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Parsonine, a Pyrrolizidine Alkaloid from *Parsonsia laevigata*

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A pyrrolizidine alkaloid was isolated from the stems of *Parsonsia laevigata* ALSTON, a plant upon which the larvae of *Idea leuconoe* ERICHSON feed, and its structure was determined to be 1-(2'*S*,3'*S*)-2',3'-dihydroxy-2'-isopropylbutanoyloxymethyl-5,6-dihydropyrrolizin-7-one.

Keywords—*Parsonsia laevigata*; Apocynaceae; pyrrolizidine alkaloid; 2,3-dihydroxy-2-isopropylbutanoic acid; viridifloric acid; 1-hydroxymethyl-5,6-dihydropyrrolizin-7-one; danaidone homologue

Genus *Parsonsia* belongs to Apocynaceae. In Japan, one species, *P. laevigata* ALSTON, grows in the southern islands, and it is known that the larvae of *Idea leuconoe* ERICHSON feed upon this plant. Three triterpenes were isolated from the leaves of *P. laevigata* by Ogiwara *et al.*,¹⁾ and pyrrolizidine alkaloids have been isolated from other species of *Parsonsia*.²⁾ In the course of our studies on the constituents of Apocynaceae plants, we have examined the alkaloids of *P. laevigata*. This paper deals with the isolation and structure determination of parsonine, a pyrrolizidine alkaloid, from the stems.

When the MeOH percolate of the stems was extracted with CHCl₃, the CHCl₃-soluble fraction showed a positive reaction to the Dragendorff reagent. The CHCl₃ extractives were fractionated by means of chromatographies on a silica gel column and a Sephadex LH-20 column, and a crystalline compound (I) was isolated.

Compound I, mp 117–118 °C, showed the molecular formula C₁₅H₂₁NO₅ on elementary analysis and fast atom bombardment (FAB)-mass spectroscopy (MS) (*m/z* 318.135, M⁺ + Na). Upon usual acetylation, a monoacetate (I-1) was formed. On the basis of the presence of an esterified carbonyl carbon signal at δ 174.2 among 15 signals in the carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum, as well as the molecular formula, I was considered to be a pyrrolizidine alkaloid composed of necic acid and necine moieties. In the electron impact (EI)-mass spectrum (MS), a base peak was observed at *m/z* 134 (C₈H₈NO), suggesting the necic acid to be composed of a 7-carbon unit. The presence of an isopropyl group and a secondary carbinyl carbon bearing a methyl group was also suggested by decoupling experiments in the proton nuclear magnetic resonance (¹H-NMR) spectrum.

In a comparison of I-1 with I by ¹H-NMR and ¹³C-NMR, the secondary carbinyl proton signal and the corresponding carbon signal in I-1 were shifted downfield by +1.18 ppm and +3.0 ppm, respectively, while the tertiary carbinyl carbon showed an upfield shift of –1.7 ppm, indicating the presence of a glycol moiety composed of secondary and tertiary carbinols. The necic acid moiety was therefore considered to be a 2,3-dihydroxy-2-isopropylbutanoic acid such as viridifloric acid (2*S*, 3*S* or 2*R*, 3*R*) or trachelanthic acid (2*S*, 3*R* or 2*R*, 3*S*), of which the former was preferred based on a comparison of the ¹H- and ¹³C-NMR spectra with those of lycopsamine and intermedine.³⁾

In the nuclear Overhauser effect (NOE) difference NMR measurements initiated by irradiation of the hydroxymethylene protons at δ 5.31, the signals at δ 6.52, 6.99, 4.30, and

Chart 1

Fig. 1. NOE Difference NMR Spectra of I

(a), irradiated at δ 5.31; (b), irradiated at δ 6.52; (c), irradiated at δ 6.99; (d), irradiated at δ 4.30; (e), irradiated at δ 3.09.

3.09 showed responses, and these signals were assignable at H-9, H-2, H-3, H-5 and H-6, respectively (Fig. 1). The carbonyl group was allocated to C-7 based on the chemical shift at δ 189.1 (conjugated carbonyl) and the ultraviolet (UV) absorption at 288 nm. In the long range ^{13}C - ^1H two dimensional (2D)-NMR spectrum in the 3J mode, cross peaks between H-2/C-8 and C-9, H-3/C-8 and C-1, H-9/C-2, C-8 and C-1' were observed as well as those between H-6' and H-7'/C-2', 2'-OH/C-1', H-4'/C-2' in the necic acid moiety, and thus, all the ^1H and ^{13}C peaks were assignable.

In order to confirm the structure, I was subjected to alkaline hydrolysis with 1% KOH in EtOH to afford I-2 as a necic acid, and I-3⁴⁾ from the pyrrolizidine moiety. Compound I-2 was identified as (2*S*,3*S*)-2,3-dihydroxy-2-isopropylbutanoic acid ((-)-viridifloric acid) based on the physical constants, NMR and chemical ionization (CI)-MS. Compound I-3 showed the molecular formula $\text{C}_{10}\text{H}_{13}\text{NO}_2$, and showed the presence of an ethoxyl group in the ^1H -NMR spectrum. While a 2H singlet peak was assignable to primary carbinyl protons at C-9, other ^1H - and ^{13}C -NMR signals due to the pyrrolizidine framework showed almost the same chemical shifts as those of I. The structure of I-3 was assigned as 1-ethoxymethyl-5,6-dihydropyrrolizin-7-one. Thus, the structure of I was established and I was named parsonine.

It is a well known fact that male butterflies of *Danaus*, belonging to the same family as *Idea*, contain danaidone (1-methyl-5,6-dihydropyrrolizin-7-one) in their hair pencils as a courtship pheromone.⁵⁾ It seems noteworthy that I is the only pyrrolizidine alkaloid having a dienone system so far found among the homologous alkaloids from the higher plants.

Experimental

Melting points were taken on a hot stage apparatus and are uncorrected. ^1H -NMR and ^{13}C -NMR spectra were recorded on a JEOL GX-400 spectrometer. Samples for NMR measurements were dissolved in CDCl_3 unless otherwise mentioned. Chemical shifts are given in δ values referred to internal tetramethylsilane, and the following abbreviations are used: s=singlet, d=doublet, dd=doublet of doublets, q=quartet, dq=doublet of quartets, m=multiplet. EI-MS, FAB-MS, and CI-MS were recorded on a JEOL D-300-FD spectrometer. UV spectra were taken in MeOH on a Shimadzu 200S double-beam spectrometer. The following solvent systems were employed for silica gel and Sephadex LH-20 column chromatography, and thin layer chromatography (TLC); solv. 1, benzene–acetone (10:1–7:1); solv. 2, CHCl_3 ; solv. 3, CHCl_3 –MeOH– H_2O (7:1:2, bottom layer).

Extraction and Isolation of I—Air-dried and powdered stems of *Parsonsia laevigata* ALSTON (2.4 kg) collected at Kikai-Jima, Kagoshima Prefecture, in July, 1983, were percolated with MeOH. The MeOH percolate was concentrated *in vacuo* to 1 l, and diluted with H_2O (1 l), then the mixture was filtered. The filtrate was extracted with CHCl_3 . The CHCl_3 extractives (9.8 g) were chromatographed on a silica gel column with solv. 1 and solv. 3, and the fraction containing I was further chromatographed on a Sephadex LH-20 column with solv. 2 to afford I as prisms from EtOAc–hexane (287 mg).

Parsonine (I)—mp 117–118 °C, $[\alpha]_D^{26} + 5.3^\circ$ ($c=0.45$, MeOH). *Anal.* Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.23; H, 7.37; N, 4.58. UV $\lambda_{\text{max}}^{\text{MeOH}}$ (ϵ): 287 nm (18700). FAB-MS m/z : 318.135 (Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_5 + \text{Na}$: 318.135). EI-MS m/z : 296.149 (Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_5 + \text{H}$: 296.150), 267, 250, 134 (base peak, $\text{C}_8\text{H}_8\text{NO}$). ^1H -NMR δ : 6.52 (1H, d, $J=2$ Hz, H-2), 6.99 (1H, d, $J=2$ Hz, H-3), 4.30 (2H, t, $J=6$ Hz, H-5), 3.09 (2H, t, $J=6$ Hz, H-6), 5.31 (2H, s, H-9), 3.98 (1H, dq, $J=5, 6$ Hz, H-3'), 1.21 (3H, d, $J=6$ Hz, H-4'), 2.17 (1H, m, H-5'), 0.88, 0.91 (3H each, d, $J=6$ Hz, H-6', 7'), 2.55 (1H, d, $J=5$ Hz, 3'-OH), 3.91 (1H, s, 2'-OH). ^{13}C -NMR δ : 118.7 (C-1), 117.1 (C-2), 122.7 (C-3), 42.2 (C-5), 39.5 (C-6), 189.1 (C-7), 130.0 (C-8), 59.5 (C-9), 174.2 (C-1'), 83.3 (C-2'), 70.6 (C-3'), 17.3 (C-4'), 32.5 (C-5'), 16.1, 17.7 (C-6', 7'). Upon acetylation of I with pyridine and Ac_2O at room temperature, I-monoacetate (I-1) was obtained as prisms from hexane–AcOEt, mp 120–122 °C. EI-MS m/z : 338.161 (Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_6 + \text{H}$: 338.160), 320, 267, 250, 134, 106. ^1H -NMR δ : 5.16 (1H, q, $J=6$ Hz, H-3'), 2.02 (3H, s, $-\text{OCOCH}_3$). ^{13}C -NMR δ : 81.6 (C-2'), 73.6 (C-3'), 15.1 (C-4'), 170.2, 21.2 ($-\text{OCOCH}_3$).

Alkaline Hydrolysis of I—Compound I (80 mg) was refluxed with 2 ml of 1% KOH in EtOH for 1 h. The mixture was concentrated *in vacuo* and then diluted with H_2O . After partition with CHCl_3 , the CHCl_3 extract was passed through a silica gel column with solv. 1 to isolate I-3 (24 mg).⁴⁾ I-3: A solid. EI-MS m/z : 179.094 (Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: 179.095), 150, 135, 106. ^1H -NMR δ : 6.55 (1H, d, $J=2$ Hz, H-2), 6.96 (1H, d, $J=2$ Hz, H-3), 4.26 (2H, t, $J=6$ Hz, H-5), 3.05 (2H, t, $J=6$ Hz, H-6), 4.63 (2H, s, H-9), 3.57 (2H, q, $J=7$ Hz, $-\text{OCH}_2\text{CH}_3$), 1.22 (3H, t, $J=7$ Hz, $-\text{OCH}_2\text{CH}_3$). ^{13}C -NMR δ : 116.9 (C-1, 2), 122.5 (C-3), 42.0 (C-5), 39.5 (C-6), 189.1 (C-7), 130.0 (C-8), 65.7 (C-9), 63.6, 15.2 ($-\text{OCH}_2\text{CH}_3$). The H_2O layer, after CHCl_3 extraction, was acidified with dil. H_2SO_4 and extracted with BuOH to give I-2 (30 mg). I-2: mp 119–121 °C, $[\alpha]_D^{26} - 2.3^\circ$ ($c=2.2$, MeOH), ((–)-viridifloric acid: mp 121.5–124 °C, $[\alpha]_D - 0.8^\circ$,^{3b)} mp 122–123 °C, $[\alpha]_D - 1.4^\circ$,^{3c)} (+)-trachelanthic acid: mp 92–93 °C, $[\alpha]_D + 2.3^\circ$,^{3d)}). CI-MS (isobutane) m/z : 163.097 (Calcd for $\text{C}_7\text{H}_{14}\text{O}_4 + \text{H}$: 163.097). EI-MS m/z : 149, 118, 103 (base peak). ^1H -NMR (in pyridine- d_5) δ : 4.56 (1H, q, $J=6$ Hz, H-3'), 1.69 (3H, d, $J=6$ Hz, H-4'), 2.65 (1H, m, H-5'), 1.23, 1.33 (3H each, d, $J=6$ Hz, H-6', 7'). ^{13}C -NMR (in pyridine- d_5) δ : 177.7 (C-1'), 83.6 (C-2'), 70.8 (C-3'), 18.7 (C-4'), 33.1 (C-5'), 18.5, 17.0 (C-6', 7').

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