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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 inflamation, ulcers, etc. [1].

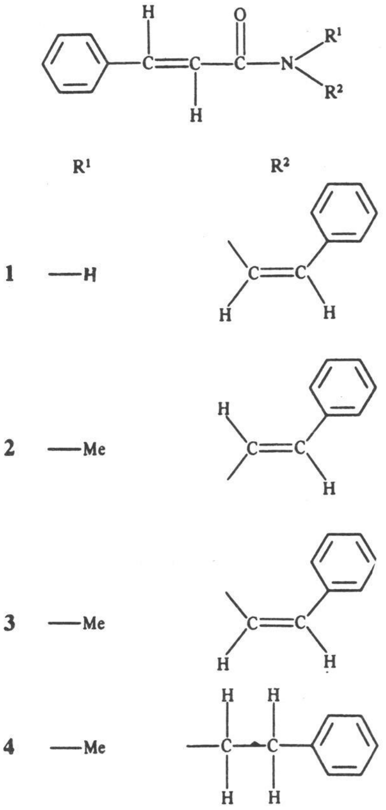
β-Sitosterol, heptaphylline, lansamide-I(*N*-methyl-*N*-styryl-cinnamamide), lansine (3-formyl-2-hydroxy-6-methylcarbazole) and three novel cyclic amides, clausenamide, neoclausenamide and cycloclausenamide, have been isolated from the leaves [2, 3]; while dehydrodicolactone and dehydroindicolactone (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**



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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 $[M]^+$, which was 14 mass units less than that of compound **3**. The ^{1}H 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; ^{1}H NMR: 100 MHz with TMS as int. standard. CC: silica gel 60; TLC: silica gel $60F_{254}$.

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 yelllow needles, mp 121–123° (n-C_6H_{12}–Et_2O). Dragendorff test: ($-$). IR ν_{max}^{KBr} cm^{-1}: 3240 ($-$NH), 1645 (C=O), 1625, 1580, 1510 (arom. C=C); UV λ_{max}^{MeOH} nm: 218, 265, 303; ^{1}H 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 $[M]^+$, 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 ν_{max}^{KBr} cm^{-1}: 1650 (C=O), 1630, 1610, 1570, 1490 (arom. C=C); UV λ_{max}^{MeOH} nm: 327, 306, 290, 218; ^{1}H NMR ($CDCl_3$): δ3.35 (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 $C_{18}H_{17}NO$: C, 82.08, H, 6.51, N, 5.34%. EIMS 12 eV, *m/z*: 263 $[M]^+$, 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 ν_{max}^{KBr} cm^{-1}: 1640 (C=O), 1610, 1570, 1490 (arom. C=C); UV λ_{max}^{MeOH} nm: 285, 226, 218; ^{1}H NMR ($CDCl_3$): δ3.08 (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, $C_{18}H_{17}NO$ requires: C, 82.08, H, 6.51, N, 5.34%. EIMS 12eV, *m/z*: 263 $[M]^+$, 133, 131, 117, 103.

Amide **4** (*lansiumamide C*, N-*methyl*-N-*phenethyl-cinnamamide*). Yellowish plates, mp 58–59° (Et_2O). Dragendorff test: (+). IR ν_{max}^{KBr} cm^{-1}: 2900 ($-CH_2-$), 1650 (C=O), 1605, 1580, 1490 (arom. C=C); UV λ_{max}^{MeOH} nm: 276, 223, 218; ^{1}H 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, $C_{18}H_{19}NO$ requires: C, 81.45, H, 7.22, N, 5.30%. EIMS 12 eV, *m/z*: 265 $[M]^+$ 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 ν_{max}^{KBr} cm^{-1}: 3250 (N$-$H), 3070 (N$-$Me), 1615, 1580, 1560, 1495 (arom. C=C); ^{1}H NMR (Me_2CO-d_6): δ 2.85 (3H, *d*, $J = 5$ Hz, $-NCH_3$), 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 $[M]^+$ (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. ^{1}H NMR ($CDCl_3$): δ2.90–2.44 (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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