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TRADITIONAL MEDICINAL PLANTS OF THAILAND VII. ALKALOIDS OF *EVODIA LEPTA* AND *EVODIA GRACILIS**

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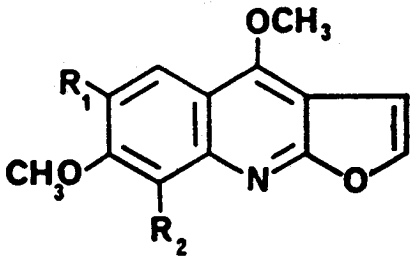
Abstract

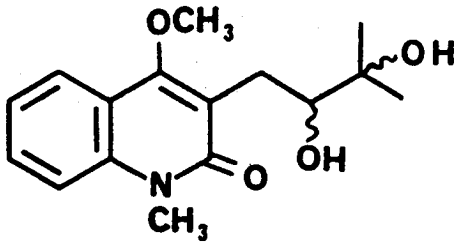
An examination of the alkaloid content of Evodia lepta *and* Evodia gracilis *has revealed that they are chemically distinct. Thus kokusaginine (1) and skimmianine (2) were obtained from* E. gracilis, *while (−)-edulinine (3), (−)-ribalinine (4) and (+)-isoplatydesmine (5) were obtained from* E. lepta. *Both 4 and 5 underwent rearrangement under basic conditions to the corresponding angular isomers. (−)-Ribalinine (4) also rearranged and underwent ring contraction in the presence of NaH to afford (+)-ψ-isoplatydesmine (7).*

Evodia is a genus of shrubs in the subfamily Rutoideae of the family Rutaceae, native to tropical Asia and Australia. In Thailand there are six species, distributed principally in the northern region[2] and here we describe phytochemical studies on two of these, *Evodia lepta* Merr. and *E. gracilis* Kurz.

E. lepta is used as an antipyretic, anti-inflammatory, and analgesic in the People's Republic of China and in Taiwan, and externally it is used for trauma, abscesses, wound infections, eczema, dermatitis and hemorrhoids[3]. *E. gracilis* has no established *in vitro* or *in vivo* activities, but in the northern part of Thailand the fresh leaves are used as a vegetable and as a bitter tonic. Preliminary screening indicated that both species contained alkaloids, but that they were of a quite different type.



	R_1	R_2
1	OCH_3	H
2	H	OCH_3



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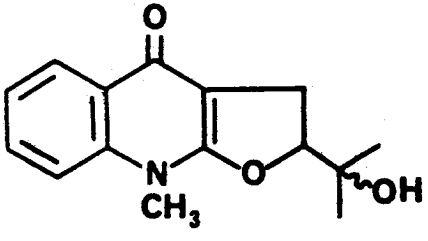

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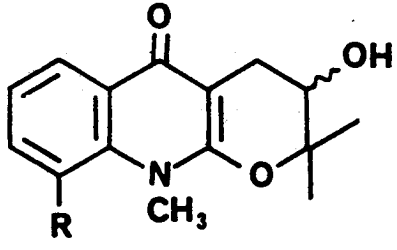
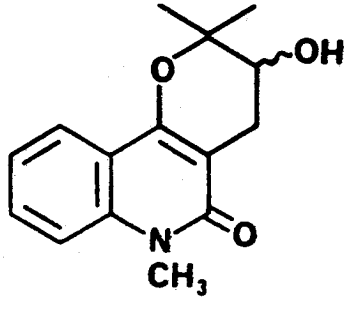


4 R = H

8 R = OCH_3



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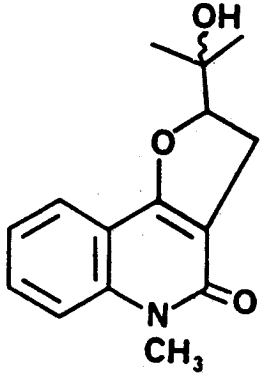

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Column chromatography led to the isolation of kokusaginine **(1)** and skimmianine **(2)** from *E. gracilis* and of (−)-edulinine **(3)**, (−)-ribalinine **(4)** and (+)-isoplatydesmine **(5)** from *E. lepta*. The range of different alkaloids from these species is of interest because

Smitinand[2] recently combined these two species into a single species. Our chemotaxonomic studies would indicate that they should remain distinct.

In the course of chemical studies on **4** and **5** it was noted that under basic conditions (e.g. refluxing with 1% methanolic KOH), both compounds rearranged quantitatively to the respective angular structures (−)-ψ-ribalinine **(6)** and (+)-ψ-isoplatydesmine **(7)**. This linear to angular isomerization is evident from the upfield shift of H-5 by ~ 0.7 ppm due to the removal of the anisotropy of the carbonyl functional in the angular isomers.

(−)-Ribalinine **(4)**, on the other hand rearranged to a mixture of **6** and **7** on standing in THF in the presence of a catalytic amount of NaH at room temperature. The linear to angular isomerization under similar conditions has been reported for balfourdine **(8)**, but the ring contraction reaction has only previously been reported for the corresponding methosulfate derivative[4].

General Experimental Methods. Melting points were determined on a Kofler hotplate apparatus and are uncorrected. Specific rotations were measured on a Perkin Elmer 241 polarimeter. The UV spectra were obtained with a Beckman DU-7 spectrophotometer. IR spectra were measured on a Nicolet MX-1 FT-IR spectrophotometer. ^{1}H-NMR and ^{13}C-nmr spectra were recorded with Nicolet NT 1280 spectrometer operating at 360 and 90.54 MHz, respectively, or on a Varian XL300 instrument at 300 MHz and 75.44 MHz, respectively. TMS was used as an internal standard. Low resolution mass spectra were obtained with a Varian MAT 112S mass spectrometer.

Plant Materials. The leaves of *E. lepta* were obtained in April, 1982 and the leaves of *E. gracilis* in May, 1983 from Doi Suthep, Chiang Mai Province, Thailand. The plant materials were authenticated by comparison with the herbarium specimens in the Botany Section, Technical Division, Department of Agriculture and Cooperatives, Bangkok, Thailand.

Extraction and Isolation of Alkaloids from E. Lepta Leaves. The dried, powdered plant material (600 g) was macerated twice for 3 day periods with 95% EtOH (5 l and 4 l). The combined alcoholic extracts were evaporated *in vacuo* and the resultant syrupy mass was mixed with glacial HOAc (500 ml), stirred thoroughly and poured into warm H_2O (4.5 l) and filtered. The filtrate was basified with NH_3 and exhaustively extracted with $CHCl_3$. After drying (Na_2SO_4), the combined $CHCl_3$ extract was filtered and evaporated *in vacuo* to a dark brown syrup (18.5 g). Chromatography of the extract portion-wise (1 g each) on a silica gel column (2.5 × 15 cm) eluting with $CHCl_3$:EtOH (9:1) afforded four fractions F-1 (4.24 g), F-2 (2.67 g, 0.45%) identified as (−)-ribalinine **(4)**, F-3 (1.82 g) and F-4 (1.53 g. 0.25%) identified as (+)-isoplatydesmine **(5)**. The residue from F-1 was rechromatographed on silica gel eluted with $CHCl_3$:acetone (9:1) to afford (−)-edulinine **(3**, 420 mg, 0.07%).

Extraction and Isolation of Alkaloids from E. Gracilis Leaves. The dried, powdered plant material (800 g) was extracted by the usual procedure (as described above) to yield a dark brown syrupy mass (10 g). The crude extract was divided into five equal portions, each of which was chromatographed on an alumina (neutral) column (5 × 7 cm) using chloroform as eluant. The result of fractionation afforded three fractions F-1 (627 mg, 0.08%) identified as kokusaginine **(1)**, F-2 (1.2 g) and F-3 (180 mg, 0.02%) identified as skimmianine **(2)**.

Kokusaginine **(1)** was obtained as colorless clusters from EtOH, mp 165-6°C (lit.[6] 168°C), ir, ν_{max} (KBr) 3130, 3000, 2950, 1625 and 1590 cm^{-1}; uv, λ_{max} (MeOH) 221 (log ε 3.87), 245 (4.39), 251 (4.42), 309 (3.77), 321 (3.79) and 335 (3.23)nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 2.7 Hz, α -furan (2'-H)), 6.94 (1H, d, J = 2.7 Hz, β -furan (3'-H)), 7.33 (1H, s, 5-H),7.27 (1H, s, 8-H), 4.27 (3H, s, 4-OCH_3), 4.00 (3H, s, 6 or 7-OCH_3) and 3.98 (3H, s, 7 or 6-OCH_3); ms, *m/z* (rel. intensity) 259 (M^+, 100%), 244 (57), 216 (26), 201 (19), 186 (21), and 173 (13).

Skimmianine **(2)** was obtained as colorless monoclinic crystals from EtOH, mp 173-4°C (lit.[7] 176-7°C), ir, ν_{max} (KBr) 3120, 2860, 1620 and 1581 cm^{-1}; uv, λ_{max} (MeOH) 249 (log ε 4.54), 320 (3.84) and 333 (3.52) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 8.4 Hz, 5-H), 7.17 (1H, d, J = 8.4 Hz, 6-H), 7.52 (1H, d, J = 2.7 Hz, α -furan (2'-H)), 6.97 (1H, d, J = 2.7 Hz, β -furan (3'-H)), 4.34 (3H, s, 4-OCH_3), 4.10 (3H, s, 8-OCH_3) and 4.00 (3H, s, 7-OCH_3); ms, *m/z* (rel. intensity) 259 (M^+, 77%), 258 (25), 245 (15), 244 (100), 242 (10), 230 (52), 229 (26), 228 (21), 216 (26), 215 (13), 213 (30), 201 (26), 200 (10), 199 (16) and 173 (14).

Edulinine **(3)** was obtained as plates from EtOH, mp 145°C (lit.[7] 140-2°C); $[\alpha]_D^{25}$ -11° (c 1.4, $CHCl_3$) (lit. (8) $[\alpha]_D^{25}$ -20°); ir, ν_{max} (KBr) 3425, 3220, 1640, and 1584 cm^{-1}; uv, λ_{max} (MeOH) 256 (log ε 4.54),340 (4.05) and 355 (4.02) nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, dd, J = 8.0, 1.5 Hz, 5-H), 7.61 (1H, dd, J = 8.5, 8.0 Hz, 7-H), 7.42 (1H, d, J = 8.5 Hz, 8-H), 7.18 (1H, dd; J = 8.5, 8.0 Hz, 6-H), 5.10 (1H, bd, OH), 3.97 (3H, s, -OCH_3), 3.75 (3H, s, -NCH_3), 3.61 (1H, dd, J = 10.0, 2.1 Hz, CHOH), 3.14 (1H, dd, J = 13.8, 2.1 Hz, -CH_2-), 2.79 (1H, dd, J = 13.8, 10.0 Hz, -CH_2-), and 1.32 (6H, s, 2 × CH_3); ms (c.i., CH_4) (rel. intensity) *m/z* 292 (M^++ 1,67%),274 (M^+ - OH, 37), 243 (23), 226 (13), 225 (100), 221 (12), 209 (12), 197 (61), 183 (10), 136 (11) and 119 (13).

(−)-Ribalinine **(4)** was obtained as white prisms from EtOH, mp 220°C (lit.[9] 220°C); $[\alpha]_D^{25}$ -151° (c 1.0, $CHCl_3$); ir, ν_{max} (KBr) 3450, 1625 and 1600 cm^{-1}, uv, λ_{max} (MeOH) 237 (log ε 4.3), 245 (4.4), 252 (4.2), 317 (4.1) and 328 nm (4.0); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, dd, J = 7.5, 1.2 Hz, 5-H), 7.51 (1H, ddd, J = 7.5, 7.5 and 1.2 Hz, 6-H), 7.25 (1H, dd, J = 7.5, 7.5 Hz, 7-H), 7.17 (1H, d, J = 7.5 Hz, 8-H), 4.35 (1H, bd, OH), 3.91 (1H, m, CHOH), 3.51 (3H, s, -NCH_3), 2.94 (2H, dd, J = 12.8, 3.7 Hz, -CH_2-), 1.55 (3H, s, -CH_3) and 1.33 (3H, s, -CH_3); ms, *m/z* (rel. intensity) 260 (M^+ + 1, 8%), 259 (M^+, 40), 189 (39), 187 (100), 134 (18), 104 (8), 77 (16), 72 (12) and 57 (14).

(+)-Isoplatydesmine (**5**) was obtained as white prisms from EtOH, mp 187°C (lit.[9] 187-9°C); $[\alpha]_D^{25}$ + 48° (c 4.0, $CHCl_3$); ir, ν_{max} (KBr) 3350 and 1640 cm^{-1}; λ_{max} (MeOH) 235 (log ε 4.40), 297 (3.97), 310 (4.05), and 319 nm (4.00); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (1H, dd, *J* = 7.8, 1.5 Hz, 5-H), 7.55 (1H, ddd, *J* = 7.8, 7.8, 1.5 Hz, 6-H), 7.33 (1H, dd, *J* = 7.8, 7.8 Hz, 7-H), 7.30 (1H, d, *J* = 7.8 Hz, 8-H, 4.84 (1H, t, *J* = 8.3 Hz, -CHOH), 3.68 (3H, s, $-NCH_3$), 3.25 (2H, d, *J* = 8.3 Hz, $-CH_2-$), 2.90 (1H, bd, -OH), 1.39 (3H, s, $-CH_3$), and 1.29 (3H, s, $-CH_3$); ms, *m/z* (rel. intensity) 260 (M^+ + 1, 13%), 259 (M^+, 68), 226 (10), 216 (32), 200 (57), 189 (37), 188 (100), 134 (19), 77 (21) and 58 (22).

Based-Catalyzed Rearrangements of **4** *and* **5**. (−)-Ribalinine (**4**, 20 mg), was heated under reflux in MeOH (50 ml) in the presence of KOH (1 g) for 4 hr. After evaporation of solvent, the residue was dissolved in $CHCl_3$, dried and evaporated, and the residue was recrystallized from EtOH to afford white plates of **6**, mp 180°C; $[\alpha]_D^{25}$ -6° (c 0.6, $CHCl_3$); ir, ν_{max} (KBr) 3450, 1645 and 1600 cm^{-1}; uv, λ_{max} (EtOH) 247 (log ε 4.61), 285 (4.60), 320 (4.57) and 322 nm (4.54); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 7.5, 1.5 Hz, 5-H), 7.50 (1H, dd, *J* = 7.5, 7.5 Hz, 6-H), 7.21 (1H, dd, *J* = 7.5, 7.5 Hz, 7-H), 7.18 (1H, d, *J* =7.5 Hz, 8-H), 3.56 (3H, s. $-NCH_3$), 3.90 (1H, m, -CHOH), 2.81 (1H, dd, *J* = 12.8 4.8 Hz, $-CH_2-$), 2.72 (1H, dd, *J* = 12.8, 5.8 Hz, $-CH_2-$), 1.46 (3H, s, $-CH_3$), 1.37 (3H, s, $-CH_3$); ms, *m/z* (rel. intensity) 260 (M^+ + 1, 15), 259 (M^+, 79), 242 (24), 226 (20), 200 (32), 189 (88), 188 (100), 187 (21), 186 (13), 134 (32), 132 (12), 104 (14) and 77 (28).

(+)-Isoplatydesmine (**5**, 18 mg) was treated as above to afford (+)-ψ-isoplatydesmine (**7**, 15 mg) which was recrystallized from EtOH, mp. 138°C, $[\alpha]_D^{25}$ + 40° (c 0.4, $CHCl_3$); ir, ν_{max} (KBr) 3340, 1642 and 1600 cm^{-1}; uv, λ_{max} 245 (log ε 4.72), 265 (4.70), 282 (4.70) and 325 nm (4.62); ^{1}H-nmr (300 MHz, $CDCl_3$) δ 7.74 (1H, dd, *J* = 7.8, 1.5 Hz, 5-H), 7.57 (1H, dd, *J* = 8.2, 7.8 Hz, 6-H), 7.35 (1H, d, *J* = 8.2 Hz, 8-H), 7.25 (1H, dd, *J* = 7.8, 8.2 Hz, 7-H), 4.88 (1H, dd, *J* = 10.5, 8.0 Hz, -CH-), 3.67 (3H, s, $-NCH_3$), 3.20 (1H, dd, *J* = 6.5, 10.5 Hz, $-CH_2-$), 3.17 (1H, dd, *J* = 6.5, 8.0 Hz, $-CH_2-$), 2.27 (1H, bd, OH), 1.38 (3H, s, $-CH_3$) and 1.29 (3H, s, $-CH_3$); ms, *m/z* (rel. intensity) 260 (M^+ + 1, 10%), 259 (M^+, 61), 244 (15), 226 (63), 202 (13), 201 (52), 200 (100), 188 (16), 144 (13), 77 (17) and 59 (74).

NaH-Catalyzed Rearrangement of **4**. NaH (3 mg, 60% suspension) was added to a solution of **4** (11 mg) in THF (2 ml) at 0°C under N_2. The solution was stirred for 20 min and stored overnight at room temp. NH_4Cl (5 mg) was added and the mixture diluted with $CHCl_3$ (25 ml), washed with H_2O, dried (Na_2SO_4), filtered and evaporated. The residue, on preparative tlc on silica, afforded **6** (5 mg) and **7** (3 mg) which were identified by comparison (tlc, ^{1}H-nmr) with samples prepared from the alcoholic KOH-catalyzed rearrangement of **4** and **5**.

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บทคัดย่อ

จากการตรวจสอบแอลคาลอยด์ ในต้นเพี้ยกระทิง *(Evodia lepta)* และต้นสเลียมดง *(Evodia gracilis)* พบว่ามีความแตกต่างกันโดยสิ้นเชิง เช่น kokusaginine **(1)** และ skimmianine **(2)** แยกได้จากต้นเพี้ยกระทิง ส่วน (−)-edulinine **(3)**, *(−)-ribalinine* **(4)** และ (+)-isoplatydesmine **(5)** แยกได้จากต้นสเลียมดง ทั้ง **4** และ **5** ต่างก็มีการจัดเรียงตัวไปเป็น angular isomers ภายใต้ความเป็นด่าง นอกจากนี้ (−)-ribalinine **(4)** ยังสามารถที่จะจัดเรียงตัวของโครงสร้างภายใต้ NaH เพื่อเกิดเป็น (+)-ψ-isoplatydesmine **(7)** ได้อีกด้วย