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 ^{1}H(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 ^{1}H-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 desacetylisoipecoside (**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.

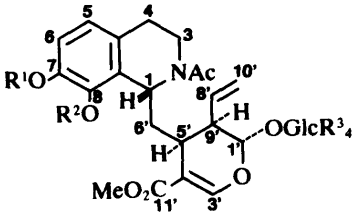
Subsequently, we determined the configuration of the C-1 of **1** from the ^{1}H-NMR and CD spectra of neoipecoside lactam hexaacetate (**8**),[7)] which was obtained from neoipecoside hexaacetate (**5**) by N-deacetylation with triethyloxonium fluoroborate, and then by treatment with $NaHCO_3$ after 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 ^{1}H-NMR spectra.[9] No anomalous acetyl signal was observed in the ^{1}H-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., ß-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-ß-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 ^{1}H-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.

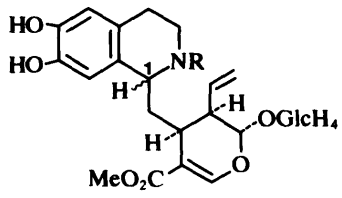
Table I. ^{13}C-NMR Data for Neoipecoside (**1**) and Ipecoside (**3**)[3]

	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	$NCO\underline{C}H_3$	21.5	21.4	5"	78.2[e]	78.2[f]
6	114.7	145.3[d]	5'	28.8	27.3	$N\underline{C}OCH_3$	172.2	172.3	6"	62.6	62.6
7	142.9[b]	144.9[d]	6'	41.0	41.1	$COO\underline{C}H_3$	51.7	51.7			

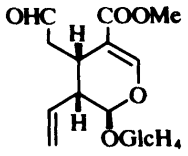
a-f) Values with the same superscript are interchangeable.



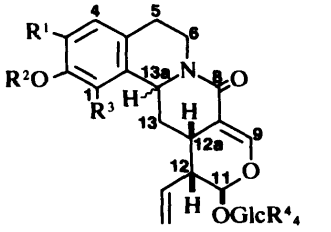
1: R^1=R^2=R^3=H
2: R^1=Me, R^2=R^3=H
5: R^1=R^2=R^3=Ac
13: R^1=Me, R^2=R^3=Ac
14: R^1=R^2=Me, R^3=Ac



1-H
3: R=Ac β
6: R=H β
7: R=H α

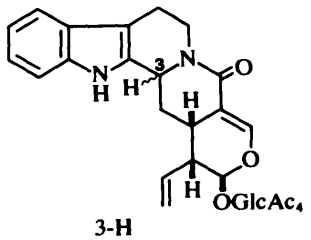


4



8: R^1=H, R^2=R^4=Ac, R^3=OAc

13a-H
β



3-H
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 ^{1}H-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 ⟶ MeO; 21%, MeO ⟶ 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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3) Some of the proton and carbon signals of **1**, **2** and **3** were accompanied with weak ones at the lower fields, probably resulting from hindered rotation about the amide bond. The values of the more intensive signals are given in the text. Their acetates showed no signal separation due to rotomers. The existence of rotomers in N-acyl tetrahydroisoquinolines has been reported.[4]

4) K. C. Rice and A. Brossi, J. Org. Chem., 45, 592 (1980).

5) ^{1}H-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').

6) N. Nagakura, G. Höfle, D. Coggiola, and M. H. Zenk, Planta Med., 34, 381 (1978); A. R. Battersby, N. G. Lewis, and J. M. Tippett, Tetrahedron Lett., 1978, 4849.

7) Neoipecoside lactam hexaacetate (**8**), $C_{36}H_{41}NO_{16}$, ^{1}H-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 λ_{max}^{EtOH} nm(Δε): 236 (-8.37).

8) S. Hanessian, Tetrahedron Lett., 1967, 1549.

9) a) K. T. D. De Silva, G. N. Smith, and K. E. H. Warren, Chem. Commun., 1971, 905; b) J. Stöckigt and M. H. Zenk, J. Chem. Soc., Chem. Commun., 1977, 646; c) G. Höfle, N. Nagakura, and M. H. Zenk, Chem. Ber., 113, 566 (1980).

10) Irradiation of C-13a ß-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(Δε): 226(-9.41), 250(-2.44); **11** λ_{max}^{EtOH} nm(Δε): 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; ^{1}H-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) ^{1}H-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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