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PIPERIDINE ALKALOIDS AND OTHER CONSTITUENTS OF *DIALYPETALUM FLORIBUNDUM*

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Key Word Index—*Dialypetalum floribundum*; Lobeliaceae; leaves; piperidine alkaloid; *N*-methyl-2-(2-hydroxybutyl)-6-(2-hydroxypentyl)-piperidine; *N*-methyl-2,6-*bis*-(2-hydroxypentyl)-piperidine; lobetyol; lobetyolin.

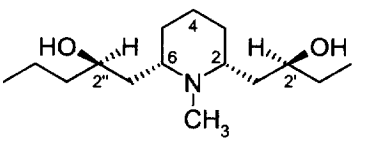
Abstract—Two piperidine alkaloids were obtained from an ethanolic extract of the leaves of *Dialypetalum floribundum*. Their structures were determined as *N*-methyl-2-(2-hydroxybutyl)-6-(2-hydroxypentyl)-piperidine and *N*-methyl-2,6-*bis*-(2-hydroxypentyl)-piperidine from spectroscopic data. Lobetyol and its 9-*O*-glucoside, lobetyolin, were also isolated.

INTRODUCTION

Dialypetalum floribundum is a plant endemic to Madagascar. The leaves are used in the area of Ambatoloana, where they have been collected, as a drug against bugs of cattle. We investigated the constituents of the leaves and have isolated two new alkaloids, *N*-methyl-2-(2-hydroxybutyl)-6-(2-hydroxypentyl)-piperidine (**1**) and *N*-methyl-2,6-*bis*-(2-hydroxypentyl)-piperidine (**2**), as well as lobetyol and lobetyolin. Piperidine alkaloids occur commonly in the Lobeliaceae [1]. Polyacetylenic compounds have also been obtained from *Lobelia* species [2].

RESULTS AND DISCUSSION

An ethanolic extract of the leaves yielded, after acid-base separation, two new alkaloids **1** and **2**. The high resolution mass spectrum of **1** led to the molecular formula $C_{15}H_{31}NO_2$ with the Mr of 257. The mass spectrum showed further peaks at *m/z* 242 $[M - CH_3]^+$, 228 $[M - C_2H_5]^+$, 214 $[M - C_3H_7]^+$, 198 $[M - C_3H_7O]^+$, 184 $[M - C_4H_9O]^+$ and 170 $[M - C_5H_{11}O]^+$. A fragmentation at *m/z* 98 is typical for *N*-methylated piperidine derivatives ($C_6H_{12}N$). The ^1H NMR spectrum showed two triplets at δ 0.92 and δ 0.94 for two methyl groups. A singlet at δ 2.18 revealed the presence of a N-CH_3 and two signals at δ 3.65 and 3.74 could be assigned to C<u>H</u>-O. A further signal for two protons at δ 3.02, together with two peaks at δ 62.1 and δ 62.3 in the ^{13}C NMR spectrum, can be attributed to two methine protons neighbouring a nitrogen. From the HH-COSY spectrum a fragment could be determined: CH_3-$(CH_2)_n$-CH(O)-CH_2-CH(N)-CH_2-. The ^{13}C NMR data (see Table 1) are in good agreement with the ^1H NMR spectrum. Two signals at δ 72.8 and 71.4



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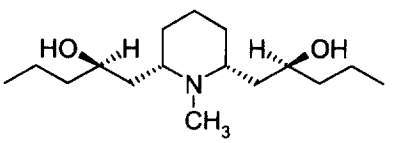

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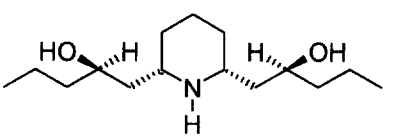

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Table 1. ^{13}C NMR chemical shift data of compounds **1** and **2** (in $CDCl_3$)

C-	1	2	3
2	62.3	62.2	56.8
3	23.2	23.2	34.3
4	25.1	25.0	25.2
5	23.2	23.2	34.3
6	62.1	62.2	56.8
1′	39.2	39.7	44.5
2′	72.8	71.2	71.5
3′	30.5	40.2	40.8
4′	9.7	18.6	19.1
5′		14.1	14.6
1″	39.8	39.7	44.5
2″	71.4	71.2	71.5
3″	40.1	40.2	40.8
4″	18.8	18.6	19.1
5″	14.2	14.1	14.6
N-Me	25.9	25.9	

can be assigned to CH-O. Furthermore, the spectrum showed eight signals for methylene and two signals for methyl groups. The *N*-methyl group had a resonance at δ 25.9. A hetero-nuclear COSY experiment led to the assignment of the peaks in the ^1H and ^{13}C NMR spectra. The configuration at C-2, C-6, C-2′ and C-2″ has been defined by comparison of NMR data with published values [3, 4, 5].

^1H and ^{13}C NMR spectra of **2** were similar to those of **1**. But because of symmetry, the number of peaks in the spectra of **2** is reduced. Again, the HH-COSY spectrum led to the fragment CH_3-$(CH_2)_n$-CH(O)-CH_2-CH(N)-CH_2-. The mass spectrum of **2** showed a $[M]^+$ at *m/z* 271 and high resolution measurement of this peak gave the molecular formula $C_{16}H_{33}NO_2$. Thus, **2** has one methylene group more than **1**. The mass spectrum revealed that both side-chains are identical. It showed peaks at *m/z* 228 $[M - C_3H_7]^+$ and *m/z* 184 $[M - C_5H_{11}O]^+$. Again, the characteristic peak at *m/z* 98 for $C_6H_{12}N$ was observed. This led to the structure of *N*-methyl-2,6-*bis*-(2-hydroxypentyl)-piperidine for compound **2**. For the stereochemistry, the ^{13}C NMR data were compared with those of andrachamine (**3**) [5]. The values are in good agreement; only the peaks for C-3 and C-5 are shifted because of the methyl group. A multiplet at δ 1.77–1.82 in the ^1H NMR spectrum of **2** for one proton must be attributed to one of the H_2-4 because of the symmetry of the molecule. This value is in good agreement with that for H-4e reported for **3** [5]. A CH COSY experiment showed correlation to the carbon peak at δ 25.0.

EXPERIMENTAL

General

Plant material was collected in March 1992 between Moramanga and Ambatoloana, Madagascar. NMR spectra (^1H 300 MHz; ^{13}C 75 MHz) were recorded in $CDCl_3$ soln with TMS as int. standard. MS were measured by direct inlet at 70 eV.

Extraction and isolation

Dried and powdered leaves of *D. floribundum* (1090 g) were extracted 3 × with 80% EtOH in H_2O at room temp. for 48 hr. After filtration and evapn of solvent, part of the residue (91 of 134 g) was partitioned between $CHCl_3$ and H_2O. The aq. phase was extracted 3 × with *n*-BuOH. Chromatography of the butanolic extract on silica gel gave lobetyol and lobetyolin. Another part of the ethanolic extract (43 of 134 g) was acidified with 2% HCl and extracted with $CHCl_3$. To the H_2O layer, NH_4OH was added to pH 9 followed by extraction with $CHCl_3$. The $CHCl_3$ soln was dried (Na_2SO_4) and then evapd to dryness, resulting in an alkaloid fr. Chromatography on Sephadex LH20 using MeOH and on silica gel using CH_2Cl_2-EtOH-NH_4OH (47:2:1) gave the two alkaloids **1** (25 mg) and **2** (28 mg).

Lobetyol and lobetyolin

^1H and ^{13}C NMR spectra were identical to lit. data [6].

N-methyl-2-(2-*hydroxybutyl*)-6-(2-*hydroxypentyl*)-*piperidine* (**1**)

EIMS *m/z* (rel. int.): 257 (21) ([M$^+$] measured 257.234924 $C_{15}H_{31}NO_2$ calculated 257.235480), 242 (10), 228 (39), 214 (40), 198 (7), 184 (84), 170 (100), 152 (37), 140 (38), 112 (39), 98 (75), 82 (39), 67 (40). ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (*m*, 1H, H-2″), 3.65 (*m*, 1H, H-2′), 3.02 (*m*, 2H, H-2 and H-6), 2.18 (*s*, 3H, N-Me), 1.78-1.84 (*m*, 1H, H-4e), 1.69–1.58 (*m*, H-1′, H-1″), 1.58–1.38 (*m*, H-4a, H-3, H-5, H_2-3′, H_2-3″, H_2-4″), 1.38–1.29 (*m*, H-1′, H-1″), 1.23–1.15 (*m*, H-3, H-5), 0.94 (*t*, J = 7.5 Hz, 3H, H_3-4′), 0.92 (*t*, J = 4.5 Hz, 3H, H_3-5″). ^{13}C NMR (75 MHz, $CDCl_3$): Table 1.

N-methyl-2,6-*bis*-(2-*hydroxypentyl*)-*piperidine* (**2**)

EIMS *m/z* (rel. int.) 271 (1) ([M$^+$] measured 271.250944 $C_{16}H_{33}NO_2$ calculated 271.251130), 228 (13), 184 (100), 98 (31). ^1H NMR (300 MHz, $CDCl_3$): 3.72 (*m*, 2H, H-2′ and H-2″), 3.01 (*m*, 2H, H-2 and H-6), 2.17 (*s*, 3H, N-Me), 1.82–1.77 (*m*, 1H, H-4e), 1.67–1.56 (*m*, H-1′, H-1″), 1.56–1.43 (*m*, H-3, H-4a, H-5), 1.43–1.35 (*m*, H_2-3′, H_2-3″), 1.40–1.30 (*m*, H_2-4′, H_2-4″), 1.33–1.26 (*m*, H-1′, H-1″), 1.22–1.13 (*m*, 2H, H-3, H-5), 0.89 (*t*, J = 6.6 Hz, 6H, H_3-5′ and H_3-5″). ^{13}C NMR (75 MHz, $CDCl_3$): Table 1.

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