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NEW ALKALOIDS FROM *GLYCOSMIS MAURITIANA**

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Key Word Index—*Glycosmis mauritiana*; Rutaceae; roots; alkaloids; glycozoline; glycozolidine; dictamnine; skimmianine; arborinine; 1-hydroxy-3-methoxy-2-(3-methylbut-2-enyl)-*N*-methylacridan-9-one; 4,8-dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone; β-sitosterol; chemotaxonomy.

Abstract—Chemical investigation of the roots of *G. mauritiana* resulted in the isolation of two new alkaloids; 1-hydroxy-3-methoxy-2-(3-methylbut-2-enyl)-*N*-methylacridan-9-one (**1**) and 4,8-dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone (**6**). The structures of these new bases have been established by chemical and spectroscopic methods and confirmed in the case of **6** by its synthesis. Interestingly, the formic acid-catalysed cyclisation of **1** gave the dealkylated product **3** along with the pyrano-[2, 3-a]-acridine (**4**).

INTRODUCTION

There has been some controversy [1–5] regarding the identification of the local variety of the genus *Glycosmis*. *Glycosmis arborea* (Roxb.) DC. (Rutaceae) is found in India, Burma and frequently across the Ghats, while *G. pentaphylla* DC. is confined to South India, Sri Lanka, Burma, Bengal and Avadh forests. The isolation of different compounds from *G. arborea* has been undertaken mainly by Chakravarti and Pakrashi [6–8], while Chakraborty [9–12] and Govindachari [13] with their co-workers reported their studies on *G. pentaphylla* (Retz.) DC. and *G. pentaphylla* (Retz.) Correa, respectively. The confusion in nomenclature of *G. arborea* and *G. pentaphylla* resulted in many taxonomic discrepancies regarding species in the genus *Glycosmis* and prompted us to undertake a detailed investigation on the roots of *G. mauritiana* (Lam.) Tanaka, available plentifully in Gorakhpur. A search in the literature revealed that only one communication dealing with the isolation of hentricontane, hentricontanol, friedelin and vitexin from stem and leaves of *G. mauritiana* has been published [14].

RESULTS AND DISCUSSION

The compounds A, B, C, D, E and F, obtained by a combination of column chromatography and Si gel PLC, were identified as glycozoline, glycozolidine, β-sitosterol, dictamnine, skimmianine and arborinine on the basis of their physical properties and spectral data. The structures were confirmed by comparison of TLC, mmp and superimposable IR spectra with authentic samples.

Compound G, mp 134–36° was isolated as deep yellow needles by column chromatography on Si gel followed by PLC in C_6H_6–EtOAc (19:1). Its UV spectrum exhibited bands at λ_{max} 227, 252, 275, 305, 330 and 428 nm characteristic of a 9-acridone system [15–17]. Surprisingly, it did not show any shift with alkali while a bathochromic shift with aluminium chloride [18] indicated the presence of a chelated phenolic group. Repeated attempts to acetylate compound G with pyridine and acetic anhydride at room temperature, or methylation with diazomethane proved unsuccessful. A similar lack of reactivity of the *peri*-hydroxyl group has been observed with noracronycine [18], thus substantiating the earlier assignment. The IR spectrum of compound G showed bands at 1630, 1580 and 1550 cm^{-1} strongly reminiscent of an acridone nucleus. The partial structure of compound G was evident from its ^1H NMR and MS data. The former showed a sharp singlet at δ 14.53, which disappeared on deuteration. This low field signal was assigned to the strongly hydrogen-bonded phenolic proton. The double doublet centered at δ 8.2 (1H) was attributed to the C-8 proton [19]. This deshielding is expected because the proton lies in close proximity to the carbonyl group. The complex multiplets in the region δ 7.4–6.9 (3H) were assigned to aromatic protons at the C-5, C-6 and C-7 positions. The sharp singlet at δ 6.28 (1H) was assigned to the lone aromatic proton either at C-2 or C-4, consistent with the observation of Pakrashi *et al.* [20] that such upfield shifts have been noted with aromatic protons flanked by oxygen or nitrogen. The sharp singlets at δ 3.85 and 3.73 (3H each) were assigned to *O*-methyl and *N*-methyl groups, respectively. As all acridone alkaloids reported to date are oxygenated either at C-1 and/or C-3 positions, the methoxyl group in compound G was placed at C-3 (C-1 position being occupied by a hydroxyl group). The multiplet at δ 3.36 (2H) was due to benzylic protons and the vinylic proton appeared as multiplet centered at δ 5.23 (1H). Two singlets at δ 1.72 and 1.71 (3H each) were assigned to two vinylic methyl groups. The MS of compound G showed a M^+ at *m/e* 323 compatible

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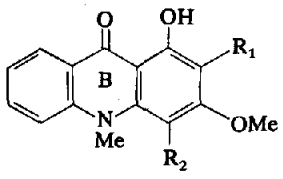
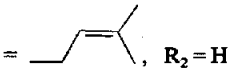
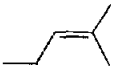
with the molecular formula $C_{20}H_{21}NO_3$. The base peak appeared at *m/e* 308 ($M^+ - 15$) and the fragmentation pattern was typical of acridone alkaloids; loss of Me from the dimethylallyl chain followed by loss of CO from ring B; an alternative mode of fragmentation involved the loss of HCO directly from ring B and was related to the presence of an *N*-methyl substituent [21]. On the basis of these observations, either structure **1** or **2** could be proposed for compound G.



1 R_1 =  , R_2 = H

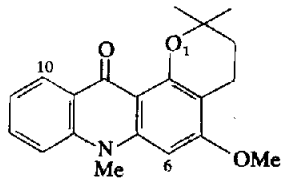
2 R_1 = H, R_2 = 

3 $R_1 = R_2 = H$

The monoacetyl derivative of compound G, prepared by heating it with pyridine and acetic anhydride, did not prove to be of much help in eliminating either of the two structures because similar chemical shifts have been noted for *ortho* and *para* positions in acridone alkaloids [18]. This difficulty was obviated by taking recourse to acid-catalysed cyclisation which could be expected to provide support in favour of either structures. Compound G, when heated with formic acid (98%) for 4 hr and after subsequent work up, gave a mixture of two compounds (G_1 and G_2) which were separated by PLC using C_6H_6–EtOAc (9:1) as developing solvent.

Compound G_1, mp 173–75° showed UV λ_{max} 253, 276 and 395 nm indicative of an acridone nucleus. It gave a positive ferric chloride test showing the presence of a phenolic hydroxyl group. The ^{1}H NMR spectrum revealed a singlet at δ 14.6 (1H) exchangeable with D_2O. The low field value was indicative of strong intramolecular hydrogen bonding between the C-1 hydroxyl and C-9 carbonyl substituents. A one-proton double doublet at δ 8.41 was assigned to the C-8 proton. The multiplets in the region 7.7–7.1 (3H) were assigned to protons at the C-5, C-6 and C-7 positions. The two-proton singlet at 6.28 could be assigned to the C-2 and C-4 protons. The singlets at 3.88 and 3.75 (3H each) were assigned to *O*-methyl and *N*-methyl protons. Surprisingly enough there were no protons for the dimethylallyl chain indicating structure **3** for G_1. This was confirmed by comparison of G_1 with an authentic sample of 1-hydroxy-3-methoxy-*N*-methylacridan-9-one [22] which was found to be identical with G_1 in all respects.

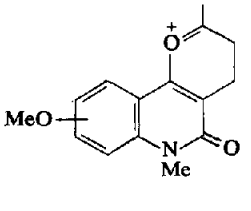
The ^{1}H NMR spectrum of compound G_2 showed a double doublet at δ 8.5 (1H) assigned to proton at C-10. The multiplets in the region 7.7–7 were assigned to the protons at the C-7, C-8 and C-9 positions. The singlet at 6.2 (1H) was assigned to the C-6 proton. The singlets at 3.89 and 3.68 (3H each) were assigned to *O*-methyl and *N*-methyl protons, respectively. The appearance of triplets at 2.64 (2H) and 1.81 (2H) and a singlet at 1.45 (6H) were reminiscent of a dimethylpyran ring confirming G_2 as a cyclised product possessing structure **4**. The UV spectrum of G_2 did not show the expected bathochromic shift on addition of aluminium chloride, confirming once again that the free phenolic hydroxyl group had participated in the cyclisation leading to structure **1** for compound G.



4

The UV spectrum of compound H exhibited bands at λ_{max} 240, 258, 285, 295 and 335 nm which remained unaffected on addition of either acid or base [23] indicating the presence of a 2-quinolone chromophore. The IR spectrum showed bands at 1635 (NCO), 1590, 1570, 735 (substituted benzene derivative) and 1235 (aromatic ether) cm^{-1}. The ^{1}H NMR spectrum showed two singlets at δ 1.67 and 1.82 (3H each) assigned to two vinylic methyl groups. A doublet at 3.5 (2H) was assigned to benzylic protons split by one neighbouring proton. Three singlets at δ 3.95, 3.88 and 3.85 (3H each) were assigned to one *N*-methyl and two *O*-methyl groups. A multiplet at 5.25 (1H) was assigned to a vinylic proton. The multiplets in the region 7.2–6.85 were assigned to two aromatic protons at C-6 and C-7. The deshielded double doublet at 7.35 (1H) could be due either to the proton at C-5 or that at C-8. The magnitude of the relative deshielding of this proton from the centre of multiplet of other aromatic protons was found to be 32 Hz confirming that H possessed a 4-alkoxy-2-quinolone system, consistent with the observation of Robertson *et al.* [24].

The MS of compound H was remarkably simple. It showed a M^+ at *m/e* 287 which was in agreement with the molecular formula $C_{17}H_{21}NO_3$ obtained by elemental analysis. The total ion current is carried by two ionic species, i.e. the M^+ at *m/e* 287 (77%) and 272 (100%; $M^+ - 15$). The high stability of the latter could be understood by the formation of a highly conjugated system (**5**) leading to either structure **6** or **7** for H.



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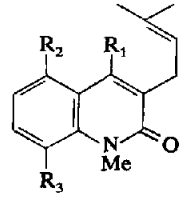
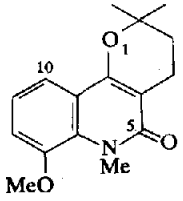


6 $R_1 = R_3 = OMe$, $R_2 = H$
7 $R_1 = R_2 = OMe$, $R_3 = H$
8 $R_1 = OMe$, $R_2 = H$, $R_3 = OH$
9 $R_1 = OH$, $R_2 = H$, $R_3 = OMe$

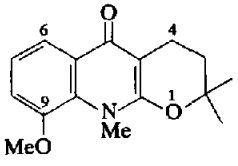
4,8-Dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone (**6**) has already been synthesized by Clarke and Grundon [25]. However, as an authentic sample of this compound could not be obtained, it was

resynthesized using essentially their procedure. Compound **6** thus obtained was identical in all respects (UV, IR, NMR and MS) with **H**, confirming its structure as 4,8-dimethoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone. It is interesting to note that its phenol (**8**) has recently been isolated as a natural product from *G. pentaphylla* [26].

Formic acid is a good hydride donor and with this ability it has probably effected deprenylation in 1-hydroxy-3-methoxy-2-(3-methylbut-2-enyl)-*N*-methylacridan-9-one under refluxing conditions to furnish **3**. To our knowledge this is the first instance of deprenylation in alkaloids using this reagent. In order to explore its suitability as a general dealkylating reagent, we have studied the reaction of 4-hydroxy-8-methoxy-3-(3-methylbut-2-enyl)-*N*-methyl-2-quinolone (**9**) with formic acid. Contrary to our expectation of a dealkylated product, two products (H_1 and H_2) were isolated by PLC and could be assigned structures **10** and **11**, respectively, on the basis of their physical characteristics.



10



11

The present work is an interesting exercise in the study of the distribution of natural products for taxonomic purposes. Furoquinoline, acridone and quinazolone alkaloids have been reported from *G. arborea*. In view of the present isolation of quinolone and carbazole bases, in addition to the furoquinolines and acridones in *G. mauritiana* and Brizicky's classification [27] of *Glycosmis* genus, the possibility that the plant on which Govindachari *et al.* and Chakraborty and coworkers reported their findings might well have been *G. mauritiana* (Lam.) Tanaka (Syn. *G. pentaphylla* DC.). The name *G. pentaphylla* (Retz.) Correa as given by Narayanaswami [28] to this species appears to be incorrect.

EXPERIMENTAL

All mps are uncorr. UV spectra were recorded in MeOH and IR spectra as KBr discs. ^{1}H NMR spectra were run in $CDCl_3$ with TMS as an int. standard either at 60 or 90 MHz. Si gel was utilized both for column chromatography and PLC. Spots on TLC plates were visualized by spraying with 1% acidic $KMnO_4$ soln.

Isolation of constituents. Air-dried roots of *G. mauritiana* (12 kg) were powdered and extracted with 95% EtOH (4×15 l.). The total EtOH extract was concentrated *in vacuo* (90 g) and diluted with H_2O (2 l.). It was extracted with hexane (4×1 l.) and $CHCl_3$ (3×1 l.) to afford hexane-soluble (18.5 g) and $CHCl_3$-soluble (10 g) materials, respectively. Part of the hexane-soluble material (12 g) was chromatographed on Si gel (450 g). Elution was carried out with hexane, hexane–C_6H_6, C_6H_6–EtOAc and EtOAc to afford glycozoline (A) (1.3 g), mp 160–62°; glycozolidine (B) (30 mg), mp 180°; β-sitosterol (C) (50 mg), mp 137–40°; dictamnine (D) (10 mg), mp 134–36°; skimmianine (E) (30 mg), mp 164–65°; G (60 mg), mp 134–36° and H (1.3 g), viscous oil. Column chromatography of the $CHCl_3$-soluble material on Si gel also afforded compounds A–E, although in low yield, along with arborinine (F) (105 mg), mp 174–76°.

1-Hydroxy-3-methoxy-2-(3-methylbut-2-enyl)-N-methylacridan-9-one (compound G) (**1**). UV λ_{max}^{MeOH} nm: 227, 252, 275, 305, 330 and 428; UV $\lambda_{max}^{MeOH-AlCl_3}$ nm: 234, 248, 286, 312, 342 and 445; IR γ_{max} cm^{-1}: 3500 (OH), 2980 (CH), 1630, 1580, 1550 (acridone nucleus), 1490, 1385, 1310, 1265 (=C—O—C), 1045, 810 and 760; ^{1}H NMR: δ 14.53 (1H, *s*, OH), 8.2 (1H, *dd*, C-8H), 7.4–6.9 (3H, *m*, C-5, C-6 and C-7H), 6.28 (1H, *s*, C-4H), 5.23 (1H, *m*, CH_2CH=$C(Me)_2$), 3.85 (3H, *s*, C-3, OCH_3), 3.73 (3H, *s*, NCH_3), 3.36 (2H, *m*, $ArCH_2$), 1.72 and 1.71 (6H, *d*, =$C(CH_3)_2$); MS *m/e* (rel. int.): 323 (M^+, 90%), 308 (100), 292 (20), 280 (22), 279 (10), 278 (15), 268 (45), 266 (60), 255 (92) and 236 (10).

Acetylation of G. A soln of **1** (25 mg) in Py (1 ml) and Ac_2O (2 ml) was heated at 110° for 4 hr. Excess solvent was removed by distillation *in vacuo*, the residue diluted with H_2O (2 ml) and extracted with CH_2Cl_2 (3×5 ml). The organic layer was washed with H_2O, dried (Na_2SO_4) and the solvent removed. The residue, a mixture of starting material and the acetylated product, was separated by PLC on Si gel using C_6H_6–EtOAc (19:1) as developing solvent. The lower spot (R_f 0.4) was recrystallized with a mixture of $CHCl_3$ and Et_2O to give 1-acetoxy-3-methoxy-2-(3-methylbut-2-enyl-*N*-methylacridan-9-one (18 mg), mp 115–16°; IR ν_{max} cm^{-1} 1760 (OCOMe) and 1620 (C=O); ^{1}H NMR δ 8.29 (1H, *dd*, C-8 H), 7.69–7.08 (3H, *m*, C-5, C-6 and C-7 H), 6.52 (1H, *s*, C-4 H), 5.1 (1H, *m*, HC=$C(Me)_2$), 3.9 (3H, *s*, OCH_3), 3.74 (3H, *s*, NCH_3), 3.47 (2H, *d*, $ArCH_2$), 2.5 (3H, *s*, $OCOCH_3$), 1.77 and 1.71 (6H, *d*, =$(CH_3)_2$).

Cyclisation of **1** *with formic acid.* A soln of **1** (30 mg) in HCO_2H (1 ml, 98%) was heated at 90° for 4 hr and left overnight. It was diluted with H_2O and extracted with CH_2Cl_2 (4×15 ml). The organic layer was washed with $NaHCO_3$ soln, H_2O, dried (Na_2SO_4) and the solvent removed. The residue (28 mg) on TLC showed two spots in C_6H_6–EtOAc (9:1) which were separated by PLC on Si gel to afford 1-hydroxy-3-methoxy-*N*-methylacridan-9-one (G_1) (R_f 0.7) (**3**) (9 mg), mp 173–75°; IR ν_{max} cm^{-1}: 3450 (OH), 2920 (CH), 1608 (C=O), 1600, 1560, 760 (substituted benzene), 1480, 1304, 1236, 1200 (=C—O—C), 1120 and 1108; ^{1}H NMR δ 8.41 (1H, *dd*, C-8 H), 7.7–7.1 (3H, *m*, C-5, C-6 and C-7 H), 6.28 (2H, *s*, C-2 and C-4 H), 3.88 (3H, *s*, OCH_3), 3.75 (3H, *s*, NCH_3) and 3,4,11,12-tetrahydro-5-methoxy-2,2,12-trimethyl-11-oxo-2H-pyrano-[2,3-a]-acridine (G_2) (R_f 0.3) (**4**) (11 mg), mp 165°; IR ν_{max} cm^{-1}: 2900 (CH), 1637 (C=O), 1600, 760 (substituted benzene), 1470, 1330, 1280 (=C—O—C), 1058, 932 and 836; ^{1}H NMR δ 8.5 (1H, *dd*, C-10 H), 7.7–7 (3H, *m*, C-7, C-8 and C-9 H), 6.2 (1H, *s*, C-6 H), 3.89 (3H, *s*, OCH_3), 3.68 (3H, *s*, NCH_3), 2.64 (2H, *t*, C-4 H_2), 1.81 (2H, *t*, C-3 H_2) and 1.45 (6H, *s*, $OC(CH_3)_2$).

4,8-Dimethoxy-3-(3-methylbut-2-enyl)-N-methyl-2-quinolone (H) (**6**). UV λ_{max} nm: 240, 258, 285, 295 and 335; IR ν_{max} cm^{-1}: 2900(CH), 1635 (NC=O), 1590, 735 (substituted benzene), 1460, 1235, 1065 and 750; ^{1}H NMR 7.35 (1H, *dd*, C-5 H), 5.25 (1H, *m*, CH_2CH=$C(Me)_2$), 3.95 (3H, *s*, C-4 OCH_3), 3.88 (3H, *s*, C-8 OCH_3), 3.85 (3H, *s*, NCH_3), 1.82 and 1.67 (6H, *d*, =$C(CH_3)_2$); MS *m/e* (rel. int.): 287 (M^+, 77%), 272 (100), 256 (30), 244 (98), 232 (35), 218 (50) and 214 (10).

Reaction of 4-hydroxy-8-methoxy-3-(3-methylbut-2-enyl)-N-methyl-2-quinolone (**9**) *with formic acid.* A soln of **9** (50 mg) in HCO_2H (3 ml, 98%) was heated at 90° for 4 hr and left overnight at room temp. It was diluted with H_2O and

extracted with CH_2Cl_2 (4×20 ml). The organic layer was washed with $NaHCO_3$ soln, H_2O, dried (Na_2SO_4) and concd *in vacuo*. The residue (47 mg) showed two spots on TLC which were separated by PLC in C_6H_6–EtOAc (2:3) to afford 3,4,5,6-tetrahydro-7-methoxy-2,2,6-trimethyl-5-oxo-2H-pyrano-[3, 2-c]-quinoline (H_1) (R_f 0.6) (**10**) (10 mg), mp 133–34°; UV λ_{max}^{MeOH} nm: 240, 280, 299 and 325; ^{1}H NMR δ 7.57 (1H, *dd*, C-10 H), 7.2–7 (2H, *m*, C-8 and C-9 H), 3.91 (3H, *s*, OCH_3), 3.85 (3H, *s*, NCH_3), 2.64 (2H, *t*, C-4 H_2), 1.82 (2H, *t*, C-3 H_2), 1.39 (6H, *s*, $OC(CH_3)_2$) and 3,4,5, 10-tetrahydro-9-methoxy-2,2,10-trimethyl-5-oxo-2H-pyrano-[2,3-b]-quinoline (H_2) (R_f 0.3) (**11**) (9 mg), mp 131–32°; UV λ_{max}^{MeOH} nm: 244, 288, 320 and 332; UV $\lambda_{max}^{MeOH-HCl}$ nm: 255 and 306; ^{1}H NMR δ 8 (1H, *dd*, C-6 H), 7.18–6.7 (2H, *m*, C-7 and C-8 H), 3.87 (3H, *s*, OCH_3), 3.77 (3H, *s*, NCH_3), 2.7 (2H, *t*, C-4 H_2), 1.8 (2H, *t*, C-3 H_2) and 1.4 (6H, *s*, $OC(CH_3)_2$).

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