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ISOPEDUNCULARINE

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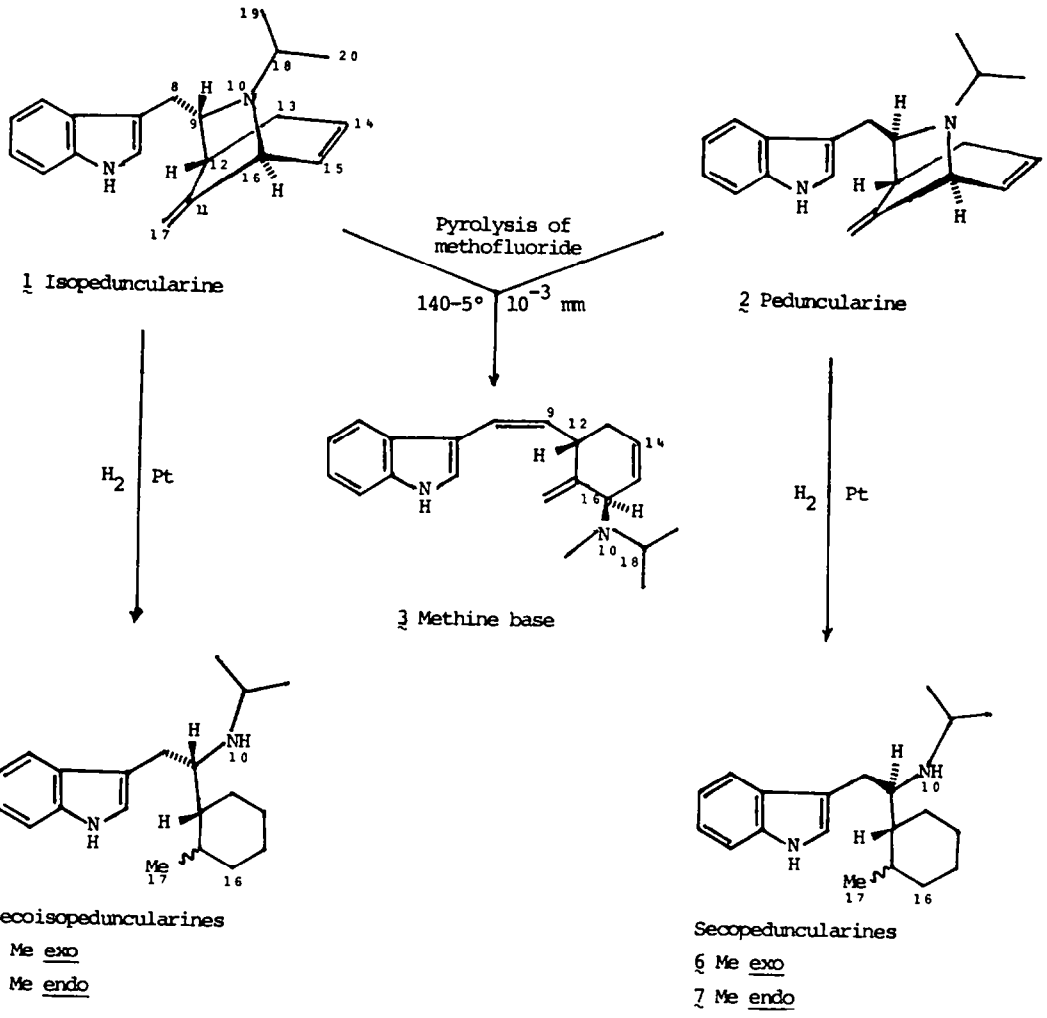
Abstract - The *Aristotelia* alkaloid isopeduncularine occurs in *A. serrata*, *A. fruticosa* and *A. peduncularis*. It has been shown to have the structure and relative stereochemistry represented in 1.

The isolation of isopeduncularine (1) was first recorded from the New Zealand elaeocarpaceous plant *Aristotelia serrata* W.R.B. Oliver[1], but at the time isopeduncularine was confused with the isomeric base peduncularine (2), the main alkaloid of the Tasmanian species *A. peduncularis* (Labill.) Hook. f.[2-4]. In the present study, isopeduncularine has been found to accompany 2 in the latter plant, and has also proved to be the major alkaloid of another New Zealand species, *A. fruticosa* Hook. f.. On the other hand, no peduncularine could be found after careful examination of several batches of both New Zealand species.

Isopeduncularine is closely similar to peduncularine in most respects, but the two bases are readily distinguished from one another on the basis of solubility: peduncularine (2) is in particular sparingly soluble in cold chloroform, while isopeduncularine (1) is readily soluble. Both crystallise in small needles with distinctly different melting points, which are depressed on admixture of the two.

From spectroscopic evidence, the same functional groups and skeleton must be present in isopeduncularine as in peduncularine, and the similarity in most of their properties, and close resemblance in their spectra suggest that they are diastereomers. The absolute stereochemistry of peduncularine (2) is still unknown; it has three chiral centres, two of which (C-12 and C-16) are at bridgeheads of interlocking ring systems[3,4]. These centres are tentatively assumed to be the same in both 1 and 2, which must then differ in configuration at the remaining centre C-9.

This presumption is supported by the fact that Hofmann degradation, which destroys the chirality of C-9 but not C-12 or C-16[4], produces a methine base 3 with identical properties from both peduncularine and isopeduncularine. On the other hand, hydrogenolysis of 1 and 2 destroys the chirality of C-16 by rupturing the link between this carbon and N-10[4], but at the same time a new chiral centre is produced at C-11, so that peduncularine (2) and isopeduncularine (1) each form two distereomeric products (4-7). The more polar product from each alkaloid has been obtained crystalline in each case; the Rf values of these two seco bases are the same, and their spectroscopic data are very similar, although there are small but significant differences in their spectra. On the other hand their specific rotations and their melting points are distinctly different, and a mixed melting point showed that they are not identical. The less polar, non-crystalline hydrogenation products of 1 and 2 likewise have the same Rf values and show a very



close resemblance to one another in spectroscopic properties, but they have distinctly different specific rotations.

These observations indicate that peduncularine and isopeduncularine are diastereomers that differ in configuration at C-9. The ^{1}H nmr signals for the protons attached to these centres are obscured in each case by other overlapping signals. In the case of peduncularine, no coupling could be detected between the H-9 and H-12 protons, which evidently make a 90° dihedral angle with one another, and in consequence the skatolyl group was assigned[3,4] an *exo* configuration to accord with molecular models. On the other hand, decoupling experiments on isopeduncularine (1) reveal a weak coupling between H-9 and H-12, and an *endo* attachment is thus indicated for the skatolyl group in this case.

The difference in stereochemistry at C-9 may account for the large difference in solubility between the two alkaloids in chloroform: an *exo* configuration would from molecular models cause obstruction of the basic nitrogen (N-10) by the bulky skatoyl group, and impede its solvation by the comparatively large molecules of chloroform. The same factor may be responsible for the considerable difference in specific rotation of 1 and 2 in chloroform as compared to methanol.

EXPERIMENTAL

Some variation in the method of extraction and in the proportion of alkaloids occurred with different batches of plant material. The following represent typical procedures and yields.

Separation of Alkaloids from *A. fruticosa* : Isolation of Isopeduncularine (1) - Air-dried roots, stems and leaves, collected near Rotorua, New Zealand in December 1977, were ground to a powder

(1.7 kg) and exhaustively extracted with cold methanol. The solvent was removed *in vacuo* at a temperature below 40°, and the concentrate was dissolved in warm glacial acetic acid (500 ml). The solution was poured in a fine stream into 7 ℓ of water, which was simultaneously agitated vigorously with a vibromixer. The precipitate that settled out was filtered off, washed with water until free from alkaloids, and discarded. The combined filtrate and washings were evaporated almost to dryness *in vacuo* at a temperature below 35°. The residue was dissolved in water and the solution was again evaporated, the procedure being repeated once more to remove as much acetic acid as possible. Finally, the residue was dissolved in water (15 ℓ) and the solution was basified to pH 8 with ammonia, then exhaustively extracted with chloroform until no more alkaloid was removed. The combined extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue of crude alkaloids (367 mg) contained one major and at least four minor components from analytical tlc (silica gel prepared with 0.5N KOH using 5% EtOH/$CHCl_3$ for development). Ptlc on a 1-metre plate under the same conditions yielded four bands; extraction of the highest Rf band gave isopeduncularine (90 mg). The remaining bands in decreasing order of Rf yielded fruticosonine[5] (33.5 mg), aristofruticosine (30 mg), and a mixture of isosorelline (4 mg) and isohobartine (3 mg), which was further separated by ptlc using 20% EtOH/$CHCl_3$ for development. The latter three alkaloids will be described in separate reports.

Separation of Alkaloids from *A. serrata*: Isolation of Isopeduncularine (1) - Air-dried roots, stems, and leaves collected near Rotorua, New Zealand (5.5 kg) in January 1980 were ground and extracted as described for *A. fruticosa* to yield 11.6 g of crude alkaloids, which were subjected to a preliminary separation in a 100-tube (each 40 ml) Craig counter-current apparatus with chloroform as stationary phase and 10^{-3} N sulphuric acid as mobile phase. The alkaloids emerged partially separated from the apparatus in order of basicity. Automatic collection of 720 40 ml samples was followed by tlc examination of every 10th sample; from the results the samples were suitably combined into 14 fractions. The recovered bases were subjected to further separation by ptlc under similar conditions to those described above for the crude *A. fruticosa* alkaloids. The following bases, in approximate order of emergence from the Craig machine, were obtained: tasmanine[6,7] (20 mg), aristomakinine (30 mg), aristoteline[1,6,8,9] (500 mg), isohobartine (55 mg), serratoline[10,11] (60 mg), isosorelline (60 mg), isopeduncularine (100 mg), aristoserratenine[7] (50 mg), aristotelinone[10] (140 mg), serratenone[11] (36 mg), makomakine[12] (74 mg), makonine[12] (33 mg), and aristoserratine[13] (50 mg). Details concerning certain of these minor alkaloids will be published separately.

Separation of Alkaloids from *A. peduncularis*: Isolation of Peduncularine (2) and Isopeduncularine (1) - Air-dried stems and roots (16.3 kg), collected around the Arve River, Tasmania in March 1969, were ground and extracted as described for *A. fruticosa*. The crude alkaloids so obtained (3 g) were partially separated by column chromatography on silica gel using chloroform with gradually increasing amounts of methanol (0-15%) for development. The fractions eluted with chloroform containing 5% methanol deposited crystals, which after recrystallisation from chloroform yielded peduncularine[2-4] (2, 450 mg). The combined mother liquors from these fractions and from the recrystallisation were subjected to a 2-stage ptlc separation on silica gel, with chloroform basified with ammonia in the first-stage development and benzene-methanol (1:1) in the second. Two bands running very close together were separated: the band with slightly lower Rf was extracted to give isopeduncularine (1, 230 mg), and a further small quantity of crystalline peduncularine (2) was obtained from the upper band. The combined alkaloidal residues were reserved for further fractionation and subsequent isolation of minor alkaloids[6,13-16].

Characterisation and Properties of Isopeduncularine (1) - Isopeduncularine crystallises from chloroform as small colourless needles, mp 113-4°; $[\alpha]_D^{19}$ -40° (C 4.1, $CHCl_3$); $[\alpha]_D^{19}$ -45° (C 4.1, MeOH); [cf peduncularine (2): small needles from chloroform, mp 155-7°[4]; $[\alpha]_D^{21}$ -76° (C 2.33, $CHCl_3$)[4]; $[\alpha]_D^{21}$ -24° (C 1.2, CH_3OH)[2]. A mixture of peduncularine (2) and isopeduncularine (1) melted at 109-110°]. λ_{max} (MeOH): 290, 282, 274, 219, 200 nm (log ε_{max} 3.52, 3.57, 3.55, 4.76, 4.82). ν_{max} (CCl_4): 3400 (NH), 1680 (C=C) cm^{-1}. ^1H nmr: 8.21 (1H, bs, exchangeable with D_2O, H-1); 7.08-7.62 (4H, aromatic protons); 6.96 (1H, d, J = 2.4 Hz, H-2); 5.93 (1H, ddt, $J_{14/15}$ = 9.5 Hz, $J_{15/16}$ = 5.1 Hz, $J_{15/13exo,13endo}$ = 2.0 Hz, H-15); 5.67 (1H, ddd, $J_{14/15}$ = 9.5 Hz, $J_{14/13exo}$ = 3.0 Hz, $J_{14/13endo}$ = 2.5 Hz, H-14); 4.96 and 4.83 (1H x 2, 2s, 2H-17); 3.86 (1H, d, $J_{16/15}$ = 5.1 Hz, H-16); 3.06-2.89 (3H, m, H-9 + H-18 + H_a-8); 2.72 (1H, dd, $J_{8a/8b}$ = 15 Hz, $J_{8b/9}$ = 10.5 Hz, H_b-8); 2.50 (1H, m, H-12); 2.47 (1H, dddd, $J_{13exo/13endo}$ = 19 Hz, $J_{13exo/12}$ = 5.0 Hz, $J_{13exo/14}$ = 3.0 Hz, $J_{13exo/15}$ = 2.5 Hz, Hexo-13); 2.04 (1H, dddd, $J_{13endo/13exo}$ = 19 Hz, $J_{13endo/14}$ = 2.5 Hz, $J_{13endo/15}$ = 2.0 Hz, $J_{13endo/12}$ < 1 Hz, H_{endo}-13; 1.32 and 1.78 δ (3H x 2, 2d, J = 6.5 Hz, 3H-19 + 3H-20). ^{13}C nmr: 149.7 (s, C-11); 136.2 (s, C-7a); 130.9 + 128.5 (2d, C-14 + C-15); 127.7 (s, C-3a); 122.1 (d, C-2); 121.5 (d, C-15); 119.5 (d, C-6); 119.2 (d, C-4); 114.8 (s, C-3); 111.1 (d, C-7); 101.2 (t, C-17); 70.1 (d, C-16); 60.7 (d, C-9); 51.0 (d, C-18); 46.2 (d, C-12); 40.3 (t, C-8); 34.2 (t, C-13); 23.6 + 22.7 δ (2q, C-19 + C-20). Ms: m/z 292 (M^+, 2%); meas.: 292.1931; calc. for $C_{20}H_{24}N_2$: 292.1939; 277 (<1), 182 (1.5), 163 (7), 162 (100), 130 (5), 120 (7), 105 (4), 103 (3), 91 (8), 70 (6). Found: C, 66.83; H, 6.60; N, 7.34. Calc. for $C_{20}H_{24}N_2$, 2/3 $CHCl_3$: C, 66.71; H, 6.68; N, 7.52%. Isopeduncularine gives a positive Ehrlich test.

Hofmann Degradation of Isopeduncularine (1) - Isopeduncularine (100 mg) in nitromethane (5 ml) was treated with 0.5 ml of methyl iodide, and the resulting solution was stirred at room temperature for 10 hr. The solvent was then removed *in vacuo*, and the gummy residue of isopeduncularine methiodide was converted into the methofluoride by ion exchange [CH_3OH/H_2O 1:1; Amberlite IRA-400 (F^-)]. The product, dissolved in methanol, was divided between 8 kugelrohrs (each 5 ml), and the solvent was evaporated *in vacuo* so as to leave a thin brown film of the compound on the internal

surfaces. The material was then pyrolysed (metal bath at 140-5°, 1 x 10^{-3} mm/Hg. The clear brown distillates were extracted with chloroform, and the solutions combined and evaporated *in vacuo*. The residue (47 mg), after purification by ptlc (cyclohexane/EtOH/ether/NH_4OH 40:40:20:1) yielded an oil (3, 21 mg, $[\alpha]_D^{19}$-12° (C 0.32, MeOH); λ_{max} (MeOH): 297 sh, 280, 258, 252 sh, 224 nm (log ϵ_{max} 3.71, 3.85, 4.21, 4.13, 4.32). ν_{max} ($CHCl_3$): 3490 (NH), 1660 cm^{-1}. ^1H nmr: 8.45 (1H, br s, exchangeable with D_2O, H-1); 7.83 (1H, d); 7.3-7.1 (3H, m); 6.7-6.28 (2H, m); 5.92-5.70 (2H, m); 5.30 (1H, s); 4.03 (1H, bs); 3.2-2.85 (2H, m); 2.4-2.1 (5H, including N-CH_3); 1.08 + 1.06 δ (2 x 3H, 2d, J = 6.0 Hz). Ms: m/z 306 (M^+, 70%), 291 (29), 235 (49), 234 (100), 233 (31), 232 (47), 220 (10), 219 (18), 218 (21), 207 (19), 180 (20), 144 (56), 143 (51), 130 (73), 118 (63). The corresponding methine base[4] prepared in the same way from peduncularine (2) had $[\alpha]_D^{19}$-14° (MeOH); the Rf values and spectroscopic data of the two products were identical (ir, uv, ^1H nmr, and ms).

Hydrogenolysis of Isopeduncularine (1) - Isopeduncularine (100 mg) was hydrogenated in 5 ml of glacial acetic acid with 25 mg of platinum oxide for 20 hr at 19° under 3 at. pressure. The catalyst was filtered off, the solution was diluted with 10 ml of water, basified with ammonium hydroxide, and extracted with chloroform (3 x 10 ml). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Two components were present in the residue (70 mg) from tlc. The mixture was separated by ptlc (silica gel prepared with 0.5 N KOH, 4% EtOH/$CHCl_3$ as solvent, double development) into two bands. The higher Rf band was extracted to give 18.3 mg of an amorphous secoisopeduncularine (4 or 5) with $[\alpha]_D^{19}$ + 53° (C 0.30, MeOH); λ_{max} (MeOH): 290.5, 282, 274 sh, 228 nm (log ϵ_{max} 3.29, 3.35, 3.31, 3.80). ν_{max} ($CHCl_3$): 3480, 3420 cm^{-1}. ^1H nmr: 8.1 (1H, bs, exchangeable with D_2O, H-1); 7.2-7.05 (4H, multiplets); 2.13 (1H, m); 1.76-1.2 (10 H); 0.98 + 0.98 + 0.85 δ (3 x 3H, 3d, J = 6.5 Hz). Ms: m/z 232 (21%), 201 (64), 168 (100), 152 (10), 130 (66), 98 (41). The corresponding secopeduncularine with the same Rf value (6 or 7), prepared[4] from peduncularine by the same method, had $[\alpha]_D^{19}$ + 35° and closely similar spectroscopic properties to the above-mentioned secoisopeduncularine 4 or 5.

Extraction of the lower Rf band from the hydrogenolysis of 1 afforded 10.8 mg of another secoisopeduncularine (5 or 4) which crystallised from cold chloroform, mp 116-120°, $[\alpha]_D^{19}$ + 126° (C 0.18, MeOH); λ_{max} (MeOH): 290.5, 282, 274, 228 nm (log ϵ_{max} 3.34, 3.39, 3.36, 3.77). ν_{max} ($CHCl_3$): 3475, 3410 cm^{-1}. ^1H nmr: 8.15 (1H, bs, exchangeable with D_2O, H-1); 7.6 (1H, m); 7.35-7.1 (3H, m); 7.02 (1H, m); 3.03-2.8 (1H, m); 2.7-2.3 (2H, m); ; 2.01-1.1 (11H, m); 1.06 + 0.92 + 0.62 δ (3 x 3H, 3d). Ms: m/z 201 (10%), 168 (100), 130 (21), 72 (8). The corresponding secopeduncularine 7 or 6 with the same Rf value crystallised from cold chloroform, mp 106-110° (mmp with the corresponding crystalline secopeduncularine 5 or 4: 101-108°), $[\alpha]_D^{19}$ + 81° (C 0.34, MeOH); λ_{max} (MeOH): 290.5, 282, 275 sh, 225.5 nm (log ϵ_{max} 3.05, 3.11, 3.08, 3.55). ν_{max} ($CHCl_3$): 3475, 3400 cm^{-1}; there were distinct differences in the fingerprint region the corresponding crystalline secoisopeduncularine 5 or 4, but the ^1H nmr spectra and the ms of the two seco bases were closely similar to one another.

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