Pergamon

0031-9422(95)00457-2

Phytochemistry, Vol. 40, No. 5, pp. 1561–1562, 1995

0031-9422/95 $9.50 + 0.00

EVOMERRINE FROM *MELICOPE SEMECARPIFOLIA*

IAN-LIH TSAI,* SHWU-JEN WU,† TSUTOMU ISHIKAWA,‡ HIROKO SEKI,§ SHU-TING YAN,* and IH-SHENG CHEN*¶

*School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan; †China Junior College of Medical Technology, Tainan Hsien, Taiwan; ‡Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Chiba, 260, Japan; §Analytical Center, Chiba University, 1-33, Yayoi-cho, Chiba, 260, Japan

(*Received in revised form* 10 *May* 1995)

Key Word Index—*Melicope semecarpifolia*; Rutaceae; leaves; furoquinoline alkaloids; evomerrine; flavonoid.

Abstract—A new phenolic furoquinoline alkaloid, evomerrine, was isolated from the leaves of *Melicope semecarpifolia*. Its structure was elucidated from spectral data and chemical evidence. Six other known furoquinoline alkaloids, platydesmine, skimmianine, kokusaginine, haplopine, heliparvifoline and confusameline, along with one flavonoid, ayanin, were also isolated.

INTRODUCTION

Melicope semecarpifolia (Merr.) T. Hartley (*Evodia merrillii* Kanehira & Sasaki ex Kanehira; *Melicope confusa* (Merr.) Liu) is a small- to medium-sized tree, distributed in Taiwan and the Philippines [1]. Investigations on the chemical constituents of this species have been reported previously [2–6]. Subsequent examination of the constituents of leaves of Formosan *M. semecarpifolia* has now led to the isolation of a new phenolic furoquinoline alkaloid, evomerrine (**1**), along with six known furoquinoline alkaloids, platydesmine (**2**) [7], skimmianine (**3**) [2], kokusaginine (**4**) [2], haplopine (**5**) [7], heliparvifoline (**6**) [8], confusameline (**7**) [2] and one flavonoid, ayanin (**8**) [9]. Ayanin (**8**) was first obtained from rutaceous plants; platydesmine (**2**) and haplopine (**5**) were first isolated from *M. semecarpifolia*. The isolation and structural elucidation of the new furoquinoline alkaloid, evomerrine (**1**), is described in this paper.

RESULTS AND DISCUSSION

Evomerrine (**1**) was obtained as colourless needles. Its molecular formula of $C_{13}H_9NO_4$ was determined by EI ($[M]^+$, *m/z* 243) mass spectrometry and elemental analysis. The IR spectrum indicated the presence of an aldehyde group at 1625 cm^{-1}. UV absorptions at 267, 273 and 332 nm showed the existence of a furoquinoline moiety [2]; after adding KOH there was no bathochromic shift, suggesting the presence of intramolecular hydrogen-bonding between the phenolic hydroxyl and the aldehyde groups in **1**. The ^1H NMR spectrum showed one set of doublets and characteristic H-3 and H-2 furan protons at δ7.09 and 7.63 (each 1H, *d*, J = 2.8 Hz) [3, 8]. The other set of *ortho*-coupling protons at δ7.08 and 8.43 (each 1H, *d*, J = 9.6 Hz) were assigned to H-6 and H-5. A methoxyl signal at δ4.46 (3H, *s*) suggested the presence of a 4-methoxyl group [2, 10]. The hydroxyl group (δ13.21, *s*, disappeared on addition of D_2O) was relatively low-field and the existence of hydrogen-bonding with the neighbouring aldehyde group (δ11.19, *s*) was further suggested. The above conclusions were further supported by ^1H–^1H COSY. From the NOESY experiment (Fig. 1), the methoxyl group at C-4 was correlated with H-3. ^{13}C NMR data was assigned by DEPT, HETCOR and HMBC techniques (Fig. 2) which also supported the structure of **1**. The locations of the hydroxyl group at C-7 and the aldehyde group at C-8 of **1** were confirmed by comparison (TLC, IR, ^1H NMR, mixed mp) of the product obtained by Reimer–Tiemann reaction [11] of confusameline (**7**) (Fig. 3) with natural **1**. Thus, the structure of **1** was unambiguously elucidated as 8-formyl-7-hydroxy-4-methoxy furoquinoline.

EXPERIMENTAL

Mps: uncorr. ^1H NMR (200 and 500 MHz) and ^{13}C NMR (125 MHz) were recorded in $CDCl_3$. Chemical

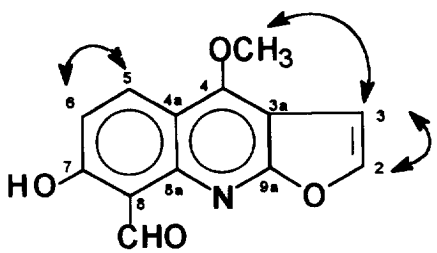


Fig. 1. NOESY of compound **1** (↷).

¶ Author to whom correspondence should be addressed.

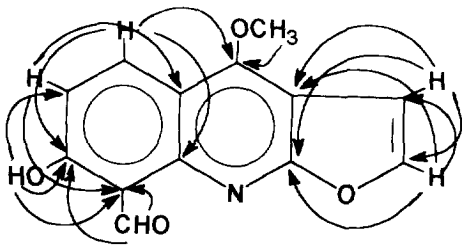
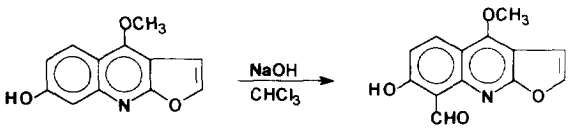


Fig. 2. HMBC of compound **1** (⤻).



7 **1**

Fig. 3. Formylation of compound **7**.

shifts are given in δ with TMS as int. standard. MS were measured using a direct inlet system. UV were determined in EtOH and IR recorded in KBr. CC was carried out on Merck silica gel (70–230 and 230–400 mesh) and TLC used Merck silica gel plates (60 GF-254).

Plant material. Leaves of *M. semecarpifolia* were collected from Man-Chou (Pingtung Hsien, Taiwan) in October, 1979. A voucher specimen is deposited in the herbarium of the School of Pharmacy (Kaohsiung Medical College, Taiwan).

Extraction and isolation. Leaves (11.9 kg) were extracted with MeOH and concd under red. pres. to a dark residue (3.12 kg). This was extracted with 5% HOAc and the acid-sol. part basified with NH_4OH and then extracted with $CHCl_3$. The $CHCl_3$ soln was extracted with 5% aq. NaOH soln, dried (K_2CO_3), then evapd to leave a light brownish residue (24.4 g) of crystalline tertiary nonphenolic bases. Excess NH_4Cl was then added to the 5% NaOH soln and extracted with $CHCl_3$ to afford a reddish orange residue (5.21 g) of tertiary phenolic bases. The tertiary nonphenolic bases were washed with MeOH and the crystals obtained recrystallized from $CHCl_3$–MeOH to yield skimmianine (**3**) (1.104 g). The mother liquor of **3** was chromatographed on a silica gel column and eluted with $CHCl_3$ to furnish kokusaginine (**4**) (83 mg). Then, the above MeOH washings were chromatographed on a silica gel column and eluted with benzene–EtOAc (5:1) to obtain platydesmine (**2**) (3.9 mg). Tertiary phenolic bases were chromatographed on a silica gel column and eluted with $CHCl_3$ to afford ayanin (**8**) (3.4 mg), evomerrine (**1**) (8.1 mg), haplopine (**5**) (46.5 mg) and heliparvifoline (**6**) (148 mg), and with $CHCl_3$–MeOH (100:1) to afford confusameline (**7**) (463 mg), respectively.

Evomerrine (**1**). Needles, mp 219–220° ($CHCl_3$–MeOH). EIMS *m/z* (rel. int.): 243 ($[M]^+$, 29), 216 (15), 215 (100), 187 (28). *Anal.* calcd., $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76; Found: C, 63.83; H, 3.69; N, 5.73. UV λ_{max} nm (log ε): 267 (4.16), 273 (4.14), 332 (3.83), no alteration with KOH. IR ν_{max} cm^{-1}: 1625 (CHO). ^1H NMR (500 MHz): 4.46 (3H, *s*, OMe-4), 7.08 (1H, *d*, J = 9.6 Hz, H-6), 7.09 (1H, *d*, J = 2.8 Hz, H-3), 7.63 (1H, *d*, J = 2.8 Hz, H-2), 8.43 (1H, *d*, J = 9.6 Hz, H-5), 11.19 (1H, *s*, CHO-8), 13.21 (1H, *s*, OH-7, disappeared after addition of D_2O). ^{13}C NMR (125 MHz): 59.12 (OMe), 102.59 (C-3a), 104.94 (C-3), 112.05 (C-8), 112.37 (C-4a), 116.63 (C-6), 132.31 (C-5), 142.92 (C-2), 147.12 (C-8a), 157.63 (C-4), 164.93 (C-9a), 166.79 (C-7), 196.98 (CHO).

Formylation of confusameline (**7**). To a soln of confusameline (**7**) (30 mg) in 10% aq. NaOH soln (0.5 ml), $CHCl_3$ (0.6 ml) was added dropwise at 75° with stirring and mixt. refluxed for 40 min. The reaction mixt. was acidified with 5% HCl, then extracted with Et_2O. The Et_2O soln was dried ($MgSO_4$), then evapd under red. pres. The residue obtained was chromatographed on a silica gel column and eluted with benzene to yield evomerrine (**1**) (5.4 mg), mp 239–241°.

Acknowledgements—This research was financially supported by the National Science Council of the Republic of China (NSC 77-0606-B-037-13).

REFERENCES

1. Chang, C. E. and Hartley, T. (1993) *Rutaceae in Flora of Taiwan*, (2nd edn), p. 522. Editorial Committee of the Flora of Taiwan, Taipei, Taiwan.
2. Yang, T. S., Lu, S. T., Wang, S. J., Wang, T. W., Lin, J. H. and Chen, I. S. (1971) *Yakugaku Zasshi* **91**, 782.
3. Kang, S. S. and Woo, W. S. (1986) *Arch. Pharm. Res.* **9**, 11.
4. Lin, L. C., Chou, C. J., Chen, K. T. and Chen, C. F. (1992) *Chin. Pharm. J.* **44**, 125.
5. Chou, C. J., Lin, L. C., Chen, K. T. and Chen, C. F. (1992) *J. Nat. Prod.* **55**, 795.
6. Lin, L. C., Chou, C. J., Chen, K. T. and Chen, C. F. (1993) *J. Nat. Prod.* **56**, 926.
7. Ishii, H., Chen, I. S., Akaike, M., Ishikawa, T. and Lu, S. T. (1982) *Yakugaku Zasshi* **102**, 182.
8. Chang, P. T. O., Aynilian, G. H., Cordell, G. A., Tin-Wa, M., Fong, H. H. S., Perdue, Jr. R. E. and Farnsworth, N. R. (1976) *J. Pharmacol. Sci.* **65**, 561.
9. Filho, R. B. and Gottlieb, O. R. (1971) *Phytochemistry* **10**, 2433.
10. Robertson, A. V. (1963) *Aust. J. Chem.* **16**, 45.
11. Wynberg, H. and Meijer, E. W. (1982) *Org. React.* **28**, 2.