NATSUCITRINE-I, -II: NEW ACRIDONE ALKALOIDS FROM CITRUS NATSUDAIDAI HAYATA[1)]

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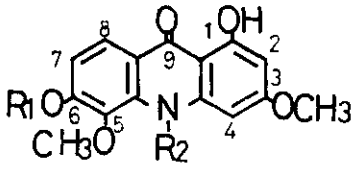
Abstract ——— Two new acridone alkaloids, natsucitrine-I (1a) and natsucitrine-II (1b) were isolated from the root bark of Citrus natsudaidai and their structures were elucidated on the basis of the spectral and chemical studies.

The chemical investigations of the alkaloid constituents of several species of the genus Citrus (Rutaceae) have indicated the presence of simple alkyl amines, quinolines and furoquinolines[2)], and recent studies have revealed the existence of many acridone alkaloids[3-6)]. We report here the isolation of two new acridone alkaloids from the root bark of Citrus natsudaidai Hayata and their structure determination.

Natsucitrine-I (1a): light yellow prisms, mp 292-293°C, $C_{15}H_{13}NO_5$. The UV spectrum (λ_{max} 214, 258, 264, 291, 328 and 365 nm) and the IR spectrum (3350, 1650 and 1600 cm^{-1}) showed the characteristic absorption of the 1-hydroxy-9-acridone system[7)]. The presence of two methoxyl groups was suggested by the CMR (δ 60.4, 55.2) and PMR (δ 3.93, 3.86) spectra[8)]. The presence of one NH and two hydroxyl groups was suggested by the three one-proton singlets at δ 14.35, 10.29 and 9.28 in the PMR spectrum. In the aromatic proton region, meta-coupled two-proton signals at δ 6.64 and 6.12 (2xd, J=1.96 Hz), and ortho-coupled two-proton signals at δ 7.90 and 6.90 (2xd, J=8.79 Hz) were observed. The lower ortho-coupled signal at δ 7.90 was characteristic of C_8-H in the 9-acridone system. Consequently, these four aromatic protons were assigned to locate at C_2, C_4, C_7 and C_8 in the 9-acridone skeleton. Furthermore, the NOE experiment showed 17.3 and 21.9% enhancements of the signals

at δ 6.64 and 6.12, respectively, on irradiation at the frequency corresponding to the O-methyl proton signal at δ 3.93. On the other hand, no NOE enhancement between C_7-H at δ 6.90 and the methoxyl protons at δ 3.86 suggested the location of a methoxyl and a hydroxyl groups at C-5 and C-6, respectively. The above data were in good accord with the structure 1a for natsucitrine-I.



1a: $R_1=R_2=H$ 2a: $R_1=H$, $R_2=CH_3$

1b: $R_1=CH_3$, $R_2=H$ 2b: $R_1=R_2=CH_3$

Natsucitrine-II (1b): light yellow needles, mp 246-247°C, $C_{16}H_{15}NO_5$, UV λ_{max} 215, 257, 266, 289 and 329 nm; IR ν_{max}^{KBr} 3360, 1640 and 1605 cm^{-1}. The UV and IR spectra indicated the characteristic absorption of the 1-hydroxy-9-acridones. The CMR studies revealed the presence of three methoxyl groups at δ 60.8, 56.2 and 55.3[8]. In the PMR spectrum, intramolecular hydrogen-bonded one hydroxyl proton signal due to the C-1 hydroxyl group in the 9-acridone skeleton was observed at δ 14.26. In addition, one NH proton singlet at δ 10.30, meta-coupled two-proton signals at δ 6.64 and 6.12 (2xd, J=1.94 Hz), and ortho-coupled two-proton signals at δ 7.11 and 8.00 (2xd, J=9.28 Hz) were observed. Treatment of 1a with diazomethane gave yellow needles, mp 244-245°C, which were identified with 1b by comparisons of TLC and IR spectrum. On the basis of these data, the structure of natsucitrine-II was assigned unequivocally to 1b.

The structures of natsucitrine-I and natsucitrine-II correspond to des N-methylated citpressine-I (2a) and citpressine-II (2b)[3], respectively. Our present study indicates the first example of the isolation of the NH type acridone alkaloids from Citrus species.

EXPERIMENTAL

Extraction and Isolation : The air-dried root bark of C. natsudaidai (1.5 Kg) was extracted with acetone. The acetone extract (119 g) was subjected to silica gel column with benzene, dichloromethane, acetone and methanol as an eluent. The dichloromethane eluate was rechromatographed on silica gel and eluted with benzene-acetone (9:1) to afford natsucitrine-II (1b), (41.6 mg). The acetone

fraction was also subjected to silica gel column chromatography and elution with acetone-dichloromethane (1:4) gave natsucitrine-I (1a) (54.5 mg).

Natsucitrine-I (1a): light yellow prisms, mp 292-293°C (from MeOH). ms m/z: 287 (M^+, base peak), 273, 272, 258, 244, 216. uv λ_{max}^{EtOH} nm (log ε): 214 (4.17), 258 (4.71), 264 (4.75), 291 (4.28), 328 (4.05), 365 (3.91). ir (cm^{-1}, KBr): 3350, 1650, 1600. ^{1}H-nmr (δ, acetone-d_6): 14.35 (1H, s), 10.29 (1H, s), 9.28 (1H, s), 7.90 (1H, d, J=8.79 Hz), 6.90 (1H, d, J=8.79 Hz), 6.64 (1H, d, J=1.96 Hz), 6.12 (1H, d, J=1.96 Hz), 3.93, 3.86 (each 3H, s). ^{13}C-nmr (δ, $CDCl_3$+DMSO-d_6): 180.3 (s), 165.1 (s), 163.8 (s), 153.6 (s), 143.4 (s), 136.5 (s), 133.0 (s), 121.4 (s), 113.7 (s), 112.6 (d), 103.9 (s), 94.7 (d), 90.0 (d), 60.4 (q), 55.2 (q).

Natsucitrine-II (1b): light yellow needles, mp 246-247°C (from benzene-acetone). ms m/z: 301 (M^+, base peak), 286, 268, 258, 243, 240. uv λ_{max}^{EtOH} nm (log ε): 215 (4.44), 257 (sh. 4.79), 266 (4.89), 289 (sh. 4.46), 329 (4.26). ir (cm^{-1}, KBr): 3360, 1640, 1605. ^{1}H-nmr (δ, acetone-d_6): 14.26 (1H, s), 10.30 (1H, s), 8.00 (1H, d, J=9.28 Hz), 7.11 (1H, d, J=9.28 Hz), 6.64 (1H, d, J=1.95 Hz), 6.12 (1H, d, J=1.95 Hz), 4.04, 3.93, 3.86 (each 3H, s). ^{13}C-nmr (δ, $CDCl_3$+DMSO-d_6): 180.5 (s), 165.4 (s), 163.8 (s), 155.0 (s), 143.6 (s), 135.9 (s), 134.5 (s), 121.6 (d), 114.9 (s), 107.4 (d), 103.9 (s), 94.8 (d), 90.1 (d), 60.8 (q), 56.2 (q), 55.3 (q).

Methylation of natsucitrine-I (1a) [Formation of natsucitrine-II (1b)]: Natsucitrine-I (1a, 8 mg) was dissolved in MeOH (10 ml) and the solution was treated with excess diazomethane. The product was chromatographed on silica gel with acetone as an eluent to give light yellow needles (4.7 mg). This was identified with natsucitrine-II (1b) by comparisons of IR and TLC.

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8) Both O-methyl and N-methyl group of acridone alkaloids resonate in the same region (δ 3.4-4.1) in the PMR spectrum and it is difficult to distinguish them.

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