Alkaloids from the Fruits of *Daphniphyllum macropodum*

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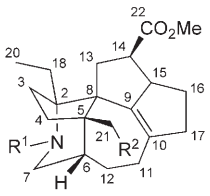
Three new alkaloids, *N*-hydroxypaxdaphnine B (**1**), 21-*O*-acetylpaxdaphnine B (**2**), and methyl 17-hydroxyhomodaphniphyllate (**3**), were isolated from the fresh fruits of *Daphniphyllum macropodum*, together with six known alkaloids. Their structures were established on the basis of extensive spectroscopic and mass-spectrometric analyses in combination with chemical transformations.

Introduction. – The *Daphniphyllum* alkaloids are a structurally diversified group of natural products with complex heterocyclic ring systems elaborated by plants of the genus *Daphniphyllum* (Daphniphyllaceae) [1]. Many of these compounds are still attracting great interest as challenging targets for total synthesis [2] as well as for biosynthetic studies [3]. In recent years, a number of novel *Daphniphyllum* alkaloids have been discovered from different species of this genus [4–10].

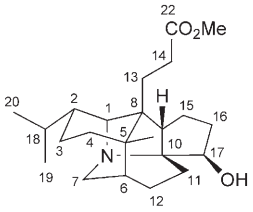
Daphniphyllum macropodum MIQ. is an evergreen shrub or small tree widely distributed in southern China [11]. The decoction of its leaves and fruits shows detoxifying, fever-clearing, and detumescent effects, and has been used in the treatment of inflammatory diseases in traditional Chinese medicine (TCM) [12]. Chemical investigations on this species growing in Japan were mainly performed from 1966 to 1975, which led to the isolation of a series of alkaloids belonging to the daphniphylline and yuzurimine types [1a]. Recently, eight additional new alkaloids have been reported from this plant collected in China [6a][8][9].

In our search for structurally unique and biogenetically interesting natural products [5], we herein report three new alkaloids, *N*-hydroxypaxdaphnine B (**1**), 21-*O*-acetylpaxdaphnine B (**2**), and methyl 17-hydroxyhomodaphniphyllate (**3**), from the fresh fruits of *D. macropodum*, together with six known alkaloids. Herein, we describe the isolation and structure elucidation of these new alkaloids.

Results and Discussion. – Compound **1** was isolated as a colorless amorphous solid. The molecular formula was determined as $C_{21}H_{31}NO_4$ on the basis of HR-EI-MS (*m*/*z* 361.2264 (M^+; calc. 361.2253)) and NMR data (*Table 1*). The IR absorption band at 1734 cm^{-1} indicated the presence of a C=O functionality. The ^{13}C-NMR data of **1** (*Table 1*) displayed signals for 21 C-atoms, including two Me groups, ten CH_2 groups (the one at δ(C) 67.4 being oxygenated, and the one at δ(C) 57.9 being linked to an N-atom), three CH groups, and six quaternary C-atoms (the one at δ(C) 79.4 being linked



	R^1	R^2
1	OH	OH
2	H	OAc
4	H	OH



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Arbitrary atom numbering

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 400/100 MHz, resp., in CD_3OD; δ in ppm, J in Hz. Arbitrary atom numbering.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
C(2)	–	79.4	–	70.7
CH_2(3)	1.86–1.92 (*m*)	24.6	1.69–1.74 (*m*)	30.5
CH_2(4)	1.50–1.58 (*m*)	36.2	1.70–1.76 (*m*)	35.6
C(5)	–	52.0	–	50.9
H–C(6)	2.13 (*t*-like, $J=8$)	41.5	1.88–1.85 (*m*)	41.2
H_α–C(7)	3.12 (*d*, $J=11.0$)	57.9	2.90 (*d*, $J=14.7$)	44.9
H_β–C(7)	2.99 (*dd*, $J=11.0$, 7.1)		3.16 (*ddd*, $J=14.7$, 6.6, 1.0)	
C(8)	–	60.4	–	60.3
C(9)	–	145.2	–	145.6
C(10)	–	137.4	–	138.8
H_α–C(11)	2.50–2.52 (*m*)	27.2	2.43–2.48 (*m*)	27.3
H_β–C(11)	1.88–1.96 (*m*)		2.10–2.18 (*m*)	
H_α–C(12)	1.47–1.54 (*m*)	28.4	1.52–1.56 (*m*)	28.0
H_β–C(12)	2.02–2.05 (*m*)		1.92–1.99 (*m*)	
H_α–C(13)	2.03 (*dd*, $J=15.3$, 9.4)	38.6	2.07 (*dd*, $J=15.2$, 9.6)	37.7
H_β–C(13)	2.52 (*dd*, $J=15.3$, 3.5)		2.50 (*dd*, $J=15.2$, 3.5)	
H–C(14)	2.93 (*td*, $J=10.6$, 3.3)	44.8	2.93 (*td*, $J=9.3$, 3.2)	44.9
H–C(15)	3.40–3.50 (*m*)	58.9	3.36–3.46 (*m*)	58.7
H_α–C(16)	1.76–1.83 (*m*)	30.9	1.82–1.87 (*m*)	30.7
H_β–C(16)	1.15–1.22 (*m*)		1.20–1.32 (*m*)	
H_α–C(17)	2.52–2.60 (*m*)	44.2	2.67–2.77 (*m*)	44.5
H_β–C(17)	2.29 (*dd*, $J=15.2$, 8.4)		2.36 (*dd*, $J=15.0$, 8.7)	
CH_2(18)	1.66 (*q*, $J=7.3$)	28.4	1.08–1.18 (*m*),	29.6
			1.61–1.69 (*m*)	
Me(20)	1.01 (*t*, $J=7.3$)	12.8	0.90 (*t*, $J=7.3$)	9.8
H_a–C(21)	3.94 (*d*, $J=11.5$)	67.4	4.48 (*d*, $J=11.8$)	70.4
H_b–C(21)	3.82 (*d*, $J=11.5$)		4.43 (*d*, $J=11.8$)	
C(22)	–	178.2	–	177.6
MeO	3.61 (*s*)	52.1	3.64 (*s*)	52.2
AcO	–	–	2.01 (*s*)	21.4
				173.5

to an N-atom, one C=O moiety at δ(C) 178.2, and one tetrasubstituted C=C bond at δ(C) 145.2 and 137.4).

The ^{1}H- and ^{13}C-NMR data of **1** were very similar to those of paxdaphnine B (**4**) [5a], a known compound also isolated in the present study. Compared with **4**, there was one more O-atom in the molecular formula of **1**. The structure of **1** was further determined by HMBC and ROESY experiments (*Fig. 1*), which revealed that the additional O-atom could only be attached to the N-atom. The signals of C(2) at δ(C) 79.4 and of C(7) at δ(C) 57.9 were both obviously downfield-shifted relative to those in **4** (δ(C) 70.8 and 45.2, resp.) [5a], which are diagnostic of the N–OH moiety.

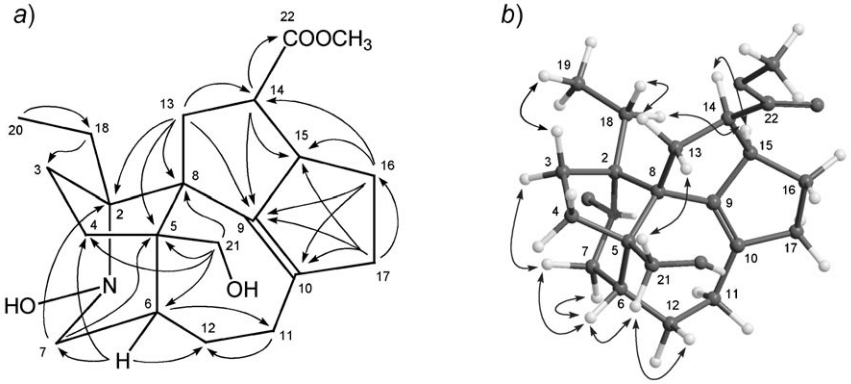

Fig. 1. *Selected HMBC* (*a*) *and ROESY* (*b*) *correlations of* **1**

Oxidation of paxdaphnine B (**4**) with 3-chloroperbenzoic acid (MCPBA) afforded, indeed, compound **1** in high yield, which further confirmed its structure, including its absolute configuration [5a]. Therefore, the structure of **1** was established as *N*-hydroxypaxdaphnine B[1]).

21-*O*-Acetylpaxdaphnine B (**2**) was isolated as a colorless oil. The molecular formula $C_{23}H_{33}NO_4$ was determined by HR-EI-MS (M^+ at *m*/*z* 387.2429 (calc. 387.2410)). The ^{1}H- and ^{13}C-NMR spectroscopic data of **2** (*Table 1*) were very similar to those of **4**, except for the presence of an AcO group at C(21) instead of the 21-OH group in **4**. The ^{1}H- and ^{13}C-NMR signals for CH_2(21) at δ(H) 4.43 and 4.48 (2*d*, J = 11.8 Hz each), and at δ(C) 70.4, respectively, were all severely shifted downfield relative to those in **4** (δ(H) 3.84, 3.99 (2*d*, J = 11.6 Hz each); δ(C) 64.7) [5a]. The signal at δ(H) 2.01 (*s*, Me), and those at δ(C) 21.4 and 173.5 confirmed the presence of an AcO group. The structure of **2** was further corroborated by chemical derivatization. Thus, acetylation of the parent compound **4** with acetic anhydride (Ac_2O) in pyridine afforded **2** in high yield, as identified by ^{1}H-NMR comparison and co-TLC. The structure of compound **2** was, thus, assigned as 21-*O*-acetylpaxdaphnine B.

Methyl 17-hydroxyhomodaphniphyllate (**3**) was obtained as a yellowish oil. HR-EI-MS Analysis showed the molecular ion at *m*/*z* 375.2753, which matched the molecular formula $C_{23}H_{37}NO_3$ (calc. 375.2773). The IR absorption at 1736 cm^{-1} was indicative of a C=O group. The ^{13}C-NMR (DEPT) spectrum of **3** (*Table 2*) displayed

[1]) For systematic names, see the *Exper. Part*.

Table 2. *^{1}H- and ^{13}C-NMR Data of* **3**. At 400/100 MHz, resp., in C_5D_5N; δ in ppm, J in Hz. Arbitrary atom numbering.

Atom	δ(H)	δ(C)	Atom	δ(H)	δ(C)
H–C(1)	2.78–2.87 (*m*)	64.2	H_β–C(12)	1.66–1.72 (*m*)	
H–C(2)	1.27–1.34 (*m*)	38.2	H_a–C(13)	1.37–1.47 (*m*)	26.0
H_α–C(3)	1.40–1.48 (*m*)	27.0	H_b–C(13)	2.08–2.17 (*m*)	
H_β–C(3)	1.62–1.73 (*m*)		H_a–C(14)	2.46 (*ddd*, *J* = 16.5, 10.4, 4.2)	32.8
H_α–C(4)	1.24–1.33 (*m*)	36.6	H_b–C(14)	2.60 (*ddd*, *J* = 16.5, 10.8, 6.2)	
H_β–C(4)	1.79–1.90 (*m*)		H_α–C(15)	1.26–1.36 (*m*)	22.5
C(5)	–	37.2	H_β–C(15)	1.48–1.55 (*m*)	
H–C(6)	1.15–1.23 (*m*)	41.6	H_α–C(16)	1.95–2.03 (*m*)	32.8
H_α–C(7)	2.76 (br. *d*, *J* = 13.5)	46.8	H_β–C(16)	1.56–1.64 (*m*)	
H_β–C(7)	3.18 (br. *d*, *J* = 13.5)		H–C(17)	4.08–4.16 (*m*)	80.6
H–C(8)	–	48.1	H–C(18)	1.66–1.78 (*m*)	31.3
H–C(9)	2.19–2.28 (*m*)	50.8	Me(19)	1.06 (*d*, *J* = 6.6)	21.5
C(10)	–	74.6	Me(20)	0.85 (*d*, *J* = 6.6)	21.1
H_α–C(11)	2.07–2.15 (*m*)	23.2	Me(21)	0.84 (*s*)	25.7
H_β–C(11)	1.48–1.56 (*m*)		C(22)	–	174.3
H_α–C(12)	1.46–1.54 (*m*)	22.0	MeO	3.69 (*s*)	51.5

23 carbon signals: four Me groups (including one MeO function at δ(C) 51.5), nine CH_2 groups (the one at δ(C) 46.8 being linked to an N-atom), six CH groups (the one at δ(C) 80.6 being oxygenated, and the one at δ(C) 64.2 being linked to an N-atom), as well as four quaternary C-atoms (the one at δ(C) 74.6 being linked to an N-atom, as well as a C=O group at δ(C) 174.3).

The NMR spectroscopic data of **3** were similar to those reported for 17-hydroxyhomodaphniphyllic acid [7b], except for an additional MeO moiety (δ(H) 3.69 (*s*, 3 H); δ(C) 51.5). The carbon skeleton of **3** was the same as that of 17-hydroxyhomodaphniphyllic acid, as determined by analysis of the HMBC spectrum (*Fig. 2*,*a*). The MeO group was placed at C(22) to form a methyl ester, in accord with the observed HMBC correlation from MeO to C(22) (δ(C) 174.3). The relative configuration of **3** was determined to be the same as that of 17-hydroxyhomodaphniphyllic acid by a ROESY experiment (*Fig. 2*,*b*). The structure of compound **3** was, thus, determined as methyl 17-hydroxyhomodaphniphyllate.

The following six known compounds were also isolated: paxdaphnine B (**4**) [5a], a zwitterionic alkaloid [13], daphnezomine S [4g], daphnilactone B [14], yuzurimine B [7b], and dehydrated daphnigracine [15]. Their structures were identified by comparison of the corresponding ^{1}H- and ^{13}C-NMR as well as MS data with those reported in the literature. Notably, compound **4**, the zwitterionic alkaloid, daphnezomine S, and dehydrated daphnigracine were isolated from *D. macropodum* for the first time.

Experimental Part

General. All solvents used were of anal. grade (*Shanghai Chemical Plant*, Shanghai, China). Thin-layer chromatography (TLC): Pre-coated silica gel GF_{254} plates (*Qingdao Haiyang Chemical Co., Ltd.*, Qingdao, China). Column chromatography (CC): silica gel (200–300 mesh), silica gel *H60*, *Sephadex*

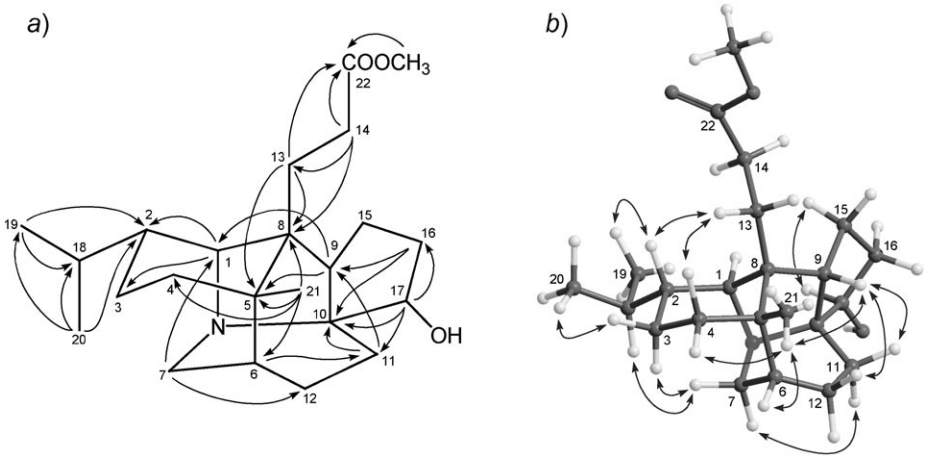

Fig. 2. *Selected HMBC* (*a*) *and ROESY* (*b*) *correlations of* **3**

LH-20 (*Amersham Biosciences*), and amino silica gel (*NH-DM 1020*, 20–45 μm; *Fuji Silysia Chemical, Ltd.*). Semi-prep. HPLC: *Waters* system, with a *515* pump, a *2487* detector (254 nm), and an *YMC-Pack ODS-A* column (250 × 10 mm, S-5 μm, 12 nm). Optical rotations: *Perkin-Elmer 341* polarimeter. IR Spectra: *Perkin-Elmer 577* spectrometer, with KBr discs; in cm^{-1}. NMR Spectra: *Varian Mercury-Plus-400* spectrometer; δ in ppm rel. to Me_4Si, *J* in Hz. Electron-impact-ionization mass spectrometry (EI-MS): *Finnigan MAT-95* mass spectrometer (70 eV); in *m*/*z* (rel. %). Low- and high-resolution electrospray-ionization mass spectrometry (ESI-MS and HR-ESI-MS): *Finnigan LC-Q^{DECA}* and *Waters Micromass-Q-TOF* mass spectrometers, resp.; in *m*/*z* (rel. %).

Plant Material. The fresh fruits of *D. macropodum* MIQ. were collected in October 2006 from Guangxi Province, P. R. China, and were authenticated by Prof. *Shao-Qing Tang* (Guangxi Normal University, P. R. China). A voucher specimen (No. DM-T-frt-zg1Y) was deposited at the Institute of Materia Medica, SIBS, Chinese Academy of Sciences.

Extraction and Isolation. The dried fresh fruits (6.0 kg) of *D. macropodum* were powdered and percolated with 95% EtOH to give a crude extract (320 g), which was dissolved in acidic H_2O (1000 ml; adjusted to pH 4 with 0.5M H_2SO_4) to form a suspension. After removal of the non-alkaloidal components by extraction with AcOEt, the aq. phase was adjusted with 2M aq. Na_2CO_3 soln. to pH 10, and then re-extracted with AcOEt to obtain the crude alkaloids (20.0 g). These were subjected to CC (SiO_2; $CHCl_3$/MeOH 1:0 → 0:1) to afford five fractions (*Fr. A* – *Fr. E*). *Fr. B* (3.0 g) was separated by CC (SiO_2; petroleum ether (PE)/AcOEt/Et_2NH 10:1:0.1), and the major fraction was further purified by CC (amino silica gel; cyclohexane/CH_2Cl_2 3:1) to afford dehydrated daphnigracine (70 mg). *Fr. C* (5.0 g) was separated by CC (SiO_2; PE/AcOEt/Et_2NH 25:1:0.1 → 4:1:0.1) to afford seven fractions (*Fr. C1* – *Fr. C7*). *Fr. C2* (0.5 g) was purified by CC (*Sephadex LH-20*; EtOH) to afford daphnilactone B (20 mg). *Fr. C3* (0.2 g) was purified by CC (amino silica gel; cyclohexane/CH_2Cl_2 2:1) to afford **2** (25 mg). *Fr. C4* (0.9 g) was separated by CC (SiO_2; PE/AcOEt/Et_2NH 5:1:0.1) to afford **4** (210 mg) and **1** (20 mg). *Fr. C6* (0.2 g) was repeatedly purified by CC (1. SiO_2, $CHCl_3$/MeOH 10:1; 2. *Sephadex LH-20*, EtOH) to provide **3** (20 mg). *Fr. D* (3.0 g) was recrystallized and further purified by semi-prep. HPLC (MeOH/H_2O 25:75, 3 ml/min) to afford the zwitterionic alkaloid (0.7 g) and daphnezomine S (26 mg). The mother liquor was purified by CC (SiO_2; $CHCl_3$/MeOH 5:1 → 1:1) to afford yuzurimine B (35 mg).

Oxidation of Paxdaphnine B (**4**). 3-Chloroperbenzoic acid (MCPBA; 10 mg) was added to a stirred soln. of **4** (10 mg) in CH_2Cl_2 (3 ml) at r.t., and the mixture was stirred for 2 h. Then, the mixture was washed with 20% aq. Na_2SO_3 soln. (3 ml) and with H_2O (6 ml). The org. layer was concentrated under reduced pressure, and the residue was purified by CC (SiO_2; PE/AcOEt/Et_2NH 6:1:0.1) to afford a major product (8 mg), which was identical with **1** by ^{1}H-NMR and TLC.

Acetylation of Paxdaphnine B (**4**). To a soln. of **4** (10 mg) in anh. pyridine (1 ml) was added Ac_2O (0.5 ml), and the mixture was stirred at r.t. for 24 h. After evaporation of excess reagent under vacuum, the residue was separated by CC (SiO_2; PE/AcOEt/Et_2NH 10 : 1 : 0.1) to afford a major product (8.6 mg), which was identical with **2** by ^{1}H-NMR and TLC.

N-*Hydroxypaxdaphnine B* (= *Methyl (2*R,*5*S,*8*S,*15*R*)-5-Ethyl-6-hydroxy-2-(hydroxymethyl)-6-azapentacyclo[9.5.1.0^{1,5}.0^{2,8}.0^{14,17}]heptadec-11(17)-ene-15-carboxylate*; **1**). Colorless, amorphous solid. $[\alpha]_D^{20} = +38.6$ ($c = 0.72$, MeOH). IR (KBr): 3423, 2949, 1734, 1624, 1437, 1383, 1198, 1171, 1039. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 361 (28, M^+), 344 (100), 314 (64), 297 (8), 229 (32), 183 (24). HR-EI-MS: 361.2264 (M^+, $C_{21}H_{31}NO_4^+$; calc. 361.2253).

21-O-*Acetylpaxdaphnine B* (= *Methyl (2*R,*5*S,*8*S,*15*R*)-2-(Acetoxymethyl)-5-ethyl-6-azapentacyclo[9.5.1.0^{1,5}.0^{2,8}.0^{14,17}]heptadec-11(17)-ene-15-carboxylate*; **2**). Colorless oil. $[\alpha]_D^{20} = +49.7$ ($c = 0.67$, MeOH). IR (KBr): 3448*w*, 2933, 1736, 1439, 1365, 1246, 1169, 1034, 814. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 387 (80, M^+), 327 (32), 314 (100), 297 (8), 229 (20), 183 (20), 149 (20). HR-EI-MS: 387.2429 (M^+, $C_{23}H_{33}NO_4^+$; calc. 387.2410).

Methyl 17-Hydroxyhomodaphniphyllate (= *Methyl (11β)-11-Hydroxydaphnan-23-oate*; **3**). Yellowish oil. $[\alpha]_D^{20} = -47.5$ ($c = 0.10$, MeOH). IR (KBr): 3400*w*, 2951, 1736, 1454, 1379, 1309, 1167, 1118, 1082, 933. ^{1}H- and ^{13}C-NMR: see *Table 2*. EI-MS: 375 (64, M^+), 360 (35), 333 (25), 302 (36), 288 (100), 274 (28), 194 (24). HR-EI-MS: 375.2753 (M^+, $C_{23}H_{37}NO_3^+$; calc. 375.2773).

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