STRUCTURE OF ACRIGNINE-A, THE FIRST NATURALLY OCCURRING ACRIDONOLIGNOID FROM *CITRUS* PLANTS

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The chemical structure of acrignine-A (**1**), an acridone alkaloid carrying lignan moiety, from roots of *Citrus* plants (Rutaceae) have been elucidated by spectrometric studies using ^{1}H-^{13}C long-range COSY and NOE experiments . The structure was confirmed by single crystal X-ray analysis. This is the first example of an acridonolignoid isolated from natural sources.

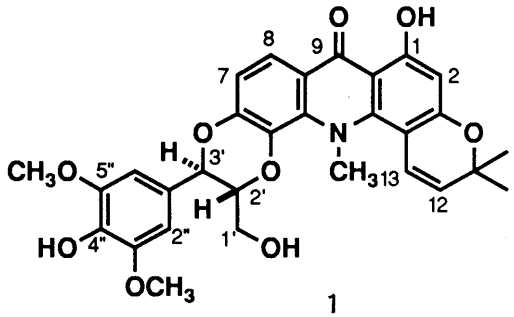
KEYWORDS acridonolignoid; acridone; *Citrus*; acrignine-A; crystal structure; lignoid

In our studies of the constituents of the *Citrus* plants, many kinds of novel acridone,[1] homo-acridone,[2] and acrimarine[3] alkaloids have been isolated and their structures characterized. We here disclose the structure of the first example of a naturally occurring "acridonolignoid," an acridone carrying a lignan moiety, which we named acrignine-A (**1**), obtained from *C. grandis* OSBECK f. *Hirado*[4] and *C. Yuko* Hort. ex TANAKA [5] (Rutaceae).

Acrignine-A (**1**) was isolated as a racemate,[6] yellow prisms, mp 177 -179°C, from the acetone extracts of roots of the plants. The molecular formula $C_{30}H_{29}NO_9$ [M^+ 547.1845. Calcd. 547.1841] was confirmed by high resolution mass spectrometry. The UV (MeOH) and IR ($CHCl_3$) spectra exhibited absorption bands typical of a 9-acridone nucleus[7] [λ_{max}: 207, 236 (sh.), 272, 316 (sh.), 340, and 400 nm; ν_{max}: 1630, 1618, 1595, and 1565 cm^{-1}]. The presence of 1-hydroxy-5,6-oxygenated 9-acridone nucleus having an angular oriented dimethylpyran ring was proposed based on the following spectral data: a) The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) using ^{1}H-^{1}H COSY and HMQC showed signals attributable to a strongly hydrogen-bonded 1-hydroxy [δ_H 14.38 (s)], a 9-carbonyl [δ_C 181.18], and an N-methyl [δ_H 3.77 (s); δ_C 49.62] group along with a lone aromatic H-2 [δ_H 6.24 (s); δ_C 98.43] and *ortho*-coupled protons including a deshielded H-8[7] [δ_H 6.94 (H-7) and 7.88 (H-8) (each d, J = 8.5 Hz)]. b) The AB-type signals at δ_H 6.58 and 5.52 (each d, J = 9.8Hz) accompanied with 6H singlet [δ_H 1.50 (s)] due to *gem*-dimethyls [δ_C 27.25 and 27.03] attached to an oxygenated carbon [δ_C 76.52] reflect the presence of a 2,2-dimethylpyran ring system attached to the acridone nucleus. c) Observation of an NOE enhancement (8 %) between the signals at δ_H 6.58 (H-13) and 3.77 (N-Me) suggested an angular orientation of the dimethylpyran ring. d) Appearances of ^{13}C signals at δ_C 133.05 and 148.43, which showed three-bond correlations to H-7 and H-8, respectively, in HMBC (J = 8 Hz) spectrum, suggested the presence of O-substituents at C-5 and C-6. e) A significant mass fragment

peak at m/z 339 ($C_{19}H_{17}NO_5$) associated with a base fragment peak at m/z 324 corresponding to ions of the pyranoacridone unit and further loss of a methyl radical, respectively, was observed.

Furthermore, remaining ^1H and ^{13}C signals in NMR spectra together with the results of ^1H-^1H COSY, HMBC, and difference NOE experiments [δ_H 3.72(1H, dd, J = 3.7, 12.5Hz, H-1'), 4.02 (1H, dd, J =7.3, 12.5Hz, H-1'), 4.14 (1H, br. d, J =8.1Hz, H-2'), 5.13 (1H, d, J =8.1Hz, H-3'), 3.95 (6H, s. 3", 5"-OCH_3), 6.72 (2H, s, H-2", 6"), and 5.68 (1H, br. s, 4"-OH); δ_C 61.81 (t, C-1'), 78.43 (d, C-2'), 76.83 (d, C-3'); NOE: H-2"(6") — OMe (18 %), H-2"(6") — H-2' (4 %), and H-2"(6") — H-3' (7 %)] indicated the presence of 3-(3,5-dimethoxy-4-hydroxy)phenylpropanol moiety bonded to the acridone skeleton through ether linkages. However, attempts to confirm the direction of the linkage [*i.e.* C(6)-O-C(3') and C(5)-O-C(2') or C(6)-O-C(2') and C(5)-O-C(3')] by spectrometric methods were unsuccessful. The complete structure and relative stereochemistry of **1** were obtained from a single-crystal X-ray analysis.[8] A perspective view of one enantiomer of **1** is provided in Fig 1.



1

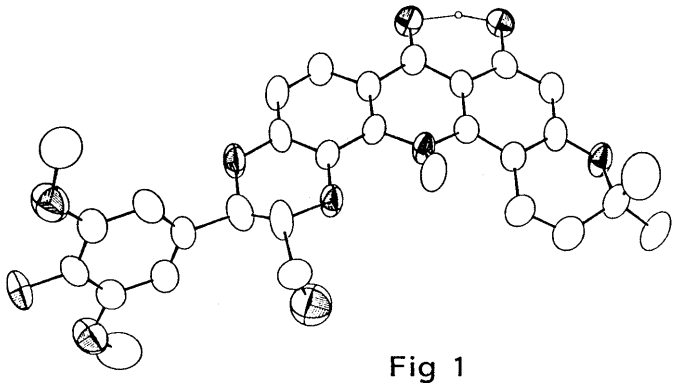


Fig 1

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4) *Hirado-buntan* grown in the orchard of Okitsu Branch, Fruit Tree Research Station, Shizuoka.

5) *Yuko* collected at Katsura, Tokushima.

6) CD 200-400 nm (MeOH): no absorption.

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8) Crystal data for **1**: $C_{33}H_{35}NO_{10}$ (acetone adduct), M = 605.65, monoclinic, a = 8.646(1), b = 12.392(1), c = 27.997(5)Å, α = 90°, β = 98.73(1)°, γ = 90°, U = 2965(6)Å^3, Z = 4, space group $P2_1/c$, Dc = 1.357 g/cm^3, μ(Mo-Kα) = 0.9 cm^{-1}. Data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-Kα radiation. Intensity data were reduced with the suite of program of SDA. The structure was solved by direct methods (MULTAN82). The hydrogen positions were idealized and included in subsequent cycles of full-matrix least-squares refinement as fixed and converged at R = 0.086.

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