Aurapten and Flindersine From Zanthoxylum coco

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Zanthoxylum coco Gill. [= Fagara coco (Gill.) Engl.] (Rutaceae) is a small tree growing at the dry western edge of the Gran Chaco in Bolivia and Argentina, and extending south into the Córdoba Sierras (1). Its morphology and ecology set it aside from most of its South American congeners, which grow in tropical or subtropical rain- or cloud-forests, and its well-worked chemistry has been considered exceptional in the literature context (2).

The alkaloids of the bark and foliage of Z. coco have been studied for more than fifty years, and the quaternary phenethylamine candicine, the quaternary aporphines magnoflorine and N-methylisocorydine, the protoberberines berberine and palmatine, the benzophenanthridines chelerythrine and nitidine, the protopine bases allo-cryptopine and fagarine (11), and the furoquinolines skimmianine (1) and γ-fagarine are all known constituents of this plant (3, 4, 5, 6). On the other hand, no attempt seems to have been made to obtain non-alkaloidal substances from this source, and the less polar hexane extracts have not been analyzed previously.

Recent contributions to the chemistry of Zanthoxylum s. l. (i.e. including Fagara) have cast further doubt on the validity of Engler's classification (7). Bishordeninylterpenes, for example, which are known as metabolites of only four geographically close Zanthoxylum species, have been found in the “primitive” subsection Pterota and in the “advanced” section Tobinia (8). The “modern” alkaloid skimmianine is now known to occur in the Pterota species Z. jagara (9) and Z. culantrillo (10) and in the American Paniculatae (Neogaeae) Z. belisense (11), Z. monophyllum (12), Z. limoncello, Z. caribaeum (9), and Z. microcarpum (8), while a few years ago Z. coco was the only species of this latter group from which any alkaloid of this type had been isolated.

When Fish and Waterman’s seminal paper on the chemosystematics of the Zanthoxylum/Fagara complex was published (2), no coumarins had been described from the Pterota, and Z. elephantiasis and Z. flavum were the only known sources in the Paniculatae (Neogaeae). Since then, coumarins have been found in Z. jagara (9) and in Z. belisense (11). If these species are indeed primitive, as can be construed from their affinities in the Englerian system (7), it would seem that the presence of anthranilate-derived alkaloids and both simple and C-prenylated coumarins is useless as a mark of advancement within Zanthoxylum s. l. Conversely, if these chemical characters are taken to imply specialization in this genus, then the subsections Pterota and Paniculatae (Neogaeae) are either more advanced than had been thought, or heterogeneous.

As part of a specific search for less polar and neutral substances in South American Zanthoxylum species, we have analyzed a hexane extract of Z. coco leaves. Besides skimmianine (1), present in alcohol extracts of this material (3), the coumarin aurapten (2)
and the angular pyranoquinoline flindersine (3) were found. Since these compounds were isolated without the use of acids, it may be concluded that flindersine is present as such in Z. coco and is not, in this case, an artifact produced by the acid hydrolysis of putative precursors as in Z. monophyllum (12).

EXPERIMENTAL

PLANT MATERIAL.—Zanthoxylum coco foliage was collected near Bialet Masé, Córdoba, Argentina, in February (summer), 1978, and identified by Professor A. T. Hunziker. Voucher specimens are retained in the herbaria of the Botanical Museum of the University of Córdoba and of the Natural History Museum in Santiago, Chile.

EXTRACTION AND FRACTIONATION.—Ground and air-dried leaves (650 g) were continuously extracted with hexane (3 liters). The extract was concentrated to a volume of 300 ml, refrigerated overnight, and filtered to remove an abundant precipitate (1.5 g) which was chromatographed (0.70 g) over a column of silica gel in chloroform (A), eluting with the same solvent. The filtrate was extracted with methanol-water (85:15), and the aqueous phase was concentrated to afford a dark oily residue which, when treated with chloroform, deposited a yellowish-white solid (430 mg) showing two major spots on tlc (Merck silica gel GF<sub>254</sub>, chloroform-hexane (9:1)). This product (360 mg) was chromatographed on a column of silica gel in chloroform-hexane (9:1) (B). After elution first with this mixture and then with chloroform, 15 ml fractions were collected and then combined according to their tlc behavior.

SKIMMIANINE (1).—Column A provided first a mixture composed mainly of fatty acid esters (ir, <sup>1</sup>H nmr) and then an alka-loidal residue which when crystallized from methanol, afforded skimmianine (30 mg), identified by comparison with an authentic sample (tlc, mp, ir, uv, <sup>1</sup>H nmr).

AURAPTEN (2).—Fractions 3-10 from Column B were concentrated, and the residue, when crystallized from methanol, yielded white crystals (120 mg), mp 68°; uv λ max (MeOH) 220 (sh), 240 (sh), 252
Aurapten and Flindersine 369

and 320 nm; ir ν max (KBr) 1720, 1610 and 1510 cm⁻¹; ¹H nmr (90 MHz) δ (CDCl₃) 1.65 (s, 3H), 1.75 (s, 3H), 1.80 (s, 3H), 2.0-2.2 (m, 4H), 4.63 (d, J 7, 2H), 5.10 (m, 1H), 5.50 (t, J 7, 1H), 6.25 (d, J 10, 1H), 6.82 (d, J 3, 1H), 6.87 (dd, J 7 and 3, 1H), 7.43 (d, J 7, 1H), 7.65 ppm (d, J 10, 1H); ms m/z (relative intensity) 299.1629 (1.4%) (M⁺, C₁₀H₁₄NO₃ requires 289.1647). The tlc, uv and ir data were identical with that of a reference sample.

FLINDERSINE (3).—Fractions 37-48 from Column B were concentrated. When the residue was crystallized from methanol, it furnished white crystals (98 mg), mp 198°; uv λ max (MeOH) 258 (sh), 310 (sh), 333, 348 and 364 nm; ir ν max (KBr) 3400, 1660 and 1625 cm⁻¹; ¹H nmr (90 MHz) δ (CDCl₃) 1.55 (s, 6H), 5.53 (d, J 10, 1H), 6.80 (d, J 10, 1H), 7.05-7.49 (m, 3H), 7.84 (dd, J 7.5 and 2, 1H), 11.55 (s, 1H); ms m/z (relative intensities) 227.0946 (21.6%) (M⁺, C₁₀H₁₄NO₂ requires 227.0946), 212.0707 (100%) (M⁺-CH₃, C₇H₁₄NO₂ requires 212.0711). The tlc, uv and ir data were identical with that of a reference sample.

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