Parsonsianine, a Macrocyclic Pyrrolizidine Alkaloid from the Leaves of *Parsonsia laevigata* (Studies on *Parsonsia*. III)[1]

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Parsonsianine, a 14-membered macrocyclic pyrrolizidine alkaloid, composed of retronecine, (2*S*, 3*R*)-2,3-dihydroxy-2-ethylbutanoic acid and (2*R*, 3*S*)-2,3-dihydroxy-2-isopropylbutanedioic acid, was isolated from the leaves of *Parsonsia laevigata* and the structure was determined by means of nuclear magnetic resonance and X-ray analysis.

Keywords *Parsonsia*; Apocynaceae; parsonsianine; pyrrolizidine alkaloid; macrocyclic pyrrolizidine alkaloid; retronecine; X-ray analysis

Parsonsia is distributed in Asian and Australian districts. In Japan, *P. laevigata* Alston grows in the coastal areas of the Ryukyu Islands, and is known as a feeding plant for the larvae of *Idea leuconoe*, the largest *Danaus* butterfly in Japan. In the preceding paper of this series, we described parsonine,[1] a pyrrolizidine alkaloid containing 1-hydroxymethyl-5,6-dihydro-7-oxo-pyrrolizine (loroquin)[2] as the necine moiety, and also lignans[3] from the caules. This paper deals with the isolation and the structure determination of parsonsianine, a new pyrrolizidine alkaloid having a macrocyclic ring structure, composed of retronecine (**1a**) and two carboxylic acids, from the leaves of *P. laevigata*.

When the MeOH extract of the fresh leaves was partitioned with benzene and $CHCl_3$, the $CHCl_3$ fraction showed the presence of alkaloids on thin layer chromatography (TLC). By means of silica gel column chromatography, the major alkaloid was isolated as crystals, mp 235—245 °C, and it was named parsonsianine (**1**). Based on the electron impact (EI)-mass spectrum (MS), **1** afforded a molecular ion peak (M^+) at m/z 441.2006 ($C_{21}H_{31}NO_9$). The base peak at m/z 120 ($C_8H_{10}N$) suggested **1** to contain a pyrrolizine framework having one additional carbon, and the necine moiety was identified as retronecine, based on ^{1}H-nuclear magnetic resonance (^{1}H-NMR) and ^{1}H–^{1}H chemical shift correlation spectroscopy (COSY) spectra, and by comparison of the chemical shifts with those of a similar macrocyclic pyrrolizidine alkaloid.[4,5]

The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **1** demonstrated the presence of two secondary and two tertiary carbinyl carbons in addition to those of C-7 and C-9 which showed downfield shifts.[5] The signals of three esterified carbonyl carbons were observed, suggesting that six oxygens in **1** were due to ester functions. Since the degree of unsaturation was 7, the necic acid moiety was considered to form a macrocyclic ring, connecting at C-7 and C-9, and one ester function was located in the macrocyclic ring. The necic acid was therefore composed of a dicarboxylic acid and a monocarboxylic acid with four hydroxyl groups in all, and linked with each other through a carboxyl group in the former and a hydroxyl group in the latter to form an ester.

In the ^{1}H-NMR and ^{1}H–^{1}H COSY spectra, the presence of terminal ethyl and isopropyl groups, and a methyl group linked to a secondary carbinyl carbon was revealed, suggesting that these groups were attached to the macrocyclic ring. In the two-dimensional (2D) nuclear Overhauser effect (NOESY) and the long-range ^{13}C–^{1}H COSY (^{3}J-mode) spectra, the sequence from the isopropyl group to the secondary carbinyl carbon (C-14) through the tertiary carbinyl carbon (C-15) was suggested. The linkage between the secondary carbinyl carbon (C-12) having the methyl group and another tertiary carbinyl carbon (C-11) was also established by the cross peak (C-11/H-19) in the ^{3}J-mode COSY spectrum, and NOE was observed between the methyl protons (H-19) and one of the methylene protons

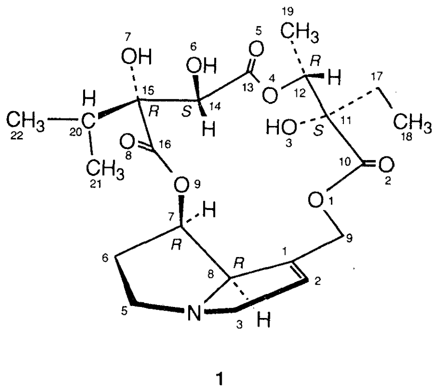

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Chart 1

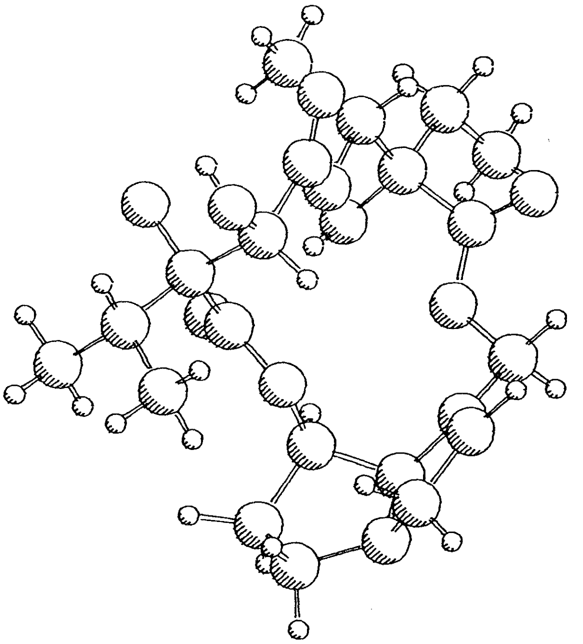

Fig. 1. Perspective View of the Crystal Structure of **1**

Table I. Atomic Parameters ($\times 10^4$) and Equivalent Thermal Parameters

Atom	x	y	z	B_{eq} (Å^2)
O1	780 (4)	5165 (2)	11340 (6)	4.14 (10)
O2	1908 (5)	6134 (2)	10476 (6)	4.81 (12)
O3	2671 (4)	4951 (2)	14640 (5)	3.61 (9)
O4	3945 (4)	4654 (2)	10973 (5)	2.93 (8)
O5	5786 (4)	4791 (2)	8907 (5)	3.56 (9)
O6	5156 (3)	3535 (2)	7075 (5)	3.34 (9)
O7	5313 (4)	3293 (2)	11747 (5)	3.78 (9)
O8	2696 (4)	3455 (2)	13256 (5)	3.53 (9)
O9	1369 (3)	3476 (2)	10137 (4)	2.40 (7)
N	−1797 (4)	3468 (2)	8121 (6)	2.90 (10)
C1	−644 (5)	4561 (3)	8564 (8)	3.46 (14)
C2	−647 (6)	4400 (4)	6583 (9)	4.44 (17)
C3	−1199 (6)	3679 (4)	6174 (7)	4.51 (18)
C5	−1435 (6)	2748 (3)	8849 (9)	3.78 (15)
C6	−773 (6)	2827 (3)	11098 (8)	3.61 (14)
C7	−30 (5)	3537 (3)	11144 (6)	2.47 (11)
C8	−1168 (5)	3965 (3)	9750 (7)	2.41 (11)
C9	−352 (7)	5255 (3)	9538 (11)	5.25 (19)
C10	1866 (6)	5642 (3)	11555 (8)	3.25 (13)
C11	3115 (6)	5476 (3)	13307 (7)	3.05 (13)
C12	4474 (6)	5269 (3)	12207 (8)	3.22 (13)
C13	4764 (5)	4465 (3)	9433 (7)	2.89 (12)
C14	4193 (5)	3773 (3)	8506 (7)	2.75 (12)
C15	4013 (5)	3235 (3)	10269 (7)	2.88 (12)
C16	2629 (5)	3409 (3)	11395 (7)	2.62 (11)
C17	3469 (8)	6139 (3)	14589 (9)	4.51 (17)
C18	2107 (10)	6427 (4)	15486 (10)	6.23 (24)
C19	5857 (7)	5063 (4)	13675 (9)	4.55 (17)
C20	3948 (6)	2479 (3)	9466 (9)	3.77 (15)
C21	2822 (7)	2342 (3)	7578 (9)	4.27 (16)
C22	3700 (9)	1968 (3)	11217 (11)	5.63 (21)

Table II. Bond Lengths (Å)

O1–C9	1.477 (8)	O1–C10	1.331 (7)
O2–C10	1.184 (7)	O3–C11	1.415 (6)
O4–C12	1.480 (6)	O4–C13	1.351 (6)
O5–C13	1.186 (6)	O6–C14	1.409 (6)
O7–C15	1.433 (5)	O8–C16	1.212 (6)
O9–C7	1.474 (5)	O9–C16	1.327 (5)
N–C3	1.484 (7)	N–C5	1.488 (7)
N–C8	1.495 (6)	C1–C2	1.328 (8)
C1–C8	1.487 (8)	C1–C9	1.490 (9)
C2–C3	1.487 (10)	C5–C6	1.531 (8)
C6–C7	1.519 (8)	C7–C8	1.531 (6)
C10–C11	1.544 (7)	C11–C12	1.525 (8)
C11–C17	1.541 (8)	C12–C19	1.533 (8)
C13–C14	1.529 (7)	C14–C15	1.568 (7)
C15–C16	1.538 (7)	C15–C20	1.547 (8)
C17–C18	1.508 (11)	C20–C21	1.529 (8)
C20–C22	1.540 (9)		

Table III. Bond Angles (°)

C9–O1–C10	115.7 (4)	C12–O4–C13	116.9 (4)
C7–O9–C16	115.7 (3)	C3–N–C5	116.3 (5)
C3–N–C8	106.9 (4)	C5–N–C8	108.4 (4)
C2–C1–C8	110.9 (5)	C2–C1–C9	127.4 (6)
C8–C1–C9	121.4 (5)	C1–C2–C3	111.1 (5)
N–C3–C2	104.2 (5)	N–C5–C6	105.3 (4)
C5–C6–C7	103.4 (4)	O9–C7–C6	107.9 (4)
O9–C7–C8	108.6 (3)	C6–C7–C8	102.2 (4)
N–C8–C1	103.9 (4)	N–C8–C7	104.7 (4)
C1–C8–C7	120.0 (4)	O1–C9–C1	108.0 (5)
O1–C10–O2	123.9 (5)	O1–C10–C11	113.4 (4)
O2–C10–C11	122.7 (5)	O3–C11–C10	112.0 (4)
O3–C11–C12	112.8 (4)	O3–C11–C17	108.3 (4)
C10–C11–C12	104.7 (4)	C10–C11–C17	108.8 (4)
C12–C11–C17	110.1 (5)	O4–C12–C11	103.9 (4)
O4–C12–C19	108.9 (4)	C11–C12–C19	113.7 (4)
O4–C13–O5	124.4 (5)	O4–C13–C14	110.1 (4)
O5–C13–C14	125.5 (5)	O6–C14–C13	110.2 (4)
O6–C14–C15	112.7 (4)	C13–C14–C15	110.0 (4)
O7–C15–C14	107.7 (4)	O7–C15–C16	107.2 (4)
O7–C15–C20	107.5 (4)	C14–C15–C16	110.7 (4)
C14–C15–C20	112.2 (4)	C16–C15–C20	111.3 (4)
O8–C16–O9	124.3 (4)	O8–C16–C15	122.4 (4)
O9–C16–C15	113.3 (4)	C11–C17–C18	112.8 (6)
C15–C20–C21	115.7 (5)	C15–C20–C22	110.7 (5)
C21–C20–C22	110.7 (5)		

(H-17a) of the ethyl group. Consequently, the two acids were considered to be 2,3-dihydroxy-2-ethylbutanoic acid (**1b**) and 2,3-dihydroxy-2-isopropylbutanedioic acid (**1c**).

Based on the fragment peak in the EI-MS at *m/z* 312, which was assignable to a fragment formed by splitting of the allyl C–O linkage at C-9 and the C–O linkage at C-12, the linkage of **1c** to the C-7 hydroxyl seemed to be likely. In order to confirm the stereochemistry of the necic acid moiety and also the linking mode of **1b** and **1c**, X-ray analysis of **1** was carried out and the structure was elucidated as presented in Chart 1.

Pyrrolizidine alkaloids having a 14-membered macrocyclic ring are characteristic of *Parsonsia* spp.[4] An alkaloid containing 2,3-dihydroxy-2-isopropylbutanedioic acid, spiraline, was obtained from *P. spiralis* Wall,[4] although the stereochemistry of the secondary carbinyl carbon has not been determined. The finding of 2,3-dihydroxy-2-ethylbutanoic acid in **1** is the first example of its occurrence in a necic acid.

Experimental

The melting point was taken on a hot stage apparatus and is uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GX-400 spectrometer in $CDCl_3+CD_3OD$. Chemical shifts are given in δ values referred to internal tetramethylsilane (TMS), and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublets, td = triplet of doublets. The EI-MS was recorded on a JEOL D-300-FD spectrometer. Optical rotation was measured on a JASCO DIP 360 polarimeter. Spots on TLC plates were detected by spraying the plates with 5% *p*-dimethylaminobenzaldehyde in diluted H_2SO_4 after chloranil in benzene (saturated).

Extraction and Isolation of 1 Fresh leaves of *Parsonsia laevigata* Alston (5.4 kg) collected at Iriomote-jima in July, 1987, were homogenized and then percolated with MeOH. The MeOH percolate was concentrated *in vacuo* and filtered. The filtrate was extracted with benzene (ext. 0.7 g) and then $CHCl_3$ (ext. 2.8 g). The $CHCl_3$ extract was subjected to a silica gel column chromatography with $CHCl_3$–MeOH–H_2O (7 : 1 : 1) to isolate **1** (55 mg), along with two minor alkaloids.

Parsonsianine (1) Prisms from MeOH, mp 235—245 °C (dec.), $[\alpha]_D^{24}$ +37.9° (c=0.7, MeOH). EI-MS *m/z*: 441.2006 (Calcd for $C_{21}H_{31}NO_9$ 441.1998). EI-MS *m/z*: 441, 384, 312 ($C_{15}H_{22}NO_6$), 236, 136, 120 (base peak, $C_8H_{10}N$). ^{1}H-NMR δ: 0.88, 1.12 (3H each, d, J=7 Hz, H-21, 22), 0.92 (3H, t, J=7 Hz, H-18), 1.29 (3H, d, J=6 Hz, H-19), 1.60, 1.81 (1H each, m, H-17a, b), 2.20—2.30 (2H, m, H-6), 2.28 (1H, m, H-20), 2.82 (1H, br q, J=9 Hz, H-5a), 3.39 (1H, br t, J=9 Hz, H-5b), 3.54 (1H, td, J=3, 14 Hz, H-3a), 3.97 (1H, dd, J=14, 1 Hz, H-3b), 4.40 (1H, s, H-14), 4.43 (1H, br s, H-8), 4.44 (1H, dd, J=14, 2 Hz, H-9a), 4.95 (1H, q, J=6 Hz, H-12), 5.32 (1H, dd, J=14, 1 Hz, H-9b), 5.53 (1H, br s, H-7), 5.85 (1H, br s, H-2). 2D-NOESY cross peaks: H-2/H-9b, H-14/H-21, H-17a/H-19. ^{13}C-NMR δ: 7.5 (C-18), 12.4 (C-19), 16.2, 17.9 (C-21, 22), 27.6 (C-17), 34.1 (C-20), 34.8 (C-6), 52.2 (C-5), 61.8 (C-9), 62.5 (C-3), 73.6 (C-14), 76.2 (C-8), 78.2 (C-7), 78.5 (C-12), 80.7 (C-11), 81.6 (C-15), 127.3 (C-2), 132.2 (C-1), 170.2 (C-16), 172.9 (C-10), 174.1 (C-13). Long range ^{13}C–^{1}H COSY (^{3}J) cross peaks: C-2/H-8 and H-9a, C-10/H-9b, C-11/H-19, C-15/H-21 and H-22, C-16/H-14.

Crystal Data for 1 $C_{21}H_{31}NO_9$, monoclinic, space group $P2_1$, $a=8.921$ (1), $b=19.254$ (4), $c=6.520$ (1) Å, $\beta=95.94$ (2)°, $V=1113.9$ (4) $Å^3$, $D_c=1.316$ g/cm^3, $F(000)=472$, μ for Cu $K_\alpha=0.824$ mm^{-1}. Intensities were collected on an Enraf-Nonius CAD4F-11 diffractometer using the ω–2θ scan mode with graphite-monochromated Cu K_α radiation up to $\theta=60°$; 1788 unique reflections with $I>2.38$ (I) were used for refinement. The structure was solved by the direct method using MULTAN 11/82. All atomic parameters, with anisotropic temperature factors for non-hydrogen atoms and isotropic ones for hydrogen atoms, were refined by a block-diagonal matrix least-squares method. The final R value was 0.039.

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