Alkaloids of *Ocotea acutangula*

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The leaves of *Ocotea acutangula* (Mez) contain, in addition to the known (*S*)-(−)-pallidine (5) and its new derivative (*S*)-(−)-*O*-methylpallidine (6), the new 8,14-dihydromorphinandienone alkaloids (*S*)-(−)pallidinine (7) and (*S*)-(−)-*O*-methylpallidinine (8) which possess a B/C *trans*-junction.

MORPHINANDIENONE alkaloids are widely distributed in many plants of the Papaveraceae and Menispermaceae families. They play an important role as biosynthetic intermediates in the formation of pharmacologically active morphinanes [1] and several reports concerning their chemical behaviour and occurrence have appeared.[2] Furthermore, the ready *in vitro* conversion of morphinandienones into aporphines may strongly suggest their role as *in vivo* precursors of aporphine alkaloids.[3] On the other hand, the corresponding 8,14-dihydromorphinandienones, whose importance and formation have yet to be clarified, are a small class of compounds found only rarely in nature, namely, 8,14-dihydrosalutaridine (1) in *Croton discolor*,[4] *Croton linearis*,[5] and *Croton plumieri*,[6] its nor-derivative (2) in *Croton linearis*,[5,7] isosinomenine (3) in *Sinomenium acutum*,[8,9] ocobotrine (4) in *Ocotea brachybotra*,[10] and the not fully elucidated delavaine in *Stephania delavayi*.[11]

In our studies on the South American Lauraceae of the genus *Ocotea*, we have found that leaves of *Ocotea acutangula* (Mez) contain only morphinandienones and 8,14-dihydromorphinandienones, namely the known (*S*)-(−) pallidine (5),[12] the unreported natural (*S*)-(−)-*O*-methylpallidine (6),[12] and two new compounds for which we have established the structures of (*S*)-(−)-pallidinine (7) and (*S*)-(−)-*O*-methylpallidinine (8).

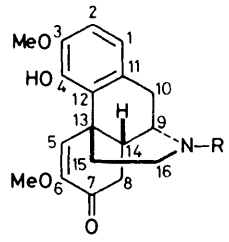
From the chemotaxonomic point of view, isolation of morphinandienone alkaloids from *Ocotea acutangula* is of interest since this type of alkaloid has been previously found only in *Cassytha pubescens*,[13] *Litsea sebifera*,[14] and *Ocotea brachybotra*.[15]

After the usual extraction and chromatographic separation, (*S*)-pallidine was isolated in a crystalline solvated form from acetonitrile, and identified by direct comparison with an authentic sample.

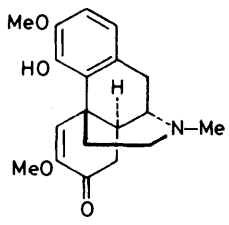
The second alkaloid (6), $C_{20}H_{23}NO_4$, crystallized from diethyl ether as colourless needles and its spectroscopic data corresponded to those of a 2,3,6-trimethoxymorphinandienone already isolated as a racemate from *Litsea sebifera* [14] and *Rhigiocarya racemifera*,[16] and as the *laevo*-isomer from *Nemuaron vieillardii*.[17]

The absolute configuration of (6), *i.e.* (*S*), is established by means of c.d. measurements, being closely related to that for (*S*)-(−)-pallidine (5).[18] In addition, (6) is obtained by methylation of (5) with dimethyl sulphate and potassium t-butoxide.†

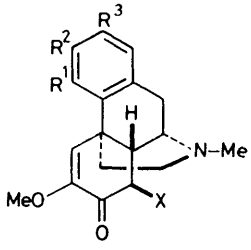
As regards the two other alkaloids (7) and (8), they are structurally related since crystalline (7), $C_{19}H_{19}NO_4$, on methylation gives rise to a product identical in all respects to *O*-methylpallidinine (8). This was a solid which did not crystallize and was characterized as the



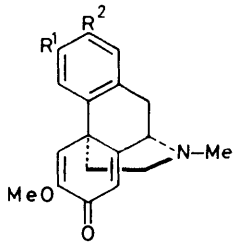
(1) R = Me
(2) R = H



(3)



(4) R^1 = OH, R^2 = OMe, R^3 = H, X = H
(7) R^1 = H, R^2 = OMe, R^3 = OH, X = H
(8) R^1 = H, R^2 = R^3 = OMe, X = H
(12) R^1 = H, R^2 = R^3 = OMe, X = Br



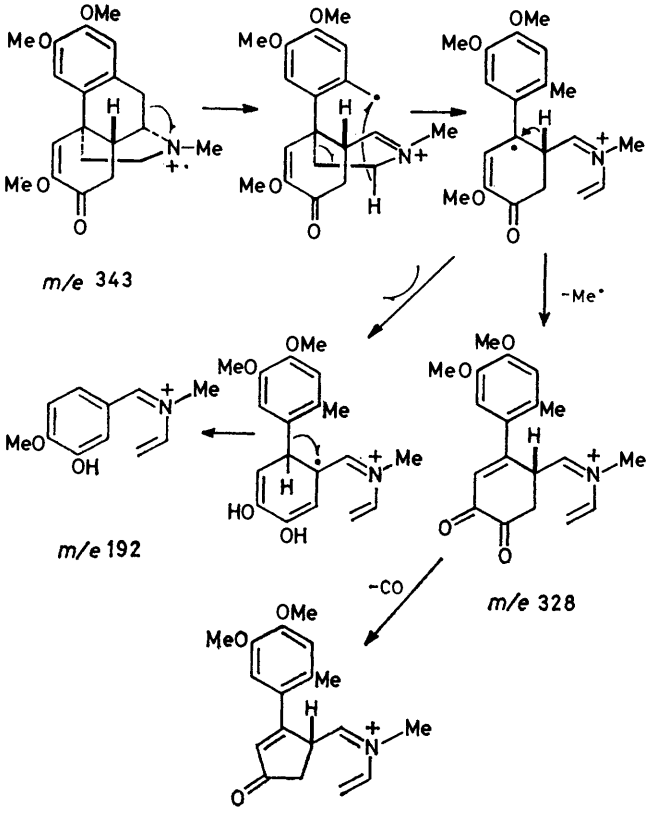
(5) R^1 = OMe, R^2 = OH
(6) R^1 = R^2 = OMe

hydrochloride. The u.v. spectrum of the base was characteristic of a 8,14-dihydromorphinandienone; this was confirmed by the i.r. spectrum which showed the presence of a conjugated enone system (see Experimental section). Apart from the stereochemistry of the B/C ring junction, supporting evidence for the structure (8) is furnished by the ^{1}H n.m.r. spectrum which exhibits *inter alia*, seven singlets for nine *O*-methyl protons, three *N*-methyl protons, and three isolated protons for H-1,

† Kametani *et al.* obtained (6) as a syrup by *O*-methylation of (−)-pallidine using diazomethane (refs. 11 and 18).

H-4, and H-5. The appearance of aromatic protons as singlets assists in fixing the positions of the aromatic substituents.

The remaining problem of determining the stereochemistry in (8) is approached by analysis of the mass spectrum, which, besides the intense molecular ion peak at *m/e* 343 (100%), displays significant fragments at *m/e* 328 ($M^{+\cdot}$ − Me), 300, and 192 and only a weak peak at *m/e* 59 (C_3H_9N) (Scheme). As *N*-methyl compounds in the B/C *cis* series show a strong peak at *m/e* 59 whereas, in all cases, B/C *trans* compounds give no peak or only a very weak peak at *m/e* 59, (8) may be assumed to possess a B/C *trans* junction. The striking difference in the mass spectra of the morphine–morphinane series as a function of the stereochemistry at C-14 is attributed to the spatial arrangement of 14-H and the nitrogen-containing side-chain that rearranges in the key fragmentation step.[19] This attribution is inferred by the ^{13}C n.m.r. spectrum and unequivocally supported by chemical correlation. The ^{13}C n.m.r. spectrum of (8) may be compared with that of ocobotrine (4) whose structure,



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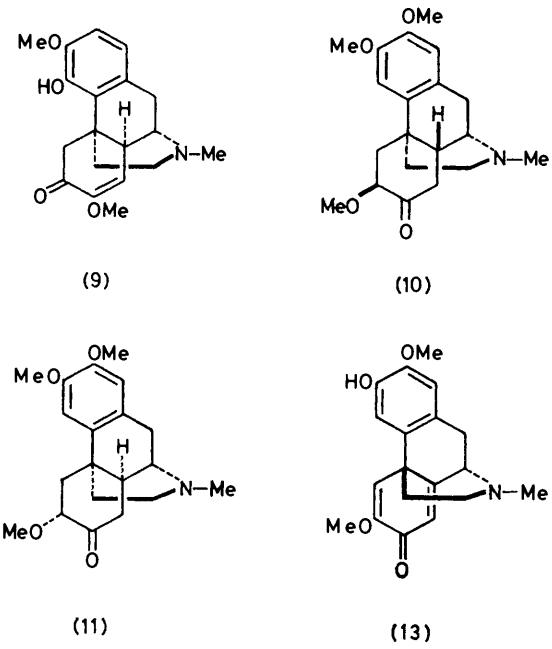
including the B/C *trans*-junction, has been previously reported by some of us.[10] In the spectrum of (4) a triplet at δ 32.15 p.p.m. is attributed to C-15 because its broadening and additional splitting due to second-order effects[20] provide evidence that it is adjacent to C-16. The aliphatic pattern of the ^{13}C n.m.r. spectrum of (8) closely resembles that of (4): the shifts of C-8, -10, -14, and -16 are almost identical, showing that (8) has the same steric arrangement of carbon atoms as in (4).*

The proposed structure (8) and its absolute configuration (*S*) are corroborated by chemical correlation with (6). Catalytic hydrogenation of (8) over 10% Pd–C in ethyl acetate at room temperature gives a mixture of dihydro-derivatives epimeric at C-6 which, after base-induced epimerization, affords the thermodynamically stable isomer (10) having an equatorial 6-OMe group. This last compound is different (t.l.c., ^1H n.m.r.) from the tetrahydro-derivative (11) obtained from (6) by a similar reduction–equilibration sequence. The catalytic reduction of morphinandienones requires the close approach of both C-8 and C-14 to the surface of the catalyst. This can only occur on the least hindered side of the molecule, *i.e.* it results in addition of hydrogen to C-14 on the same side as the nitrogen-containing bridge[5,21] to give a B/C *cis*-fusion. Thus (8) has a B/C *trans*-fusion.



Finally, the absolute configuration (*S*) of (8) was confirmed by dehydrogenation to (6). Thermodynamically controlled bromination of (8) in trifluoroacetic acid–HBr gave the α-bromo-ketone (12) which possesses a *cis*-pseudo-equatorial–axial relationship between its 8β-Br and 14β-H atoms, as confirmed by the magnitude of the 8-H–14-H coupling constant (^3J 13 Hz). Dehydrobromination of (12) in neat 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) at room temperature provided a single product which was identical in all respects to (6). The elimination probably proceeds through a base-catalysed

* Details of the ^{13}C n.m.r. spectra of compounds (4) and (8) are available as Supplementary Publication No. SUP 22906 (2 pp.) (see Notice to Authors No. 7, in *J.C.S. Perkin I*, 1979, Index issue).

isomerization 8β-Br(*eq*) ⟶ 8α-Br(*ax*) since the C-14-hydrogen and the 8β-bromine atoms are unable to adopt a 180° *trans* relationship to allow concerted elimination.

Turning now to pallidinine (7), this alkaloid could, at least *a priori*, possess the same aromatic substitution pattern as flavinantine (13) (OMe and OH in positions 2 and 3 respectively) or pallidine (5). The 100-MHz ^{1}H n.m.r. spectrum of pallidinine was obtained and extensive spin–spin decoupling experiments carried out to determine the substitution at C-2 and -3. The spectrum exhibits complex unresolved signals spread between δ 1.8 and 3.8 due to the aliphatic protons, three singlets at δ 2.36, 3.70, and 3.90 for NMe, 3-OMe, and 6-OMe, and three slightly broad singlets at δ 6.38, 6.71, and 6.86 which we assign to 1-H, 4-H, and 5-H, respectively. In fact, irradiation at δ 3.70 and 3.90 caused the signals at δ 6.71 and 6.86 to collapse into sharp singlets due to vanishing of long-range couplings.* Furthermore, irradiation of the aliphatic region near δ 2.70 (benzylic protons) simplifies only the δ 6.38 singlet, so that the methoxy-group on the aromatic ring of pallidinine must be located at C-3 as depicted in (7).

EXPERIMENTAL

Analytical and preparative t.l.c. was performed on Kieselgel 60 F_{254}; column chromatography was carried out on Kieselgel G. I.r. spectra were recorded for KBr discs on a Perkin-Elmer 257 instrument and u.v. spectra for solutions in methanol on a Perkin-Elmer 124 instrument. ^{1}H N.m.r. spectra were run with NEVA 14 or XL-100 spectrometers operating at 60 and 100 MHz, respectively, with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Pulsed Fourier-transform ^{13}C n.m.r. spectra were recorded with a Varian XL-100 spectrometer operating at 25.2 MHz. Chemical shifts are expressed in p.p.m. downfield from tetramethylsilane. Electron-impact mass spectra were obtained on a Varian Mat CH-7 spectrometer operating at 70 eV. Optical rotations were measured with a Perkin-Elmer spectropolarimeter and circular dichroism curves on a Roussel–Jouan dichrograph.

Extraction and Isolation.—Dried finely ground leaves of *Ocotea acutangula* (28.8 kg) were extracted with 95% ethanol (80 l; ×4). The alcoholic extracts were concentrated *in vacuo* ($T < 35$ °C) and the aqueous layer was acidified with acetic acid to pH 4. After filtration, the extracts were basified with concentrated ammonia and extracted (×4) with chloroform (5 l). The combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alkaloids (40.5 g, 0.14%) which were chromatographed on silica gel (500 g). Gradient elution with dichloromethane and methanol afforded four main fractions. The fraction obtained with dichloromethane–methanol (98 : 2 v/v) gave pure O-*methylpallidinine* (8) as a gum (3.2 g); $\lambda_{max.}$ (log ε) 206 (4.51), 228 (3.98), and 262 nm (3.99); $\nu_{max.}$ 1 690 and 1 620 cm^{-1}; δ_H (60 MHz) 2.37 (s, 3 H, N-Me), 3.69 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 6.32 (s, 1 H, 1-H), 6.62 (s, 1 H, 4-H), and 6.85 (s, 1 H, 5-H); *m/e* 343 (100%, $M^{+\cdot}$), 328 (90), 312 (9), 300 (30), 257 (15), 232 (10), 215 (10), 203 (10), 192 (45), 165 (10), and 59 (2.5). The hydrochloride had m.p. 195—200 °C (from acetone); $[\alpha]_D^{20}$ −50° (methanol) (Found: C, 60.0; H, 6.9; N, 3.35; Cl, 8.65. $C_{20}H_{25}NO_4 \cdot H_2O \cdot HCl$ requires C, 60.37; H, 7.09; N, 3.52; Cl, 8.91%).

The fraction obtained with dichloromethane–methanol (97 : 3 v/v) gave a mixture (9 g) of O-*methylpallidinine* (8) and (6), which on further chromatography gave additional (8) (1.7 g) and O-*methylpallidine* (6) (1.8 g), m.p. 118—120 °C (from diethyl ether); $[\alpha]_D^{20}$ +25.2° (chloroform); $\lambda_{max.}$ (log ε) 208 (4.49), 238 (4.19), and 280 nm (3.82); $\nu_{max.}$ 1 660, 1 640, and 1 615 cm^{-1}; δ_H (60 MHz) 2.45 (s, 3 H, N-Me), 3.75 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 6.25 (s, 1 H, 8-H), 6.33 (s, 1 H, 1-H), 6.59 (s, 1 H, 4-H), and 6.78 (s, 1 H, 5-H); *m/e* 341 (100%, $M^{+\cdot}$), 326 (40), 313 (30), 298 (40), 282 (30), 270 (20), and 256 (20); c.d. (methanol) $[\theta]_{330}$ 0, $[\theta]_{312}$ +3 760, $[\theta]_{310}$ +3 640, $[\theta]_{296}$ +5 580, $[\theta]_{286}$ 0, $[\theta]_{280}$ −2 230, $[\theta]_{271}$ 0, $[\theta]_{265}$ +880, $[\theta]_{260}$ 0, $[\theta]_{252}$ −750, $[\theta]_{246}$ −450, $[\theta]_{233}$ −32 370 [the c.d. data agree with those reported by Kametani for synthetic (6) [11,18]].

The fractions obtained with dichloromethane–methanol (95 : 5 v/v) (3.2 g) after further chromatography, were subjected to preparative t.l.c. on silica gel to yield *pallidinine* (7), (180 mg), m.p. 234—236 °C, $[\alpha]_D^{20}$ −80° (chloroform, *c* 0.5); $\lambda_{max.}$ (log ε) 205 (4.45), 228sh, and 260 nm (3.99); $\nu_{max.}$ 1 688, 1 685, and 1 620 cm^{-1}; δ_H (100 MHz) 2.36 (s, 3 H, NMe), 3.70 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.38 (s, 1 H, 1-H), 6.71 (s, 1 H, 4-H), and 6.86 (s, 1 H, 5-H); *m/e* 329 (100%, $M^{+\cdot}$), 314 (100), 286 (50), 243 (15), 218 (15), and 192 (60) (Found: C, 66.65; H, 6.2; N, 4.1. $C_{19}H_{19}NO_4 \cdot H_2O$ requires C, 66.46; H, 6.16; N, 4.08%).

Finally from the fractions eluted with 20% methanol, *pallidine* (5) (1.2 g) was obtained, m.p. 120—122 °C (from acetonitrile); $[\alpha]_D^{20}$ −39.3° (methanol, *c* 1); $\lambda_{max.}$ (log ε) 210 (4.51), 240 (4.20), and 286 nm (3.91); $\nu_{max.}$ 1 670, 1 650, and 1 620 cm^{-1} (Found: C, 68.1; H, 6.45; N, 7.0. $C_{19}H_{21}NO_4 \cdot$ MeCN requires C, 68.46; H, 6.57; N, 7.11%); c.d. (methanol) $[\theta]_{328}$ 0; $[\theta]_{313}$ +3 850; $[\theta]_{309}$ +3 710; $[\theta]_{296}$ +5 670; $[\theta]_{288}$ 0; $[\theta]_{279}$ −2 320; $[\theta]_{268}$ 0; $[\theta]_{263}$ +450; $[\theta]_{260}$ 0; $[\theta]_{252}$ −2 250; $[\theta]_{246}$ −1 800; $[\theta]_{233}$ −31 800 (i.r., u.v., and c.d. data agree with those reported by Kametani for amorphous *pallidine* [12]).

Methylation of pallidine (5) *to* (6).—The hydrochloride of (5) (1 g) was suspended in anhydrous t-butyl alcohol (15 ml) and heated with dimethyl sulphate (630 mg) and potassium t-butoxide (870 mg) at 35 °C for 4 h. The reaction mixture was diluted with water and extracted with chloroform. The organic extract was chromatographed on silica gel (20 g) with dichloromethane–methanol (99 : 1 v/v) giving (6) (400 mg), m.p. 120—122 °C (from diethyl ether); $[\alpha]_D^{20}$ +23° (chloroform, *c* 0.5), identical in all respects to the natural product.

Conversion of O-*Methylpallidinine* (8) *into* O-*Methylpallidine* (6).—The hydrochloride of (8) (300 mg) in trifluoroacetic acid (0.25 ml) was treated at 0 °C successively with 30% HBr in acetic acid (0.5 ml), acetic acid (7 ml), acetic anhydride (3 ml), and bromine (0.044 ml). The solution was stirred at 0 °C for 2 h, left at room temperature for 15 h, and then evaporated to dryness *in vacuo* ($T < 25$ °C). The residue was chromatographed on silica gel (6 g) with dichloromethane–methanol (99 : 1 v/v) giving amorphous (12) (120 mg); δ_H (60 MHz) 2.41 (s, 3 H, N-Me), 3.72 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 5.58 (d, 1 H, ^3J 13 Hz, 8-H), 6.46 (s, 1 H, 1-H), 6.63 (s, 1 H, 4-H), and 6.83 (s, 1 H, 5-H); *m/e* 423/421 (10%; $M^{+\cdot}$), 408/406 (8), 343 (40), 342 (100), 328 (15), 314 (10), 313 (91), and 298 (10).

* For long-range couplings between the OMe methyl protons and the *ortho* ring protons or β-protons in methyl enol-ethers see ref. 22.

The bromomorphinane (12) (30 mg) in neat 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0.2 ml) was stirred for 15 h at room temperature, then the solution was diluted with dichloromethane (10 ml) and filtered through silica gel (2 g). The eluate was concentrated and the residue purified on preparative t.l.c. eluting with cyclohexane–diethylamine (1 : 1 v/v) to give *O*-methylpallidine (8 mg), identical (t.l.c., i.r., and c.d.) with the natural product.

Dihydro-O-methylpallidinine (10).—The hydrochloride of (8) (200 mg) in ethyl acetate (50 ml) was hydrogenated at 1.5 kg cm^{-2} for 8 h in the presence of 10% Pd–C (100 mg). The catalyst was filtered off and the filtrate evaporated to dryness. The residue was taken up in methanol (5 ml) containing 5% potassium hydroxide in methanol (2.2 ml) and stirred at room temperature for 48 h. The brown solution was evaporated and the residue purified by preparative t.l.c. eluting with cyclohexane–diethylamine (3 : 2 v/v) (R_F 0.45) to yield amorphous dihydro-*O*-methylpallidinine (10) (50 mg); δ_H (60 MHz) 2.38 (s, 3 H, NMe), 3.58 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 6.65 (s, 1 H, 1-H), and 6.75 (s, 1 H, 4-H); *m/e* 345 (100%, $M^{+\cdot}$), 330 (30), 317 (15), 314 (20), 286 (20), 253 (35), 238 (50), 244 (40), 194 (35), and 166 (20).

Tetrahydro-O-methylpallidine (11).—*O*-methylpallidine (6) (200 mg) was hydrogenated and equilibrated as for (8) giving, after preparative t.l.c. [cyclohexane–diethylamine (3 : 2 v/v)] amorphous (11) (R_F 0.35) (47 mg); δ_H (60 MHz) 2.45 (s, 3 H, N-Me), 3.47 (s, 3 H, OMe), 3.93 (s, 6 H, 2 OMe), 6.72 (s, 1 H, 1-H), and 6.97 (s, 1 H, 4-H); *m/e* 345 (80%, $M^{+\cdot}$), 330 (15), 286 (13), and 194 (80).

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