Communications to the Editor

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THE SYNTHESIS OF LUPIN ALKALOIDS. I. TOTAL SYNTHESIS OF (±)-LEONTIFORMINE AND (±)-LEONTIFORMIDINE

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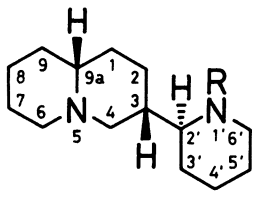
The novel total synthesis of the lupin alkaloids (±)-leontiformine (**1**) and (±)-leontiformidine (**2**) has been achieved by using the 1,3-dipolar cycloaddition reaction of 1-piperine 1-oxide (**4**) twice in the synthesis process.

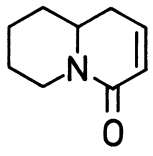
KEYWORDS ——— lupin alkaloid; 3-(2'-piperidyl)quinolizidine; (±)-leontiformine; (±)-leontiformidine; 1,3-dipolar cycloaddition; 1-piperine 1-oxide; 2,3-dehydroquinolizidin-4-one

Lupin alkaloids are usually found in plants of the Leguminosae family. Most of them have a trans-quinolizidine ring system and some have a cis-ring system. Many methods for synthesizing various types of lupin alkaloids have been reported, but there are only a few reports on 3-(2'-piperidyl)quinolizidine derivatives, such as leontiformine (**1**)[1a] and leontiformidine (**2**).[1b]

Recently, we have reported[2] on the alternative total synthesis of indolizidine alkaloids, elaeokanine homologues, using the 1,3-dipolar cycloaddition reaction of 1-pyrroline 1-oxide as a key reaction. As an extension of this work, we have synthesize some lupin alkaloids. Kakisawa et al.[3] reported the syntheses of the lupin alkaloids (±)-lupinine and (±)-α-isosparteine using the cycloaddition reaction of cyclic nitrone. In our first trial, a total synthesis of (±)-**1** and (±)-**2** was attained by using the cycloaddition reaction of the conjugated enone (**3**) with 1-piperine 1-oxide (nitrone **4**) as a key step. The key intermediate (**3**) was prepared by three steps from the 1,3-dipolar cycloaddition product (**6**) formed from the same nitrone (**4**) with ethyl 3-butenoate (**5**).



leontiformine (**1**) R = CHO
leontiformidine (**2**) R = H



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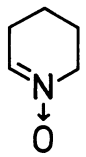

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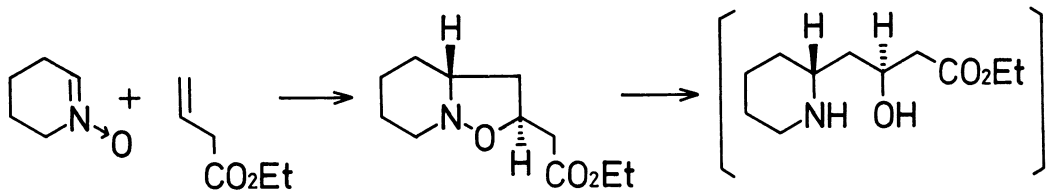
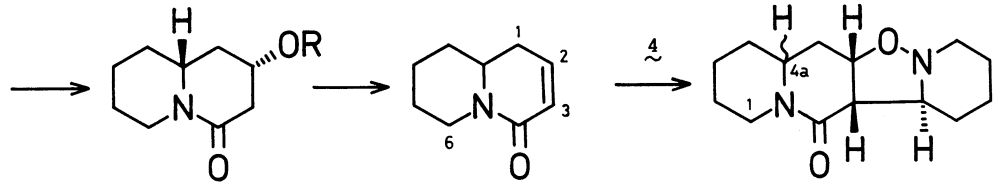
Procedures for preparing the intermediate (**3**) are as follows. The cycloaddition reaction of **4** with **5** was carried out according to the method of Tufariello et al.[4] [reflux in toluene, 15 h, N_2], and the exo-adduct (**6**) was obtained[5] in 87% yield. The stereochemistry of **6** is supported by the following evidence. The next recyclized product **7** formed from **6** has a rigid structure, and appeared in the ^{1}H-NMR spectrum at δ3.93 [1H, m, $W_{1/2}$=24 Hz, which was assigned to axial C2-βH]. And the spectral data of both **6** and **7** indicated the presence of a single isomer. Catalytic hydrogenolysis of **6** [10% Pd-C, H_2, 100 Kg/cm^2, in EtOH, r.t., 3 day] caused a reductive N-O bond cleavage resulting in a recyclized product (**7**) in 90% yield. The dehydration of **7** applying acidic conditions [for example, 75% H_2SO_4, 130°C, 3 h, 76% yield] gave the unconjugated enone (**8**) [1,2-dehydroquinolizidin-4-one (**8**); MS m/e 151 (M^+, base peak), 136, 122, 108; ^{1}H-NMR($CDCl_3$) δ2.96 (2H, m, C3-H), 4.86 (1H, m, C6-eqH), 5.63 (2H, m, C1-H and C2-H); IRν_{max}^{film} 1620 cm^{-1}].



4 **5** **6**



7 R = H
7' R = OMs

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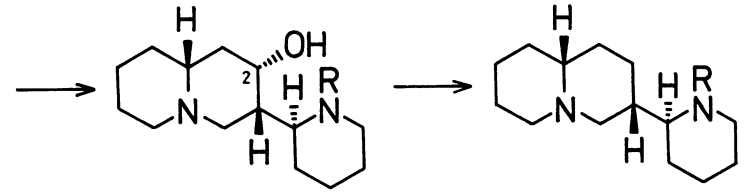
9a C4a - βH
9b C4a - αH



10 R = H
11 R = $PhCH_2$-

12 R = $PhCH_2$-
(±) - **2** R = H
(±) - **1** R = CHO

The desired **3** was finally prepared under basic conditions via the methanesulfonate (**7'**) [1) methanesulfonyl chloride 1.25 eq, excess Et_3N, in CH_2Cl_2, r.t., 2 h; 2) DBU 1.1 eq, in fresh dry THF, reflux, 2 h, N_2] in 89% yield [2,3-dehydroquinolizidin-4-one (**3**); MS m/e 151 (M^+), 136, 122, 84 (base peak); ^{1}H-NMR($CDCl_3$) δ4.50 (1H, dm, J=13.8 Hz, C6-eqH), 5.87 (1H, ddd, J=1.5, 2.3, and 9.8 Hz, C3-H), 6.87 (1H, ddd, J=3.4, 4.9, and 9.8 Hz, C2-H); IRν_{max}^{film} 1668, 1615 cm^{-1}].

Next, the 1,3-dipolar cycloaddition reaction of the key intermediate (**3**) with **4** [reflux in $CHCl_3$, over night, N_2] afforded an inseparable stereoisomeric mixture of the adducts (**9**) in 99% yield. The formation ratio of **9a** and **9b** was shown to be 5.7:1 by its ^{1}H-NMR (400 MHz) spectrum[6], comparing the signals due to C1-H. The structures **9a** and **9b** were identified as C4a-βH and C4a-αH forms, respectively, by comparison of the spectral data of the final synthetic products and authentic samples prepared by the method of Bohlmann.[7a] Formation of the stereoisomers (**9a** and **9b**) is attributable to the exo-addition of nitrone (**4**) from both sides of the enone system of **3**. The major product **9a** is probably derived from the less steric effect of the C9a-position of **3**. The adduct (**9**) was treated with $LiAlH_4$ [3 eq, reflux in dry Et_2O, 12 h, N_2], and the resulting product was converted to (±)-2-hydroxyleontiformidine (**10**) by catalytic hydrogenolysis [10% Pd-C, H_2, 6.5 Kg/cm^2, in MeOH, r.t., 3 day] in 80% yield. The aminoalcohol (**10**) was converted into the N-benzyl derivative (**11**) by successive benzoylation and reduction [1) 3 eq PhCOCl, Et_3N, r.t., over night, 79% yield; 2) 8 eq $LiAlH_4$, reflux in dry Et_2O, over night, N_2, 96% yield]. Then the hydroxyl group of **11** was replaced with bromine followed by hydrogenation to give (±)-N-benzylleontiformidine (**12**) [1) 10 eq PBr_3, reflux in CCl_4, 10 h; 2) 3 eq Super-H, r.t., over night, N_2] in 90% yield from **11**.

The conversion of (±)-**12** to (±)-leontiformidine (**2**) was carried out by catalytic hydrogenolysis in AcOH [1) preparation of (±)-**12**-HCl salt, 2) Pd black, H_2, 6-7 Kg/cm^2, in AcOH, r.t., 3 day]. The product thus obtained was subjected to column chromatography [SiO_2, CH_2Cl_2-MeOH-28% NH_4OH(90:9:1)] to separate (±)-**2** and its C-9a epimer along with a fair amount of unchanged (±)-**12**. The sum of the yields of (±)-**2** and its C-9a epimer was 32% in the ratio of 5:1 obtained by GC [(±)-**2** ; MS m/e 222 (M^+), 164, 150, 138, 110, 98, 84 (base peak); ^{13}C-NMR($CDCl_3$) δ24.70 (t), 25.12 (t), 25.97 (t), 26.81 (t), 27.37 (t), 30.02 (t), 33.29 (t), 33.32 (t), 42.02 (d), 47.62 (dd), 56.80 (dd), 59.47 (t), 60.52 (d), 62.96 (d); IR$\nu_{max}^{CCl_4}$ 2928, 2853, 2802, 2767, 1445, 1115 cm^{-1} : C-9a epimer ; MS m/e 222 (M^+), 164, 150, 138, 110, 98, 84 (base peak); ^{13}C-NMR($CDCl_3$) δ24.79 (t), 24.95 (t), 25.06 (t), 25.71 (t), 26.82 (t), 29.60 (t), 31.15 (t), 32.85 (t), 40.06 (d), 47.47 (dd), 56.27 (d), 56.89 (dd), 58.26 (dd), 63.22 (d); IR$\nu_{max}^{CCl_4}$ 3315, 2933, 2857, 2800, 2763, 1443, 1114 cm^{-1}]. These products were identified with the authentic samples[1a,7a] by comparison of all available spectroscopic data (MS, ^{13}C-NMR, IR, TLC, and GC).

On the other hand, catalytic hydrogenolysis of (±)-**12** in formic acid [10% Pd-C, H_2, 6-7 Kg/cm^2, in 98% HCO_2H, r.t., 3 day] was performed in a similar manner and (±)-leontiformine (**1**) was obtained in 24% yield as a result of formylation of released (±)-**2** with the solvent [(±)-**1** ; IR$\nu_{max}^{CCl_4}$ 2935, 2855, 2800, 2770, 1673 cm^{-1}]. In this case, much (±)-**12** was recovered but there was no C-9a epimer. The product was identified with the formylation product of (±)-**2** by comparison of IR,[1b,7b] TLC, and GC. The debenzylation of (±)-**12** is being improved.

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6) Adduct **9a** showed signals at δ2.58 (0.85H, ddd, J=3.5, 11.8, and 13.4 Hz, C1-axH) and δ4.59 (0.85H, dm, J=13.4 Hz, C1-eqH), **9b** signals appeared at δ2.48 (0.15H, m, C1-axH) and δ4.66 (0.15H, dm, J=13.7 Hz, C1-eqH). The spectral data were obtained in pyridine-d_5 at 100°C, since most of the signals are broad in $CDCl_3$ at 25°C. However some signals are also broad in pyridine-d_5 at 100°C.
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