A New Coumarin and Carbazole Alkaloid from *Clausena vestita* D. D. TAO

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Phytochemical investigation of the EtOH extract of *Clausena vestita* D. D. TAO led to the isolation of one new coumarin, clauslactone U (**1**), and one new carbazole alkaloid, clauszoline N (**2**), together with 28 known compounds. The structures of these compounds were established by using MS and 1D- and 2D-NMR techniques, and by comparison with known analogues.

Introduction. – The genus *Clausena* belongs to the tribe Clauseneae of the Rutaceae subfamily Aurantioideae, and it was reported that this genus comprises 15 species and six varieties [1]. The plants are shrubs or small trees mainly distributed in south and southeast Asia [1–4]. Plants of the genus *Clausena* have been extensively subjected to phytochemical investigations [1–23]. In addition, various biological activities have been demonstrated, such as antimycobacterial [2], antifungal [2], antiplatelet [5][6], antitumor [7], antiplasmodial [8], antimicrobial [9], antituberculosis [24], and anti-HIV activities [25]. *Clausena vestita* D. D. TAO is an endemic species of China distributed in Yunnan Province. It can be found in dry and hot valleys and bushy places. To the best of our knowledge, no chemical study has been performed on this plant.

In the present study, the fractionation of the EtOH extract of *Clausena vestita* led to the isolation of one new coumarin (**1**), named clauslactone U, and one new carbazole alkaloid (**2**), named clauszoline N, together with 28 known compounds. Herein, we describe the isolation and structure elucidation of two new compounds (*Fig. 1*).

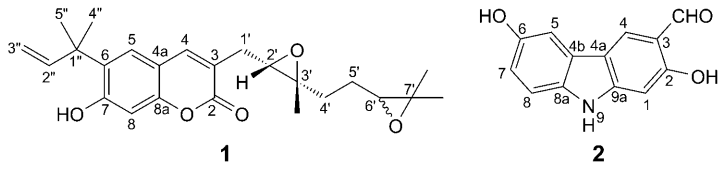

Fig. 1. *Chemical structures of compounds* **1** *and* **2**

Results and Discussion. – Clauslactone U (**1**) was obtained as colorless needles, and the molecular formula was determined to be $C_{24}H_{30}O_5$ by HR-EI-MS (M^+ at m/z 398.2091; calc. 398.2093). The IR absorption at 3435 cm^{-1} showed the presence of a OH

group. In the ^{1}H- and ^{13}C-NMR spectra (*Table 1*), a set of three aromatic H-atom *singlet* signals at δ(H) 6.68, 7.16, and 7.46 coupled with eight sp^2 C-atom signals at δ(C) 97.1, 112.9, 123.1, 124.3, 130.6, 138.0, 154.6, and 160.2, and one COO signal at δ(C) 162.6 were observed. These data suggested the presence of a 3,6,7-trisubstituted coumarin skeleton [10]. In the ^{1}H-NMR spectrum, a *singlet* signal at δ(H) 1.45 corresponding to two equivalent Me groups and an isolated *ABX* type signal at δ(H) 6.15 (*dd*, $J = 11.3$, 17.0), 5.07 (*d*, $J = 10.5$), 5.06 (*d*, $J = 18.0$) were assigned to a 1,1-dimethylallyl moiety [10]. To confirm the location of the linkage of this side chain, a HMBC experiment was used (*Fig. 2*). The observed HMBCs of H–C(5) with C(6) and C(1″), and of Me(4″,5″) with C(1″) and C(6) supported a C–C linkage between C(1″) and C(6) on the coumarin nucleus. Analysis of the ^{1}H- and ^{13}C-NMR spectra, including HSQC, coupled with biogenetic considerations, suggested the presence of a C_{10} terpenoid side chain with two trisubstituted oxirane rings in the molecule. The ^{1}H-NMR chemical shifts of the 3-H *singlet* (*Me*–C(3′)) and the CH double *doublet* (H–C(2′)) coupled with ^{13}C-chemical shifts of C(2′) and a fully substituted C-atom C(3′), and the ^{1}H-chemical shifts of two 3 H-*singlet*s (*Me*$_2$–C(7′)) and the CH double *doublet* (H–C(6′)) coupled with ^{13}C-chemical shifts of C(6′) and a fully substituted C-atom C(7′) suggested the presence of two trisubstituted oxirane rings, respectively. The connectivity of these signals was elucidated by HMBCs of H–C(2′) with C(3′) and *Me*–C(3′), of H–C(6′) with *Me*$_a$–C(7′), *Me*$_b$–C(7′), and C(7′). The HMBCs of CH_2(1′) with C(2′) and C(3′), of C(3′) with CH_2(4′) and CH_2(5′), of C(6′) with CH_2(4′) and CH_2(5′), and of CH_2(4′) with C(5′) suggested that CH_2(1′) was connected to C(2′), and the two trisubstituted oxirane rings were connected *via* two CH_2 groups (C(4′), C(5′)), respectively. The location of the linkage of the C_{10} terpenoid side chain at C(3) on the coumarin nucleus was revealed by observation of HMBCs of H–C(1′) with C(4) and C(2). Similarly, HMBCs of H–C(8) with C(4a), C(8a), and C(2) revealed that the OH group was attached to C(7). All these data led to the assignment of the constitutional formula of compound **1**.

The relative configuration of C(2′) and C(3′) was deduced as (*S**) and (*R**), respectively, by the interaction of H–C(2′)/*Me*–C(3′) observed in the ROESY

Table 1. *^{1}H- and ^{13}C-NMR Data of Clauslactone U* (**1**). In $CDCl_3$; at 300 (^{1}H) and 100 MHz (^{13}C), resp.; δ in ppm, *J* in Hz.

	δ(H)	δ(C)		δ(H)	δ(C)
C(2)		162.6	*Me*–C(3′)	1.20 (*s*)	22.6
C(3)		112.9	H–C(4′)	1.85–1.92 (*m*)	26.2
H–C(4)	7.16 (*s*)	123.1	H$_a$–C(5′)	1.96–2.04 (*m*)	33.8
C(4a)		124.3	H$_b$–C(5′)	1.73–1.80 (*m*)	
H–C(5)	7.46 (*s*)	138.0	H–C(6′)	3.89 (*dd*, $J = 6.8$, 8.1)	87.2
C(6)		130.6	C(7′)		70.6
HO–C(7)		160.2	*Me*$_a$–C(7′)	1.22 (*s*)	27.5
H–C(8)	6.68 (*s*)	97.1	*Me*$_b$–C(7′)	1.13 (*s*)	24.0
C(8a)		154.6	C(1″)		40.2
H$_a$–C(1′)	3.23 (*dd*, $J = 9.5$, 16.2)	30.5	H–C(2″)	6.15 (*dd*, $J = 11.3$, 17.0)	145.6
H$_b$–C(1′)	3.06 (*dd*, $J = 7.8$, 15.9)		H$_a$–C(3″)	5.07 (*d*, $J = 10.5$)	12.0
H–C(2′)	4.84 (*dd*, $J = 8.1$, 9.3)	89.4	H$_b$–C(3″)	5.06 (*d*, $J = 18.0$)	
C(3′)		84.0	Me(4″,5″)	1.45 (*s*)	26.0

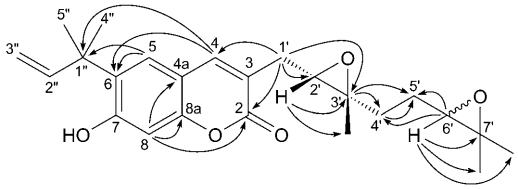

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Fig. 2. *Key HMBCs for compound* **1**

spectrum of compound **1**. In respect that the two oxirane rings were linked *via* an acyclic C-atom chain, the relative configuration of C(6′) remained uncertain.

Clauszoline N (**2**) was obtained as a yellow powder and the molecular formula was determined to be $C_{13}H_9NO_3$ by a HR-EI-MS peak at *m/z* 227.0580 (calc. 227.0582). Based on the analysis of the IR, ^{1}H- and ^{13}C-NMR spectra (*Table 2*), compound **2** was recognized as a carbazole alkaloid. The IR spectrum showed the presence of NH (3317 cm^{-1}), OH (3375 cm^{-1}), and conjugated C=O (1647 cm^{-1}) functions, which were also observed in the ^{1}H- and ^{13}C-NMR spectra (δ(H) 11.23 (*s*, NH), 10.97 (*s*, OH), 9.06 (br. *s*, OH), 10.07 (*s*, CHO), and δ(C) 192.8 (CHO)). In the ^{1}H-NMR spectrum, two different benzene rings could be observed, one with a set of two *singlet*s at δ(H) 6.77 and 8.33, suggesting the presence of two substituents in the first benzene ring attached to C(2) and C(3), the other with a set of *ABX*-type signals at δ(H) 6.82 (*dd*, $J = 2.4$, 8.4), 7.21 (*d*, $J = 8.4$), and 7.36 (*d*, $J = 2.4$), suggesting the presence of one substituent in the second benzene ring attached to either C(6) or C(7). The sites of linkage of all the substituents were determined according to the ROESY, HSQC, and HMBC experiments. In the ROESY spectrum (*Fig. 3*), correlations of the NH H-atom at δ(H) 11.23 with the H-atoms at δ(H) 6.77 and 7.21, and the OH group at δ(H) 10.97 with the H-atoms at δ(H) 6.77 and 10.07 suggested that the OH group at δ(H) 10.97 was attached to C(2) and the aldehyde group at δ(H) 10.07 was attached to C(3). Similarly, the

Table 2. *^{1}H- and ^{13}C-NMR Data of Clauszoline N* (**2**). In (D_6)DMSO; at 300 (^{1}H) and 100 MHz (^{13}C), resp.; δ in ppm, *J* in Hz.

	δ(H)	δ(C)
H–C(1)	6.77 (*s*)	95.9
HO–C(2)	10.97 (*s*)	159.7
C(3)		115.2
CHO	10.07 (*s*)	192.8
H–C(4)	8.33 (*s*)	125.0
C(4a)		146.2
C(4b)		116.9
H–C(5)	7.36 (*d*, $J = 2.4$)	105.1
HO–C(6)	9.06 (br. *s*)	151.6
H–C(7)	6.82 (*dd*, $J = 2.4$, 8.4)	114.4
H–C(8)	7.21 (*d*, $J = 8.4$)	111.5
C(8a)		134.3
H–N(9)	11.23 (*s*)	
C(9a)		123.7

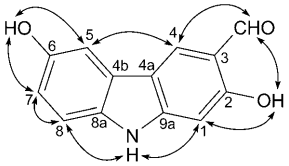

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Fig. 3. *ROESY Correlations for compound* **2**

correlation of the H-atom at δ(H) 7.36 with the H-atom at δ(H) 8.33 and the OH group at δ(H) 9.06 suggested that the OH group at δ(H) 9.06 was attached to C(6). This assumption was confirmed by the ^{1}H,^{13}C long-range correlations from the OH group at δ(H) 10.97 to C(1), C(2), and C(3), from the aldehyde H-atom at δ(H) 10.07 to C(2), C(3), and C(4), and from the OH group at δ(H) 9.06 to C(5), C(6), and C(7). Consequently, these results determined the structure of the compound **2** to be 2,6-dihydroxy-9*H*-carbazole-3-carbaldehyde.

The structures of the additional 28 known compounds 1-allyl-3,5-dimethoxybenzene [26], (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde [27], grinimibine [11], dictamine [12], γ-fagarine [24], 4-methoxy-1-methylquinolin-2-one [13], 4-methoxy-3-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one [14], clausine-P [15], methyl carbazole-3-carboxylate [7][16], 3-formyl-2-hydroxy-7-methoxycarbazole [17], mukonidine [5], mukonal [6], methyl 6-methoxycarbazole-3-carboxylate [16], clauszoline-K [17], carbalexin B [18], 3-formyl-2,7-dihydroxy-1-(3′-methylbut-2′-en-1′-yl)carbazole [19], 2-hydroxy-3-methylcarbazole [6], 2,3-dimethoxycarbazole [28], 7-hydroxy-1-methoxy-3-methylcarbazole [29], 7-methoxy-*O*-methylmukonal [25], clauszoline-C (clausine-H) [20], caluszoline-I [6][7], clauszoline-M [17], clausine-O [21], clauszoline-J (clausine-K) [15], clausine-Z [22], clausenolid [21], and eleutheroside E_2 [23] were established by using MS and 1D- and 2D-NMR techniques, and by comparison with reference values.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; *Qingdao Haiyang Chemical Group Co.*, 100–200 and 200–300 mesh), *Sephadex LH-20* (*Pharmacia Fine Chemical Co.*), *RP-18* (0.015–0.040 mm, *Merck*). Thin-layer chromatography (TLC): silica gel GF_{254} (*Qingdao Marine Chemical Factory*) and *RP-18* F_{254} plates (*Merck*); detection under UV light and visualized by spraying with 10% H_2SO_4 in EtOH (*v*/*v*), followed by heating. Optical rotations: *Perkin-Elmer M341* polarimeter. M.p.: *Fisher-Johns* melting point apparatus; uncorrected. IR Spectra: *Nicolet Magna 750 FT-IR* spectrophotometer with KBr discs; in cm^{-1}. NMR Spectra: *Varian Mercury* NMR spectrometer, at 300 Hz for ^{1}H and 100 Hz for ^{13}C; with TMS as standard, chemical shifts δ in ppm and coupling constants *J* in Hz. EI- and HR-EI-MS: *Finnigan*/*MAT-95* spectrometer; in *m*/*z* (rel. %).

Plant Material. The whole plants of *Clausena vestita* were collected in the Yunnan Province, P. R. China, in July 2008 and identified by Prof. *Jin-Gui Shen* of the Shanghai Institute of Materia Medica, and a voucher specimen (SIMM 20080716) was deposited with the Herbarium of Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, CAS, P. R. China.

Extraction and Isolation. The air-dried whole plants *Clausena vestita* (3.5 kg) were chopped into pieces and extracted with 95% EtOH (5 × 10 l, 2 h each). After removing the solvents by evaporation under reduced pressure, 130 g of crude extract was obtained. This extract was then chromatographed on a

SiO_2 column (100–200 mesh, 3 kg, 58 × 14 cm) eluted with $CHCl_3$/MeOH 40:1, 20:1, 10:1, 5:1 and $CHCl_3$/MeOH/H_2O 1:1:2. A total of 268 sub-fractions (*ca.* 500 ml each) were collected and combined on the basis of TLC analysis, leading to seven main fractions (*F1–F7*).

F1 (1.757 g) was chromatographed over a SiO_2 column (200–300 mesh, 34 × 3 cm) eluted with petroleum ether (PE)/acetone gradients (100:1, 50:1, 20:1, 10:1) to give four sub-fractions (*F1a–F1d*). *F1a* (600 mg) was purified by *Sephadex LH-20* column (70 g, 100 × 2 cm, MeOH) to afford 1-allyl-3,5-dimethoxybenzene [26] (171 mg). Treated in the same manner as *F1a*, grinimibine [11] (37 mg) was isolated from *F1c* (126 mg), and clausine-P [15] (4 mg) and (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde [27] (1 mg) were isolated from *F1d* (77 mg).

F2 (1.180 g) was chromatographed over a SiO_2 column (200–300 mesh, 52 × 4 cm) eluted with PE/acetone gradients (10:1, 9:1, 8:1, 5:1) to yield methyl carbazole-3-carboxylate [7][16] (10 mg).

F3 (9.832 g) was chromatographed over a SiO_2 column (200–300 mesh, 43 × 4 cm) eluted with PE/acetone gradients (10:1, 9:1, 7.5:1, 6:1, 5:1, 4:1) to give eleven sub-fractions (*F3a–F3k*). 3-Formyl-2-hydroxy-7-methoxycarbazole [17] (131 mg) was obtained by direct crystallization in PE/acetone from *F3a*. *F3c* (440 mg) was purified by *Sephadex LH-20* CC (70 g, 100 × 2 cm, MeOH) to afford mukonidine [5] (4 mg). Treated in the same manner as *F3c*, dictamine [12] (48 mg) and mukonal [6] (21 mg) were isolated from *F3d* (200 mg). Compound **1** (171 mg) and methyl 6-methoxycarbazole-3-carboxylate [16] (20 mg) were isolated from *F3e* (1.722 g). Clauszoline-K [17] (13 mg) was isolated from *F3f* (190 mg). Carbalexin B [18] (10 mg), 3-formyl-2,7-dihydroxy-1-(3′-methylbut-2′-en-1′-yl)carbazole [19] (14 mg), and 2-hydroxy-3-methylcarbazole [6] (10 mg) were isolated from *F3g* (147 mg). 3-Formyl-2,7-dihydroxy-1-(3′-methylbut-2′-en-1′-yl)carbazole [19] (9 mg) was also isolated from *F3h* (60 mg). γ-Fagarine [24] (10 mg), 2,3-dimethoxycarbazole [28] (6 mg), and 7-hydroxy-1-methoxy-3-methylcarbazole [29] (6 mg) were isolated from *F3i* (103 mg). 7-Methoxy-*O*-methylmukonal [25] (10 mg) and 4-methoxy-1-methylquinolin-2-one [13] (16 mg) were isolated from *F3j* (200 mg). *F3k* (210 mg) was further chromatographed over a SiO_2 column (200–300 mesh, 36 × 2 cm) with PE/acetone 6:1 to give a crude compound, which then was applied to *Sephadex LH-20* (30 mg, 36 × 2 cm) with $CHCl_3$/MeOH 1:1 to afford clauszoline-J (clausine-K) [15] (52 mg).

F4 (3.8 g) was chromatographed over a SiO_2 column (200–300 mesh, 43 × 4 cm) eluted with PE/acetone gradients (10:1, 9:1, 8:1, 7:1, 6:1, 4:1, 1:1) to give six sub-fractions, *F4a–F4f*. *F4a* (122 mg) was purified by *Sephadex LH-20* (30 g, 36 × 2 cm) eluted with $CHCl_3$/MeOH 1:1 to afford 4-methoxy-3-(3-methylbut-2-en-1-yl)-2*H*-chromen-2-one [14] (26 mg). *F4d* (157 mg), treated in the same manner as *F4a*, afforded caluszoline-I [6][7] (83 mg) and clauszoline-M [17] (2 mg).

F5 (4.867 g) was chromatographed over a SiO_2 column (200–300 mesh, 43 × 4 cm) eluted with PE/acetone gradients (6.5:1 to 1:1, with increasing polarity by an acetone 2% gradient) to give eight sub-fractions, *F5a–F5h*. *F5b* (285 mg) was further chromatographed over a SiO_2 column (200–300 mesh, 36 × 2 cm) with PE/acetone 4:1 to give clausenolid [21] (43 mg). *F5c* (178 mg) was further chromatographed over a SiO_2 column (200–300 mesh, 36 × 2 cm) eluted with PE/AcOEt gradients (3.5:1, 2.5:1, 2:1) to afford caluszoline-I [6][7] (30 mg). *F5e* (600 mg) was further chromatographed over SiO_2 column (200–300 mesh, 34 × 3 cm) with PE/AcOEt 2.5:1 to afford compound **2** (12 mg) and clausine-O [21] (9 mg). *F5h* (244 mg) was further chromatographed over a SiO_2 column (200–300 mesh, 34 × 3 cm) with $CHCl_3$/MeOH 35:1 to afford clauszoline-J (clausine-K) [15] (30 mg).

F6 (4.012 g) was chromatographed over SiO_2 (200–300 mesh, 43 × 4 cm) with $CHCl_3$/MeOH 20:1 and then further applied to *Sephadex LH-20* (30 g, 36 × 2 cm) to afford clausine-Z [22] (84 mg).

F7 (6.033 g) was chromatographed over a SiO_2 column (200–300 mesh, 43 × 4 cm) with $CHCl_3$/MeOH 12:1 to give one main sub-fraction. Then, it was rechromatographed on a *RP-18* column (70 g, 23 × 3 cm) eluted with H_2O/MeOH (90:10 to 30:70, with decreasing polarity by a MeOH 5% gradient) to afford eleutheroside E_2 [23] (23 mg).

Clauslactone U (=*2,3:6,7-Dianhydro-1,4,5-trideoxy-1-[7-hydroxy-6-(2-methylbut-3-en-2-yl)-2-oxo-2*H*-chromen-3-yl]-3,7,7-trimethyl*-D-erythro-*heptitol*; **1**). Colorless needles. M.p. 129–130°. $[\alpha]_D^{23} = 19.5$ ($c = 1.00$, MeOH). IR (KBr) 3435, 2972, 2872, 1707, 1626, 1579, 1485, 1375, 1269, 1163, 1128, 989, 785. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 398 (12, M^+), 383 (2), 255 (5), 143 (100), 125 (25), 107 (3), 85 (13), 59 (4). HR-EI-MS: 398.2091 (M^+, $C_{24}H_{30}O_5^+$; calc. 398.2093).

Clauszoline N (=*2,6-Dihydroxy-9*H-*carbazole-3-carbaldehyde*; **2**). Yellow powder. IR (KBr) 3375, 3317, 1647, 1630, 1358, 1217, 1142, 793. ^{1}H- and ^{13}C-NMR: see *Table 2.* EI-MS: 227 (100, M^+), 226 (53), 198 (11), 170 (12). HR-EI-MS: 227.0580 (M^+, $C_{13}H_9NO_3^+$; calc. 227.0582).

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