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ALKALOIDS FROM *MELODINUS SUAVEOLENS*

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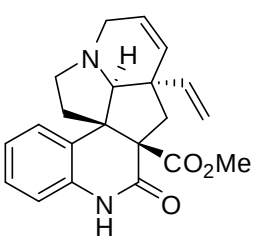
Abstract – Two new quinoline alkaloids, 14,15-*β*-epoxyscandine (**3**) and meloscine *N*-oxide (**6**), along with six known alkaloids scandine (**1**), scandine *N*-oxide (**2**), meloscandonine (**4**), meloscine (**5**), tubotaiwine (**7**), polyneuridine (**8**) were isolated from the twigs and leaves of *Melodinus suaveolens*. The structures of the new compounds were elucidated on the basis of spectroscopic methods and circular dichroism experiments.

The genus *Melodinus* (Apocynaceae) comprises 53 species mainly distributed in tropical or subtropical Asia and Australia.[1] This genus has been regarded as a rich source of monoterpenoid indole alkaloids, which originate from the condensation of tryptophan with secologanin.[2] Up to now, more than 100 monomeric and dimeric indole alkaloids as well as quinoline alkaloids have been isolated from *Melodinus* sp. The interesting chemical significance of the *Melodinus* plants prompted us to initiate a phytochemical study on the twigs and leaves of *Melodinus suaveolens*, which led to the isolation of two new quinoline alkaloids, 14,15-*β*-epoxyscandine (**3**) and meloscine *N*-oxide (**6**), along with six known alkaloids scandine (**1**),[3] scandine N-oxide (**2**),[3] meloscandonine (**4**),[4] meloscine (**5**),[5] tubotaiwine (**7**),[6] and polyneuridine (**8**).[7]



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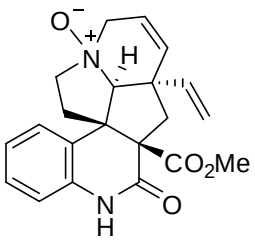

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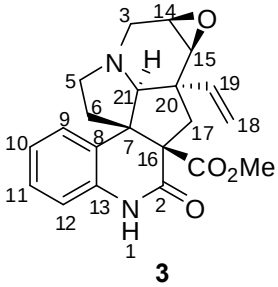

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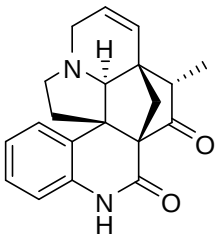

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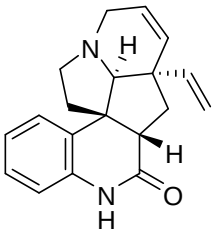

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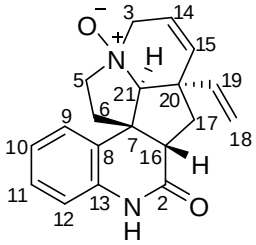

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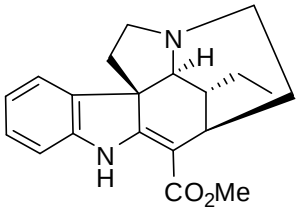

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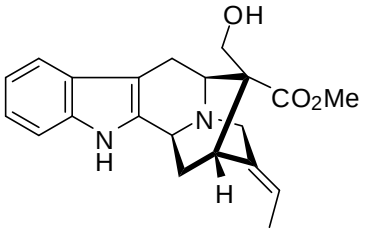

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14,15-*β*-Epoxyscandine (**3**) was obtained as yellow oil. The molecular formula of **3** was established to be $C_{21}H_{22}N_2O_4$ by its HR-ESI-MS (*m/z* 367.1648 $[M+H]^+$, calcd for $C_{21}H_{23}N_2O_4$, 367.1652). The IR spectrum of **3** suggested the presence of NH (3456 cm^{-1}), carbonyl (1744, 1663 cm^{-1}) and aromatic ring (1596, 1498 cm^{-1}). The UV spectrum showed absorption maxima at 341, 326, 287, 257 and 214 nm, suggesting that **3** was a quinoline alkaloid. The ^1H NMR spectrum of **3** displayed signals for an *ortho*-disubstituted phenyl ring [δ_H 7.30 (1H, dd, J = 7.9, 1.3 Hz, H-9), 7.12 (1H, td, J = 7.9, 1.3 Hz, H-11), 7.03 (1H, td, J = 7.9, 1.3 Hz, H-10), and 6.74 (1H, dd, J = 7.9, 1.3 Hz, H-12)], a terminal double bond [δ_H 5.63 (1H, dd, J = 17.8, 11.1 Hz, H-19), 4.93 (1H, d, J = 17.8 Hz, H-18a) and 4.92 (1H, d, J = 11.1 Hz, H-18b)], and a methoxyl group [δ_H 3.63 (3H, s, CO_2Me)]. The ^{13}C NMR spectrum showed twenty-one carbon signals, including two carbonyls, eight olefinic carbons, three quaternary carbons, one methoxyl, three methines and four methylenes. With the aid of ^1H-^1H COSY, HSQC and HMBC experiments, the ^1H and ^{13}C NMR signals of **3** were assigned as shown in Table 1.

Comparison of the NMR data of **3** with those of the known compound scandine (**1**)[3] revealed their structural similarity, except for an epoxy group [δ_C 58.2, 55.5; δ_H 3.48 (1H, m), 3.03 (1H, d, J = 3.7 Hz)] instead of a double bond [δ_C 132.7, 124.2; δ_H 5.72 (1H, m, H-14), 5.65 (1H, overlapped, H-15)]. The ^1H-^1H COSY spectrum of **3** revealed the presence of the spin system (C-3 to C-15) and the HMBC cross peaks between H-3*α*/H-3*β*/H-15/H-19/H-17*α*/H-17*β* and C-21 indicated that epoxy group was located at C-14 and C-15 (Figure 1). Based on the above evidence, the planar structure of **3** was elucidated as 14,15-epoxyscandine.[4] However, the relative configuration of the epoxy group was not clearly defined in the previous work. In this paper, the relative stereochemistry of **3** was deduced by a ROESY experiment,

in which correlations between H-19 and H-15/H-21 suggested that these protons had the same orientation. Furthermore, the CD spectrum of **3** showed the same Cotton effects as scandine (**1**) (Figure 2), indicating the presence of *S*, *R*, *R*, *R* configurations at C-7, C-16, C-20 and C-21, respectively. Thus, the structure of **3** was elucidated as 14,15-*β*-epoxyscandine.

Table 1. NMR Data of Compounds **3** and **6** (CD_3OD, δ in ppm, J in Hz) [a]

		3[b]			**6**[c]	
No		δ_H	δ_C		δ_H	δ_C
2			170.8			171.3
3	*β*	3.43 dd (12.8, 5.7)	50.4	*β*	4.05 dd (14.9, 6.6)	61.4
	α	2.59 d (12.8)		*α*	3.89 m	
5	*β*	3.09 dd (8.0, 8.0)	54.9	*α*	3.99	68.1
	α	2.69 m		*β*	3.32	
6	*α*	2.18 dd (13.6, 5.7)	44.8	*α*	2.51 m	38.4
	β	1.93 m		*β*	2.20	
7			58.2			59.0
8			129.9			125.9
9		7.30 dd (7.9, 1.3)	129.1		7.90 dd (7.7, 1.4)	129.7
10		7.03 td (7.9, 1.3)	124.8		7.17 td (7.7, 1.3)	125.6
11		7.12 td (7.9, 1.3)	128.6		7.24 td (7.7, 1.4)	129.8
12		6.74 dd (7.9, 1.3)	116.5		6.90 dd (7.7, 1.3)	117.0
13			135.8			136.6
14		3.48 m	55.5		6.21 m	125.7
15		3.03 d (3.7)	58.2		6.08 dd (9.8, 2.8)	136.4
16			66.1		2.75 dd (13.7, 5.5)	49.2
17	*β*	3.13 d (12.9)	41.6	*β*	2.23	44.5
	α	2.64 dd (12.9, 1.2)		*α*	1.93 dd (13.7, 12.8)	
18	a	4.93 d (17.8)	117.8	a	5.16 d (17.2)	114.6
	b	4.92 d (11.1)		b	5.04 d (10.4)	
19		5.63 dd (17.8, 11.1)	140.0		5.79 dd (17.2, 10.4)	141.2
20			49.6			52.7
21		2.61 s	83.9		4.48 s	98.3
CO_2Me			172.3			
CO_2*Me*		3.63 s	53.0			

[a] Overlapped signals were reported without designating multiplicity.
[b] Measured at 600 MHz. [c] Measured at 400 MHz.

Meloscine *N*-oxide (**6**) was isolated as yellow oil with a molecular formula of $C_{19}H_{20}N_2O_2$, as determined by the HR-ESI-MS at *m/z* 309.1597 $[M+H]^+$ (calcd for $C_{19}H_{21}N_2O_2$, 309.1598). The IR and UV spectra of

6 were similar to those of **3**, suggesting that **6** was also a quinoline alkaloid. The ^{1}H NMR spectrum of **6** showed signals for an *ortho*-disubstituted phenyl ring [δ_H 7.90 (1H, dd, J = 7.7, 1.4 Hz, H-9), 7.24 (1H, td, J = 7.7, 1.4 Hz, H-11), 7.17 (1H, td, J = 7.7, 1.3 Hz, H-10), 6.91 (1H, dd, J = 7.7, 1.3 Hz, H-12)], a double bond [δ_H 6.21 (1H, m, H-14) and 6.08 (1H, dd, J = 9.8, 2.8 Hz, H-15)], and a terminal double bond [δ_H 5.79 (1H, dd, J = 17.2, 10.4 Hz, H-19), 5.16 (1H, d, J = 17.2 Hz, H-18a) and 5.04 (1H, d, J = 10.4 Hz, H-18b)]. The ^{13}C NMR spectrum displayed nineteen carbon signals, including one carbonyl, ten olefinic carbons, two quaternary carbons, two methines and four methylenes. Detailed examination of 1D and 2D NMR spectra of **6** and comparison with those of the known compound meloscine (**5**)[5] revealed that **6** was the N-oxide of compound **5**, in particular the characteristic downfield shifts of the C-21 [δ_c 98.3; δ_H 4.48 (1H, s)] in **6**. In the HMBC spectrum, the correlations between H-3α/H-3β/H-5α/H-5β/H-15/H-19/H-17α/H-17β and C-21 further confirmed the oxidation of N_4 (Figure 1). In the ROESY spectrum, correlations between H-9 and H-6α/H-21 suggested that H-6α and H-21 were α-oriented, whereas the correlations H-16 and H-6β/H-17β suggested that H-16 was β-oriented. Furthermore, H-19, H-17α and H-21 were assigned on the same side on the basis of the ROESY correlations among them. The absolute configuration of **6** was identical to that of meloscine **(5)**, since they showed similar Cotton effects in the CD measurement (Figure 2). Accordingly, the structure of **6** was determined as meloscine *N*-oxide.

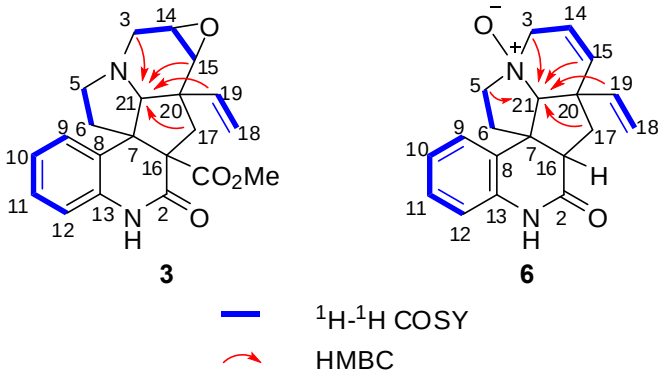

Figure 1. Key ^{1}H-^{1}H COSY and HMBC correlations of **3** and **6**

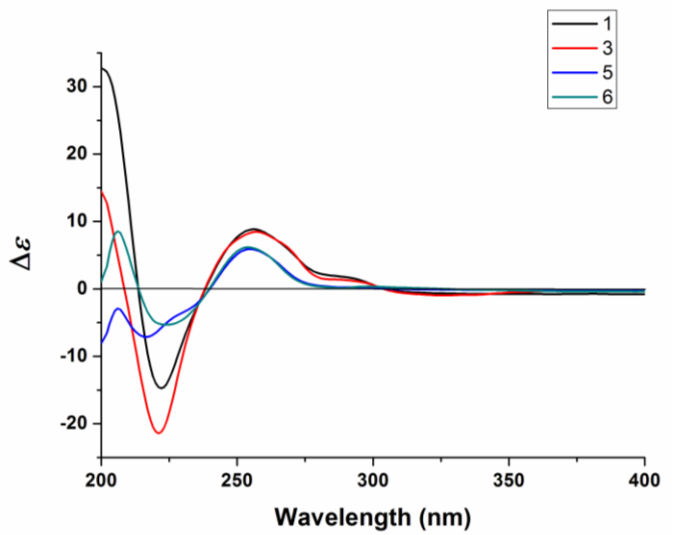

Figure 2. CD spectra of compounds **1**, **3**, **5** and **6**

The structures of the known compounds were identified by the comparison of their spectroscopic data (UV, IR, ^{1}H NMR, ^{13}C NMR, MS) with the data from the corresponding values in the literature as scandine (**1**),[3] scandine *N*-oxide (**2**),[3] meloscandonine (**4**),[4] meloscine (**5**),[5] tubotaiwine (**7**),[6] and polyneuridine (**8**),[7] respectively.

EXPERIMENTAL

General experimental procedures: Optical rotations were carried out using a Jasco P-1020 digital polarimeter. UV spectra were measured on a Jasco V-550 UV/VIS spectrophotometer with a 1 cm length cell. IR spectra were recorded on a Bruker Equinox 55 infrared spectrometer with KBr disc. CD spectra were measured on a Chirascan spectrometer (Applied Photophysics Ltd) at 25 ºC for 200-400 nm with a quartz cell of path length 1 cm. HR-ESI-MS data were measured on an Agilent 6210 ESI/TOF mass spectrometer. NMR experiments were performed on Bruker AV-400 and AV-600 spectrometers. Column chromatography (CC) were performed on silica gel (200-300 mesh; Qingdao Marine Chemical Inc., Qingdao, China) and ODS (YMC, Kyoto, Japan), respectively. Preparative high-performance liquid chromatography (HPLC) was carried on a Agilent 1260 system equipped with a G1310B Iso pump, a G1365D MWD VL detector and a CAPCELL PAK MGII C_{18} reversed-phase column (20×250 mm, 5 μm, Shiseido Fine Chemicals Ltd, Japan).

Plant material: The leaves and twigs of *M. suaveolens* were collected in Jinxiu, a Yao Autonomous County of Guangxi Province of China, in September 2010, and authenticated by Dr. Jing-Quan Yuan (Guangxi Medicinal Herb Garden). A voucher specimen (No. CP2010093001) is deposited in the herbarium of the College of Pharmacy, Jinan University, Guangzhou, China.

Extraction and isolation: The air-dry leaves and twigs (18 kg) of *M. suaveolens* was powdered and extracted with 95% EtOH (50 L) three times at room temperature, and the solution was concentrated under reduced pressure to afford a brownish residue (1700 g), which was suspended in water, and then successively partitioned with petroleum ether, EtOAc and *n*-BuOH, respectively. The EtOAc extract (326 g) was subjected to a silica gel column with gradient $CHCl_3$-MeOH (100:0□0:100) to afford 9 fractions (Fr-E1~Fr-E9). Fraction E2 was then subjected to sephadex LH-20 ($CHCl_3$-MeOH, 1:1) and ODS (MeOH-H_2O, 30:90→90:10) column chromatography (CC) to yield **1** (17.5 mg) and **8** (2.3 mg). The *n*-BuOH extract (306 g) was subjected to a silica gel column with gradient $CHCl_3$-MeOH (100:0→0:100) to afford 11 fractions (Fr-B1~Fr-B11). Fraction B3 was further separated on silica gel column eluting with $CHCl_3$-MeOH (100:1→90:10), followed by HPLC (MeOH-H_2O+0.1‰ Et_2NH, 65:35) to afford **3** (2.4 mg), **4** (3.2 mg) and **5** (13.5 mg). The Fr-B5 was purified by Sephadex LH-20 column ($CHCl_3$-MeOH, 1:1) and HPLC (MeOH-H_2O+0.1‰ Et_2NH, 60:40) to afford **2** (2.4 mg), **6** (2.5 mg) and **7** (2.7 mg).

14,15-*β*-Epoxyscandine (3). Yellow oil; $[\alpha]_D^{25}$ +109.8° (*c* 0.9, MeOH); UV λ_{max}^{MeOH} (log ε): 341 (3.38), 326 (3.43), 287 (3.74), 257 (4.12), 214 (4.56) nm; CD (MeOH, $\Delta\varepsilon$) λ_{max} 257 (+8.5), 221 (−21.4) nm; IR ν_{max}^{KBr}: 3456, 2924, 1744, 1663, 1634, 1596, 1498, 1384, 1235, 1115, 756 cm^{-1}; HR-ESI-MS *m*/*z* 367.1648 $[M+H]^+$ (calcd for $C_{21}H_{23}N_2O_4$, 367.1652).

Meloscine *N*-oxide (6). Yellow oil; $[\alpha]_D^{25}$ +128.6° (MeOH, *c* 0.6); UV λ_{max}^{MeOH} (log ε): 252 (4.40), 210 (3.91) nm; CD (MeOH, $\Delta\varepsilon$) λ_{max} 254 (+6.2), 224 (−5.3) nm; IR ν_{max}^{KBr}: 3455, 2923, 1665, 1594, 1491, 1384, 763 cm^{-1}; HR-ESI-MS *m/z* 309.1597 $[M+H]^+$ (calcd for $C_{19}H_{21}N_2O_2$, 309.1598).

ACKNOWLEDGEMENTS

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