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MINOR LIGNANS OF *PIPER CLUSII*

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Key Word Index—*Piper clusii*; Piperaceae; new lignans.

Abstract—Further investigations on the petrol extract of *Piper clusii* have afforded four more new lignans. These are 2*S*,3*R*,4*R*,2-ethoxy-3-(3,4,5-trimethoxyphenyl)methyl 4-(1,3-benzodioxol-5-yl) methyl tetrahydrofuranol; 3*R*,4*R*,*bis*-3,4-(3,4,5-trimethoxyphenyl) methyl tetrahydrofuran-2-one; 2*R*,3*R*,2-(7-methoxy-1,3-benzodioxol-5-yl) methyl 3-(3,4,5-trimethoxyphenyl) methyl butan-1,4-diol and 2*R*,3*R*,2-(1,3-benzodioxol-5-yl) methyl 3-(3,4,5-trimethoxyphenyl) methyl butan-1,4-diol. This is the first report of these compounds from a natural source.

INTRODUCTION

Recently we have reported the presence of a new lignan, (−)-clusin **1** from the petrol extract of *Piper clusii* [1]. It is the precursor of an active anti-cancer compound namely steganacin [2] and could also be one of the possible biogenetic precursors of the same. Further exhaustive chemical investigations on the petrol extract of this plant have resulted in the isolation and characterisation of four more new minor lignans, viz **2**–**5**. Two of these, **2** and **5**, belong to the same aromatic substitution class as clusin. The compounds characterized are 2*S*,3*R*,4*R*,2-ethoxy-3-(3,4,5-trimethoxyphenyl) methyl 4-(1,3 benzodioxol-5-yl) methyl tetrahydrofuranol (**2**), 3*R*,4*R-bis*-3,4-(3,4,5-trimethoxyphenyl) methyl tetrahydrofuran-2-one (**3**), 2*R*,3*R*,2-(7-methoxy 1,3-benzodioxol-5-yl) methyl 3-(3,4,5-trimethoxy phenyl) methyl butan-1,4-diol (**4**), and 2*R*,3*R*,2-(1,3-benzodioxol-5-yl) methyl 3-(3,4,5 trimethoxyphenyl) methyl butan-1,4-diol (**5**).

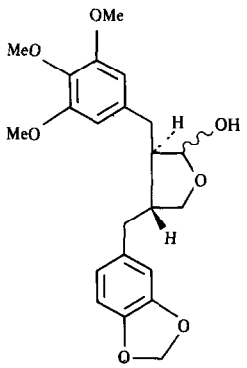
RESULTS AND DISCUSSION

Lignan **2** is a semi-solid which analysed for $C_{24}H_{30}O_7$ and is also corroborated by its mass spectrum ($[M]^+$ at *m/z* 430). It differs from clusin by an ethyl group in its molecular formula. In the IR of the compound no absorption was observed for carbonyl or alcoholic functions. In the ^{1}H NMR methylenedioxy protons were observed at δ 5.90 as a sharp singlet. Another broad singlet at δ 4.30 is assigned to an acetalic proton. The weak coupling of this proton with the vicinal methine proton is explained when both have the *cis* orientation. The signals for methine as well as four benzylic protons were located as an envelope between δ 2.0–2.8. A triplet at δ 1.20 (J = 7 Hz) for three protons shows the presence of a methyl group adjacent to a methylene. The presence of such a signal is indicative of an ethoxyl grouping. The signals for OCH_2 protons were however, submerged in the other proton signals for methoxyls and the tetrahydrofuran system observed between δ 3.4 and 4.2. This data clearly indicates that **2** is the ethyl ether of clusin—a hemiacetalic lignan which is also supported by its molecular formula.

The possibility of **1** being an artifact is ruled out from the fact that at no stage of the processing was ethanol used and its presence has also been confirmed by comparison with the original extract on TLC.

Paucity of this compound prevented us from doing any further chemical reaction on it. However, the proof for its final structure came when clusin was converted into **2** by reaction with ethanol and *p*-toluenesulphonic acid. One of the products obtained during this transformation was found to be same as **2** which was confirmed by its superimposable IR and co-TLC. As clusin and **2** both have the same sign of rotation, their configuration at C-2 and C-3 should also be same. The structure has also been supported by mass spectrometry.

Lignan **3** is a semi-solid which analysed for $C_{24}H_{30}O_8$. The mass spectrum showed $[M]^+$ at *m/z* 446. In the IR of the compound a strong absorption was observed at 1770 cm^{-1} which clearly indicated the presence of a five membered lactone system. No absorption was observed for a hydroxyl group. The ^{1}H NMR (CCl_4) showed a four proton envelope at δ 2.43 and a narrow two proton envelope at δ 2.76 assigned to benzylic and methine (β, β') protons, respectively. The presence of two such envelopes is indicative of the *trans* stereochemistry of the two methine protons [3]. Two sharp singlets each integrating for two protons at δ 6.10 and 6.23, respectively, were assigned to two symmetrical pairs of protons (2′ and 6′) on the aromatic ring. The signals for six methoxyls were observed at δ 3.78–3.85 and for OCH_2 protons in the form



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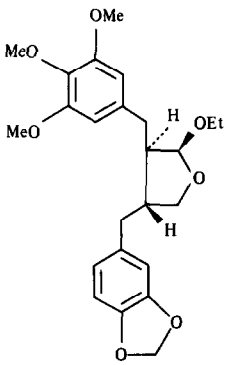

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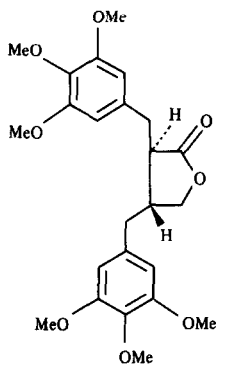

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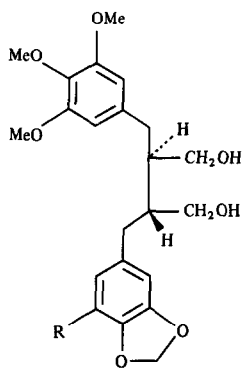

R
4 OMe
5 H

of a multiplet at δ 4.00. On the basis of the above data structure **3** has been assigned to this compound. The structure has finally been ascertained through its mass fragmentation pattern wherein the base peak is observed at *m/z* 181. The other fragments are in full concordance with the proposed structure.

Lignan **4** is a crystalline solid mp 58–60° and was analysed for $C_{23}H_{30}O_8$ supported by $[M]^+$ at *m/z* 434. IR showed a strong band at 3450 cm^{-1} indicating hydroxyl functions. IR showed no evidence for the presence of a carbonyl function. In the ^1H NMR (CCl_4), signals for methylenedioxy protons were observed at δ 5.90 as a sharp singlet. The presence of four methoxyls was shown by signals at δ 3.90 integrating for 12 protons. The CH_2O proton signals were located as a broad multiplet centred at δ 3.60 (part of this signal is obscured by methoxyl proton signals). Benzylic proton signals were observed in the form of an envelope centred at δ 2.6. Another envelope (2H) at δ 2.0 is assigned to methine protons. In the aromatic part of the spectrum a three proton broad singlet was observed at δ 6.20 which is attributed to the two symmetrical protons 2′, 6′ of ring A and the 2′ proton of ring B. An isolated one proton doublet (J = 2 Hz) at δ 6.6 is assigned to the 6′-proton of ring B. Acetylation of **4** gave a semi-solid diacetate which analysed for $C_{27}H_{34}O_{10}$, $[M]^+$ at *m/z* 518. In the ^1H NMR of this compound signals for CH_2O were shifted to δ 4.0. Other signals remained essentially at their original positions.

From the above spectral data structure **4** has been proposed for the new lignan. Its stereochemistry has been established as *trans* at β, β' by analogy with (−)-dihydrocubebin and its acetate [1]. The structure is in agreement with its mass fragmentation pattern. As both dihydrocubebin and **4** have a negative sign of optical rotation, the configuration at C-2 and C-3 should also be the same in **4** as in dihydrocubebin.

Lignan **5** is a crystalline solid mp 68–70° analysing for $C_{22}H_{28}O_7$ which was also corroborated by its mass spectrum ($[M]^+$ at *m/z* 404). The IR is clearly marked by the absence of a carbonyl function. The broad band at 3250 cm^{-1} and the bands at 1120 and 1130 cm^{-1} are also indicative of hydroxyl functions. ^1H NMR shows a sharp singlet for a methylenedioxy group at δ 5.90. The signals for three methoxyls were observed at δ 3.80. Benzylic protons were observed as an envelope between δ 2.30 and 2.80. Another envelope (2H) at δ 1.83 is assigned to methine protons. The four methylene protons of the primary alcoholic group were located at δ 3.60 as a multiplet. In the aromatic region a singlet for two protons at δ 6.30 was assigned to the symmetrical protons on the ring bearing the three methoxyl groups. The other protons on the aromatic ring were located at δ 6.60 as a three proton multiplet. Acetylation produced a diacetate which analysed for $C_{36}H_{32}O_9$ ($[M]^+$ at *m/z* 488). In the ^1H NMR the signals for methylene protons shifted to δ 4.10. The other signals remained essentially at the same positions.

Comparison of the ^1H NMR spectra of dihydroclusin and its diacetate with dihydrocubebin and its diacetate points to a close resemblance between the two. This analogy establishes the stereochemistry of the β, β' protons in **5** as *trans*. Further proof of the structure was obtained when a sample of clusin was reduced with lithium aluminium hydride in ether. A comparison of the ^1H NMR spectrum of the reduced product with that of the natural substance indicated that both the compounds were the same. TLC and mass spectrometry also substantiated these observations. This establishes the structure and configuration at C-2 and C-3 in dihydroclusin which also has the negative optical rotation exhibited by clusin.

EXPERIMENTAL

IR spectra were recorded in KBr pellets or as neat samples. ^1H NMR were recorded at 60 MHz in CCl_4 with TMS as int. standard. Specific rotations were determined in MeOH solns. All mps determined are uncorr. MS were measured at 70 eV.

The petrol extract [1] of *P. clusii* after exhaustive CC and prep. TLC over silica gel using mixtures of petrol–C_6H_6 and C_6H_6–EtOAc as eluants in increasing proportions furnished four isolates in pure form designated as **2**, **3**, **4** and **5**.

Compound **2**. Gummy solid, $[M]^+$ *m/z* 430 analysed for $C_{24}H_{30}O_7$ (requires C, 66.96; H, 7 023 observed C, 67.10; H, 7.13%). $[\alpha]_D^{36}$ −31 6°, ν_{max} 1595, 1504, 1490, 1460, 1440, 1330, 1240, 1120 and 920 cm^{-1}. ^1H NMR: δ 5.90 (2H, OCH_2O), 1.20 (3H, *t*, J = 7 Hz, $C\underline{H}_3CH_2O$), 2.0–2.8 (6H, envelope, $-C\underline{H}$ and ϕ protons), 3.4–4.2 (11H, 3 × OMe and OCH_2), 4.73 (1H, *s*, acetalic proton), 6.4 (5H, *m*, ArH), MS $[M]^+$ *m/z* 430 (16.2), 384 (6.2), 249 (22.1), 197 (9.8), 182 (100), 181 (62.7), 167 (13.7), 161 (14.2), 151 (17.9), 136 (15.2) and 135 (47.3).

Compound **3** Semi-solid, analysed for $C_{24}H_{30}O_8$ $[M]^+$ *m/z* 446 (requires C, 64.56; H, 6.77 observed C, 65.01; H, 6.08%). $[\alpha]_D^{34}$ −42.4°, ν_{max} 1770 cm^{-1} (γ-lactone), 1600, 1508 1468, 1435, 1350, 1245, 1120 and 1005 cm^{-1}, ^1H NMR: δ 2.43 (4H, envelope, ϕ-

CH_2), 2.76 (2H, envelope, CH), 3.78–3.85 (18H, 6 × OMe), 4.00 (2H, *m*, OCH_2), 6.10 and 6.23 (2H each, *s*, ArH). MS *m/z* 446 (45.3), 211 (27), 210 (29.4), 207 (14.1), 197 (25.9), 195 (18.3), 181 (100), 169 (16.9), 167 (18.9), 151 (28.0), 148 (10.8), 137 (24.7) and 136 (10.8).

Compound **4**. Crystallized from EtOH as colourless crystals, mp 58–60°, analysed for $C_{23}H_{30}O_8$ (requires C, 63.58; H, 6.95 observed C, 63.93; H, 7.12%). $[\alpha]_D^{36} - 28°$; ν_{max} 3450 (OH) 1594, 1500, 1460, 1230, 1110, 1020 and 918 cm^{-1}. ^1H NMR: δ 5.90 (2H, *s*, OCH_2O), 2.00 (2H, envelope, CH), 2.6 (4H envelope, ϕ-CH_2), 3.60 (4H, *m*, OCH_2), 3.90 (12H, 4 × OMe), 6.20 (3H, *br s*, ArH) and 6.6 (1H, *d*, J = 2 Hz, ArH). Acetylation with Ac_2O–pyridine gave a diacetate, semisolid, $[M]^+$ *m/z* 518 analysed for $C_{27}H_{34}O_{10}$ (requires C, 62.53; H, 6.60 observed C, 63.00; H, 6.62%). IR showed two bands at 1732 and 1252 cm^{-1} (OCOMe). ^1H NMR δ 1.98 (6H, *s*, OAc), 2.13 (2H, envelope, CH), 2.6 (4H, *m*, ϕ-CH_2), 3.83 (12H, *s*, 4 × OMe), 4.0 (4H, *m*, 2 × $C\underline{H}_2OAc$), 5.87 (2H, *s*, OCH_2O), 6.2 (3H, *br s*, ArH) and 6.8 (1H, *d*, J = 2 Hz, ArH). MS *m/z* 518 (74.7), 488 (44.3), 233 (11.2), 187 (18.3), 181 (100), 166 (38 4), 165 (50.1), 162 (10.1), 151 (14.0) and 135 (61.0).

Compound **5**. Crystallized from EtOH, mp 68–70°, analysed for $C_{22}H_{28}O_7$ (requires C, 65.33; H, 6.97 observed C, 65.86; H, 7.14%). $[\alpha]_D^{28} - 48°$; ν_{max} 3350, 1590, 1500, 1480, 1440, 1330, 1240, 1130, 1120, 1030 and 920 cm^{-1}. ^1H NMR δ 5.90 (2H, *s*, OCH_2O), 1.85 (2H, envelope, CH), 2.30–2.80 (4H, envelope, ϕ-CH_2), 3.60 (4H, envelope, 2 × OCH_2) 3.80 (9H, *s*, 3 × OMe), 6.30 (2H, *s*, ArH) and 6.60 (3H, *m*, ArH). MS $[M]^+$ *m/z* 404 (3.5), 387 (23.2), 386 (10.1), 238 (22.1), 225 (10), 219 (27.4), 202 (10.5), 183 (31.8), 182 (70.6), 181 (71), 167 (63.4), 151 (100) and 105 (33.1). Acetylation with Ac_2O–pyridine gave a diacetate, semi-solid, ($[M]^+$ *m/z* 488) analysed for $C_{26}H_{32}O_9$ (requires C, 63.92; H, 6.60 observed C, 64.10; H, 6.63%). IR showed the disappearance of the band at 3350, and appearance of two bands at 1720 and 1240 cm^{-1} (OCOMe). ^1H NMR: δ 2.03 (6H, *s*, OAc), 2.16 (2H, *m*, CH), 2.56 (4H, *m*, ϕ-CH_2), 3.73–3.83 (9H, *s*, 3 × OMe), 4.10 (4H, *m*, $C\underline{H}_2OAc$), 5.86 (2H, *s*, OCH_2O), 6.30 (2H, *s*, ArH) and 6 60 (3H, *m*, ArH).

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NEOLIGNANS FROM *OCOTEA ACIPHYLLA**

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Key Word Index—*Ocotea aciphylla*; Lauraceae; hydrobenzofuranoid neolignans; bicyclo[3.2.1]octanoid neolignans.

Abstract—The trunk wood of the central Brazilian *Ocotea aciphylla* contains two hydrobenzofuranoid and three bicyclo[3.2.1]octanoid neolignans. The former comprise a novel representative of the rare ferrearin (3a-allyl-2-aryl-7a-hydroxy-3-methyl-2,3,3a,4,7,7a-hexahydro-7-oxobenzofuran) type.

INTRODUCTION

Ocotea aciphylla, a lauraceous tree popularly known as canela-amarela, ranges in central Brazil from Minas Gerais and Espirito Santo to Santa Catarina. Its heartwood resists termites and is used for flooring [2]. Trunk wood, collected in the vicinity of Brasilia, D.F., yielded five neolignans. The three bicyclo[3.2.1]octanoids **1** (canellin-A), **2a** and **2b** (5-methoxyguianin) have been isolated from *Licaria canella* [3], *Ocotea catharinensis* [4] and *Aniba affinis* [5], respectively, and were identified by direct comparison with authentic samples. The neolignan **3a** was identified with ferrearin-B previously isolated from *Aniba ferrea* [6]. Compound **3b** proved to be novel and was designated ferrearin-C.

*Part LXXVI in the series "The Chemistry of Brazilian Lauraceae". For Part LXXV see ref. [1]. Based in part on the M.Sc. thesis submitted by P.R. to Universidade de São Paulo (1982).

RESULTS AND DISCUSSION

The HR mass spectra of **3a** and **3b** were superimposable