A New Pyranoacridone Alkaloid from the Bark of *Medicosma subsessilis* (*Rutaceae*)

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The alkaloids evolitrine, acronycidine, melicopine, melicopidine, normelicopine, normelicopidine, acronycine, noracronycine, 12-desmethylnoracronycine, (+)-*cis*-1,2-dihydroxy-1,2-dihydroacronycine, and (-)-*trans*-1,2-dihydroxy-1,2-dihydroacronycine were isolated from *Medicosma subsessilis* bark, together with the new 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine. The structure of the latter compound was elucidated on the basis of spectral data and partial synthesis.

**Key words:** *Medicosma subsessilis*, Alkaloids, 1-Oxo-2-hydroxy-1,2-dihydro-12-desmethylacronycine

**Introduction**

According to the last revision published by Hartley, the genus *Medicosma* L. (*Rutaceae*) consists of some 22 species of trees and shrubs, endemic to eastern Australia, southern New Guinea, and New Caledonia [1]. Until now, only three of these species have been studied from a chemical point of view for their alkaloid contents. In both *Medicosma fareana* (F. Mueller) T. Hartley and *Medicosma leratii* (Guillaumin) T. Hartley (= *Melicope leratii* Guillaumin), furo[2,3-\(b\)]quinolines were accompanied by acridones and related oxidation products, such as fareanine [2, 3]. In contrast, acridones were not isolated from *Medicosma cunninghamii* (Hooker) Hooker f., which was only shown to contain furo[2,3-\(b\)]quinolines and the furo[2,3-\(b\)]pyrano[3,2-\(f\)]quinoline medicosmine [4, 5]. In a continuation of our studies on the Rutaceae from the Pacific area [6, 7], we describe here the isolation and structure elucidation of the alkaloids of the bark of *Medicosma subsessilis* T. Hartley.

**Results and Discussion**

Twelve alkaloids were isolated from the bark of *Medicosma subsessilis*. Two furo[2,3-\(b\)]quinolines were identified with evolitrine and acronycidine [8 – 10]. The UV spectra of the ten other compounds displayed typical absorptions associated with the acridone chromophore [11, 12]. These alkaloids included the simple acridones melicopine, melicopidine, normelicopine, and normelicopidine, and the angular pyranoacridones acronycine, noracronycine, 12-desmethylnoracronycine, (+)-*cis*-1,2-dihydroxy-1,2-dihydroacronycine, and (-)-*trans*-1,2-dihydroxy-1,2-dihydroacronycine were isolated from *Medicosma subsessilis* bark, together with the new 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine. The structure of the latter compound was elucidated on the basis of spectral data and partial synthesis.

1–Oxo–2–hydroxy–1,2–dihydro–12–desmethylnor–acronycine (1) was obtained as a yellow amorphous product. The empirical formula was determined by accurate mass measurement as C\(_{18}\)H\(_{13}\)NO\(_5\). The UV spectrum recorded in MeOH showed absorption maxima attributable to an acridone chromophore [11]. The IR spectrum showed characteristic bands accounting for the acridone carbonyl and for a second conjugated carbonyl group, at 1610 and 1652 cm\(^{-1}\), respectively. In the aromatic region, the \(^1\)H NMR
spectrum displayed the characteristic set of four coupled signals associated with the unsubstituted A ring of a 9-acridone, whereas a 1H singlet indicated the presence of three substituents on the C ring. Two downfield resonances at $\delta$ 12.88 and 15.43 were typical for an acridone NH and a hydroxyl group strongly bonded to the acridone carbonyl, respectively. At higher field, signals at $\delta$ 6.19 (1H, d, $J = 5$ Hz, D$_2$O exch.), 4.27 (1H, d, $J = 5$ Hz), 1.47 (3H, s), and 1.33 (3H, s) accounted for a fused 2,2-dimethyl-3-hydroxy-4-oxo-3,4-dihydro-2H-pyrane subunit. This statement is in full agreement with a series of signals observed at 20.4, 26.1, 75.7, 84.7, and 194.8 ppm in the $^{13}$C NMR spectrum [15, 16]. The observation of a strong NOESY correlation between the signals of H-11 at $\delta$ 7.88 and NH-12 and the lack of correlation between NH-12 and the singlet at $\delta$ 6.10 strongly suggested an angular fusion of the dimethylpyran ring onto the acridone tricyclic system. In order to confirm this hypothesis, the synthesis of 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine was achieved by oxidation of the readily available 3,12-dihydro-3,3-dimethyl-7H-pyrano[2,3-c]acridin-7-one (2) [17] with potassium permanganate in aqueous acetone [15, 16]. The synthetic product obtained was identical in all respects with the new natural alkaloid, whose structure was consequently established as 1. Despite the presence of a chiral center at C-2, natural 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine (1) has been isolated as a racemate. The equilibrium of 1 with the tautomeric achiral 1,2-dihydroxy-12-desmethylnoracronycine form most probably accounts for this lack of optical rotatory properties.

From a chemotaxonomic point of view, it is interesting to note that the alkaloids isolated from Medicosma subsessilis include common furo[2,3-b]quinolines and acridones, together with six different pyrano[2,3-c]acridin-7-ones. Alkaloids deriving from the latter ba-

The optical rotation was measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Nermag R-10-10C spectrometer, using electron impact ionization (70 eV) technique. UV spectra ($\lambda_{max}$ in nm) were recorded in spectroscopic grade EtOH on a Beckman Model 34 spectrophotometer. IR spectra ($\nu_{max}$ in cm$^{-1}$) were obtained from potassium bromide pellets on a Nicolet 510 FT instrument. $^{1}$H NMR (δ [ppm], $J$ [Hz]) and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz respectively, using a Bruker AVANCE-400 spectrometer. Multi-impusional 2D NMR experiments ($^{1}$H-1H COSY, $^{1}$H-1H NOESY, $^{13}$C- $^{1}$H HMOC, and $^{13}$C-1H HMBC) were performed using standard Bruker microprograms. Column chromatographies were carried out with silica gel 20 – 45 µm. Flash column chromatographies were conducted using silica gel 60 Merck (35 – 70 µm) with an overpressure of 300 mbar [21].

**Plant material**

Bark of Medicosma subsessilis T. Hartley was collected in the Vallée de la Nodela (New Caledonia), on 30 October 1997. A voucher sample (LIT 372) is kept in the herbarium of the Centre IRD of Nouméa, New Caledonia.

**Extraction and isolation**

Dried, pulverized bark of Medicosma subsessilis (1 kg) was extracted successively with Et$_2$O (4 × 1 l) and MeOH (2 × 1 l) at room temperature. The solvents were removed under reduced pressure to give crude Et$_2$O and MeOH extracts (8.5 g and 1.2 g, respectively). The Et$_2$O extract (1.5 g) was subjected to flash column chromatography on silica gel, using a CH$_2$Cl$_2$-MeOH gradient of increasing polarity to yield 6 fractions. Further column chromatographies on silica gel 20 – 45 µm, performed on fractions 4 and 5 (eluted with CH$_2$Cl$_2$-MeOH 95:5 v/v) successively gave evolutrine (100 mg), acronycinide (7 mg), normelicopine (5 mg), normelicopidine (7 mg), melicopine (30 mg), melicopidine (35 mg), noracronycine (32 mg), acronycine (200 mg), and 12-desmethylacronycine (120 mg). Similarly, flash chromatography performed on the MeOH extract (0.3 g), followed by column chromatogra-
phies on silica gel 20–45 μm, successively afforded (+)-cis-1,2-dihydroxy-1,2-dihydroacronycine (27 mg), (-)-trans-1,2-dihydroxy-1,2-dihydroacronycine (34 mg) and 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine (3.5 mg).

Spectroscopic data

1-Oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine (1), UV (EtOH): λ_max (log ε) = 221 (4.98), 255 (4.99), 383 nm (4.04). – IR (KBr): ν = 3444, 2923, 2854, 1652, 1610, 1549, 1464, 1171, 1089, 1054, 829 cm⁻¹. – ¹H-NMR (DMSO-d₆, 400 MHz): δ = 1.33 (s, 3H, CH₃-3), 1.47 (s, 3H, CH₃-3), 4.27 (d, J = 5 Hz, 1H, H-5), 6.10 (s, 1H, H-5), 6.19 (d, J = 5 Hz, 1H, D₂O excl., OH-2), 7.45 (t, J = 8 Hz, 1H, H-9), 7.85 (t, J = 8 Hz, 1H, H-10), 7.88 (d, J = 8 Hz, 1H, H-11), 8.23 (d, J = 5 Hz, 1H, D₂O excl., OH-12), 15.43 (s, 1H, D₂O excl., OH-6). – 13C-NMR (DMSO-d₆, 100 MHz): δ = 20.4 (CH₃-3), 26.1 (CH₃-3), 75.7 (C-2), 84.7 (C-3), 97.1 (C-5), 97.5 (C-12b), 104.3 (C-6a), 119.9 (C-11), 121.2 (C-7a), 128.4 (C-9), 125.9 (C-8), 135.7 (C-10), 140.4 (C-11a), 144.4 (C-12a), 167.6 (C-4a), 171.1 (C-6), 181.1 (C-7), 194.8 (C-1). – MS (EI, 70 eV): m/z 325 [M⁺], 310, 296, 281, 267, 254, 238, 226, 211, 197, 182, 169. – HR-EIMS found: 325.0947 (calcd. for [C₁₉H₁₅NO₅]⁺, 325.0950).

Synthesis

Permanganate oxidation of 3,12-dihydro-3,3-dimethyl-7H-pyrano[2,3-c]acridin-7-one (2): A suspension of powdered KMnO₄ (0.096 g, 0.6 mmol) in H₂O (2 ml) was added dropwise within 30 mn to a solution of 2 (0.030 g, 0.1 mmol) in acetonitrile (4 ml). The reaction mixture was stirred for 15 h at 20 °C and extracted with 2-butanol (3 × 10 ml). The organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel 35–70 (solvent, CH₂Cl₂-MeOH 98:2 v/v) gave 1-Oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine (1) (0.010 g, 31%), as a yellow amorphous powder, identical with the natural product (TLC, IR, MS, ¹H and ¹³C NMR).