Isolation and X-Ray Structure Determination of a Novel Pyrimidinone from *Aglaia odorata*

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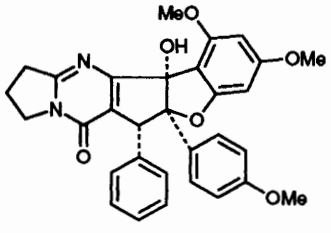
A new pyrimidinone has been isolated from the Thai medicinal plant *Aglaia odorata* Lour., and its structure elucidated by X-ray crystallography and NMR spectroscopy; the results reveal a unique structural backbone of fused five- and six-membered rings.

Aglaia odorata Lour., a traditional medicinal plant found in Thailand, Malaysia, China and the Philippines, is a shrubby tree of the Meliaceae family.[1] Aqueous extracts from the leaves and roots have found use in herbal medicine as an emetic, heart stimulant, febrifuge and decongestant. Several novel, naturally occurring substances have been isolated from *A. odorata*,[2–10] and the cytostatic activity of one of these has been reported. Further investigation of extracts from the dried plant roots has led to the isolation of a novel product reported here, with a particularly unusual backbone of fused five- and six-membered rings.

Extraction of 3.8 kg of the dried, ground roots of *A. odorata* with methanol gave 355 g of a red-brown material. After prior extraction with hexane, this crude residue was further extracted with dichloromethane to yield 23.5 g of material which was chromatographed on silica. Elution was performed beginning with hexane, progressing through dichloromethane–hexane mixtures to dichloromethane, and thence to dichloromethane–methanol mixtures. Early fractions yielded the steroids compesterol, β-sitosterol, stigmasterol, compesteryl-3-*O*-glucopyranoside, β-sitosteryl-3-*O*-glucopyranoside, stigmasteryl-3-*O*-glucopyranoside along with a mixture of saturated long-chain alcohols (C_{24}–C_{28}). A fraction consisting of a single product, compound **1**, was obtained from the dichloromethane–methanol eluent.



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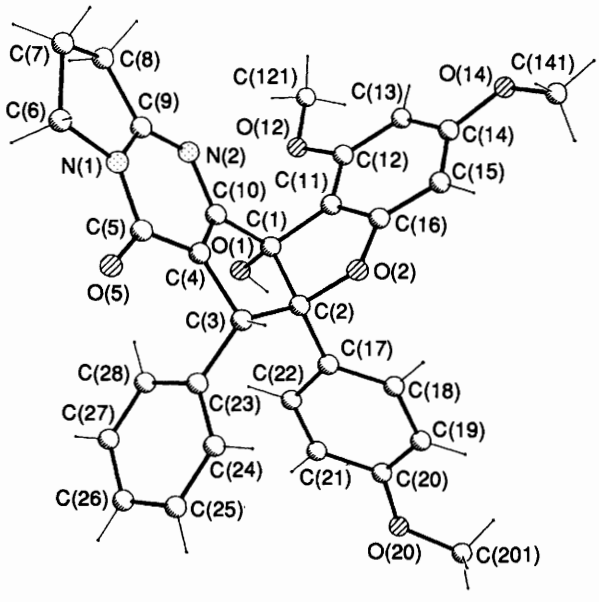
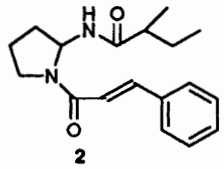


Crystallisation of compound **1** from CH_2Cl_2–MeOH gave colourless plates. Analytical data and high-resolution mass spectroscopy confirmed the formulation $C_{31}H_{28}N_2O_6$.† The X-ray crystal structure solution‡ revealed the novel fusion of five- and six-membered rings shown in Fig. 1, with the OH substituent and the O atom of the cyclic ether in the positions shown. Bond lengths within the six-membered rings C(11)–C(16), C(17)–C(22) C(23)–C(28) are entirely consistent with all-carbon aromatic ring systems. The *p*-methoxyphenyl substituent at C(2) is reflected in the observation of doublets at δ 6.55 and 7.09 (*J* 9 Hz) in the ^{1}H NMR spectrum. Doublets at δ 6.04 and 6.19 correlate to the *meta*-related methoxyl peaks (δ 3.83 and 3.78 respectively) in the COSY spectrum, in accordance with the observed substitution pattern in the C(11)–C(16) aromatic ring. The monosubstituted benzene ring C(23)–C(28) gives rise to two further multiplets in the aromatic region a 3H peak at δ 7.06 and a 2H peak at δ 6.89. An appropriate COSY correlation is again observed.

Assignment of the linear sequence of CH_2 groups at C(6), C(7) and C(8) was supported by the observation of peaks in appropriate positions for H atoms in a difference-Fourier map and by the ^{1}H and COSY spectra. Similar support was obtained for the methine H atom at C(3), with a 1H singlet at δ 4.69 in the ^{1}H NMR spectrum. The alternative singlet proton resonance at δ 3.34 is removed by exchange with D_2O and may be assigned to the OH proton signal.

The two nitrogen atoms required by the analytical data and the high-resolution mass spectrum would thus appear to be in the same ring as the carbonyl grouping. One must be between C(9) and C(10) as there are no unaccounted for low-field signals in the ^{1}H NMR spectrum and no evidence for additional electron density close to the N(2) atom in the final difference-Fourier map. The IR spectrum suggests a conjugated amide (ν_{max} 1670 cm^{-1}), thus the remaining nitrogen could be at C(4) or between C(5) and C(6). Molecular modelling (PCMODEL-P1)[13] gives bond length data for the latter structure, Fig. 1, which matches the observed X-ray data much more closely than the alternative. Furthermore least-



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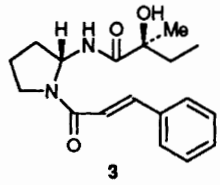

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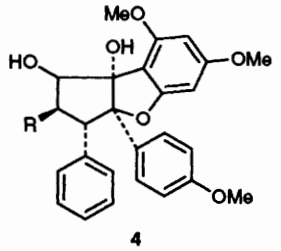

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R = $CONMe_2$, CONHMe, CO_2Me or H

squares refinement with C(4) and N(1) transposed gave a significant increase in the conventional R index which lends further weight to the assignment of the final structure detailed in Fig. 1. Strong IR absorptions at ν_{max} 1670, 1600, 1500 cm^{-1} are also consistent with a pyrimidinone ring system. Comparison of the ^1H NMR data with those reported for desoxyvasicinone,[14] which has a comparable cyclopentapyrimidinone ring system, shows excellent agreement for the methylene proton multiplets (δ 2.25, 3.20, 4.09 for **1**; 2.26, 3.14 4.17 for desoxyvasicinone).

In accordance with the proposed structure, the ^{13}C NMR spectrum showed 27 distinct peaks. The chemical shifts of the methylene carbon resonances (δ 19.4, 32.7, 46.7) also matched those of desoxyvasicinone[14] (19.4, 32.3, 46.3).

Structure **1** encapsulates features of some previously identified metabolites of *A. odorata*. Odorine **2** and odorinol **3**[3,5] both possess the azole ring system found in **1**, and have the requisite components in the side chains to assemble the pyrimidinone unit. The substituted 1*H*-cyclopentatetrahydro[*b*]benzofurans **4** have been reported recently[10] and a crystal structure obtained for one of them.[15] Clearly these contain the components of the remainder of **1**.

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Footnotes

† Mp 256–257 °C. IR ν_{max}/cm^{-1} 3400 (OH); 1670, 1600, 1530, 1500 (pyrimidone) NMR ^1H, δ 2.25 (m, $W_{\frac{1}{2}}$ 60, 2H), 3.20 (m, $W_{\frac{1}{2}}$ 66, 2H), 3.34 (s, 1H, exchanges with D_2O), 3.65 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 4.09 (m, $W_{\frac{1}{2}}$ 50, 2H), 4.69 (s, 1H), 6.04 (d, J 2, 1H), 6.19 (d, J 2, 1H), 6.55 (d, J 9, 2H), 6.89 (m, $W_{\frac{1}{2}}$ 10, 2H), 7.06 (m, $W_{\frac{1}{2}}$ 13, 3H) 7.08 (d, J 9 Hz, 2H); ^{13}C δ 19.4 (CH_2), 32.7 (CH_2), 46.7 (CH_2), 54.9 (OCH_3), 55.5 (OCH_3), 55.6 (OCH_3), 56.9 (CH), 89.0 (CH), 90.3 (C), 92.6 (CH), 103.6 (C), 107.2 (C), 112.2 (2 × CH), 121.4 (C), 126.7 (CH), 127.0 (C), 127.6 (2 × CH), 128.9 (2 × CH), 129.2 (2 × CH), 136.9 (C), 158.0 (C), 158.6 (C), 159.0 (C), 160.8 (C), 163.4 (C), 166.0 (C), 166.7 (C). MS *m/z* 524.1947; $C_{31}H_{28}N_2O_6$ requires 524.1947.

‡ *Crystal data* for **1**: $C_{31}H_{28}N_2O_6 \cdot CHCl_3$, M 643.92, orthorhombic space group $P2_12_12_1$ (no. 19), a = 10.200(11), b = 10.842(2), c = 27.282(9) Å; U = 3017(3) $Å^3$, D_c = 1.418 gm cm^{-3}, Z = 4, $F(000)$ = 1336, λ = 0.71069 Å, μ(Mo-Kα) = 0.35 mm^{-1}, T = 295(2) K. 3035 Measured reflections, 3008 unique of which 3003 were employed in the refinement, $2\theta_{max}$ = 25°, $R(\Sigma|F_o| - |F_c|/\Sigma|F_o|) = 0.062$ ($F > 2\sigma F$, 1465 reflections), and $wR2 = [\Sigma w(F_o^2\text{-}F_c^2)^2/\Sigma wF_o^4]^{\frac{1}{2}} = 0.204$ (all data), S = 1.009, $w^{-1} = \sigma^2(F_o^2) = (0.198P)^2 + 2.03P$, and $P = (F_o^2 + 2F_c^2)/3$. Residual electron density, max = 0.29, min = −0.33 e $Å^{-3}$.

Data were collected on a CAD4 diffractometer using graphite-monochromated Mo-Kα radiation. The structures were solved by direct methods using SHELXS-86.[11] The O, N, methyl, C atoms and the Cl atoms of the $CHCl_3$ solvate were refined anisotropically, other C atoms were refined isotropically by full-matrix least squares based on F^2 with SHELXL-93.[12] Hydrogen atoms were input in calculated positions, with fixed, isotropic thermal parameters. The $CHCl_3$ solvate showed evidence of positional disorder and two distinct Cl atom positions were found for Cl(1). High and increasing temperature factors for the Cl atoms indicated that the disorder was not fully resolved which contributes to the relatively high residual observed in the final refinement. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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