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ISONOYAINE, A NEW C-RING SECOCULARINE ALKALOID†

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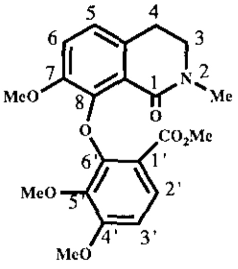
Abstract- We report the isolation of isonoyaine (**1**), a new C-ring secocularine alkaloid, from *Sarcocapnos saetabensis*. Its structure was established on the basis of its spectroscopic data and confirmed by total synthesis.

As a continuation of our work on the alkaloid content of Sarcocapnos species,[1] we now report the isolation of a new C-secocularine alkaloid,[2] isonoyaine (**1**), from *Sarcocapnos saetabensiss* Mateo & Figuerola (Fumariaceae).[3] Its structure was established on the basis of its spectroscopic data and confirmed by total synthesis.



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Isonoyaine (**1**) was obtained as an amorphous optically inactive, colourless substance. Its ir spectrum showed absorption peaks at 1720 and 1650 cm^{-1} revealing the presence of an ester and an amide group in the molecule. The ^{1}H-nmr spectrum exhibited two multiplets centred at δ 2.87 (2H) and 3.45 (2H), a singlet at δ 3.08 (3H, NMe), four singlets at δ 3.49, 3.56, 3.75 and 3.85 (3H each) corresponding to four methoxyl groups, and two AB systems in the aromatic region, one of them centred at δ 6.58 and 7.58 with a coupling constant of 8.8 Hz ($H_{2'}$ and $H_{3'}$) and the other at δ 6.80 and 6.87 (J=8.2 Hz, H_5 and H_6). The ^{13}C-nmr spectrum, with two singlets at δ 166.37 and 162.57, confirmed the presence of two carbonyl groups in the molecule. It also showed four quartets at δ 60.48, 56.65, 55.76 and 51.52 corresponding to four methoxyl groups, the last of them appearing at an unusually high field for a typical aromatic methoxyl group. This feature and the presence of a second carbonyl group established a carboxymethyl group as a benzene ring substituent. There were also, in the aromatic region, five singlets (156.76, 152.01, 150.50, 147.45 and 139.59) due to quaternary oxygenated carbons, three singlets (131.91, 121.25 and 115.72) corresponding to quaternary non-oxygenated carbons, and

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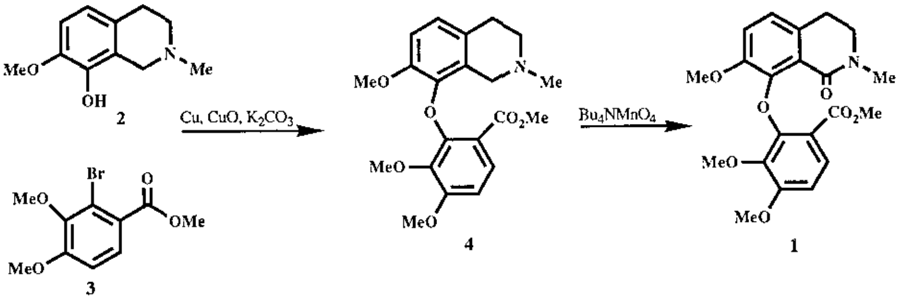
† This paper is dedicated to the memory of our colleague and friend J. M. Boente.

four doublets (126.48, 121.15, 115.89 and 105.04) due to methine carbons, and in the aliphatic part two triplets (48.14 and 28.72) due to the methylene groups and one quartet at δ 34.79 for the N-methyl group.

The mass spectrum showed the molecular ion at m/z 401 (26), which corresponds to the molecular formula $C_{21}H_{23}NO_7$. *This was confirmed by high resolution ms (calculated for* $C_{21}H_{23}NO_7$: 401.14736, found 401.14744). There were also other significant peaks at m/z 370 (12), 204 (100), 190 (12) and 176 (8).

In order to confirm the structure of isonoyaine (**1**) we carried out its total synthesis as shown in Scheme 1. Ullmann condensation of 1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (**2**)[4] and methyl 2-bromo-3,4-dimethoxybenzoate (**3**)[5] afforded 1,2,3,4-tetrahydroisoquinoline **4** in 26% yield. Oxidation of **4** with tetrabutylammonium permanganate gave isonoyaine (**1**) in 40% yield.



Scheme 1

EXPERIMENTAL

Melting point is uncorrected. Infrared spectra were determined in film with a Perkin Elmer 1420 spectrophotometer. Ultraviolet spectra were recorded in ethanol solution on a Milton-Ray Spectronic 3000 Array. Mass spectra were obtained with a Kratos MS 50 instrument at 70 eV ionizing energy. Proton and carbon nmr spectra were measured on a Bruker WM 250 (250 MHz for ^1H and 62.83 MHz for ^{13}C) in $CDCl_3$ solutions with TMS as internal standard; all signals are expressed as δ values ppm downfield from TMS. Column chromatography was carried out on Merck type 60 silica gel and Woelm N (grade IV) neutral alumina. Tlc was performed on Merck GF-254 type 60 silica gel and 60 GF-254 type E neutral alumina plates with the solvent systems CH_2Cl_2 and CH_2Cl_2-MeOH (19:1 and 9:1), alkaloids were detected by uv and spraying with Dragendorff's reagent or iodine vapour.

Isolation of isonoyaine **1** - Powdered dried aerial parts of *Sarcocapnos saetabensis* (400 g) were extracted in a Soxhlet with methanol (2 l) until a negative Dragendorff test was achieved. The solvent was evaporated and the residue (103 g) was taken up in 5% HCl and filtered.This solution was washed with ether to remove neutral components and then extracted with CH_2Cl_2 at pH 6, 8 and 12, (achieved by successive addition of NH_4OH and NaOH). The extracts were dried over sodium sulphate and the solvent was evaporated in vacuo. The extract obtained at pH 6 (3.397 g) was fractionated on a silica gel column eluted with CH_2Cl_2 containing increasing percentages of MeOH. The fraction eluted with CH_2Cl_2-MeOH (9:1) was purified by column chromatography on alumina with CH_2Cl_2 as eluent followed by preparative tlc on alumina (CH_2Cl_2) and finally tlc on silica with CH_2Cl_2-MeOH (19:1) as eluent, affording isonoyaine(**1**,10 mg) as an amorphous powder. Uv λ_{max} nm: 241, 292, 313. Ir υ_{max} cm^{-1} 1650, 1720. ^{1}H-Nmr: 2.87 (m, 2H, H_4), 3.08 (s, 3H, NMe), 3.45 (m, 2H, H_3), 3.49, 3.56, 3.75 and 3.85 (4s, 3H each, 4xOMe), 6.58 and 7.58 (AB, J= 8.8Hz, 2H, $H_{2'}$ and $H_{3'}$), 6.80 and 6.87 (AB, J= 8.2Hz, 2H, H_5 and H_6).^{13}C-Nmr: 28.72 (t), 34.79 (q), 48.18 (t), 51.52 (q), 55.76 (q), 56.65 (q), 60.48 (q), 105.04 (d), 115.72 (s), 115.89 (d), 121.15 (d), 121.25 (s), 126.48 (d), 131.91 (s),139.59 (s), 147.45 (s), 150.50 (s), 152.01 (s), 156.76 (s), 162.57 (s), 166.37 (s). Ms m/z (%): 401 (M^+, 26), 370 (12), 224 (11), 205 (16), 204 (100), 192 (16), 190 (12), 176 (8), 149 (11), 104 (10). Hrms m/z M^+ calcd for $C_{21}H_{23}NO_7$ 401.14736, found 401.14744.

Ullmann condensation of **2** and **3**

A mixture of 1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (**2**)[4] (340 mg, 1.76 mmol), methyl 2-bromo-3,4-dimethoxybenzoate (**3**)[5] (440 mg, 1.60 mmol), potassium carbonate (87 mg, 5.8 mmol), copper powder (667 mg, 10.4 mmol), cupric oxide (335 mg, 4.19 mmol) and pyridine (15 ml) was heated at 115°C with vigorous stirring for 24 h. The mixture was then filtered over silica gel, water was added and the product was extracted with chloroform. The extract was dried with sodium sulphate and the solvent was evaporated off to afford a dark syrup which was purified by column chromatography on silica gel using CH_2Cl_2-MeOH (19:1) as eluent to give **4** in 26% yield (159 mg), mp 138 °C. ^{1}H-Nmr: 2.45 (s, 3H, NMe), 2.65 (t, J=5.8Hz, 2H, H_3), 2.87 (t, J=5.8Hz, 2H, H_4), 3.81 (s, 2H, H_1), 3.37, 3.44, 3.68 and 3.84 (4s, 3H each, 4xOMe), 6.62 and 6.66 (AB, J= 8.9Hz, 2H, H_5 and H_6), 6.76 and 7.52 (AB, J= 8.6Hz, 2H, $H_{2'}$ and $H_{3'}$). Ms m/z (%): 386 (M^+-1, 3), 372 (3), 328 (6), 313 (5), 190 (4), 177 (14), 176 (100), 174 (5).

Isonovaine (1)

71 mg (0.196 mmol) of tetrabutylammonium permanganate were added in small portions to a solution of 95 mg of isoquinoline **4** (0.245 mmol) in dry pyridine (10 ml),and the mixture was stirred at room temperature for 24 h. This solution was poured into cold dilute HCl containing sodium hydrogen sulphite,[6] and the product was extracted with chloroform. The extract was dried with sodium sulphate and the solvent was evaporated off. Purification by tlc on silica gel (CH_2Cl_2-MeOH 19:1) gave **1** in 40% yield (38 mg).^{1}H-Nmr and ^{13}C-nmr were identical to those of the natural product.

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