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Acridone and furoquinoline alkaloids from *Teclea gerrardii* (Rutaceae: Toddalioideae) of southern Africa

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This paper is dedicated to the memory of the late Ms Sawsan Mekki El Amin.

Abstract

The combined hexane/CH_2Cl_2 extract of the stem bark of *Teclea gerrardii* (Rutaceae: Toddalioideae) has yielded two acridone alkaloids, 3-hydroxy-1-methoxy-*N*-methylacridone (tegerrardin A) (**1**) and 3-hydroxy-*N*-methyl-1-(γ,γ-dimethylallyloxy)acridone (tegerrardin B) (**2**), three known acridones (**3**–**5**), two known furoquinolines (**6**,**7**), and the acridone precursor tecleanone (**8**). Arborinine (**3**) and evoxine (**6**) displayed moderate antiplasmodial activity against the CQS D10 strain of *Plasmodium falciparum*, with IC_{50} values of 12.3 and 24.5 μM, respectively.

Keywords: *Teclea gerrardii*; Rutaceae; Stem bark; Acridone alkaloids; Furoquinoline alkaloids; 3-Hydroxy-1-methoxy-*N*-methylacridone (tegerrardin A); 3-Hydroxy-*N*-methyl-1-(γ,γ-dimethylallyloxy)acridone (tegerrardin B); Arborinine; Evoxanthine; 1,3-Dimethoxy-*N*-methylacridone; Evoxine; 7-(γ,γ-Dimethylallyloxy)-γ-fagarine; Tecleanone; *Plasmodium falciparum*; Antiplasmodial activity

1. Introduction

Teclea gerrardii I.Verd., the Flaky cherry-orange, is an aromatic shrub or tree (to 15 m) occurring in riverine thicket and dry forest along the eastern seaboard of southern Africa, in which region it is known from South Africa, Swaziland and southern Mozambique. As a genus of about 22 species, *Teclea* Del. is restricted to Africa and the Mascarenes (Victor, 2000) and has been assigned to the subtribe Amyridinae in the subfamily Toddalioideae of the Rutaceae (Engler, 1931). Continentally, *Teclea* is the most widely distributed of the African Toddalioideae (Verdoorn, 1926) though with most taxa localised in the tropics, only three species are known from the Flora of Southern Africa (FSA) region. *T. gerrardii* is known to the Zulu as *umboza* or *umozane* and is employed in traditional medicine; bark decoctions are taken for chest complaints (Hutchings et al., 1996). Whilst South African material of *T. natalensis* has previously been the subject of phytochemical study (Tarus et al., 2005), *T. gerrardii* has not. Accordingly, the current investigation sought chemically to profile this medicinal plant and to interpret findings in view of earlier chemotaxonomic assessments of African Toddalioideae (Waterman, 1973; Waterman et al., 1978; Dagne et al., 1988).

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2. Results and discussion

In continuation of our studies on southern African rutaceaeus taxa (Naidoo et al., 2005; Tarus et al., 2005, 2006; Mbala, 2006), we report the isolation of two novel acridone alkaloids, together with three known acridones, two known furoquinolines, and an aminobenzophenone, from the combined hexane/CH_2Cl_2 extract of the stem bark of *T. gerrardii*.

An HREIMS of tegerrardin A **1** showed an $[M]^+$ peak at *m/z* 255.0896, corresponding to the molecular formula $C_{15}H_{13}NO_3$. Inspection of the IR, ^1H and ^{13}C NMR spectra of **1** showed it to possess a carbonyl carbon (δ_C 180.6(C); 1639 cm^{-1}, C=O stretch), an aromatic methoxy group (δ_H 3.86 *s*, 3H; δ_C 55.5 (CH_3)), an *N*-methyl group (δ_H 3.73 *s*, 3H; δ_C 34.0 (CH_3)), and six aromatic proton signals. A correlation in the HMBC spectrum between the C-9 carbonyl resonance and a 1H doublet signal at δ_H 8.39 ($J = 8.1$ Hz) established this as H-8, with correlations in the COSY spectrum then permitting the assignment of 1H multiplet resonances at δ_H 7.24 and 7.65, and a 1H doublet signal at δ_H 7.43 ($J = 8.6$ Hz), to H-7, H-6 and H-5, respectively, of the unsubstituted A ring of an acridone alkaloid. These assignments were confirmed by a correlation in the NOESY spectrum between the latter signal and that of the *N*-methyl group, which also displayed a further correlation to the more upfield signal of a pair of *m*-coupled aromatic protons (δ_H 6.23, 6.24, each *d*, $J = 2.2$ Hz), which was assigned to H-4. A further correlation in the NOESY spectrum between the methoxy group resonance and that at δ_H 6.24, assigned to H-2, but not to that of H-4, placed this at C-1, and the remaining O and H atoms are accounted for by placing a hydroxy group at C-3. As 3-hydroxy-1-methoxy-*N*-methylacridone, tegerrardin A **1** is reported here for the first time from a natural source, although it has previously been synthesized (Hlubucek et al., 1970; Su and Chou, 1994), while the closely related 1-hydroxy-3-methoxy-*N*-methylacridone and 1,3-dimethoxy-*N*-methylacridone are widespread in the Rutaceae (Dictionary of Natural Products, 2006).

The ^1H and ^{13}C NMR spectra of tegerrardin B **2** were similar to those of **1** (δ_C 180.8 (C), C-9; δ_H 8.39, *d*, $J =$ 8.1 Hz, H-8; δ_H 7.27, *m*, H-7; δ_H 7.71, *m*, H-6; δ_H 7.43, *d*, $J = 8.8$ Hz, H-5; δ_H 3.77 *s*, 3H, δ_C 34.1 (CH_3), *N*-methyl; δ_H 6.34, *d*, $J = 2.2$ Hz, H-4; δ_H 6.33, *d*, $J = 2.2$ Hz, H-2). However, the methoxy group proton and carbon resonances observed in the NMR spectra of **2** have disappeared, having been replaced by the signals of a γ,γ-dimethylallyloxy (prenyloxy) substituent (δ_H 4.61, 2H, *d*, $J = 6.6$ Hz, 2H-1′; δ_H 5.50, 1H, *m*, H-2′; δ_H 1.76, 3H, *s*, 3H-4′; δ_H 1.81, 3H, *s*, 3H-5′; δ_C 65.2, CH_2, C-1′; 118.8, CH, C-2′; 142.3, C, C-3′; 18.3, CH_3, C-4′; 25.9, CH_3, C-5′), which was placed at C-1, as before, on the basis of correlations in the NOESY spectrum between 2H-2′ and H-2, but not between 2H-2′ and H-4. As 3-hydroxy-*N*-methyl-1-(γ,γ-dimethylallyloxy)acridone, tegerrardin B **2** is reported here, for the first time, from either natural or synthetic sources, although the 3-prenyloxy isomer vebilocine has previously been isolated from *Vepris bilocularis* (Wight et Arn.) Engl. (Brader et al., 1996).

The known compounds were identified as arborinine **3** (Chakravarti et al., 1953; Bergenthal et al., 1979), evoxanthine **4** (Hughes and Neill, 1949; Rasoanaivo et al., 1999), 1,3-dimethoxy-*N*-methylacridone **5** (Reisch et al., 1991), evoxine **6** (Moulis et al., 1981; Ali et al., 2001), 4,8-dimethoxy-7-(γ,γ-dimethylallyloxy)furo[2,3-*b*]furoquinoline **7** (Bessonova et al., 1974; Al-Rehaily et al., 2003) and tecleanone **8** (Casey and Malhotra, 1975; Waterman, 1975) by comparison of their physical properties and spectral data with the literature values.

As rutaceaeus taxa often feature as antimalarials or febrifuges in African traditional medicine (Watt and Breyer-Brandwijk, 1962; Kokwaro, 1976; Neuwinger, 2000), and the significant antiplasmodial activity of a variety of both furoquinoline and acridone alkaloids has earlier been demonstrated (Nkunya, 1992; Basco et al., 1994; Weniger et al., 2001), compounds **1**–**8** were tested against the CQS D10 strain of *P. falciparum*. While compounds **2** and **8** were found to be completely inactive, compounds **1**, **3** and **4**–**7** displayed mild activity, with IC_{50} values of 12.3, 95.3, 70.6, 46.8, 24.5 and 132.4 μM, respectively, against a value of 57.5 nM for CQ as positive control. At 12.3 μM, the activity of arborinine **3** compares reasonably with values of 2.5, 5.3 and 11.1 μM recently reported for three acridones from *Swinglea glutinosa* Merr. against a Nigerian CQS strain (Weniger et al., 2001), while the 24.5 μM of evoxine **6** makes it more active than haplopine, at 38.8 μM the most active of five furoquinolines tested against the Honduran CQS strain HB3 (Basco et al., 1994).

Although numerous studies on the cytotoxicity of acridones against a variety of cell lines have been carried out (Su et al., 1992; Su and Chou, 1994; Kawaii et al., 1999; Teng et al., 2005), Weniger et al. (2001) remains, to our knowledge, the only investigation to date in which antiplasmodial activity and cytotoxicity were simultaneously established. Selectivity indices for the four compounds evaluated were 0.3 and 0.5 for those compounds with a methoxy group at C-4, compared to 9.0 and 7.7 for those without. As some 65% of the more than 150 acridone alkaloids identified to date (Dictionary of Natural Products, 2006) fall into this category, there is scope for much future study.

In contrast, the furoquinoline alkaloids have been much less investigated, with only one cytotoxicity study (Chen et al., 2003) to date. No inferences can thus currently be made about this group of compounds.

Whereas Dagne et al. (1988) recognized two groups within the genus *Teclea*, defined by the production of either acridone or furoquinoline alkaloids, both the current report on *T. gerrardii* and earlier ones on *T. natalensis* (Pegel and Wright, 1969; Tarus et al., 2005) indicate that at least the southern African representatives produce both alkaloid classes. As all of the constituent classes isolated in the present investigation have previously been recorded from the genus *Teclea* (Dagne et al., 1988), only minor

extensions of the biosynthetic range are evident, and as such no new subtribal or subfamilial chemotaxonomic insights are revealed. However, the two novel acridone alkaloids (tegerrardins A-B **1**–2) may presently be considered taxonomic markers for *T. gerrardii*.

3. Experimental

3.1. General

Melting points were determined on a Kofler micro-hot stage melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature on a 400 MHz Varian UNITY-INOVA spectrometer. ^{1}H NMR spectra were referenced against the C*H*Cl$_3$ signal at δ_H 7.27, and ^{13}C NMR spectra against the corresponding signal at δ_C 77.0. Coupling constants are given in Hz. IR spectra were recorded on a Nicolet Impact 400D Fourier-transform infrared (FT-IR) spectrometer, using NaCl windows with $CHCl_3$ as solvent against an air background. LREIMS and HREIMS were taken on Perkin–Elmer 6890-Agilent 5975 GCMS and Micromass VG 70 SEQ instruments, respectively.

3.2. Plant material

Stem bark from a cultivated specimen of *T. gerrardii* I.Verd. was sourced in Durban, South Africa. A voucher (Crouch 1045, NH) has been lodged for verification purposes.

3.3. Extraction and isolation of compounds

The air-dried, ground stem bark material of *T. gerrardii* (800 g) was extracted for 72 h each with hexane, CH_2Cl_2 and MeOH at room temperature, affording 15.1, 30.6, and 65.7 g of extract, respectively, on concentration under reduced pressure. A ^{1}H NMR spectrum of the MeOH extract showed it to contain mostly sugars and it was not investigated further, while the hexane and CH_2Cl_2 extracts were combined on the basis of similar TLC profiles. Repeated combinations of vacuum liquid and gravity column chromatography on Merck 7729 and 9385 silica gels, and PTLC on aluminium backed analytical TLC (Merck 5554) plates, using hexane:EtOAc:MeOH mixtures, afforded tegerrardins A **1** (7.2 mg) and B **2** (5.0 mg), together with arborinine **3** (85.0 mg), evoxanthine **4** (50.0 mg), 1,3-dimethoxy-*N*-methylacridone **5** (74.1 mg), evoxine **6** (4.0 mg), 7-(γ,γ-dimethylallyloxy)-γ-fagarine **7** (6.0 mg) and tecleanone **8** (1.219 g).

3.3.1. 3-Hydroxy-1-methoxy-N-methylacridone, tegerrardin A *1*

Pale yellow powder; m.p. 158–159 °C, ν_{max}(NaCl) cm^{-1} 3449, 1639, 1600, 1461, 1329, 1228, 1159; HREIMS (70 eV) *m*/*z* 255.0896 (calc. for $C_{15}H_{13}NO_3$ 255.0895); EIMS (70 eV) *m*/*z* (rel. int.) 255 (100), 226 (29), 212 (9), 128 (3), 113 (5); ^{1}H NMR spectral data (400 MHz, $CDCl_3$) δ_H 8.39 (1H, *d*, *J* = 8.1 Hz, H-8), 7.65 (1H, *m*, H-6), 7.43 (1H, *d*, *J* = 8.6 Hz, H-5), 7.24 (1H, *m*, H-7), 6.24 (1H, *d*, *J* = 2.2 Hz, H-2), 6.23 (1H, *d*, *J* = 2.2 Hz, H-4), 3.86 (3H, *s*, 1-OCH$_3$), 3.73 (3H, *s*, *N*-CH$_3$); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

3.3.2. 3-Hydroxy-N-methyl-1-(γ,γ-dimethylallyloxy)acridone, tegerrardin B *2*

Pale yellow gum, ν_{max}(NaCl) cm^{-1} 3450, 1637, 1600, 1459, 1331, 1228, 1150; HREIMS (70 eV) *m*/*z* 309.1358 (calc. for $C_{19}H_{19}NO_3$ 309.1365); EIMS (70 eV) *m*/*z* (rel. int.) 309 (27), 242 (22), 241 (100), 212 (12), 204 (30), 189 (24), 175 (22), 161 (10), 148 (10), 115 (11), 95 (16); ^{1}H NMR spectral data (400 MHz, $CDCl_3$) δ_H 8.39 (1H, *d*, *J* = 8.1 Hz, H-8), 7.71 (1H, *m*, H-6), 7.43 (1H, *d*, *J* = 8.8 Hz, H-5), 7.27 (1H, *m*, H-7), 6.34 (1H, *d*, *J* = 2.2 Hz, H-4), 6.33 (1H, *d*, *J* = 2.2 Hz, H-2), 5.50 (1H, *m*, H-2′), 4.61 (2H, *d*, *J* = 6.6 Hz, 2H-1′), 3.77 (3H, *s*, N–CH$_3$), 1.81 (3H, *s*, 3H-5′), 1.76 (3H, *s*, 3H-4′); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

3.4. Antiplasmodial assay

All samples were tested in duplicate on a single occasion against a chloroquine sensitive (CQS) strain of *Plasmodium falciparum* (D10). Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen (1976). Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler et al. (1993).

The compounds were prepared to a 2 mg/mL stock solution in 10% methanol, 10% ethanol or 10% DMSO. Chlo-

Table 1
^{13}C NMR spectral data for tegerrardins A **1** and B **2**

Carbon	**1**	**2**
1	166.0 (C)[a]	165.4 (C)
2	89.9 (CH)	94.5 (CH)
3	165.8 (C)[a]	166.0 (C)
4	94.0 (CH)	90.9 (CH)
5	114.5 (CH)	114.4 (CH)
6	134.0 (CH)	134.1 (CH)
7	121.4 (CH)	121.4 (CH)
8	126.6 (CH)	126.8 (CH)
9	180.6 (C)	180.8 (C)
4a	144.6 (C)	144.7 (C)
1a	105.2 (C)	105.4 (C)
8a	120.9 (C)	121.4 (C)
5a	142.3 (C)	142.3 (C)
1-O*C*H$_3$	55.5 (CH$_3$)	–
N–*C*H$_3$	34.0 (CH$_3$)	34.1 (CH$_3$)
1′	–	65.2 (CH$_2$)
2′	–	118.8 (CH)
3′	–	142.3 (C)
4′	–	18.3 (CH$_3$)
5′	–	25.9 (CH$_3$)

[a] values interchangeable within column.

roquine (CQ) was used as the reference drug in all experiments. Compounds were stored at −20 °C until use. A full dose–response was performed with a starting concentration of 100 μg/mL, which was serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.195 μg/mL. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/mL. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not shown). The 50% inhibitory concentration (IC_{50}) values were obtained using a non-linear dose–response curve fitting analyses via GraphPad Prism v.4.0 software.

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