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FAREANINE AND FAREANOL FROM LEAVES OF *MEDICOSMA FAREANA*

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Key Word Index—*Medicosma fareana*; Rutaceae; leaves; alkaloids; fareanine; fareanol.

Abstract—Two new compounds, named fareanine (1-methyl-3ξ-hydroxy-2,2-dimethoxy-3ξ-methoxycarbonyl-1,4H-quinoline-[2,3:*b*]-cyclopentan-4,5-dione) and fareanol (1ξ,2-dihydroxy-1ξ-(4-hydroxy-3,5-dimethoxyphenyl)-ethane, together with the known compounds 1,3,4-trimethoxy-10-methyl acridone, normelicopicine, melicopidine, and *p*-hydroxybenzaldehyde, have been isolated from leaves of *Medicosma fareana*. The identity of the new compounds was established from their spectroscopic data. Fareanine appears to be the product of fission of the C-ring of a normal acridone precursor. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Medicosma fareana is a small tree occurring in the rain forest areas of North-Eastern Queensland, Australia, between sea-level and *ca* 800 m [1]. Previous phytochemical work on this species resulted in the isolation of the furoquinoline alkaloids, skimmianine and acronycidine, the acridones, melicopine, melicopidine and melicopicine, and the common triterpene, lupeol [2]. In the present study, we report the isolation of four known compounds (*p*-hydroxybenzaldehyde and **1**–**3**) and the structural elucidation of two new compounds, fareanine (**4**) and fareanol (**7**), from the leaves of *M. fareana*.

RESULTS AND DISCUSSION

The ethanol extract of leaves of *M. fareana* was suspended in water and successively re-extracted with hexane, chloroform, ethylacetate and butanol. Vacuum liquid chromatography (VLC) followed by column and preparative TLC of the chloroform fraction gave the known compounds 1,3,4-trimethoxy-10-methylacridone (**1**) [3], normelicopicine (**2**) [4], melicopidine (**3**) [2, 5, 6], *p*-hydroxybenzaldehyde and two new compounds, fareanine (**4**) and fareanol (**7**).

The high-resolution EI and FAB mass spectra of compound **4** analysed for $[M]^+$ 347 ($C_{17}N_{17}NO_7$). The IR spectrum showed a broad band between 3500 and 3000 cm^{-1} (OH), and bands in the carbonyl region at 1713 (ester) and 1620 and 1618 cm^{-1}, characteristic of α,β-unsaturated carbonyls. The ^1H and ^{13}C NMR spectra revealed typical signals for the *N*-methyl-4-quinolone part of the acridone skeleton unsubstituted in the aromatic ring [3–6] (Table 1). The structural assignments and the chemical shift values of the A and B rings were further substantiated by HMBC studies (Table 2).

The C ring of alkaloid **4**, which differs from that of all known acridones, was established from HMBC and NOESY studies. In the HMBC spectrum (Table 2), a ^3J interaction between the protons of two methoxyl substituents (δ 3.53 and 3.59) and a carbon signal at δ 99.6 required the methoxyls to be placed geminal on an sp^3

Table 1. ^1H and ^{13}C data for compound **4** (400 MHz, $CDCl_3$)

H/C	δ_H	σ_C
1		186.9
2		81.8
3		168.7
4		99.6
5	7.59 *d* (8.4)	116.3
6	7.77 *td* (7.1, 1.6)	133.8
7	7.51 *td* (8.0, 0.9)	126.1
8	8.52 *dd* (8.0, 1.4)	128.1
9		173.5
10		
11		164.4
12		116.3
13		129.2
14		141.7
N-Me	3.88 *s*	36.0
OMe-4_A	3.53 *s*	52.5
OMe-4_B	3.59 *s*	53.3
Ester-Me	3.80 *s*	54.1
OH-2	4.53 *br s*	

Coupling constants (Hz) in parentheses.

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Table 2. HMBC correlations for compound **4**

H	^1J	^2J	^3J
5		133.8	126.1, 129.2
6		116.3	128.1, 141.7
7		133.8	116.3, 129.2
8	128.1		133.8, 141.7, 173.5
N-Me	36.0		141.1, 164.4
OMe-4_A	52.5		99.6
OMe-4_B	53.3		99.6
Ester-Me	54.1		168.7
OH-2		81.8	99.6, 168.7

carbon, while a ^3J coupling between a third methoxyl group (δ 3.80) and the carbonyl ester carbon (δ 168.7) indicated the presence of a methyl ester functional group. A further interaction (which must be ^3J) of these methoxyl-bearing carbons (δ 99.6 and 168.7) with a broad hydroxyl singlet at δ 4.53 established the partial structure **6**. Given that the compound possessed an *N*-methyl 4-quinolone nucleus combined with **6** and a further carbonyl (δ_C 186.9), it could be assigned as either structure **4** or **5**. The unusually deshielded position of the carbon signal of C-11 (δ 164.4) (cf. in normal acridones this is at *ca* σ 143 [7]) supports the placement of the carbonyl β to that position (structure **4**) rather than in an α-position (as in structure **5**). The identity of the new compound as **4** and discrimination against the alternative structure **5** was also supported by a NOESY spectrum (Fig. 1), which revealed interactions between the *N*-Me and 4_A-OMe. This can occur only if the methoxyls are placed as in compound **4** rather than in compound **5**.

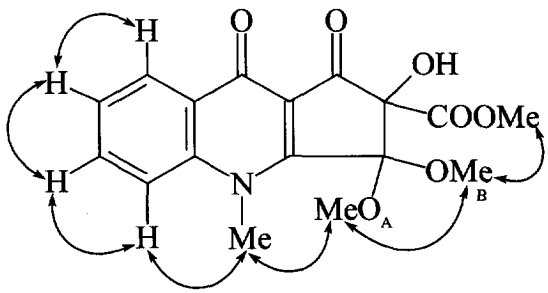
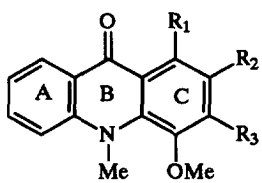
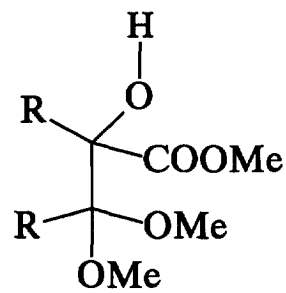


Fig. 1. NOE interactions for compound **4**.

Alkaloid **4** (trivial name fareanine) is likely to be a degraded product of the highly oxygenated C-ring of acridone alkaloids of the type isolated in the present and in previous studies on this species. A possible route to the formation of compound **4** is shown in Scheme 1b and receives support from synthetic studies. In their attempt to find a convenient method of degrading the oxygenated ring of acridones, Prager and Thredgold [7] brominated moelicopine (**8**) and this yielded compound **10**, presumably through the unstable intermediate **9** (Scheme 1a). Their oxidation–reduction reactions did not lead to compound **4**, but similar degradation pathways are likely to be involved in the formation of **4**, (cf. Scheme 1b). Following the formation of an



1 R_1=R_3=OMe, R_2=H
2 R_1=OH, R_2=R_3=OMe
3 R_1=OMe, R_2,R_3= -OCH_2O-



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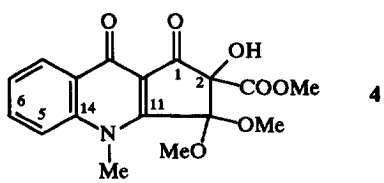

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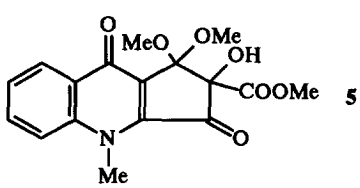

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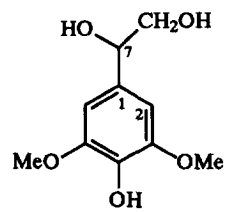

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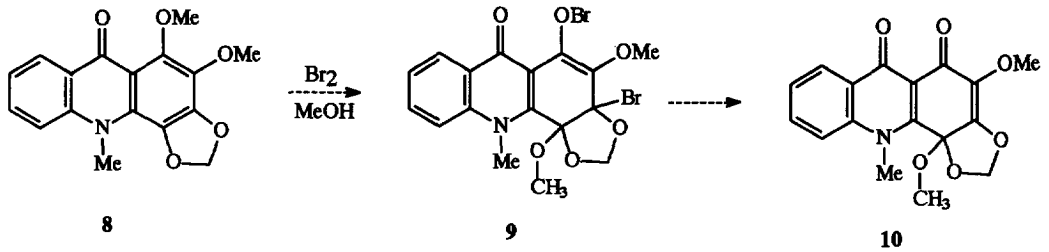
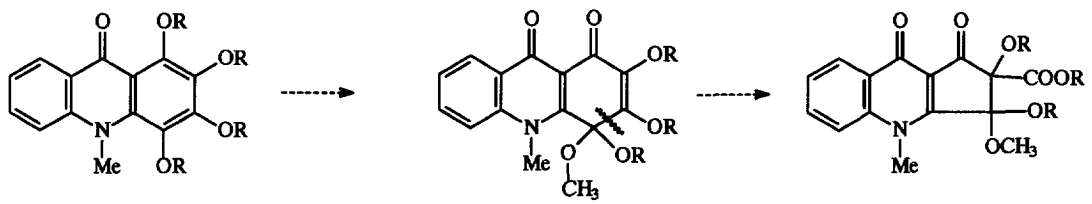


8 9 10

Scheme 1a



11 12 13

Scheme 1b

intermediate, such as **12**, the C_3–C_4 bond of the C-ring must be broken with oxidation of C-3 and recyclization through C_2–C_4 leading to compounds such as **13** or **4**.

The high-resolution EI-mass spectrum of the second new compound **7** revealed an empirical formula of $C_{10}H_{14}O_5$. The ^1H and ^{13}C NMR spectra (Table 3) revealed signals for one primary and one secondary alcohol functional group. The broad hydroxyl doublet signal in the ^1H NMR spectrum showed coupling to the oxymethine which, in turn, showed coupling to the two oxymethylene protons (^1H–^1H COSY). The ^1H NMR further revealed signals for two, chemically equivalent, aromatic protons, one olefinic hydroxyl and two identical methoxyls. Because the ^{13}C NMR also showed signals in the aromatic region for only four carbons signals (one methine), compound **7** must possess a symmetrical aromatic skeleton. The two methoxyls must then be assigned at C-3 and C-5 and the hydroxyl at C-4 position.

Table 3. ^1H and ^{13}C chemical shift data for compound **7** (400 MHz, $CDCl_3$)

H/C	^1H	^{13}C
1		132.0
2	6.59 *s*	103.0
3		147.4
4		137.6
5		147.4
6	6.59 *s*	103.0
7	3.10 *m*	86.3
8	3.90, 4.30 *m*	72.0
OMe-3, OMe-5	3.90 *s*	56.5
OH-4	5.50 *br s*	
OH-7	5.50 *br d* (4.4)	

Coupling constant (Hz) in parentheses.

Both compounds **4** and **7** were isolated as a result of bioassay-guided separation. Their biological activity will be discussed elsewhere.

EXPERIMENTAL

General. Silica gel (Merck 7749) was used for VLC and silica gel 60 PF_{254} for prep. TLC. Spots and bands were detected by spraying with 5% vanillin in concd H_2SO_4. UV: EtOH and IR: KBr. ^1H, ^{13}C, ^1H–^1H COSY, NOESY (mixing time d_8 = 0.8 s) and HMBC (d_6 set for *ca* J = 7 Hz) NMR spectra were recorded on a Bruker AMX-400 instrument. Chemical shifts are reported in ppm relative to $CDCl_3$. EI-MS were obtained by direct probe insertion at 70 eV.

Plant material. Leaves of *M. fareana* (F. Muell) T. G. Hartley were collected from Northern Queensland in 1991. A voucher specimen TGH-15147, was identified by Dr T. G. Hartley and deposited at the Australian National Herbarium, Canberra.

Extraction and isolation. Ground leaves (590 g) were Soxhlet-extracted to exhaustion. Removal of solvent yielded a residue (90 g) which was suspended in H_2O and subjected to successive partitioning against hexane, $CHCl_3$, EtOAc and MeOH. The $CHCl_3$ fr. (14 g) was further subjected to VLC over silica gel, eluting with hexane and hexane–$CHCl_3$ mixts of increasing polarity and finally $CHCl_3$ containing increasing amounts of MeOH. The hexane–$CHCl_3$ (1:9) eluent was collected and chlorophyll removed by elution through Sephadex LH 20 ($CHCl_3$–MeOH, 1:1).

The resulting gum was subjected to repetitive prep. TLC (silica gel, $CHCl_3$–MeOH, 24:1) to give 1,3,4-trimethoxy-10-methyl acridone (**1**, 5 mg, 0.0009%), normelicopicine (**2**, 6 mg, 0.001%) and melicopidone (**3**, 50 mg, 0.009%). Similar treatment of the $CHCl_3$ VLC eluent gave *p*-hydroxybenzaldehyde (4 mg, 0.0007%), fareanine (**4**, 8 mg, 0.0013%) and fareanol (**7**, 6 mg, 0.001%).

1,3,4-*Trimethoxy*-10-*methyl acridone* (**1**), *normelicopicine* (**2**), *melicopidine* (**3**) p-*hydroxybenzaldehyde*. All gave UV, IR, EI-MS and ^{1}H NMR data in close agreement with those reported [3–6].

Fareanine (1-*methyl*-3ξ-*hydroxy*-2,2-*dimethoxy*-3ξ-*methoxycarbonyl*-1,4*H*-*quinoline*-[2,3:*b*]-*cyclopentan*-4,5-*dione*, **4**). Gum. $[\alpha]_D$ −2° ($CHCl_3$, *c* 0.7). UV λ_{max}, nm: 305. IR ν_{max} cm^{-1}: 3450 *br*, 3020, 1713, 1620, 1618, 1602, 1538, 1506, 1463, 1421, 1074 and 1046. ^{1}H and ^{13}C NMR (400 MHz, $CDCl_3$: see Table 1). (HREI-MS: Found 347.1229. calcd for $C_{17}H_{17}NO_7$, 347.1005). EI-MS *m/z* (rel. int.): 347 $[M]^+$ (30.4), 332 (23.8), 287 (26.5), 272 (100) 244 (60), 77 (67.5).

Fareanol (1ξ,2-*dihydroxy*-1ξ-(4-*hydroxy*-3,5-*dimethoxyphenyl*, **7**). Gum. $[\alpha]_D$ −18° ($CHCl_3$, *c* 0.4). UV λ_{max}, nm: 265, 340 sh. IR ν_{max} cm^{-1}: 3398 br, 2929, 1616, 1521, 1456, 1521, 1215, 1115. ^{1}H and ^{13}C NMR (400 MHz, $CDCl_3$: see Table 3). (HREI-MS: Found 214.0312. calcd 214.0841 for $C_{10}H_{14}O_5$). EI-MS *m/z* (rel. int.): 214 $[M]^+$ (10.9), 213 (14.2), 201 (22.7), 199 (15.1), 193 (99.8), 93 (100).

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