# ACRIDONE ALKALOIDS IV[1]. STRUCTURES OF FOUR NEW ACRIDONE ALKALOIDS FROM GLYCOSMIS CITRIFOLIA (WILLD.) LINDL.

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Abstract —— Four new acridone alkaloids, glyfoline (2a), glycocitrine-I (4), -II (5a) and its O-methyl ether (5b) were isolated from the root- and stem-bark of Glycosmis citrifolia, and characterized.
Glyfoline (2a) is the most oxygenated acridone alkaloid from natural sources.

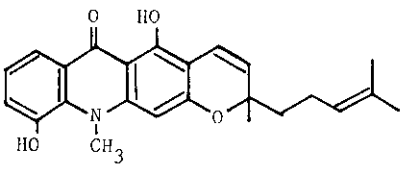
In previous paper[1], we have reported the first isolation of monoterpenoid acridone alkaloid glycofoline (1) from Glycosmis citrifolia(Willd.) Lindl. collected in Taiwan. Continuing the investigation of the constituents of the same plant, four new acridone alkaloids named glyfoline, glycocitrine-I, -II, and O-methylglycocitrine-II were isolated from the root- and stem-bark and characterized for the structure 2a, 4, 5a, and 5b, respectively.

Glyfoline (2a), orange plates, m.p. 215-217°(from acetone). The molecular formula $C_{18}H_{19}NO_7$ was fixed on the basis of the elemental analysis. The UV spectrum [ λ max(MeOH)(log ε): 223(sh, 4.17), 261(sh, 4.50), 272(4.56), 333(4.12) and 409(3.83) nm] showed the typical absorption associated with 9-acridone nucleus[2]. The bathochromic shifts of UV band with $NaOCH_3$ or $AlCl_3$, IR bands at 3400 and 1610 $cm^{-1}$, and $^1$H-n.m.r. signals at δ 14.10 and 8.76 (disappeared on $D_2O$) indicated the presence of two phenolic hydroxyl groups in glyfoline, and at least one of them chelated with 9-carbonyl moiety. In the aromatic proton region of the $^1$H-n.m.r. spectrum of glyfoline, only two-protons signals at δ 6.90 and 7.93 (each 1H doublet, J=10Hz) ortho-coupled each other were observed. The lower signal at δ 7.93 was characteristic to H-8 deshielded by 9-carbonyl moiety in an acridone system. Other signals in $^1$H-n.m.r. spectrum of glyfoline appeared at δ 3.78, 3.81, 3.84, 3.89, and 4.09 (each 3H singlet) were assigned to four methoxyls and an N-methyl group. These data, coupled with the empirical formula of glyfoline indicated the structure of glyfoline would be hexa-oxygenated N-methyl-9-acridone.

The foregoing evidence suggested the assignment of structure 2a for glyfoline.

The mass spectrum of glyfoline showed fragment peaks at m/z 361 ($M^+$, 13%), 346 (73%), 316 (100%), and 204 (75%). The fragment peak at m/z 204 could be assigned to the ion 3 which resulted from the cleavage of ring C and associated transfer of a hydrogen. This fragmentation is known as the characteristic of the 1,2,3,4-tetra-O-substituted acridone alkaloids[3].

The location of a hydroxyl group at C-6 (not at C-5) was confirmed by the following evidence. Treatment of 2a with chloromethylmethyl ether and NaOH in the presence of phase-transfer catalyst (Adogen 464 from Aldrich)[4] afforded 2b as orange needles, m.p. 105-109°, $C_{20}H_{23}NO_8$. $^1$H-n.m.r. δ 7.14(1H, d, J=9Hz, H-7), 8.04(1H, d, J=9Hz, H-8), 13.89(1H, s, $C_1$-OH), 3.80, 3.82, 3.91, 3.96, and 4.15(15H, 5s, 4 $OCH_3$ & N-$CH_3$). In addition of these signals, the methoxymethyl signals appeared at δ 3.57(3H, s) and 5.36(2H, s). The NOE experiment of this compound was carried out and 12% enhancement of the signal at δ 7.14 (H-7) on irradiation at the frequency corresponding to the methylene protons of the methoxymethyl ether moiety at δ 5.36 was observed.



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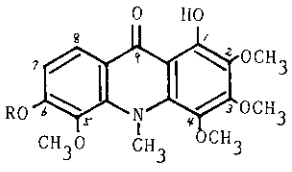
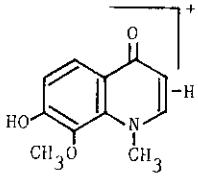
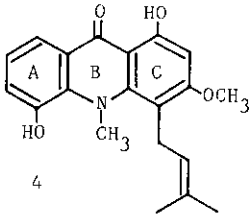


2a R=H
2b R=-$CH_2OCH_3$



3 m/z 204



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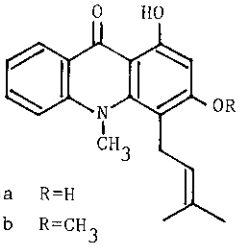

5a R=H
5b R=$CH_3$

On the result of this, the location of a phenolic hydroxyl group at C-6 in glyfoline was established. Consequently, glyfoline should be represented by the structure of 2a.

Glyfoline (2a) is the first base having hexa-O-substituents in N-methyl-9-acridone to be isolated from Nature.

Glycocitrine-I (4), m.p. 210-212°, $C_{20}H_{21}NO_4$, was isolated as orange yellow needles from $CHCl_3$ solution. The spectral data of this alkaloid were listed in Table 1. The UV and IR spectra exhibited bands characteristic 1-hydroxy-9-acridone system. This was also supported by the presence of one-proton sharp singlet at δ 14.23 which was assigned to the strongly hydrogen-bonded phenolic proton at C-1. In the aromatic proton region, ABX-pattern signals and one-proton sharp singlet were observed. Among them, one proton double-doublet at δ 7.72, X-part of the ABX-type signals was attributed to C-8 proton. This deshielding is expected because the proton lies in peri-position to the 9-carbonyl group. The presence of a prenyl moiety in glycocitrine-I was suggested by $^1$H-n.m.r. signals shown in Table 1, and MS fragments at $M^+$-15, $M^+$-55 and $M^+$-68 together with $^{13}$C-n.m.r.($CDCl_3$+DMSO-$d_6$) signals at δ 25.7(q), 18.0(q), 26.3(t), and 93.4(d). In $^{13}$C-n.m.r. spectrum of glycocitrine-I, N-methyl carbon signal was observed at δ 48.09. This lower chemical shift is characteristic of N-methyl carbon having substituents at both peri-positions (C-4 & C-5) in 9-acridone nucleus[6]. Thus, a sharp singlet at δ 6.37 in $^1$H-n.m.r was assigned to a lone aromatic proton of H-2[5]. Furthermore, appearance of the methylene carbon signal at δ 26.27 in $^{13}$C-n.m.r. was suggestive of the location of a prenyl moiety at C-4[6]. In NOE experiment on irradiation at the frequency corresponding to the methoxy group at δ 3.93, 24% enhancement of the singlet signal at δ 6.37(H-2) was

Table 1.

| | | Glycocitrine-I (4) | Glycocitrine-II (5a) |
|---|---|---|---|
| UV λ max nm(log ε) in MeOH | | 228(4.17),268(4.57), 322(sh,4.01),337(4.07), 415(3.58) | 226(4.27),251(4.48),268(sh,4.54), 275(4.74),304(4.12),334(3.95), 405(3.77) |
| IR ν max(KBr) $cm^{-1}$ | | 3240, 1620, 1585, 1565 | 3400, 1610, 1585, 1560 |
| $^1$H-n.m.r. δ (4): in $(CD_3)_2CO$ (5a): in $(CD_3)_2CO$ +$CDCl_3$ | $C_1$-OH | 14.23 | 14.63 |
| | $C_5$-OH | 9.25 | 9.46 |
| | $N^5$-$CH_3$ | 3.65 | 3.88 |
| | O-$CH_3$ | 3.93 | ..... |
| | H-8 | 7.72(1H,dd, J=2 & 8Hz) | 8.18(1H,dd, J=2 & 8Hz) |
| | H-7 | 7.12(1H,t, J=8Hz) | 7.20(1H,t, J=8Hz) |
| | H-6 | 7.28(1H,d, J=8Hz) | 7.70(1H,t, J=8Hz) |
| | H-5 | ..... | 7.54(1H,d, J=8Hz) |
| | H-2 | 6.37(1H,s) | 6.24(1H,s) |
| | Prenyl | 1.68(3H,s), 1.77(3H,s) 3.47(2H,d, J=7Hz) 5.30(1H,m) | 1.70(3H,s), 1.76(1H,s) 3.47(2H,d, J=7Hz) 5.26(1H,m) |
| MS m/z | | 339($M^+$, 50%), 324(51%), 308(16%) 294(25%), 284(37%), 282(50%), 271(100%) | 309($M^+$, 51%), 294(37%), 264(10%) 254(25%), 252(46%), 241(100%) |

observed. However, on the irradiation to the N-methyl group at δ 3.65, no NOE enhancement was observed at any aromatic protons, expectedly.

On the basis of these spectral data, coupled with the facts of a positive Gibbs' reaction and giving no cyclization product with acids, the structure 4 was proposed for glycocitrine-I.

Glycocitrine-II (5a), orange needles from acetone, m.p. 168-169°, $C_{19}H_{19}NO_3$, showed a deep green color reaction with $FeCl_3$. The UV and IR spectra, and $^1$H-n.m.r. signal at δ 14.63 (Table 1) revealed a typical 1-hydroxy-9-acridone as similar in 4. Furthermore, four aromatic protons signals coupled each other due to the protons in non-substituted A ring, and a one-proton singlet assigned at either H-2 or H-4 were observed[5]. In addition, the presence of a prenyl moiety in glycocitrine-II as in glycocitrine-I (4) was also suggested by $^1$H-n.m.r. and MS spectra shown in Table 1. Treatment of glycocitrine-II with diazomethane or $CH_3I/K_2CO_3$ in acetone afforded a mono-methyl ether as orange needles, m.p. 134-135° (acetone), $C_{20}H_{21}NO_3$. $^1$H-n.m.r.(acetone-$d_6$) δ : 3.86(3H,s, N-$CH_3$), 3.93(3H,s, $OCH_3$), 6.34(1H,s, H-2), 7.21(1H,t, J=8Hz, H-7), 7.52(1H,d, J=8Hz, H-5), 7.70(1H,t, J=8Hz, H-6), 8.18(1H,dd, J=2 & 8Hz, H-8), 14.70(1H,s, $C_1$-OH); 1.72(3H,s), 1.76(3H,s), 3.42(2H,d, J=7Hz), 5.30(1H,m): prenyl. This compound was also isolated from the same plant and identified by comparisons of $^1$H-n.m.r., MS, and IR spectra, and mixed m.p. The $^{13}$C-n.m.r. spectrum of this compound showed the signals at δ 43.8 and 27.1 assigned to an N-methyl carbon and a methylene carbon of the prenyl moiety, respectively. The chemical shift values of these carbons suggested the location of the prenyl moiety at C-4[7,8]. The structure of glycocitrine-II, and its O-methyl ether can thus be assigned to formula 5a[9] and 5b, respectively.

AKNOWLEDGEMENT We thank Dr. Y. Terada in our University for the measuring NOE n.m.r. spectra.

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5. The probability of H-3 can ruled out by the biogenetic consideration of naturally occurring hydroxylated acridone alkaloids[11].
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7. In our knowledge, if the prenyl moiety attached at C-2, signals of these carbons were expected to appear higher field at $\delta$ 33-35[8] and 21.5-22.5, respectively[6].
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Received, 19th February, 1982