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LETTERS

Ancisheynine, a novel naphthylisoquinolinium alkaloid from *Ancistrocladus heyneanus*

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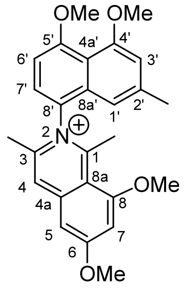
Abstract—A novel naphthylisoquinoline alkaloid, ancisheynine **1**, was isolated from the aerial part of *Ancistrocladus heyneanus* Wallich ex J. Graham (Ancistrocladaceae). Ancisheynine **1** contained a previously undescribed N-2,C-8′–linkage between the isoquinoline and naphthalene units and its structure was established by spectroscopic methods.

Many naphthylisoquinoline alkaloids have been isolated from plants of the genera *Ancistrocladaceae* and *Dioncophyllaceae*.[1,2] These alkaloids consist of naphthalene and isoquinoline units with varying degrees of hydroxylation and *O*-methylation, as well as different oxidation states of the isoquinoline ring.[1] The position of biaryl linkage between the two units also varies, with C-5,C-1′–, C-5,C-8′–, C-7,C-1′–, C-7,C-3′–, C-7,C-6′– and C-7,C-8′–linkages known.[1] This paper describes the isolation and structure elucidation of a novel naphthylisoquinoline alkaloid, ancisheynine **1**, with a previously undescribed N-2,C-8′–linkage, from *Ancistrocladus heyneanus* Wallich ex J. Graham (Ancistrocladaceae).[3]

An MeOH/CH_2Cl_2 (1:1) extract (7.5 g) of the aerial part of *A. heyneanus* (72 g dry weight) was chromatographed on diol VLC, followed by silica gel using centrifugal TLC (3% MeOH/CH_2Cl_2 saturated with NH_3 vapor) and Sephadex LH-20 (50% MeOH/CH_2Cl_2) to yield a minor compound **1** (4 mg), which showed a positive test to the Dragendorff's reagent.[4]

The new alkaloid **1**[5] had a cationic molecular formula of $C_{26}H_{28}NO_4^+$ on the basis of a (+)-HR-ESIMS of the $[M]^+$ ion peak at *m*/*z* 418.2006 (Δ −2.8 ppm). Examination of the ^{1}H NMR spectrum of **1** obtained in $CDCl_3$ (Table 1) revealed seven clearly resolved aromatic protons, four methoxy and three aromatic methyl reso-



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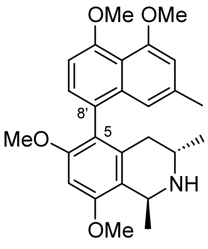

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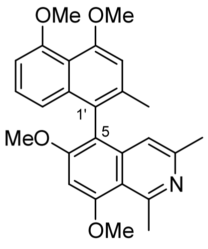

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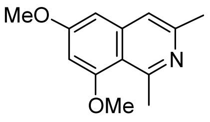

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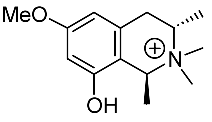

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Keywords: *Ancistrocladus heyneanus*; Ancistrocladaceae; naphthylisoquinoline; quaternary alkaloid; ancisheynine.

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Table 1. ^{15}N (50 MHz), ^{13}C (125 MHz), ^{1}H (500 MHz), COSY, HMBC, ^{15}N HMBC and ROESY NMR data for ancisheynine **1** in $CDCl_3$

No.	^{15}N (δ)^{a}	^{13}C (δ)	^{1}H δ, m, J (Hz)	COSY	HMBC (H to C)	^{1}H–^{15}N HMBC	ROESY
1		160.5					
2	197.0						
3		146.5					
4		124.8	8.30, br s	3-CH_3	3, 5, 8, 8a, 3-CH_3	2	5
4a		143.9					
5		101.0	7.34, d, 2.1	7	4, 6, 7, 8a		4, 6-OCH_3
6		168.6					
7		103.6	6.76, d, 2.1	5	5, 6, 8, 8a		8-OCH_3
8		162.2					
8a		116.4					
1′		112.0	6.05, br s	3′, 2′-CH_3	3′, 4a′, 8′, 8a′, 2′-CH_3		2′-CH_3
2′		141.9					
3′		110.8	6.79, br s	1′, 2′-CH_3	1′, 4′, 4a′, 2′-CH_3		2′-CH_3, 4′-OCH_3
4′		159.3					
4a′		117.3					
5′		160.4					
6′		105.3	6.98, d, 8.4	7′	4a′, 5′, 8′		7′, 5′-OCH_3
7′		127.5	7.54, d, 8.4	6′	5′, 8′, 8a′	2	6′
8′		128.2					
8a′		132.4					
1-CH_3		23.5	2.86, s		1, 8a	2	
3-CH_3		22.2	2.24, s	4	3, 4	2	
6-OCH_3		58.1	4.14, s		6		5
8-OCH_3		57.5	4.04, s		8		7
2′-CH_3		23.3	2.35, s	1′, 3′	1′, 2′		1′, 3′
4′-OCH_3		57.4	4.02, s		4′		3′
5′-OCH_3		57.6	4.08, s		5′		6′

[a] Chemical shift obtained from the ^{1}H–^{15}N HMBC NMR and referenced to liq. NH_3.

nances. Analysis of the 2D NMR data of **1** (Table 1) allowed these resonances to be assigned to a naphthalene and an isoquinoline unit.

The naphthalene unit consisted of two *ortho*-coupled doublets at δ 7.54 (H-7′) and 6.98 (H-6′), two broad aromatic singlets at δ 6.79 (H-3′) and 6.05 (H-1′), two methoxy groups at δ 4.08 (5′-OCH_3) and 4.02 (4′-OCH_3) and an aromatic methyl at δ 2.35 (2′-CH_3). These data are typical of an 8′-linked 2′-methyl-4′,5′-dimethoxynaphthalene unit[6–9] except for the higher field shift of H-1′. For example, H-1′ resonated at δ 6.64 in ancistrotectoriline A **2**,[6] compared to δ 6.05 in **1**.

The isoquinoline unit of **1** consisted of two *meta*-coupled aromatic methines (^{1}H: δ 7.34 and 6.76; ^{13}C: δ 101.0 and 103.6), one aromatic methine singlet (^{1}H: δ 8.30; ^{13}C: δ 124.8), two methoxy groups (^{1}H: δ 4.14 and 4.04; ^{13}C: δ 58.1 and 57.5) and two aromatic methyl groups (^{1}H: δ 2.86 and 2.24; ^{13}C: δ 23.5 and 22.2). HMBC correlations (Fig. 1) allowed the structure of the isoquinoline unit to be assigned as 1,3-dimethyl-6,8-dimethoxy-isoquinoline.

As there were no other available points of attachment, C-8′ of the naphthalene unit must be attached to N-2 of the isoquinoline unit to form an isoquinolinium cation. No correlations between the naphthalene and isoquinoline units were observed in the HMBC and ROESY spectra of **1**. Confirmation of the N-2,C-8′–link was obtained by the observation of ^{1}H–^{15}N HMBC correlations from H-7′ on the naphthalene unit and H-4, 1-CH_3 and 3-CH_3 on the isoquinoline unit to a nitrogen resonance at δ 197.0. The chemical shift was consistent with those previously reported for a quinolinium salt (δ 190).[10] The downfield shift of H-4 (δ 8.30) was also in accordance with those reported for *N*-substituted pyridinium derivatives,[11,12] when compared with H-4 at δ 6.43 for 6-*O*-methyl-hamateine **3**[9] and δ 7.08 for the parent alkaloid 6,8-dimethoxy-1,3-dimethylisoquinoline **4**.[13,14] The identity of the counter ion was not pursued. Therefore, the structure of **1** was assigned as shown and given the trivial name ancisheynine.

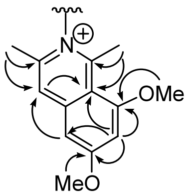

Figure 1. Selected HMBC correlations for the isoquinoline unit of **1**.

Many of the naphthylisoquinoline alkaloids reported to date have been shown to contain an axis of chirality originating from restricted rotation between the naphthalene and isoquinoline units.[1,2,6–9] The optical rotation of **1** was found to be 0 ($[\alpha]^{30}_{D}$ (c 0.42, $CHCl_3$)), which suggested that **1** was a racemic mixture.

Ancisheynine **1** is the first reported naphthylisoquinoline alkaloid that is not coupled via a C,C–linkage. Although numerous naphthylisoquinoline alkaloids have been found in the genus *Ancistrocladus*, no quaternary alkaloids have been reported except for the tetrahydroisoquinoline, gentrymine B **5**, from *A. korupensis*.[15]

Acknowledgements

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References

1. Bringmann, G.; Pokorny, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 46, pp. 127–271.
2. Bringmann, G.; Saeb, W.; Rückert, M.; Mies, J.; Michel, M.; Mudogo, V.; Brun, R. *Phytochemistry* **2003**, *62*, 631–636 and references cited therein.
3. A large woody climber collected from Ambavne, Pune District, India, which grows on trees like *Symplocos racemosa* and *Garcinia talbotii* in moist forest areas. Local names: 'Kardal'; 'Mothi Taan'. Voucher specimen: *Godbole and Sarnaik 45005*, January 10, 1994 (deposited at the Herbarium of the Field Museum, Chicago, USA).
4. Harbourne, J. B. *Phytochemical Methods*: *A Guide to Modern Techniques of Plant Analysis*, 3rd ed.; Chapman & Hall: London, 1998; p. 208.
5. Yellow solid; UV (MeOH) $\lambda_{\max}$ nm (log ε) 233 (4.47), 264 (4.29), 307 (3.89), 358 (3.71); IR $\nu_{\max}$ cm^{-1}: 1610, 1459, 1284, 1116.
6. Tang, C. P.; Yang, Y. P.; Zhong, Y.; Zhong, Q. X.; Wu, H. M.; Ye, Y. *J. Nat. Prod.* **2000**, *63*, 1384–1387.
7. Bringmann, G.; Hamm, A.; Günther, C.; Michel, M.; Brun, R.; Mudogo, V. *J. Nat. Prod.* **2000**, *63*, 1465–1470.
8. Bringmann, G.; Günther, C.; Busemann, S.; Schäffer, M.; Olowokudejo, J. D.; Alo, B. I. *Phytochemistry* **1998**, *47*, 37–43.
9. Anh, N. H.; Porzel, A.; Ripperger, H.; Bringmann, G.; Schäffer, M.; God, R.; Sung, T. V.; Adam, G. *Phytochemistry* **1997**, *45*, 1287–1291.
10. Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **1999**, *63*, 543–585.
11. Nawwar, M. A. M.; Hussein, S. A. M.; Merfort, I. *Phytochemistry* **1994**, *37*, 1175–1177.
12. Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*; Springer-Verlag: Berlin Heidelberg, 2000; Chapter 5, p. 187.
13. Rizzacasa, M. A.; Sargent, M. V.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 79–86.
14. Montagnac, A.; Hadi, A. H. A.; Remy, F.; Païs, M. *Phytochemistry* **1995**, *39*, 701–704.
15. Hallock, Y. F.; Cardellina, J. H., II; Kornek, T.; Gulden, K. P.; Bringmann, G.; Boyd, M. R. *Tetrahedron Lett.* **1995**, *36*, 4753–4756.