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ALKALOIDS OF *ZANTHOXYLUM MONOPHYLLUM* AND *Z. PUNCTATUM*

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Key Word Index—*Zanthoxylum monophyllum*; Rutaceae; zanthophylline; desmethylzanthophylline; columbianetin; *Z. punctatum*; berberine; *N*-methylcorydine; magnoflorine; chemosystematics.

Abstract—The known alkaloids *N*-methylcorydine and magnoflorine were major constituents of stems and branches of *Zanthoxylum punctatum* (Rutaceae). Berberine was the major alkaloid of *Z. monophyllum*, which also contained a new pyrano-2-quinolone alkaloid, zanthophylline, and its desmethyl analog. Zanthophylline has an —NCH_2OAc functional group which is readily hydrolyzed by dilute acid. Methyl vanillate and the furocoumarin columbianetin were also found in *Z. monophyllum*.

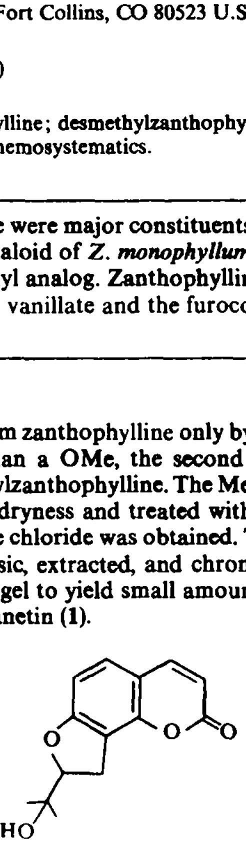
INTRODUCTION

The genus *Zanthoxylum* (Rutaceae) is a rich source of alkaloids, coumarins, furocoumarins and other metabolites [1, 2]. Two of the alkaloids, nitidine and fagaronine, have shown promise as antitumor agents. There have been problems with the taxonomy of *Zanthoxylum* (many species of which were previously included under the name *Fagara*) and extensive reviews of pertinent chemosystematic work are available [1–3]. In contrast to the well-investigated species from Africa and Asia, those of Central America and the West Indies have been relatively little studied. In the hope of contributing to the chemosystematics of the genus and perhaps discovering new alkaloids, we have begun a chemical investigation of the *Zanthoxylum* of the West Indies and Central America. In the present work, results of studies on two Puerto Rican species, *Z. monophyllum* Lam. and *Z. punctatum* Vahl., are described. According to the Engler classification [4] the former belongs to the widespread American subsection Neogaeae, section Macqueria. Engler lists [4] 90 species in this subsection and a few have been chemically studied. *Z. punctatum* is one of 25 species placed by Engler in the section Tobinia and none of these have previously been investigated.

RESULTS

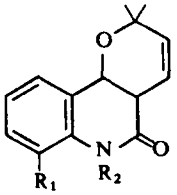
Z. monophyllum

Stems and branches of *Z. monophyllum* were extracted successively with petrol, $CHCl_3$ and MeOH. TLC indicated the presence of alkaloids in all fractions, but only traces were in the petrol extract. The $CHCl_3$ extract was divided into two, one of which was evaporated to dryness, the residue taken up in acetone–water, extracted with petrol and the acetone solution removed *in vacuo*. The crude residue was chromatographed on silica gel using a low pressure system (LPLC). Berberine was found to be a major alkaloid along with an unknown which was named zanthophylline. A small amount of a second unknown was present and, since it was soon found to differ from zanthophylline only by having a phenolic OH rather than a OMe, the second unknown was named desmethylzanthophylline. The MeOH extract was evaporated to dryness and treated with HCl. A precipitate of berberine chloride was obtained. The acidic solution was made basic, extracted, and chromatographed by LPLC on silica gel to yield small amounts of Me vanillate and columbianetin (1).



1 columbianetin

Half of the original $CHCl_3$ extract was treated with 2N HCl and the acidic layer was then made basic to pH 9. This was extracted with $CHCl_3$ and the $CHCl_3$ residue chromatographed as before. In addition to berberine, an unknown alkaloid was found whose spectral properties (MS, IR, PMR and UV) suggested that it could be assigned the structure of 8-methoxyflindersine (2). This was proved to be correct since 2 had identical spectra (PMR, IR and UV) with an authentic synthetic sample [5].

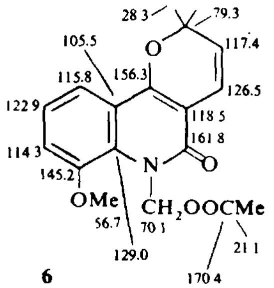


2 R_1 = OMe, R_2 = H (8-methoxyflindersine)
3 R_1 = OMe, R_2 = $C_2H_5O_2$
4 R_1 = OMe, R_2 = CH_2OCOMe (zanthophylline)
5 R_1 = OH, R_2 = CH_2OCOMe (desmethylzanthophylline)

Zanthophylline was shown by combustion analysis and MS to have the molecular formula $C_{18}H_{19}NO_5$. The UV, IR and PMR spectra indicated that zanthophylline was an angular pyrano-2-quinolone with one OMe group. Comparison with **2** and with the spectra of a standard sample of flindersine [6] confirmed this assignment so that the part structure **3** could be assigned to zanthophylline. Since no zanthophylline but rather 8-methoxyflindersine was found in the extract which was treated with acid, the missing $C_2H_5O_2$ fragment would have to be an easily hydrolyzable group on the nitrogen. PMR showed a 3 proton singlet at 2.14 ppm and the IR a major absorption at 1742 cm^{-1}. Taken together these data indicated a —OCOMe grouping and this was conformed by the ^{13}C spectrum of zanthophylline which revealed carbons at 170.40 ppm for the ester carbonyl and at 21.07 for a Me on a carbonyl. If —O_2CMe is subtracted from $C_2H_5O_2$, the remainder is CH_2 and hence the substituent on the nitrogen should be —CH_2O_2CMe. A two proton singlet appeared in the PMR at 6.6 ppm and a carbon resonance at 70.11 ppm. These were assigned to the N—CH_2—O protons and carbon respectively. If these assignments are correct, the structure of zanthophylline should be **4**. This was confirmed by mild hydrolysis of zanthophylline which yielded 8-methoxyflindersine and formaldehyde (identified as the 2,4-DNP derivative).

Only a few mg of the second unknown was obtained as a semi-solid, but PMR analysis showed only trace impurities. Sufficient material was not available for complete characterization and structural proof. IR showed the ester carbonyl absorption and also an OH band. The UV spectrum was very similar to that of zanthophylline and a slight base shift occurred. In the PMR, the OMe peak was missing but the spectrum was otherwise nearly identical with that of zanthophylline. The MS showed a M$^+$ at m/e 315 which would correspond to $C_{17}H_{17}NO_5$ and gave fragmentation peaks which were in accord with our assignment of the desmethylzanthophylline (**5**) structure to this unknown.

There are no published ^{13}C NMR spectra of pyranoquinoline alkaloids, and, since this aided in the structure proof for zanthophylline, we give our assignments for zanthophylline and flindersine in structures **6** and **7**. These were based on models such as carbostyril as well as assignments given recently [7] for some simple substituted 2- and 4-quinolones.



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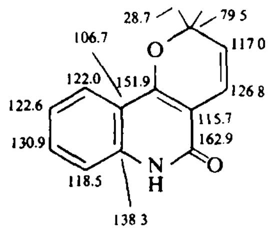

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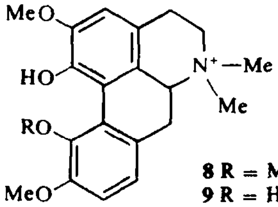
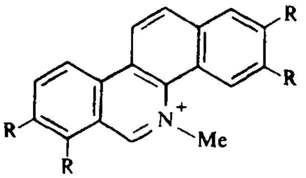
Z. punctatum

Ground stems and branches of *Z. punctatum* were extracted in a similar manner to that given above and, again, the petrol extract showed little of interest. The MeOH extract was reduced in volume and crystals formed which were shown to be sucrose (about 0.5% dry wt). The MeOH evaporated residue was treated with HCl, made basic to pH 9 and extracted with $CHCl_3$. The residue was chromatographed on Sephadex LH 20 and yielded pure samples of (+)-N-methylcorydine (**8**) and magnoflorine (**9**). Traces of other polar alkaloids were present but not in sufficient quantity to isolate at this time.



8 R = Me (N-methylcorydine)
9 R = H (magnoflorine)

When the $CHCl_3$ extract was evaporated nearly to dryness, 5 mg of an orange–yellow solid alkaloid, named punctatine, was obtained. High resolution MS established its molecular formula as $C_{21}H_{20}NO_4$ and the fragmentation pattern as well as the UV spectrum were very characteristic of those of benzophenanthridine alkaloids. The UV spectrum showed a base shift in keeping with the presence of a phenolic group. A benzophenanthridine with 3 OMe groups and one phenolic OH is in keeping with the data on punctatine. Many *Zanthoxylum* species have yielded benzophenanthridines related to either nitidine and fagaronine or to chelerythrine. We have previously [8] synthesized all possible trimethoxymonohydroxy benzophenanthridines of the nitidine–fagaronine type and none were identical with punctatine. These alkaloids all have a characteristic light yellow–green color, while only the chelerythrine–sanguinarine type are generally orange–yellow. Based upon these ideas as well as the MS fragmentation pattern, part structure **10** is suggested for punctatine.



10 R = 3 × OMe, 1 OH (punctatine)

DISCUSSION

Zanthophylline and desmethylzanthophylline are new alkaloids and contain the rare —NCH_2CO_2CMe grouping. As far as we are aware, the only other report of such a function was in a 4-quinolone from *Boronia ternata* [9], also a Rutaceous plant. No N-demethyl compounds are found when acid is not used in the isolation scheme and this raises the question as to whether or not alkaloids such as flindersine (**7**) are artifacts rather than natural constituents. Either possibility seems equally valid at this time since biological N-demethylations apparently proceed through conversion of N—Me to N—CH_2OH. Acetylation in *Z. monophyllum* has apparently completely intercepted the intermediate leading to N-demethylation.

A current hypothesis [3, 10] in the evolution of *Zanthoxylum* is that alkaloids from the benzylisoquinoline biosynthetic pathway are markers of more primitive species, while occurrence of quinoline-type alkaloids (anthranilic acid pathway) and furocoumarins are indicative of more advanced species. If this holds true in the present case, then *Z. punctatum* would represent a more primitive species and, since this is the first species of the section Tobinia to be studied, might point to that section as a more primitive one. Unfortunately, the Engler classification [4] places the section Tobinia late in development. Our work thus indicates that either the use of the benzylisoquinoline pathway as a primitive marker is not valid or the Engler classification is in error.

The situation with *Z. monophyllum* is equally unclear. As a member of the Neogaeae, the species should be primitive, but it contains a quinolone alkaloid as a major constituent and the furocoumarin columbianetin. The presence of berberine as the major alkaloid is unique in *Zanthoxylum* since it has only been detected in trace amounts in two previous species. Interestingly, both other occurrences are in American species: *Z. caribeum* [11] from Central America and *Z. coco* [12] from South America. It should also be pointed out that zanthophylline represents the first angular pyranoquinoline to be found in *Zanthoxylum*. If future research shows that the Neogaeae is indeed primitive, then *Z. monophyllum* might represent a bridge from the more primitive to the more advanced sections. A previous occurrence of columbianetin was in *Z. arnottianum* [13], an Asian species.

EXPERIMENTAL

Plant material. Stems, branches and leaves of *Z. monophyllum* (Lam.) P. Wilson (known as 'Palo rubio' or yellow prickly ash) were collected on May 22, 1975, northeast of Salinas on Road 712 near the town of Carmen, Puerto Rico. Plant material was collected from one roadside tree with two stems *ca* 10 cm and 5 cm in diameter. It had new foliage and flower buds. All specimens were separately air dried and were ground to coarse powders. Stems, branches and leaves of *Z. punctatum* Vahl. (known as 'Alfiler' or toothache-ache) were collected on May 29, 1975, from the Susua Forest, just beyond the dam, northwest of Yauco and northeast of Sabana Grande, Puerto Rico. It was a shiny small tree *ca* 100 m south of the road. It had fairly new foliage, flower buds and some of the old fruit. It was the only tree with leaves on it, and the leaves were mostly trifoliate. These collections were made by Drs Roy Woodbury and Luis Amoros and the identification was by Dr Woodbury, University of Puerto Rico.

Z. monophyllum. Powdered stems and branches (1328 g) were successively extracted to exhaustion in a Soxhlet with petroleum (bp 40–60°), $CHCl_3$ and finally with MeOH. Analysis of the MeOH extracts by TLC on Si gel (*n*-BuOH–Py–H_2O (6:4:3) used throughout unless otherwise noted) indicated the presence of alkaloids. The petrol extract contained very low concns of the same alkaloids as the $CHCl_3$ extract and was not investigated further. The $CHCl_3$ extract was concd under red. pres. to a vol. of 200 ml. It was divided into two 100 ml parts. One part was evapd under red. pres. and the residue dissolved in Me_2CO–H_2O and extracted with petrol. Evaporation of the Me_2CO soln left 3.4 g of crude material. This was mixed with 1 g of Si gel (Woelm 0.032–0.063 mm) placed in the top of a column (2.5 × 100 cm) which was packed with the same kind of Si gel and chromatographed on a LPLC system. Elution was with C_6H_6–EtOAc (9:1). After alkaloids ceased being eluted, the column was back-flushed with MeOH. The MeOH back-flush was evapd to dryness and prep-TLC of a portion yielded an alkaloid which, after addition of H_2SO_4, was confirmed as berberine sulfate by TLC, IR, UV and PMR (yield 900 mg). Fractions 49–52 of the LPLC showed a single spot on TLC ($R_f = 0.66$). These fractions were combined and evapd to yield 600 mg of zanthophylline which was washed with hexane and then recrystallized from hot MeOH–H_2O to give white crystals, mp 126–127°. IR (KBr): 1742 (RCOO), 1640 and 1660 (2-quinolone), 1610 peak, and a minimum between 1500–1565 cm^{-1} (2-quinolone); PMR ($CDCl_3$) ppm: 1.5 (*s*, 6H, Me—C—Me), 2.14 (*s*, 3H, MeC=O), 3.94 (*s*, 3H, OMe), 5.6 (*d*, 1H, $J = 10$ Hz, —CH=CH—), 6.6 (*s*, 2H, O—CH_2—N), 6.8 (*d*, 1H, $J = 10$ Hz, —CH=CH—), 7.08 (*m*, 1H, $J = 3$ Hz, aromatic), 7.15 (*t*, 1H, $J = 7$ Hz, aromatic), 7.58 (*dd*, 1H, $J = 3$ Hz); UV λ_{max}^{EtOH} nm (log ε), 220 (4.43), 247 (4.36), 254 *sh* (4.34), 320 (3.91), 333 (4.02), 346 (3.96) and 366 (3.78); MS *m/e* 329 ($C_{18}H_{19}NO_5$, 30%, M^+), 314 (M^+-Me, 36%), 270 (M^+-$MeCO_2$), 242 (314-$MeCO_2CH$, 55%), 227 (18%), 226 (M^+-2Me, —$MeCO_2CH_2$, 40%). Found: C, 65.98; H, 5.65; N, 4.25%. $C_{18}H_{19}NO_5$ requires: C, 65.65; H, 5.77; N, 4.25%. ^{13}C NMR was determined in $CDCl_3$ using an instrument in the proton noise decoupled mode and absorptions are given on structure **6**. A total of 25 mg of partially impure dark brown semi-solid was obtained from fractions 46 and 47. This was washed with hexane, but did not crystallize. PMR ($CDCl_3$) ppm: 1.54 (*s*, 6H, Me—C—Me), 2.14 (*s*, 3H, $MeCO_2$), 5.54 (*d*, 1H, $J = 10$ Hz, —CH=CH—), 6.35 (*s*, 2H, O—CH_2—N), 6.73 (*d*, 1H, $J = 10$ Hz, —CH=CH—), 7.4 (*m*, 2H, aromatic), 8 (*q*, 1H $J = 3$ Hz): IR ($CHCl_3$): 3500 (O—H broad), 1750 MeCOO), 1660 and 1640 peaks and a minimum from 1500 to 1565 cm^{-1} (2-quinolone); UV λ_{max}^{EtOH} 365 (3.79), 350 (4.02), 333 (4.01), 320 (3.97), 308 *sh* (3.84), 253 *sh* (4.23), 220 (4.71) and 207 nm (4.86). Upon addition of NaOH a base shift of the 253 nm peak in the UV was observed. MS *m/e* 315 ($C_{17}H_{17}NO_5$, M^+, 22%), 300 (M^+-Me, 9%), 299 (M^+-Me and H, 18.6%), 273 (M^+-MeCO, 37%), 257 (M^+-$MeCO_2$, 26%), 244 (M^+-$MeCO_2CH$, 24.3%), 227 (15%), 212 (57%). This unknown was named desmethylzanthophylline. Insufficient material was available for further work. The MeOH extract was evapd down and 450 ml of 2N HCl was added to the heavy syrup. The acidic soln was made alkaline to pH 9 and the basic soln was extracted with $CHCl_3$. The $CHCl_3$ soln was evapd and the residue was chromatographed by LPLC. Elution started with $CHCl_3$–MeOH 49:1 and finished with 1:1. Fractions 9–15 contained a mixture of two compounds which were separated by PLC on Si gel ($CHCl_3$–MeOH, 99:1). A band at R_f 0.45 proved to be Me vanillate, whose IR, PMR and MS were identical with lit. A band at R_f 0.2 which gave a positive color test with Dragendorff reagent and fluoresced light blue under UV was scraped from the plate and extracted with $CHCl_3$–MeOH (9:1). A brown–orange viscous oil which was obtained gave the following spectral data: PMR (100 MHz, $CDCl_3$) ppm: 1.22 (*d*, 6H, $J = 10$ Hz), 1.44 (*s*, 1H, OH), 3.2 (*d*, 2H, $J = 8.5$ Hz), 4.64 (*t*, 1H, $J = 8.5$ Hz), 6 (*d*, 1H, $J = 9$ Hz), 6.54 (*d*, 1H, $J = 8$ Hz), 7.04 (*d*, 1H, $J = 8$ Hz), and 7.38 (*d*, 1H, $J = 9$ Hz); IR (KBr): 3420 (OH), 1720, 1740 (C=O), and 1620 cm^{-1}; UV λ_{max}^{EtOH} 328, 264, 252, 220 *sh* and 212 nm; high resolution MS: *m/e* 246.0858 (28.4%, 246.0875 calculated for $C_{14}H_{14}O_4$), 231 ($C_{13}H_{11}O_4$. 3.2%, M^+-Me), 228 ($C_{14}H_{12}O_3$, 12.7%, M^+-H_2O), 213 ($C_{13}H_9O_3$, 41.5%, M^+-H_2O—Me), 188 ($C_{11}H_8O_3$, 67.7%, M^+-$C(Me)_2O$), 187 ($C_{11}H_7O_3$, base peak, M^+-$C(Me)_2OH$), 185 ($C_{11}H_5O_3$, 10.2%), 160 ($C_{10}H_8O_2$, 31.3%, 188-CO) and 159 ($C_{10}H_7O_2$, 15.7%, 187-CO). The above spectral data are identical with those given for columbianetin [13]. Fractions 86–110 of the LPLC yielded 700 mg of berberine.

Hydrolysis of zanthophylline. Zanthophylline (30 mg) was dissolved in 1 ml MeOH and 9 ml H_2O added. To this soln 3 drops of conc H_2SO_4 was added and the soln refluxed for 3 hr. The soln was then made alkaline (pH 9) by adding dry $Ba(OH)_2$ and the ppt. of $BaSO_4$ removed by centrifugation. Hydrolyzed zanthophylline was extracted ×3 with $CHCl_3$ (5 ml) and IR and PMR recorded. To the aq. layer 5–6 drops of dil. H_2SO_4 was added to ppt. the extra Ba^{2+}. To this soln a few drops of 2,4-dinitrophenylhydrazine was then added and the yellow-orange ppt. was separated by centrifugation. It was recrystallized from EtOH, mp 160°. R_f 0.74 ($CHCl_3$–MeOH, 99:1), and 0.69 n-BuOH–Py–H_2O, 6:4:3) These data were identical with those obtained from formaldehyde-DNP. The PMR and IR spectra of hydrolyzed zanthophylline were identical with an authentic synthetic [5] sample of 8-methoxyflindersine. Half of the original $CHCl_3$ extract of *Z monophyllum* stems and branches was treated with 2N HCl and the acidic layer separated This was made basic to pH 9 and extracted with $CHCl_3$. The $CHCl_3$ was evapd to dryness and the residue chromatographed on Si gel (LPLC). No zanthophylline was found, but 8-methoxyflindersine was isolated.

Z. punctatum. Dried and ground stems and branches (817 g) were extracted as above. The MeOH extract was concd under red. pres. to a vol. of 200 ml. On standing, crystals separated which were filtered out and washed with MeOH. These were identified as sucrose by PMR and comparison with a known sample (0.5% dry wt). To the MeOH soln, 200 ml of 5% HCl was added and the soln extracted with $CHCl_3$ and then made alkaline to pH 9. This basic soln was reextracted with $CHCl_3$ and 7.2 g of crude alkaloid mixture was obtained. Preliminary TLC and UV tests indicated this to be a mixture of two aporphine quaternary alkaloids. They had PC R_f values of 0.2 and 0.75 on Whatman No. 1 (0.1 N HCl). Therefore 3.4 g of the mixture was dissolved in 4 ml H_2O and a satd soln of KI was added dropwise until no further ppt. was formed. Repeated recrystallization of the ppt. from MeOH yielded white crystals which were chromatographed on Sephadex LH 20 using $CHCl_3$–MeOH (1:1). Fractions containing $R_f = 0.75$ were combined and were rechromatographed on Sephadex. Fractions containing only the $R_f = 0.75$ spot were combined. Upon evaporation of solvent 3.2 g of a white–yellow solid was formed which was recrystallized from MeOH to yield pure white crystals, mp 217°. IR (KBr): 3440 (OH) and 1600 cm^{-1} (C=C): PMR (D_2O) ppm: 2.7 (*s*, 3H, N—Me), 3.1 (*s*, 3H, N—Me), 3.3 (*s*, 3H, OMe), 3.62 (*s*, 3H, OMe), 3.7 (*s*, 3H, OMe), 6.65 (*s*, 2H, aromatic), 6.78 (*s*, 1H, aromatic) and unresolved signals of aliphatic protons between 2.5–4; UV λ_{max}^{EtOH} 302 *sh*, 270 and [illegible] nm and λ_{min}^{EtOH} 295, 250 nm; UV base shift: λ_{max}^{EtOH} 350, 280 *sh*, 250 *sh* and 232 nm; MS *m/e* 356 M^+, 355 (M^+-H), 343 (M^+-Me), 341; $[\alpha]_D^{22}$ + 152 ($c = 0.7$, MeOH). These data are identical in all respects with those of (+)-corydine methiodide [14]. Fractions containing alkaloid PC R_f 0.2 (Whatman No. 1, 0.1 HCl) were combined. This crude material was rechromatographed on Sephadex and the eluate yielded 45 mg of a quaternary aporphine alkaloid which by spectral analysis and comparison with an authentic sample was identified as magnoflorine. The $CHCl_3$ extract was concd *in vacuo* until a yellow ppt. formed. This was separated by centrifugation to yield 5 mg of an orange–yellow solid (punctatine). The UV spectrum in acidified EtOH showed λ_{max} 390, 340 *sh*, 325 *sh*, 318, 305 *sh*, 280 *sh* and 270 nm and λ_{min} at 355 and 295 nm. Addition of base gave λ_{max} 335 *sh*, 302 (enhancement of 270 nm peak), 288 and 255 nm. The MS showed a very weak M^+ peak at *m/e* 350 but, in keeping with the behavior of many quaternary bases, showed an M^+-1 peak at *m/e* 349. Other prominent peaks were at *m/e* 333, 319 (base peak), 304 and 276. Both the UV-visible and MS data suggest that punctatine is a benzophenanthridine alkaloid containing 3 OMe groups and one OH. Spectral data for all possible combinations of these substituents in the nitidine–fagaronine pattern were available from synthetic [8] benzophenanthridines. Punctatine was not identical with any of these. The UV-visible and MS of punctatine suggest that it has the part structure **10**.

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