THREE TETRAHYDROISOQUINOLINE-MONOTERPENE GLUCOSIDES FROM *ALANGIUM LAMARCKII*: THE FIRST OCCURRENCE OF GLUCOSIDES WITH THE SAME ABSOLUTE CONFIGURATIONS AS DEACETYLISOIPECOSIDE, A KEY INTERMEDIATE IN THE BIOSYNTHESIS OF IPECAC ALKALOIDS

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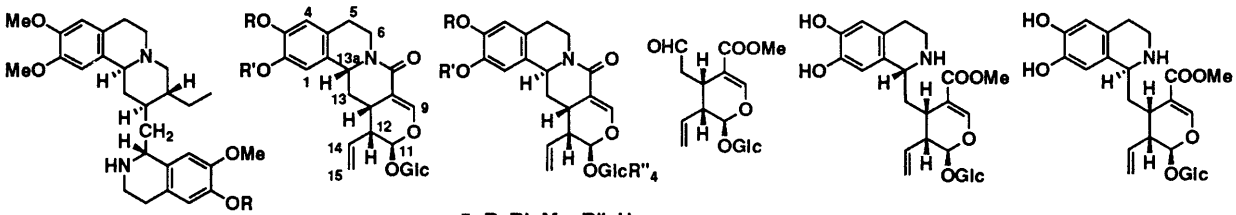
From the fruits of *Alangium lamarckii*, three new tetrahydroisoquinoline-monoterpene glucosides, isoalangiside, 3-*O*-demethyl-2-*O*-methylisoalangiside and methylisoalangiside, were isolated. Their structures were determined by spectroscopic and chemical methods. This is the first instance of the isolation of glucosides with the same absolute configurations as deacetylisoipecoside, and strongly supports the intermediacy of the latter compound in ipecac alkaloid biosynthesis.

KEYWORDS *Alangium lamarckii*; Alangiaceae; tetrahydroisoquinoline-monoterpene glucoside; isoalangiside; 3-*O*-demethyl-2-*O*-methylisoalangiside; methylisoalangiside

Alangium lamarckii Thwaites (Alangiaceae) is a deciduous shrub with a wide distribution in India and SE Asia. Extracts of the root bark of this plant have been used medicinally as an anthelmintic, purgative, emetic and febrifuge as well as in the treatment of leprosy and other skin diseases. The previous phytochemical studies on this plant resulted in the isolation of a variety of bases including ipecac alkaloids, represented by emetine (**1**) and cephaeline (**2**).[1] Alangiside (**3**), a tetrahydroisoquinoline-monoterpene glucoside, whose structure is closely related to these alkaloids, was also isolated from the fruits of this plant.[2] In the course of our chemical studies on nitrogenous glycosides,[3] we have recently investigated the constituents of the fruits of *A. lamarckii* and isolated 3-*O*-demethyl-2-*O*-methylalangiside (**4**).[4] This preliminary study prompted us to further examine the glycosidal fraction of this plant material. In this paper, we report the isolation and characterization of three new unusual tetrahydroisoquinoline-monoterpene glucosides and discuss their biogenetic significance.

Dried fruits of *A. lamarckii* were crushed and extracted with hot MeOH. The extract was partitioned between H_2O and $CHCl_3$ and then between H_2O and *n*-BuOH. The *n*-BuOH layers were separated by a combination of chromatographic procedures to yield three novel tetrahydroisoquinoline-monoterpene glucosides **5**, **6** and **7**.

Compound **5**[5] was isolated as an amorphous powder, $[\alpha]_D$ -141° (MeOH). The HR-SI mass spectrum of **5** exhibited a strong peak at *m/z* 520.2179 ($[M+H]^+$), indicating a molecular formula of $C_{26}H_{33}NO_{10}$ for **5**. It showed an UV maximum at 235 nm, an IR band at 1657 cm^{-1} and ^{1}H-NMR signal at δ 7.33 (d, *J*=2.5 Hz); all these suggested the presence of β-alkoxyacrylic amide chromophore. Its ^{1}H-NMR spectrum, moreover, exhibited signals for two methoxy



1: R=Me
2: R=H

3: R=Me, R'=H
4: R=H, R'=Me
8: R=R'=Me

5: R=R'=Me, R''=H
6: R=Me, R'=R''=H
7: R=R''=H, R'=Me
10: R=R'=Me, R''=Ac
11: R=Me, R'=R''=Ac
12: R=R''=Ac, R'=Me

9

13

14

groups at δ 3.80 and 3.83 (each s), two acetal protons at δ 4.61(d, J=8.0 Hz) and 5.42 (d, J=1.5 Hz), a terminal vinyl group at δ 5.32 (dd, J=10.0 and 2.0 Hz), 5.39 (dd, J=17.0 and 2.0 Hz) and 5.67 (dt, J=17.0 and 10.0 Hz) and two aromatic protons at δ 6.74 (s) and 6.83 (s). These spectral features indicated its structural similarity to methylalangiside (**8**).[4] However, when the ^{1}H-NMR data of the new compound **5** were compared with those of **8**, there were remarkable differences in the coupling constants between H_2-13 and H-13a [**5**: δ 2.00 (ddd, J=14.0, 12.5 and 5.5 Hz, H-13), 2.46 (ddd, J=14.0, 4.5 and 3.0 Hz, H-13), 4.78 (brt, J=4.5 Hz, H-13a); **8**: δ 1.36 (td, J=13.0 and 11.5 Hz, H-13), 2.39 (dt, J=13.0 and 3.5 Hz, H-13), 4.79 (m, H-13a)], whereas $J_{11,12}$ (1.5 Hz) and $J_{12,12a}$ (5.5 Hz) were identical in both cases. Careful inspection of the coupling constants of all protons suggested that each quinolizidinone ring of **5** and **8** adopts a respective conformation as illustrated in Fig. 1, and therefore compound **5** should be methylisoalangiside with an *S*-configuration at C-13a; this has previously been prepared from secologanin (**9**) and 3-hydroxy-4-methoxyphenethylamine.[2] This suggestion was consistent with the observation that there were significant differences between **5** and **8** in the chemical shifts of C-6, C-12a and C-13 in the ^{13}C-NMR spectra (Table I) .[6] The α orientation of H-13a in **5** was also supported by the NOESY experiments with **5** and its acetate **10**, where NOE interactions were observed between H-1 and H-13 and between H-1 and H-12a, but not between H-12a and H-13a, in contrast to alangiside (**3**) which has an *R*-configuration at C-13a. Further evidence for the stereochemistry was obtained from an alcoholic acetyl signal resonating at an anomalously high field (δ 1.57) in the ^{1}H-NMR spectrum of **10**,[7] which is typical of the acetates having α-H at C-13a, such as methylisoalangiside tetraacetate.[6] For a final structural confirmation, methylisoalangiside and methylisoalangiside tetraacetate were prepared from secologanin (**9**) and dopamine by a modification of the procedure in ref. 6. As a result of direct comparison, the synthetic compounds were completely identical in all respects including CD spectra with the isolate **5** and its acetate **10**. Accordingly, compound **5** was established as methylisoalangiside.

Table I. ^{13}C-NMR Data of Glucosides **3**-**8** in CD_3OD*

C	3	4	8	6	7	5
1	112.6[a]	110.3	110.8[c]	111.7	108.9	109.3
2	146.4	148.2	149.4[d]	146.2	147.9	149.2[f]
3	148.0	146.5	149.5[d]	148.3	147.0	149.9[f]
4	113.3[a]	116.1	113.2[c]	113.6	117.1	114.1
4a	127.3	128.9[b]	128.7[e]	127.9	129.6	129.6[g]
5	29.5	29.4	29.6	29.2	29.1	29.3
6	41.0	40.8	40.7	43.9	43.8	43.8
8	166.0	166.0	166.0	166.6	166.6	166.7
8a	109.3	109.3	109.2	109.4	109.4	109.4
9	148.8	148.8	148.9	148.8	148.8	148.8
11	97.5	97.6	97.6	98.2	98.2	98.2
12	44.5	44.5	44.5	44.9	44.8	44.8
12a	27.8	27.9	27.9	24.4	24.4	24.4
13	35.1	35.3	35.2	28.3	28.4	28.4
13a	57.0	57.3	57.3	56.4	56.7	56.7
13b	130.3	128.8[b]	130.1[e]	130.4	129.0	130.3[g]
14	134.0	134.0	134.0	134.4	134.5	134.4
15	120.4	120.4	120.4	120.5	120.5	120.5
OMe	56.4	56.7	56.5	56.5	56.9	56.5
			56.8			57.0

* Glucosides **3**-**8** showed signals of C-1' to C-6' of glucose moiety at δ 100.6, 74.5, 78.1, 71.5, 78.3 and 62.7 or close to them, respectively.
[a)-g)] Values with the same superscript are interchangeable.

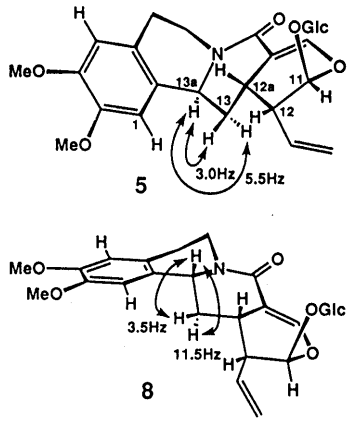


Fig.1

The other glucosides, **6** and **7**,[8] were also obtained as amorphous powder. The HR-SIMS measurements of **6** and **7** revealed the same molecular formula $C_{25}H_{31}NO_{10}$ isomeric with alangiside (**3**) and 3-*O*-demethyl-2-*O*-methylalangiside (**4**). The ^{1}H- and ^{13}C-NMR (Table I) spectral features of **6** and **7** were analogous to those of methylisoalangiside (**5**), except for the absence of one aromatic methoxyl signal and the chemical shifts of the signals arising from the aromatic

ring. These results suggested **6** and **7** are two possible demethylates of methylisoalangiside (**5**), i.e. C-13a epimers of alangiside (**3**) and 3-*O*-demethyl-2-*O*-methylalangiside (**4**). Further evidence of α disposition of H-13a in **6** and **7** was provided by characteristic anomalous acetyl signals in the ^{1}H-NMR spectra of their acetates **11** and **12**,[9] and by comparison of their CD curves with that of methylisoalangiside (**5**).

The placement of the methoxy group in both compounds was deduced from the comparison of their ^{1}H- and ^{13}C-NMR (Table I) spectral data with those of **3** and **4**. The chemical shifts of proton and carbon signals due to the aromatic moiety of **6** agreed with those of **3**, but not with those of **4**, indicating that the methoxyl group was located at C-3 in **6**. This was further corroborated by the NOESY experiments with **6**. The NOE interaction between the signal at δ 6.72 and H-13 at δ 2.35 allowed us to assign the aromatic protons at δ 6.72 and 6.71 to H-1 and H-4, respectively. The methoxy signal showed a strong interaction with H-4, but not with H-1, thereby establishing the C-3 methoxyl group. As in the case of **6**, the position of the methoxyl group at C-2 in **7** was substantiated by comparative studies on the ^{1}H- and ^{13}C-NMR spectra as well as by the NOESY experiments with **7**, where cross peaks between H-13 and H-1 and between OMe and H-1 were observed. Thus, **6** and **7** could unequivocally be assigned to isoalangiside and 3-*O*-demethyl-2-*O*-methylisoalangiside, respectively.

The occurrence of glucosides **5**, **6** and **7** gives important clues with regard to the biosynthesis of ipecac alkaloids represented by emetine (**1**) and cephaeline (**2**). Previous biosynthetic investigations demonstrated that deacetylipecoside (**13**) was exclusively incorporated into alangiside (**3**), but not into alkaloids **1** and **2**, and that deacetylisoipecoside (**14**) is a true key intermediate for the alkaloids.[10] However, all of the tetrahydroisoquinoline-monoterpene glucosides isolated so far have a β-H at the chiral center, but no glucoside with α-H such as **14** has been isolated from natural sources. This is the first instance of the isolation of this type of glucoside, and strongly supports the intermediacy of deacetylisoipecoside (**14**) in the biosynthetic pathway to ipecac alkaloids.

REFERENCES AND NOTES

1) T. Fujii, M. Ohba, "The Alkaloids," Vol. XXII, ed. by A. Brossi, Academic Press, Inc., New York, 1983, Chapter 1.
2) A. Shoeb, K. Raj, R.S. Kapil, S.P. Popli, *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1245.
3) A. Itoh, T. Tanahashi, N. Nagakura, *Phytochemistry* , **30**, 3117 (1991).
4) A. Itoh, T. Tanahashi, N. Nagakura, H. Nayeshiro, *Phytochemistry* , **36**, 383 (1994).
5) **5**, UV λmax (MeOH) nm (log ε): 235 (4.31), 282 (3.65), 292sh (3.52). IR νmax (KBr) cm^{-1}: 3406, 1657, 1589, 1516, 899. CD (MeOH) Δε (nm): -8.7 (224), +1.5 (242), -0.2 (255), +0.1 (274).
6) G. Höfle, N. Nagakura, M.H. Zenk, *Chem. Ber.*, **113**, 566 (1980).
7) **10**, ^{1}H-NMR ($CDCl_3$) δ: 1.57, 1.96, 2.01, 2.09 (each s, 4 X OAc), 3.85, 3.90 (each s, 2 X OMe), 5.32 (dd, *J*=10.0, 1.5 Hz, H-15), 5.36 (dd, *J*=17.0, 1.5 Hz, H-15), 5.64 (dt, *J*=17.0, 10.0 Hz, H-14), 6.62, 6.63 (each s, H-1 and H-4), 7.33 (d, *J*=2.5 Hz, H-9). EIMS *m/z*: 687 $[M]^+$.
8) **6**, $[\alpha]_D$ -118° (MeOH), UV λmax (MeOH) nm (log ε): 233 (4.26), 284.5 (3.64). IR νmax (KBr) cm^{-1}: 3400, 1660, 1592,1516, 900. ^{1}H-NMR (CD_3OD) δ: 1.96 (ddd, *J*=14.0, 13.0, 5.5 Hz, H-13), 2.35 (ddd, *J*=14.0, 4.5, 3.0 Hz, H-13), 3.82 (s, OMe), 4.61 (d, *J*=8.0 Hz, H-1'), 4.72 (brt, *J*=4.5 Hz, H-13a), 5.31 (dd, *J*=10.5, 2.0 Hz, H-15), 5.38 (dd, *J*=17.0, 2.0 Hz, H-15), 5.41(d, *J*=1.5 Hz, H-11), 5.66 (dt, *J*=17.0, 10.5 Hz, H-14), 6.71 (s, H-4), 6.72 (s, H-1), 7.32 (d, *J*=2.5 Hz, H-9). SIMS *m/z*: 506 $[M+H]^+$. CD (MeOH) Δε (nm): -5.6 (224), +1.3 (240), -0.7 (254), +0.5 (280). **7**, $[\alpha]_D$ -169° (MeOH), UV λmax (MeOH) nm (log ε): 234 (4.25), 284 (3.61). IR νmax (KBr) cm^{-1}: 3400, 1653, 1578, 1516, 901. ^{1}H-NMR (CD_3OD) δ: 1.99 (ddd, *J*=14.0, 12.5, 5.0 Hz, H-13), 2.45 (ddd, *J*=14.0, 4.5, 3.0 Hz, H-13), 3.85 (s, OMe), 4.62 (d, *J*=8.0 Hz, H-1'), 4.76 (brt, *J*=4.0 Hz, H-13a), 5.32 (dd, *J*=10.0, 2.0 Hz, H-15), 5.39 (dd, *J*=17.0, 2.0 Hz, H-15), 5.42 (d, *J*=1.5 Hz, H-11), 5.67 (dt, *J*=17.0, 10.0 Hz, H-14), 6.59 (s, H-4), 6.80 (s, H-1), 7.33 (d, *J*=2.5 Hz, H-9). SIMS *m/z*: 506 $[M+H]^+$. CD (MeOH) Δε (nm): -9.9 (225), +0.3 (243), -1.0 (254), -0.7 (283).
9) **11**, ^{1}H-NMR ($CDCl_3$) δ: 1.64, 1.96, 2.01, 2.09, 2.33 (each s, 5 X OAc), 3.80 (s, OMe), 5.31 (dd, *J*=10.0, 2.0 Hz, H-15), 5.34 (dd, *J*=17.0, 2.0 Hz, H-15), 5.61 (dt, *J*=17.0, 10.0 Hz, H-14), 6.72 (s, H-4), 6.83 (s, H-1), 7.32 (d, *J*=2.5 Hz, H-9). EIMS *m/z*: 715 $[M]^+$. **12**, ^{1}H-NMR ($CDCl_3$) δ: 1.52, 1.96, 2.01, 2.09, 2.30 (each s, 5 X OAc), 3.87 (s, OMe), 5.33 (dd, *J*=10.0, 1.5 Hz, H-15), 5.36 (dd, *J*=17.0, 1.5 Hz, H-15), 5.63 (dt, *J*=17.0, 10.0 Hz, H-14), 6.73 (s, H-1), 6.83 (s, H-4), 7.35 (d, *J*=2.5 Hz, H-9). EIMS *m/z*: 715 $[M]^+$.
10) N. Nagakura, G. Höfle, D. Coggiola, M.H. Zenk, *Planta Med.*, **34**, 381 (1978).

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