Pergamon

Tetrahedron Letters, Vol. 38, No. 7, pp. 1253-1256, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00051-8

seco-Benzyltetrahydroisoquinolines from *Polyalthia insignis* (Annonaceae)

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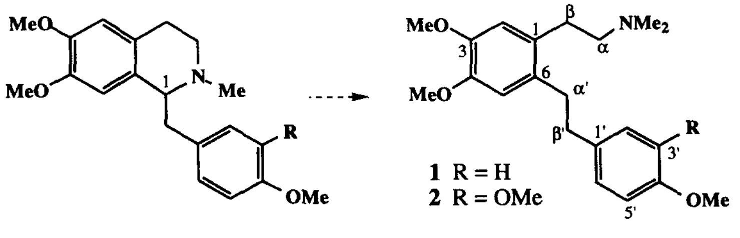
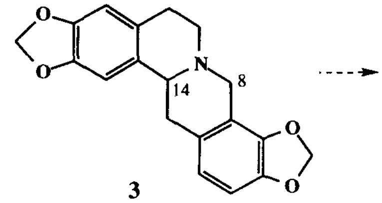
***Abstract*:** Polysignine (**1**) and methoxypolysignine (**2**), two *seco*-benzyltetrahydroisoquinoline alkaloids, together with (-)-asimilobine, oxostephanine, *O*-methylmoschatoline and liriodenine, have been isolated from bark of *Polyalthia insignis* and their structures elucidated by spectroscopic methods. © 1997, Elsevier Science Ltd. All rights reserved.

The biosynthesis of alkaloids from phenylethylamines (e.g. dopamine) provides a family of isoquinoline alkaloids which include benzylisoquinolines, benzyltetrahydroisoquinolines, bisbenzylisoquinolines, morphinandienones, aporphines, protoberberines, benzophenanthridines and phenanthrene alkaloids[1,2]. These alkaloids comprise many bioactive principles of medicinal importance and they are provided by many genera of the plant kingdom. Although the isoquinoline ring is a general feature of these alkaloids, simple *seco*-benzyltetrahydroisoquinolines (C1-N ring-opened alkaloids) such as polysignine(**1**) and methoxypolysignine (**2**) have not been reported while few related examples found are likely derived from protoberberines[3-6], e.g. cheilanthifoline (**3**) provides protopine (**4**). More commonly, cleavage of C14-N bonds of **3** to *seco*-berberine derivatives can be facilitated after cleavage of the C8-N bond[4,6]; for example, peshawarine (**5**)[3] from *Hypecoum parviflorum* and *N*-methylhydrosteine (**6**) can also arise from derivatives of torulosine (**7**)[4] from *Dactylicapnos torulosa*. First examples of *seco*-benzyltetrahydroisoquinolines, **1** and **2**, probably derived directly from simple



1 R = H
2 R = OMe

benzyltetrahydroisoquinolines, are now furnished as major alkaloids by *P. insignis* [7], a Malaysian plant of the Annonaceae family.



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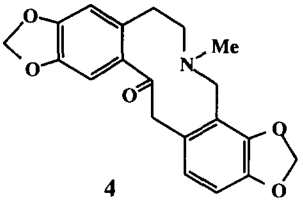

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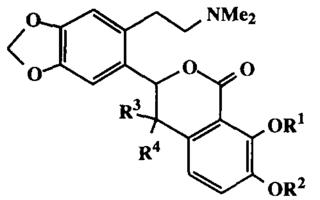
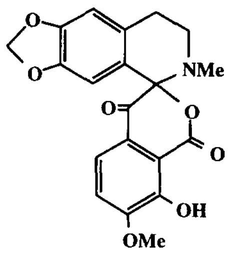


5 $R^1 = R^2 = CH_2$, $R^3 = R^4 = H_2$

6 $R^1 = R^2 = Me$, $R^3 = R^4 = O$



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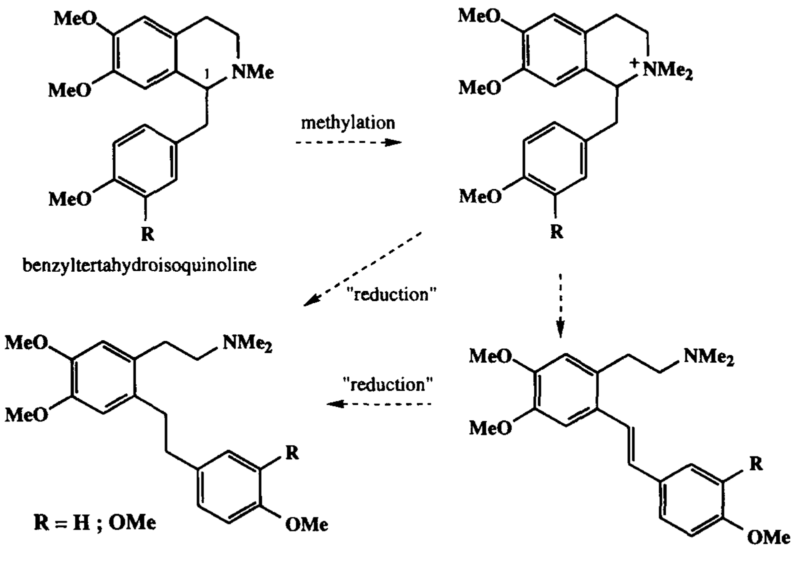
Ethanol extracts from the bark of *P. insignis* [7](1.1 kg) were partitioned into dilute HCl and then treated with NH_4OH to give a crude alkaloidal mixture, which on repeated silica-gel chromatography afforded pure alkaloids **1**, **2**, (-)-asimilobine, oxostephanine, *O*-methylmoschatoline and liriodenine. The mass spectrum of polysignine (**1**) shows a molecular ion at m/z 343 corresponding to the molecular formula $C_{21}H_{29}NO_3$ (found $M^{+\cdot}$ 343.2127, calcd. 343.2147). The ^1H NMR spectrum ($CDCl_3$, 270 MHz) shows two proton singlets at δ 6.67 and 6.58 in the aromatic region which is characteristic of a 1,3,4,6-tetrasubstituted phenyl ring (ring A). Another set of two 2H-doublets at δ 6.82 and 7.07 is due to the 1,4-disubstituted benzene ring system (A_2B_2, $J_{AB} = 8.8$ Hz, H-2', H-6' and H-3', H-5' respectively). The remaining resonances were for the aliphatic protons H-α and H-β observed as multiplets (due to possible conformational preferences) centered at δ 2.44 and 2.71 respectively; H-α' and H-β' (overlapped as a broad singlet) at δ 2.81, and two NMe groups (6H, s, δ 2.33). The ^{13}C NMR spectrum of **1** shows signals of 12 aromatic carbons, constituting the two phenyl rings, three methoxy groups, four methylenes of which one carbon (C-α, 61.4 ppm) is N-linked and two other NMe groups. Based on spectral data from ^1H NMR, ^{13}C NMR, DEPT, difference nOe, COSY and HETCOR experiments, the assignment of **1** is as shown[8].

The second new alkaloid, methoxypolysignine (**2**), shows a molecular ion at m/z 373 corresponding to the formula of $C_{22}H_{31}NO_4$ (found 373.2242; calcd. 373.2253). The ^1H NMR spectrum ($CDCl_3$, 270 MHz), showed two proton singlets at δ 6.67 and 6.61 similar to **1** but with four methoxyl groups (6H, δ 3.86; 3H, 3.83 and 3H, 3.81). A marked difference is observed in the other set of three aromatic protons belonging to the 1,3,4-trisubstituted benzene ring system with absorptions at δ 6.70 (1H, dd, $J = 8.0$ and 2.0 Hz), 6.79 (1H, d, $J = 8.0$)

and 6.64 (1H, d, $J = 2$ Hz). The additional methoxy group in ring B is placed at C-3' and is consistent with the MS and the ^{13}C & ^{1}H NMR data. The chemical shifts for the methylene protons and two NMe groups are similar to those of **1**. Based on spectral data from ^{1}H NMR, ^{13}C NMR, DEPT, difference nOe, COSY and HETCOR experiments, the assignment of **2** is as shown[8].

A possible biosynthetic scheme is given below, whereby *seco*-benzyltetrahydroisoquinoline can be formed directly after *N*-methylation and reductive cleavage of the C1-N bond, or stepwise by β-elimination followed by reduction steps. Whereas the latter reactions are common in chemical synthesis[2], these transformations or the net reductive C1-N bond cleavage of the isoquinoline ring appears to be rare in the biosynthesis of these alkaloids.

The other alkaloids isolated from the bark of *P. insignis*, readily identified based spectral data from the literature[9-13], are (-)-asimilobine, oxostephanine, *O*-methylmoschatoline and liriodenine. Another related species *P. microtus* collected from the same location provided only aporphinoid alkaloids (i.e. oxostephanine, *O*-methylmoschatoline, liriodenine and lanuginosine) but no *seco*-benzyltetrahydroisoquinolines.



Acknowledgements: We thank the University of Malaya, Ministry of Science, Technology and the Environment (Malaysia) and the German Research Foundation for financial support, and the Forest Research Centre (L. Madani, K. M. Wong and J. T. Pereira), Sabah, for taxonomic authentication. S. H. Goh acknowledges the support of the National University of Singapore.

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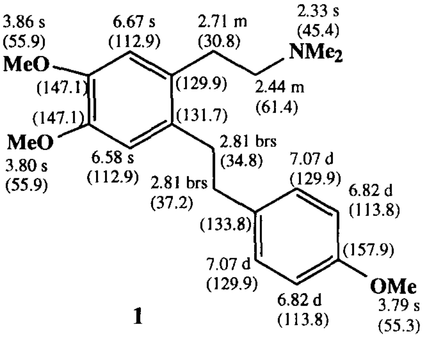
8. A summary of the ^{1}HNMR and ^{13}CNMR (in parenthesis) spectra of **1** and **2** is given below :-



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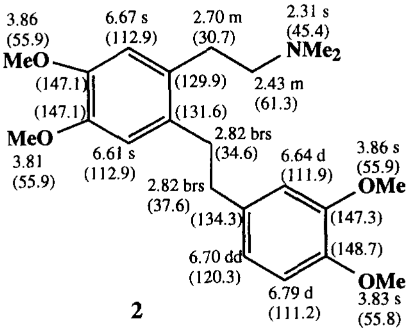

2

EIMS of **1** : 343 (M$^{+\cdot}$, 1%), 285 (3), 164 (10), 121 (41), 91 (8), 77 (8), 58 (100). EIMS of **2** : 373 (M$^{+\cdot}$, 70), 328 (7), 315 (6), 164 (55), 151 (81), 121 (28), 107 (20), 91 (16), 77 (13), 58 (100).

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(*Received in UK* 20 *November* 1996; *revised* 2 *January* 1997; *accepted* 10 *January* 1997)