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ALKALOIDS OF THE LEAVES OF *GLYCOSMIS BILOCULARIS*

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Key Word Index—*Glycosmis bilocularis*; Rutaceae; alkaloids; 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (5-hydroxyarborinine); arborine; arborinine; glycorine; kokusaginine; skimmianine.

Abstract—Six alkaloids have been isolated from the leaves of *Glycosmis bilocularis*, 5 of which are known compounds viz. arborine, arborinine, glycorine, kokusaginine and skimmianine, all previously isolated from other species of *Glycosmis*. The sixth alkaloid was identified as 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (5-hydroxyarborinine).

INTRODUCTION

As part of our examination of Asian Rutaceae, we have investigated the alkaloids of the leaves of *Glycosmis bilocularis* [1], Thw., a rare species found in the dry zone of Sri Lanka. Other species of *Glycosmis* have been reported [2–5] to contain acridone, furoquinoline and quinazoline alkaloids, but no 5-hydroxyacridones have been reported from this genus, although their occurrence in Rutaceae has been established [6–8]. We now report the isolation of a new 5-hydroxyacridone, along with 5 known alkaloids, from the leaves of *G. bilocularis*.

RESULTS AND DISCUSSION

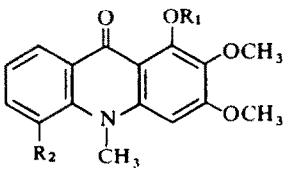
The leaves were boiled with water in a flask equipped with a trap [9] to separate the essential oil and the aqueous extract obtained was evaporated to dryness. Preparative-TLC of a chloroform extract of the resulting solid yielded the alkaloids arborine (**2a**), glycorine (**2b**) and skimmianine (**3a**).

The leaves after extraction were oven-dried, powdered and extracted in a Soxhlet apparatus successively with petrol (bp 60–80°), chloroform and methanol. On standing (24 hr), a yellow solid separated from the petrol extract, and preparative-TLC of this solid yielded arborinine (**1a**), skimmianine and an unknown alkaloid (A).

The petrol mother liquors and the chloroform extract were separately extracted with N HCl followed by N NaOH and the acid- and base-soluble compounds were recovered from their respective extracts. The base-soluble fraction in each case consisted solely of alkaloid A. Both acid-soluble fractions contained arborinine, kokusaginine (**3b**) and skimmianine, and the acid-soluble fraction of the chloroform extract contained in addition arborine and glycorine.

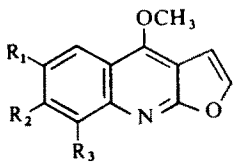
From the aqueous, petroleum, and chloroform extracts of the leaves of *G. bilocularis* we have, therefore, isolated 6 alkaloids: arborine (0.011%), arborinine (0.012%), glycorine (0.005%), kokusaginine (0.005%), skimmianine (0.015%) and alkaloid A (0.014%). The known alkaloids were identified by comparison (TLC, mp, mmp, spectra) with authentic samples.

Alkaloid A was not identifiable with any of the known Rutaceae alkaloids. Its UV spectrum suggested an acri-



1a $R_1 = R_2 = H$
1b $R_1 = H; R_2 = OH$
1c $R_1 = H; R_2 = OCH_3$
1d $R_1 = CH_3; R_2 = OCH_3$
1e $R_1 = H; R_2 = OCOCH_3$
1f $R_1 = COCH_3; R_2 = OCOCH_3$

2a $R = CH_2Ph$
2b $R = H$



3a $R_1 = H; R_2 = R_3 = OCH_3$
3b $R_1 = R_2 = OCH_3 = R_3 = H$

done nucleus and the IR spectrum was very like that of arborinine (**1a**) with peaks at 3230 (OH) and 1630 cm^{-1} (CO) suggesting hydrogen bonding and the presence of a *peri*-OH group. Accurate mass measurement gave the molecular formula as $C_{16}H_{15}NO_5$ (M^+, 301) and PMR indicated the presence of 3 Me groups at δ 3.79 (OCH_3), 3.81 (NCH_3), and 3.95 (OCH_3), the assignment of the NCH_3 peak being based on shifts in the peak positions in the presence of TFA [10, 11]. The PMR of alkaloid A in DMSO-d_6/CD_3SOCD_2Na showed shifts for all the aromatic protons, indicating that anion substituents were present on both ring A and ring C and the aromatic proton absorptions (particularly well defined in acetone-d_6 solution) showed an ABX pattern similar to that of tecleanthine [6], *N*-methylatalaphylline [7] and 3,12-dihydro-6,11-dihydroxy-3,3,12-trimethylpyrano(2,3-c)acridin-7-one [8], suggesting the presence of a OH group at position 5 of the acridone. A singlet at δ 6.37 was considered, on comparison with other noracridones, to be at too high a field for a C-2 proton and it was therefore assigned to a C-4 proton and the methoxyls were assigned to C-2 and C-3. A sharp singlet at δ 13.97 confirmed the presence of a *peri*-OH group. We therefore propose structure **1b** (1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone) for alkaloid A and suggest the trivial name 5-hydroxyarborinine.

This assignment is supported by MS, being very similar to that of arborinine with major peaks occurring at M^+-15, M^+-30, M^+-43, M^+-58, arising from concerted losses of small fragments such as Me, CO, CH_2N, CHO and CH_2O. In both cases the base peak was due to the fragment M^+-15, as would be expected for *N*-methyl-acridones [13].

Methylation of alkaloid A with diazomethane gave a monomethyl derivative (**1c**) whilst use of methyl iodide or dimethyl sulphate produced a mixture of mono-(**1c**) and di-Me (**1d**) derivatives which were easily separated by preparative-TLC. Similarly, on acetylation, both mono- (**1e**) and di-acetyl (**1f**) derivatives were obtained, as expected since the resistance of 1-hydroxyacridones to methylation and acetylation is well known.

TLC of cold chloroform extracts of the leaves revealed the presence of all 6 alkaloids, indicating that none were produced as a result of the extraction and purification procedures, and, in particular, that the noracridones isolated were present as such in the plant. We could not detect 1-methoxyacridones in our extracts.

5-Hydroxyacridones also occur in *Atalantia* which is taxonomically very close to *Glycosmis*. Engler [14] placed both genera in the same subtribe (Hesperethusinae) of the sub-family Aurantioideae, whilst Swingle [15], in his sub-division of this sub-family, placed the two genera in adjacent tribes. 5-Methoxyacridones occur in Rutaceae in *Teclea* species [6, 16] (sub-family Toddalioideae) and it has been suggested [17] that the Aurantioideae may have evolved from a Rutoideae/Toddalioideae complex. The occurrence of 5-oxygenated acridones in both sub-families may provide additional biochemical support for this concept.

EXPERIMENTAL

All TLC separations were carried out on Si gel. TMS was used as internal standard for all PMR spectra which were recorded in $CDCl_3$ unless otherwise stated

The leaves of *G. bilocularis* [1] (600 g) were steam distilled in a Likens and Nikerson [9] apparatus for 12 hr, filtered, and the aq. extract evapd to a dry powder (87 g). $CHCl_3$ (Soxhlet) extraction of this solid followed by separation by TLC ($CHCl_3$–MeOH; 19:1) yielded 3 alkaloids, C, D and F. The leaves after steam distillation were oven-dried (40°), powdered and extracted successively (Soxhlet, 32 hr) with petrol, (60–80°), $CHCl_3$ and MeOH (8 l. of each). The extracts were concd to 200 ml and left in a refrigerator for 24 hr. A yellow solid separated from the petrol extract and prep.-TLC of this solid (C_6H_6–EtOAc–MeOH, 40:40:1; or $CHCl_3$–MeOH, 19:1) gave alkaloids A, B and D.

The petrol mother liquor was extracted with N HCl (5 × 200 ml) which was neutralized ($NaHCO_3$) and extracted with $CHCl_3$. The evapd $CHCl_3$ extract was separated by prep.-TLC ($CHCl_3$–MeOH, 19:1) into 3 fractions and elution of these with $CHCl_3$ and MeOH yielded alkaloids B, D and E. The residual petrol extract was extracted with N NaOH (5 × 200 ml) which was acidified (HCl) and extracted with $CHCl_3$. Prep.-TLC of the evapd $CHCl_3$ soln gave alkaloid A.

The $CHCl_3$ extract of the leaves was treated in a similar manner to the petrol mother liquor: the acid-soluble fraction yielding alkaloids B, C, D, E and F, and the base-soluble fraction again yielding only alkaloid A.

Similar alkaloid fractions were combined

Alkaloid A (*1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone*, **1b**) (92 mg) was purified by TLC (C_6H_6–EtOAc, 6:4) and crystallized (Et_2O–petrol) as an orange-yellow solid (82 mg, 0.014%), mp 206–207°. R_f (C_6H_6–EtOAc, 6:4) 0.63, R_f (C_6H_6–EtOH, 9:1) 0.35. λ_{max}^{EtOH} nm 272 (log ε 4.60), 321 (4.32), 335 (sh 4.26), 405 (3.48). $\lambda_{max}^{EtOH\ NaOH}$ nm: 273 (4.65), 298 (sh 4.47), 338 (4.31). ν_{max}^{KBr} cm^{-1}: 3230 (OH), 1630 (CO), 1598, 1560, 1545, 1490, 1445, 1400, 1358, 1265, 1248, 1200, 1182, 1148, 1115, 1090, 1062, 1000, 910, 850, 800, 765, 740. δ (100 MHz): 3.79 (*s*, 3H, OCH_3, C-2), 3.81 (*s*, 3H, NCH_3), 3.95 (*s*, 3H, OCH_3, C-3), 6.37 (*s*, 1H, C-4), 7.18 (*m*, 2H, C-6 and C-7), 7.9 (*dd*, 1H, C-8), 13.97 (*s*, 1H, OH, C-1); δ (100 MHz, CD_3COCD_3) 3.76 (*s*, 3H, OCH_3, C-2), 3.82 (*s*, 3H, NCH_3), 3.97 (*s*, 3H, OCH_3, C-3), 6.4 (*s*, 1H, C-4), 7.14 (*t*, 1H, C-7, $J_{6,7} = J_{7,8} = 8$ Hz), 7.3 (*dd*, 1H, C-6, $J_{6,7} = 8$ Hz, $J_{6,8} = 2$ Hz), 7.79 (*dd*, 1H, C-8, $J_{6,8} = 2$ Hz, $J_{7,8} = 8$ Hz). δ (100 MHz, $CDCl_3$ + trace TFA) 3.85 (*s*, 3H, OCH_3, C-2), 4.03 (*s*, 6H, NCH_3 and OCH_3 at C-3); δ (100 MHz, $CDCl_3$ + 10% TFA) 3.87 (*s*, 3H, OCH_3 C-2), 4.06 (*s*, 3H, OCH_3, C-3), 4.13 (*s*, 3H, NCH_3). MS (*m/e*) 301 (M^+ 77%), 286 (100), 285 (33), 271 (44), 243 (41), 228 (21), 226 (31), 215 (33), 185 (39), m* 271.7 (301 → 286). (Accurate mass 301.0952: $C_{16}H_{15}NO_5$ requires: 301.0950. Found: C, 63.5; H, 4.99; N, 4.63. $C_{16}H_{15}NO_5$ requires: C, 63.8; H, 5.02, N, 4.65%)

Methylation of alkaloid A. (a) *Using diazomethane.* Alkaloid A (20 mg) in MeOH (5 ml) was cooled (0°) and excess of a cooled soln of CH_2N_2 in Et_2O added. After stirring at room temp. for 2 days, the solvent was evapd and the residual yellow solid (20 mg) purified by prep.-TLC (toluene–EtOAc, 3:2). The major product (R_f 0.81) crystallized from EtOH as yellow needles, mp 168–169° and was characterized as the monoMe derivative (1-hydroxy-2,3,5-trimethoxy-10-methyl-9-acridone, **1c**). λ_{max}^{EtOH} nm: 266 (log ε 4.52) 276 (sh, 4.34), 283 (sh 4.52), 316 (4.08), 337 (sh, 3.96), 350 (3.82), 410 (3.76); $\lambda_{max}^{EtOH\ NaOMe}$ nm: 266 (4.52), 284 (sh, 4.26), 318 (3.92), 336 (sh, 3.73), 418 (3.46); $\lambda_{max}^{EtOH\ AlCl_3}$ nm: 267 (sh, 4.52), 279 (sh, 4.16), 289 (4.02), 350 (3.92), 468 (3.76) ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1630, (C=O) δ (100 MHz) 3.73 (*s*, 3H, CH_3), 3.76 (*s*, 3H, CH_3), 3.94 (*s*, 3H, CH_3), 3.97 (*s*, 3H, CH_3), 6.35 (*s*, 1H, C-4), 7.1–7.24 (*m*, 2H, C-6, C-7), 7.91 (*dd*, 1H, C-8, $J_{7,8} = 7.5$ Hz, $J_{6,8} = 3.5$ Hz), 13.98 (*s*, 1H, OH at C-1, exchanging with D_2O). MS (*m/e*) 315 (85%), 301 (65), 300 (100), 285 (66), 284 (54), 270 (43), 257 (34), 256 (36), 242 (33), 228 (21), 224 (27), 200 (25), 158 (44), 135 (28), 115 (35), 91 (41), 77 (54). (M^+, 315.1104; $C_{17}H_{17}NO_5$ requires: 315.1106.) (b) *Using MeI.* Alkaloid A (20 mg), dry K_2CO_3 (500 mg) and MeI (1 ml) in dry Me_2CO (5 ml) was stirred at room temp. and the reaction monitored by TLC. Formation of the monoMe derivative (**1c**) was very rapid but the dimethylated compound (**1d**) was produced more slowly. After 4 days the reaction mixture was

filtered and evapd to give a brown solid which was purified by prep.-TLC (toluene–EtOAc, 3:2). Two products were isolated, the minor product being the monoMe derivative (**1c**). The major product was characterized as the diMe ether of alkaloid A (1,2,3,5-tetramethoxy-10-methyl-9-acridone, **1d**). R_f 0.17, yellow needles (from EtOH), mp 97–98°. λ_{max}^{EtOH} nm: 267 (log ε, 4.88), 308 (4.42), 324 (sh, 4.01), 390 (3.67). ν_{max}^{KBr} cm^{-1}: 1630 (C=O). δ (100 MHz): 3.64 (*s*, 3H, CH_3), 3.79 (*s*, 3H, CH_3), 3.98 (*s*, 9H, 3 × CH_3), 6.36 (*s*, 1H, C-4), 7.05 7.28 (*m*, 2H, C-6, C-7), 7.87 (*dd*, 1H, C-8, J_{7-8} = 7 Hz, J_{6-8} = 4 Hz). MS (*m/e*) 329 (85%), 314 (100), 300 (59), 298 (61), 286 (59), 284 (52), 270 (80), 256 (60), 242 (46), 228 (43), 200 (44), 198 (45), 149 (41), 126 (39), 115 (37), 77 (53). (M$^+$ 329.1260; $C_{18}H_{19}NO_5$ requires: 329.1263.)

Acetylation of alkaloid A. (a) *Monoacetate* (**1e**). Alkaloid A (30 mg), HOAc (0.3 ml), Ac_2O (1 ml) and NaOAc (1 g) were stirred (room temp.) for 3 days, diluted with H_2O and extracted with $CHCl_3$. Evapn of the dried $CHCl_3$ extract gave a yellow solid which crystallized (Me_2CO–hexane) as yellow prisms, mp 128–129°. λ_{max}^{EtOH} nm: 267 (sh), 273, 309, 416. $\lambda_{max}^{EtOH-NaOMe}$ nm: 266 (sh), 275, 320, 337 (sh), 432. $\lambda_{max}^{EtOH\ AlCl_3}$ nm: 276, 286, 318, 335, 466. ν_{max}^{KBr} cm^{-1}: 1763 (acetyl C=O), 1630 (acridone C=O). δ (60 MHz): 2.36 (*s*, 3H, acetate CH_3), 3.83 (*s*, 3H, OCH_3), 3.9 (*s*, 3H, NCH_3), 4.01 (*s*, 3H, OCH_3), 6.64 (*s*, 1H. C-4), 7.33 (*m*, 2H, C-7, C-6), 8.22 (*m*, 1H, C-8). 14.67 (*s*, 1H, OH at C-1, exchanging with D_2O). M$^+$ at 343 for $C_{18}H_{17}NO_6$. (b) *Diacetate* (**1f**). Alkaloid A (30 mg), Ac_2O (1 ml) and Py (1 ml) were heated at 100° for 2 hr, poured into H_2O and extracted with $CHCl_3$. Evapn of the dried $CHCl_3$ extract gave a yellow residue which was purified by TLC (toluene–EtOAc, 3:2) yielding the diacetate as the main product (R_f 0.43). It crystallized from Me_2CO–hexane as pale yellow prisms, mp 192–193°. λ_{max}^{EtOH} nm: 272.5, 301 (sh), 402. ν_{max}^{KBr} cm^{-1}: 1763 (acetyl C=O), 1630 (acridone C=O). δ (60 MHz): 2.44 (*s*, 3H, acetate CH_3), 2.56 (*s*, 3H, acetate CH_3), 3.82 (*s*, 3H, OCH_3), 3.9 (*s*, 3H, NCH_3), 4.02 (*s*, 3H, OCH_3), 6.61 (*s*, 1H, C-4), 7.42 7.72 (*m*, 2H, C-6, C-7), 8.32 (*d*, 1H, C-8, J_{7-8} = 8 Hz). M$^+$ 385 for $C_{20}H_{19}NO_7$.

Alkaloid B (*arborinine*, **1a**) (80 mg) was purified by TLC (C_6H_6–EtOAc, 3:2) to give a yellow powder (72 mg, 0.012%), crystallized from EtOH–Et_2O as yellow needles (65 mg), mp 174–176°, undepressed on admixture with authentic arborinine. R_f (Me_2CO–petrol–Et_2NH, 2:7:1) 0.18; R_f (C_6H_6–EtOAc: 3:2) 0.48; R_f ($CHCl_3$–MeOH, 19:1) 0.79. UV, IR, PMR and MS data identical with an authentic sample. (M$^+$ 285.0999, $C_{16}H_{15}NO_4$ requires: 285.1001.)

Alkaloid C (*arborine*, **2a**) (78 mg) was purified by TLC (C_6H_6–EtOAc; 3:2) to give a white powder (68 mg, 0.011%) which crystallized from C_6H_6–EtOAc (60 mg), mp 154–156°, undepressed on admixture with authetic arborine. R_f ($CHCl_3$–MeOH, 19:1) 0.52; R_f (C_6H_6–EtOH, 9:1) 0.22; R_f (*n*-BuOH–HOAc–H_2O, 6:1:1) 0.65. UV and IR spectra identical with an authentic sample. δ(100 MHz) 3.62 (*s*, 3H, NCH_3), 4.27 (*s*, 2H, benzyl CH_2), 7.25–7.80 (*m*, 8H, phenyl ring protons and protons at C-6, C-7 and C-8), 8.33 (*dd*, 1H, C-5). MS (*m/e*) 250 (M$^+$, 81%), 249 (100), 235 (44), 234 (40), 205 (22), 180 (25), 133 (24), 132 (31), 125 (24), 121 (29), 105 (65), 104 (68), 91 (65), 78 (56), 77 (61).

Alkaloid D (*skimmianine*, **3a**) (103 mg) was purified by TLC (C_6H_6–EtOAc, 3:2) giving a white solid (92 mg, 0.015%) which crystallized from EtOH (85 mg), mp 174–176°, mmp 176°. R_f (Me_2CO–petrol–Et_2NH, 2:7:1) 0.27; R_f ($CHCl_3$–MeOH, 19:1) 0.75; R_f (C_6H_6–EtOH, 9:1) 0.41. Identical in all respects with an authentic sample of skimmianine. (M$^+$ 259.0844; $C_{14}H_{13}NO_4$ requires: 259.0844.)

Alkaloid E (*kokusaginine*, **3b**) (38 mg) was purified by TLC (C_6H_6–EtOAc, 3:2) yielding a pale brown powder (32 mg, 0.005%), mp 170–172°. R_f (Me_2CO–petrol–Et_2NH: 2:7:1) 0.27; R_f (C_6H_6–EtOAc, 3:2) 0.50; R_f ($CHCl_3$–MeOH, 19:1) 0.79. UV, IR, PMR and MS data were identical with those of an authentic sample of kokusaginine. (M$^+$ 259.0841; $C_{14}H_{13}NO_4$ requires: 259.0844).

Alkaloid F (*glycerine*, **2b**) (32 mg, 0.005%) was purified by TLC (C_6H_6–EtOAc; 3:2) and crystallized (C_6H_6–EtOAc) as a white powder, mp 145–146°. R_f ($CHCl_3$–MeOH: 19:1) 0.13; R_f (*n*-BuOH–HOAc–H_2O, 6:1:1) 0.34; R_f (C_6H_6–EtOH, 9:1) 0.05. λ_{max}^{EtOH} nm 268 (log ε, 3.94), 277 (3.99), 306 (4.23), 317 (4.14); $\lambda_{max}^{EtOH\ AlCl_3}$ nm. 278 (4.09), 294 (4.04), 305 (3.90). ν_{max}^{KBr} cm^{-1}: 3340, 1705, 1665, 1600, 1518, 1463, 1380. δ (100 MHz): 3.76 (*s*, 3H, NCH_3), 7.27–7.88 (*m*, 4H), 8.12–8.44 (*m*, 2H). MS (*m/e*) 160 (M$^+$ 100%), 133 (47), 132 (71), 105 (66). 83 (42), 78 (30).

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