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ALKALOIDS FROM *PELEA BARBIGERA**

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Abstract—From the rutaceous Hawaiian shrub *Pelea barbigera* we have isolated the furoquinoline alkaloid kokusaginine, the 4-quinolone isoplatydesmine, and a dextrorotatory edulinine which was shown to be an artefact. An *in vitro* experiment showed it to be unlikely that isoplatydesmine is derived from edulinine.

ENDEMIC Hawaiian Rutaceae include several species of the cosmopolitan genus *Fagara*, the entire genus *Platydesma*, which consists of 4 species, and the genus *Pelea* comprising some 70 species, only two of which have been described from elsewhere, viz the Marquesas. The genus *Pelea*, which is named after Pele, the goddess of the Hawaiian volcanoes, is one of the most diversified genera of the Hawaiian flora.[1]

In the course of our research on alkaloids from Hawaiian plants we identified the benzophenanthridine bases chelerythrine and dihydrochelerythrine from *Fagara semiarticulata*.[2] From *Platydesma spathulatum*, syn. *P. campanulata*,[3] we isolated four furoquinoline and two 4-quinolone derivatives.[4] All species of *Pelea* are more or less fragrant, and many are anise-scented.[5–7] During our alkaloid survey[8–10] we screened some 10 species of *Pelea* for the presence of alkaloids. A majority showed only marginal response, but *P. barbigera* (Gray) Hillebrand proved to be moderately positive, sufficiently so for detailed study. *P. barbigera* is endemic to the island of Kauai and its leaves are only slightly fragrant. Botanists had previously assigned it to the genera *Melicope* or *Evodia*.[11]

Pelea barbigera is a shrub or small tree which occurs predominantly in the Kokee area of Kauai at 2000–3000 ft (700–1000 m) elevation. An hexane extract of the leaves and stems yielded kokusaginine (**1**) as the major alkaloidal constituent. Kokusaginine is known

* Part XV in the series "Hawaiian Plant Studies". For Part XIV see JORDAN, W. and SCHEUER, P. J. (1965) *Tetrahedron* **21**, 3731.

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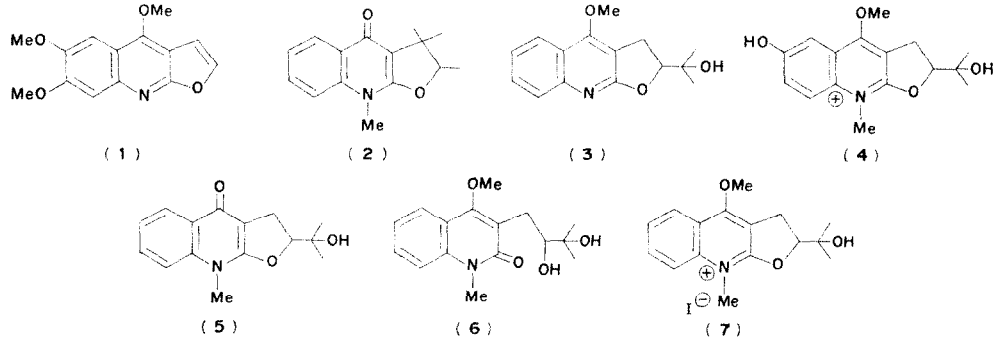
[11] STONE, B. C. (1969) *The Genus Pelea A. Gray*, p. 59, Cramer, Lehre, Germany.

from some ten rutaceous genera.[12] It was identified by comparison with an authentic sample.[4]

Following hexane treatment, the plant material was extracted with methanol. The methanol extract showed a number of alkaloidal spots on TLC. Two of these were isolated by preparative TLC on alumina and characterized. The minor component, R_f 0·12, was recrystallized from benzene–chloroform, m.p. 208–210°. It had UV spectra in neutral and acidic ethanol that were virtually identical with the published UV data of the alkaloid ifflaiamine (**2**),[13] thereby indicating a 2-alkoxy-4-quinolone chromophore for the alkaloid. In the MS of the alkaloid, a molecular ion at *m/e* 259 supported a formula of $C_{15}H_{17}NO_3$ and ready loss of 59 m.u. suggested an isopropanol side chain, by analogy with the MS behavior of platydesmine (**3**)[4] and of ribalinium (**4**).[14] IR absorption at 3400 cm^{-1} confirmed the side chain hydroxyl. The combined spectral data pointed to structure **5** for the *Pelea* alkaloid. This compound, isoplatydesmine, has been known as a synthetic substance,[15] but has not been isolated before from a natural source. We proved structure **5** for the *Pelea* alkaloid by treating natural platydesmine (**3**)[4] with methyl iodide. The resulting isoplatydesmine (**5**), m.p. 187–189°, was identical in all respects with the *Pelea* alkaloid, except for m.p. This apparent dimorphism of isoplatydesmine had been observed by Bowman and Grundon[15] in the synthetic (±)-series.



The second alkaloid from the methanol work-up, R_f 0·30 on alumina, was recrystallized from benzene-petroleum ether as colorless plates, m.p. 136–138°. Spectral analysis (IR, UV, NMR, MS) indicated a 3-alkylated 2-quinolone of structure **6**. This was proven through conversion of platydesmine (**3**) to compound **6** by treatment with methyl iodide, followed by heating with base. Compound **6** is known as edulinine, which was first isolated from the Mexican rutaceous tree *Casimiroa edulis*.[16] Structure **6** was assigned to edulinine on the basis of spectral data,[17] and Boyd and Grundon[18] recently proved the structure by synthesis of (−)-edulinine from (+)-platydesminium metho-salt (**7**), which they had isolated from *Skimmia japonica*.* Boyd and Grundon[18] transformed the metho-salt **7** into edulinine

* The related balfourodinium salt has recently been shown to be an *in vitro* plant growth inhibitor (GARESTIER, R. and RIDEAU, M. (1972) *Compt. Rend.* **274**, 3541).

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(**6**) with aqueous ammonia at 20° and suggested that edulinine might be an artefact and that the metho-salt is the plant constituent, in analogy with similar observations on the furoquinoline alkaloids from *Balfourodendron riedelianum*.[19] We could also show that edulinine (**6**) could only be isolated from *P. barbigera* when an aqueous alkaline solution was allowed to stand at room temperature for several hours or by continuous chloroform extraction of an alkaline solution. Conversely, chloroform extracts of acidic or neutral aqueous solutions contained no edulinine. We have not, however, isolated an edulinine precursor in *P. barbigera*.

Since we did isolate the closely related isoplatydesmine (**5**), we wondered whether this compound might have been derived from edulinine (**6**) by ring closure and ether cleavage during work-up. Treatment of edulinine (**6**) with *p*-toluenesulfonyl chloride in pyridine yielded starting material and a new uncharacterized substance, but no isoplatydesmine.

Edulinine from *Pelea barbigera* is dextrorotatory, $[\alpha]_D$ + 27·2°, while the two previous isolations from *Casimiroa edulis*[16] and *Skimmia japonica*[18] yielded levorotatory (−15° and −20°) material. Isolation of enantiomers is not without precedent in the Rutaceae: it had been observed with balfourolone[19] and hydroxylunacridine,[20] and with the related pair balfourodine[19] and hydroxylunacrine.[21]

EXPERIMENTAL

All m.ps were determined on a Fischer-Johns block and are uncorrected. Combustion analysis by University of California Chemical Analytical Services, Berkeley, Calif. MS were recorded by Sr. M. Roger Brennan and NMR spectra by Mr. James Loo. *Pelea barbigera* was collected in the Kokee area of Kauai and a voucher specimen DH2636 has been deposited in the herbarium of the Pacific Tropical Botanical Garden.

General procedure of isolation. Dried and ground leaves and twigs of *Pelea barbigera* were extracted in a Soxhlet with *n*-hexane for 16–24 hr. The solution was concentrated and the residue was washed with 0·5 M HCl. The aq. soln was 2 × extracted with Et_2O, made alkaline, and again extracted with Et_2O until the soln showed no precipitate with Mayer's reagent. The ethereal soln was dried (K_2CO_3) and concentrated to furnish crude product. In some experiments the crude product was already crystalline (kokusaginine) at this stage and was therefore purified by recrystallization. The plant material was next extracted with boiling MeOH for 72 hr. After evaporating the solvent the residue was taken up in a minimum amount of $CHCl_3$ and thoroughly extracted with 0·5 M HCl. The aq. soln was successively extracted with $CHCl_3$ at pH 7, 8 and 10. In some experiments the acidic soln was made alkaline (pH 12) and extracted with $CHCl_3$. The aqueous layer after these extractions was still positive to Mayer's reagent and was therefore continuously extracted with $CHCl_3$ for 48–72 hr. Each of these extracts showed several spots on TLC, but only 3 of them were isolated and characterized in the present work.

Kokusaginine (**1**). The crude crystalline product (27 mg from 30 g of the plant) from the hexane extract was recrystallized from hexane–ether to furnish 7 mg yellow crystals, m.p. 160–165°. Further recrystallization from 95% EtOH afforded pure kokusaginine as colourless needles; m.p. 170–171° (lit.[22] m.p. 170–171°); IR (KBr), 3130 (m), 2995 (w), 2950 (w), 1625 (m), 1587 (s), 1363 (s), 1250 (s) and 1202 (s). The picrate melted at 205–207° (dec) [lit.[4] m.p. 205–207° (dec)] and the m.m.p. with an authentic sample[4] was undepressed.

Isoplatydesmine (**5**). Treatment of a MeOH extract from 130 g of *P. barbigera* gave rise to 130 mg of basic components. Preparative TLC (alumina G, C_6H_6–$CHCl_3$, 1:4) of this mixture afforded a crystalline compound which upon recrystallization from C_6H_6–$CHCl_3$ furnished 2·5 mg of fine crystals; m.p. 208–210°; R_f 0·12 (alumina G, C_6H_6–$CHCl_3$, 1:4), 0·45 (alumina G, MeOH–$CHCl_3$, 3:100). The compound was identified as isoplatydesmine by IR (KBr), 3400 (s, broad), 2975 (w), 1623 (s), 1585 (s), 1544 sh. (s), 1537 (s), 1515 (s) and 1508 sh. (s) cm^{-1}; UV (EtOH) λ_{max} (log ε), 215 (4·45), 235 (4·40), 250 sh. (4·18), 298 infl. (3·96), 307 (4·06), 318 (4·01) nm; (EtOH–HCl): 216 (4·49), 233 (4·56), 292 (4·08), 300 sh (4·06), 313 infl. (3·85) nm; and MS, *m/e* 259 (M^+), 244 (–Me), 242 (–OH), 226 (–Me, $–H_2O$), 216 (–Me, –CO), 202 (–CO, N–Me), 200 ($–C_3H_7O$), 189, 188 (base, $–C_4H_7O$), and 134 ($–C_4H_7O$, $–C_3H_2O$).

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Conversion of platydesmine to isoplatydesmine. Platydesmine (3·3 mg) and 1 ml MeI were left at room temp. for 24 hr. After removing excess MeI, 0·5 ml dry pyridine was added to the residue and the mixture was heated at 80–100° for 15 hr. Pyridine was removed under vacuum and the residue was partitioned between $CHCl_3$ (5 ml) and H_2O (1 ml). The organic soln was dried and the solvent evaporated to yield crude solid which upon treatment with charcoal and recrystallization from C_6H_6 afforded 2·0 mg of isoplatydesmine, m.p. 187–189° (lit.[15] m.p. 186–187°). UV (95% ethanol, IR (KBr) and MS were identical to those of **5** isolated from *P. barbigera.*

Edulinine (**6**). A continuous $CHCl_3$ extract at pH 10 afforded 190 mg of mixture (from 130 g of the plant material). Two chromatographies of the mixture on TLC (alumina G, MeOH–$CHCl_3$, 1:50, R_f 0·69) and subsequent recrystallization from C_6H_6–petrol. gave 50 mg edulinine as colorless plates; m.p. 136–138° (lit.[16] m.p. 140–142°); UV (95% EtOH or ethanolic HCl) λ_{max} (log ϵ), 227 (4·59), 244 sh. (4·11), 266 infl (3·78), 273 (3·92), 283 (3·89), 315 infl (3·80), 325 (3·90), and 335 sh. (3·76); IR (KBr), 3425 (m), 3220 (m), 1640 sh. (m), 1621 (s), and 1585 cm^{-1} (s); NMR ($CDCl_3$), δ 1·26 (6H, *s*), 2·10 (1H, *s*), 2·66 (1H, *dd*, 14·0, 10·0 Hz), 3·08 (1H, *dd*, 14·0, 2·2), 3·55 (1H, *dd*, 10·0, 2·5), 3·70 (3H, *s*), 3·92 (3H, *s*), 6·98 (1H, br *s*), 7·22–7·88 (4H, complex); MS, *m/e* 276 (–Me), 274 (–OH), 273 ($-H_2O$), 258 (–Me, $-H_2O$), 233, 232 (base, $-C_3H_7O$), 203 ($-C_3H_7O$, –NMe), 202, 200 and 188. (Found: C, 65·81, H, 7·18, N, 4·80. Calc. for $C_{16}H_{21}NO_4$: C, 65·96, H, 7·26, N, 4·80%). $[\alpha]_D^{26.5}$ + 27·2° (*c* 13·6 × 10^{-3}, C_6H_6).

Conversion of platydesmine to edulinine. Platydesmine (2·2 mg) and 0·7 ml MeI were stirred at room temp. for 24 hr. After evaporation of excess MeI, the residue was dissolved in 10 ml H_2O and the UV spectrum recorded ($\lambda_{max}^{H_2O}$ 217, 234, 293, 304 sh and 314 infl). The soln was made alkaline to pH 13, allowed to stand at room temp. for 5 hr and heated at 80° for an additional 2 hr. The UV spectrum of the soln at this stage was completely different from that of the metho-salt but nearly identical to a spectrum of edulinine. The solution was acidified to pH 2 and extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ layer was dried, concentrated, and chromatographed on a thin layer plate (alumina G, MeOH–$CHCl_3$, 1:50) to yield *ca* 1 mg of crystalline compound which showed the same R_f 0·70 on TLC as a sample of **6** isolated from *P. barbigera.* IR ($CHCl_3$) and UV (95% EtOH) spectra were also identical to those of the natural product.

Attempted conversion of edulinine to isoplatydesmine. To a soln of 7·6 mg (0·04 mmol) of toluenesulfonyl chloride in 50 μl dry pyridine was added 11·7 mg (0·04 mmol) of **6** in 150 μl dry $CHCl_3$ at 0°. The mixture was allowed to stand at this temp. for 30 min, then at room temp. (27°) for 10 hr, and heated at 80° for 15 min. After adding a soln of NaI (6·0 mg) in 150 μl dry pyridine the mixture was heated at 80–100° for 9·5 hr, solvent removed, and partitioned between $CHCl_3$ (2 ml) and H_2O (2 ml). The H_2O layer was extracted with $CHCl_3$ (2 × 2 ml). The combined organic layers were washed with H_2O (2 ml), dried and concentrated to yield a mixture which upon chromatography (TLC on alumina G in MeOH–$CHCl_3$ 1:50) furnished 3·5 mg of starting material (R_f 0·67, violet fluorescence in UV) and 6·3 mg of a crystalline compound (R_f 0·81, yellow fluorescence in UV). The latter compound whose chromatographical behavior did not agree with that of furoquinolone **5** (R_f 0·45, violet fluorescent) has not been characterized.

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