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QUININE- AND QUINICINE-DERIVED ALKALOIDS FROM *GUETTARDA NOUMEANA*

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Key Word Index—*Guettarda noumeana*; Rubiaceae; bark; quinoline alkaloids.

Abstract—A new quinicine-type alkaloid, *N*-methylquinicinol, has been isolated from the bark of *Guettarda noumeana*, together with the known alkaloids, cupreine, dihydrocupreine and *N*-methyldihydroquinicinol. Complete NMR chemical shift assignments based on 2D experiments are reported for all the alkaloids.

INTRODUCTION

From the bark of *Guettarda noumeana*, which was collected in New Caledonia, we have isolated the known *O*-demethylquinine and *O*-demethyldihydroquinine derivatives, cupreine (**1**) and dihydrocupreine (**2**), together with the quinicine derived alkaloids **3** and **4**. The alkaloids **1** and **2** have been isolated previously from two other Rubiaceae species, *Remijia pedunculata* [1] and *Timonius kanensis* [2], respectively. Compound **1** has also been found in *Picrolemma pseudocoffea* (Simaroubaceae) [3]. *N*-methyldihydroquinicinol (**4**) has been isolated recently from *Guettarda trimera*. [4]. However, the closely related *N*-methylquinicinol (**3**) has not been described previously. The structure of alkaloid **3** was established by spectral means and chemical correlation with the known alkaloid **4**. In addition, we report complete ^{1}H and ^{13}C chemical shift assignments of the four alkaloids based on 2D NMR experiments.

RESULTS AND DISCUSSION

N-methylquinicinol (**3**), $[\alpha]_D - 70°$, showed a $[MH]^+$ peak in the HRCI mass spectrum at *m/z* 341.2224, that matched the molecular formula $C_{21}H_{28}N_2O$ (Δ −0.5 mmu). The ^{1}H NMR exhibited two methyl singlets (3H each) at δ 3.93 and 2.33, corresponding to a OMe and NMe group, respectively. The spectrum further exhibited five aromatic signals (1H each), similar to the one of quinine and *N*-methyldihydroquinicinol, one oxymethine proton at δ 5.30 and resonances typical of a terminal vinyl group (Table 1). The ^{13}C NMR showed, apart of the aromatic signals and the signals of the oxymethine and of the vinyl group (Table 1), the resonances of five methylenes and two methines with chemical shifts reminiscent of the ones previously described for alkaloid **4**. Thus, alkaloid **3** is *N*-methylquinicinol. C-2, C-5 and C-6 gave weak signals in the ^{13}C spectrum and no cross-peak in the ^{1}H^{13}C COSY, due to rapid inversion of the nitrogen ring. However, cross-peaks were observed in the HMBC experiment.

Catalytic hydrogenation of the double bond compound **3** over Pd/C gave alkaloid **4** with known absolute configuration at the three chiral carbons, thus establishing the stereochemistry of **3** as shown. Cupreine (**1**) and dihydrocupreine (**2**) have been described as metabolites of quinine in the human body [5], but are rare in the plant-kingdom. They were not found in *Cinchona* species, which is a rich source of quinine and other related alkaloids. The quinicinol derivatives at the present time appear to be specific to the genus *Guettarda* [4], however the corresponding ketonic alkaloid quinicine is common to both *Guettarda* and *Cinchona* [4, 5].

EXPERIMENTAL

General. UV: MeOH. ^{1}H NMR: 300 or 400 MHz. ^{13}C NMR: 75 MHz. 2D experiments: 300 or 400 MHz. CC: Merck silica gel H 60.

Plant material. The collection (bark, Port Boisé-Forêt, New-Caledonia, 1994) and identification of *G. noumeana* Baill. were done by one of us (M.L.) and J.M. Veillon (Centre ORSTOM, Noumea, New Caledonia). Voucher specimens (LIT 074) are in the Herbarium of the centre ORSTOM, Noumea, New Caledonia.

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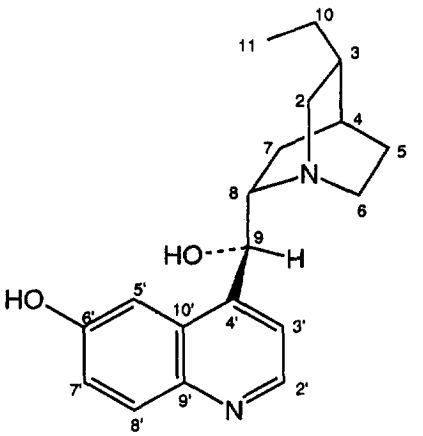
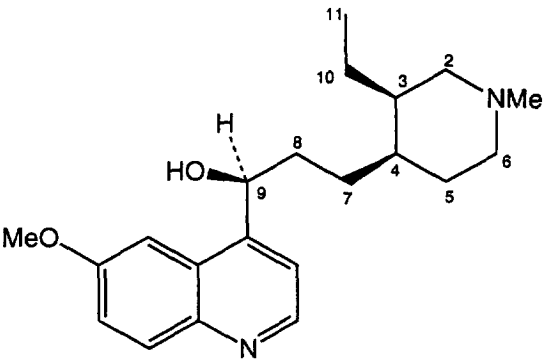


1 Δ^{10}
2



3 Δ^{10}
4

Table 1. ^{13}C (75 MHz) and ^{1}H NMR* data for alkaloids **1–4** in CD_3OD

Position	**1**† δ_C	**1**† δ_H (*J* Hz)	**2**† δ_C	**2**† δ_H (*J* Hz)	**3**‡ δ_C	**3**‡ δ_H (*J* Hz)	**4** δ_C	**4** δ_H (*J* Hz)
2	57.8	2.85 *m*	57.2	2.87 *m*	61.2§	2.45 *m*	58.5	2.15 *m*
		3.20 *m*		3.45 *m*		2.75 *m*		
3	41.1	2.40 *m*	36.5	1.84 *m*	44.1	2.41 *m*	41.4	1.50 *m*
4	30.0	1.85 *m*	25.6	1.95 *m*	38.1	1.38*m*	36.6§	1.50 *m*
5	28.3	1.65 *m*	25.7	1.80 *m*	29.4§	1.57 *m*	28.5§	1.50 *m*
		1.95 *m*		2.12 *m*				
6	45.5	2.85 *ddd* (13, 13,5)	44.4	3.15 *ddd* (13, 13,5)	55.9§	2.31 *m*	54.8§	2.38 *m*
		3.80 *m*		4.15 *ddd* (13)		2.90 *m*		
7	22.1	1.40 *ddd* (13)	18.8	1.50 *ddd* (13)	28.7	1.38 *m*	28.9	1.40 *m*
		1.93 *m*		2.12 *m*		1.56 *m*		1.55 *m*
8	62.0	3.20 *m*	60.6	3.52 *m*	36.8	1.85 *m*	36.8	1.80 *m*
						1.95 *m*		
9	72.0	5.62 *br s*	68.5	5.85 *br s*	71.1	5.30 *dd* (8,4)	70.7	5.34 (7.5, 5)
10	142.6	5.67 *ddd* (17, 10,8)	27.2	1.30 *dq* (7)	138.4	6.00 *ddd* (17, 10,10)	21.0	1.28 *m*
11	116.6	4.87 *d* (10)	11.4	0.85 *t* (7)	117.6	5.05 *d* (10)	12.3	0.87 *t* (7)
		4.97 *d* (17)				5.01 *d* (17)		
2′	148.5	8.55 *d* (4.5)	147.0	8.63 *d* (4.5)	148.5	8.63 *d* (4.5)	148.3	8.63 *d* (4.5)
3′	120.9	7.60 *d* (4.5)	119.6	7.71 *d* (4.5)	119.4	7.59 *d* (4.5)	119.1	7.60 *d* (4.5)
4′	150.0		146.7		152.5		152.3	
5′	106.2	7.32 *d* (2.5)	104.5	7.45 *d* (2.5)	103.1	7.35 *d* (2.5)	102.6	7.33 *d* (2.5)
6′	158.9		157.0		159.4		159.1	
7′	124.4	7.30 *m*	123.0	7.35 *dd* (9, 2.5)	123.2	7.39 *dd* (9, 2.5)	123.0	7.38 *dd* (9, 2.5)
8′	132.6	7.87 *d* (9)	131.1	7.92 *d* (9)	131.5	7.92 *d* (9)	131.2	7.92 *d* (9)
9′	145.0		143.5		144.9		144.7	
10′	129.2		127.3		128.3		128.0	
OMe					56.3	3.93 *s*	56.0	3.90 *s*
NMe					46.3	2.33 *s*	46.7	2.15 *s*

* At 300 MHz for compounds **1**, **2** and **4** and 400 MHz for compound **3**.
† Assignments based on ^{1}H-^{1}H and ^{1}H-^{13}C COSY.
‡ Assignments based on ^{1}H-^{1}H COSY and HMQC.
§ Low intensity peak.

Extraction and isolation of akaloids. Alkaloids were extracted by the classical method after alkalinization of the plant material. A total of 0.6 g of crude alkaloids was obtained from the bark (0.5 kg). The crude product underwent cc on silica gel with EtOAc–MeOH–H_2O–NH_4OH (100:17:13:0.5), yielding cupreine (**1**) (50 mg), a mixt. of dihydrocupreine (**2**) and *N*-methylquinicinol **3** (150 mg) and *N*-methyldihydroquinicinol **4** (90 mg). Further prep. TLC of the mixt. of **2** and **3** (95 mg) using MeOH–NH_4OH (49:1) afforded alkaloids **3** (41 mg) and **2** (45 mg).

Identification of known compounds was carried out

by comparison of their physical and spectral data with lit. data [6, 7] and, for **4**, by comparison with an authentic sample. NMR data are listed in Table 1, since only ^{1}H NMR data (DMSO-d_6) were available for cupreine **1** (7) and partial ^{1}H and ^{13}C NMR data ($CDCl_3$) for alkaloid **4** (4).

N-*methylquinicinol* (**3**). Amorphous gum. $[\alpha]_D$ 70° ($CHCl_3$, *c* 0.5). UV λ_{max} nm (log ε): 224 (4.55), 277 (3.97), 308 sh (3.51). HRCIMS: $[MH]^+$ *m/z* 341.224. $C_{21}H_{28}N_2O$ (Δ −0.5 mmu) ^{1}H and ^{13}C NMR: Table 1.

Hydrogenation of N-*methylquinicinol* (**3**) *to* N-*methyldihydroquinicinol* (**4**). A mixt. of MeOH soln (4 ml) of **3** (13 mg), 10% Pd/C (*ca* 10 mg) and two drops of HOAc was shaken for 3 hr under an atmosphere of H_2. After removal of catalyst and solvent, the residue was dissolved in CH_2Cl_2 and the soln washed with aq. 1 H NaOH. The organic layer was washed with H_2O, dried (Na_2SO_4) and evapd, yielding **4** (10 mg). Spectral data (^{1}H and ^{13}C NMR) identical to those of natural **4**.

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