

MEDELLINE, FIRST BISBENZYLISOQUINOLINE ALKALOID WITH A METHYLENEDIOXY BRIDGE¹

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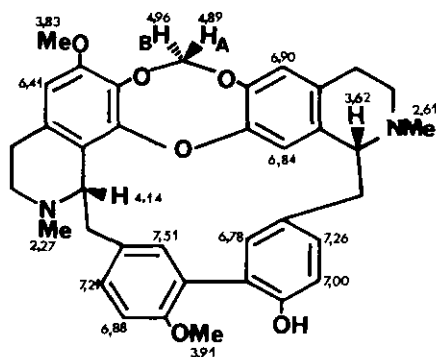
Abstract - High resolution MS and ¹H-NMR studies indicate that medelline, a minor alkaloid isolated from the bark of *Pseudoxandra* aff. *lucida*, is the first known example of a bisbenzylisoquinoline alkaloid with a methylenedioxy bridge joining both halves of the molecule. Medelline is probably biosynthesized via intramolecular condensation of the accompanying major bisbenzylisoquinoline alkaloid, antioquine.

Several bisbenzyltetrahydroisoquinoline alkaloids have been isolated from the bark of the Columbian plant, *Pseudoxandra* aff. *lucida* (Annonaceae)². These are all characterised by the presence of a diphenyl bridge between rings C and C' of the benzylisoquinoline moieties^{3,4}.

Medelline, 1, is one of the minor alkaloids (0.1% of total alkaloidal fraction) isolated from the bark of *P.* aff. *lucida*. It has been obtained in an amorphous state⁵; the molecular formula, C₃₇H₃₈N₂O₆ has been determined by high resolution mass spectrometry⁶, and confirmed by high resolution mass spectrometry of its acetate⁷. The fragmentation pattern of medelline indicates a bisbenzyltetrahydroisoquinoline with a diphenyl bridge^{8,9}, as in antioquine, 2, the major alkaloid isolated from the same plant^{2,4}. The molecular ions of medelline, 1, and antioquine, 2, as well as their singly and doubly charged bisisoquinoline fragment ions differ only in two mass units. This suggests that medelline, 1, has a bisbenzyltetrahydroisoquinoline structure, either with three bridges two of which join the isoquinoline moieties, or with two bridges and a methylenedioxy group as in cepharanthine, 3¹⁰.

High resolution mass spectroscopy of O-acetylmedelline shows a molecular ion peak at m/z 648.276 and a significant peak at m/z 379.166, showing that medelline, 1, has only one hydroxyl group in the diphenyl part of the molecule⁷.

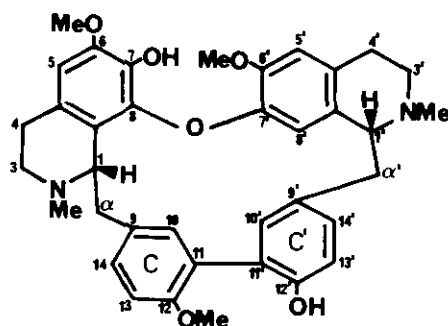
¹H-NMR analysis of medelline, 1, confirms the structural relationship with antioquine, 2. The noteworthy feature in the ¹H-NMR spectrum of 1, is the presence of an



1, medelline : ^1H -NMR, 360 MHz

$J_{10-14} = J_{10'-14'} = 2 \text{ Hz}$; $J_{A-B} = 4 \text{ Hz}$;

$J_{14-13} = J_{14'-13'} = 8 \text{ Hz}$



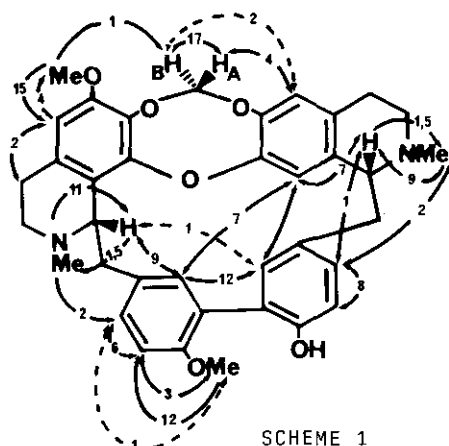
2, antioquine

AB system (4.89 and 4.96 ppm ; $J=4 \text{ Hz}$) attributable to the two protons of a methylenedioxy group. The signal at 3.83 ppm in medelline, 1, is assigned to the protons of the methoxyl group attached to position 6 in the isoquinoline part of the molecule, as in antioquine, 2⁴. The chemical shift of the methoxyl group in medelline, 1, is evidence for an intramolecular methylenedioxy linkage between positions 7 and 6' rather than between positions 6 and 7, for it is well known that a methoxyl group at 6' appears at a higher field (δ 3.49 for antioquine, δ 3.66 for cepharanthine). The hypothesis of a methylenedioxy linkage between 7 and 6' is supported by the difference in the chemical shifts of the protons of the OCH_2O group of medelline, 1 (clearly more shielded than the protons of the methylenedioxy linkage in alkaloids of the cepharanthine type, 3^{9,10}). Further support for the hypothesis is obtained from the coupling constant ($J=4 \text{ Hz}$), characteristic of the protons of an OCH_2O group in a large ring. The coupling constant for the protons of the OCH_2O group in a five membered ring is below 2 Hz¹¹. The ^{13}C -NMR spectrum of medelline, 1, shows that the carbon atom of the methylenedioxy group (δ 94.8 (t)⁵) is definitely more shielded than the carbon atom of a methylenedioxy group in a five membered ring (δ 101.0 (t)¹¹).

The structure of medelline, 1, has been further confirmed by a detailed examination of its ^1H -NMR spectrum at 360 MHz as well as by the determination of the Nuclear Overhauser Effects^{12,4} of medelline, 1, and that of 12'-O-acetylmedelline (see Scheme 1). It should be noted that the negative NOE¹³ between H-1 and H-10' ascribed to a collinear arrangement of H-1, H-10 and H-10' is consistent with the high rigidity of a Dreiding model of the molecule. Finally, the NOE's observed on irradiation of the protons of the methylenedioxy group confirm that H_A is close to H-5', while H_B is far from H-5'. The protons of the methylenedioxy group are only affected by irradiation of H-5' and the protons of the 6-OMe group, thus confirming their position (see Scheme 1).

The CD curve of medelline, 1⁵, is superimposable with that of antioquine, 2⁴. Further, the NOE observed for the protons in the 1 and 1' position of these alkaloids are of the same order⁴ (see Scheme 1). Medelline has therefore the same absolute configuration as antioquine namely 1S,1'R.

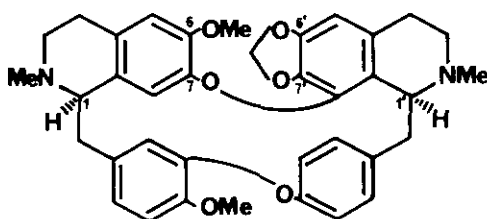
This is the first report of the isolation of a bisbenzyltetrahydroisoquinoline alkaloid with an intramolecular methylenedioxy bridge. Medelline, 1, can be considered to be formed by intramolecular condensation through enzymatic oxidation of antioquine, 2, the major alkaloid of the bark of *Pseudoxandra* aff. *lucida*.



SCHEME 1

1, medelline : NOE

→ NOE +
--- NOE -



3, cepharanthine

¹H-NMR of methylenedioxy : two doublets,
J=1 Hz at 5,53 and 5,55 ppm

REFERENCES AND NOTES

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5. Medelline, 1 : $[\alpha]_D^{25} -38^\circ$ (c=0.16, MeOH ; UV λ_{max} , EtOH, nm (log ϵ) : 220 (4.38), 250 sh (3.98), 282 (3.82) ; EtOH+NaOH : 222 (4.58), 300 (3.95) ; IR, ν_{max} , film : 3325, 2930, 2840, 1610, 1580, 1500, 1120, 1070, 1020, 990, 910 cm^{-1} ; CD, EtOH (c=2.57.10⁻⁴), $\Delta\epsilon$ (nm) : 0 (300), +12.5 (288), +68 (249), 0 (232), -109 (218) ; ¹H-NMR : see 1 and scheme 1 ; ¹³C-NMR of 12'-O-methyl-medelline, CDCl₃, δ ppm : 62.1 (C₁), 44.8 (C₃), 24.5 (C₄), 105.9 (C₅), 134.2 (C₁₀), 120.0 (C₁₃), 128.7 (C₁₄), 66.1 (C₁), 44.8 (C₃), 25.3 (C₄), 110.8 (C₅), 124.5 (C₉), 133.1 (C₁₀), 112.3 (C₁₃), 129.1 (C₁₄), 42.5 (NMe₂), 43.5 (NMe₂), 56.0 (OMe₆), 56.2 (OMe₁₂), 56.4 (OMe₁₂), 94.8 (OCH₂O).

6. High resolution MS of medelline, 1 : M^{+} 606.270 (found), 606.272 (calc.) : $C_{37}H_{38}N_2O_6$; m/z 379.145 (found), 379.165 (calc.) : $C_{22}H_{23}N_2O_4$; m/z 174.053 (found), 174.055 (calc.) : $C_{10}H_8NO_2$; MS (EI) m/z (%) : 606 (11) (M^{+}), 380 (20), 379 (29), 349 (1), 190 (67), 174 (100).
7. 12'-O-acetyl-medelline. Prepared from 1 (Ac_2O /Pyr). $[\alpha]_D -42^\circ$ ($c=0.60$, $CHCl_3$) ; UV, λ_{max} , EtOH, nm ($\log \epsilon$) : 222 (4.60), 283 (3.90) ; IR, ν_{max} , film : 1765, 1605, 1580, 1500 cm^{-1} ; 1H -NMR, $CDCl_3$, 360 MHz, δ ppm : 2.10 (s, 3H, OAc-12'), 2.34 (s, 3H, NMe-2), 2.60 (s, 3H, NMe-2'), 3.72 (s, 3H, OMe-12), 3.83 (s, 3H, OMe-6), 3.60 (m, 1H, H-1'), 4.37 (m, 1H, H-1), 4.88 and 4.94 : AB system ($J=4$ Hz) (OCH_2O), 6.41 (s, 1H, H-5), 6.94 (s, 1H, H-5'), 6.66 (s, 1H, H-8'), 7.49 (d, 1H, H-10), 6.77 (d, 1H, H-13), 7.21 (dd, 1H, H-14), 6.73 (d, 1H, H-10'), 7.15 (d, 1H, H-13'), 7.34 (dd, 1H, H-14') ; $J_{10-14}=J_{10'-14'}=2$ Hz ; $J_{14-13}=J_{14'-13'}=8$ Hz ; MS (EI) m/z (%) : 648 (84) (M^{+}), 380 (22), 379 (68), 307 (11), 235 (24), 190 (97), 170 (100).
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