A New Prenylated Flavone from *Artocarpus champeden*

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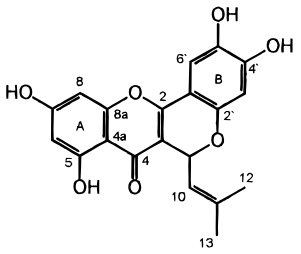
Received February 28, 1996[⊗]

A new prenylated flavone, named cyclochampedol (**1**), together with four known triterpenes—cycloeucalenol, glutinol, cycloartenone, and 24-methylenecycloartanone—as well as β-sitosterol were isolated from *Artocarpus champeden*. The structure of the new compound was determined on the basis of spectral evidence and by comparison with known related compounds. Compound **1** is active in the brine shrimp lethality assay.

In the Indonesian indigenous system of medicine, several *Artocarpus* plants (Moraceae) such as *A. communis* and *A. elastica* have established use, while the fruits of *A. champeden* Spreng (Moraceae) are eaten as a staple food and its wood is used commercially as timber.[1] As part of our continuing investigation of Indonesian tropical plants,[2,3] we now report the isolation of a new prenylated flavone, together with the known triterpenes, cycloeucalenol,[4,5] glutinol,[6] a mixture of cycloartenone[7] and 24-methylenecycloartanone,[8] and the sterol, β-sitosterol, from the tree bark of *A. champeden*, an endemic species found throughout the Indonesian archipelago. The structure of the new compound **1**, named cyclochampedol, was determined on the basis of spectroscopic evidence.



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The dried, powdered tree bark of *A. champeden* was extracted with hexane and then with Me_2CO. The $CHCl_3$-soluble portion of the Me_2CO extract was fractionated by vacuum−liquid chromatography (VLC) to give a number of fractions that contained a major compound. Repeated flash chromatography of the combined fractions yielded cyclochampedol (**1**) as yellow crystals, mp 205−206 °C. The HRFABMS gave an $[MH]^+$ ion at *m/z* 369.0979 (calcd 369.0975) consistent with a molecular formula of $C_{20}H_{16}O_7$. The IR spectrum showed absorptions for hydroxyl (3568 cm^{-1}) and conjugated carbonyl (1701, 1626 cm^{-1}) functionalities and the UV spectrum [269 nm (log ϵ 4.42), 315 (3.98), 399 (4.29)] was consistent with the presence of a flavone structure. The ^{1}H-NMR spectrum included signals for an isoprenyl group (δ 1.65, 1.89, each a doublet, J = 1.2 Hz) in which the vinylic proton (δ 5.39, br d, J = 9.5 Hz) was coupled to a benzylic oxymethine (δ 6.05, d, J = 9.5 Hz), similar to the arrangement found for a related compound, cyclocommunol.[9] The remaining signals in the ^{1}H-NMR spectrum indicated the presence of two meta-coupled protons, consistent with a 5,7-dihydroxy substitution of the A-ring,[10] and two uncoupled protons in accord with a 1,2,4,5-tetrasubstituted B-ring.[11] HMBC measurements allowed the quaternary carbons observed at δ 153.1 and 141.9 to be assigned to C-4′ and C-5′, respectively. Supporting evidence for the structure assigned to cyclochampedol (**1**) came from comparison of the ^{13}C-NMR spectrum, assigned with the aid of HMQC and HMBC measurements, to those reported for the related compounds cyclocommunol[9] and cycloaltilisin,[11] and from UV and MS data[12] (see Experimental Section). Cyclochampedol (**1**) is active (LC_{50} 15.1 μg/mL) in the *Artemia salina* shrimp bioassay,[13] suggesting that it is comparable to other prenylated flavonoids isolated from *A. communis*, which have been reported to exhibit strong cytotoxic activity.[14]

Experimental Section

General Experimental Procedures. All melting points were determined on a micro-melting point apparatus and are uncorrected. UV and IR spectra were measured with Beckman DU-7000 and Shimadzu FT-IR 8501 spectrophotometers, respectively. ^{1}H- and ^{13}C-NMR spectra were recorded with either a Bruker AM 300 spectrometer, operating at 300.1 MHz (^{1}H-) and 75.4 MHz (^{13}C-), or a JEOL JNM A5000 spectrometer, operating at 500 MHz (^{1}H-) and 125.6 MHz (^{13}C-), using TMS as an internal standard. MS were obtained with either a VG Autospec mass spectrometer using the EI mode (8000 V) or a JMS-HM20 mass spectrometer. VLC was carried out using Merck Si gel 60 GF_{254}, flash chromatography with Merck Si gel 60 (230−400 mesh), and TLC analysis on precoated Si gel plates (Merck Kieselgel 60 F254, 0.25 mm).

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[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

S0163-3864(96)00330-8 CCC: $12.00

Plant Material. Samples of the tree bark of *A. champeden* were collected in July, 1994, from plantation trees growing in Bogor District, West Java, Indonesia. The plant was identified by staff at the Herbarium Bogoriense, Bogor Botanical Garden, Bogor, Indonesia, and a voucher specimen has been deposited at the herbarium.

Extraction and Isolation. The milled, dried bark (0.96 kg) was extracted exhaustively with hexane and then with Me_2CO. The Me_2CO extract, on removal of solvent under reduced pressure, gave a light brown residue (42.0 g, 4.4%). The residue was solubilized in a mixture of H_2O-Me_2CO (75:25), and the soluble portion extracted with $CHCl_3$. A portion (7 g) of the total $CHCl_3$ extract (32 g) was fractionated by Si gel VLC (95 g, 6.5 × 7.5 cm, $CHCl_3$, $CHCl_3$−EtOAc, EtOAc, EtOAc−Me_2CO, Me_2CO, in order of increasing polarity) to give 35 fractions. This chromatographic step was repeated five times on portions of 5 g each of the $CHCl_3$ extract. Nine fractions were ultimately obtained on combining the eluates on the basis of TLC. The sixth fraction (2.1 g) was further fractionated by Si gel VLC (44 g, 4.5 × 5.5 cm, hexane, hexane−EtOAc, EtOAc, in order of increasing polarity) to afford 75 fractions. From fractions 29−34 a precipitate was obtained (180 mg), which was further purified by Si gel flash chromatography [29 g, 2.5 × 15 cm, $CHCl_3$−MeOH (93:7)] to yield a crude compound (75 mg), which was crystallized from $CHCl_3$−MeOH to afford cyclochampedol (**1**) (11 mg). Using the same methods, five known compounds were identified from the hexane extract: cycloeucalenol,[4,5] glutinol,[6] cycloartenone,[7] 24-methylenecycloartanone[8] and β-sitosterol.

Cyclochampedol (1): obtained as yellow crystals; mp 205−206 °C; $[\alpha]^{25}_D$ +141.6° (*c* 0.12, MeOH); IR (KBr) ν max 3568 (OH), 1701 (C=O, ketone), 1626, 1599, 1512, 1454 cm^{-1}; UV (MeOH) λ max (log ϵ) 212 (4.64), 269 (4.42), 315 (sh, 3.98), 399 (4.29) nm; (MeOH + NaOH) 214 (4.99), 276 (4.49), 305 (sh, 4.25), 315 (sh, 4.26), 4.38 (4.54) nm; (MeOH + $AlCl_3$) 212 (4.68), 278 (4.33), 303 (sh, 3.98), 338 (sh, 3.91), 470 (4.43) nm; (MeOH + NaOAc) 214 (4.87), 270 (4.36), 421 (4.33) nm; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.09 (1H, s, H-6′), 6.33 (1H, d, J = 2.2 Hz, H-8), 6.30 (1H, s, H-3′), 6.12 (1H, d, J = 2.2 Hz, H-6), 6.05 (1H, d, J = 9.5 Hz, H-9), 5.39 (1H, br d, J = 9.5 Hz, H-10), 1.89 (3H, d, J = 1.2 Hz, Me-12), 1.65 (3H, d, J = 1.2 Hz, Me-13); ^{13}C NMR (CD_3OD, 125.6 MHz) δ 179.5 (s, C-4), 165.4 (s, C-7), 163.3 (s, C-8a), 158.6 (s, C-5), 157.6 (s, C-2), 153.1 (s, C-4′), 152.5 (s, C-2′), 141.9 (s, C-5′), 139.5 (s, C-11), 122.4 (d, C-10), 110.5 (s, C-3), 109.9 (d, C-6′), 107.8 (s, C-1′), 105.6 (s, C-4a), 105.4 (d, C-3′), 99.9 (d, C-6), 95.0 (d, C-8), 70.2 (d, C-9), 26.0 (q, C-13), 18.7 (q, C-12); EIMS *m/z* $[M]^+$ 368 (16), 353 (22), 313 (38), 153 (13), 69 (16), 56 (67), 41 (100); HRFABMS (glycerol) *m/z* $[MH]^+$ 369.0979 (calcd for $C_{20}H_{17}O_7$, 369.0975).

Biological Evaluation. Compound **1** exhibited an LC_{50} of 15.1 μg/mL when evaluated in the brine shrimp lethality assay as described by Meyer *et al.*[13]

Acknowledgment. This work was supported by a grant from the National Research Council, Ministry for Research and Technology, Republic of Indonesia, awarded to E.H.H. We also thank the Herbarium Bogoriense, Bogor, Indonesia, for help in identification of the plant specimen.

References and Notes

(1) Heyne, K. *The Useful Indonesian Plants*; Research and Development Agency, Ministry of Forestry: Jakarta, Indonesia, 1987; p 668.
(2) Achmad, S. A.; Ghisalberti, E. L.; Hakim, E. H.; Makmur, L.; Manurung, M. *Phytochemistry* **1992**, *31*, 2153−2154.
(3) Hakim, E. H.; Achmad, S. A.; Effendy; Ghisalberti, E. L.; Hockless, D. C. R.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 1355−1362.
(4) Kocor, M.; St. Pyrek, J. *J. Org. Chem.* **1973**, *38*, 3688−3690.
(5) Conner, A. H.; Foster, D. O. *Phytochemistry* **1981**, *20*, 2543−2546.
(6) Matsunaga, S.; Tanaka, R.; Akagi, M. *Phytochemistry* **1988**, *27*, 535−537.
(7) Pavanasasivam, G.; Sultanbawa, M. U. S. *Phytochemistry* **1973**, *12*, 2725−2726.
(8) Schulte, K. E.; Rucker, G.; Matern, H. U. *Planta Med.* **1979**, *35*, 76−83.
(9) Lin, C. N.; Shieh, W. L. *Phytochemistry* **1992**, *31*, 2922−2924.
(10) Nomura, T.; Fukai, T.; Katayanagi, M. *Chem. Pharm. Bull.* **1978**, *26*, 1453−1458.
(11) Chen, C. C.; Huang, Y. L.; Ou, J. C.; Lin, C. F.; Pan, T. M. *J. Nat. Prod.* **1993**, *56*, 1594−1597.
(12) Nomura, T.; Fukai, T.; Yamada, S.; Katayanagi, M. *Chem. Pharm. Bull.* **1978**, *26*, 1394−1402.
(13) Meyer, N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, D. E.; Nichols, D. E.; McLaughlin, J. L. *Planta Med.* **1982**, *45*, 31−34.
(14) Fujimoto, Y.; Zhang, X. X.; Kirisawa, M.; Uzawa, J.; Sumatra, M. *Chem. Pharm. Bull.* **1990**, *38*, 1787−1789.

NP960330Q