THE STRUCTURES OF SPIRAMINES E, F AND G; THE NEW DITERPENE ALKALOIDS FROM *SPIRAEA JAPONICA* VAR. *ACUMINATA* FRANCH[1]

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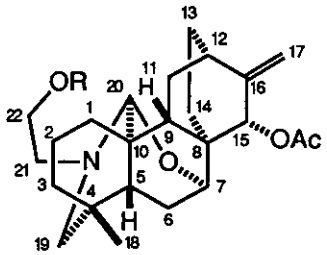
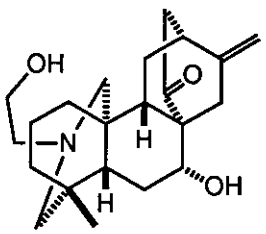
Abstracts - Structures of spiramines E (**1**), F (**2**) and G (**3**) were elucidated by chemical and spectroscopic means.

In the previous paper,[2] we reported the isolation and structures of four new atisine type alkaloids, spiramines A~D, from the roots of *Spiraea japonica* var. *acuminata* which has been used as a folk medicine in China.[3] In the course of the investigation on the constituents of the plant, we isolated three new atisine type alkaloids; spiramines E (**1**), F (**2**), and G (**3**). Here we report a full account on the structures of these alkaloids.

The formula for spiramine E (**1**), amorphous, $[\alpha]_D$ - 97 ° ($CHCl_3$), was determined as $C_{26}H_{37}NO_5$ on the basis of high resolution mass spectrum and elemental analysis. An atisine type skeleton for spiramine E was deduced by comparing its ^{13}C-nmr shift values with literature data of spiramines A ~ D.[1,4] Other spectroscopic analysis showed the presence of an exo-methylene group [δ 5.28, 5.03 (each 1H, t, J = 1.5 Hz, 2H-17); ν 1650 cm^{-1}], a secondary acetoxy group [δ 1.68 (3H, s), 5.46 (1H, br s); ν 1710, 1240 cm^{-1}], and a primary acetoxy group [δ 1.75 (3H, s), 4.16 (2H, t, J = 6 Hz, 2H-22)]. The presence of an ether linkage between C-7 and C-20 in spiramine E (**1**) was presumed by the signals of ^1H-nmr [δ 4.53 (1H, br s, H-20), 3.60 (1H, d, J = 5 Hz, H-7β)], which were the same as those of spiramine A (**4**).[2] On irradiation at δ 5.46, both of the signals at δ 5.28 and 5.03 were changed to doublets with J = 1.5 Hz, demonstrating the location of the secondary acetoxy group on C-15, and the α-configuration of the 15-acetoxy group was presumed from the ^{13}C-nmr shifts values of C-7 and C-15 in spiramine E (**1**) which were very close to those of spiramine A (**4**). Spectral data (Table 1) for spiramine F (**2**), amorphous, $[\alpha]_D$ -101° ($CHCl_3$), $C_{24}H_{35}NO_4$, indicated that this compound was the deacetyl spiramine E. In fact, acetylation of spiramine F (**2**) afforded spiramine E (**1**). In order to comfirm the deduced structures for spiramines E and F, spiramine F (**2**) was treated with sodium borohydride to give triol (**6**), which had already been obtained from spiramine A (**4**) in the same way.[2] The existence of an ether linkage between C-7 and C-20 in spiramines E and F was chemically proved by the following oxidative cyclization using triol (**6**). Oxidation of triol (**6**) with $K_3Fe(CN)_6$ [5] gave deacetylspiramine F (**5**) which was identical with the product obtained by the hydrolysis of spiramine F (**2**). It was interesting that an ether linkage between C-7 and C-20 was formed from triol (**6**) while an oxazolidine ring was formed from dihydroajaconine (**7**).[5] The difference of the two compounds is just the configuration of 15-hydroxy group.



1 : R = Ac
2 : R = H



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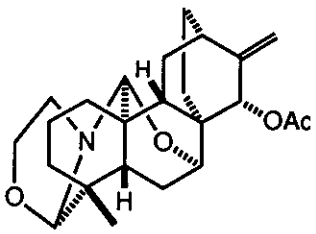

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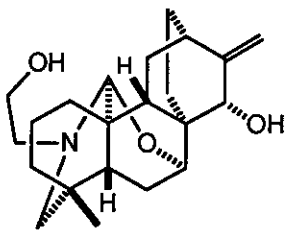

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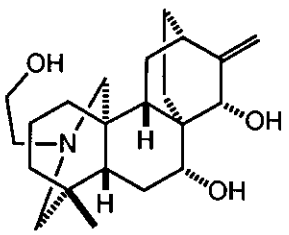

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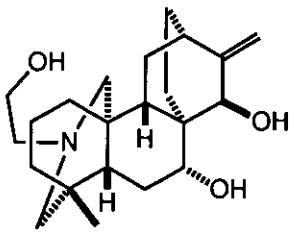

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Spectroscopic analysis of spiramine G (**3**), needles, mp 160-162 °C, $[\alpha]_D$ -16° ($CHCl_3$), $C_{22}H_{31}NO_3$, indicated the presence of an exo-methylene group [δ 4.92, 4.74 (each 1H, m), ν 1650 cm^{-1}], a primary hydroxy group [δ 3.60 (2H, m, 2H-22); ^{13}C-nmr, δ 60.3 (t)], a secondary hydroxy group [δ 3.20 (1H, ddd, J = 6, 8, 11 Hz), ^{13}C-nmr, δ 76.2 (t)], and a carbonyl group [ν 1700 cm^{-1}; ^{13}C-nmr, δ 219.8 (s)]. The secondary hydroxy group was assigned to be of 7-α configuration by its chemical shift and the coupling constant value of ^{1}H-nmr which were similar to those of triol (**6**).[2] The location of the carbonyl group was deduced as follows: the NOE experiment between the signals of δ 4.92 (17-H) and δ 2.70 indicated the latter should be H-12 (Figure 1).

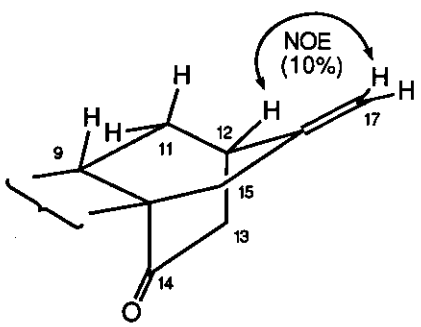

Fig. 1 NOE of spiramine G(**3**)

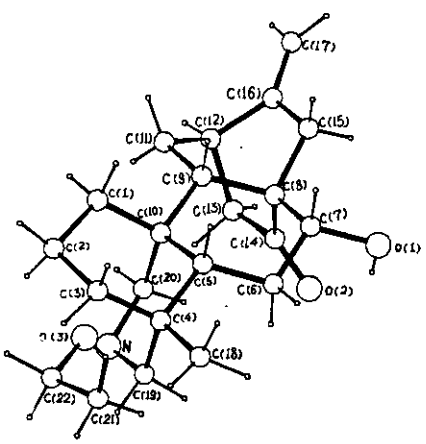

Fig. 2 Crystal structure of **3**, showing the atom-labeling scheme

Irradiated at δ 2.70, the signal at δ 2.31 (1H, dt, J = 3, 20 Hz, 13β-H) changed to a doublet of doublet (J = 3, 20 Hz, long range coupling with H-11) and the signal at δ 2.19 (1H, dd, J = 3, 20 Hz, 13α-H) changed to a doublet (J = 20 Hz). This shows that there is no proton at C-14. A close inspection of ^{13}C-nmr spectra of spiramine G (**3**) and triol (**6**) revealed that the quaternary carbon signal at δ 51.8 in spiramine G (**3**) was shifted to the down field about 10 ppm, which indicated that the carbonyl group was located at C-14. Three-dimensional single-crystal X-ray analysis provided the total structure for spiramine G (**3**) (Figure 2). Spiramine G (**3**) is the first C-20 diterpene alkaloid containing the carbonyl group at C-14.

Table I. ^{13}C Chemical Shifts[a] for Spiramines and Their Derivatives

carbon	E (**1**)	F (**2**)	(**5**)	G (**3**)
1 (t)	41.2	41.2	41.3	39.5
2 (t)	21.2	21.2	21.1	22.8
3 (t)	30.1	30.1	30.1	41.1
4 (s)	34.6	34.8	34.6	33.5
5 (d)	44.8	44.5	44.6	48.4
6 (t)	25.2	25.1	25.2	28.1
7	74.6 (d)	74.5 (d)	74.6 (d)	76.2 (d)
8 (s)	41.0	40.8	40.3	51.8
9 (d)	44.6	44.9	44.6	49.4
10 (s)	34.6	33.6	34.6	38.2
11 (t)	23.8	23.8	23.7	27.3
12 (t)	36.9	36.9	37.1	38.6
13 (t)	25.2	25.1	25.1	45.6
14	20.7 (t)	21.2 (t)	21.1 (t)	219.8 (s)
15	69.7 (d)	70.0 (d)	70.2 (d)	38.2 (t)
16 (s)	150.3	150.2	155.6	146.3
17 (t)	114.1	114.2	112.4	107.7
18 (q)	26.1	26.0	26.5	26.3
19 (t)	53.0	51.9	51.6	59.6
20	87.3 (d)	87.4 (d)	87.6 (d)	52.4 (t)
21 (t)	53.4	57.7	57.5	58.0
22 (t)	62.1	57.9	58.0	60.3
O<u>C</u>OCH$_3$	171.1	171.1		
O<u>C</u>OCH$_3$	170.9			
OCO<u>C</u>H$_3$	21.0	21.0		
OCO<u>C</u>H$_3$	21.2			

[a] Determined in CDCl$_3$.

EXPERIMENTAL

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. ^{1}H-Nmr spectra and double irradiation spectra were recorded on a JOEL-GX 400 spectrometer. ^{13}C-Nmr were recorded on a VARIAN VXR-200 spectrometer and their assignments are given in Table 1. Optical rotations were measured with a JASCO DIP-181 polarimeter. Ir spectra were measured with a JASCO IR-180 spectrophotometer. Ms spectra were mesured with a JEOL JMSDX 300 mass spectrometer.

Isolation of spiramines:

Fraction B[2] (30 g) was chromatographed on alumina column and eluted with CH_2Cl_2, Et_2O, EtOAc, and MeOH respectively to give five fractions. Fraction 4 (eluted with EtOAc, 2.4 g) was subjected to SiO_2 flash column and eluted with hexane - Et_2NH (20 : 1) to give I (520 mg) and II (589 mg) fraction. Fraction I (520 mg) was subjected to the SiO_2 flash column (eluted with hexane-Et_2NH, 30 : 1) and SiO_2 preparative tlc (developed with hexane-Et_2O, 1 : 1) gave spiramine E (**1**) (40 mg) and spiramine F (**2**) (70 mg). Fraction II was subjected to SiO_2 flash column (eluted with Et_2O-Et_2NH-hexane, 10 : 1 : 10) to give spiramine F (**2**) (210 mg) and two other components. Fraction 5 (eluted with MeOH, 2.3 g) was subjected to SiO_2 flash column and eluted with hexane-Et_2NH-Et_2O (10 : 3 : 10) to give spiramine G (**3**) (45 mg) and a mixture of spiramine C and D.[2]

Spiramine E (**1**): amorphous, $[\alpha]_D^{20}$ -97° (c 1.9, $CHCl_3$); ms m/z 443. 269 (50), 370 (100); Anal. Calcd for $C_{26}H_{37}NO_5$: C, 70.43; H, 8.85; N, 3.16. Found. C, 70.63; H, 8.54; N, 3.12. Ir ($CHCl_3$) ν 1710, 1650, 1240 cm^{-1}; ^{1}H-nmr (C_6D_6) δ 5.46 (1H, brs, H-15β), 5.28, 5.03 (each 1H, t, *J* = 1.5 Hz, 2H-17), 4.51 (1H, br s, H-20), 4.16 (2H, t, *J* = 6 Hz, 2H-22), 3.60 (1H, d, *J* = 5 Hz, H-7β), 2.98, 2.64 (each 1H, dt, *J* = 6, 13.5 Hz, 2H-21), 2.60, 2.16 (each 1H, d, *J* = 11 Hz, 2H-19), 2.55 (1H, m, H-12), 1.80 (1H, m, H-6α), 1.75 (3H, s, $OCOCH_3$), 1.73 (1H, m, H-6β), 1.68 (3H, s, $OCOCH_3$), 0.63 (3H, s, 18-CH_3).

Spiramine F (**2**): amorphous, $[\alpha]_D^{18}$ -101° (c 2.5, $CHCl_3$), ms m/z 401.257 Calcd 401.257 for $C_{24}H_{35}NO_4$. Ir ($CHCl_3$) ν 3450, 1705, 1650 cm^{-1}; ^{1}H-nmr (C_6D_6) δ 5.38 (1H, br s, H-15β), 5.23, 5.02 (each 1H, br s, 2H-17), 4.49 (1H, br s, H-20), 3.75 (2H, m, 2H-22), 3.53 (1H, d, *J* = 5 Hz, H-7β), 3.42, 2.86 (each 1H, m, 2H-21), 2.81, 2.73 (each 1H, m, 2H-19), 2.35 (1H, m, H-12), 1.78 (1H, m, H-6α), 1.68 (1H, m, H-6β), 1.71 (3H, s, $OCOCH_3$), 0.61 (3H, s, 18-CH_3), 0.60 (1H, m, H-5β).

Spiramine G (**3**): needles, mp 160 - 162 °C (Et_2O), $[\alpha]_D^{20}$ -16 °C (c 0.95, $CHCl_3$), ms m/z 359.249 Calcd 359.249 for $C_{22}H_{31}O_3N$. Ir ($CHCl_3$) ν 3500, 1705, 1650 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 4.29, 4.74 (each 1H, m, 2H-17), 3.60 (2H, m, 2H-22), 3.48 (1H, d, *J* = 8 Hz, OH), 3.20 (1H, ddd, *J* = 6, 8, 11 Hz, H-7β), 3.07 (1H, dt, *J* = 2.5, 11 Hz, H-15β), 2.70 (1H, m, H-12), 2.40 (2H, m, 2H-21), 2.52, 2.45, 2.20, 2.12 (each 1H, 2 x AB type, 2H-20 and 2H-19), 2.31 (1H, dt, *J* = 3, 20 Hz, H-13β), 2.25 (1H, dt, *J* = 2, 17 Hz, H-15α), 2.19 (1H, dd, *J* = 3, 20 Hz, H-13α), 1.95 (1H, m, H-11), 1.67 (1H, m, H-11), 0.80 (3H, s, 18-CH_3).

Acetylation of spiramine F (**2**)

Spiramine F (80 mg, 0.2 mmol) was dissolved in 2 ml (21 mmol) of Ac_2O and 2 ml (25 mmol) of pyridine. The solution was allowed to stand overnight at room temperature. After addition of water (10 ml), the reaction mixture was made basic (pH 8 - 9) with 5% aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4, and evaporated. The residue was subjected to SiO_2 flash column (eluted with ether-hexane-Et_2NH, 10 : 3 : 10) to give 75 mg (85%) of spiramine E (**1**) which was identified by ^{1}H-nmr, ir, and tlc.

Reduction of spiramine F (**2**)

To a solution of spiramine F (**2**) (70 mg, 0.17 mmol) in MeOH (7 ml) was added 120 mg (3.2 mmol) of $NaBH_4$ at 0 °C, and the mixture was stirred for 8 h at room temperature. Removal of the solvent was followed by partition between H_2O and $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to give 58 mg (92%) of triol (**6**) which was identified by ^{1}H-nmr, ir, and tlc.[2]

Oxidative cyclization of triol (**6**)using $K_3Fe(CN)_6$ [5]

To a solution of 200 mg (0.55 mmol) of triol (**6**) in 10 ml of MeOH was added a solution of 700 mg (2.1 mmol) of $K_3Fe(CN)_6$ in 10 ml of H_2O and 8 ml of 8 % aqueous KOH solution and stirred for 30 min at room

temperature. The reaction mixture was extracted with CH_2Cl_2 (3x40 ml), washed with H_2O, dried over Na_2SO_4, and the solvent was removed to give 170 mg of residue. The residue was subjected to preparative tlc (developed with Et_2O-hexane-Et_2NH, 4 : 2 : 1) to give 110 mg (77%) of deacetylspiramine F (**5**): amorphous, $[\alpha]_D^{20}$ -110° (c 1.5, $CHCl_3$), ms m/z 259.248 Calcd 259.246 for $C_{22}H_{33}NO_3$. Ir ($CHCl_3$) ν 3650, 3400, 1650 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 5.01, 4.99 (each 1H, br s, 2H-17), 4.55 (1H, br s, H-20), 3.91 (1H, br s, H-15), 3.75 (1H, d, J = 5 Hz, H-7), 3.55 (2H, m, 2H-22), 3.30 (2H, m, 2H-21), 0.73 (3H, s, 18-CH_3).

Hydrolysis of spiramine F (**2**):

Spiramine F (30 mg, 0.075 mmol) was dissolved in 5 ml (4.5 mmol) of 5% KOH-MeOH and left standing overnight at room temperature. Removal of the solvent was followed by the partition between H_2O and CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give 20 mg(100%) of deacetylspiramine F (**5**) which was identified with the authentic sample by ^{1}H-nmr, ir and tlc.

X-Ray Analysis of Spiramine G

Crystal data : $C_{22}H_{33}NO_3$, MW=359.5, orthorhombic, $P2_12_12_1$, a =11.408(2), b =12.906(2), c = 13.031(3) Å, V=1918.6 $Å^3$, Z=4, DX=1.244 g cm^{-3}. The colorless crystal with dimensions 0.3 x 0.3 x 0.3 mm was used for the data collection on a Rigaku AFC-5RU diffractometer with a 2θ-ω scan mode using graphite-monochromated Cu $K\alpha$ radiation (λ=1.54178 Å). The structure was solved by direct methods using MULTAN78[6], and refined to R=0.052 and Rw=0.079 for 1823 observed reflections with Fo larger than 3σ(Fo).

Table II. Atomic Coordinates and Isotropically Equivalent Thermal Paramaters with Their Standard Deviation in Parentheses for Non-hydrogen Atoms of Spiramine G (**3**)

Atom	x	y	z	Beq($Å^2$)
C (1)	0.3986(2)	0.9730(2)	0.6254(2)	3.56(12)
C (2)	0.3339(2)	0.8706(2)	0.6174(2)	3.87(12)
C (3)	0.4140(3)	0.7774(2)	0.6412(2)	4.26(14)
C (4)	0.5350(3)	0.7818(2)	0.5907(2)	3.66(10)
C (5)	0.5938(2)	0.8853(2)	0.6186(2)	3.27(10)
C (6)	0.7242(2)	0.8931(2)	0.5887(2)	3.78(12)
C (7)	0.7768(2)	0.9957(2)	0.6172(2)	3.71(12)
C (8)	0.7113(2)	1.0880(2)	0.5702(2)	3.05(10)
C (9)	0.5780(2)	1.0807(2)	0.5961(2)	3.01(8)
C (10)	0.5206(2)	0.9738(2)	0.5728(2)	2.83(8)
C (11)	0.5114(2)	1.1749(2)	0.5519(2)	3.48(10)
C (12)	0.5962(3)	1.2472(2)	0.4939(3)	3.87(10)
C (13)	0.6898(3)	1.2829(2)	0.5682(2)	4.01(12)
C (14)	0.7549(2)	1.1927(2)	0.6145(2)	3.72(12)
C (15)	0.7309(2)	1.1014(2)	0.4553(2)	3.54(12)
C (16)	0.6563(3)	1.1859(2)	0.4088(2)	4.24(14)
C (17)	0.7107(3)	1.3818(2)	0.5905(3)	5.22(16)
C (18)	0.6055(4)	0.6879(2)	0.6307(3)	5.17(14)
C (19)	0.5263(3)	0.7715(2)	0.4737(2)	3.69(10)
C (20)	0.5105(2)	0.9577(2)	0.4559(2)	2.87(8)
C (21)	0.4641(3)	0.8469(2)	0.3134(2)	3.65(12)
C (22)	0.3867(3)	0.9240(2)	0.2576(2)	3.97(12)
N (1)	0.4626(2)	0.8573(2)	0.4257(2)	3.14(8)
O (1)	0.8992(2)	1.0008(2)	0.5920(2)	4.46(8)
O (2)	0.8056(2)	1.0540(2)	0.4067(2)	4.62(10)
O (3)	0.4364(2)	1.0252(2)	0.2455(2)	4.34(8)

H atoms were located in a ΔF map. Non-H atoms were anisotropically and H atoms were isotropically refined by H atoms were located in a ΔF map. Non-H atoms were anisotropically and H atoms were isotropically refined by the block-diagonal least-squares. All computations were undertaken on a FACOM M780 in the Data Processing Center of Kyoto University, using KPPXRAY program system.[7] The atomic scattering factors used were obtaind from International Tables for X-ray Crystallography IV(1974).

Table III. Bond Lengths (Å) and Bond Angles (degree) with Their Standard Deviations in Parentheses for Spiramine G (3)

Bond	Length	Bond	Length	Bond	Length
C (1) - C (2)	1.517(4)	C (1) - C (10)	1.551(3)	C (2) - C (3)	1.542(4)
C (3) - C (4)	1.530(5)	C (4) - C (5)	1.538(4)	C (4) - C (18)	1.545(4)
C (4) - C (19)	1.534(4)	C (5) - C (6)	1.541(3)	C (5) - C (10)	1.536(4)
C (6) - C (7)	1.500(4)	C (7) - C (8)	1.534(4)	C (7) - O (1)	1.436(3)
C (8) - C (9)	1.561(3)	C (8) - C (14)	1.551(4)	C (8) - C (15)	1.524(4)
C (9) - C (10)	1.557(4)	C (9) - C (11)	1.545(4)	C (10) - C (20)	1.542(4)
C (11) - C (12)	1.542(4)	C (12) - C (13)	1.513(5)	C (12) - C (16)	1.525(4)
C (13) - C (14)	1.507(4)	C (13) - C (17)	1.331(4)	C (15) - C (16)	1.510(4)
C (15) - O (2)	1.225(3)	C (19) - N (1)	1.465(4)	C (20) - N (1)	1.460(4)
C (21) - C (22)	1.516(4)	C (21) - N (1)	1.470(4)	C (22) - O (3)	1.433(4)

Bond	Angle	Bond	Angle	Bond	Angle
C (2) - C (1) - C (10)	114.3(2)	C (1) - C (2) - C (3)	112.2(2)	C (2) - C (3) - C (4)	114.8(2)
C (3) - C (4) - C (5)	108.9(2)	C (3) - C (4) - C (18)	107.2(2)	C (3) - C (4) - C (19)	111.5(3)
C (5) - C (4) - C (18)	112.0(3)	C (5) - C (4) - C (19)	109.8(2)	C (18)-C (4) - C (19)	107.5(2)
C (4) - C (5) - C (6)	114.7(2)	C (4) - C (5) - C (10)	108.5(2)	C (6) - C (5) - C (10)	112.2(2)
C (6) - C (7) - O (1)	111.9(2)	C (8) - C (7) - O (1)	110.3(2)	C (7) - C (8) - C (9)	110.0(2)
C (7) - C (8) - C (14)	111.8(2)	C (7) - C (8) - C (15)	114.1(2)	C (9) - C (8) - C (14)	106.5(2)
C (9) - C (8) - C (15)	111.2(2)	C (14)-C (8) - C (15)	102.7(2)	C (8) - C (9) - C (10)	114.9(2)
C (8) - C (9) - C (11)	110.6(2)	C (10)-C (9) - C (11)	114.7(2)	C (1) - C (10)-C (5)	108.1(2)
C (1) - C (10)-C (9)	107.3(2)	C (1) - C (10)-C (20)	111.6(2)	C (5) - C (10)-C (9)	110.8(2)
C (5) - C (10)-C (20)	108.9(2)	C (9) - C (10)-C (20)	110.1(2)	C (9) - C (11)-C(12)	110.5(2)
C (11)-C (12)-C (13)	108.3(3)	C (11)-C (12)-C (16)	108.9(2)	C (13)-C (12)-C (16)	107.8(3)
C (12)-C (13)-C (14)	111.6(2)	C (12)-C (13)-C (17)	123.9(3)	C (14)-C (13)-C (17)	124.4(3)
C (8) - C (14)-C (13)	111.5(2)	C (8) - C (15)-C (16)	113.2(2)	C (8) - C (15)-O (2)	123.6(2)
C (16)-C (15)-O (2)	123.0(3)	C (12)-C (16)-C (15)	109.6(2)	C (4) - C (19)-N (1)	113.0(2)
C (10)-C (20)-N (1)	114.4(2)	C (22)-C (21)-N (1)	114.3(2)	C (21)-C (22)-O (3)	114.9(3)
C (19)-N (1) - C (20)	111.7(2)	C (19)-N (1) - C (21)	110.5(2)	C (20)-N (1) - C (21)	110.2(2)

REFERENCES

1. Preliminary communication: X. Hao, J. Zhou, S. Chen, K.Fuji, and M.Node, *Acta Botanica Yunnanica*, **1991**, *13*, 452.
2. a) X. Hao, M. Node, T. Taga, Y. Miwa, J. Zhou, S. Chen, and K. Fuji, *Chem.Pharm. Bull.*, **1987**, *35*, 1670.
   b) M. Node, X. Hao, J. Zhou, S. Chen, T. Taga, Y. Miwa, and K. Fuji, *Heterocycles*, **1990**, *30*, 635.
3. "Zhong Yao Da Ci Dian", ed. by Jiangshu new medical College, Shanghai people's publishing House, 1971, p. 117.
4. For known atisine type alkaloids, see: N.W. Mody and S.W. Pelletier, *Tetrahedron*, **1978**, *34*, 2421.

5. S. W. Pelletier, N. V. Mody, H. D. Desai, J. F. Moore, J.Nowacki, and B. S. Joshi, *J. Org. Chem.*, **1983**, *48*, 1787.

6 P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, *Multan 78 system*, Universities of York, Great Britain, and Louvain, Bergium, 1987.

7 T. Taga, T. Higashi, and H. Iizuka, *KPPXRAX system*, Kyoto University, Japan, 1985.

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