13-epi-Hydroxysparteine and Desoxyangustifoline, New Alkaloids from Thermopsis mongolica

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13-*epi*-HYDROXYSPARTEINE AND DESOXYANGUSTIFOLINE, NEW ALKALOIDS FROM *THERMOPSIS MONGOLICA*

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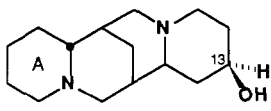
ABSTRACT.—Two new quinolizidine alkaloids, 13-*epi*-hydroxysparteine [**1**] and desoxyangustifoline [**2**], have been isolated from the hitherto uninvestigated species *Thermopsis mongolica*. Also, (+)-sparteine, 17-oxosparteine, 5,6-dehydrolupanine, α-isolupanine, (+)-hydroxysparteine, (−)-anagyrine, (−)-thermopsine, (−)-cytisine, and *N*-methylcytisine have been found.

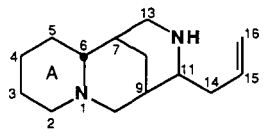
The genus *Thermopsis* (Fabaceae) includes some 18 species (1), among which 9 are found in Mongolia. The species investigated so far contain quinolizidine alkaloids, including some anagyrine-type toxins. Extracts of some species have been used in folk medicine as expectorants (1).

From the aerial parts of Mongolian *Thermopsis mongolica* Czefr., the following eleven compounds were isolated and identified on the basis of spectral data and some chemical transformations. Nine are the known alkaloids (+)-sparteine, 17-oxosparteine, 5,6-dehydrolupanine, α-isolupanine, (+) 13-hydroxysparteine, (−)-anagyrine, (−)-thermopsine, (−)-cytisine, and *N*-methylcytisine. The remaining two compounds, 13-*epi*-hydroxysparteine [**1**] and desoxyangustifoline [**2**], are new alkaloids.

The eims of **1**, *m/z* 250 $[M]^+$ and fragments *m/z* 233 $[M-17]^+$, 137, and 98, was identical with that of (+)-13-hydroxysparteine, but the two differed in their R_f values. The epimerization of the hydroxyl group in the latter (2) yields a compound whose ms and tlc are identical with those of **1**. To determine the position of H-11, (+)-13-hydroxysparteine was dehydrogenated with mercuric acetate and subsequently rehydrogenated to give two 13-hydroxy-α-isosparteine isomers: 13-α-hydroxy-α-isosparteine and 13-β-hydroxy-α-isosparteine (3). The ms of these compounds corresponded to 13-hydroxysparteine. They differed from **1** by their R_f values. Thus, the structure of the new alkaloid, 13-*epi*-hydroxysparteine, was identified. This compound has hitherto not been known as a natural compound.



1



2

The cims of **2** showed an ion with *m/z* 221 $[M+1]^+$, and the eims (70 eV) showed fragments *m/z* 220 $[M]^+$, 179 $[M-41]^+$, and 98. The fragment *m/z* 179 is formed upon C-11–C-14 bond cleavage, similar to the fragmentation of angustifoline and tinktorine (4,5). The fragment at *m/z* 98 arises from ring A following the fragmentation pattern of the sparteine-type alkaloids (6); hence, the structure of **2** is similar to that of angustifoline but without a carbonyl group.

The ^{1}H-nmr spectrum of **2** exhibited signals for three vinylic protons at δ 5.78 (m, 1H, H-15), 5.07 (br d, J = 17.5 Hz, 1H, H-16), and 5.02 (br d,

J = 9 Hz, 1H, H-16′); a peak at δ 3.75 (br, =NH) exchanged with D_2O. This spectrum also supported an angustifoline-like structure. An unambiguous proof of structure **2** was its cyclization into 13-*epi*-hydroxysparteine [**1**], carried out in a phosphate buffer (pH = 5.5) in the presence of HCHO (7). The latter was compared by ms and tlc with 13-*epi*-hydroxysparteine obtained after epimerization of 13-hydroxysparteine. Compound **1** and 4-α-hydroxysparteine, prepared from 4-α-hydroxylupanine after reduction with $LiAlH_4$ in THF, differed in their ms and R_f values. This excluded the possibility of an open A ring, i.e., a propylene chain at C-6 of a sparteine structure.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were measured on a Kofler-microscope (uncorrected). Ir spectra were run in KBr and Nujol on a SPECORD 75 IR Carl Zeiss. ^{1}H-nmr spectra were recorded using a Bruker WM-250 spectrometer at 250 MHz. Eims spectra were obtained with a JEOL JMS D 300 instrument by direct inlet probe at 70 eV; cims was performed with isobutane. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

PLANT MATERIAL.—The above-ground parts of *T. mongolica* were collected in July 1989 in Baishint, Somona Baiandalai, Aimak Omnogobi, Mongolia. The voucher specimen has been deposited at the Herbarium of the Institute of Botany, Mongolian Academy of Sciences, Ulan Bator, Mongolia, under number 297. The identification of the species was made by Dr. N.S.B. Ganbold.

EXTRACTION, ISOLATION, AND IDENTIFICATION.—The dried aerial parts (3 kg) were treated with 10% NH_3 and extracted with $CHCl_3$; the solvent was evaporated and the residue dissolved in 10% H_2SO_4. The acidic solution was basified, and extracted with $CHCl_3$ to afford 6 g (2%) of the total alkaloid mixture, which was fractionated by cc over neutral Al_2O_3 eluting with petroleum ether/Et_2O and Et_2O/MeOH gradients. Final purification was made by preparative tlc on Si gel plates (Merck) using the following systems: petroleum ether-diethylamine (2:0.2), Et_2O-MeOH (2:0.5) with a drop of NH_3, and $CHCl_3$-MeOH (2:0.5) with a drop of NH_3.

13-epi-*Hydroxysparteine* [**1**].—Compound **1** (2 mg): ms *m/z* (%) $[M]^+$ 250 (25), 233 (9), 209 (16), 152 (15), 137 (100), 113 (16), 98 (73), 84 (21); R_f 0.38 [petroleum ether-diethylamine (2:0.5)].

Epimerization of 13-hydroxysparteine.—13-Hydroxysparteine (30 mg) was dissolved in C_6H_6-pyridine (1:1); tosylchloride (80 mg) was added; and the mixture was left overnight at room temperature, basified with $NaHCO_3$, and extracted with $CHCl_3$. After evaporation of the solvent the residue was dissolved in glacial HOAc, 70 mg of NaOAc was added, and the material was heated at 120° for 4 h. Finally the mixture was made alkaline with Na_2CO_3 and extracted with $CHCl_3$ to furnish 1 mg of 13-*epi*-hydroxysparteine [**1**] after purification by preparative tlc. R_f values and ms spectra were identical with those of **1**.

Isomerization of 13-hydroxysparteine.—13-Hydroxysparteine (35 mg) was dissolved in 5% HOAc, $Hg(OAc)_2$ (150 mg) was added, and the mixture was heated at 60° for 12 h. The reaction mixture was filtered, acidified with 70% $HClO_4$, and evaporated to dryness to afford a residue that was dissolved in 10 ml MeOH. $NaBH_4$ (70 mg) was added while stirring, the inorganic sediment was filtered off, and the solution was evaporated to dryness. The residue was dissolved in H_2O, basified with 50% KOH, and extracted with $CHCl_3$. 13-α-Hydroxy-α-isosparteine and 13-β-hydroxy-α-isosparteine (1 mg) each were obtained after preparative tlc purification: R_f 0.22 and 0.19, respectively; R_f = 0.06 for 13-*epi*-hydroxysparteine [Si gel, dichloroethane-MeOH (2:0.5)].

Desoxyangustifoline [**2**].—Compound **2** (4 mg): cims *m/z* $[M + 1]^+$ 221, eims *m/z* (%) $[M]^+$ 220 (9), 180 (6), 179 (51), 137 (9), 136 (9), 123 (4), 122 (3), 110 (7), 98 (100), 96 (13), 84 (18), 69 (7), 55 (11); ^{1}H nmr δ 5.78 (m, 1H, H-15), 5.07 (br d, J = 17.5 Hz, 1H, H-16), 5.02 (br d, J = 9 Hz, 1H, H-16′), 3.75 (br, =NH exchanged with D_2O).

Cyclization of **2**.—Compound **2** (3 mg) was dissolved in 2 ml of an aqueous solution of NaH_2PO_4/Na_2HPO_4 (pH 5.5); 3 drops of HCHO were added, and the mixture was heated at 90° for 4 h. Finally, the mixture was basified with NH_3 and extracted with $CHCl_3$. Compound **1** (2 mg) was obtained after preparative tlc purification. R_f values and ms spectra were identical with those of **1** [Si gel, petroleum ether-diethylamine (2:0.5)].

IDENTIFICATION OF KNOWN ALKALOIDS.—(+)-Sparteine (100 mg): oil; $[\alpha]_D$ +19° (c = 0.02, MeOH). (−)-Anagyrine (50 mg): oil, $[\alpha]_D$ −124° (c = 0.01, MeOH). (−)-Thermopsine (35 mg), mp 198–201°, $[\alpha]_D$ −175° (c = 0.02, MeOH). (−)-Cytisine (150 mg): mp 155°, $[\alpha]_D$ −118° (c = 0.01, MeOH). These compounds identified by ir and ms (6).

17-Oxosparteine (1 mg), α-isolupanine (3 mg), and *N*-methylcytisine (2 mg) were identified by ms and tlc comparisons with authentic samples (6,8).

Catalytic reduction (2 mg) of 5,6-dehydrolupanine (4 mg), oil, ms (9) with 5% Pd/C in glacial HOAc afforded lupanine, compared by ms and tlc.

13-Hydroxysparteine (65 mg), mp 151–153°, $[\alpha]_D$ +25° (c = 0.01, MeOH), compared by ir, ms (6) and R_f values with 13-hydroxysparteine [Si gel, petroleum ether-diethylamine (2:0.5)] obtained after reduction of 13-hydroxylupanine with $LiAlH_4$ in THF.

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ERRATA

For the paper by Were *et al.*, entitled "Pyrrolizidine Alkaloids of *Senecio hadiensis*," *J. Nat. Prod.*, **54**, 491 (1991), the physical properties reported for hadienecine [**10**] were those of a salt. The free base has the following properties: mp 140–141° (Me_2CO), ν max (KBr) 3343 (br s), 2945–2885 (br s), 1350 (w), 1341 (w), 1319 (w), 1281 (m), 1260 (s), 1192 (s), 1125 (s), 1076 (w), 1061 (w), 1045 (s), 1020 (s), 974 (w), 882 (w), 835 (s), 746 (s), 669 (m), 602 (m), 534 (m), 488 (m), 475 (m) cm^{-1}; ^{1}H-nmr (pyridine-d_5 ref. δ 123.5) δ 82.4 (C-1), 36.9 (C-2), 55.5 (C-3), 54.7 (C-5), 37.8 (C-6), 70.9 (C-7), 80.5 (C-8), 66.4 (C-9) ppm; ^{1}H nmr (pyridine-d_5, ref. 7.19) δ 2.65 (1H, ddd, J = 9.6, 9.6, and 12 Hz, H_a-2), 1.99 (1H, ddd, J = 2.3, 6.8, and 12 Hz, H_b-2), 3.77 (1H, ddd, J = 9.8, 9.8, and 6.8 Hz, H_a-3), 2.95 (1H, ddd, J = 9.6, 9.6, and 2.3 Hz, H_b-3), δ 3.36 (1H, dd, J = 8.0 and 8.3 Hz, H_a-5), 3.12 (1H, ddd, J = 6.3, 8.3, and 11.4 Hz, H_b-5), 2.04 (1H, dd, J = ca. 6 and ca. 12 Hz, H_a-6), 1.90 (1H, dddd, J = 3.4, 8.2, 11.6, and 11.9 Hz, H_b-6), 4.59 (1H, dd, J = ca. 3 and ca. 3 Hz, H-7), 3.76 (1H, d, J = 3 Hz, H-8), 4.49 (1H, d, J = 10.9 Hz, H_a-9), 4.46 (1H, d, J = 10.9 Hz, H_b-9); eims *m/z* (%) $[M]^+$ 173.1050 (5) (calcd for $C_8H_{15}NO_3$, 173.1052), 156 (12), 155 (40), 129 (28), 112 (20), 99 (92), 98 (95), 82 (100), 56 (25), 55 (25), 51 (8), 41 (43); hydrochloride salt mp 160–161° ($EtOH/Et_2O$).

Also, in Table 2, the missing resonance for the acetyl carbonyl is δ 170.5 ppm.

For the paper by Shide *et al.*, *J. Nat. Prod.*, **54**, 573 (1991) the title should read "Studies on Peroxides of *Artemisia lancea*."