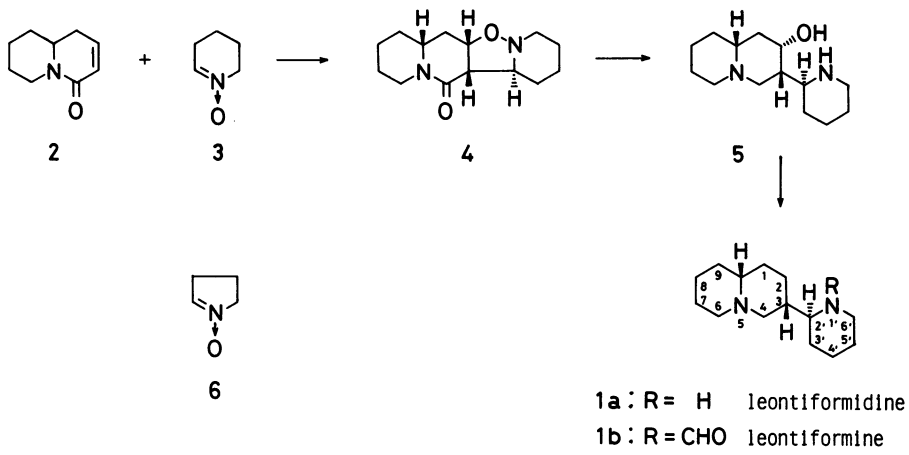

Chart 1

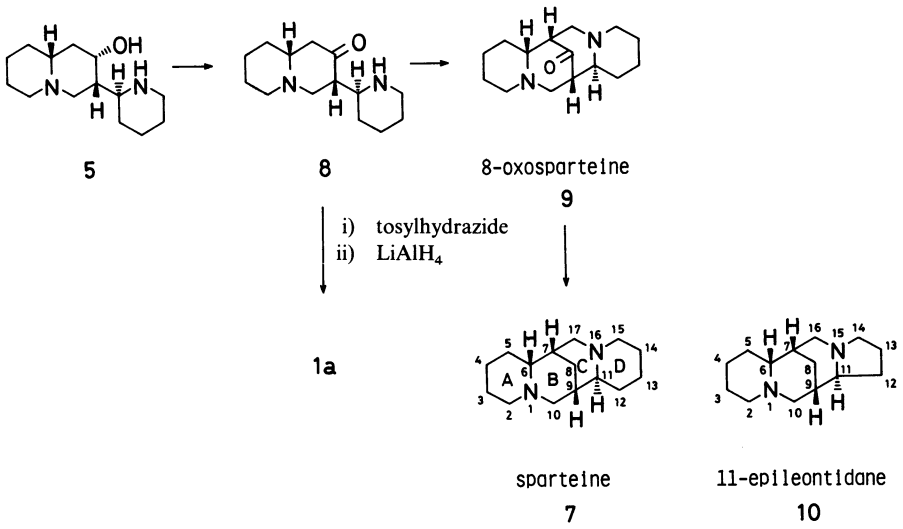

Chart 2

Thus, we have achieved a novel synthesis of sparteine, maintaining the stereo-structure from 2-hydroxyleontiformidine (**5**). This method should be applicable to the total synthesis of naturally occurring homologous alkaloids. For example, the quinolizidine-indolizidine alkaloid 11-epileontidane[4] has the structure **10**, in which the D-ring of sparteine (**7**) is replaced by a five-membered ring and the stereochemistry of chiral centers is the same as that of **7**. Accordingly, it is expected that the synthesis of **10** should be possible by using 1-pyrroline 1-oxide (**6**) instead of nitrone (**3**) in the foregoing procedures. The correctness of this assumption is now under investigation in our laboratory.

Experimental

Infrared (IR) spectra were measured with a Hitachi 215 spectrometer and MS with a JEOL JMS-D300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX 400 FT NMR with tetramethylsilane as an internal standard.

(±)-2-Oxoleontiformidine (8)——i) Oxidation of **5** with PCC: A solution of **5** (500 mg, 2.10 mmol) in dry CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (0.90 g, 4.18 mmol) and molecular sieves 3A powder (2.10 g) in dry CH_2Cl_2 (10 ml) at room temperature. Stirring was continued for 6 h, then water and K_2CO_3 were added and the solvent was evaporated off *in vacuo*. The residue was extracted with CH_2Cl_2 in a Soxhlet extractor for 12 h and the extract was evaporated *in vacuo*. The resulting product was chromatographed on silica gel with CH_2Cl_2–CH_3OH–28%NH_4OH (90 : 9 : 1) to give colorless crystals of **8**. Yield, 263 mg (53.0%).

ii) Jones Oxidation. Fresh Jones reagent (a mixture of CrO_3 5.34 g, H_2SO_4 4.6 ml, and water 8 ml make 20 ml) was added to a stirred suspension of **5** (200 mg, 0.84 mmol) in acetone (20 ml) to form a clear solution at 0°C. After being stirred for 2 h, the reaction mixture was warmed to room temperature and then stirred for a further 3 h. The resulting mixture was concentrated to half the initial volume, water and K_2CO_3 were added, and the solvent was evaporated off. The residue was extracted with CH_2Cl_2 in a Soxhlet extractor for 12 h, and the extract was concentrated to dryness. The solid obtained gave a single spot on thin layer chromatography (TLC). Yield, 190 mg, 96.1%. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3370(NH), 2930, 2850, 2800 (Bohlmann band), 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, m), 2.78 (1H, ddd, J=2.4, 7.2, 10.9 Hz), 2.96 (1H, m), 3.03 (1H, m), 3.16 (1H, dd, J=5.9, 11.2 Hz). MS *m/z*: 236(M^+), 152, 110, 98, 84 (base peak). High MS *m/z* 236.1887 (Calcd for $C_{14}H_{24}N_2O$: 236.1887).

(±)-Leontiformidine (1a) From the Tosylhydrazone of 8——A solution of **8** (50 mg, 0.21 mmol) and tosylhydrazide (47 mg, 0.25 mmol) in EtOH (70 μl) was heated at 90°C under an N_2 atmosphere for 20 h and then concentrated to dryness *in vacuo*. The residue was dissolved in dry tetrahydrofuran (THF) (2 ml) and this solution was added to a stirred suspension of $LiAlH_4$ (80 mg, 2.11 mmol) in dry THF under an N_2 atmosphere. The mixture was stirred for 12 h at ambient temperature, then the reaction was quenched by the addition of water. The insoluble material formed was filtered off and washed with CH_2Cl_2. The combined filtrate was dried and evaporated to give the residue, which was subjected to preparative TLC on silica gel with CH_2Cl_2–CH_3OH–28% NH_4OH (90 : 9 : 1) to give (±)-**1a** as a pale yellow syrup (34.3 mg, 73%). Spectral data of (±)-**1a** were consistent with those of an authentic sample.[1]

Mannich Reaction of 8: Formation of (±)-8-Oxosparteine (9)——A solution of **8** (190 mg, 0.80 mmol) and 35% formalin (64 μl, 0.81 mmol) in EtOH (0.5 ml) was adjusted to pH 7—8 with 50% AcOH and then heated at 110°C with stirring for 2 h. After the solution had cooled, the solvent was evaporated off *in vacuo* and then water, CH_2Cl_2 and K_2CO_3 were added and the whole was extracted with CH_2Cl_2. The organic layer was dried and evaporated *in vacuo* to give the residue, which was subjected to column chromatography on silica gel. Elution with CH_2Cl_2–CH_3OH–28%NH_4OH (90 : 9 : 1) afforded (±)-8-oxosparteine (**9**) as a pale yellow solid (74.3 mg, 37.2%). The spectral data of **9** were consistent with those reported by Bohlmann and Zeisberg.[2] IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2935, 2855, 2803, 2770 (Bohlmann band), 1738, 1720 (C=O). ^{13}C-NMR ($CDCl_3$) δ: 23.32 (t), 23.65 (t), 25.41 (t), 25.52 (t), 29.86 (t), 34.90 (t), 51.88 (d), 54.39 (dd), 54.63 (d), 55.13 (dd), 55.92 (t), 62.16 (dd), 66.64 (d), 66.77 (d), 213.16 (s). MS *m/z*: 248 (M^+), 166, 165, 164, 152, 151, 150, 124, 110, 98 (base peak), 97, 96.

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