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ALKALOID AND LIGNAN CONSTITUENTS OF *CINNAMOSMA MADAGASCARIENSIS*

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Key Word Index—*Cinnamosma madagascariensis*; Canellaceae; N_b-coumaroyltryptamine; N_b-feruloyltryptamine; (±)-lyonyresinol; 5-methoxy-9-β-xylopyranosyl-(−)-isolariciresinol.

Abstract—A new lignan glycoside, 5-methoxy-9-β-xylopyranosyl-(−)-isolariciresinol and two indole alkaloids have been characterised from the bark of *Cinnamosma madagascariensis*.

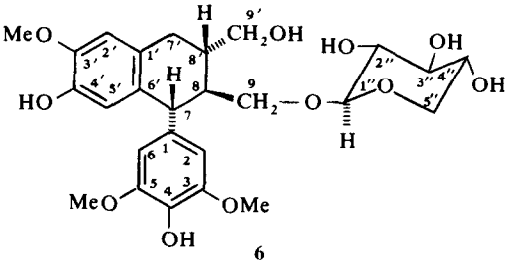
In a previous investigation on *Cinnamosma madagascariensis* (Canellaceae) bark, [1] a quaternary aporphine alkaloid (chakranine) was found in the alcohol extract, and essential oils in the acetone extract. A more thorough examination of the latter has now enabled us to isolate other substances.

Two alkaloids were isolated and identified as N_b-(*p*-coumaroyl) **1** and N_b-feruloyltryptamine **2**. Both these indole derivatives had previously been isolated in very small amounts (140 and 40 μg/kg, respectively) from *Zea mays* kernels and identified by GC–MS of their TMSi derivatives and the TMSi derivatives of their acid hydrolysis products [2]. These compounds have now been isolated with an overall yield of 0.03% from *C. madagascariensis* and completely characterized and synthesized (see Experimental). Tryptamine and other related indole amines occur in a wide variety of higher plants and have been identified in each of their parts [3]. Conversely, their N_b-acyl derivatives are rare. N_b-Acetyltryptamine has been found in *Prosopis nigra* [4] and *Passiflora edulis* [5] leaves; behanoyltryptamine in cocoa shells [6]; C_{20}, C_{22} and C_{24} N_b-acylamides of 5-hydroxytryptamine [7] have been found in the fat of coffee seeds. An etherocyclic amid of tryptamine has also been isolated from Thermo actinomyces strain TM-64 [8].

Two lignan derivatives were also isolated. One obtained in a yield of 0.0054% was identified as (±)-lyonyresinol **5** by comparison with an authentic sample [9]. The other lignan derivative has been isolated with a yield of 0.031% and to our knowledge was a new compound for which we propose the structure of 5-methoxy-9β-xylopyranosyl-(−)-isolariciresinol **6**.

The reactions reported in the Experimental are in agreement with the structure suggested for **6**. It gave an hexaacetate **7** by acetylation, a diMe ether by methylation with MeI/K_2CO_3, which provides a dimethoxy tetraacetate **8** by further treatment with Ac_2O/Py, and finally (−)-5-methoxy-isolariciresinol **9** and D-xylose by acid hydrolysis.

The tabulated ^{13}C NMR spectra were of particular help in elucidating the structure of **6**. The spectra of **5**, lyoniresinol tetraacetate **10**, lyoniside **11** [10] and



6

lyoniside hexaacetate **12** [10] are also reported (Table 1). The values were in agreement with the assignments made for **6**, considering the changes due to the presence of a methoxy group at C-5′. C-1 and C-7 sterically hindered were affected and some signals cannot be attributed because they were overlapped by DMSO signals.

The assignments of the carbon resonances of **6** were made on the basis of those reported for β-methylxyloside [11] and similar lignan derivatives [12]. It has also been considered that only one of the aromatic rings was symmetric and that during acetylation an upfield shift occurred for the aromatic carbon bearing the OH group whilst a downfield shift took place for the carbon *ortho* and *para* to the OH group.

In the ^{13}C NMR spectrum of **6** three doublets were present at δ 46.7, 43.4 and 38.5 which were attributed to C-7, C-8 and C-8′, respectively. In the ^1H NMR spectrum of **8**, which was the best resolved, the benzylic proton at C-7 was readily identifiable as a doublet at δ 4.05 ($J_{7,8}$ = 9 Hz). The signal of the C-8 proton was localized at 1.79 by decoupling experiments with the C-7 proton. Finally, by irradiating selectively at δ 1.79, the signal of C-8 at 43.4 appeared as a singlet whilst the other carbon signals showed the multiplicity of their C-H couplings. In the ^{13}C NMR spectra of the acetates **7** and **8** of the 3 signals in question, only that at 38.5 undergoes an upfield shift whilst the other two remained unchanged. As acetylation is known to cause an upfield shift of the carbon atoms β to the OH group, the CH_2OH capable of acetylation was linked to C-8′ which gave the signal at

Table 1. ^{13}C NMR chemical shifts (ppm from internal TMS)

Carbon	Compounds 5	11	10	12	6	7	8
1	137.6	137.4	144.9	145.1	135.5	142.7	137.0
2	106	106	105	105	106.4	106.2	106.7
3	147.4	147.4	151.9	151.9	147.5	151.8	152.9
4	133.35	133.35	127.3	127.0	133.5	127.0	140.6
5	147.4	147.4	151.9	151.9	147.5	151.8	152.9
6	106	106	105	105	106.4	106.2	106.7
7	*†	*†	43.0*	42.5*	46.7	47.4	47.6
8	46.6*	44.5*	44.4*	45.0*	43.4	43.9	44.5
9	62.3	69.0	63.1	68.2	67.9	67.3	67.6
1′	128.5	128.5	135.2	135.4	126.9	134	127.9
2′	106.6	106.6	106.8	106.8	111.5	111.6	110.9
3′	146.3	146.4	151.3	151.4	145.3	149.1	147.4
4′	137.1	137.1	131.7	131.7	143.8	137.8	147.2
5′	146.8	146.7	150.9	150.8	115.9	124.0	113.1
6′	124.9	124.9	124.3	124.3	131.7	131.2	131.0
7′	32.2	32.5	33.6	33.5	32.2	33.2	32.9
8′	†	38.8	35.5	35.3	38.5	34.4	34.7
9′	64.6	65.6	66.3	66.2	65.5	65.8	66.1
1″	—	103.8	—	101.0	103.2	101.1	101.2
2″	—	73.2	—	70.9	73.1	71.2	71.2
3″	—	76.7	—	71.4	76.3	71.8	71.9
4″	—	69.5	—	68.8	69.4	69.4	69.1
5″	—	63.7	—	62.1	63.0	62.4	62.5
OMe	55.6	55.6	56.0	56.0	55.3	55.7	55.8
	56.1 × 2	56.0 × 2	56.25 × 2	56.3 × 2	55.8 × 2	56.0 × 2	56.05 × 2
	58.9	58.9	60.1	60.0			60.8 × 2

Solvents: compounds **5**, **6** and **11** in DMSO-d_6; compounds **7**, **8**, **10** and **12** in $CDCl_3$.
* Signals may be reversed.
† Masked by DMSO.

38.5 in compound **6**, shifted upfield in **7** and **8**. Consequently the point of attachment of the CH_2-O-oxylose was at C-8 which gave the signal at 43.4 in **6**, unchanged by acetylation. The third signal at 46.7, also unchanged by acetylation, was assigned to C-7. The coupling constants reported above have also established the stereochemistry of the protons in C-7, C-8 and C-8′, which were all *trans*-diaxial.

The absolute stereochemistry of genine **9**, which was opposite to that of (+)-5,5′-dimethoxy-isolariciresinol, has been established on the basis of the CD spectrum that was specular as compared with that reported for the above lignan derivative [10]*.

The β nature of the xylosidic linkage, inferred from the ^{13}C NMR spectra, is supported by the ^1H NMR analysis of **6**. In effect, the signal of the acetalic proton appeared as a doublet at δ 4.57 (J = 7 Hz confirmed by double resonance experiment). The values of the chemical shift and coupling constant were in agreement with the axial nature of this proton. Moreover, the difference between the molar rotation of xyloside **6** and genine **9** were also in agreement with the β nature of the linkage. As far as we know, **6** would therefore be the first derivative of (−)-isolariciresinol.

EXPERIMENTAL

Isolation. Ground bark of *C. madagascariensis* (190 kg) was extracted with Me_2CO at room temp. (3 × 415 l.). The Me_2CO extract was evapd *in vacuo* to 40 l. A 10 l. portion of the concentrate was diluted with an equal vol. of H_2O and extracted successively with $CHCl_3$ and BuOH. The $CHCl_3$ extracts were concd to dryness. The residue was extracted with petrol (bp 60–80°) in order to eliminate most of the essential oils. The residue (230 g) was chromatographed on Al_2O_3 with CH_2Cl_2 containing increasing amounts of MeOH. The fractions containing compounds **1**, **2** and **5** (30 *g*) were further chromatographed on Si gel with cyclohexane–EtOAc to give a mixture of **1** and **2** (15.2 g, 0.032%) and **5** (2.6 g, 0.0054%). Two crystallizations from MeCN of the mixture of **1** and **2** and a crystallization from EtOAc gave 9.6 g of **1**. The mother liquors of crystallization rechromatographed on Si gel with CH_2Cl_2–MeOH (97:3) gave a further 3.4 g of **1** and 1.1 g of **2**. The BuOH extract was concd to dryness giving a residue of 580 g. One tenth of this residue (58 g) was chromatographed on Si gel with EtOAc–MeOH (9:1). A fraction of 15 g was obtained. When further chromatographed on Al_2O_3 with CH_2Cl_2–MeOH, it gave 1.5 g of **6**.

N_b-(p-*Coumaroyl*)-*tryptamine* (**1**). Mp 164–166° (EtOAc). UV λ_{max}^{MeOH} nm (log ε): 310 (4.34), 292 (4.42), 224 (4.64). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3370, 1650, 1540, 1610, 1590, 1510. ^1H NMR (DMSO-d_6): δ 2.95 (2H, *m*, $\underline{CH_2}$-CH_2-N), 3.6 (2H, *m*, CH_2-$\underline{CH_2}$-N), 6.45 and 7.5 (2H, *d*, J = 16 Hz, CH$\overset{E}{=}$CH), 7.35 and 6.6 (4H, *d*, J = 10 Hz, *p*-substituted C_6H_5), 7.6–6.8 (5H, *m*, Ar$\underline{H}$, after exchange with D_2O). MS identical to that reported in lit. [2].

N_b-*Feruloyl-tryptamine* (**2**). Mp 163–165° (MeCN). UV λ_{max}^{MeOH} nm (log ε): 316 (4.32), 252 (4.32), 222 (4.68). IR ν_{max}^{Nujol} cm^{-1}: 3360, 3300, 1650, 1570, 1525. ^1H NMR (DMSO-d_6): δ 3.07 (2H, *m*, $\underline{CH_2}$-CH_2-N), 3.6 (2H, *m*, CH_2-$\underline{CH_2}$-N), 6.52 and 7.48 (2H, *d*, J = 16 Hz, CH$\overset{E}{=}$CH), 3.92 (3H, *s*, OMe), 7.7–6.9 (8H, *m*, Ar$\underline{H}$, after exchange with D_2O). MS identical to that reported in lit. [2].

* The difference of a methoxyl cannot account for this specularity.

Synthesis of **1**. Tryptamine HCl (272 mg) was suspended in Py (3 ml) and *p*-acetoxycinnamoyl chloride [13] prepared from the corresponding acid (250 mg) was added. The reaction mixture was stirred at room temp. for 15 hr, poured into H_2O and extracted with $CHCl_3$. The organic extract was concd and the residue purified by chromatography on Si gel using CH_2Cl_2–MeOH (99:1) as eluent giving **3** (250 mg), mp 127–128° ($CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3200, 1770, 1665, 1620, 1605, 1515. ^1H NMR ($CDCl_3$): δ 2.25 (3H, *s*, MeCO), 3 (2H, *t*, J = 7 Hz, $\underline{CH_2}$-CH_2-N), 3.7 (2H, *q*, CH_2-$\underline{CH_2}$-N). An identical product (mp, TLC and IR) was obtained from **1** by reaction with Ac_2O–Py. **3** (40 mg) in 2 N methanolic KOH (8 ml) was refluxed (N_2) for 2 hr, and the MeOH then evapd. The residue was dissolved in H_2O and acidified (HCl, 2 N) giving **1** (27 mg), identical (mmp, TLC, NMR) with the natural product.

Synthesis of **2**. By proceeding as for **1** but starting from *p*-acetoxyferulyl chloride [13], **4**, mp 139–141° (C_6H_6) was obtained. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3440, 1760. Saponification as for **3** gave **2**, identical (mmp, TLC, NMR) to the natural product.

5-Methoxy-9β-xylopyranosyl-(−)-isolariciresinol **6**. Plates (MeOH), mp 200–203°. (Found: C, 57.63; H, 6.72. $C_{26}H_{34}O_{11}\cdot 2MeOH$ requires: C, 57.34; H, 7.17%). $[\alpha]_D^{25}$ − 53° (MeOH). UV λ_{max}^{MeOH} nm (log ε): 280 (3.65). IR ν_{max}^{Nujol} cm^{-1}: 3650, 3440, 3300, 1620, 1520, 1460, 1220, 1130, 1050. ^1H NMR (C_5D_5N after exchange with D_2O): δ 2.5 (2H, *m*, H-8 and H-8′), 3–3.16 (2H, *m*, H-7′), 3.63 (6H, *s*, 2 × OMe), 3.94 (3H, *s*, OMe), 3.5–4.4 (10H, *m*, H-7, H-9, H-9′, H-2″, H-3″, H-4″, H-5″), 4.57 (1H, *d*, J = 7 Hz, H-1″), 6.74 (2H, *s*, H-2 and H-6), 6.76 (1H, *s*, H-5′), 6.84 (1H, *s*, H-2′). MS *m/e* (rel. int.): 522 (M^+, 16), 391 (58), 390 (100), 389 (50), 372 (92), 371 (100), 342 (100), 341 (100), 314 (58), 311 (50), 309 (83), 271 (83). CD (in MeOH, c = 0.001): $[\theta]_{288}$ + 16709, $[\theta]_{272}$ − 13953, $[\theta]_{254}$ − 2583, $[\theta]_{240}$ − 13 780. Hexaacetate **7** (Ac_2O–Py, 12 hr room temp.) mp 155–157° (C_6H_6–hexane). MS *m/e*: 774 (M^+). ^1H NMR ($CDCl_3$): δ 1.96–2 (12H, *s*, 4 × MeCO), 2.12 (3H, *s*, MeCO), 2.22 (3H, *s*, MeCO), 6.36 (2H, *s*, H-2 and H-6), 6.4 (1H, *s*, H-5′), 6.62 (1H, *s*, H-2′).

Dimethylethertetraacetate **8**. **6** (375 mg) was methylated with excess MeI/K_2CO_3 in Me_2CO (5 ml) at room temp. for 24 hr. The reaction mixture was concd, diluted with H_2O and extracted with EtOAc. The organic extract was concd and the residue (175 mg, MS *m/e*: 550 (M^+), $FeCl_3$ neg.) without further purification was acetylated (Ac_2O–Py, room temp.). After usual work-up and chromatography on Si gel with EtOAc–C_6H_6 (1:3), **8** (137 mg) was obtained. Needles, mp 134–136° (EtOAc). MS *m/e*: 718 (M^+). ^1H NMR ($CDCl_3$): δ 1.79 (1H, *br dd*, $J_{8\text{-}7}$ = 9 Hz, H-8; irradiation of this *dd* collapsed the *d* at 4.05 to a *s*), 2.02 (6H, *s*, 2 × MeCO), 2.08 (6H, *s*, 2 × MeCO), 2–2.5 (1H, *m*, H-8′), 2.78–2.85 (2H, *m*, H-7′), 3.6 (3H, *s*, OMe), 3.8 (6H, *s*, 2 × OMe), 3.9 (6H, *s*, 2 × OMe), 3.2–4.1 (4H, *m*, H-9 and H-5″), 4.05 (1H, *d*, $J_{7\text{-}8}$ = 9 Hz, H-7; irradiation at this frequency collapsed the *dd* at 1.79 to a *br d*, J = 9 Hz), 4.17 (2H, *q*, H-9′), 4.4 (1H, *d*, J = 7 Hz, H-1″), 4.7–5.3 (3H, *m*, H-2″, H-3″ and H-4″), 6.6 (1H, *s*, H-2′), 6.26 (1H, *s*, H-5′), 6.36 (2H, *s*, H-2 and H-6).

5-Methoxy-(−)-isolariciresinol **9**. **6** (60 mg) was hydrolysed by heating with 5% H_2SO_4 (40 ml) for 3 hr at 100°. The genine was separated by extraction with EtOAc and purified on Si gel with EtOAc–MeOH (99:1). It was crystallized from MeOH into colourless crystals (22 mg), mp 175–178°, $[\alpha]_D^{25}$ − 46.4 (MeOH). CD (in MeOH, c 0.0007): $[\theta]_{286}$ + 12 309, $[\theta]_{272}$ − 9636, $[\theta]_{254}$ − 1435, $[\theta]_{240}$ − 12 309. MS *m/e*: 390 (M^+). In the aq. layer D-xylose was identified (TLC).

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