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The Constituents of *Schizandra chinensis* Baill. VIII.[1] The Structures of Two New Lignans, Tigloylgomisin P[2] and Angeloylgomisin P

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Two new dibenzocyclooctadiene lignans, tigloylgomisin P(1), and angeloylgomisin P(2) were isolated from the fruits of *Schizandra chinensis* Baill. (Schizandraceae). Their absolute structures were elucidated by means of chemical and spectral studies.

Keywords——*Schizandra chinensis* Baill; Schizandraceae; dibenzocyclooctadiene; lignan; tigloylgomisin P; angeloylgomisin P; NOE; ^{13}C-NMR

In the previous papers of this series, we have reported a number of dibenzocyclooctadiene lignans isolated from the fruits of *Schizandra chinensis* Baill. (Schizandraceae).[4] This paper deals with two additional new lignans, tigloylgomisin P (**1**, yield 0.0013%) and angeloylgomisin P (**2**, 0.0008%) from the same source.

Tigloylgomisin P (**1**) was isolated as a white amorphous powder, $C_{28}H_{34}O_9$, $[\alpha]_D^{22}$ $-64.2°$ ($CHCl_3$). The ultraviolet (UV) spectrum of **1**, with absorption maxima at 217 (log ε 4.68), 255 (sh 3.99) and 282 nm (3.51), and the infrared (IR) spectrum, with bands at 3480 (OH), 1712 (ester), 1645 (C=C), 1616 and 1595 (aromatic) cm^{-1}, indicate that **1** is a dibenzocyclooctadiene lignan[4] possessing a hydroxyl and an ester linkage. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum (Table I) and the carbon (^{13}C)-NMR spectrum (Table II) indicate the presence of a methylenedioxy moiety and four methoxyl groups on the aromatic rings and also the presence of a tertiary methyl group attached to a carbon carrying a hydroxyl group (CH_3-$\overset{|}{\underset{|}{C}}$-OH), a secondary methyl group, a benzylic methine and a tigloyl group[^{13}C-NMR, δ in $CDCl_3$, tigloyl: 12.2 (α-Me), 14.4 (β-Me), 128.8, 137.5 ($\rangle$C=C$\langle$), 166.6 ($\rangle$C=O)].[5] The mass spectral analysis also supports the presence of a tigloyl group in **1** (see "Experimental").

On hydrolysis with 3% ethanolic potassium hydroxide, **1** afforded a tiglic acid and a diol (**3**), named gomisin P, $C_{23}H_{28}O_8$, mp 114—116°, $[\alpha]_D^{25}$ $-94.3°$ ($CHCl_3$). The circular dichroism (CD) spectrum of **3** shows a positive Cotton effect at 221 nm ($[\theta]$ $+62000$) and two negative Cotton effects at 242 nm ($[\theta]$ -66000, sh) and 253 nm ($[\theta]$ -76000), indicating that **3** possesses an *S*-biphenyl configuration.[4a]

The singlet at δ 4.32 in the ^{1}H-NMR spectrum of **3**, which appeared at δ 5.37 (in C_6D_6) (δ 5.54 in $CDCl_3$) in **1**, was assigned to a benzylic methine. This shows that the tigloyl group in **1** is linked to a benzylic hydroxyl group. On the basis of a comparison of the ^{1}H-NMR spectrum of **3** with that of deangeloylgomisin B (**4**),[4a] **3** is assumed to be a diastereomer of **4** at the C-6 and C-7 positions, as discussed below. In the ^{1}H-NMR spectrum, the tertiary

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[1] Part VII: Y. Ikeya, H. Taguchi, and I. Yosioka, *Chem. Pharm. Bull.*, **28**, 2422 (1980).

[2] Preliminary communication of this work: Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *Chem. Pharm. Bull.*, **26**, 3257 (1978).

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[4] *a*) Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *Chem. Pharm. Bull.*, **27**, 1383 (1979); *b*) Y. Ikeya, H. Taguchi, I. Yosioka, Y. Iitaka, and H. Kobayashi, *ibid.*, **27**, 1395 (1979); *c*) Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *ibid.*, **27**, 1576 (1979); *d*) *Idem*, *ibid.*, **27**, 1583 (1979); *e*) *Idem*, *ibid.*, **27**, 2695 (1979); *f*) Y. Ikeya, H. Taguchi, H. Sasaki, K. Nakajima, and I. Yosioka, *ibid.*, **28**, 2414 (1980).

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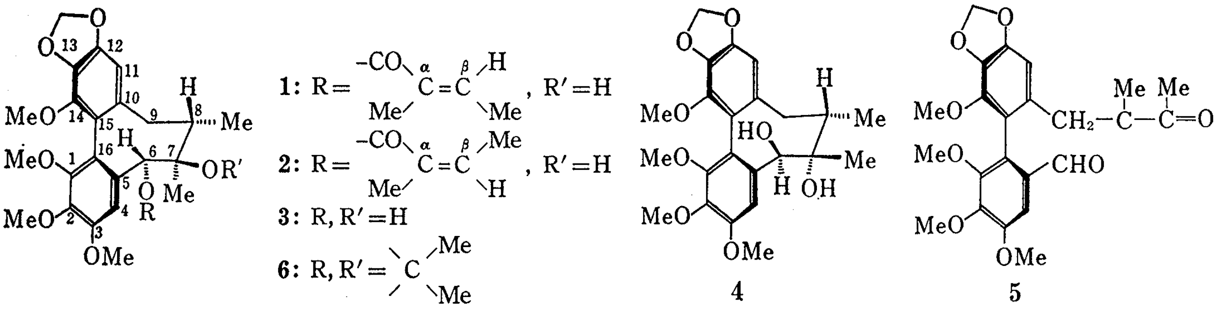
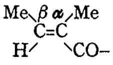


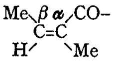
Chart 1

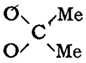
Table I. ¹H-NMR Spectral Data[δ in $CDCl_3$, 60 MHz for **2**,**3**,**6** and 100 MHz for **1**,**4**]

Compd.	4-H, s 11-H, s	6-H s	OCH_2O s	OCH_3 s	9α-H dd(J=Hz)	9β-H dd(J=Hz)	6-OH[c] s	HO[c]–C(7)–Me		H–C(8)–Me[d]	
								s	s	m	d(J=Hz)
1[a,b]	6.95 6.13	5.90	5.37	3.53, 3.70 3.83, 3.92	2.10 (center) (2H ,m)		—	2.07	1.13	1.98	1.10 (7)
2[a,b]	6.97 6.49	5.97	5.37	3.53, 3.71 3.85, 3.92	2.10 (center) (2H, m)		—	1.80	1.11	1.88	1.08 (7)
3	7.10 6.47	4.32	5.93	3.58, 3.83 3.92(×2)	2.10 (center) (2H, m)		2.40	2.40	1.00	1.77	1.07 (7)
4	6.62 6.51	4.59	5.95	3.61, 3.90 3.93(×2)	2.35 (12/8.5)	2.05 (12/1)	1.56	1.56	1.40	1.85	1.11 (7)
6[b]	7.07 6.50	4.57	5.99	3.62, 3.78 3.93, 3.95	2.10 (center) (2H, m)		—	—	0.83	1.77	1.08 (6)

a) Measured in C_6D_6.

b) Other signals: 1:

$$\overset{\text{Me}\diagdown\beta\ \alpha\diagup\text{Me}}{\underset{\text{H}\diagup\quad\diagdown\text{CO–}}{\text{C=C}}}$$
: 1.38 (3H, dq, J=7/1 Hz, β-Me), 1.68 (3H, m, α-Me), 6.85 (1H, m, β-H).

2:

$$\overset{\text{Me}\diagdown\beta\ \alpha\diagup\text{CO–}}{\underset{\text{H}\diagup\quad\diagdown\text{Me}}{\text{C=C}}}$$
: 1.80 (3H, s, α-Me), 1.87 (3H, dq, J=7/1.5 Hz, β-Me), 5.70 (1H, m, β-H).

3:

$$\overset{\text{O}\diagdown\quad\diagup\text{Me}}{\underset{\text{O}\diagup\quad\diagdown\text{Me}}{\text{C}}}$$
: 1.27, 1.55 (each 3H, s)

c) Confirmed by addition of D_2O.

d) Confirmed by decoupling experiments.

e) d=doublet, m=multiplet, q=quartet, s=singlet.

methyl of **3** appears at higher field than that of **4** (δ 1.40), indicating that it is shielded by the aromatic rings, and one of the aromatic protons (δ 7.10) appears at lower field than that of **4** (δ 6.62), suggesting the presence of a C-6α-oriented hydroxyl group. This view is also supported by the ¹³C-NMR spectra of **3** and **4**.[4f)]

Oxidation of **3** with chromium trioxide in pyridine afforded a ketoaldehyde (**5**),[4a)] $C_{23}H_{26}O_8$, which was identical with **5** prepared from **4** by oxidation with chromium trioxide in acetic acid. This further supports the above considerations. On the other hand, treatment of **3** with $CuSO_4$ and 0.25% H_2SO_4 (in acetone) afforded an acetonide (**6**), $C_{26}H_{32}O_8$ (M^+, m/z 472), $[\alpha]_D^{22}$ −135° ($CHCl_3$). Dreiding model examination indicated that the structure of the acetonide is represented by the formula **6**.

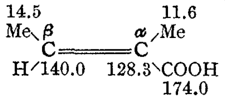
Finally, the structure of **1**, including the conformation of the cyclooctadiene ring, was confirmed by measurements of intramolecular nuclear Overhauser effects (NOE) (in C_6D_6), as shown in Fig. 1.[4a,b)] Irradiation of a methoxyl signal (δ 3.53) caused a 14% increase in the integrated intensity of the lower field aromatic proton signal at δ 6.95 ($C_{(4)}$–H), while the higher field aromatic proton at δ 6.13 ($C_{(11)}$–H) was unaffected by irradiation of any methoxyl signal. Irradiation of the benzylic methylene protons (irradiated at δ 2.01) caused a 13% increase in the integrated intensity of the $C_{(11)}$–proton signal, while the $C_{(4)}$-proton was unaf-

Table II. ^{13}C-NMR Spectral Data for **1** and **2** [δ in $CDCl_3$, ^{13}C: 20 MHz at 25°]

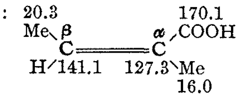
Carbon	**1**	**2**	Carbon		**1**	**2**
1	151.1(s)[a)]	151.1(s)[a)]		17	18.8(q)	18.8(q)
2	141.1(s)[b)]	141.1(s)[b)]		18	17.5(q)	17.5(q)
3	152.4(s)[a)]	152.4(s)[a)]	OMe	C-1, 14	60.6, 59.9(q)	60.6, 59.9(q)
4	106.2(d)	106.5(d)		C-2	60.9(q)	60.9(q)
5	133.1(s)	132.9(s)		C-3	55.9(q)	55.9(q)
6	77.6(d)	77.3(d)		OCH_2O	101.0(t)	101.0(t)
7	75.2(s)	75.2(s)	Tigloyl[d)]	α-Me	12.2(q)	
8	46.6(d)	46.7(d)		β-Me	14.4(q)	
9	36.7(t)	36.7(t)		C=C	128.8(s)	
10	136.7(s)	136.7(s)			137.5(d)	
11	103.0(d)	103.0(d)		C=O	166.6(s)	
12	149.5(s)	149.5(s)	Angeloyl[e)]	α-Me		15.8(q)
13	135.6(s)	135.7(s)		β-Me		20.8(q)
14	141.5(s)[b)]	141.5(s)[b)]		C=C		127.6(s)
15	122.9(s)[c)]	122.9(s)[c)]				138.7(d)
16	119.6(s)[c)]	119.6(s)[c)]		C=O		166.4(s)

a, *b*, *c*) Assignments within any vertical column may be reversed.

d) Tiglic acid (δ in $CDCl_3$):



e) Angelic acid (δ in $CDCl_3$):



f) d=doublet, q=quartet, s=singlet, t=triplet.

fected by irradiation of the benzylic methine (δ 5.90, $C_{(6\beta)}$–H). Irradiation of the $C_{(8)}$-methine (δ 1.98) caused a 13% increase in the integrated intensity of the $C_{(6)}$-methine signal (δ 5.90). These findings indicate that the methylenedioxy moiety is located adjacent to the $C_{(11)}$-proton, and that the $C_{(6)}$- and $C_{(8)}$-protons are β-oriented. Irradiation of the tertiary methyl signal (δ 1.13) affected the $C_{(4)}$-proton, indicating that the tertiary methyl and the $C_{(4)}$-proton must be close to each other. On the other hand, the aromatic protons were unaffected by irradiation of the secondary methyl signal (δ 1.10).

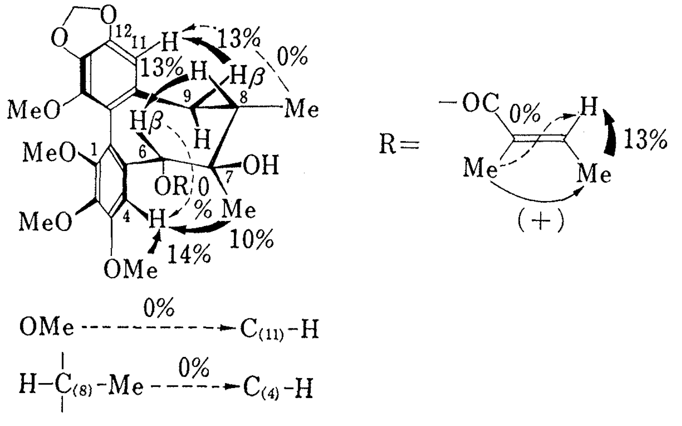


Fig. 1. NOE in **1** (in C_6D_6)

On the basis of the above results, the absolute structure of tigloylgomisin P was elucidated as **1**, possessing a twist-boat-chair conformation of the cyclooctadiene ring.

Angeloylgomisin P (**2**) was isolated as a white amorphous powder, $C_{28}H_{34}O_9$, $[\alpha]_D^{23}$ −98.5° ($CHCl_3$). The UV, mass, ^{1}H-NMR and ^{13}C-NMR spectra of **2** indicate that **2** is a dibenzocyclooctadiene lignan possessing the same skeleton as **1** and an angeloyl group[^{13}C-NMR, δ in $CDCl_3$, angeloyl: 15.8 (α-Me), 20.8 (β-Me), 127.6, 138.7 (C=C), 166.4 (C=O)].[5)] On hydrolysis with 3% ethanolic potassium hydroxide, **2** gave **3** and angelic acid.[6)] The structure of angeloylgomisin P was thus elucidated as **2**.

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6) Angelic acid was partly isomerized to tiglic acid during hydrolysis.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (a hot stage type) and are uncorrected. The UV spectra were recorded with a Hitachi 624 digital spectrophotometer and the IR spectra with a Hitachi EPI-G2 machine. The ^{1}H-NMR spectra were recorded with Varian T-60 and JEOL PS-100 spectrometers and ^{13}C-NMR spectra with a Varian FT-80A spectrometer, with tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi double-focusing mass spectrometer. The specific rotations were measured with a JASCO DIP-SL unit and the circular dichroism (CD) spectrum with a JASCO J-20. Gas liquid chromatography (GLC) was carried out on a Hitachi 073 gas chromatograph with FID. For silica gel column chromatography, Kieselgel 60 (Merck) was used. Thin-layer chromatography (TLC) was carried out on Merck plates precoated with Kieselgel 60F$_{254}$. Preparative layer chromatography (PLC) was carried out on plates (20 × 20 cm) coated with Kieselgel PF$_{254}$ (Merck).

Isolation of 1 and 2——In the previous paper,[4a] it was reported that the pet. ether and methanolic extracts of the fruits of *Schizandra chinensis* Baill. (4.671 kg) afforded twelve fractions (fr. 1—12) on silica gel column chromatography, developing with hexane, acetone-benzene and acetone solvent systems. Fr. 6 (10.97 g) was rechromatographed on silica gel (240 g, 4.5 × 29 cm) with a hexane–EtOAc solvent system. The fractions eluted with hexane–EtOAc (4: 1) were concentrated to give a residue (1104 mg), which was rechromatographed on silica gel (30 g, 2 × 17 cm) with a benzene–ether solvent system. The fractions eluted with benzene–ether [(49: 1) and (24: 1)] were combined and concentrated to give a residue (385 mg). Repeated PLC [i) hexane–acetone (7: 3), *Rf* 0.62, ii) benzene–ether (2: 1), *Rf* 0.67, iii) CHCl$_3$–EtOH (20: 1), *Rf* 0.91] of this residue gave **2** (39 mg, yield 0.0008%). The fractions eluted with benzene–ether (47: 3) were concentrated to give a residue (548 mg), which was purified by PLC [hexane–ether (1: 2), *Rf* 0.47] to give **1** (24 mg). The fractions eluted with hexane–EtOAc (3: 1) were concentrated to give a residue (238 mg). Repeated PLC [i) benzene–ether (7: 3), *Rf* 0.56; ii) hexane–ether (1: 2), *Rf* 0.47] of this residue gave **1** (35 mg, 0.0013%).

Tigloylgomisin P(1)——Pure tigloylgomisin P was obtained as a white amorphous powder (from ether–hexane), $[\alpha]_D^{22}$ −64.2° (c=0.436, CHCl$_3$). UV λ_{max}^{EtOH} nm (log ε): 217 (4.68), 255 (sh 3.99), 282 (3.51). IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1712 (ester), 1645 (C=C), 1616, 1595 (aromatic). High resolution MS (*m/z*), Calcd for $C_{28}H_{34}O_9$(M$^+$): 514.2208. Found: 514.2180. MS, *m/z* (%): 514 (M$^+$, 12), 414 [M$^+$−CH$_3$CH=C(CH$_3$)COOH, 19], 343 (43), 83 [CH$_3$CH=C(CH$_3$)CO$^+$, 100], 55 (CH$_3$CH=C$^+$−CH$_3$, 90). *Anal.* Calcd for $C_{28}H_{34}O_9$: C, 65.36; H, 6.66. Found: C, 65.62; H, 6.85. The ^{1}H-NMR and ^{13}C-NMR data are given in Tables I and II, respectively.

Angeloylgomisin P(2)——Pure angeloylgomisin P was obtained as a white amorphous powder, $[\alpha]_D^{23}$ −98.5° (c=2.18, CHCl$_3$). UV λ_{max}^{EtOH} nm (log ε): 3500 (OH), 1720 (ester), 1644 (C=C), 1618, 1598 (aromatic). High resolution MS (*m/z*), Calcd for $C_{28}H_{34}O_9$(M$^+$): 514.2208. Found: 514.2202. MS, *m/z* (%): 514 (M$^+$, 28), 414 [M$^+$−CH$_3$CH=C(CH$_3$)COOH, 36], 343 (57), 83 [CH$_3$CH=C(CH$_3$)CO$^+$, 73], 55 (CH$_3$CH=C$^+$−CH$_3$, 100). The ^{1}H-NMR and ^{13}C-NMR data are given in Tables I and II, respectively.

Hydrolysis of 1——A solution of **1** (38 mg) in 3% KOH–EtOH (2 ml) was kept at 55° for 2 hr, then diluted with H$_2$O (20 ml) and extracted with ether (15 ml × 3). The combined ethereal extract was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated to give a residue, which was purified by PLC [benzene–ether (3: 2)] to give a diol (**3**), colorless needles (from ether–hexane), mp 114—116°, $[\alpha]_D^{25}$ −94.3° (c=0.530, CHCl$_3$) (30 mg). UV λ_{max}^{EtOH} nm (log ε): 220 (4.59), 254 (sh 4.02), 283 (sh 3.49), 294 (sh 3.37). IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1615, 1595 (aromatic). CD (c=0.0183, MeOH), $[\theta]^{23}$ (nm): +62000 (221), −66000 sh (242), −76000 (253). *Anal.* Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 63.80; H, 6.63.

The aqueous solution was acidified with 1 N HCl and extracted with ether. The ethereal extract was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated to give a residue, which was sublimed (70°, 15 mmHg) to give colorless needles (2 mg), mp 63—64°. This compound was identified as tiglic acid by direct comparison with an authentic sample [GLC, IR and mixed mp; GLC conditions: column, SP-1200 (10%) + H$_3$PO$_4$ (1%) on Chromosorb WAW (80—100 mesh) 3 mm × 2 m; column temperature, 130°; injection temperature, 150°; carrier gas, N$_2$, 30 ml/min; tiglic acid, t_R(min), 8.7].

Oxidation of 3 with Chromium Trioxide in Pyridine——CrO$_3$ (25 mg) was added to a solution of **3** (12 mg) in pyridine (0.5 ml). The reaction mixture was stirred at 15° for 30 min, then diluted with H$_2$O and extracted with ether (15 ml × 3). The combined ethereal extract was washed with 1 N HCl, then H$_2$O, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by PLC [hexane–acetone (7: 3)] to give **5** as a colorless oil (8 mg), $[\alpha]_D^{26}$ $\simeq$0° (c=0.277, CHCl$_3$). The ^{1}H-NMR of **5** was identical with that of an authentic sample.[4a] Treatment of **5** (5 mg) with 1% 2,4-dinitrophenylhydrazine in 2 N HCl–EtOH (2: 1) gave reddish needles (from acetone–EtOH), mp 129.5—132.5° (6 mg). This compound was identical with the di-2,4-dinitrophenylhydrazone of **5** on direct comparison (^{1}H-NMR and mixed mp).

Preparation of 6——Anhydrous CuSO$_4$ (80 mg) and 0.25% H$_2$SO$_4$ (in acetone) (0.05 ml) were added to a solution of **3** (11 mg) in dry acetone (4 ml). The reaction mixture was stirred at 22° for 3 hr, then diluted with H$_2$O (20 ml) and extracted with ether (15 ml × 3). The combined ethereal extract was washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated to dryness. The residue was purified by PLC [benzene–ether

(4: 1)] to give **6** as a white amorphous powder, $[\alpha]_D^{22}$ $-135°$ ($c=0.615$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1619, 1599 (aromatic). MS, m/z (%): 472 [$C_{26}H_{32}O_8$(M^+), 93], 457 (M^+-CH_3, 100), 414 (10), 343 (43).

Hydrolysis of 2——A solution of **2** (27 mg) in 3% KOH–EtOH (1 ml) was kept at 50° for 1.5 hr, then the reaction mixture was treated as described for the hydrolysis of **1** to give a diol and an acid. The former was obtained as colorless needles (17 mg), mp 113.5—116°, $[\alpha]_D^{24}$ $-96.7°$ ($c=1.62$, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 64.10; H, 6.60. This compound was identified as **3** by direct comparison with an authentic sample (IR, $[\alpha]_D$ and mixed mp). The latter was sublimed (70°, 15 mmHg) to give a colorless oil (1 mg). The presence of angelic acid and tiglic acid in this sublimate in a ratio of 3: 1 was demonstrated by GLC.(6) GLC conditions were the same as in the case of **1**; angelic acid, t_R(min), 6.5; tiglic acid, t_R(min), 8.4.

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