The Structure of Yuzurimine-C

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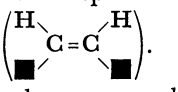
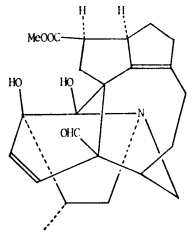
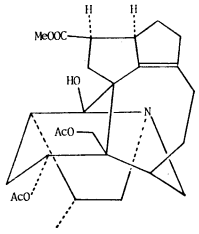
The structure of yuzurimine-C, one of the yuzurimine-type alkaloids, was unambiguously determined on the basis of chemical evidences coupled with its spectral data. Particularly, application of the ^{13}C NMR spectra plays an important role in the structural elucidation.

As described in the previous paper,[1] yuzurimine-C was isolated, as one of the minor components, from the plant *Daphniphyllum macropodum* Miquel (Japanese name "Yuzuriha"). In the present paper, we wish to describe the structure of yuzurimine-C on the basis of chemical evidences coupled with comparison of its ^{13}C NMR spectrum with those of yuzurimine and its derivatives.

Yuzurimine-C (**1**, mp 186—187 °C; $C_{23}H_{29}O_5N$) is one of the minor alkaloids, that has a secondary methyl group [δ 1.04 ppm (2H, d, J=6 Hz)] and a carbomethoxyl group [ν_{max} 1736 cm^{-1} and δ 3.58 ppm (2H, s)] analogous to those of yuzurimine (**2**).[2] The IR spectrum of **1** indicates the presence of two different carbonyl groups (ν_{max} 1736 and 1723 cm^{-1}), one of which can be due to an aldehyde group [ν_{max} 1723 cm^{-1} and δ 9.99 ppm (1H, s)], instead of a tertiary acetoxymethyl group in yuzurimine (**2**). Furthermore, two sharp doublets at δ 5.61 (1H, d, J=10 Hz) and 6.20 ppm (1H, d, J=10 Hz) in the NMR spectrum must be due to two olefinic protons  . From a biogenetic point of view, the above spectral data suggests that yuzurimine-C, which co-occurs with yuzurimine (**2**) in the plant, may have a tentative structure (**1**). In fact, this tentative structure (**1**) can be confirmed, as follows.



(**1**)



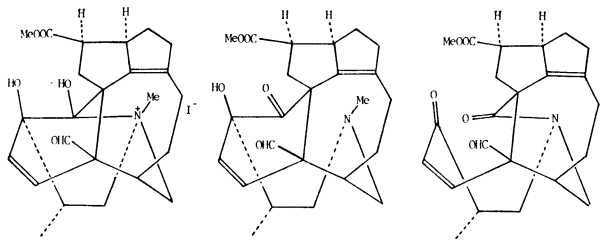
(**2**)

When heated with methyl iodide in acetone under reflux for 6 hr,* yuzurimine-C was converted into the corresponding methiodide (**3**, mp 209—210 °C; $C_{24}H_{32}O_5NI$) in almost quantitative yield. In the mass spectra of the methiodides corresponding to daphniphylline[3] and daphnilactone-B,[4] usually, they have the fragment peaks resulting from the loss of MeI from each molecular ion. In the case of **3**, however, the strong peak can be observed at m/e 413 resulting from the loss of HI, indicating that the original alkaloid (**1**) must have a HO–C–N< grouping. In fact, yuzurimine-C methiodide (**3**) was readily converted into a keto-amine (**4**, mp 199—200 °C; $C_{24}H_{31}O_5N$) only by contact with aqueous alkaline solution, as seen in the case of yuzurimine methiodide.[2] In the IR spectrum of **4**, extraordinary low C=O frequency (ν_{max} 1640 cm^{-1}) assigned to the newly formed keto-group must result from proximity of the nitrogen atom with a lone pair of electrons.

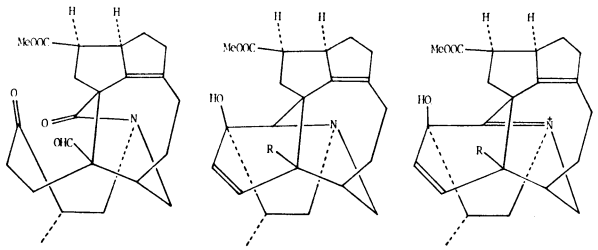
The presence of a vicinal glycol [HO–C–C(OH)–N<] can be confirmed on the basis of the following experiments. When treated with $NaIO_4$ in aqueous MeOH–THF (room temp., 16 hr), yuzurimine-C was converted into a keto-lactam [**5**, mp 179—181 °C; $C_{23}H_{27}O_5N$ (m/e 397 (M^+))], in good yield. In the IR spectrum of **5** [ν_{max} 1737, 1705 br. and 1660 cm^{-1}; no OH band], the absorption band at 1660 cm^{-1} is attributable to the newly formed lactam carbonyl. Furthermore, it is clear from the molecular model of **5** that the other newly formed keto-group can not conjugate well with the disubstituted double bond [ν_{max} 1705 br. cm^{-1} and λ_{max} 215 nm (ε, 6590)] which is readily reduced on catalytic hydrogenation leading to the formation of a dihydro-compound [**6**, mp 168—169 °C; $C_{23}H_{29}O_5N$ (m/e 399 (M^+))]. Further information of the disubstituted double bond can be obtained from the NMR spectrum of the keto-lactam (**5**), which has two doublets assigned to the  grouping [δ 5.61 (1H, d, J=14 Hz) and 6.01 ppm (1H, d, J=14 Hz)]. Clearly, this disubstituted double bond in **5** (J=14 Hz) must be included in a medium ring, and not in the original six-membered ring (J=10 Hz in **1**, **3**, and **4**).[5]

As mentioned earlier, yuzurimine-C (**1**) seems to have an aldehyde group (–C–CHO) instead of the acetoxymethyl group in yuzurimine (**2**). This is also supported by the following chemical evidences: when treated with limited amounts of $LiAlH_4$ in THF (room temp., 5 hr), yuzurimine-C (**1**) was converted into the corresponding hydroxy-compound [**7**, mp 168—170 °C; $C_{23}H_{31}O_4N$ (m/e 385 (M^+) ν_{max} 3470, 3420, and 1715 cm^{-1}]. The NMR spectrum of **7** indicates two doublets at δ 3.75 and 4.06 ppm (each one proton, J=12 Hz) due to the newly formed hydroxymethyl group instead of the aldehyde group in yuzurimine-C (**1**). These doublets in **7** are further shifted to δ 4.48 ppm (2H, br. s) on acetylation with Ac_2O–pyridine (room temp., overnight) leading to the formation of the corresponding mono-acetate [**8**, mp 171—173 °C; $C_{25}H_{33}O_5N$ (m/e 427 (M^+)); ν_{max} 3440,

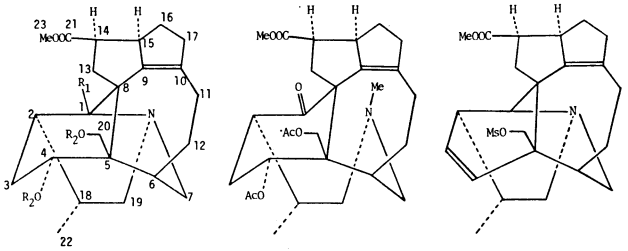
* The starting material was recovered under milder conditions (room temp., overnight).



(3) (4) (5)



(6) (7) R=CH_2OH (8) R=CH_2OAc (9) R=CHO or CH_2OH



(10) R_1=OH R_2=H (11) R_1=H R_2=Ac (12) (13)

1745, and 1735 cm^{-1}]. In the course of reduction, an anti-Bredt's rule imine (**9**) as an unstable intermediate must be produced,[6] as found in the case of yuzurimine (**2**).[2] Finally, the structure (**1**) for yuzurimine-C is supported by comparison of its ^{13}C NMR spectrum with those of yuzurimine (**2**) and its derivatives (**10**—**13**).[2]

Generally, partially relaxed Fourier transform (PRFT) ^{13}C NMR technique[7] is known to be very useful in the structural study on complex natural products, because methyl, methylene, methine and quaternary carbon signals are easily differentiated.

Thus, proton noise decoupled (PND) and partially relaxed FT ^{13}C NMR spectra of yuzurimine-C were measured, as shown in Fig. 1, in which the PRFT spectrum was obtained by using the pulse sequence (180 °–τ–90 °–T).

In the PRFT spectrum at τ=0.6 s, methylene and disubstituted olefin peaks appear as positive signals, while methine and secondary methyl peaks are nulled. Quaternary carbon and tetrasubstituted olefin peaks remain negative. The results of ^{13}C NMR experiments of yuzurimine-C (**1**), yuzurimine (**2**), and several derivatives (**10**—**13**) are summarized in Table 1.

In the Table 1, the signals of the quaternary carbon C-1 connected to the hydroxyl group and the nitrogen atom are seen in the spectra of **1** (δ 91.6 ppm), **2** (δ 96.8 ppm), and **10** (δ 97.3 ppm), whereas the spectra of **11**, **12**, and **13** lack the signal attributed to the above quaternary carbon. Nine methylene and six methine signals are observed in the spectra of **4** and **10**, whereas seven methylene, four methine, and one carbonyl (δ 207.0 ppm) signals are found in the case of yuzurimine-C (**1**). Furthermore, four olefinic signals are seen in the

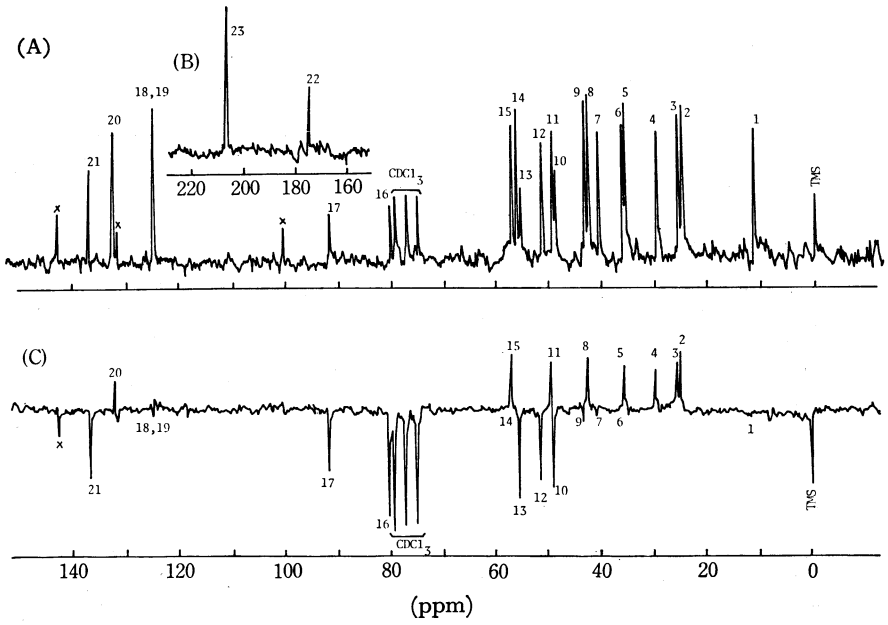


Fig. 1. (A, B) Proton noise decoupled (PND) natural abundance FT ^{13}C NMR spectra of yuzurimine-C (1) in $CDCl_3$ (100 mg/1.7 ml) at 15.04 MHz; (A): recycle time=1 s, number of scans=3600, sweep width=2500 Hz; (B): low field part, recycle time=1 s, number of scans=5400, sweep width=5000 Hz. (C): PRFT ^{13}C NMR spectrum of yuzurimine-C (1); interval time τ=0.6 s, recycle time T=10 s, number of scans=5000, sweep width=2500 Hz.

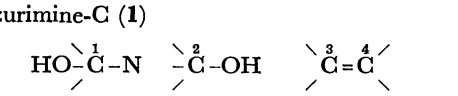
TABLE 1. ^{13}C CHEMICAL SHIFTS OF YUZURIMINE-C (**1**), YUZURIMINE (**2**), AND ITS DERIVATIVES (**10**—**13**)

Functional group	Compound						Assignment
	1	**2**	**10**	**11**	**12**	**13**	
-Me	11.4	14.7	14.9	15.5	14.2	18.4	C-22
	51.2	51.0	51.5	51.1	51.1	51.3	C-23
					a)47.6*	b)37.2*	a) N-Me b) $-SO_2-Me$
$-CH_2-$	24.8	25.2	25.6	25.4	24.9	25.1	C-3, 11, 12, 13,
	25.6	27.1	27.4	26.9	26.8	25.6	16, 17
	29.6	27.3	29.7	27.2	28.7	27.7	
	35.5	28.7	30.7	28.2	29.8	39.9	
	42.4	37.4	36.7	39.1	40.4	43.3	
		43.1	43.3	42.8	42.4		
	49.1	58.6	59.2	58.1	67.1	51.7	C-7, 19, 20
	56.8	64.4	64.8	64.8	67.1	63.7	
		67.0	66.7	67.1	68.4	71.6	
C=O	a)207.0				b)189.3		a) C-20 b) C-1
-CH-	36.0	34.3	32.3*	35.1*	39.0**	32.9	C-6
	40.6	34.3	34.4*	37.6*	39.7**	35.1**	C-18
		42.2*	42.5**	38.3*	41.9**	39.2**	C-2
	43.0	43.1*	43.6**	42.8	43.2**	42.9	C-15
	55.9	57.5	57.9	54.0	56.7	54.8	C-14
		72.9	71.7	73.4	71.5		C-4
				67.0		66.8	C-1
-C-	48.7	45.0	45.9	41.1	44.3*	39.9*	C-5
	55.2	52.1	51.7	46.4	60.0	42.9*	C-8
	91.6	96.8	97.3				C-1
	80.1						C-2
-COOMe	175.6	175.3	177.6	175.0	175.5	175.2	C-21
>C=C<	125.0	136.7	136.7	133.4	132.9	138.6	C-9, 10
	136.9	144.0	144.0	144.5	145.0	140.2	
	125.0					127.8	C-3, 4
	132.5					131.5	
AcO-		21.0		21.1	21.1		Me-COO-
		21.0		21.1	21.1		
		170.1		170.1	170.1		Me-COO-
		170.8		170.8	170.6		

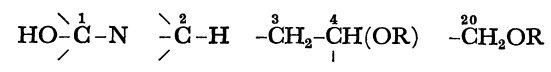
1) Chemical shifts are given in ppm relative to TMS. 2) Assignment of chemical shifts for close-lying peaks marked with asterisk may be reversed. 3) The ketonic ^{13}C NMR signal in **12** is observed at extraordinary high field (δ 189.3 ppm), indicating the presence of a strong interaction between the keto-group and the nitrogen atom, as suggested by the IR spectrum (ν_{max} 1633 cm^{-1})[2].

spectra of **1** and **13**. These facts are in good agreement with the partial structures, as shown below. The

Yuzurimine-C (**1**)



2 and **10**



presence of the hydroxyl group on C-2 in yuzurimine-C (**1**) rationalized the upfield shift of C-19 and C-22 signals and the down field shift of C-18 signal. The PRFT spectrum of **1** which lacks the signal at δ 125.0 ppm clearly indicates that the signal of one disubstituted olefinic carbon overlaps with that of one of the two tetra-substituted olefinic carbon atoms. The other signals show the one to one correspondence to each carbon atom.

The present study indicates that partially relaxed Fourier transform ^{13}C NMR technique must be very useful in the structural study on the daphniphyllum alkaloids of undetermined complex structure.[8,9]

From a structural point of view,[8] yuzurimine-C (**1**) belongs to be yuzurimine group of alkaloids as suggested in the previous paper,[1] and is the most highly oxygenated product among them.

Experimental

All mps were uncorrected. The IR and UV spectra were recorded on a JASCO Model IR-S and on a Perkin-Elmer 202 spectrophotometer, respectively. The ^1H and ^{13}C NMR spectra were obtained on a Nihondenshi JNM-PS 100 (100 MHz) and on a Nihondenshi JNM-PFT 60 (15.04 MHz), respectively. Chemical shifts for all NMR spectra are given in ppm from TMS as an internal standard using $CDCl_3$ as

solvent, unless otherwise stated. Only prominent peaks are cited. (d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet). The mass spectra were recorded on a Hitachi RMU-6C mass spectrometer with an ionization energy of 70 eV. Column chromatography was carried out on basic alumina (Nakarai Chemical Co. Ltd., *ca.* 200 mesh). Thin layer chromatography (tlc) was performed on Kieselgel 60 PF_{254} using *n*-hexane–ether–diethylamine (10: 10: 1), unless otherwise stated.

Physical Properties of Yuzurimine-C (1). Mp 186—187 °C (from *n*-hexane–acetone); $[\alpha]_D^{25} = +28°$ ($c=1.33$ in $CHCl_3$); ν_{max} (KBr) 3450 br. s, 1736, 1722, and 1660 cm^{-1}; λ(EtOH) 210 nm (ε, 8410), end absorption; δ 1.04 (3H, d, $J=6.0$ Hz), 3.58 (3H, s), 5.61 (1H, d, $J=10.0$ Hz), 6.20 (1H, d, $J=10.0$ Hz), and 9.99 ppm (1H, s); *m/e* 399 (M^+), 381, 353, 352, and 324 (Found: C, 69.01; H, 7.22; N, 3.57%. Calcd for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; N, 3.51%).

Formation of Yuzurimine-C methiodide (3). A solution of yuzurimine-C (20 mg) and MeI (2 ml) in acetone (5 ml) was heated under reflux for 6 hr, and then concentrated under reduced press to leave pale yellow crystals in quantitative yield, which were recrystallized from acetone–Et_2O to give needles of the corresponding methiodide (**3**), mp (decomp.) 209—210 °C; ν_{max} (Nujol) 3280, 1745, and 1720 cm^{-1}; δ($CDCl_3$–CD_3OD) 1.17 (3H, d, $J=6.0$ Hz), 3.20 (3H, s), 3.65 (3H, s), 3.56—4.60 (4-5H, complex), 5.88 (1H, d, $J=10$ Hz), 6.45 (1H, d, $J=10$ Hz) and 9.99 ppm (1H, s); *m/e* 413 (M^+—HI), 398, 384, 370, 356, and 327 (Found: C, 53.15; H, 6.04; N, 2.09%. Calcd for $C_{24}H_{32}O_5NI$: C, 53.24; H, 5.96; N, 2.59%).

Formation of the Keto-amine (4). A solution of **3** (30 mg) in $CHCl_3$ (20 ml) was shaken well with water (15 ml) containing Na_2CO_3 (30 mg). The chloroform solution was washed with sat. NaCl aq. solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded white crystals of **4** in almost quantitative yield, mp 199—200 °C (from acetone–*n*-hexane); ν_{max} (Nujol) 3400, 1725, 1715 sh., and 1640 cm^{-1}; δ 0.92 (3H, d, $J=7.0$ Hz), 2.17 (3H, s), 3.63 (3H, s), 4.08 (2H, br.), 5.83 (1H, d, $J=10$ Hz), 6.34 (1H, d, $J=10$ Hz), and 10.1 ppm (1H, s); *m/e* 413 (M^+), 398, 384, 370, 356, and 327 (Found: C, 69.27; H, 7.52; N, 3.20%. Calcd for $C_{24}H_{31}O_5N$: C, 69.70; H, 7.51; N, 3.39%).

Oxidation of Yuzurimine-C (1) with $NaIO_4$. To a solution of yuzurimine-C (100 mg) in MeOH–THF (4: 1; 8 ml) was added a solution of $NaIO_4$ (150 mg) in 50% aq. MeOH (3 ml) with stirring. The resulting solution was further stirred at room temperature for 16 hr, and then concentrated under reduced press. The remaining reaction mixture was dissolved in water and extracted with $CHCl_3$. The extract was washed with sat. NaCl aq. solution and then dried over anhydrous Na_2SO_4. Removal of the solvent gave an amorphous solid (*ca.* 107 mg), which was chromatographed on alumina (0.5 g) and eluted with Et_2O to give colorless needles of the keto-lactam (**5**), mp 179—181 °C (from Et_2O); ν_{max} (Nujol) 1737, 1705 br., and 1660 cm^{-1} (no OH absorption band); λ_{max} (MeOH) 215 nm (ε, 6590); δ 1.01 (3H, d, $J=7.0$ Hz), 3.06—3.50 (3H, complex), 3.64 (3H, s), 3,85 (1H, q, $J=13$, 8 Hz), 4.40 (1H, q, $J=12$, 8 Hz), 5.61 (1H, d, $J=14$ Hz), 6.01 (1H, d, $J=14$ Hz), and 9.95 ppm (1H, s); *m/e* 397 (M^+), 383, 369, 355, 350, 337, 311, and 310 (Found: C, 69.83; H, 7.02; N, 3.56%. Calcd for $C_{23}H_{27}O_5N$: C, 69.50; H, 6.85; N, 3.52%).

Catalytic hydrogenation of the Keto-lactam (5). Catalytic hydrogenation of **5** (15 mg) in EtOAc (2 ml) was carried out over 10% Pd–C (5 mg) at room temp. overnight, and then the catalysts were filtered. The filtrates were evaporated under reduced press. to give an almost colorless oil, which was chromatographed on alumina. Elution with Et_2O afforded white crystals (13 mg) which were recrystallized from Et_2O–*n*-hexane to give colorless plates of **6**, mp 168—169 °C; ν_{max} (Nujol) 1735, 1710, 1695, and 1623 cm^{-1}; δ 1.02 (3H, d, $J=7.0$ Hz), 3.05—3.50 (3H, complex), 3.64 (3H, s), 3.66 (1H, q, $J=13$, 8 Hz), 4.56 (1H, q, $J=12.5$, 8 Hz), and 10.01 ppm (1H, s); *m/e* 399 (M^+), 371, 339, 313, 312, 311, and 301 (Found: C, 69.12; H, 7.32; N, 3.35%. Calcd for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; N, 3.51%).

$LiAlH_4$ Reduction of Yuzurimine-C (1). To a solution of yuzurimine-C (69 mg) in THF (3 ml) was added $LiAlH_4$ (14 mg) with stirring, and then the heterogeneous solution was continuously stirred at room temperature for 5 hr. After excess $LiAlH_4$ was decomposed with EtOH, the reaction mixture was poured into sat. potassium sodium tartarate aq. solution and extracted with $CHCl_3$. The extract was washed with sat. NaCl aq. solution and then dried over anhydrous Na_2SO_4. Removal of the solvent gave a white solid (56 mg) which was recrystallized from Et_2O–acetone to afford white crystals of **7**, mp 168—170 °C; ν_{max}(Nujol) 3470, 3420, and 1715 cm^{-1}; δ 1.16 (3H, d, $J=7.0$ Hz), 3.62 (3H, s), 3.75 (1H, d, $J=12$ Hz), 4.06 (1H, d, $J=12$ Hz), 5.69 (1H, d, $J=10$ Hz) and 5.83 ppm (1H, d, $J=10$ Hz); *m/e* 385 (M^+ for $C_{23}H_{31}O_4N$), 368, 354, and 326.

Acetylation of 7. A solution of **7** (15 mg) in dry pyridine (1 ml) and acetic anhydride (1 ml) was allowed to stand at room temperature overnight, and then concentrated under reduced press. to give a pale brown oil, which was chromatographed on alumina and eluted with EtOAc to give colorless needles of **8** (12 mg), mp 171—173 °C (from *n*-hexane–acetone); ν_{max} (Nujol) 3440, 1745, and 1735 cm^{-1}; δ 1.12 (3H, d, $J=7.0$ Hz), 2.09 (3H, s), 3.66 (3H, s), 4.48 (2H, br. s) and 5.72 ppm (2H, br. s); *m/e* 427 (M^+), 387, 368, 345, and 300 (Found: *m/e* 427.2336. Calcd for $C_{25}H_{33}O_5N$: *m/e* 427.2359).

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