AZACRIDONE-A, THE FIRST NATURALLY OCCURRING AZAACRIDONE ALKALOID FROM A *CITRUS* PLANT

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Azacridone-A (1), the first naturally occurring azaacridone alkaloid, was isolated from the roots of Marsh grapefruit (*Citrus paradisi* Macf.), and its structure was determined by spectroscopic evidence.

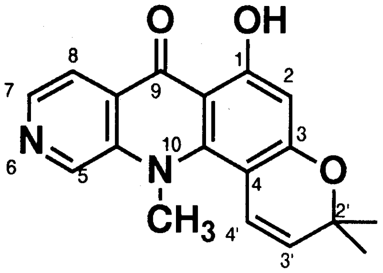
KEYWORDS azacridone-A; acridone alkaloid; *Citrus paradisi*; Marsh grapefruit; Rutaceae

Many acridone alkaloids have been isolated[1)] mainly from Rutaceous plants, and some of them are of interest to possess a variety of biological activities, including antitumor,[2)] antiviral,[3)] and antiprotozoal[4)] activities. On continuing our phytochemical studies[5)] on the constituents of *Citrus* plants (Rutaceae), we investigated the constituents of the roots of Marsh grapefruit (*C. paradisi* Macf.) and isolated a novel acridone alkaloid, named azacridone-A (1). The new compound was characterized as containing pyridine moiety.

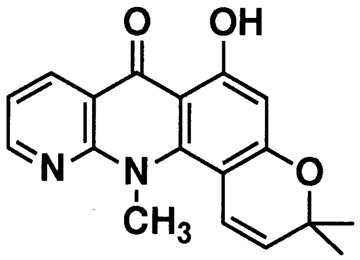
The dried roots of the plant (1.2 Kg) were extracted with acetone under reflux, and the extract was concentrated under reduced pressure. Column chromatography of the extract on silica gel and subsequent preparative TLC gave azacridone-A (1, 1.7 mg).

Azacridone-A (1), light brown oil, $C_{18}H_{16}N_2O_3$ (M^+, 308.1160. Calcd 308.1161). The IR ($CHCl_3$) (1630, 1580, 1445 cm^{-1}) and UV (EtOH) [λmax 224(sh), 276(sh), 290, 321, 360(sh) nm] spectra were diagnostic to 9-acridone.[6)] The most striking characteristic of (1) is the difference from all the other acridone alkaloids isolated so far by the presence of a second nitrogen atom. The ^{1}H-NMR (acetone-d_6, 500MHz) spectrum showed the presence of hydrogen-bonded hydroxy group (δ 14.35), an aromatic proton (δ 6.19) and a 2,2-dimethylpyran ring [δ 6.83 (1H, d, J=9.8 Hz), 5.68 (1H, d, J=9.8 Hz) and δ 1.54 (6H, s)]. Usually, aromatic protons at H-8, H-7, H-6, H-5 of acridone alkaloids resonate at about δ 8.3, 7.2, 7.7 and δ 7.4, respectively.[7)] A remarkable lower field resonance was observed at δ 9.19 (1H, s), 8.54 (1H, d, J=4.9 Hz) and 8.06 (1H, d, J=4.9 Hz), and its coupling constants suggested the presence of a 3,4-disubstituted pyridine ring. The signals resonating at δ 4.14 (3H, s) in ^{1}H-NMR and at δ 43.90 (q) in ^{13}C-NMR[8)] spectra indicated the presence of an N-methyl group. In the NOE experiments, irradiation of N-methyl signal showed 10% and 9% increments on the signals at δ 6.83 and 9.19, respectively, indicating that the locations of these protons were C-4' and C-5. The above results proved the structure of azacridone-A to be represented by formula (1).

Although the synthetic compound (2)[9] is known as the only example of aza-type acridone alkaloid, (1) is the first example of this type compound obtained from natural sources.



(1)



(2)

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8) The ^{13}C-NMR (acetone-d_6, 125MHz) : δ 181.33 (C-9), 165.96 (C-3), 163.35 (C-1), 142.61 (C-5), 142.19 (C-7), 126.52 (C-8a), 124.31 (C-4'), 122.17 (C-3'), 117.57 (C-8), 108.12 (C-4), 102.55 (C-9a), 98.45 (C-2), 77.69 (C-2'), 43.90 (N-CH_3), 27.10 (2'-CH_3 x 2). Because of the small quantity obtained, other quarternary carbon signals could not be assigned.

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