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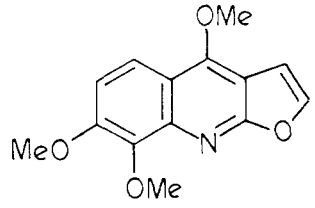
AURAPTEN AND FLINDERSINE FROM *ZANTHOXYLUM COCO*

MIGUEL A. MUÑOZ, RENÉ TORRES and BRUCE K. CASSELS

Universidad de Santiago de Chile, Facultad de Ciencia, Departamento de Química, Santiago 2, Chile

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 allocryptopine and fagarine II, 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.



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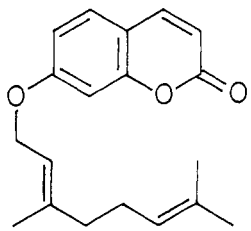
Recent contributions to the chemistry of *Zanthoxylum s. l.* (i.e. including *Fagara*) have cast further doubt on the validity of Engler's classification (7). Bishordeninylterpenes, for example, which are known as metabolites of only four geographically close *Zanthoxylum* species, have been found in 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. fagara* (9) and *Z. culantrillo* (10) and in the American Paniculatae (Neogaeae) *Z. belizense* (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. fagara* (9) and in *Z. belizense* (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**)



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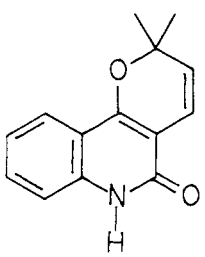
and the angular pyranoquinoline flindersine (**3**) were found. Since these compounds were isolated without the use of acids, it may be concluded that flindersine is present as such in *Z. coco* and is not, in this case, an artifact produced by the acid hydrolysis of putative precursors as in *Z. monophyllum* (12).



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These results lend further support to the notion that coumarins are rather widespread in American *Zanthoxylum* species belonging to different sections. In fact, comparing data for American and Old World species (13), the number of occurrences in each group appears to be merely a reflection of the number of species examined. Aurapten is not a common *Zanthoxylum* metabolite, and in this genus it has only been isolated from *Z. ovalifolium* (14), of the Asian Paniculatae (Gerontogaeae). It is also the only known *O-prenylated* coumarin from these plants, but more information is needed before its systematic value can be assessed.

Angular pyranoquinolines, such as flindersine, are also quite unusual in *Zanthoxylum*, where they have been found only in *Z. monophyllum* (12) and *Z. chalybeum* (15), of the American and African Paniculatae, respectively. Here again we cannot draw any reasonable conclusion from such isolated data, which may or may not point to an exceptional position for *Z. coco* among its South American relatives. Further analyses of these plants should pay special attention to the possible presence of coumarins, anthranilate-derived alkaloids, and protopine bases. With regard to these latter compounds, *Z. coco* still appears to be unique among all studied American *Zanthoxylum* species unless one considers a report on the presence of allocryptopine in an extract believed to be of the very variable *Z. rhoifolium* Lam. (16) [=*Fagara rhoifolia* (Lam.) Engl.]. The report could not be confirmed in later work (6).

EXPERIMENTAL

PLANT MATERIAL.—*Zanthoxylum coco* foliage was collected near Bialet Massé, 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_{254}, 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, ^{1}H nmr) and then an alkaloidal residue which when crystallized from methanol, afforded skimmianine (39 mg), identified by comparison with an authentic sample (tlc, mp, ir, uv, ^{1}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

and 320 nm; ir ν max (KBr) 1720, 1610 and 1510 cm^{-1}; ^1H nmr (90 MHz) δ ($CDCl_3$) 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^+, $C_{19}H_{22}NO_3$ requires 299.1647). 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 ($CDCl_3$) 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^+, $C_{14}H_{13}NO_2$ requires 227.0946), 212.0707 (100%) (M^+–CH_3, $C_{13}H_{10}NO_2$ requires 212.0711). The tlc, uv and ir data were identical with that of a reference sample.

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