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Furoquinoline alkaloids from the southern African Rutaceae *Teclea natalensis*

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Abstract

The chloroform and ethyl acetate extracts of the leaves of *Teclea natalensis* have yielded two furoquinoline alkaloids, 6-[(2,3-epoxy-3-methylbutyl)oxy]-4,7-dimethoxyfuro[2,3-*b*]quinoline and 4,7-dimethoxy-6-[(3-methyl-2-butenyl)oxy]furo[2,3-*b*]quinoline, and the known alkaloids 4,7-dimethoxy-8-[(3-methyl-2-butenyl)oxy]furo[2,3-*b*]quinoline, flindersiamine and dictamnine.

Keywords: *Teclea natalensis*; Rutaceae; Leaves; Isolation; Furoquinoline alkaloids; 6-[(2,3-Epoxy-3-methylbutyl)oxy]-4,7-dimethoxyfuro[2,3-*b*]-quinoline; 4,7-Dimethoxy-6-[(3-methyl-2-butenyl)oxy]furo[2,3-*b*]quinoline; 4,7-Dimethoxy-8-[(3-methyl-2-butenyl)oxy]furo[2,3-*b*]quinoline; Tecleanatalensine A; Tecleanatalensine B; Flindersiamine; Dictamnine

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1. Introduction

Teclea natalensis (Sond.) Engl., or the Natal Cherry–Orange, uMozane or iZinyana, is a shrub or small (2–8 m) tree widespread in southern and eastern Africa, where it occurs on rock outcrops and forest margins (Pooley, 1994).

Previous investigations of the bark of *T. natalensis* have yielded the novel acridone alkaloid tecleanthine, together with the known acridone alkaloids arborinine, evoxanthine, melicopidine and melicopine (Pegel and Wright, 1969), and tecleanine, an alkaloid of unknown structure (Wright and Pegel, 1967). No furoquinoline alkaloids have yet been reported from *T. natalensis*, but they have been found in the related species *T. verdoorniana* Exell & Mendonça (Fish et al., 1976; Okogun and Ayafor, 1977; Ayafor and Okogun, 1982a,b), *T. ouabanguiensis* Aubrév & Pellegr. (Ayafor et al., 1982), *T. nobilis* Delile (Dagne and Yenesew, 1987; Yenesew and Dagne, 1988; Dagne et al., 1988), *T. simplicifolia* (Engl.) I. Verd. (Wondimu et al., 1987; Dagne et al., 1988), and *T. borenensis* M.G. Gilbert (Dagne et al., 1988).

2. Results and discussion

Two novel furoquinoline alkaloids, and the known alkaloids 4,7-dimethoxy-8-[(3-methyl-2-butenyl)oxy] furo[2,3-*b*]quinoline, dictamnine and flindersiamine were isolated from the chloroform and ethyl acetate extracts of the leaves of *T. natalensis*.

The ^{1}H NMR spectrum of teclenatalensine A **1** displayed a pair of coupled doublet resonances at δ 7.54

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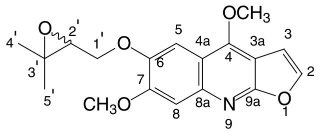
and δ 7.02 (each 1H, *J* = 2.8 Hz), characteristic of the H-2 and H-3 furan ring protons, and a downfield 3H singlet resonance at δ 4.41, characteristic of the methoxy group at C-4 in a furoquinoline alkaloid. Two 1H singlet proton resonances at δ 7.53 and δ 7.32 were assigned to H-5 and H-8, respectively, by a correlation in the NOESY spectrum between the C-4 methoxy group resonance and the resonance at δ 7.53. A further NOESY correlation between the H-8 resonance and a second methoxy group resonance at δ 3.99 placed this at C-7.

In addition to the resonances assigned above, and those required for the furoquinoline nucleus, the ^{13}C NMR spectrum contained an additional five signals, in the form of two methyl (δ 24.5, C-4′: δ 19.1, C-5′), an oxymethylene (δ 67.7, C-1′), a methine (δ 61.2, C-2′), and a fully substituted carbon (δ 58.9, C-3′) resonances. These were assigned to a (2,3-epoxy-3-methylbutyl)oxy group, whose presence was supported by coupling in the COSY spectrum between the two proton multiplet at δ 4.27 (2H, 2H-1′), and the triplet at δ 3.25 (1H, H-2′), and the appearance, on closer inspection, of the ^{1}H NMR spectrum of two non-equivalent singlet methyl group proton signals at δ 1.390 and 1.387 (each 3H, 3H-4′, 3H-5′), and confirmed by the fragmentation pattern of the mass spectrum, in which the base peak occurs at *m/z* 245, consistent with the loss of a C_5H_9O fragment (*m/z* 85), via a β-H transfer mechanism common in aromatic ethers (Kemp, 1991), from the molecular ion at *m/z* 329. This group was placed at C-6 on the basis of a correlation in the NOESY spectrum between the 2H-1′ resonance and that of H-5. Tecleanatalensine A **1** is thus the novel 6-[(2,3-epoxy-3-methylbutyl)oxy]-4,7-dimethoxyfuro[2,3-*b*]quinoline, although the closely related 7-[(2,3-epoxy-3-methylbutyl)oxy]-4,8-dimethoxy isomer anhydroevoxine has been reported from *Evodia xanthoxyloides* F. Muell., *Haplophyllum ferganicum* Vved. and *H. perforatum* (M. Bieb.) Kar. & Kir. (Dreyer, 1970; Bessonova and Yusunov, 1982; Razakova et al., 1985).

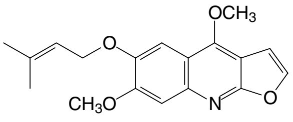
Comparison of the ^{13}C NMR spectra of tecleanatalensines A **1** and B **2** showed them to be very similar, except that the resonances assigned to the C-2′, C-3′ epoxide ring in **1** were absent, while two alkene carbon resonances at δ 119.3 (*d*) and δ 138.0 (*s*) had appeared in **2**. The mass spectral fragmentation patterns of **1** and **2** were equally comparable, other than the molecular ion of **2** appearing 16 mass units less, relative to **1**, at *m/z* 313. The 2,3-epoxy-3-methylbutyl ether side chain in **1** has thus been replaced by a 3-methyl-2-butenyl ether side chain in **2**, which was placed at C-6, as in **1**, by a NOESY correlation between H-5 at δ 7.48 (*s*) and the downfield allylic 2H-1′ protons at δ 4.70 (*d*, *J* = 6.8 Hz). Tecleanatalensine B **2** is thus the novel 4,7-dimethoxy-6-[(3-methyl-2-butenyl)oxy]furo[2,3-*b*]-quinoline, although the closely related 4,6-dimethoxy-7-[(3-methyl-2-butenyl)oxy] isomer nobiline has been reported from *Teclea nobilis* (Yenesew and Dagne, 1988).

Inspection of the ^{1}H and ^{13}C NMR spectra of tecleanatalensine B **2** and compound **3** also showed them to be very similar, with **3** also possessing a furoquinoline nucleus, a methoxy group at C-4, a second methoxy group, and a 3-methyl-2-butenyl ether side chain. A faint correlation in the NOESY spectrum between the C-4 methoxy group singlet proton resonance and the more downfield of a pair of *ortho*-coupled 1H doublet resonances at δ 7.98 (*d*, *J* = 9.3 Hz) assigned this as H-5. A further NOESY correlation between the corresponding upfield doublet at δ 7.20 (*d*, *J* = 9.3 Hz), ascribed to H-6, and the second methoxy group singlet resonance at δ 7.20 placed this at C-7, and thus the 3-methyl-2-butenyl ether side chain at C-8. Compound **3** is thus the known, but uncommon, 8-[(3-methyl-2-butenyl)oxy]-4,7-dimethoxyfuro[2,3-*b*]quinoline, reported only from *Zanthoxylum arborescens* Rose (Grina et al., 1982) and *T. simplicifolia* (Wondimu et al., 1987; Dagne et al., 1988).[1] The ^{13}C NMR data for **3** has not been previously reported and is presented here for the first time.

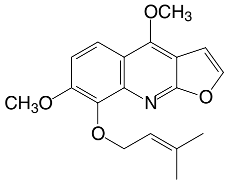
Also isolated in this study were the ubiquitous Rutaceae alkaloids flindersiamine and dictamnine.



tecleanatalensine A **1**



tecleanatalensine B **2**



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3. Experimental

3.1. General

NMR spectra were recorded at room temperature on a 400 MHz Varian UNITY-INOVA spectrophotometer. Chemical shifts (δ) are expressed in ppm rela-

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[1] The 4,8-dimethoxy-7-[(3-methyl-2-butenyl)oxy] isomer, from *Ptelea aptera* Parry (Dreyer, 1969), *Haplophyllum perforatum* (Bessonova et al., 1974; Abdullaeva et al., 1978; Razakova et al., 1983; Rasulova et al., 1992), *H. latifolium* Kir. & Kar. (Nesmelova et al., 1977; Nesmelova et al., 1978), *H. ferganicum* (Bessonova and Yusunov, 1982), *H. glabrinum* (Rozsa et al., 1986), *H. tuberculatum* (Forssk.) A. Juss (Khalifa and Youssef, 1999) and *Skimmia reevesiana* (Fortune) Fortune (Wu, 1987), is far more widespread.

tive to tetramethylsilane (TMS) as internal standard and coupling constants are given in Hz. ^{1}H NMR spectra were referenced against the $C\underline{\underline{H}}Cl_3$ signal at δ_H 7.27, and ^{13}C NMR spectra to the corresponding signal at δ_C 77.0. UV spectra were obtained on a Varian DMS 300 UV–visible spectrometer. 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 were acquired on a Perkin–Elmer 6890 – Agilent 5975 GCMS instrument. Optical rotations were measured at room temperature in CH_2Cl_2 on a Perkin–Elmer 341 Polarimeter, using a 100 mm quartz Microcell flow tube.

3.2. Plant material

T. natalensis (Sond.) Engl. was collected in March 2003 near the Long Tom Pass in Mpumalanga, South Africa, and a voucher specimen (*N. Crouch/O. Grace*, 993, NH) retained for verification purposes.

3.3. Extraction and isolation of compounds

The air-dried, powdered leaf material (585 g) was extracted successively for 24 h in a Soxhlet apparatus with hexane, $CHCl_3$, ethyl acetate and methanol, yielding extracts of masses 4.65, 8.21, 6.04, and 22.79 g, respectively. The hexane and methanol extracts were shown by ^{1}H NMR to contain only fatty acids and sugars, respectively, and were not examined further.

Compounds were isolated by repeated combinations of vacuum liquid column and preparative thin layer chromatography on silica gel, and column chromatography on Sephadex-LH-20. Tecleanatalensine A **1** (12.3 mg), Tecleanatalensine B **2** (8.5 mg), and 8-[(3-methyl-2-butenyl)oxy]-4,7-dimethoxyfuro[2,3-*b*]quinoline **3** (21.8 mg) were isolated from the $CHCl_3$ extract, and flindersiamine (5.6 mg) and dictamnine (7.4 mg) from the ethyl acetate extract.

3.3.1. 6-[(2,3-epoxy-3-methylbutyl)oxy]-4,7-dimethoxyfuro[2,3-b]quinoline, tecleanatalensine A 1

Pale yellow gum; $[\alpha]_D$ +11° (*c* 0.19 in CH_2Cl_2); ν_{max} (NaCl) cm^{-1} 3054, 2928, 2854, 1625, 1589, 1507, 1367, 1265, 1210; HREIMS (70 eV) not obtained due to sample decomposition; EIMS (70 eV) *m/z* (rel. int.) 329 (31), 245 (100), 230 (38), 186 (15), 85 (33); UV λ_{max} (CH_2Cl_2) nm (log ε): 246 (4.51), 253 (4.47), 310 (3.85), 322 (3.88), 334 (3.79); ^{1}H NMR spectral data (400 MHz, $CDCl_3$) δ_H 7.54 (1H, *d*, J = 2.8 Hz, H-2), 7.53 (1H, *s*, H-5), 7.32 (1H, *s*, H-8), 7.02 (1H, *d*, J = 2.8 Hz, H-3), 4.41 (3H, *s*, 4-OC$\underline{H}_3$), 3.99 (3H, *s*, 7-OC$\underline{H}_3$), 4.27 (2H, *m*, 2H-1′), 3.25 (1H, *t*, J = 5.1 Hz, H-2′); 1.390, 1.387 (each 3H, *s*, 3H-4′, 3H-5′); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

Table 1
^{13}C NMR spectral data for compounds **1**–**3** ($CDCl_3$, 100 MHz)

Carbon no.	1	2	3
2	142.5 (CH)	142.5 (CH)	142.9 (CH)
3	104.6 (CH)	104.7 (CH)	104.6 (CH)
3a	102.2 (C)	102.0 (C)	101.9 (C)
4	155.7 (C)	156.0 (C)	157.1 (C)
4a	112.9 (C)	112.0 (C)	114.8 (C)
5	102.4 (CH)	101.5 (CH)	118.0 (CH)
6	146.7 (C)	147.0 (C)	112.0 (CH)
7	152.8 (C)	153.0 (C)	152.6 (C)
8	107.0 (CH)	106.0 (CH)	140.8 (C)
8a	142.8 (C)	143.0 (C)	141.9 (C)
9a	163.2 (C)	164.0 (C)	164.2 (C)
1′	67.7 (CH_2)	65.7 (CH_2)	70.4 (CH_2)
2′	61.2 (CH)	119.3 (CH)	121.1 (CH)
3′	58.9 (C)	138.0 (C)	137.6 (C)
4′	19.1 (CH_3)[a]	18.3 (CH_3)[a]	18.0 (CH_3)[a]
5′	24.5 (CH_3)[a]	25.9 (CH_3)[a]	25.8 (CH_3)[a]
4-O$\underline{C}H_3$	58.5 (CH_3)	58.9 (CH_3)	58.9 (CH_3)
7-O$\underline{C}H_3$	56.0 (CH_3)	56.1 (CH_3)	56.8 (CH_3)

[a] Values interchangeable within column.

3.3.2. 4,7-Dimethoxy-6-[(3-methyl-2-butenyl)oxy]furo-[2,3-b]quinoline, tecleanatalensine B 2

Pale yellow gum; ν_{max}(NaCl) cm^{-1} 3054, 2986, 1629, 1579, 1506, 1440, 1364, 1267, 1100; HREIMS (70 eV) *m/z* 313.1348 (calcd. for $C_{18}H_{19}NO_4$ 313.1314); EIMS (70 eV) *m/z* (rel. int.) 313 (95), 245 (100), 230 (74), 186 (35), 69 (10); UV λ_{max} (CH_2Cl_2) nm (log ε): 248 (4.4), 253 (4.4), 310 (3.7), 322 (3.7), 336 (3.7); ^{1}H NMR spectral data (400 MHz, $CDCl_3$) δ_H 7.56 (1H, *d*, J = 2.6 Hz, H-2), 7.48 (1H, *s*, H-5), 7.36 (1H, *s*, H-8), 7.03 (1H, *d*, J = 2.6 Hz, H-3), 5.58 (1H, *br t*, J = 6.8 Hz, H-2′), 4.70 (2H, *d*, J = 6.8 Hz, 2H-1′), 4.43 (3H, *s*, 4-OC$\underline{H}_3$), 3.98 (3H, *s*, 7-OC$\underline{H}_3$), 1.79 (6H, *s*, 3H-4′, 3H-5′); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

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