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LIGNANS OF *PIPER CLUSII**

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Key Word Index—*Piper clusii*; Piperaceae; lignans; (−)-hinokinin; (−)-cubebin; (−)-deoxypodorhizon; (−)-dihydrocubebin; (−)-clusin; asaronaldehyde; ^{13}C NMR; CD.

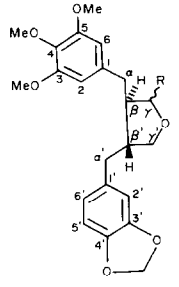
Abstract—From the petrol extract of *Piper clusii* five lignans were isolated. One of the lignans (−)-clusin is assigned the structure (−)-2-furanol-4(1,3-benzodioxol-5-ylmethyl) tetrahydro-3(3,4,5-trimethoxyphenyl) methyl. This is the first report of this compound from a natural source. Asaronaldehyde and sitosterol were also present.

INTRODUCTION

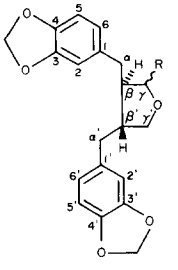
Piper clusii is reported to have some medicinal properties [1]. Previous work reports the presence of piperine and sesamin as the only lignans from the leaves of the plant [2]. The present investigations on this plant have proved it to be a rich source of lignans, viz. (−)-hinokinin, (−)-cubebin, (−)-dihydrocubebin and (−)-deoxypodorhizone. One of the lignans named (−)-clusin (**1**) is being reported for the first time. It has been assigned the structure (−)-2-furanol-4(1,3-benzodioxol-5-ylmethyl) tetrahydro-3(3,4,5-trimethoxyphenyl)methyl. The presence of sitosterol and asaronaldehyde is also reported.

RESULTS AND DISCUSSION

Chromatographic separation of the extract (benzene–ethyl acetate) resulted in the isolation of compound **1** (viscous mass). Elemental analysis gave a molecular formula of $C_{22}H_{26}O_7$, M^+ *m/z* 402. IR gave a strong absorption at 3400 cm^{-1} indicating the presence of a hydroxyl function. ^1H NMR in $CDCl_3$ showed a sharp singlet at δ 5.86 for two protons assigned to the methylenedioxy group. Signals for three methoxyl groups were observed at δ 3.90. Signals for benzylic protons and methine protons were observed as an envelope between δ 2.20 and 2.80. A broad singlet at δ 5.10 is ascribed to a hemiacetalic proton. Aromatic protons were located between δ 6.20 and 6.70. The –O–CH_2– protons were observed from δ 3.9 to 4.1 as a multiplet.



1 R=OH
5 R= =O



2 R= =O
6 R=OH

Acetylation gave a monoacetate (**1a**), a semi-solid, which analysed for $C_{24}H_{28}O_8$. The ^1H NMR, showed a signal for the hemiacetal C-1 shifted to δ 6.10 whereas the signal at δ 5.10 disappeared. The other signals remained unchanged.

Oxidation with Collin's reagent gave one product which analysed for $C_{22}H_{24}O_7$. IR showed a strong signal at 1770 cm^{-1} indicative of a γ-lactone while the band at 3460 cm^{-1} (observed in **1**) disappeared. The ^1H NMR ($CDCl_3$) showed a four proton envelope at δ 2.43 and a narrow two proton envelope at δ 2.70 assigned to benzylic and β,β'-protons, respectively. This situation of the two envelopes arises when the stereochemistry at β and β' is *trans* [10]. Moreover, a multiplet centred at δ 4.00 also supports the *trans* stereochemistry at β and β'. In the case of *cis*-β,β' the signals for benzylic and methine protons are generally observed as a multiplet between δ 2.1 and 3.3. Other signals remained practically unchanged. The spectral data of the compound, including the mass spectral fragmentation, are in agreement with deoxypodorhizon [7]. An additional proof of the stereochemistry at β and β' was obtained by comparing the CD curve of the lactone with that of (−)-hinokinin [3]. Both show a negative Cotton effect. This further confirms that the stereochemistry at β and β' in the parent compound (**1**) is also *trans*.

A compound with a similar structure to **1** has also been synthesized by Kiyoshi *et al* [4] as an intermediate during the synthesis of the anticancer lactone (+)-steganacin. However, Tomioka's compound is dextrarotatory with $[\alpha]_D$ +48.1 (EtOH) while **1** is laevoratotory with $[\alpha]_D$ −34.4 ($CHCl_3$). Therefore, clusin appears to be the enantiomer of the compound synthesized by Kiyoshi *et al.* The structure is also supported by its mass spectrum.

^{13}C NMR proved to be invaluable in confirming the structure of **1**. A comparison of the ^{13}C NMR spectrum of (−)-cubebin (**6**) with that of **1** and its lactone (**5**) is presented in Table 1. The values at the β and β'-carbons are in complete accordance with that of (−)-cubebin. The values of the hemiacetal carbons observed at δ 103.1 are also close to those in cubebin (δ 103.5). The other values are also similar and further support the proposed structure of (−)-clusin.

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Table 1. ^{13}C chemical shift values of 1, 5 and 6

Carbon position	1	5	6
α	39.0	35.37	39.5
α′	38.7	38.5	38.7
β	51.5	41.42	53.1
β′	45.1	46.7	45.1
γ	103.1	178.0	103.5
γ′	73.9	71.28	72.7
1	130.7	129.24	132.3
1′	133.9	133.9	133.9
2	105.9	107.2	108.3
6	105.9	107.2	121.9
2′	108.0	108.0	109.3
5′	108.8	108.5	109.0
6′	121.1	121.95	121.6
3	153.1	153.7	147.5
5	153.1	153.77	109.5
4	145.9	146.8	145.9
3′	148.3	147.07	147.5
4′	147.5	147.37	145.9
O–CH_2O	101.1	101.2	101.1
OMe	56.3	56.3	—

EXPERIMENTAL

All mps determined are uncorr. IR spectra were recorded in KBr pellets. ^1H NMR at 60 MHz in $CDCl_3$ and MS at 70eV. Specific rotations were determined in $CHCl_3$ soln.

Dried plant material of *P. clusii* Cass DC. (200 g) was extracted with petrol (60–80°) in a Soxhlet. Removal of solvent yielded a resinous mass (16 g) which on repeated CC over Si gel and elution with C_6H_6 and C_6H_6–EtOAc in increasing proportions furnished seven isolates in pure form designated 1–7.

1. Gummy solid, M^+ *m/z* 402, analysed for $C_{22}H_{26}O_7$ (requires C, 65.65; H, 6.52; observed C, 65.39; H, 6.51%); $[\alpha]_D^{26}$ −34.5° ($CHCl_3$; *c* 1.0). IR prominent bands at 1590 (C=C), 3400 (–OH), 928 cm^{-1} (–O–CH_2–O); other bands at 1487, 1440, 1320, 1230, 1120 and 1020 cm^{-1}. ^1H NMR: envelope between δ 2.20 and 2.80 (6H, four benzylic and two methine protons), *s* at 3.90 (9H, aromatic OMe), 5.86 (2H, *s*, –O–CH_2–O) and *m* 6.20–6.70 (five aromatic protons), *m* 3.9–4.1 (2H, O–CH_2–) and *br s* at 5.10 (1H) for a hemiacetal proton. The signal at δ 4.30 was exchangeable with D_2O. MS *m/z* 402 (base peak), 385, 384, 249, 182, 181, 127, 121 and 119. Acetylation with pyridine–Ac_2O gave the monoacetate (**1a**), a semi-solid, M^+ *m/z* 444, analysed for $C_{24}H_{28}O_8$. IR showed disappearance of the band at 3400 and appearance of two bands at 1730 and 1245 cm^{-1} (–O–C(=O)–Me). ^1H NMR showed a downfield shift of the hemiacetalic proton observed at δ 6.10 (1H) while the other signals were observed at δ 3.89 (9H, aromatic OMe), 5.90 (2H, *s*, –O–CH_2–O), 6.21–6.73 (*m*, five-aromatic protons), 3.9–4.16 (*m*, –O–CH_2) and 2.23 and 2.86 as an envelope (6H, four benzylic and two methine protons). MS *m/z* 444, 402, 385, 384, 249, 182, 181, 121, 119 and 117.

Oxidation of **1** with Collin's reagent gave a gummy mass, analysed $C_{22}H_{24}O_7$. M^+ *m/z* 400.4125 (requires C, 65.99; H, 6.04; observed C, 66.12; H, 6.12%), $[\alpha]_D^{26}$ −11.1° ($CHCl_3$; *c* 0.72) negative Cotton effect at 280 nm. From the spectral data the compound was identified as (−)-deoxypodorhizon in comparison with an authentic sample [7], (co-TLC, superimposable IR).

2. Semisolid analysed for $C_{29}H_{18}O_6$, M^+ at *m/z* 354 (requires C, 67.69; H, 5.12; observed C, 68.00; H, 5.08%). $[\alpha]_D^{26}$ −19.1°. IR bands at 1772, 1600 and 923 cm^{-1}. ^1H NMR signals: δ 2.43 (4H, *m*, φ-CH_2) 3.9 (envelope, 2H, –OCH_2), 2.83 (envelope, 2H, –C–H), 5.86 (1H, *s*, –O–CH_2–O) and 6.5 (6H, *m*, Ar–H). The compound was identified as (−)-hinokinin by comparison with an authentic sample [5] (co-TLC, superimposable IR).

3. Crystals from EtOH, mp 114–115°. The compound was identified as asaronaldehyde by comparison with an authentic (lit. [6] mp 114°) (co-TLC and superimposable IR).

4. Mp 137°, analysed for $C_{29}H_{50}O$, M^+ at *m/z* 414. The compound was identified as sitosterol by comparison with an authentic sample (lit. [6] mp 137°) (co-TLC and superimposable IR).

5. Semisolid, analysed for $C_{22}H_{24}O_7$, M^+ at *m/z* 400 (requires C, 65.99; H, 6.04; observed C, 65.83; H, 6.13%). $[\alpha]_D^{36}$ −26.1°. From the spectral data (IR, ^1H NMR and MS) the compound was identified as (−)-deoxypodorhizon by comparison with an authentic sample [7]. (Co-TLC and superimposable IR).

6. Mp 131.5°, analysed for $C_{20}H_{20}O_6$, M^+ at *m/z* 356 (requires C, 67.40; H, 5.65; observed C, 67.49; H, 5.59%). IR bands at 3330, 1605 and 930 cm^{-1}. ^1H NMR signals δ 2.66 (envelope, 2H, φ-CH_2), 3.96 (envelope, 2H, O–CH_2–), 5.26 (1H, *br s*–CH), 5.96 (4H, *s*, –O–CH_2–O) and 6.6 (6H, *m*, Ar–H). Monoacetate analysed for $C_{22}H_{22}O_7$, M^+ *m/z* 398 (requires C, 66.32; H, 5.56; observed C, 66.39; H, 5.59%). ^1H NMR signals: δ 2.0 (3H, *s*, –OCOMe), 3.8 (envelope, 2H, –OCH_2) 6.1 (1H, *s*, –CH OAc). The compound was identified as (−)-cubebin by comparison with an authentic sample (lit. [8] mp 131°) (Co-TLC and superimposable IR).

7. Mp 102°, analysed for $C_{20}H_{22}O_6$, M^+ at *m/z* 358 (requires C, 67.21; H, 6.20; observed C, 67.38; H, 6.23%). $[\alpha]_D^{28}$ −32.1°. IR bands at 3310, 1601 and 924 cm^{-1}. ^1H NMR signals: δ 2.63 (4H, *d*, *J* = 7 Hz, φ-CH_2), 3.56 (envelope 4H, –OCH_2), 4.03 (2H, *br s*, exchangeable with D_2O), 5.93 (4H, *s*, –O–CH_2–O) and 6.63 (6H, *m*, Ar–H). Diacetate (gummy solid), ^1H NMR signals for methyleneoxy and methine proton were shifted to δ 4.06 and 3.80, respectively, and the other signals remained essentially unchanged. MS fragments at *m/z* 442, 382, 322, 187 (base peak), 186, 174, 136 and 135. **7** was identified as (−)-dihydrocubebin (lit. [9] mp 101–102°) (Co-TLC, mmp and superimposable IR).

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