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-desmethylacronycine, (+)-*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.

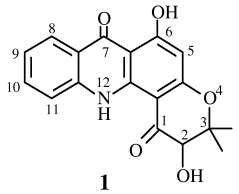
Key words: Medicosma subsessilis, Alkaloids, 1-Oxo-2-hydroxy-1,2-dihydro-12-desmethyl-acronycine

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-desmethylacronycine, (+)-*cis*-1,2-dihydroxy-1,2-dihydroacronycine, (-)-*trans*-1,2-dihydroxy-1,2-dihydroacronycine [12 – 14], and 1-oxo-2-hydroxy-1,2-dihydro-12-desmethylnoracronycine (**1**), which is a new product.



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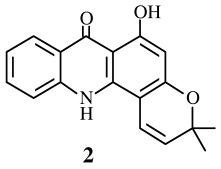
1–Oxo–2–hydroxy–1,2–dihydro–12–desmethylnoracronycine (**1**) was obtained as a yellow amorphous product. The empirical formula was determined by accurate mass measurement as $C_{18}H_{15}NO_5$. The UV spectrum recorded in MeOH showed absorption maxima attributable to an acridone chromophore [11]. The 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 ^1H NMR



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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 substitents on the C ring. Two downfield resonances at δ 12.88 and 15.43 were typical for an acridone NH and a hydroxyl group stongly bonded to the acridone carbonyl, respectively. At higher field, signals at δ 6.19 (1H, d, J = 5 Hz, D_2O 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-2*H*-pyran 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 δ 7.88 and NH-12 and the lack of correlation between NH-12 and the singlet at δ 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-7*H*-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 basic skeleton are seldom encountered within the Rutaceae family, and generally bear a hydroxy group at C-6 [18]. Indeed, 6-methoxypyrano[2,3-*c*]acridin-7-ones have been previously isolated only from *Melicope leptococca* (Baill.) Guill. and also from all the species of *Sarcomelicope* studied until now [19, 20]. The isolation of several angular pyranoacridones of this type, including 12-desmethylacronycine and acronycine, from *Medicosma subsessilis* raises questions about the position of this species within the Rutaceae family and suggests the need for a revision of the genus *Medicosma*, which includes species unusually diverse from a morphological point a view [1].

Experimental Section

General experimental procedures

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 (λ_{max} in nm) were recorded in spectroscopic grade EtOH on a Beckman Model 34 spectrophotometer. IR spectra (ν_{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-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{13}C-^{1}H HMQC, and ^{13}C-^{1}H 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_2O (4 × 1 l) and MeOH (2 × 1 l) at room temperature. The solvents were removed under reduced pressure to give crude Et_2O and MeOH extracts (8.5 g and 1.2 g, respectively). The Et_2O extract (1.5 g) was subjected to flash column chromatography on silica gel, using a CH_2Cl_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_2Cl_2-MeOH 95:5 v/v) successively gave evolitrine (100 mg), acronycidine (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} (lg ε) = 221 (4.98), 255 (4.99), 383 nm (4.04). – IR (KBr): ν = 3444, 2923, 2854, 1652, 1610, 1459, 1464, 1171, 1089, 1054, 829 cm^{-1}. – ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 1.33 (s, 3H, CH_3-3), 1.47 (s, 3H, CH_3-3), 4.27 (d, J = 5 Hz, 1H, H-2), 6.10 (s, 1H, H-5), 6.19 (d, J = 5 Hz, 1H, D_2O exch., 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 = 8 Hz, 1H, H-8), 12.88 (s, 1H, D_2O exch., NH-12), 15.43 (s, 1H, D_2O exch., OH-6). – ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 20.4 (CH_3-3), 26.1 (CH_3-3), 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), 124.8 (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 $[C_{18}H_{15}NO_5]^+$, 325.0950).

Synthesis

*Permanganate oxidation of 3,12-dihydro-3,3-dimethyl-7H-pyrano[2,3-c]acridin-7-one (**2**)*: A suspension of powered $KMnO_4$ (0.096 g, 0.6 mmol) in H_2O (2 ml) was added dropwise within 30 mn to a solution of **2** (0.030 g, 0.1 mmol) in acetone (4 ml). The reaction mixture was stirred for 15 h at 20 °C and extracted with 2-butanone (3 × 10 ml). The organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography over silica gel 35 – 70 μm (solvent, CH_2Cl_2-MeOH 98:2 v/v) gave -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, ^{1}H and ^{13}C NMR).

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