A Novel Quinoline Alkaloid Possessing a 7-Benzyl Group from the Centipede, *Scolopendra subspinipes*

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The novel quinoline alkaloid scolopendrine was isolated from the centipede, *Scolopendra subspinipes mutilans* L. KOCH. The structure was determined to be 2-hydroxy-7-[(4-hydroxy-3-methoxyphenyl)methyl]-3-methoxy-8-quinolyl sulfate on the basis of high-resolution electron-spray ionization mass spectroscopy and two-dimensional NMR spectral data. Unlike quinoline alkaloids so far reported, scolopendrine is unique in having a 7-benzyl moiety in the quinoline ring.

Key words centipede; *Scolopendra subspinipes*; 7-benzyl quinoline alkaloid; scolopendrine

The centipede, *Scolopendra subspinipes mutilans* L. KOCH,[1] has been used in the traditional Chinese medicine Wu Gong prescribed for tetanus and childhood convulsions.[2] This drug has also been used for many other clinical purposes, such as the treatment of acute heart attack and as a toxicide, in Korea.[3] Concerning the constituents of this animal, only two compounds, 3,8-dihydroxyquinoline, called jineol,[4] and 8-hydroxy-1*H*-2-benzopyran-1-one,[3] have been recently isolated from the centipede by Korean researchers.

In our search for biologically active compounds from crude drugs, especially animal crude drugs originating from various species of invertebrates,[5] we investigated the constituents of this drug, and isolated a novel quinoline alkaloid with a benzyl group at the C-7 position, which is called scolopendrine.

The dried whole bodies (800 g) of centipedes (commercial crude drug) were extracted with MeOH, and the methanolic extract was shaken with $CHCl_3$–MeOH–H_2O (1 : 1 : 1) to give an upper and a lower fraction. The upper fraction was subjected to a combination of Diaion HP-20, Sephadex LH-20, silica gel column chromatography and HPLC separation to give scolopendrine (**1**, 24.6 mg).[6]

The molecular formula of **1** was determined to be $C_{18}H_{16}NO_8S$ using high-resolution electron-spray ionization mass spectroscopy (HR-ESI-MS) and its ^{13}C-NMR spectral data. The presence of one sulfate was substantiated by an IR absorption band at 1257 cm^{-1} and negative FAB-MS ion peaks at *m/z* 406 [M(SO_3^-)] and 326 [M$-SO_3$]$^-$. The ^{1}H-NMR spectrum showed signals due to two methoxyl (δ 3.79, 3.90) and one benzylic methylene groups (δ 4.14) together with six aromatic proton signals. All the proton and carbon signals arising from **1** were assigned with the aid of ^{1}H–^{1}H and ^{1}H–^{13}C chemical shift correlation spectroscopy (COSY) analyses. These assignments revealed that the two methoxyl and one benzyl moieties in addition to two hydroxyl and one sulfate groups were located at the C-2, C-3, C-7, C-8, C-3′, or C-4′ positions. In the ^{1}H-detected heteronuclear multiple-bond connectivity (HMBC) spectrum, the methoxyl protons (δ 3.90) gave a long-range correlation with the C-3 carbon (δ 149.4) and the other (δ 3.79) showed a correlation with the C-3′ carbon (δ 149.0). In addition, the methylene protons (δ 4.14) clearly showed long-range correlations with C-6, C-7, and C-8 as well as with C-1′, C-2′, and C-6′ (Fig. 1). These findings demonstrated that the benzyl moiety was located at C-7, and therefore the positions of the remaining two hydroxyl and one sulfate groups were determined to be C-2, C-8, or C-4′.

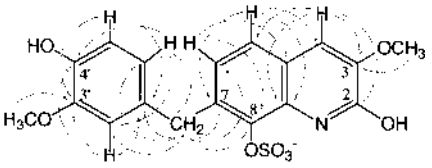

Fig. 1. HMBC Correlation of Scolopendrine (**1**)

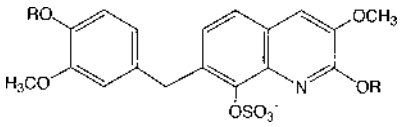

Fig. 2. Scolopendrine (**1**): R=H
2: R=CH_3

Treatment of **1** with diazomethane gave **2**.[7] In the ^{1}H-NMR spectrum of **2**, in addition to the signals ascribable to the 3- and 3′-methoxyl groups, two signals due to methoxyl groups appeared at δ 3.78 and 4.19. The locations of the latter two were revealed to be C-2 and C-4′ by HMBC analysis. From the information described above, the position of the sulfate group was concluded to be C-8, and thus the structure of scolopendrine (**1**) was determined to be 2-hydroxy-7-[(4-hydroxy-3-methoxyphenyl)methyl]-3-methoxy-8-quinolyl sulfate (Fig. 2).

With regard to C-substituted quinoline alkaloids, only 2-,[8] and 3-substituted[9] compounds have been reported. Scolopendrine (**1**) isolated in this study is the first example of a naturally occurring quinoline alkaloid with a 7-C substituted group. Since TLC examination of the upper fraction indicated the presence of several quinoline derivatives in addition to **1**, the isolation of these compounds is in progress.

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References and Notes

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6) Scolopendrine (**1**): Yellow powder, mp 192—194 °C. IR (KBr) cm^{-1}: 1257, 1043, 698. Negative ion FAB-MS *m/z*: 406 [$M(SO_3^-)$], 326 $[M-SO_3]^-$. HR-ESI-MS *m/z*: 406.0592 (Calcd for $C_{18}H_{16}NO_8S$: 406.0596). ^{1}H-NMR (CD_3OD) δ: 3.79 (3H, s, 3′-OCH_3), 3.90 (3H, s, 3-OCH_3), 4.14 (2H, s, CH_2), 6.70* (*J*=8.1 Hz, 5′-H), 6.71* (*J*=1.2, 8.1 Hz, 6′-H), 6.91 (d, *J*=1.2 Hz, 2′-H), 6.96 (d, *J*=8.1 Hz, 6-H), 7.22 (s, 4-H), 7.31 (d, *J*=8.1 Hz, 5-H). ^{13}C-NMR (CD_3OD) δ: 36.5 (CH_2), 56.4 (3-OCH_3), 56.6 (3′-OCH_3), 113.5 (4-C), 114.3 (2′-C), 116.0 (5′-C), 121.5 (4a-C), 122.9 (6′-C), 124.4 (5-C), 126.0 (6-C), 128.7 (8a-C), 133.5 (1′-C), 137.0 (7-C), 138.0 (8-C), 145.8 (4′-C), 149.0 (3′-C), 149.4 (3-C), 159.9 (2-C). Signals marked with asterisks appear as singlet-like signals of the AB type.
7) **2**: White powder, mp 204—206 °C. Negative ion FAB-MS *m/z*: 434 [$M(SO_3^-)$], 354 $[M-SO_3]^-$. ^{1}H-NMR (CD_3OD) δ: 3.76 (3H, s, 3′-OCH_3), 3.78 (3H, s, 4′-OCH_3), 3.91 (3H, s, 3-OCH_3), 4.19 (3H, s, 2-OCH_3), 4.31 (2H, s, CH_2), 6.84* (*J*=8.1 Hz, 5′-H), 6.85* (*J*=1.2, 8.1 Hz, 6′-H), 6.99 (d, *J*=1.2 Hz, 2′-H), 7.09 (d, *J*=8.1 Hz, 6-H), 7.38 (s, 4-H), 7.42 (d, *J*=8.1 Hz, 5-H). ^{13}C-NMR (CD_3OD) δ: 36.3 (CH_2), 54.8 (2-OCH_3), 56.3 (3-OCH_3), 56.5 (3′-OCH_3), 56.7 (4′-OCH_3), 113.2 (5′-C), 114.0 (4-C), 114.7 (2′-C), 122.7 (6′-C), 124.2 (5-C), 127.6 (6-C), 127.7 (4a-C), 134.7 (7-C), 136.1 (1′-C), 136.7 (8a-C), 145.6 (3-C), 146.2 (8-C), 148.8 (4′-C), 150.5 (3′-C), 155.7 (2-C). Signals marked with asterisks appear as singlet-like signals of the AB type.
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