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(−)-*N*-ETHYLCYTISINE, A LUPIN ALKALOID FROM THE FLOWERS OF *ECHINOSOPHORA KOREENSIS**

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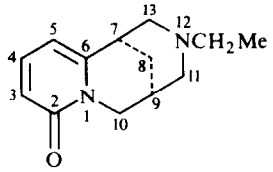
Key Word Index—*Echinosophora koreensis*; Leguminosae; lupin alkaloid; (−)-*N*-ethylcytisine; (−)-cytisine.

Abstract—A new lupin alkaloid, (−)-*N*-ethylcytisine, was isolated from the fresh flowers of *Echinosophora koreensis*. Its structure has been confirmed by spectroscopic data and by direct comparison with a synthetic sample prepared from (−)-cytisine and ethylbromide.

INTRODUCTION

As part of our chemical [1–9] and biochemical [11–13] studies on the lupin alkaloids in Japanese leguminous plants, we have recently isolated (−)-*N*-(3-oxobutyl)cytisine [4], (−)-cytisine, (−)-*N*-formylcytisine, (−)-*N*-methylcytisine, (−)-rhombifoline, (−)-baptifoline, (−)-anagyrine, (−)-lupanine and 5,6-dehydrolupanine from the fresh leaves, stems and roots of *Echinosophora koreensis* [10]. *E. koreensis* is a deciduous shrub, which is a native of Korea and closely related to the genus *Sophora* (Leguminosae). Further examination of the basic constituents in the fresh flowers has resulted in the isolation of a new lupin alkaloid, (−)-*N*-ethylcytisine (**1**); this paper deals with its structure determination.



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*This work was presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan at Kumamoto, 2 April 1981 (*Meeting Abstract* p. 518).

RESULTS AND DISCUSSION

From the freshly harvested flowers of *E. koreensis*, a new lupid alkaloid (**1**) was isolated in a yield of 0.001% of the fr. wt as colourless needles, mp 112°, $[\alpha]_D^{27}$ −216.7°; UV λ_{max}^{EtOH} nm (log ε): 235 (3.98), 310 (4.07).

The mass spectrum of 1 showed a $[M]^+$ at *m/z* 218 (28%) with predominant ions at *m/z* 160 (6) and 146 (7), characteristic of lupin alkaloids containing an α-pyridone ring [1, 2, 4, 6, 9]. The UV spectrum of **1** also suggested the presence of an α-pyridone moiety in the molecule [1, 2, 4, 6, 9]. The ^{1}H NMR spectrum ($CDCl_3$) of **1** clearly indicated the presence of aromatic protons at δ 5.97 (1 H, *dd*, *J* = 1.5 and 7 Hz), 6.43 (1 H, *dd*, *J* = 1.5 and 9 Hz) and 7.27 (1 H, *dd*, *J* = 7 and 9 Hz) attributable to the C-5, C-3 and C-4 positions, respectively, of an α-pyridone ring in a cytisine-type lupin alkaloid [1, 2, 4, 6, 9]. Other significant signals revealed in the NMR spectrum included an *N*-ethyl side chain at δ 0.91 (3 H, *t*, *J* = 7 Hz) and 2.32 (2 H, *q*, *J* = 7 Hz), and an equatorial H on C-11 and C-13 at δ 2.92 (2 H, *m*) very similar to those of (−)-*N*-methylcytisine and (−)-*N*-(3-oxobutyl)cytisine [4]. A base peak at *m/z* 72 in the mass spectrum of **1** was also indicative of the presence of an ethyl function at the *N*-12 position of the cytisine ring in contrast to the characteristic base peak of (−)-*N*-methylcytisine at *m/z* 58. From the above spectroscopic results, the new lupin alkaloid (**1**) was presumed to be (−)-*N*-ethylcytisine. Further confirmation of the identity of the new alkaloid as **1** was obtained by comparing the

natural compound directly with a synthetic material prepared from (−)-cytisine and ethylbromide.

EXPERIMENTAL

General procedures. Mps were uncorr. UV spectra were determined in EtOH. MS were measured at 70 eV. ^{1}H NMR spectra were recorded on a 100 MHz instrument with TMS as an int. standard. TLC was conducted on Si gel (Merck, GF_{254}, type 60) plates with solvents: (1), CH_2Cl_2–MeOH–28% NH_4OH (90:9:1); (2), Et_2O–MeOH–28% NH_4OH (40:2:1) and (3), 10% MeOH in Et_2O–28% NH_4OH–H_2O (500:5:1). Analytical HPLC was carried out with solvent (4), 15% MeOH in Et_2O–2.5% NH_4OH (50:1) using a LiChrosorb SI 100 (Merck, particle size 10 μm) column employing a monitoring flow system (220 nm) at a flow rate of 1 ml/min.

Extraction and isolation of **1**. The fresh flowers (422 g) of *E. koreensis* Nakai were collected in April 1980 at the medical garden of the University of Chiba. The alkaloid fraction (2.49 g), obtained from the 75% MeOH extract of the fresh flowers, was chromatographed on a Si gel (Merck, type 60, 100 g) column using solvent (2), 30 ml fractions being collected. **1** mainly appeared in fraction 19–30. **1**-rich fractions were re-chromatographed using a Si gel column with solvent (3). **1** was obtained as colourless needles (C_6H_6–n-C_6H_{14}), mp 112° (4.7 mg), $[\alpha]_D^{27}$ − 216.7° (EtOH; *c* 0.31). UV λ_{max}^{EtOH} nm (log ϵ): 235 (3.98), 310 (4.07). MS (70 eV) *m/z* (rel. int.): 218 $[M]^+$ (28), 203 (8), 160 (6), 146 (7), 72 ($CH_2{=}\overset{+}{N}\!\!<^{Et}_{Me}$, 100), 58 (8). ^{1}H NMR ($CDCl_3$): δ 0.91 (3 H, *t*, J = 7 Hz, Me), 1.81 (2 H, *m*, 8-H_2), 2.32 (2 H, *q*, J = 7 Hz, N–CH_2–), 2.92 (3 H, *m*, 7-H, 11-H_e and 13-H_e), 3.7–4.1 (2 H, *m*, 10-H_2), 5.97 (1 H, *dd*, J = 7 and 1.5 Hz, 5-H), 6.43 (1 H, *dd*, J = 9 and 1.5 Hz, 3-H), 7.27 (1 H, *dd*, J = 9 and 7 Hz, 4-H). The R_f values of **1** on Si gel TLC using solvents (1), (2) and (3) were 0.67, 0.38 and 0.62. respectively. The R_t (min) value of an analytical HPLC using solvent (4) was 5.7.

Synthesis of **1**. A mixture of (−)-cytisine (60 mg, 0.32 mmol), isolated from *E. koreensis* and EtBr (52.5 μl, 0.66 mmol) in C_6H_6, in the presence of Et_3N (0.5 ml), was heated at 80° for 1.5 hr. After evaporation of solvent *in vacuo* the residue was purified by Si gel CC developed with solvent (2). **1** was obtained as colourless needles, mp 112° (35 mg), $[\alpha]_D^{27}$ − 216.7 (EtOH; *c* 0.30). The synthetic product was found to be identical with the natural product by UV, MS, ^{1}H NMR and chromatographic comparisons.

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