Tetrahedron 74 (2018) 441–452

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Biphenyl ether and biphenyl quinolizidine lactone alkaloids from *Heimia salicifolia*

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ARTICLE INFO

Article history:
Received 21 October 2017
Received in revised form
30 November 2017
Accepted 6 December 2017
Available online 9 December 2017

Keywords:
Alkaloid
Quinolizidine
Heimia salicifolia

ABSTRACT

Three new biphenyl ether quinolizidine lactone alkaloids (**1**–**3**) and 13 new biphenyl quinolizidine lactone alkaloids (**4**–**16**) were isolated from *Heimia salicifolia* (Lythraceae) together with seven known alkaloids. Their structures were determined by spectroscopic analyses and chemical conversions.

1. Introduction

Heimia salicifolia[1] belonging to Lythraceae has been used in folk medicine because of its antisyphilitic, antipyretic, laxative, diuretic, and anti-inflammatory effects. On the other hand, this plant is the main ingredient of the law-evading drug "sinicuichi", which exerts a psychoactive effect when consumed.[1b] *H. salicifolia* is known to contain biphenyl quinolizidine lactone alkaloids and phenyl quinolizidine alkaloids, but the active principles and the mechanism of action underlying its neurotropic effects have not been clarified until now. As part of our continuous chemical studies on new and bioactive alkaloids,[2] we have started an investigation of the constituents of *H. salicifolia*. Herein we report the structure elucidation of three new biphenyl ether quinolizidine lactone alkaloids (**1**–**3**) which were the first examples of biphenyl ether quinolizidine lactones having a hydroxy group at C-14, and 13 new biphenyl quinolizidine lactone alkaloids (**4**–**16**) from *H. salicifolia*, based on spectroscopic analyses and chemical conversions (Fig. 1).

2. Results and discussion

Compound **1** was found to have the molecular formula $C_{25}H_{29}NO_6$ from HRESIMS (*m/z* 440.2068 $[M+H]^+$) (Fig. 2). The ^{1}H NMR spectral data (Table 1) included signals assignable to the aromatic protons of 1,4-disubstituted benzene [δ_H 7.69 (dd, J = 8.5, 2.0 Hz, H-4′), 7.34 (dd, J = 8.5, 2.2 Hz, H-3′), 6.94 (dd, J = 8.5, 2.0 Hz, H-6′), 6.51 (dd, J = 8.5, 2.2 Hz, H-1′)], two singlet aromatic protons [δ_H 6.75 (s, H-6″), 6.97 (s, H-3″)], two oxymethine protons [δ_H 5.05 (dd, J = 10.8, 5.0 Hz, H-14), 4.85 (br s, H-2)], two aminomethine protons [δ_H 3.36 (br d, J = 10.5 Hz, H-4), 3.03 (m, H-10)], and a methoxy group [δ_H 3.92 (3H, s, 5″-OMe)]. ^{13}C NMR (Table 1) and HMQC analyses indicated the presence of an ester carbonyl carbon [δ_C 169.4 (C-12)], 12 aromatic carbons, including four oxygenated ones [δ_C 161.9 (C-2′), 148.7 (C-1″), 146.3 (C-5″), 143.2 (C-4″)], two oxygenated sp^3 carbons [δ_C 72.1 (C-14), 68.2 (C-2)], a methoxy group [δ_C 56.0 (5″-OMe)], two aminomethine carbons [δ_C 56.7 (C-10), 44.8 (C-4)], and an aminomethylene carbon [δ_C 50.4 (C-6)]. In the HMBC spectra (Fig. 2), correlations between H-10 and H-6 and C-4, between H-4 and C-1″ and C-2″ aromatic carbons, and between H-4′ and H-6′ and C-14 were observed. The above data suggested that **1** was a biphenyl ether quinolizidine lactone alkaloid having a hydroxy group at C-14 and an analog of vertaline (**17**).[3]

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https://doi.org/10.1016/j.tet.2017.12.012
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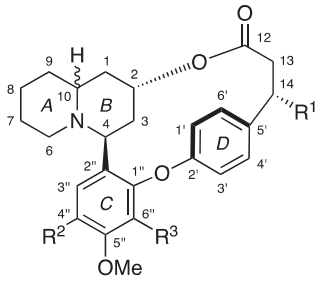
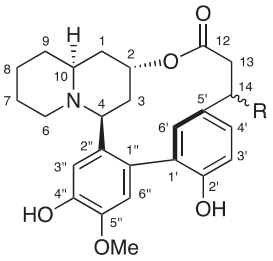
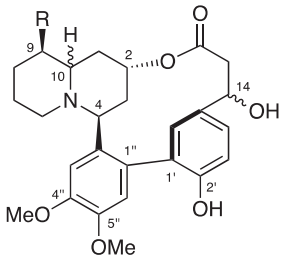


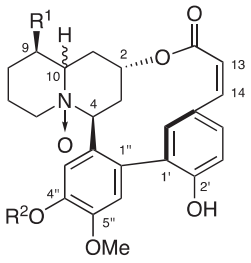
10β-H, R^1=OH, R^2=OH, R^3=H:
4''-*O*-demethyl-14-hydroxyvertaline (**1**)
10β-H, R^1=OH, R^2=H, R^3=OH:
14-hydroxylagerine (**2**)
10α-H, R^1=OH, R^2=OH, R^3=H:
4''-*O*-demethyl-14-hydroxydecaline (**3**)
10β-H, R^1=H, R^2=OMe, R^3=H: vertaline (**17**)
10β-H, R^1=H, R^2=H, R^3=OH: lagerine (**18**)
10α-H, R^1=H, R^2=OMe, R^3=H: decaline (**19**)



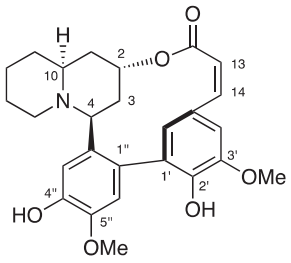
R=α-OH: 4''-*O*-demethyllythridine (**4**)
R=α-OH, *N*-oxide:
4''-*O*-demethyllythridine *N*-oxide (**5**)
R=β-OH:
14-*epi*-4''-*O*-demethyllythridine (**6**)
R=β-OMe: 14-*epi*-4''-*O*-demethyl-
14-*O*-methyllythridine (**7**)



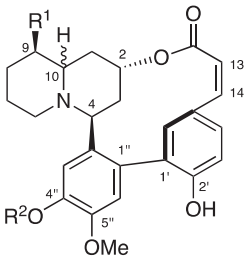
10α-H, 14β-OH, R=H:
14-*epi*-lythridine (**8**)
10β-H, 14β-OH, R=H:
14-*epi*-heimidine (**9**)
10β-H, 14β-OH, R=OH:
14-*epi*-9β-hydroxyheimidine (**10**)
10β-H, 14α-OH, R=OH:
9β-hydroxyheimidine (**11**)
10α-H, 14α-OH, R=H: lythridine (**20**)
10β-H, 14α-OH, R=H: heimidine (**21**)



10α-H, R^1=H, R^2=H: lyfoline *N*-oxide (**12**)
10α-H, R^1=H, R^2=Me: lythrine *N*-oxide (**13**)
10β-H, R^1=H, R^2=Me: vertine *N*-oxide (**14**)
10β-H, R^1=OH, R^2=Me: 9β-hydroxyvertine *N*-oxide (**15**)



3'-methoxylyfoline (**16**)



10α-H, R^1=H, R^2=H: lyfoline (**22**)
10α-H, R^1=H, R^2=Me: lythrine (**23**)
10β-H, R^1=H, R^2=Me: vertine (**24**)
10β-H, R^1=OH, R^2=Me:
9β-hydroxyvertine (**25**)

Fig. 1. Structures of new biphenyl quinolizidine lactone alkaloids **1**–**16** isolated from *Heimia salicifolia* and known alkaloids **17**–**25**.

The NOE correlations of H-4 to H-7 (δ_H 1.65, m) and H-9 (δ_H 1.73, dddd), and of H-10 to H-6 (δ_H 2.42, br dd) indicated the presence of *cis*-quinolizidine having a chair-chair form and that H-4 and H-10 assumed α-axial and β-orientations, respectively. The downfield chemical shift of H-10 (δ_H 3.03) was observed and it could be explained by the deshielding effect of the syn-oriented nitrogen lone pair.[4] That H-2 was observed as a broad singlet revealed that H-2 was in an equatorial orientation. The methoxy group on C-5″ was confirmed from the NOE correlations of the methoxy protons to H-6″ and of H-3 to H-3″. The NOE correlations of H-4 to H-3′, of H-4′ to H-13 (δ_H 2.37, dd), and of H-14 to H-6′ and the coupling constants between H_2-13 and H-14 ($J_{13\alpha,14\beta}$ = 10.8 Hz, $J_{13\beta,14\beta}$ = 5.0 Hz) suggested that the hydroxy group at C-14 was α-oriented. From these data, **1** was deduced to be 4″-*O*-demethyl-14-hydroxyvertaline.

Compound **2** was found to have the same molecular formula $C_{25}H_{29}NO_6$ as **1** on the basis of HRESIMS (*m/z* 440.2071 $[M + H]^+$) (Fig. 3). Its ^1H and ^{13}C NMR spectral data (Table 1) were very similar to those of **1**. The difference in the ^1H NMR data was the presence of two additional doublet aromatic protons in **2** [δ_H 6.87 (d, J = 9.0 Hz, H-3″), 6.75 (d, J = 9.0 Hz, H-4″)] in place of two singlet aromatic protons in **1**. HMBC correlations between H-4 (δ_H 3.34) of the quinolizidine ring and the oxygenated aromatic carbon at δ_C 143.2 (C-1″) and the aromatic methine carbon at δ_C 119.7 (C-3″), between H-3″ and C-4 and the oxygenated aromatic carbons at δ_C 143.2 (C-1″) and δ_C 146.5 (C-5″), between H-4″ and the oxygenated aromatic carbon at δ_C 138.2 (C-6″), and between methoxy protons and the carbon at δ_C 146.5 (C-5″) were observed, indicating that **2** was a biphenyl ether quinolizidine lactone alkaloid with oxygenated C-1″, C-5″, and C-6″, as was observed in lagerine (**18**).[5] The NOE correlations confirmed the presence of a 14α-hydroxy group and a 5″-methoxy group, and the stereochemistry of the quinolizidine ring. From these data, **2** was deduced to be 14-hydroxylagerine.

Compound **3** was found to have the same molecular formula $C_{25}H_{29}NO_6$ as **1** and **2** from HRESIMS (*m/z* 440.2072 $[M + H]^+$) (Fig. 4). The ^1H NMR spectral data (Table 1) included signals assignable to the aromatic protons of 1,4-disubstituted benzene [δ_H 7.67 (dd, J = 8.5, 2.1 Hz, H-4′), 7.27 (dd, J = 8.5, 2.6 Hz, H-3′), 6.90 (dd, J = 8.4, 2.1 Hz, H-6′), 6.46 (dd, J = 8.4, 2.6 Hz, H-1′)], two singlet aromatic protons [δ_H 6.96 (s, H-3″), 6.73 (s, H-6″)], two oxymethine protons [δ_H 5.05 (dd, J = 10.9, 5.4 Hz, H-14), 4.84 (m, H-2)], two aminomethine protons [δ_H 2.50 (dd, J = 12.1, 2.3 Hz, H-4), 1.89 (br dd, J = 10.7, 10.7 Hz, H-10)], and a methoxy group [δ_H 3.91 (3H, s, 5″-OMe)]. The ^{13}C NMR data (Table 1) indicated the presence of an ester carbonyl carbon [δ_C 169.5 (C-12)], 12 aromatic carbons, including four oxygenated ones [δ_C 161.8 (C-2′), 148.8 (C-1″), 145.9 (C-5″), 142.8 (C-4″)], two oxygenated sp^3 carbons [δ_C 72.2 (C-14), 68.1 (C-2)], a methoxy group [δ_C 56.00* (5″-OMe)], two