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Incisol, an alcohol with a novel sesquiterpene skeleton from *Xenophyllum incisum*

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1. Subject and source

Aerial parts of *Xenophyllum incisum* (Phil.) V. A. Funk (syn. *Werneria incisa* Phil.) were collected at 4300 m above sea level in the Departamento Susques, between Susques and Paso de Jama, 30 km before arriving in Paso de Jama. A voucher specimen (LIL 606089) is deposited in the herbarium of the Instituto Miguel Lillo, Tucumán. Aerial parts of this species of the highlands of Northwestern Argentina, Northern Chile and Bolivia, known under the common names ''pupusa de agua'', ''pupusa del cerro'', ''poposa'', and ''popusa'', are used locally to prepare infusions for the treatment of hepatic disorders, ''apunamiento'' (altitude sickness) and chills and for washing rheumatic feet. This species is frequently confused with *Xenophyllum poposum* (Phil.) V. A. Funk (syn. *Werneria poposa* Phil.). In folk medicine the uses for both species are essentially the same (Giberti, 1983; Shemluck, 1982).

2. Previous work

X. incisum (Phil.) V. A. Funk (Senecioneae, Asteraceae) is one of the 21 species of the Andean genus *Xenophyllum* that has recently been removed from *Werneria s.l.* (Funk, 1997). The literature contains reports on the chemistry of *Xenophyllum ciliolatum* (Lock de Ugaz et al., 1984; Lock de Ugaz and Peralta, 1988; Piacente et al., 1992, 1994), *Xenophyllum dactylophyllum* (Bonilla Rivera et al., 1991; De Tommasi et al., 1992), *Xenophyllum decorum* (Lock de Ugaz et al., 1990) and *X. poposum* (Ponce and Gros, 1991, 1995; Cordova et al., 1998; Abella et al., 2000), all reported as species of *Werneria*. Typical constituents are prenylated *p*-hydroxyacetophenone derivatives, their benzofuran cyclization products and, in several instances diterpenes with *ent*-labdane and *ent*-kaurane skeletons.

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3. Present work

3.1. General procedures

X. incisum has a pungent and somewhat unpleasant odor. The volatile oil was obtained by hydrodistillation in a Clevenger-type apparatus for 4 h. From 653 g of aerial parts 2.87 g of yellow essential oil was obtained. The oil was analyzed by GC–MS using a 5973 Hewlett–Packard selective mass detector coupled to a Hewlett–Packard 6890 GC fitted with an HP-5 capillary column, helium as carrier gas at 1.0 ml min^{-1} (constant flow) and the following temperature program: 60 °C (5 min), 60–100 °C (3 °C min^{-1}), 100–160 °C (1 °C min^{-1}), 160–240 °C (10 °C min^{-1}), 240 °C (10 min). The injector, GC–MS interphase, ion source and selective mass detector temperatures were 250 °C, 275 °C, 280 °C and 150 °C, respectively; ionization energy, 70 eV; injection size 0.4 μL (split mode). The components' percentage was taken from capillary GC traces with FID. Identification of the individual components was based on (a) computer matching with commercial mass spectra libraries (Hewlett Packard NBS75K library; NIST, 1999; McLafferty and Stauffer, 1994) and comparison with spectra in our files; (b) comparison of retention indices (RI) on an HP-5 column. RI's were obtained by injection of a series of *n*–C_8–C_{16} hydrocarbon mixtures with the oil sample under the same conditions and comparison with data in the literature (Adams, 2001). For RI measurements an oven temperature program suggested by Adams (60–246 °C at 3 °C min^{-1}: Adams, 2001) was used; (c) co-injection with authentic samples whenever available; (d) additionally the main oxygenated sesquiterpenoids were isolated by fractionating 2.50 g of the oil by column chromatography on Si gel 230–400 mesh using hexane with increasing amounts of EtOAc (0–10%) followed by semi-preparative HPLC of the fractions of interest using either a C18 or a C8 column with MeOH–H_2O mixtures (90:10, 85:15, 80:20) as eluting solvent. The compounds obtained in this manner were analyzed by NMR spectrometry.

Mps' were taken on an E. Leitz Mikroskopheiztich 350 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively on a Varian Inova spectrometer. Mass spectra were run on a JEOL MS route 600 instrument.

Table 1 lists data obtained by GC–MS analysis of the oil together with information gleaned from column chromatography of 2.50 g of the oil over Si gel (100 g) using hexane with increasing amounts of EtOAc (0, 1, 2 and 4%) to obtain somewhat larger amounts of the main oxygenated constituents, each such fraction being analyzed further by GC–MS. HPLC of the oxygenated fractions (C18 column, eluent MeOH, H_2O 9:1 at 2.0 ml min^{-1} followed by re-chromatography on a C8 column, MeOH–H_2O 85:15 at 2.0 ml min^{-1}) permitted isolation of several components in amounts sufficient to allow analysis by NMR spectrometry. New alcohol **1** which we have named incisol was the main oxygenated sesquiterpene (13%) of the essential oil and the second most abundant component after β-pinene. One sesquiterpene (sesquiterpene A), one sesquiterpene ether (oxide A), and two sesquiterpene alcohols (alcohols A and B) were present in amounts too small to permit identification or had decomposed prior to study of the ^{13}C NMR spectrum.

To identify non-volatile constituents, air-dried aerial parts of *X. incisum* (695 g) were extracted twice with $CHCl_3$ (4.5 l) for 5 days. Evaporation at reduced pressure produced 103 g of residue (14.8%) a portion of which (73.75 g) was suspended in EtOH (630 ml) at 60 °C, diluted with water (480 ml) and extracted successively with hexane (2 × 400 ml) and $CHCl_3$ (2 × 400 ml). Evaporation of the hexane extract at reduced pressure gave 33.8 g of residue that was not investigated further. The $CHCl_3$ extract on evaporation at reduced pressure furnished 23.6 g of residue a portion of which (10.2 g) was subjected to CC over Si gel (Merck 70–230 mesh) using hexane with increasing amounts of ethyl acetate (0, 5, 8, 10, 15, 20, 50 and 100%) to yield 27 fractions which were re-chromatographed over Si gel (Merck 230–400 mesh) or by HPLC (C18 column). The constituents were examined by GC–MS, IR, UV and NMR spectrometry. Fr. 1 (61 mg) after preparative TLC yielded 6 mg of unidentified material and 2 mg of cadalene. Fr. 2 (68 mg) after preparative TLC gave cadalene (6 mg), 6-hydroxytremetone (**5**, 11 mg, Bohlmann and Zdero, 1979) and 28 mg of euparin (**4b**, Proksch et al., 1983). Fr. 3 (196 mg) after re-crystallization afforded an additional 141 mg of **5**. Fr. 4 (429 mg) after repeated CC on Si gel gave 201 mg of 2,2-dimethyl-6-acetyl chromene (**3**, Bohlmann and Grenz, 1970) and 49 mg of **5**. Fr. 5 (399 mg) after re-chromatography over Si gel furnished 210 mg of a substance identical with oxide A, $C_{15}H_{26}O$, mp 110–112 °C, found in the essential oil which decomposed on keeping, 11 mg of toxol angelate (**6b**, Bohlmann and Dutta, 1979) and 30 mg of zerumbone (Dev et al., 1968; Dai et al., 1997). Fr. 6 (293 mg) on re-chromatography on Si gel afforded 40 mg of dehydrotremetone (**4a**, Zalkow et al., 1962) and 25 mg of toxol acetate (**6a**, Bohlmann and Dutta, 1979). Fr. 7 (121 mg) after repeated HPLC using the C18 and C8 columns with MeOH–H_2O mixtures as eluting solvents furnished T-muurolol (7 mg), γ-eudesmol

Table 1
Essential oil constituents of *Xenophyllum incisum*

Compound	RI	%	Identification
α-Pinene	938	2.5	MS, RI, co-GC
Camphene	954	trace	MS, RI, co-GC
β-Pinene	977	19.4	MS, RI, co-GC
Myrcene	990	0.2	MS, RI, co-GC
α-Phellandrene	1001	0.5	MS, RI, co-GC
p-Cymene	1025	0.4	MS, RI, co-GC
β-Phellandrene (major) limonene (minor)	1029	4.0	MS, RI, co-GC
Nopinone	1138	trace	MS, RI, co-GC
trans-Pinocarveol	1141	0.1	MS, RI
Pinocarvone	1162	trace	MS, RI, co-GC
Cryptone	1183	0.1	MS, RI
Myrtenal	1190	0.1	MS, RI
Myrtenol	1193	0.1	MS, RI
Carvacrol methyl ether	1244	trace	MS, RI, co-GC
endo-Bornyl acetate	1288	trace	MS, RI
trans-pinocarveol acetate	1295	trace	MS, RI
Didehydro-cycloisolongifolene	1311	0.2	MS, RI
Neryl acetate	1362	trace	MS, RI, co-GC
α-Copaene	1375	0.1	MS, RI
Geranyl acetate	1378	trace	MS, RI, co-GC
Sesquiterpene A, $C_{15}H_{22}$	1413	6.4	[a]
α-Humulene	1451	1.4	MS, RI, co-GC
Acetovanillone (**2**)	1480	0.3	MS, RI, H NMR
γ-Muurolene	1481	0.1	MS, RI
Germacrene D	1483	1.1	MS, RI, co-GC
β-Selinene	1485	0.7	MS, RI
α-Selinene	1498	trace	MS, RI
α-Muurolene	1500	0.1	MS, RI
γ-Cadinene	1512	0.2	MS, RI
Kessane	1523	2.9	MS, RI[b]
δ-Cadinene	1525	trace	MS, RI
Liguloxide	1530	1.5	MS, RI[c]
Incisol (**1**)	1540	13.0	see text
β-Calacorene	1546	0.7	MS, RI
Elemol	1550	trace	MS, RI, co-GC
Oxide A, $C_{15}H_{26}O$	1608	11.0	[d]
γ-Eudesmol	1632	0.1	MS, RI
epi-α-Muurolol	1640	1.0	MS, RI
β-Eudesmol	1649	0.2	MS, RI
α-Eudesmol	1653	1.3	MS, RI
2,2-Dimethyl-6-acetyl-3-chromene (**3**)	1657	5.9	MS, ^{1}H NMR

(*continued on next page*)

Table 1 (*continued*)

Compound	RI	%	Identification
Alcohol A, $C_{15}H_{24}O$	1673	2.1	[e]
Cadalene	1677	1.4	MS, RI, ^{1}H NMR
Alcohol B, $C_{15}H_{24}O$	1682	2.4	[f]
4-Isopropyl-6-methyl-1,2,3,4-tetrahydronaphthalenone	1705	trace	MS, RI
Zerumbone	1732	2.2	MS, RI, ^{1}H NMR
α-Cyperone	–	0.1	MS
6-Hydroxytremetone (**5b**)	–	1.0	MS, UV, ^{1}H NMR
Euparin (**4b**)	–	0.3	MS, UV, ^{1}H NMR

[a] MS *m/z* (%): 202 (M^+, 30), 187 (27), 173 (4), 159 (77), 147 (24), 146 (52), 145 (31), 131 (63), 129 (23), 128 (17), 119 (21), 118 (22), 117 (100), 116 (10), 115 (24), 105 (40), 93 (21), 91(68), 79 (34), 77 (26), 67 (10), 65 (11), 55 (8), 53 (9), 43 (10), 41 (19).

[b] Identified by MS, ^{1}H and ^{13}C NMR spectrometry (Southwell and Tucker, 1993).

[c] Identified by MS, ^{1}H and ^{13}C NMR spectrometry (Lee et al., 1992; Wang et al., 2003).

[d] MS *m/z* (%) 207 ($M^+ - 15$, 1) 189 (3), 164 (36), 149 (64), 135 (30), 122 (13), 121 (20), 109 (10), 108 (26), 107 (37), 105 (12), 95 (21), 94 (16), 93 (23), 92 (5), 91 (23), 81 (24), 79 (19), 77 (14), 69 (5), 68 (8), 67 (14), 59 (100), 55 (16), 43 (22), 41 (19); ^{1}H NMR ($CDCl_3$) δ 5.46 (dd, $J = 4.3$, 2.7 Hz), 2.37 (m), 1.22 (s, 3H), 1.21 (s, 3H), 1.05 (d, $J = 7$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H). The substance had partially decomposed by the time the ^{13}C NMR spectrum was run.

[e] MS *m/z* (%) 207 (0.2, $M^+ - CH_3$), 204 (15, $M^+ - H_2O$), 189 (9.6), 175 (2.7), 161 (31), 149 (36), 135 (14), 133 (12), 122 (14), 121 (20), 119 (12), 109 (10), 108 (15), 107 (29), 105 (16), 95 (19), 94 (17), 93 (26), 91 (20), 81 (35), 79 (25), 77 (12), 69 (9), 68 (8), 67 (16), 59 (100), 55 (15), 53 (7), 43 (20), 41 (22). The ^{1}H NMR spectrum indicated that the substance had decomposed.

[f] MS *m/z* (%): 218 (M^+,18), 203 (9), 200 (5), 190 (2), 189 (2), 185 (2), 175 (62), 161 (20), 157 (57), 147 (66), 133 (45), 120 (90), 119 (67), 107 (69), 105 (100), 91 (99), 79 (46), 77 (42), 69 (12), 67 (15), 65 (19), 55 (27), 53 (18), 43 (20), 41 (45); ^{1}H NMR ($CDCl_3$) δ 4.81 (quint, $J = 1$ Hz), 4.68 (quint, $J = 1$ Hz), 2.64 (dd, $J = 17$, 8.4 Hz), 2.55 (d, $J = 6$ Hz), 1.65 (sext, $J = 7$ Hz), 0.96 (d, $J = 7$ Hz, 3H), 0.94 (d, $J = 7$ Hz, 3H), 0.91 (s, 3H).

(2 mg), β-eudesmol (8 mg) and α-eudesmol (6 mg) identified by GC–MS and RI. Frs. 8–11 (2.256 g) on elution from the mother column with hexane–EtOAc (95:5) gave solid material which on re-crystallization from hexane–ethyl acetate afforded 1.44 g, mp 96 °C, of 4-hydroxy-3-(isopenten-2-yl)-acetophenone (**7**, Bohlmann and Grenz, 1970). This prenylated *p*-hydroxyacetophenone was by far the main component of the extract and has significant antifungal properties (Tomás-Barberán et al., 1990; Takasugi and Masuda, 1996). It has previously been found in the closely related species *X. poposum* (as *Werneria poposa*, Ponce and Gros, 1991). Frs. 12 and 13 (510 mg) after repeated preparative TLC yielded 103 mg of acetovanillone called also apocynin (4-hydroxy-3-methoxyacetophenone) (**2**), a potent and selective inhibitor of the NADH oxidase-dependent production of reactive oxygen species (Simons et al., 1990; Stolk et al., 1994) and 9 mg of pregnenolone identified by mp, MS, co-chromatography with an authentic sample and by NMR spectroscopy (Szendi et al., 1995). It is interesting to note that occurrence of mammalian hormones in plants is well established (Bennett et al., 1969). Frs. 14–27 (2.20 g) yielded no identifiable material or decomposed during the workup.

*3.2. Incisol (incisa-3(E),6(14),11-trien-9α-ol) (**1**)*

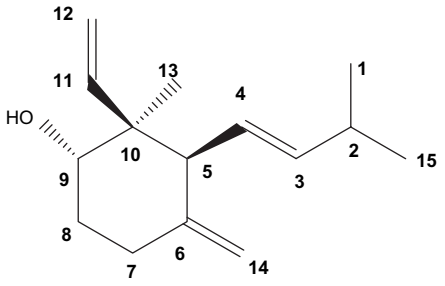
This triply unsaturated secondary alcohol with a new sesquiterpene skeleton was the main constituent of the oil fraction containing monooxygenated sesquiterpenes. We have given the name incisane to the novel skeleton of **1**. Oil; HRMS 220.18272 (calcd for $C_{15}H_{24}O$, 220.18272); MS 220 (M^+, 2), 205 ($M^+ - CH_3$, 4), 202 ($M^+ - H_2O$, 12), 187 (25), 177 (18), 159 (49), 145 (29), 133 (30), 131 (45), 121 (45), 119 (49), 117 (35), 109 (39), 107 (56), 105 (80), 93 (90), 91 (100), 81 (86), 79 (82), 77 (64), 69 (37), 55 (74), 43 (50), 41 (70). Its ^{1}H and ^{13}C NMR spectra (numbering of carbons as in farnesol) are listed in Table 2 together with the results of decoupling, COSY, NOESY and HMBC experiments that led to the various assignments. These demonstrated that (1) ring closure had occurred between C-5 and C-10 of the 12-carbon chain of a farnesol derivative, (2) an exocyclic methylene group was located on C-6 adjoining the 5-carbon side chain attached to C-5, (3) that two double bonds were located at C-3, C-4 (E configuration) and C-11, C-12, (4) that a secondary hydroxyl group was located on C-9, and (5) that the latter was *cis* to the methyl group on C-10 and *trans* to the 5-carbon side chain as shown in formula **1**. Since in the spectrum in chloroform the vinyl protons H-3 and H-4 appear at δ 5.41 as an unresolved multiplet, measurement in benzene

Table 2
^{1}H and ^{13}C NMR spectroscopic data of incisol (**1**)[a]

Position	δ_H (*J*)	δ_H (*J*,C_6D_6)	δ_C (DEPT)	COSY	NOESY*	HMBC*
1	0.98d(6.5)[b]	0.95d(6.5)[b]	22.7			3,15
2*	2.27c	2.21c	31.2	1,15	1,15	3,4,15
3*	5.41c	5.38dd (15.5, 6.5)	124.8	2,5	1,2,5,14a(w), 14b,15	5,6
4*	5.41c	5.49ddd (15.5,9.5,1)	140.6	2,5	5,12a(w)	3,5,6
5	2.76brd (7.5)	2.94brd(9)	53.6	3,4, 14a,b	13(w)	3,4,6,9(w),10, 11,14
6			148.7			
7a*	2.27c	2.15ddd (14,5.5,5)	29.8	7b,8a,b 14a,b	7b,8a,b	5,6,8,9,14
7b	2.38dddd (14,9,5,1.2)	2.43brddd (14,9,5)		7a,8a,b	7a,8a,b	5,8,9,14
8a	1.89dddd (14,9,5,3.5)	1.78dddd (14,9,5,3.5)	29.9			
8b	1.64dddd (14,7,7,5.5)	1.51 (14,7,7,5)				7,9,10
9	3.67dd (7,3.5)	3.41dd (7,3.5)	73.2	8a,b		5(w),8, 13(w)
10			45.8			
11	5.98dd (17.6,11)	6.05dd (17.6,11)	143.0	12a,b		
12a	5.06dd (17.6,1.4)	5.01 (17.6,1.5)	114.1			
12b	5.13dd (11,1.4)	5.07dd (11, 1.5)				
13	1.04s[b]	1.08s[b]	19.3			5,9,10
14a	4.80quint (1.2)	4.87brs	109.7	5,7a,b, 14b	7a,b	5
14b	4.64brt (1.2)	4.81brs		5,7a,b, 14a	5(w)	5
15	0.96d (6.5)[b]	0.94d (6.5)[b]	22.7			1,3

*N.B.: Protons H-3 and H-4 as well as H-2 and H-7a appear as unresolved signals in $CDCl_3$.
[a] Assignments based on HSQC, COSY, NOESY and HMBC experiments in $CDCl_3$ at 500 MHz relative to TMS; coupling constants are in Hz.
[b] Intensity of three protons.

was also performed whereby the signals appear nicely resolved at δ 5.38 as brdd (H-3; $J_{2,3} = 6.5$, $J_{3,4} = 15.5$ Hz) and δ 5.49 as ddd (H-4; $J_{3,4} = 15.5$, $J_{4,5} = 9.5$, $J_{2,5} = 1$ Hz). Thus, the magnitude of $J_{3,4}$ dictates an E configuration of the C-3–C-4 double bond. The relative stereochemistry of the chiral centers is based on the coupling constants looking at the model and the NOESY's listed in Table 2. Thus, H-5 (δ 2.76) showed correlation with Me-13 (δ 1.04) indicating a *cis* relationship between them; consequently, the 5-carbon side chain attached to C-5 must be *cis* to the vinyl group at C-10, a fact confirmed by the NOESY correlation between H-4 (δ 5.41) and H-12a (δ 5.06). The broadening of the doublet assigned to H-5 (δ 2.76) is due to allylic couplings with H-14a,b as shown by the COSY experiment which corroborates the HMBC experiment indicating that an exocyclic methylene group is located on C-6. The coupling values of the dd at δ 3.65 ($J_{8b,9} = 7$, $J_{8a,9} = 3.5$ Hz) assigned to the carbinol hydrogen are indicative of a quasi-axial orientation for H-9; consequently, the secondary hydroxyl group is quasi-equatorial and *cis* to the methyl group on C-10 as shown in formula **1** (relative stereochemistry). The absolute configuration of incisol (**1**) is not known. The optical rotation could not be determined since this unsaturated alcohol decomposed extensively after several months in the refrigerator.



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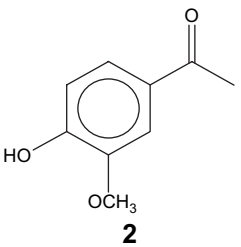

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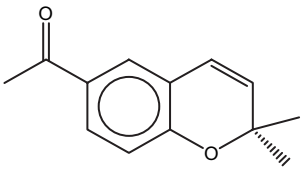

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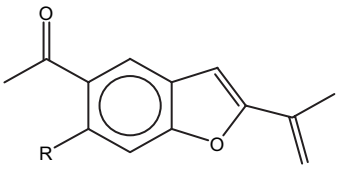

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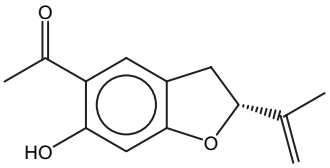
b R= OH

4



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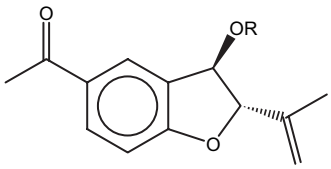
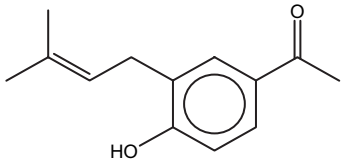


6a R= Ac
b R= Ang

6



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4. Chemotaxonomic significance

Analysis of the essential oil of *X. incisum* indicated the presence of a greater variety of constituents than reported earlier for its close relative *X. poposum* (Abella et al., 2000) that has a similar use in folk medicine. Aerial parts contained significant amounts of the antifungal agent 4-hydroxy-3-(isopenten-2-yl)-acetophenone (**7**) which was previously found also in *X. poposum* (Ponce and Gros, 1991). Other constituents of the aerial parts were identical with compounds previously reported from other members of this genus although diterpenes were notably absent. In this respect *X. incisum* resembles the two *Werneria s. str.* species on which reports are extant, *Werneria stuebeli* (Bohlmann et al., 1984) and *Werneria nubigena* (Piacente et al., 1997). The latter species also contained pyrrolizidine alkaloids (Piacente et al., 1997; Roeder et al., 1992).

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