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A DIHYDROCHALCONE FROM *LINDERA LUCIDA*

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Abstract—A new dihydrochalcone, 3′,5′-dihydroxy-2′,4′,6′-trimethoxydihydrochalcone and five known compounds, methyl linderone, 5-hydroxy-6,7,8-trimethoxyflavone (alnetin), 2′-hydroxy-3′,4′,5′,6′-tetramethoxydihydrochalcone (dihydrokanakugiol), 2′-hydroxy-3′,4′,5′,6′-tetramethoxychalcone (kanakugiol) and 2′,3′,4′,5′,6′-pentamethoxychalcone (pedicellin) were isolated from twigs of *Lindera lucida*. The structures of these compounds were determined by spectral analyses and chemical correlations.

The Shiny Laurel, *Lindera lucida* (Bl.) Boerl. belongs to the large family Lauraceae which consists of mostly trees or shrubs from the warmer regions of the earth. *L. lucida* itself is common in both lowland and montane forests of Malaysia and Singapore [1]. Previous studies of this species have afforded 5,6,7,8-tetramethoxyflavone, 5,6,7,8-tetramethoxy-3′,4′-methylenedioxyflavone and 5,7-dihydroxy-6,8-dimethoxy-3′,4′-methylenedioxyflavone (lucidin) from the roots [2] and the cyclopentenedione derivatives methyllinderone (**1**), lucidone and methyl lucidone from the fruits [3].

CC and HPLC separation of the hexane extract of the twigs of *L. lucida* collected in Malaysia gave five known compounds, viz methyllinderone (**1**) [3], 2′-hydroxy-3′,4′,5′,6′-tetramethoxychalcone (kanakugiol) (**2**) [4–6], 2′-hydroxy-3′,4′,5′,6′-tetramethoxydihydrochalcone (dihydrokanakugiol) (**3**) [6], 2′,3′,4′,5′,6′-pentamethoxychalcone (pedicellin) (**4**) [7, 8] and 5-hydroxy-6,7,8-trimethoxyflavone (alnetin) (**5**) [9]. Methyllinderone has previously been found in the fruits of *L. lucida* [3] whereas the other four compounds have not previously been reported from this species. Kanakugiol and dihydrokanakugiol have been found in *L. erythrocarpa* [5, 6] whilst methyllinderone has been reported from *L. erythrocarpa* [6] and *L. pipericarpa* [10]. All of the known compounds were identified by comparison of their physical data (see Experimental) with literature values and, for the chalcone derivatives, by chemical correlation (see Scheme 1). In the case of pedicellin, the ^{13}C NMR spectrum published for a synthetic sample [11] is at variance with that recorded during this work. Previously, six separate signals were reported for the A-ring but this is incompatible with the symmetry of the molecule. The other physical values reported for pedicellin are in agreement with those in the literature [7, 8].

The final compound, 3′,5′-dihydroxy-2′,4′,6′-trimethoxydihydrochalcone (**6**), mp 108–110°, $C_{18}H_{20}O_6$ (*m/z* 332.1273) exhibited UV absorptions at 286 and 358 nm and IR absorptions at 3481 (OH) and 1625 cm^{-1} (conjugated C=O) which, along with a positive reaction with ferric chloride, were indicative of a hydroxylated dihydrochalcone. The ^1H and ^{13}C NMR spectra of **6** (see Experimental) showed resonances for a ketone [205.2 (s, C=O)], two phenolic hydroxyl groups [δ_H 9.91 (2H, br s, 3′-OH and 5′-OH, exchangeable with D_2O], three methoxyl groups [δ_H 4.09, (3H, s, 4′-OMe) and 3.85 (6H, s, 2′-OMe and 6′-OMe); δ_C 61.4 (2 × q, 2′-OMe and 6′-OMe) and 61.0 (q, 4′-OMe)], and two coupled deshielded methylene groups [δ_H 3.43 (2H, t, J = 7.8 Hz, H_2-α) and 3.02 (2H, t, J = 7.8 Hz, H_2-β); δ_C 45.7 (t, C-α) and 30.3 (t, C-β)] in addition to twelve aromatic carbons, five of which were unsubstituted [δ_H 7.27 (4H, m, H-2, H-3, H-5, H-6) and 7.20 (1H, tt, J = 2.0 and 6.9 Hz, H-4); δ_C 152.1 (s, C-4′), 151.0 (2 × s, C2′/C-6′), 141.4 (2 × s, C-3′/C-5′), 132.1 (s, C-1), 128.45 (2 × d, C-2/C-6 or C-3/C-5), 128.40 (2 × d, C-3/C-5 or C-2/C-6), 126.0 (d, C-4), and 105.1 (s, C-1′)]. The multiplicity of the most

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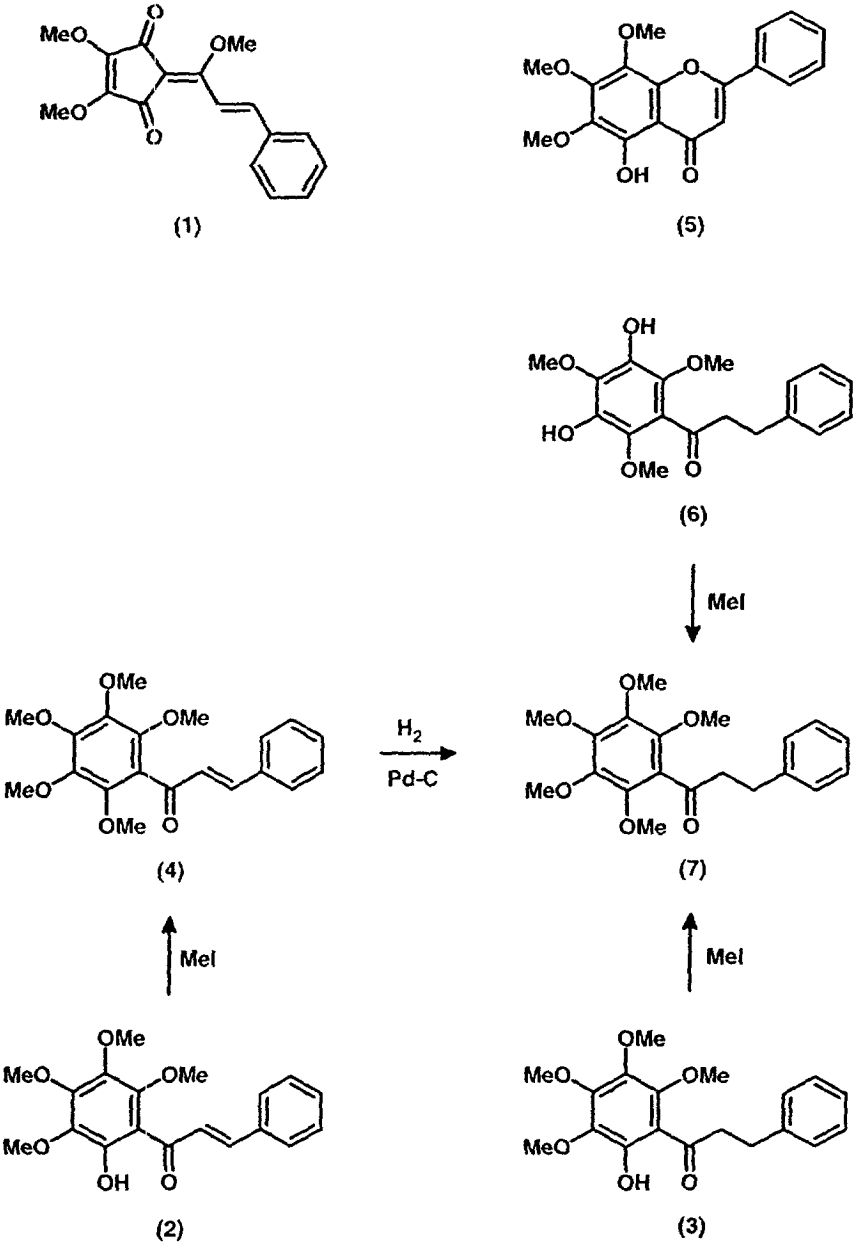

Scheme 1.

shielded aromatic proton signal revealed that the five aromatic protons were part of a phenyl group and it then followed that the second aromatic ring was symmetrically substituted by the methoxyl and phenolic hydroxyl groups. Combination of the above fragments gave a dihydrochalcone structure. The fully oxygenated ring must be conjugated with the carbonyl since α-cleavage of the carbon—C-α bond gave mass spectral fragments of *m/z* 227.0534 ($C_{10}H_{11}O_6$) and 105.0710 (C_8H_9) whilst the peak at *m/z* 91.0539 (C_7H_7) arose from cleavage of the CH_2—CH_2 bond. No chelated hydroxyl resonances were observed in the ^1H NMR spectrum, leading to structure **6** 3′,5′-dihydroxy-2′,4′,6′-trimethoxydihydrochalcone, for the compound. Methylation of **6** afforded the expected pentamethyl ether (**7**) which was also obtained by methylation of dihydrokanakugiol (**3**) and by hydrogenation of pedicellin (**4**).

EXPERIMENTAL

General

Mps: uncorr. UV: EtOH. IR: CCl_4. NMR: $CDCl_3$ relative to TMS at $\delta = 0.00$. ^{13}C multiplicities were determined using the DEPT pulse sequence. CC: silica

gel (Baker, 40 μm) or C_{18} (Bakerbond, 40 μm). HPLC: silica gel (Partisil, 5 μm, 4.6 × 250 mm) or C_{18} (Whatman ODS2, 5 μm, 4.6 × 250 mm); RI detection.

Extraction and isolation

Twigs of *Lindera lucida* were collected in the grounds of the Forest Research Institute of Malaysia. After air-drying, the ground material (450 g) was extracted with hot hexane. The crude extract (6.5 g) was chromatographed on silica gel eluting with an EtOAc–hexane step gradient to give 14 frs. Frs 7–8 (200 mg) were subjected to repeated CC (5–10% EtOAc-hexane) and HPLC (6% acetone–hexane) to give, in order of elution, **2** (5 mg) and **3** (75 mg). Frs 9–10 (1.3 g) were chromatographed (5–70% EtOAc–hexane) to give five frs, A–E. Fr. A (605 mg) was divided into two portions, A1 and A2, by CC (6% acetone–hexane). Fr. A1 afforded **4** (62.5 mg) and **5** (3.5 mg) upon reversed-phase HPLC (78% MeOH–H_2O) whilst A2 was identified as **6** (436 mg). Fr. B (204 mg) was subjected to reversed phase CC (77% MeOH–H_2O) to give **6** (141 mg) and, after HPLC (5% acetone–hexane), **5** (7.4 mg) and **1** (5.9 mg).

Methyl linderone (**1**)

Pale yellow solid, mp 75° (lit. 83–85° [10]). UV λ_{max} nm: 248, 364. IR ν_{max} cm^{-1}: 1671, 1639 (C=O), 1614, 1558, 1461 (benzene ring). EIMS *m/z* (rel. int.): 300 $[M]^+$ (68), 241 (100), 225 (26), 103 (59). HREIMS: $[M]^+$ *m/z* 300.0991 ($C_{17}H_{16}O_5$ requires *m/z* 300.0998). ^1H NMR (300 MHz): δ 7.95 (1H, d, *J* = 15.8 H-α), 7.60 (2H, dd, *J* = 7.6, 1.9 Hz, H-2 and H-6), 7.52 (1H, d, *J* = 15.8 Hz), 7.39 (3H, m, H-3, H-4 and H-5), 4.21 (3H, s, OMe), 4.20 (3H, s, OMe), 4.11 (3H, s, OMe). ^{13}C NMR (75 MHz): 187.3 (s), 184.8 (s), 165.5 (s), 149.0 (s), 147.8 (s), 141.3 (d), 135.6 (s), 130.0 (d), 128.9 (2 × d), 128.4 (2 × d), 121.2 (s), 109.5 (s), 64.3 (q), 60.0 (q), 59.9 (q).

2′-Hydroxy-3′,4′,5′,6′-tetramethoxychalcone (*kanakugiol*) (**2**)

Yellow oil [4, 5]. ^1H NMR (500 MHz): δ 13.16 (1H, s, OH-2′), 7.92 and 7.84 (2H, ABq, J_{AB} = 15.6 Hz, H-α and H-β), 7.64 (2H, m, H-2 and H-6), 7.42 (3H, m, H-3, H-4 and H-5). 4.10 (3H, s, 6′-OMe), 3.89 (6H, s, 3′-OMe and 5′-OMe), 3.86 (3H, s, 4′-OMe). UV, IR, EIMS, HREIMS data are comparable with lit. values [4, 5].

Methylation of (**2**)

The chalcone (1.0 mg) was methylated with MeI–K_2CO_3 in Me_2CO to give 2′,3′,4′,5′,6′-pentamethoxychalcone (**4**) (0.8 mg) as a pale yellow solid identical to the natural product.

2′-Hydroxy-3′,4′,5′,6′-tetramethoxydihydrochalcone (*dihydrokanakugiol*) (**3**)

Pale yellow oil [6]. UV, IR, EIMS, HREIMS, ^1H NMR comparable with lit. values [6].

Methylation of (**3**)

The dihydrochalcone (8.2 mg) was methylated with MeI–K_2CO_3 in Me_2CO. HPLC of the crude product (silica gel, 5% acetone–hexane) afforded 2′,3′,4′,5′,6′-pentamethoxydihydrochalcone (**7**) (7.0 mg) as an oil. UV λ_{max} nm: 278 and 338. IR ν_{max} cm^{-1}: 1709 (C=O), 1585, 1496, 1468 (benzene ring). EIMS *m/z* (rel. int.): 360 $[M]^+$ (100), 329 (53), 240 (44), 228 (83), 105 (26), 91 (46). HREIMS: $[M]^+$ *m/z* 360.1574 ($C_{20}H_{24}O_6$ requires *m/z* 360.1573). ^1H NMR (500 MHz): δ 7.26 (4H, m, H-2, H-3, H-5 and H-6), 7.18 (1H, br t, *J* = 7.0 Hz, H-4), 3.94 (3H, s, 4′-OMe), 3.86, 3.77 (each 6H, s, 2′-OMe, 3′-OMe, 5′-OMe and 6′-OMe), 3.09 (2H, m, H_2-α), 3.03 (2H, m, H_2-β). ^{13}C NMR (125 MHz): 202.5 (s), 148.7 (s), 145.5 (s), 143.0 (s), 141.2 (s), 128.5 (2 × d), 128.4 (2 × d), 126.0 (d), 125.8 (s), 62.1 (2 × q), 61.4 (q), 61.2 (2 × q), 46.5 (t), 29.6 (t).

2′,3′,4′,5′,6′-Pentamethoxychalcone (*pedicellin*) (**4**)

Pale yellow solid, mp 94–95° (hexane) (lit. 98° [7], 93–94° [8]). UV data identical to lit. [8]. IR ν_{max} cm^{-1}: 1654 (C=O), 1608, 1578, 1467 (benzene ring). EIMS *m/z* (rel. int.): 358 $[M]^+$ (100), 240 (22), 225 (26), 103 (59). HREIMS: $[M]^+$ *m/z* 358.1414 ($C_{20}H_{22}O_6$ requires *m/z* 358.1416). ^1H NMR (360 MHz): δ 7.53 (2H, m, H-2 and H-6), 7.36 (3H, m, H-3, H-4 and H-5), 7.35 (1H, d, *J* = 14.7 Hz, H-β), 6.99 (1H, d, *J* = 14.7 Hz, H-α), 3.98 (3H, s, 4′-OMe), 3.89, 3.80 (each 6H, s, 2′-OMe, 3′-OMe, 5′-OMe and 6′-OMe). ^{13}C NMR (90 MHz): 193.5 (s, C=O), 148.8 (s, C-4′), 146.2 (2 × s, C-2′/C-6′ or C-3′/C-5′), 145.7 (d, C-β), 143.0 (2 × s, C-3′/C-5′ or C-2′/C-6′), 134.5 (s, C-1), 130.6 (d, C-α), 128.9 (2 × d, C-2/C-6 or C-3/C-5), 128.5 (3 × d, C-4 and C-3/C-5 or C-2/C-6), 124.0 (s, C-1′), 62.0 (2 × q, OMe), 61.5 (q, 4′-OMe), 61.3 (2 × q, OMe).

Hydrogenation of (**4**)

Catalytic hydrogenation of **4** (6.5 mg) (10% Pd-C/H_2/EtOAc) gave **7** (6.2 mg).

5-Hydroxy-6,7,8-trimethoxyflavone (*alnetin*) (**5**)

Pale yellow solid, mp 101–102° (hexane) (lit. 100–101° [9]). UV λ_{max} nm: 282, 318 and 368. IR ν_{max} cm^{-1}: 3413 (OH), 1654 (C=O), 1612, 1596, 1462 (benzene ring). EIMS *m/z* (rel. int.): 328 $[M]^+$ (80), 313 (100). HREIMS: $[M]^-$ *m/z* 328.0965 ($C_{18}H_{16}O_6$ requires *m/z* 328.0947). ^1H NMR (500 MHz): δ 12.48 (1H, s, 5-OH), 7.94 (2H, dd, *J* = 8.0, 1.6 Hz, H-2′ and H-6′), 7.56 (3H, m, H-3′, H-4′ and H-5′), 6.70 (1H, s, H-3), 4.12, 3.99, 3.96 (each 3H, s, OMe). ^{13}C NMR (125

MHz): δ 183.2 (s), 164.1 (s), 153.2 (s), 149.6 (s), 145.9 (s), 136.7 (s), 133.1 (s), 132.1 (d), 131.3 (s), 129.2 (d), 126.3 (d), 107.2 (s), 105.3 (d), 62.2 (q), 61.7 (q), 61.2 (q).

3′,5′-Dihydroxy-2′,4′,6′-trimethoxydihydrochalcone (**6**)

Yellow solid, mp 108–110° (hexane). UV λ_{max} nm: 286 and 358. IR ν_{max} cm^{-1}: 3481 (OH), 1625 (C=O), 1492, 1456 (benzene ring). EIMS *m/z* (rel. int.): 332 $[M]^+$ (100), 227 $[M-PhCH_2CH_2]^+$ (72), 105 $[PhCH_2CH_2]^+$ (11), 91 (94). HREIMS: *m/z* 332.1273 ($C_{18}H_{20}O_6$ requires *m/z* 332.1260), 227.0534 ($C_{10}H_{11}O_6$ requires *m/z* 227.0556), 105.0710 (C_8H_9 requires *m/z* 105.0704), 91.0538 (C_7H_7 requires *m/z* 91.0548). ^1H (360 MHz) and ^{13}C NMR (90 MHz): see text.

Methylation of (**6**)

The dihydrochalcone (11.3 mg) was methylated with MeI–K_2CO_3 in Me_2CO. HPLC of the crude product (5% acetone–hexane) afforded **7** (8.3 mg).

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