NEOIPECOSIDE AND 7-METHYLNEOIPECOSIDE, NEW UNUSUALLY-CYCLIZED TETRAHYDROISOQUINOLINE-MONOTERPENE GLUCOSIDES FROM *CEPHAELIS IPECACUANHA*

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Two new monoterpene glucosides with unusually 7,8-disubstituted tetrahydroisoquinoline nucleus, neoipecoside and 7-methylneoipecoside, have been isolated from *Cephaelis ipecacuanha* A. Richard. Their structures were elucidated as 1 and 2 by spectroscopic and chemical means.

KEYWORDS *Cephaelis ipecacuanha*; Rubiaceae; neoipecoside; 7-methylneoipecoside; tetrahydroisoquinoline-monoterpene glucoside; dopamine; secologanin; ipecoside; NOE; CD

Ipecac, *Cephaelis ipecacuanha* A. Richard (Rubiaceae), is one of the most important medicinal plants. The roots and emetine, the main alkaloid of the plant, are still used as an emetic and as an anti-amebic.¹⁾

The presence of ipecoside, along with emetine and its derivatives in the roots of *C. ipecacuanha*, was reported,²⁾ but detailed investigations of the constituents of the polar fractions were lacking until now.

As part of our chemical studies on alkaloids and related compounds, we have re-examined the roots of this plant and isolated two new glucosides with unusually disubstituted tetrahydroisoquinoline nucleus, neoipecoside (1) and 7-methylneoipecoside (2), together with several new nitrogen-containing glucosides. They were obtained from the mother liquors of ipecoside (3), the major component of the BuOH soluble fraction, through a combination of chromatographic methods. This paper deals with the structures of the new glucosides 1 and 2, and their elucidation.

Neoipecoside (1) was obtained as colorless needles, mp 184-185°C (MeOH), $C_{27}H_{35}NO_{12}$, (positive ion FABMS m/z 566 $[M+H]^+$, negative ion FABMS m/z 564 $[M-H]^-$), $[\alpha]_D^{28}$ -161° (MeOH), and IR ν_{max}^{KBr} cm^{-1} : 3400, 1690, 1640, UV λ_{max}^{EtOH} nm (log ϵ): 227sh (4.18), 282 (3.30). Its 1H (200 MHz, CD_3OD)- and ^{13}C (50 MHz, CD_3OD , Table I)-NMR spectral features resembled those of ipecoside (3) except for the signals of the aromatic region, which suggested that it and ipecoside (3) have the same skeleton. The 1H -NMR spectrum of 1 showed a signal of the N-acetyl group at δ 2.20 and signals due to the secologanin (4) moiety at δ 7.36 (1H, d, $J=1.5$ Hz, H-3') and 3.65 (3H, s, $COOCH_3$).³⁾ The aromatic protons of 1 appeared as a pair of ortho coupled doublets ($J=8.0$ Hz) at δ 6.45 (1H) and 6.61 (1H), instead of two singlets at δ 6.44 (1H) and 6.50 (1H) as in the spectrum of 3.³⁾ Acetylation of 1 afforded neoipecoside hexaacetate (5), $C_{39}H_{47}NO_{18}$, mp 181-183°C (Et_2O -petroleum ether), $[\alpha]_D^{25}$ -146° ($CHCl_3$), which showed one N- and two phenolic acetyl signals at δ 2.26, 2.38 and 2.39, respectively.⁵⁾ These spectral data showed that neoipecoside (1) is an isomer of ipecoside (3) in regard to the position of the phenolic hydroxyl groups.

In *C. ipecacuanha*, secologanin (4) is coupled with the C-6 of 3,4-dihydroxyphenethylamine (dopamine) in Pictet-Spengler manner to desacetylipecoside (6), which is converted to ipecoside (3), and desacetyli-ipecoside (7), the precursor of the ipecac alkaloids.⁶⁾

Condensation of secologanin (4) with the C-2 of dopamine should result in the formation of a glucoside with a 7,8-dioxygenated tetrahydroisoquinoline moiety, which would be metabolized to a glucoside (1) on N-acetylation. This assumption was confirmed by the NOE experiments on neoipecoside hexaacetate (5). Irradiation of the C-4 methylene protons at δ 2.72 resulted in an 18% enhancement of a doublet at δ 6.90 (H-5') and irradiation of the latter proton caused 23% and 3% increases of a doublet at δ 7.24 (H-6) and a triplet at δ 2.72, respectively. These findings indicated that the aromatic hydroxyl groups were located at C-7 and C-8.

Subsequently, we determined the configuration of the C-1 of 1 from the 1H -NMR and CD spectra of neoipecoside lactam hexaacetate (8),⁷⁾ which was obtained from neoipecoside hexaacetate (5) by N-deacetylation with tri-ethyloxonium fluoroborate, and then by treatment with $NaHCO_3$ after the method of Hanessian.⁸⁾ One of the acetyl signals of methylisoalangiside tetraacetate (9) and strictosamide tetraacetate (10), which have an S-configuration at C-13a and C-3 respectively, appears at an anomalous high field [δ 1.57 (9), 1.23 (10)]. On

the other hand, all acetyl signals of methylalangiside tetraacetate (11) and vincoside lactam tetraacetate (12) with the *R*-configuration at the corresponding carbons, resonate at normal field in the ^1H -NMR spectra.⁹⁾ No anomalous acetyl signal was observed in the ^1H -NMR spectrum of 8, and the NOE experiments supported the *R*-configuration at the C-13a of the lactam (8). Irradiation of the 13a-H of 8 caused a 10% enhancement of 12a-H at δ 2.90, suggesting that the two were located on the same side, i.e., β -orientation.¹⁰⁾ Moreover, the splitting pattern of 13a-H (br d, $J=10.5$ Hz) also suggested the *R*-configuration at the C-13a of 8, because the 13a- β -H of 11 appears as a double doublet ($J=11, 2.5$ Hz), whereas the 13a- α -H of 9 shows a triplet ($J=4.5$ Hz).^{9c)} This evidence obtained from the ^1H -NMR spectroscopies confirmed that neoipecoside (1) has the same stereochemistry as ipecoside (3). Finally, the similar CD curves of 8 and 11, not 9, suggested that the former two lactams had the same configuration at the asymmetric carbons.^{7,11)} Accordingly, the structure 1 was assigned to neoipecoside.

Table I. ^{13}C -NMR Data for Neoipecoside (1) and Ipecoside (3)³⁾

	1	3		1	3		1	3		1	3
1	47.6	48.8	8	143.9 ^{b)}	114.3 ^{c)}	8'	135.7	135.9	1"	100.5	100.4
3	32.2	35.9	8a	125.9 ^{a)}	130.3	9'	44.8	44.9	2"	74.8	74.7
4	29.1	29.1	1'	98.7	98.7	10'	120.6	120.4	3"	78.1 ^{e)}	78.1 ^{f)}
4a	126.7 ^{a)}	125.3	3'	152.9	153.0	11'	169.3	169.2	4"	71.4	71.4
5	120.6	116.2 ^{c)}	4'	111.8	111.6	NCOCH ₃	21.5	21.4	5"	78.2 ^{e)}	78.2 ^{f)}
6	114.7	145.3 ^{d)}	5'	28.8	27.3	NCOCH ₃	172.2	172.3	6"	62.6	62.6
7	142.9 ^{b)}	144.9 ^{d)}	6'	41.0	41.1	COOCH ₃	51.7	51.7			

a-f) Values with the same superscript are interchangeable.

- 1: $\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$
 2: $\text{R}^1=\text{Me}, \text{R}^2=\text{R}^3=\text{H}$
 5: $\text{R}^1=\text{R}^2=\text{R}^3=\text{Ac}$
 13: $\text{R}^1=\text{Me}, \text{R}^2=\text{R}^3=\text{Ac}$
 14: $\text{R}^1=\text{R}^2=\text{Me}, \text{R}^3=\text{Ac}$

- 1-H
 3: $\text{R}=\text{Ac}$ β
 6: $\text{R}=\text{H}$ β
 7: $\text{R}=\text{H}$ α

- 8: $\text{R}^1=\text{H}, \text{R}^2=\text{R}^4=\text{Ac}, \text{R}^3=\text{OAc}$

- 13a-H β
 3-H α
 10: α

The second glucoside (2) was obtained as a white powder, $C_{28}H_{37}NO_{12}$, (positive ion FABMS m/z 580 $[M+H]^+$), $[\alpha]_D^{20}$ -150° (EtOH),¹²⁾ which afforded the pentaacetate (13) on acetylation with Ac_2O -Py.¹³⁾ The 1H -NMR spectrum (CD_3OD) of glucoside (2) showed an additional methoxyl signal at δ 3.80, one more than neoipecoside.¹²⁾ On treatment with CH_2N_2 followed by Ac_2O -Py, 2 afforded 7,8-dimethylneoipecoside tetraacetate (14), suggesting that 2 is 7- or 8-methylneoipecoside. This was resolved by the occurrence of the NOE enhancements between H-6 and methoxyl protons of 13 (8%, $H-6 \rightarrow MeO$; 21%, $MeO \rightarrow H-6$). Thus, the second glucoside is 7-methylneoipecoside (2). Neoipecoside and 7-methylneoipecoside are the first examples of the unusual cyclization products of dopamine with secologanin.

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- 5) 1H -NMR (200 MHz, pyridine- d_5) of **5** δ : 1.98, 2.02, 2.03, 2.06, 2.26, 2.38, 2.39(21H, each s, 7xAc), 2.72(2H, br t, $J=6.0$ Hz, H-4), 3.62(3H, s, $COOCH_3$), 3.94(2H, br t, $J=6.0$ Hz, H-3), 6.27(1H, dd, $J=12.0$, 5.0 Hz, H-1), 6.90(1H, d, $J=8.5$ Hz, H-5), 7.24(1H, d, $J=8.5$ Hz, H-6), 7.53(1H, d, $J=2.3$ Hz, H-3').
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- 7) Neoipecoside lactam hexaacetate (**8**), $C_{36}H_{41}NO_{16}$, 1H -NMR (200 MHz, $CDCl_3$) δ : 1.97, 2.02, 2.04, 2.10, 2.29, 2.38(18H, each s, 6xOAc), 4.71(1H, br d, $J=10.5$ Hz, H-13a), 7.08(2H, s, 2xAr-H), 7.49(1H, d, $J=2.5$ Hz, H-9); $CD \lambda_{max}^{EtOH}$ nm($\Delta\epsilon$): 236 (-8.37).
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- 10) Irradiation of C-13a β -proton at δ 4.72(1H, br d, $J=10.5$ Hz) of **11** resulted in a 11% enhancement of H-12a at δ 2.94, whereas no NOE was observed between the corresponding protons of the 13a- α -H-isomer (**9**).
- 11) CD of **9** and **11**. **9** λ_{max}^{EtOH} nm($\Delta\epsilon$): 226(-9.41), 250(-2.44); **11** λ_{max}^{EtOH} nm($\Delta\epsilon$): 234(-14.7).
- 12) 7-Methylneoipecoside (**2**) UV λ_{max}^{EtOH} nm(log ϵ): 227sh(3.80), 280(3.65) and 312sh(3.43); IR ν_{max}^{KBr} cm^{-1} : 3400, 1710, 1630; 1H -NMR (CD_3OD) δ : 2.23(3H, s, NAc), 3.64(3H, s, $COOCH_3$), 3.80(3H, s, OCH_3), 4.64(1H, d, $J=7.8$ Hz, H-1'), 6.59(1H, d, $J=8.0$ Hz, Ar-H), 6.77(1H, d, $J=8.0$ Hz, Ar-H), 7.40(1H, d, $J=1.5$ Hz, H-3').
- 14) 1H -NMR ($CDCl_3$) of **13** δ : 1.90, 2.00, 2.03, 2.14, 2.26, 2.29(18H, each s, 6xAc), 3.62(3H, s, $COOCH_3$), 3.76(3H, s, OCH_3), 6.83(1H, d, $J=8.3$ Hz, H-6), 6.99(1H, d, $J=8.3$ Hz, H-5).

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