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5,7-Dihydroxychromones and 8-hydroxytetrahydrochromones from *Horsfieldia irya*

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Abstract

Wood of *Horsfieldia irya* contained 2-*n*-nonyl- and 2-(6-phenylhexyl)-5,7-dihydroxychromone, 2-*n*-nonyl-8-hydroxy- and 2-(6-phenylhexyl)-8-hydroxy-5,6,7,8-tetrahydrochromone as well as dihydrocubebin.

Keywords: *Horsfieldia irya*; Myristicaceae; 2-Alkyl-5,7-dihydroxychromones; 2-Alkyl-8-hydroxy-5,6,7,8-tetrahydrochromones

1. Introduction

Horsfieldia (Myristicaceae) is a genus of about 80 South East Asian trees several members of which enjoy a reputation in indigenous medicine. Previous workers have reported lignans, resorcinol and phloroglucinol derivatives from various parts of *Horsfieldia glabra* (Gonzalez et al., 1988; Pinto et al., 1988) and *Horsfieldia iryaghedi* (Kitagawa et al., 1972; Gunatilaka et al., 1982; Tillekeratne et al., 1982). A bioactive flavan from *Horsfieldia amygdalina* has been mentioned in the patent literature (Yamamoto et al., 1991) and an oxindole alkaloid has been isolated from *Horsfieldia superba* (Jossang et al., 1991). More recently Sri Lankan workers have isolated 1-(2,6)-dihydroxyphenyldodecan-1-one and the lignans, asarinin and horsfieldin, as well as myristic acid and trimyristicin from the seeds of *Horsfieldia irya* (Wimalasena and Karunawansha, 1994). We now describe the isolation of two chromones **1a,b** and two 2-hydroxy-5,6,7,8-tetrahydrochromones **2a,b** as well as the lignan, dihydrocubebin, from the wood of *H. irya* whose bark and leaves are used in Thai popular medicine to treat intestinal infections. The bark is also used as a remedy for sores and pimples.

2. Results and discussion

The MeOH extract of the wood on concentration and extraction with $CHCl_3$ followed by column and thin layer chromatography of the $CHCl_3$ extract afforded five substances one of which was dihydrocubebin previously found in extracts of *H. iryaghedi* (Tillekeratne et al., 1982) and *H. glabra* (Pinto et al., 1988). Two others were the 2-alkyl-5,7-dihydroxychromones **1a** and **1b** as deduced from the mass, IR and UV spectra and the ^1H and ^{13}C NMR spectroscopic data listed in the Experimental section, the assignments being based on decoupling, HMBC and COSY experiments. Although chromones have not previously been reported from *Horsfieldia* species **1a** and **1b** are presumably formed by cyclization of the corresponding acylphloroglucinol derivatives. Oliver et al. (1987) have described both **1a** and **1b** and its precursor phloroglucinol derivatives as components of a mixture of phenolic acetogenins secreted by the *Rhododendron* lace

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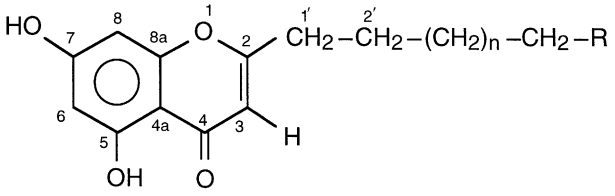

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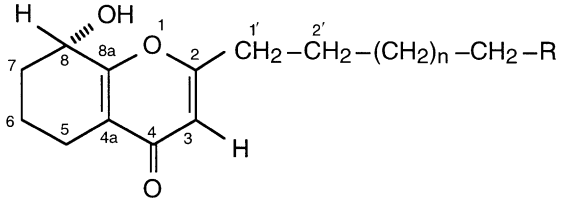
b n = 3, R = phenyl



2 a n = 5, R = CH_3
b n = 3, R = phenyl

bug and have prepared **1a** by cyclization of the corresponding phloroglucinol although it was not characterized by NMR spectrometry.

A second pair of constituents consisted of the two optically active 2-alkyl-8-hydroxytetrahydrochromones **2a** and **2b**. The location of the hydroxyl groups at C-8 of the aromatic rings could be inferred from the IR and NMR spectra (see Experimental) which indicated absence of hydrogen bonding between the hydroxyl and carbonyl groups, thus excluding location of the hydroxyl at C-5 as did the failure of the UV spectra to undergo shifts on addition of $AlCl_3$ and, in both instances, from the multiplicity of the signal of the proton under the hydroxyl group which excluded location of the latter at C-6 or C-7. Additional support for the location of the hydroxyl group at C-8 in **2a**,**b** was provided by the HMBC correlations shown in Figs. 1 and 2. In the case of **2a**, the presence of cross peaks between the proton under the hydroxyl and C-4a, C-6, C-7 and C-8, but not with C-4, again excluded location of the hydroxyl at C-6 or C-7. Unequivocal assignment of C-2, C-3 and C-2′ was made possible by cross peaks between H-1′ at δ 2.48 with C-2 at δ 169.38 and C-3 at δ 112.71 while in turn H-3 at δ 6.11 gave cross peaks with C-1′, C-4a, C-8a and, surprisingly, weak cross peaks with C-1 and C-8. In the case of **2b** the correspondence of chemical shifts with those in **2a** and the correlations shown in Fig. 2b again excluded all positions but C-8 for location of the hydroxyl group whose absolute configuration remains in question.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded at ambient temp on a Bruker AMC instrument operating at 300.13 and 75.47 MHz respectively. EI mass spectra were measured on a Hitachi Perkin-Elmer RMV-6M instrument. For HRMS samples were run using + FAB ionization with Xe gas at 6 KV on a Kratos Concept III, 2 sector mass spectrometer. The accelerating voltage was 8 KV. Rotations were determined using a Polarotronic Universal Schmidt and Haensch polarimeter. Si gel for chromatography was Si gel 60 (0.2–0.5 mm) Merck, for analytical and preparative TLC Si gel G-60 GF 254 Merck.

3.2. Plant material

H. irya (Gaertn.) Warb. (Myristicaceae) was collected from Nonthaburi, Thailand in August 2000. A voucher of the specimen was deposited at the Department of Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

3.3. Extraction and isolation

Dried powdered wood (2 kg) of *H. irya* was percolated by MeOH to exhaustion (8 l). Evaporation of the methanolic solution at reduced pressure gave 350 g of crude viscous MeOH extract (350 g) which was reextracted using $CHCl_3$ with the aid of an ultrasound bath. Evaporation of the $CHCl_3$ extract at reduced pressure

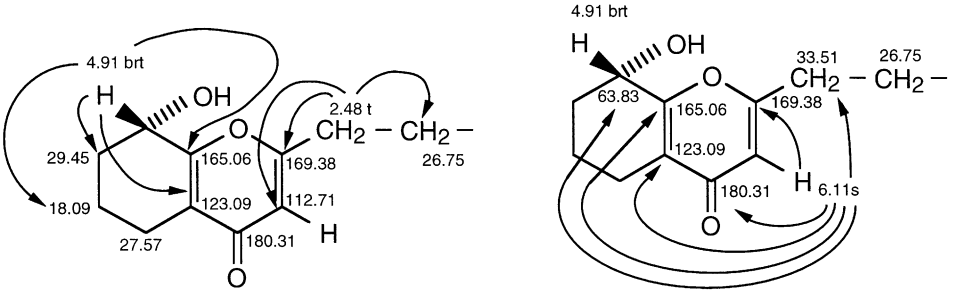


Fig. 1. HMBC correlations in **2a**.

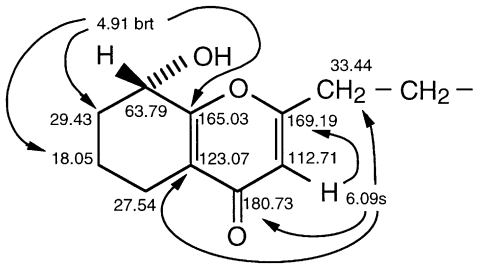


Fig. 2. HMBC correlations in **2b**.

furnished a syrupy $CHCl_3$ extract (13.6 g). The latter (13.4 g) was applied to a silica gel 60 column (450 g) and eluted with petrol–$CHCl_3$ and $CHCl_3$–$(CH_3)_2O$, with 250 ml fractions being collected as follows: Frs. 1–28 (petrol–$CHCl_3$, 9:1), 29–55 (petrol–$CHCl_3$, 4:1), 56–124 (petrol–$CHCl_3$, 3:2), 125–151 (petrol–$CHCl_3$, 1:1), 152–212 (petrol–$CHCl_3$, 3:7), 213–230 (petrol–$CHCl_3$, 1:9), 231–242 ($CHCl_3$), 243–291 ($CHCl_3$–$(CH_3)_2O$, 9:1). Frs. 121–177 (1.1 g) were combined and purified by TLC (Si gel, petrol–EtOAc–HCO_2H, 7:3:0.1) to give **1** (27 mg) and **1b** (23 mg). Frs. 178–267 were combined, applied to a Si gel 60 column (50 g) and eluted with petrol–$CHCl_3$ and $CHCl_3$–$(CH_3)_2O$, 50 ml subfrs being collected as follows: Sbfrs. 1–22 (petrol–$CHCl_3$, 4:1), 23–112 (petrol–$CHCl_3$, 3:2), 113–152 (petrol–$CHCl_3$, 1:1), 154–182 (petrol–$CHCl_3$, 2:3), 183–203 (petrol–$CHCl_3$, 3:7), 204–228 (petrol–$CHCl_3$, 1:4), 229–254 ($CHCl_3$), 255–272 ($CHCl_3$–Me_2O, 9:1). Subfrs. 104–138 (116 mg) were combined and purified by TLC (Si gel, petrol–EtOAc–HCOOH, 7:3:0.1) to give **2a** (15 mg) and a mixture of **1a** and **1b** (21 mg) which on resubmission to TLC by the same procedure furnished additional amounts of **1a** (5 mg) and **1b** (9 mg). Subfrs. 139–168 (95 mg) were combined and purified by TLC (Si gel, petrol–EtOAc–HCO_2H, 7:3:0.1) to give **2b** (12 mg). Sbfrs. 203–256 (160 mg) were combined and purified by TLC (Si gel, petrol-EtOAc-HCOOH, 3:2:0.1) to give 65 mg of dihydrocubebin identified by ^1H and ^{13}C NMR spectrometry and MS (Pinto et al., 1988).

3.4. 5,7-Dihydroxy-2-n-nonylchromen-4-one (*1a*)

Gum, EI MS *m/z* (%): 304 (M^+, 94), 205 (100), 192 (55), 153 (54), 124 (42), 69 (47); HRMS + FAB 304.16752, $C_{18}H_{24}O_4$ requires 304.16746; ^1H NMR δ: 12.77 (*s*, 5-OH), 6.33 (*brs*, H-6), 6.26 (*brs*, H-8), 6.03 (*s*, H-3), 2.57 (2p, *t*, $J = 7.2$ Hz, H-1′), 1.69 (2p, *m*, H-2′), 1.61 (2p, *brs*, H-3′), 1.34 *m*, 1.27 *brs*, 1.25 *brs* (8p, H-4′- H-8′), 0.88 (3p, *t*, $J = 6.9$ Hz, H-9′), ^{13}C NMR δ 182.57 (C-4), 170.63 (C-2), 162.41 (C-5), 161.87 (C-8a), 158.24 (C-7) 107.94 (C3), 105.34 (C-4a), 99.17 (C-6), 93.99 (C-8), 34.17 (C-1′), 31.82, 29.69, 29.38, 29.23, 28.93 (C-3′- C-7′), 26.73 (C-2′), 22.64 (C-8′), 14.10 (C-9′).

3.5. 5,7-Dihydroxy-2-(6-phenylhexyl)-chromen-4-one (*1b*)

Mp 138–140 °C (from $CHCl_3$); EI MS *m/z* (%): 338 (M^+, 75), 247 (20), 205 (100), 192 (25), 163 (15), 91 (60); HRMS + FAB 338.15184, $C_{21}H_{24}O_4$ requires 338.15183; IR (KBr) ν cm^{-1}: 3849, 3801, 3674, 3626, 2916, 2629, 1655, 1620, 1558, 1496, 1462, 1348, 1315, 1188, 1014, 837; UV (MeOH) λ_{max} nm (log ε): 204 (4.2), 248 (3.9) 295 (3.6); UV (MeOH + NaOH) λ_{max} nm (log ε): 214 (4.6), 264 (3.9), 341 (3.7); UV (MeOH + $AlCl_3$) λ_{max} nm (log ε): 205 (4.3) 255 (3.9), 310 (3.6); UV (MeOH + $AlCl_3$ + HCl)) λ_{max} nm (log ε): 205 (4.3), 255 (3.9), 310 (3.6). ^1H NMR δ 12.64 (5-OH), 7.19 (2p, *t*, $J = 7.9$ Hz, H-3″, 5″), 7.11*t*, $J = 7.9$ Hz, H-4″), 7.10 (2p, *d*, $J = 7.9$ Hz, H-2″, 6″), 6.41 *brs*, 7-OH), 6.23 (*brs*, H-6), 6.20 (*brs*, H-8), 5.95 (*s*, H-3), 2.54 (2p, *t*, $J = 7.4$ Hz, H-6′), 2.49 (2p, *t*, $J = 7.7$ Hz, H-1′), 1.5–1.7 (4p, *m*, H-3′, 5′),1.2–1.4 (4p, *m*, H-2′, 4′); ^{13}C NMR δ: 182.58 (C-4), 170.11 (C-2), 162.36 (C-5), 158.26 (C-7) 142.50 (C-1″), 128.37 (C-2″, 6″), 125.67 (C-4″), 107.89 (C-3), 105.25 (C-4a), 99.26 (C-6), 94.05 (C-8), 35.82 (C-6′), 31.20 (C-5′), 29.69, 28.80 (C-2′, C-4′), 26.64 (C-3′).

3.6. 8-Hydroxy-2-n-nonyl-5,6,7,8-tetrahydrochromone (*2a*)

Gum, $[\alpha]_D$ +42.2° ($c = 0.0043$ g/ml, $CHCl_3$); EI MS *m/z* 292 (M^+, 55), 291 (80), 264 (80), 236 (75), 221 (20), 165 (100), 152 (40), 137 (40); HRMS + FAB 292.203.82, $C_{18}H_{28}O_3$ requires 292.20385; IR (KBr) ν cm^{-1}: 3425, 2926, 2854, 2362, 1660, 1608, 1435, 1173, 1082, 949, 856; UV (MeOH) λ_{max} nm (log ε): 214 (4.1), 251 (3.9); UV (MeOH + $AlCl_3$), λ_{max} nm (log ε): 213 (4.1), 251 (3.9): ^1H NMR ($CDCl_3$) δ: 6.11 (*s*, H-3), 4.91 (brt, H-8), 4.60 (*br*, 8-OH), 2.52–2.70 (*c*, H-5a,b), 2.48 (2p, *t* $J = 7.7$ Hz, H-1′a,b), 2.05 (*c*, 2p) and 1.75 (c, 2p−H-6a,b and H-7a,b), 1.63 (sp, *q*, $J = 7.4$ Hz, H-2′a,b), 1.27–1.31 (14p, *c*, H-3′-H-7″), 0.88 (3p, *t* $J = 6.4$ Hz, H-9′) ^{13}C NMR δ: 180.81 (C-4), 169.38 (C-2), 165.06 (C-8a), 123.09 (C-4a), 112.71 (C-3), 63.83 (C-8), 33.51 (C-1′), 31.78 (C-7′), 29.45 (C-7), 29.34, 29.18, 29.17, 28.83 (C-3′-C-6′), 27.57 (C-5), 26.75 (C-2′), 22.60 (C-8′), 18.09 (C-6), 14.06 (C-9′).

3.7. 8-Hydroxy-2-(6′-phenylhexyl)-5,6,7,8-tetrahydrochromone (*2b*)

Gum, $[\alpha]_D$ +60° ($c = 0.0023$ g/ml, $CHCCl_3$); EI MS *m/z* 326 (M^+, 100) 298 (15), 270 (20), 207 (15), 165 (60), 137 (20), 109 (15), 91 (50); HRMS + FAB 326.18810, $C_{21}H_{26}O_3$ requires 326.18819; IR (KBr) ν cm^{-1}: 3444, 2920, 2852, 2362, 2337, 1657, 1618, 1558, 1460, 1427, 1350, 1163, 744, 698; UV (MeOH), λ_{max} nm (log ε): 207 (3.8), 250 (3.8); UV (MeOH + NaOH),), λ_{max} nm (log ε): 217 94.0), 250 (3.6); UV (MeOH + $AlCl_3$), λ_{max} nm (log ε): 206 (3.9), 251 (3.7); UV (MeOH + $AlCl_3$ + HCl), λ_{max}

nm (log ε): 206 (3.7), 250 (3.6). ^{1}H NMR ($CDCl_3$) δ: 7.28 (2p, *t*, $J=7.8$ Hz, H-3″, 5″), 7.18 (*m*, 3p, H-2″, 4″, 6″), 6.09 (*s*, H-3) 4.91 (*brt*, H-8), 4.47 (*br*, OH), 2.61 (2p, *t*, $J=7.8$ Hz, H-6′), 2.47 (2p, *t*, $J=7.8$ Hz, H-6′), 2.47 (2p, *t*, $J=7.7$ Hz, H-1′), 2.52 (2p, *c*, H-5a,b), 1.62 (*c*, 4p, H-2′, 5′), 1.36 (4p, *d*, $J=7$ Hz, H-3′, 4′),; ^{13}C NMR δ: 180.73 (C-4), 169.19 (C-2), 165.03 (C-8a), 142.43 (C-1′), 128.29 (C-2″, 6″), 128.19 (C-3″, 5″), 125.60 (C-4″), 123.07 (C-4a), 112.71 (C-3), 63.79 (C-8), 35.76 (C-6′), 33.44 (C-1′), 31.15 (C-5′), 29.43 (C-7), 28.73 and 28.67 (C-3′,4′), 27.54 (C-5), 26.63 (C-2′), 18.05 (C-6).

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