TWO NEW ACRIDONE ALKALOIDS FROM A *CITRUS* PLANT[1]

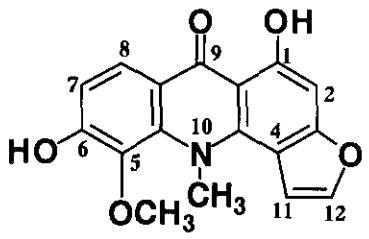
Yuko Takemura,[a] Yoko Matsushita,[a] Satomi Onishi,[a] Tomomi Atarashi,[a] Junichi Kunitomo,[a] Motoharu Ju-ichi,*,[a] Mitsuo Omura,[b] Chihiro Ito,[c] and Hiroshi Furukawa*,[c]

Faculty of Pharmaceutical Sciences, Mukogawa Women's University,[a] Nishinomiya, Hyogo 663, Japan, Fruit Tree Research Station,[b] Ministry of Agriculture, Forestry and Fisheries, Okitsu, Shimizu, Shizuoka 424-02, Japan, and Faculty of Pharmacy, Meijo University,[c] Tempaku, Nagoya 468, Japan

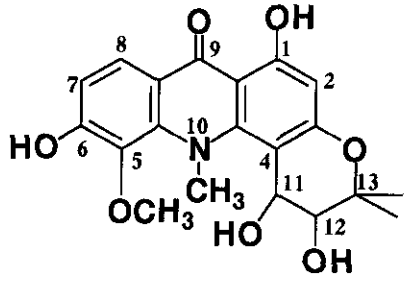
Abstracts ——Two new acridone alkaloids, named furoparadine (1) and *trans*-dihydroxycitracridone-I (2), were isolated from the root of Marsh grapefruit (Rutaceae) and their structures were elucidated on the basis of spectroscopic methods.

In our continuing research on the constituents of *Citrus* plants, we have reported the isolation and structure elucidation of many acridone alkaloids and coumarins.[2] As a part of this program, we recently reported the isolation of new acridone alkaloids, named citbismine-A,[3] marshdine, and marshmine[4] from the roots of Marsh grapefruit (*Citrus paradisi* Macf.). Further investigation of this plant furnished to isolate two new acridone alkaloids, furoparadine (1) and *trans*-dihydroxycitracridone-I (2). This paper deals with details of structure elucidation of these new alkaloids.

Furoparadine (1) was isolated as a yellow oil. The molecular formula $C_{17}H_{13}NO_5$ was established by HRms (m/z 311.0788). The ir (ν_{max} 1625, 1600, 1560 cm^{-1}) and uv [λ_{max} 261, 290, 313, 334 (sh), 367 nm] spectra indicated the presence of 1-hydroxy-9-acridone skeleton.[5] The ^{1}H-nmr spectrum showed the presence of hydrogen-bonded hydroxy group (δ 14.65), two pairs of *ortho*-coupled [δ 8.10, 7.06 (each 1H, d, J= 9.2 Hz), 7.80, 7.40 (each 1H, d, J= 2.4 Hz)] and a lone [δ 6.76 (1H, s)] aromatic protons. The lowest signal among these aromatic protons at δ 8.10 was deshielded by 9-carbonyl group and one of *ortho*-coupled protons were assigned to H-8 and H-7. The chemical shifts and a small coupling constants (J= 2.4 Hz) of another *ortho*-coupled protons suggested the presence of furan moiety. Two singlets at δ 4.26, 3.89 (each 3H) in the ^{1}H- and two quartets at δ 45.65, 69.34 in the ^{13}C-nmr spectra indicated the presence of each one *N*-methyl and *O*-methyl groups. In the nOe experiment, irradiation of *N*-methyl signal at δ 4.26 induced 14% increment on the signal at δ 7.40 , indicating the angular orientation of furan ring. When the methoxy signal at δ 3.89 was irradiated, no increments were observed on any aromatic protons,



(1)



(2)

showing the location of methoxyl group to C-5. From the above results, the structure of furoparadine was concluded to be 1.

As acridone alkaloid having furan ring, furofoline-I and -II[6] from *Glycosmis citrifolia,* thehaplosine[7] from *Haplophyllum thesioides*, chaloridone[8] from *Ruta chalepensis*, and hallacridone[9] from *Ruta graveolens*, have been isolated. Furoparadine is the first example of this type acridone alkaloid isolated from *Citrus* plant.

trans-Dihydroxycitracridone-I (2) was isolated as yellow cubes, mp 235-238°C. The EIms of 2 showed the molecular ion at m/z 387, indicating the molecular formula $C_{20}H_{21}NO_7$. The ir and uv spectra suggested the presence of 1-hydroxy-9-acridone skeleton.[5] The ^1H nmr spectrum indicated the characteristic hydrogen-bonded hydroxyl group (δ 14.66), *ortho*-coupled [δ 7.83, 6.93 (each 1H, d, J= 8.6 Hz)], and a lone [δ 6.00 (1H, s)] aromatic protons. The lowest signal of aromatic proton at δ 7.83 was easily assigned to H-8, hence *ortho*-coupled aromatic protons were assigned to H-8 and H-7. The signals at δ 5.64 (1H, d, J= 5.5 Hz) and 4.99 (1H, d, J= 7.9 Hz), 4.63 (1H, t, J= 7.9 Hz, changed to d, J= 7.9 Hz with D_2O), 3.34 (1H, overlapped with the signal of H_2O, changed to d, J=7.9 Hz with D_2O), and 1.40, 1.24 (each 3H, s) indicated the presence of dihydroxylated dihydropyran ring. The other signals at δ 3.73 and 3.75 (each 3H, s) in the ^1H-nmr, coupled with the signals at δ 45.09 and 60.55 in the ^{13}C nmr showed the presence of each one *N*-methyl and *O*-methyl groups. In the nOe experiment, irradiation the signal at δ 3.73 (N-Me) induced 11% increments on the signal at δ 4.63 (H-11). The result suggested the angular orientation of dihydroxylated dihydropyran ring. On the other hand, when the signal at δ 3.75 (O-Me) was irradiated, no increments were observed on any protons. Thus the location of methoxy group was concluded at C-5. The *trans* orientation of two hydroxyl groups was estimated by the coupling constants (J= 7.9 Hz) of H-11 and H-12. Mitaku and co-workers[10] have reported the isolation of *trans*-1,2-dihydroxy-1,2-dihydroacronycine from *Sarcomelicope glauca*. Comparisons of ^1H-nmr data showed good accordance except for the signals due to substituents on aromatic rings. Thus the presence of *trans*-3,4-dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-pyran system was determined. From the results mentioned above, the structure of *trans*-dihydroxycitracridone-I was concluded to be 2.

EXPERIMENTAL

Extraction and Isolation: The dried roots (1.2 kg) of Marsh grapefruit cultivated and collected at the Fruit Tree Research Station was extracted with acetone for 40 h under reflux (3x 2 l). The acetone extract (138 g) was chromatographed over silica gel (1 kg) with successive elution with hexane, benzene, CH_2Cl_2, acetone-CH_2Cl_2, acetone and MeOH. The CH_2Cl_2 eluate was submitted to repeated preparative thin layer chromatography (ptlc) [solvent: isopropyl ether, $CHCl_3$:acetone (9:1), benzene:acetone (8:2), $CHCl_3$:MeOH (19:1)] furnished to give furoparadine (1) (1.3 mg). The acetone-CH_2Cl_2 eluate was subjected to repeated ptlc [solvent: acetone:hexane (1:1), $CHCl_3$:MeOH (9:1), benzene:MeOH (9:1)] to give *trans*-dihydroxycitracridone-I (2)(5.9 mg).

Furoparadine (1): Yellow oil, high ms: m/z 311.0788 (M^+, found), 311.0794 (calcd for $C_{17}H_{13}NO_5$); EIms m/z: 311 (M^+, base peak), 298, 297, 296, 295, 268, 267, 253, 240, 155, 148; ir ν_{max} ($CHCl_3$, cm^{-1}): 1625, 1600, 1560; uv λ_{max} (EtOH, nm): 261, 290, 313, 334 (sh), 367; ^1H nmr (acetone-d_6, δ): 14.65 (1H, s, 1-OH), 8.10 (1H, d, J= 9.2 Hz, H-8), 7.80 (1H, d, J= 2.4 Hz, H-12), 7.40 (1H, d, J= 2.4 Hz, H-11), 7.06 (1H, d, J= 9.2 Hz, H-7), 6.76 (1H, s, H-2), 4.26 (3H, s, N-Me), 3.89 (3H, s, OMe); ^{13}C nmr (acetone-d_6, δ): 154.15 (C-6), 143.45 (C-12), 138.50 (C-4a), 137.00 (C-10a), 129.66 (C-8), 123.54 (C-7), 108.91 (C-11), 93.03 (C-2), 69.34 (OMe), 45.65 (N-Me).

trans-Dihydroxycitracridone-I (2): Yellow cubes, mp 235-238°C, $[\alpha]_D$ +107° (c= 0.056, EtOH); EIms m/z: 387 (M^+), 370, 369 (base peak), 342, 341, 326, 311, 300, 298, 283; uv λ_{max} (EtOH, nm): 228 (sh), 271, 334; ir ν_{max} ($CHCl_3$, cm^{-1}): 3450 (br), 1625, 1600, 1565; ^1H nmr (DMSO-d_6, δ): 14.66 (1H, s, 1-OH), 7.83 (1H, d, J= 8.6 Hz, H-8), 6.93 (1H, d, J= 8.6 Hz, H-7), 6.00 (1H, s, H-2), 5.64 (1H, d, J= 5.5 Hz, 12-OH), 4.99 (1H, d, J= 7.9 Hz, 11-OH), 4.63 (1H, t, J= 7.9 Hz, H-11), 3.75 (3H, s, 5-MeO), 3.73 (3H, s, N-Me), 3.34 (1H, overlapped with D_2O, H-12), 1.40, 1.24 (each 3H, s, 13-Me); ^{13}C nmr (DMSO-d_6, δ): 180.28 (C-9), 162.74 (C-3), 159.89 (C-1), 156.15 (C-6), 148.49 (C-4a), 142.16 (C-5), 136.21 (C-10a), 121.48 (C-8), 116.33 (C-8a), 113.18 (C-7), 106.33 (C-4), 104.64 (C-9a), 96.48 (C-2), 78.58 (C-13), 75.97 (C-12), 68.08 (C-11), 60.55 (OMe), 45.09 (N-Me), 22.06 (13-Me), 17.56 (13-Me).

ACKNOWLEDGEMENT

The authors express their deep gratitude to Misses K. Suwa and S. Takeyama, Mukogawa Women's University, for measurements of ms and nmr spectra.

REFERENCES AND NOTES

1 Part XXII of "Studies of the constituents of domestic Citrus plants". Part XXI: Y. Takemura, M. Ju-ichi, K. Hatano, C. Ito, and H. Furukawa submitted to Chem. Pharm. Bull..

2 Y. Takemura, T. Nakata, M. Ju-ichi, M. Okano, N. Fukamiya, C. Ito, and H.

Furukawa, Chem. Pharm. Bull., 1994, **42**, 1213; Y. Takemura, M. Ju-ichi, M. Omura, M. Haruna, C. Ito, and H. Furukawa, Heterocycles, 1994, **38**, 1937, and references cited therein.

3 Y. Takemura, M. Ju-ichi, T. Hashimoto, Y. Kan, S. Takaoka, Y. Asakawa, M. Omura, C. Ito, and H. Furukawa, Chem. Pharm. Bull., 1994, **42**, 1548

4 Y. Takemura, J. Kuwahara, N. Nagareya, M. Ju-ichi, M. Omura, I. Kajiura, C. Ito, and H. Furukawa, Heterocycles, accepted.

5 J. Reish, K. Szendri, E. Minker, and I. Novak, Pharmazie, 1972, **27**, 208.

6 T. -S. Wu, H. Furukawa, C. -S. Kuoh, and K. -S. Hsu, J. Chem. Soc., Perkin Trans. I, **1983**, 1681.

7 A. Ulubelen, A. H. Mericli, F. Mericli, U. Sonmez, and R. Ilarslan, Nat. Prod.Lett., 1993, **1**, 269.

8 A. Ulubelen and B. Terem, Phytochemistry, 1988, **27**, 650.

9 A. Baumert, D. Groeger, J. Schmidt, and C. Mugge, Pharmazie, 1987, **42**, 67; J. Reisch, G. M. K. B. Gunaherath, J. Chem. Soc., Perkin Trans. I, **1989**, 1047.

10 S. Mitaku, A-L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and G. Chauviere, J. Nat. Prod., 1986, **49**, 1091.

Received, 28th September, 1994