Megistolactone, a New Alkaloid from Sarcomelicope megistophylla

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A new quinolone alkaloid, megistolactone (1) was isolated from the bark of Sarcomelicope megistophylla. Its structure has been elucidated on the basis of MS and NMR data. From a biogenetic point of view, this compound should be considered as an oxidation product of 1,2,3,4-tetra-O-substituted acridone alkaloids, which are also present in the bark.

Introduction

Sarcomelicope megistophylla Hartley (Rutaceae) is an 8–12 m high tree, easily recognized by its pubescent leaves, exceptionally large for the genus (up to 35 cm long). This species is endemic to the region of Nouméa, New Caledonia (Hartley, 1986). Recently, we described the chemical constituents of its leaves (Skaltsounis et al., 1995; Fokialakis et al., 1999) and the major alkaloids of the bark (Papageorgiou et al., 2000; Fokialakis et al., 2000). In a continuation of our studies of the genus Sarcomelicope (Tillequin, 1997), we report here the isolation and structure determination of a novel 4-quinolone alkaloid, from the bark of Sarcomelicope megistophylla.

Results and Discussion

Megistolactone (1) was obtained as a yellowish amorphous product. The molecular formula was determined by HRMS as C₁₄H₁₂NO₃. The UV spectrum recorded in MeOH was suggestive of a quinolone derivative. A typical hypsochromic shift observed upon addition of acid gave evidence for a 4-quinolone basic skeleton (Rapoport and Holden, 1960; Hâ-huy-Kê et al., 1970). The IR spectrum showed two characteristic bands at 1647 cm⁻¹ and 1789 cm⁻¹. The first one corresponds to the carbonyl group of the quinolone and the second one to the carbonyl group of a 5-membered lactone ring. In the aromatic region, the ¹H NMR spectrum displayed the characteristic signals associated with the four aromatic protons of the A ring of a 4-quinolone. At higher field, typical signals accounted for one OMe group and one NMe group, whereas the signal of one deshielded methine proton appeared as a singlet at 6.15 ppm. The ¹³C NMR spectrum showed two carbonyl resonances, at 172.3 and 164.8 ppm. The former confirmed the presence of the quinolone system and the latter was assigned to an unsaturated lactone. Additionally, the signal of a methine carbon joined with two oxygen atoms was observed at 96.8 ppm. Further information on the structure of 1 was obtained from the long range C–H correlations in the HMBC spectrum (Fig. 1). Three bond correlations between the methine proton at δ 6.15 and the OMe carbon at 56.6 ppm on one hand, and the carbonyl group at 164.8 ppm on the other hand, indicated that the aliphatic methine carbon bore the methoxy group and was also included in the

Fig. 1. Selected HMBC (——) and NOESY (-----) correlations for megistolactone (1).
lactone ring. Correlation between the three-proton singlet of the NMe group and the two quarternary carbon signals of C-2, at 160.3 ppm, and C-10, at 140.9 ppm, gave incidentally additional evidence for the 4-quinolone basic skeleton. Finally, determination of the structure of the new natural product as 1, and discrimination against the alternative structure 2 (Fig. 2), was provided by a NOESY experiment, which showed a strong cross peak between the signals of the NMe and the aliphatic methine proton. The absolute configuration of the chiral center at C-11 could not be determined, due to the small amount of the product isolated. When evaluated for its cytotoxic activity against L1210 leukemia cells, megistolactone only showed a moderate activity (IC50 = 70 μM).

Biogenetically, megistolactone (1) should be considered as resulting from the oxidation of the A aromatic ring of an acridone, such as melicopine, melicopidine, or melicopicine which are the major alkaloids of the bark. The presence of four electron-donating groups on the A ring of these 1,2,3,4-tetra-O-substituted acridones should greatly facilitate their oxidative cleavage. From a chemotaxonomic point of view, it is interesting to note that a similar biogenesis, involving the oxidative ring opening of the aromatic ring of an acridone, had been postulated for 1-methyl-4-quinolone-2,3-dicarboxylic acids dimethylester, previously isolated from Sarcomelicope dogniensis (Mitaku et al., 1995).

**Experimental**

**General experimental procedures**

Optical rotation was measured with a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a Shimadzu-160A spectrophotometer. The IR spectrum was obtained on a Perkin-Elmer Paragon 500 instrument. NMR spectra were recorded on Bruker DRX 400 and Bruker AC 200 spectrometers [1H (400 and 200 MHz) and 13C (50 MHz)]; chemical shifts are expressed in ppm downfield to TMS. The 2D NMR experiments were performed using standard Bruker microprograms. EIMS and HRMS were determined on HP-6890 and AEI MS-902 spectrometers, respectively.

**Plant material**

The plant material was collected at Nouméa (New Caledonia) in May 1984. Herbarium samples (Pusset-Chauvière 261) are deposited in the herbarium of the Centre ORSTOM at Nouméa (New Caledonia).

**Extraction and isolation**

Extraction of alkaloids as described (Papageorgiou et al., 2000). The dichloromethane bark extract was chromatographed over a CC silica gel Merck 0.04-0.06 mm (flash), using cyclohexane-EtOAc gradient to give 6 fractions. Fraction 5 was rechromatographed to afford megistolactone 1 (10 mg).

**Spectroscopic data**

*Megistolactone (1)*, [α]D -3° (0.1 g/100 ml, CH2Cl2); UV (MeOH) λmax (log ε) 245 (3.88), 252 (sh), 299 (sh), 310 (3.75), 323 (3.69) nm; IR (CH2Cl2) νmax 2951, 2928, 1789, 1647, 1261, 1207 cm⁻¹; 1H NMR (CDCl3, 400 MHz, δ ppm): 3.85 (3H, s, N-CH3), 8.48 (1H, dd, J = 8, J = 1.5 Hz, H-6), 7.48 (1H, t, J = 8 Hz, H-7), 7.76 (1H, td, J = 8, J = 1.5 Hz, H-8), 7.56 (1H, d, J = 8, H-9), 6.15 (H, s, H-11) 3.64 (3H, s, CH3O-11); 13C NMR (CDCl3, 50 MHz, δ ppm): 35.0 (N-CH3), 160.3 (C-2), 104.4 (C-3), 172.3 (C-4), 128.9 (C-5), 127.5 (C-6), 125.8 (C-7), 133.6 (C-8), 115.9 (C-9), 140.9 (C-10), 96.8 (C-11), 56.6 (CH3O-11), 164.8 (C-12); HRMS found: 245.0647 (caled for C13H11O4N, 245.0688); MS-DCI m/z 246 [M+H]+.

**Cytotoxicity assay**

The murine leukemia was from the American Type Culture Collection (Rockville Pike, MD). Cells were grown in RPMI medium supplemented with 10% fetal calf serum, 2 mm L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin and 10
toxicity was measured by the microculture tetrazolium assay (Pierre et al., 1991).


