

SHORT REPORTS

CINNAMAMIDE DERIVATIVES FROM *CLAUSENA LANSIUM*

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Key Word Index—*Clausena lansium*; Rutaceae; cinnamamide; lansiumamides; lansamide-I; cinnamic acid derivative.

Abstract—From the ether extract of the seeds of *Clausena lansium*, three new amide derivatives have been isolated, and their structures elucidated by chemical and spectroscopic methods. They were shown to be *N*-*cis*-styryl-cinnamamide, *N*-methyl-*N*-*cis*-styryl-cinnamamide and *N*-methyl-*N*-phenethyl-cinnamamide, which we have named lansiumamides A, B and C, respectively. In addition, a known amide, lansamide-I was identified.

INTRODUCTION

Clausena lansium Skeels, grows in the southern area of mainland China and is cultivated in Taiwan. The leaves have been used as a folk medicine for the treatment of coughs, asthma and gastro-intestinal diseases, while the fruits are used for digestive disorders, and the seeds for gastro-intestinal diseases such as acute and chronic gastro-intestinal inflammation, ulcers, etc. [1].

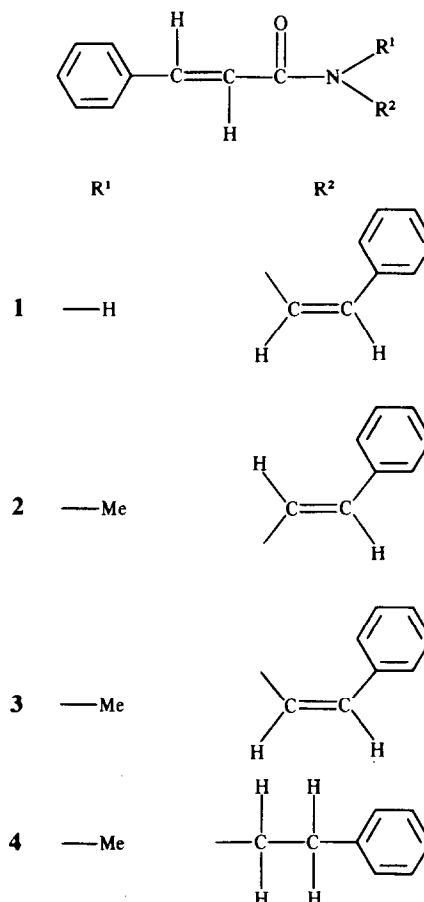
β -Sitosterol, heptaphylline, lansamide-I (*N*-methyl-*N*-styryl-cinnamamide), lansine (3-formyl-2-hydroxy-6-methylcarbazole) and three novel cyclic amides, clausenamide, neoclausenamide and cycloclausenamide, have been isolated from the leaves [2, 3]; while dehydrodicolactone and dehydroindicolactone (wampetin) are present in the bark [4, 5]. This paper deals with the structure determination of three novel amides and a known amide (lansamide-I) isolated from the seeds of this plant.

RESULTS AND DISCUSSION

The ether extract of the seeds was treated as described in the Experimental section to give four amides (1–4). Amide 2, $[M]^+$ 263, analysed for $C_{18}H_{17}NO$. Its 1H NMR spectrum contained signals of an *N*-methyl group (δ 3.35), two pairs of *trans*-olefinic protons (δ 6.04, 7.70 and δ 6.94, 7.40, each 1H, *d*, J = 16 Hz) and ten aromatic protons of two monosubstituted benzene rings (δ 7.10–7.40, *m*). Alkaline hydrolysis of 2 gave *trans*-cinnamic acid, while acid hydrolysis afforded *N*-methyl-cinnamamide. Amide 2 was thus found to be identical with lansamide-I which had been isolated from the leaves of the same plant [2].

Amide 3 has the same molecular formula as 2, but the 1H NMR spectrum is different from that of 2, showing signals of *cis*-olefinic protons (δ 6.44 and 6.18, each 1H, *d*, J = 8 Hz). Alkaline and acid hydrolysis of 3 afforded cinnamic acid and *N*-methylcinnamamide, respectively. Isomerization of 3 to the *trans* form with iodine under UV light gave compound 2. Thus, the structure of amide 3 was confirmed to be *N*-methyl-*N*-*cis*-styryl-cinnamamide.

Amide 4 gave a molecular peak at m/z 265 $[M]^+$ in the EIMS, and elemental analysis confirmed the formula of $C_{18}H_{19}NO$. Comparison of the 1H NMR spectra of 4



and **2** showed that the signals of a pair of *trans*-olefinic protons in **2** are replaced by four proton signals (δ 3.67, 2.90, each 2H, *t*, *J* = 7.5 Hz) assignable to two ethylenes. Cinnamic acid was obtained by alkaline hydrolysis. Hydrogenation of **4** gave the same product as that formed on hydrogenation of **2**. Therefore, the structure of amide **4** was established to be *N*-methyl-*N*-phenethyl-cinnamamide.

Amide **1** gave IR absorption bands of —NH group at 3250 cm^{-1} and of an amide at 1645 cm^{-1} . Its EIMS exhibited a molecular peak at m/z 249 $[\text{M}]^+$, which was 14 mass units less than that of compound **3**. The ^1H NMR spectrum showed a signal pattern similar to that of **3**, except for the absence of a methyl group. Cinnamic acid was obtained by alkaline hydrolysis. Therefore, the structure of amide **1** was determined to be *N*-*cis*-styrylcinnamamide.

EXPERIMENTAL

Mps: uncorr; IR: KBr; ^1H NMR: 100 MHz with TMS as int. standard. CC: silica gel 60; TLC: silica gel 60F₂₅₄.

Plant material. The seeds of *Clausena lansium* were collected in Hua-lian, Taiwan, and the plant was identified by Mr M. C. Kao, National Taiwan University.

Extraction and isolation. The dried seeds of *C. lansium* (3 kg) were powdered and extracted ($\times 3$) with Et_2O at room temp. The combined extracts were concd to ca 1 l. After standing for several days, yellowish plates (amide **2**) were obtained, which were collected by filtration. The filtrate, after concn, was subjected to silica gel CC (1.5 kg). Elution successively with C_6H_6 , CHCl_3 – C_6H_6 and Me_2CO – CHCl_3 – C_6H_6 gave three amides, (**1**, **3** and **4**).

Amide 1 (lansiumamide A, N-cis-styryl-cinnamamide). Pale yellow needles, mp 121–123° (*n*- C_6H_{12} – Et_2O). Dragendorff test: (–). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3240 (–NH), 1645 (C=O), 1625, 1580, 1510 (arom. C=C); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 218, 265, 303; ^1H NMR (CDCl_3): δ 5.79 (1H, *d*, *J* = 8 Hz), 6.33 (1H, *d*, *J* = 16 Hz), 7.43 (1H, *d*, *J* = 8 Hz), 7.44–7.06 (11H in total, *m*), 7.72 (1H, *d*, *J* = 16 Hz); EIMS 12 eV, m/z : 249 $[\text{M}]^+$, 131, 119, 103, 71.

Amide 2 (lansamide-I, N-methyl-N-styryl-cinnamamide). Yellowish plates, mp 119–120° (*n*- C_6H_{12} – C_6H_6). Dragendorff test: (+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1650 (C=O), 1630, 1610, 1570, 1490 (arom. C=C); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 327, 306, 290, 218; ^1H NMR (CDCl_3): δ 3.35 (3H, *s*), 6.04 (1H, *d*, *J* = 16 Hz), 6.94 (1H, *d*, *J* = 16 Hz), 7.10–7.39 (10H in total, *m*), 7.40 (1H, *d*, *J* = 16 Hz), 7.70 (1H, *d*, *J* = 16 Hz). Found: C, 82.16, H, 6.49, N, 5.68. calc. for $\text{C}_{18}\text{H}_{17}\text{NO}$: C, 82.08, H, 6.51, N, 5.34%. EIMS 12 eV, m/z : 263 $[\text{M}]^+$, 172, 146, 133, 131, 103.

Amide 3 (lansiumamide B, N-methyl-N-cis-styryl-cinnamamide). Yellowish plates, mp 72–73° (Et_2O). Dragendorff test: (+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1640 (C=O), 1610, 1570, 1490 (arom. C=C); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 285, 226, 218; ^1H NMR (CDCl_3): δ 3.08 (3H, *s*), 6.18 (1H, *d*, *J* = 8 Hz), 6.44 (1H, *d*, *J* = 8 Hz), 6.87 (1H, *d*, *J* = 16 Hz), 7.59 (1H, *d*, *J* = 16 Hz), 7.10–7.40 (10H in total, *m*). Found: C, 82.07, H, 6.54, N, 5.56, $\text{C}_{18}\text{H}_{17}\text{NO}$ requires: C, 82.08, H, 6.51, N, 5.34%. EIMS 12 eV, m/z : 263 $[\text{M}]^+$, 133, 131, 117, 103.

Amide 4 (lansiumamide C, N-methyl-N-phenethyl-cinnamamide). Yellowish plates, mp 58–59° (Et_2O). Dragendorff test: (+).

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2900 (– CH_2 –), 1650 (C=O), 1605, 1580, 1490 (arom. C=C); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 276, 223, 218; ^1H NMR (CDCl_3): δ 2.90 (2H, *t*, *J* = 7.5 Hz), 3.04 (3H, *s*), 3.67 (2H, *t*, *J* = 7.5 Hz), 6.52 (1H, *d*, *J* = 16 Hz), 7.00–7.50 (10H in total, *m*), 7.66 (1H, *d*, *J* = 16 Hz). Found: C, 81.02, H, 7.28, N, 5.64, $\text{C}_{18}\text{H}_{19}\text{NO}$ requires: C, 81.45, H, 7.22, N, 5.30%. EIMS 12 eV, m/z : 265 $[\text{M}]^+$, 174, 131, 103.

Alkaline hydrolysis of amides 1–4. Amides **1** (21 mg), **2** (53 mg), **3** (500 mg) and **4** (300 mg) were separately hydrolysed for 8 hr with 25% KOH–MeOH (w/v), 2–3 ml. The resulting ppts were collected by filtration, and washed with a little MeOH. The ppts were dissolved in H_2O and acidified with dil. HCl to give colourless plates, mp 133–134°, which were identified as cinnamic acid (IR, co-TLC and mmp).

Acid hydrolysis of compounds 2 and 3. Compounds **2** (40 mg) and **3** (300 mg) were each hydrolysed for 15 min with 10% HCl–EtOH (3 ml). The reaction mixture, after cooling, was neutralized with 10% NaOH, the EtOH evapd off and the aq. soln extracted with Et_2O . The Et_2O layer was evapd to small vol then *n*- C_6H_{12} was added to give colourless needles (**5**), mp 108°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (N–H), 3070 (N–Me), 1615, 1580, 1560, 1495 (arom. C=C); ^1H NMR ($\text{Me}_2\text{CO}-d_6$): δ 2.85 (3H, *d*, *J* = 5 Hz, –NCH₃), 6.67 (1H, *d*, *J* = 16 Hz), 7.60 (1H, *d*, *J* = 16 Hz), 7.67–7.33 (6H in total, *m*); EIMS 12 eV, m/z (rel. int.): 161 $[\text{M}]^+$ (100), 131 (80), 103 (9).

Hydrolysis of **5** with 10% HCl–EtOH for 16 hr gave colourless plates, mp 132–134°, which were identified as cinnamic acid (IR, co-TLC and mmp).

Trans-isomerization of compound 3. A mixture of compound **3** (5 mg) and a small piece of I_2 (in 2 ml of *n*- C_6H_{14} and 2 drops of EtOAc) was kept under a UV lamp for 1.5 hr. The reaction mixture gave two spots on TLC, which were identified as compounds **2** and **3**.

Hydrogenation of compounds 2–4. Compounds **2–4** (each 100 mg) in 20 ml of EtOH were separately shaken with Pd/C (10%) under an atmosphere of H_2 for 1 hr. After removal of the catalyst by filtration, the filtrate was concd to yield the same product. ^1H NMR (CDCl_3): δ 2.90–2.44 (6H in total, *m*), 3.02 (3H, *s*), 3.48 (2H, *t*, *J* = 7.5 Hz), 7.24 (10H in total, *m*).

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