

Diamide Derivatives and Cycloartanes from the Leaves of *Aglaia elliptica*

Akira INADA,^{*,a} Takako SORANO,^a Hiroko MURATA,^a Yuka INATOMI,^a Dedy DARNAEDI,^b and Tsutomu NAKANISHI^a

Faculty of Pharmaceutical Sciences, Setsunan University,^a 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan and Herbarium Bogoriense,^b Jalan Ir, H. Juanda, Bogor 16122, Indonesia. Received April 23, 2001; accepted June 9, 2001

Chemical examination of the leaves of *Aglaia elliptica* led to the isolation of two new diamides, 10-*O*-acetyl-aglain B (1) and 4-epiaglain A (2), two known diamides, aglain A (3) and odorine (4), and three known cycloartanes (5—7). The structures of 1 and 2 were elucidated by interpretation of the spectral data.

Key words *Aglaia elliptica*; diamide; 10-*O*-acetylglain B; 4-epiaglain A; aglain A; Meliaceae

The genus *Aglaia* (Meliaceae) consists of about 130 species that are dioecious trees or shrubs and the plants of this genus are mainly distributed in tropical and subtropical regions. Several novel amides containing a cyclopenta-*[bc]*benzopyran moiety (=aglain-type) and a cyclopenta-*[b]*benzofuran moiety (=rocaglamide-type) as the acid part have been characterized from this genus,^{1–20} some of which were shown to exhibit cytotoxic^{1,3,5,7,10,19,20} insecticidal,^{2,6,8,9,11–15,17} and antifungal⁴) activities. In our series of studies of this genus,¹⁶ we have investigated the constituents of the leaves of *Aglaia elliptica* Bl. Rocaglamide derivatives from the fruits⁹) and rocaglamide derivatives and dammaranes from the stems and fruits of this plant¹⁰) have already been characterized. However, to our knowledge there have been no phytochemical reports on the leaves.

Repeated column chromatography and HPLC separation of a MeOH extract of the leaves resulted in the isolation of two new aglain derivatives, 10-*O*-acetylglain B (1) and 4-epiaglain A (2), two known diamides (3, 4), and three known cycloartanes (5—7). Compounds 3 and 4 were identified as aglain A⁵) and aminopyrrolidine-diamide, odorine,^{21,22}) by a

combination of spectroscopic analyses and comparisons with reported data. Compounds 5—7 were known cycloartanes^{23,24}) previously isolated from *Aglaia harmsiana* and identified by direct comparisons with authentic samples. Compound 1, [α]_D +20.4° (MeOH), gave a molecular ion peak (M⁺) of C₃₈H₄₄N₂O₉ by high resolution (HR)-electron ionization (EI)-MS and showed absorptions at 1750 (ester), 1680, 1620 (amide), and 1595 cm⁻¹ (benzene ring) in the IR spectrum. The ¹H-NMR spectrum of 1 (Table 1) analyzed with the aid of two-dimensional (2D)-NMR studies [¹H–¹H and ¹³C–¹H shift-correlated spectroscopy (COSY), and nuclear Overhauser enhancement spectroscopy (NOESY) experiments] indicated the presence of three methoxy methyls (δ 3.76, 3.78, 3.91), an acetoxy methyl (δ 2.08), three methines [δ 4.11 (d, *J*=5.7 Hz), 4.87 (d, *J*=5.7 Hz), 4.78 (s-like)], and 11 benzene protons comprised of two meta-coupled protons of a benzene ring, four protons of a *p*-disubstituted benzene ring, and five protons of a monosubstituted benzene ring. In addition, a 2-amino-pyrrolidine ring and aliphatic side chain moiety reminiscent of those reported for odorine (4) were observed.^{21,22}) In addition to these units, the

Table 1. ¹H-NMR Spectral Data of 1—3 in CD₃OD (600 MHz)^a

Proton No.	1	2	3
3-H	4.87 (d, 5.7)	5.24 (d, 7.4)	4.39 (d, 5.3)
4-H	4.11 (d, 5.7)	3.94 (d, 7.4)	3.93 (d, 5.3)
10-H	4.78 (s-like) ^b	5.37 (s)	6.42 (s)
13-H	5.73 (d, 5.7)	6.11 (d, 5.4)	6.19 (d, 5.7)
14-H ₂	2.00—2.08 (m), 2.10—2.18 (m)	2.05—2.15 (m), 2.15—2.23 (m)	1.95—2.05 (m), 2.14—2.20 (m)
15-H ₂	1.95—2.00 (m), 2.00—2.08 (m)	1.90—1.95 (m), 1.95—2.00 (m)	1.90—1.95 (m), 1.95—2.05 (m)
16-H ₂	3.50—3.58 (m), 3.60—3.65 (m)	3.46—3.52 (m), 3.55—3.65 (m)	3.53—3.60 (m)
19-H	1.77—1.83 (m)	1.83—1.90 (m)	1.82—1.90 (m)
20-H ₂	1.18—1.28 (m), 1.32—1.42 (m)	1.20—1.30 (m), 1.35—1.44 (m)	1.05—1.14 (m), 1.18—1.28 (m)
21-H ₃	0.74 (t, 7.0)	0.74 (t, 7.5)	0.47 (t, 7.3)
22-H ₃	0.72 (d, 6.9)	0.78 (d, 6.8)	0.82 (d, 7.0)
OCOCH ₃	2.08 (s)	2.05 (s)	1.76 (s)
6-OCH ₃	3.91 (s)	4.03 (s)	4.02 (s)
8-OCH ₃	3.78 (s)	3.81 (s)	3.76 (s)
4'-OCH ₃	3.76 (s)	3.77 (s)	3.76 (s)
Aromatic protons			
7-H	6.20 (d, 1.9)	6.32 (d, 2.0)	6.31 (d, 2.4)
9-H	6.06 (d, 1.9)	6.20 (d, 2.0)	6.02 (d, 2.4)
2', 6'-H ₂	7.63 (d, 9.2)	7.61 (d, 9.2)	7.44 (d, 9.0)
3', 5'-H ₂	6.89 (d, 9.2)	6.88 (d, 9.2)	6.86 (d, 9.0)
2'', 6''-H ₂	6.85—6.87 (m)	7.00—7.05 (m)	6.48—6.50 (m)
3'', 4'', 5''-H ₃	7.03—7.08 (m)	7.06—7.09 (m)	6.95—7.06 (m)

^a) Chemical shifts are in δ -values from internal tetramethylsilane (TMS) and are followed by multiplicities and *J*-values (in Hz). ^b) A small long-range coupling (W-shaped) between 4 α -H was further observed in the COSY spectrum.

Table 2. ^{13}C -NMR Spectral Data of 1–3 in CD_3OD (150 MHz, δ -Values)

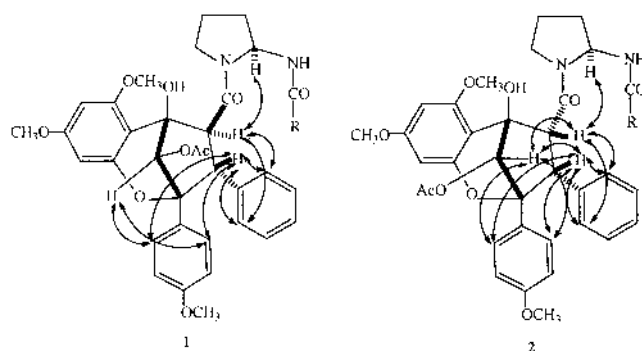
Carbon No.	1	2	3	Carbon No.	1	2	3
1a	154.8	154.8	155.6	20	28.3	28.3	27.9
2	92.0	89.5	86.8	21	12.1	12.2	12.1
3	55.1	55.4	56.6	22	17.5	17.6	17.3
4	61.6	62.2	58.2	1'	131.0	130.2	131.9
5	84.8	83.9	80.1	2', 6'	129.0	128.9	128.4
5a	109.8	112.2	108.5	3', 5'	114.1	114.3	114.3
6	157.6	157.7	159.4	4'	160.7	160.9	160.6
7	93.3	93.8	93.5	1''	138.2	138.8	137.6
8	162.7	162.8	162.6	2'', 6''	130.7	130.9	130.6
9	94.6	95.3	94.8	3'', 5''	129.8	129.5	128.8
10	81.2	80.9	74.8	4''	128.0	127.8	127.9
11	173.7	170.7	172.5	6-OCH ₃	56.3	56.6	56.8
13	65.8	65.5	65.2	8-OCH ₃	56.0	56.0	56.0
14	35.2	35.0	34.8	4'-OCH ₃	55.7	55.7	55.7
15	22.3	22.0	22.2	OCOCH ₃	170.4	171.7	171.6
16	47.8	47.3	47.3		21.2	22.0	20.7
18	178.0	178.0	178.2				
19	43.0	43.1	43.2				

^{13}C -NMR spectrum of **1** (Table 2) analyzed with the aid of ^{13}C - ^1H -COSY and heteronuclear multiple-bond correlation spectroscopy (HMBC) experiments exhibited signals due to two amide carbonyl carbons (δ 173.7, 178.0), an ester carbonyl carbon (δ 170.4), and two aliphatic quaternary carbons bearing an oxygen atom (δ 84.8, 92.0). The results indicate that compound **1** is an aglain derivative.^{5,12,13,16,18–20}

Among them, the spectral data of **1** were very similar to those of aglain B (**8**).⁵ However the signal due to a 10-OH in **8** was absent in **1** and this signal was replaced with an acetoxy group (δ_{H} 2.08; δ_{C} 21.2, 170.4). Accordingly, the 10-H of **8** (δ 4.10)⁵ was downfield-shifted to δ 4.78 in **1**. This substitution was also supported by the selective NOESY correlations, as shown in Fig. 1. That is, compound **1** gave significant cross peaks between 10-H/2', 6'-H₂, between 3-H/2', 6'-H₂, 2'', 6''-H₂, and between 4-H/2'', 6''-H₂. Thus the relative stereochemistry of 10-H, 3-H, and 4-H is as shown in Fig. 2.²⁵

Finally, the unambiguous structure of **1** was established from the following HMBC experiments and significant correlation peaks between 3-H/C-2, C-4, C-5, C-1'' and between 4-H/C-3, C-5, C-5a, C-10, C-1'' were observed.²⁶ In addition, correlation peaks between 3-H/C-1', and between 4-H/C-11 indicated the connectivities of C-3 to the monosubstituted benzene ring and of C-4 to the C-11 amide carbonyl carbon. Based on the evidence, the structure of **1** is as shown in Fig. 2.

4-Epiaglain A (**2**), $[\alpha]_{\text{D}} -1.0^\circ$ (CHCl_3), had the same molecular formula ($\text{C}_{38}\text{H}_{44}\text{N}_2\text{O}_9$) as **1** based on HR-EI-MS. The IR spectrum of **2** showed absorptions at 1750 (ester), 1660, 1620 (amide), and 1595 cm^{-1} (benzene ring). The ^1H -NMR spectrum of **2** (Table 1) analyzed with the aid of 2D-NMR studies showed the presence of the same functional groups and moiety as in **1**. The ^{13}C -NMR spectrum of **2** (Table 2) exhibited signals due to two amide carbonyl carbons (δ 170.7, 178.0) and an ester carbonyl carbon (δ 171.7), suggesting that **2** is also an aglain derivative.^{5,12,13,16,18–20} The ^1H -NMR-spectral data of **2** were similar to those of aglain A (**3**).⁵ However, the chemical shifts and J -values of the signals due to 3-H (**2**, δ 5.24, d, $J=7.4\text{ Hz}$; **3**, δ 4.39, d, $J=5.3\text{ Hz}$) and 4-H (**2**, δ 3.94, d, $J=7.4\text{ Hz}$; **3**, δ 3.93, d, $J=5.3\text{ Hz}$) are

Fig. 1. Selected NOESY Correlations of **1** and **2**

obviously different to each other. The results indicate that compound **2** is a stereoisomer of **3**.

Dreiding model inspections suggested the presence of either $3\beta\text{-H}/4\beta\text{-H}$ or $3\alpha\text{-H}/4\alpha\text{-H}$ relative stereochemistry in **2** instead of the $3\beta\text{-H}/4\alpha\text{-H}$ relative stereochemistry in **3** (and also in **1**). The $3\beta\text{-H}/4\beta\text{-H}$ stereochemistry in **2** was determined as follows. In the NOESY experiments as shown in Fig. 1, a methine proton ascribable to 10-H (δ 5.37) showed significant correlations with both 3-H and 4-H. In addition, correlation peaks between 10-H/2', 6'-H₂, between 3-H/2', 6'-H₂, 2'', 6''-H₂, and between 4-H/2'', 6''-H₂, were observed. Hence the relative stereochemistry of 10-H, 3-H, and 4-H of **2** is as shown in Fig. 2.²⁵ The final structure of **2** was established from the HMBC experiments, and **2** exhibited similar and significant correlation peaks to those observed in **1**.²⁷ Based on the evidence, the structure of 4-epiaglain A is **2**. In accordance with the biogenetic hypothesis of aglain derivatives,^{5,12,13} one supposed precursor, odorine (**4**),^{21,22} was also isolated and identified from this plant.

Experimental

The IR spectra were recorded on a JASCO A-302 spectrophotometer. Optical rotations were measured on a JASCO-DIP-140 digital polarimeter. The EI-, FAB-, and HR-EI-MS were recorded on JEOL JMS-DX 300 and JMS-700T spectrometers. The ^1H - and ^{13}C -NMR spectra were recorded on a GE-OMEGA 600 spectrometer (600 and 150 MHz, respectively), with $\text{MeOH-}d_4$ as a solvent and tetramethylsilane (TMS) as an internal standard. HPLC was performed on a JAILC-908 instrument with JAIGEL-ODS-S343-15 and JAIGEL-GS310 columns with a differential refractometer.

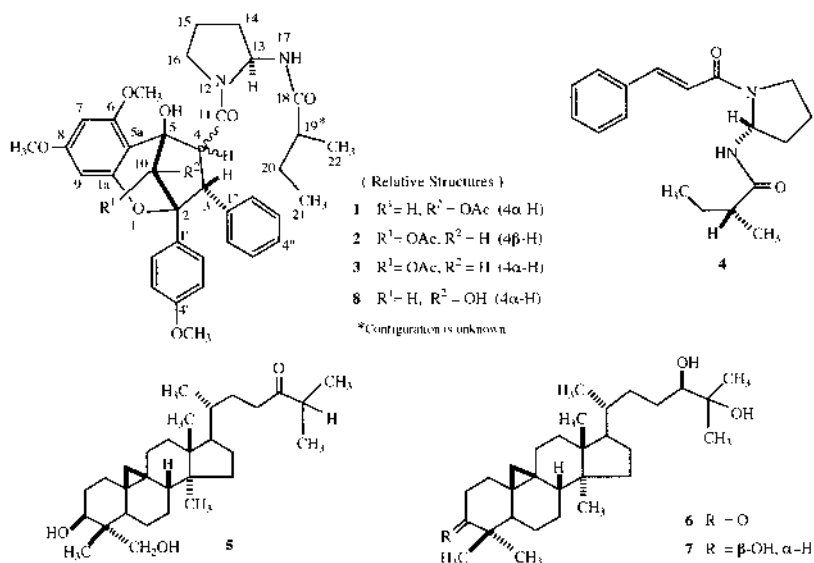


Fig. 2. Structures of Compounds 1—8

Plant Material The leaves of *A. elliptica* Bl. were harvested in 1993 at the Herbarium Bogoriense, Java, Indonesia, and voucher specimens have been deposited at the Herbarium of the Faculty of Pharmaceutical Sciences, Setsunan University.

Extraction and Isolation The dried leaves (395 g) were extracted with MeOH and the solvent was evaporated. The MeOH extract (39.0 g) was suspended with H₂O and the aqueous suspension was extracted in succession with hexane and EtOAc. The combined hexane and EtOAc extract (19.0 g) was chromatographed on silica gel with CHCl₃–MeOH containing increasing MeOH concentrations. Each fraction containing 1—7, was further purified with repeated HPLC separation to afford **1** (10.1 mg), **2** (5.3 mg), **3** (15.8 mg),⁵⁾ **4** (250 mg),^{21,22)} **5** (6.8 mg),²³⁾ **6** (57 mg),²³⁾ and **7** (75 mg)²⁴⁾ along with β -sitosterol (25 mg) and β -sitosterol glucoside (140 mg). Known compounds (**3**—**7**) were identified by direct comparison with authentic samples or by comparisons of their spectral data.

10-*O*-Acetylglain B (**1**): An amorphous powder; $[\alpha]_D^{20} + 20.4^\circ$ ($c = 0.83$, MeOH); IR (KBr) cm^{-1} : 3370, 1750, 1680, 1620, 1595, 1520, 1150; EI- and HR-EI-MS: m/z (%) 672.3049 (M^+ , C₃₈H₄₄N₂O₉ requires 672.3047, >1), 571 (18), 442 (65), 313 (100), 200 (39), 131 (79), 73 (98); FAB-MS: m/z 673 [$M+H$]⁺, 695 [$M+Na$]⁺; ¹H- and ¹³C-NMR: Tables 1 and 2, respectively.

4-Epiaglain A (**2**): An amorphous powder; $[\alpha]_D^{20} - 1.0^\circ$ ($c = 0.97$, CHCl₃); IR (KBr) cm^{-1} : 3450, 1750, 1660, 1620, 1595, 1515, 1150; EI- and HR-EI-MS: m/z (%) 672.3042 (M^+ , C₃₈H₄₄N₂O₉ requires 672.3047, >1), 571 (18), 442 (40), 313 (100), 200 (23), 131 (49), 73 (61); FAB-MS: m/z 673 [$M+H$]⁺, 695 [$M+Na$]⁺; ¹H- and ¹³C-NMR: Tables 1 and 2, respectively.

Aglain A (**3**)⁵⁾: An amorphous powder; ¹H- and ¹³C-NMR: Tables 1 and 2, respectively.

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- 25) Based on the reported results,^{5,13)} the correlation peak between 4-H/13-H and between 21-H/ 2', 6"-H₂ indicated a 13S-relative configuration in **1**—**3** and **8**.
- 26) Correlations between 10-H and carbon atoms in **1** were obscure due to the overlapping 10-H and OH proton of MeOH-*d*₄.
- 27) Correlations between 10-H/C-2, C-3, C-4, OCO, between 3-H/C-2, C-4, C-5, C-11, C-1', C-1," and between 4-H/C-3, C-5, C-5a, C-10, C-11, C-1" were observed.