

ACRIDONE ALKALOIDS V¹. NEW FURO- AND PYRANO-ACRIDONE
ALKALOIDS FROM GLYCOSMIS CITRIFOLIA (WILLD.) LINDL.

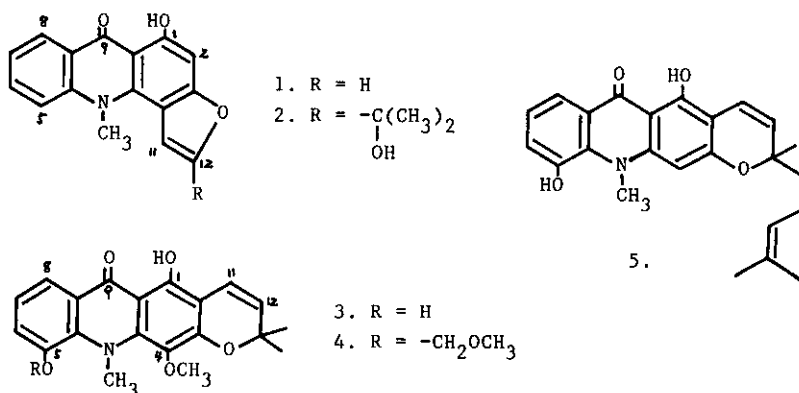
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Abstract — Two new furoacridone alkaloids, furofoline-I(1) and -II(2), and a new linear pyranocacridone alkaloid, pyranofoline(3) were isolated from the root and stem bark of Glycosmis citrifolia (Willd.) Lindl., and their structures were elucidated.

In continuations of studies of acridone alkaloids in Rutaceous plants, we have isolated five new acridone alkaloids, glyfoline¹, glycocitrine-I¹, -II¹, O-methyl-glycocitrine-II¹, and glycofoline² from Glycosmis citrifolia (Willd.) Lindl. collected in Taiwan. Here, we describe the structure elucidation of additional new furo- and linear pyranocacridone alkaloids named furofoline-I, -II, and pyranofoline, respectively obtained from the root and stem bark of the same plant.

Furofoline-I (1), yellow plates from acetone, m.p. 245-246°, C₁₆H₁₁NO₃. The UV spectrum [λ_{max}(MeOH) nm (log ε): 226(4.27), 245(4.43), 266(sh, 4.62), 274(4.76), 312(inf, 4.01), 323(4.02), and 405(3.62)] revealed the typical 9-acridone nucleus³. The presence of a phenolic hydroxyl group in furofoline-I was suggested by a positive FeCl₃ reaction. Further, this hydroxyl group must be situated peri to the carbonyl group in 9-acridone nucleus, since the alkaloid could not be methylated by diazomethane and showed no band attributable to the hydroxyl group in its IR spectrum [ν_{max}(CHCl₃) cm⁻¹: 1620, 1590, and 1570]. This was supported by the appearance of a singlet at δ 14.76 (disappeared in D₂O) in the ¹H-n.m.r. spectrum, due to a strongly hydrogen bonded phenolic proton at C-1. In the ¹H-n.m.r. of this alkaloid, the double doublets centered at δ 8.45 (J=2 & 8Hz) was characteristic to the H-8 in 9-acridones⁴, and the presence of signals at δ 7.33(1H, t, J=8Hz), 7.56(1H, t, J=8Hz), and 7.74(1H, dd, J=2 & 8Hz) due to H-7, -6, and -5, respectively, indicated that the ring A was unsubstituted. A sharp three-protons singlet due to an N-methyl group appeared at δ 4.20. In addition, three one-proton signals at δ 6.78(1H, d, J=1Hz), 7.15(1H, dd, J=2 &

1Hz), and 7.60(1H, d, J=2Hz) coupled each other, especially having a long range coupling between signals at δ 6.78 and 7.15 assigned to H-2 (or H-4) and H-11, respectively suggested the presence of 4,5,6-tri-substituted benzofuran moiety in this alkaloid⁵. In the NOE experiments, 18.4% enhancement of the signal at δ 7.15 (H-11) was observed on irradiation at the frequency corresponding to the N-methyl proton at δ 4.20. Therefore, the furan ring must have an angular orientation and the signal at δ 6.78 was assigned to H-2. The above data supported the structure 1 for furofoline-I.



Furofoline-II, yellow needles from acetone, m.p. 213-215°, $\text{C}_{19}\text{H}_{17}\text{NO}_4$. FeCl_3 test : positive. UV $\lambda_{\text{max}}(\text{MeOH})$ nm ($\log \epsilon$): 226(4.29), 247(4.43), 268(sh,4.61), 276(4.77), 312(inf, 4.03), 323(4.07), and 409(3.55). IR $\nu_{\text{max}}(\text{CHCl}_3)$ cm^{-1} : 3390, 1620, 1590, and 1535. $^1\text{H-n.m.r.}$ (CDCl_3) δ : 14.84(1H, s, washed out by D_2O), 8.43(1H, dt, J=2 & 8Hz, H-8), 7.70(1H, dd, J=2 & 8Hz, H-5), 7.40(1H, dd, J=2 & 8Hz, H-6), 7.34(1H, td, J=2 & 8Hz, H-7), 7.14(1H, d, J=1Hz, H-11), 6.71(1H, d, J=1Hz, H-2), 4.50(1H, s, washed out by D_2O), 4.31(3H, s, N- CH_3), and 1.67(6H, s, C- $(\text{CH}_3)_2$). The UV spectrum of furofoline-II showed a good similarity to that of furofoline-I, indicating it to have furo[2,3-c]acrid-6-one nucleus, the same as 1. Furthermore, the presence of a chelated hydroxyl group at C-1 and the non-substituted ring A in furofoline-II molecule were suggested by a lower field singlet at δ 14.84 and the signal pattern in aromatic proton region in $^1\text{H-n.m.r.}$, respectively. Appearance of a six-protons singlet at δ 1.67 accompanying with an alcoholic hydroxyl group signal at δ 4.50 instead of one of two protons signals of the furan ring at δ 7.60(H-12) in 1, and observation of the long range coupling between the signals at δ 6.71(H-2) and 7.14(H-11) were suggested with the presence

of an isopropanol group attached at C-12. This feature was also supported by the mass fragmentation pattern of furofoline-II: m/z 323(M^+), 308($M^+ - CH_3$, base peak), 305($M^+ - H_2O$), 290($M^+ - H_2O - CH_3$), 264($M^+ - C(OH)(CH_3)_2$), and 262. In the NOE experiments, irradiation of the N-methyl signal at δ 4.31 produced 15.2% enhancement of the signal at δ 7.14(H-11), and therefore, the furan ring was established as an angular orientation. On the basis of these results, furofoline-II should be represented by formula 2.

Several dihydro derivatives of furoacridones have been isolated from Rutaceae plants, and the first member of this series was rutacridone^{6,7}. However, occurrence of furoacridone itself has not been known in Nature. This is the first case for the isolation of the furoacridone alkaloids from natural sources.

Pyranofoline(3), orange needles from acetone, m.p. 212-214°, $C_{20}H_{19}NO_5$. IR $\nu_{max}(CHCl_3)$ cm^{-1} : 3240, 1630, 1610, and 1585. The UV spectrum [$\lambda_{max}(MeOH)$ nm (log ϵ): 230(4.26), 284(sh,4.53), 306(4.74), 332(sh,4.23), and 427(3.64)] was considerably close to that of glycofoline(5)² isolated from the same plant. The presence of phenolic hydroxyl groups was clear from the deep green $FeCl_3$ test, the IR band at 3240 cm^{-1} , and 1H -n.m.r. ($CDCl_3$) signals at δ 14.26 and 6.76 (disappeared in D_2O). The lower field signal indicated the presence of a strongly intramolecular hydrogen bonded hydroxyl group. And the 1H -n.m.r. ($CDCl_3$) of this alkaloid showed signals at δ 3.79 and 3.84(each 3H,s) due to a methoxyl and an N-methyl functions, respectively. The signals at δ 7.87(1H, dd, $J=3$ & 7Hz) and δ 7.00-7.20(2H, m)⁸ were assigned to H-8, being deshielded by the 9-carbonyl group, and other two protons on ring A, respectively. In addition, a six-protons singlet at δ 1.64, together with an AB-type signals at δ 5.58 and 6.77(each 1H, d, $J=10$ Hz) revealed the presence of a dimethylchromen system. The linear orientation of this was proposed by the following evidences: (1) The most intense UV absorption band of this alkaloid shows characteristic shift to longer wavelength at 306 nm than that of angular ones (at 270-295 nm)⁹. (2) In the 1H -n.m.r., the chemical shift value of H-11 at δ 6.77 is similar to that of glycofoline(5) having linear oriented chromen system. In this case, the proton signal of H-11 appeared at 0.1-0.2 ppm lower field than that of usual N-methylacridone alkaloids carrying angular chromen system. (3) In the ^{13}C -n.m.r. ($CDCl_3+DMSO-d_6$), C-11 signal appeared at δ 116.0 similar to that of glycofoline(5) at δ 116.3. These chemical shift values are about 4 ppm higher than those of N-methylacridones with angular oriented chromen system¹¹. N-Methyl carbon signal in the ^{13}C -n.m.r. observed at δ 46.4, indicating it to be substituted at both peri-positions of

N-methyl group^{11,12}. Next, in order to determine the location of a hydroxyl group, methoxymethyl ether derivative was prepared. Treatment of pyranofoline with chloromethyl methylether and NaOH in the presence of phase-transfer catalyst (Adogen 464 from Aldrich) afforded orange needles, m.p.112-114°, C₂₂H₂₃NO₆. UV λ max(MeOH) nm (log ε): 230(4.34), 280(sh, 4.45), 306(4.74), and 425(3.72). IR ν max(CHCl₃) cm⁻¹: 1630, 1610, 1585, and 1555. ¹H-n.m.r. (CDCl₃) δ: 14.13 (1H, s, 1-OH), 7.88(1H, dd, J=2 & 8Hz, H-8), 7.35(1H, dd, J=2 & 8Hz, H-6), 7.10 (1H, t, J=8Hz, H-7), 6.70(1H, d, J=10Hz, H-11), 5.53(1H, d, J=10Hz, H-12), 3.76 (6H, s, N-CH₃, O-CH₃), and 1.52(6H, s, C(CH₃)₂). In addition of these signals, methoxymethyl protons signals at δ 3.51(3H, s) and 5.25(2H,s) were observed. The NOE experiment showed 11.2% enhancement of the double doublet signal at δ 7.35(H-6) on irradiation at the frequency corresponding to the methylene proton signal at δ 5.25. And no NOE enhancement was observed at any protons signals on irradiation at the N-methyl and O-methyl signals at δ 3.76, expectedly.

On the basis of these results, pyranofoline should be represented by the formula 3.

This is the second example of the occurrence of the linear pyranocridone alkaloid from natural sources.

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8. The spectrum in CDCl₃+DMSO-d₆ solution showed clearly splitted signals as a typical ABC-type [δ 7.76(1H, dd, J=2 & 8Hz, H-8), 7.22(1H, dd, J=2 & 8Hz, H-6), and 7.08(1H, t, J=8Hz, H-7)].
9. Comparisons of the UV absorption spectra of linear pyranocridones with that of angular ones reveal that the main difference is in the position of the

most intense band. The UV spectra of acridone alkaloids, except for linear pyranoacridones have been reported by Brown et al.¹⁰

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11. Our unpublished data.

12. Detail discussions of ¹³C-n.m.r. spectra of acridone alkaloids will be reported elsewhere.

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