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4-HYDROXYNORNANTENINE, A 4-HYDROXYLATED NORAPORPHINE

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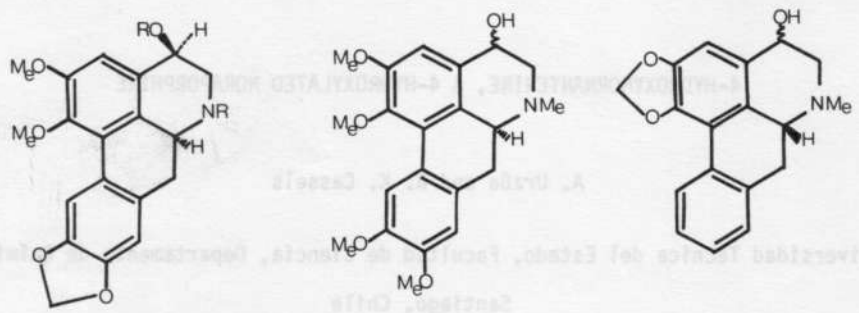
Several aporphines and 7-oxoaporphines have been isolated previously from the bark of *Laurelia philippiana* Looser (Atherospermataceae).[1] Continuing with the study of the minor bases of this Chilean tree, a new alkaloid was separated and shown to belong to the heretofore unknown class of the 4-hydroxylated noraporphines.

4(*S*)-Hydroxy-6a(*S*)-nornantenine (I) was isolated by repeated preparative TLC of the non-phenolic alkaloid fraction as a colourless oil which darkened rapidly in contact with air, PMR ($CDCl_3$) δ 3.65 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.51 (1H, m, half band width 4 Hz, H geminal to OH), 5.97 (2H, s, OCH_2O), 6.68 (1H, s, aromatic-H), 6.90 (1H, s, aromatic-H), 7.89 (1H, s, aromatic-H). Acetylation of I with acetic anhydride-pyridine afforded the stable *N*,*O*-diacetyl derivative (II), mp 179-181° (EtOH), ν_{max}^{KBr} 1770, 1640 cm^{-1}, PMR ($CDCl_3$) δ 2.30 (6H, s, *N*-Ac, *O*-Ac), 3.71 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.77 (1H, dd, J = 10, J' = 5 Hz, H geminal to OAc), 5.98 (2H, s, OCH_2O) 6.74 (1H, s, aromatic-H), 6.80 (1H, s, aromatic-H), 7.95 (1H, s, aromatic-H). These data suggested the presence of an aporphine skeleton with two methoxyl groups at C-1 and C-2, one methylenedioxy group at C-9 and C-10, one hydroxyl group at C-4 or C-5, and a secondary nitrogen atom. The mass spectrum of II showed the molecular ion at m/e 425.1475 (calc. for $C_{23}H_{23}NO_7$, 425.1475) and fragments at m/e 365, 354, 353, 311 (100 %), and 252, presumably originating in the processes depicted in Scheme 1, indicating that the acetoxy group (and the hydroxy group in I) is located at C-4.

The optical rotations of I and II were not determined due to lack of material.

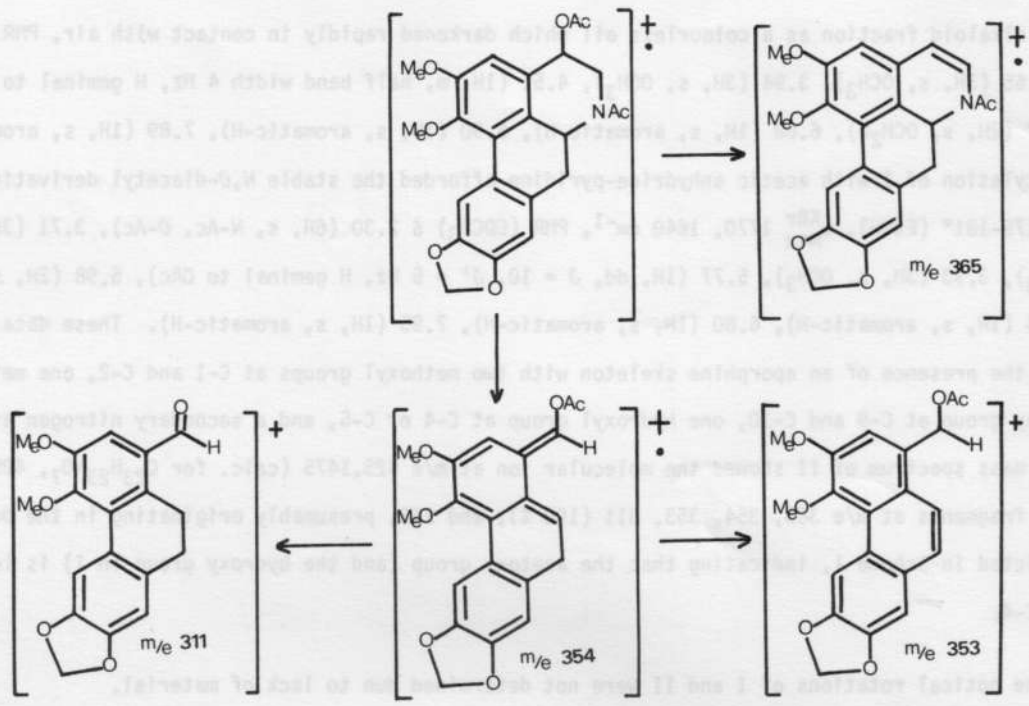


I : R=H
II : R=Ac

III

IV and V

Scheme 1.



Although this alkaloid is the first 4-hydroxynoraporphine to be investigated, three tertiary 4-hydroxyaporphines have been described before: steporphine (IV),[2] cataline (III),[3] and episteporphine (V).[4] The 6a(*S*) configuration was proposed for cataline on the basis of its hydrogenolysis to afford (*S*)(+)-glaucine,[3] and the negative Cotton effect of episteporphine near 235 nm shows that it belongs to the 6a(*R*) series.[4,5]

Regarding cataline, Ribas et al.[3] state that in $CDCl_3$ the proton at C-4 appears as a poorly-resolved triplet at 4.83 ppm with half-band width 4 Hz, while in the *O*-acetyl derivative the corresponding signal is shifted to 6.03 ppm retaining its multiplicity. According to these authors, "examination of Dreiding models ... clearly shows" that the relative configuration should be either 4(*S*):6a(*S*) or the opposite. These PMR data indicate that in both the alkaloid and its derivative, the C-4 proton lies in a plane which approximately bisects the H-C-H angle at C-5, and is therefore pseudoequatorial. However, Dreiding models built in the 4(*S*):6a(*S*) and 4(*R*):6a(*S*) configurations with pseudoequatorial C-4 protons do not suggest any clear differences as far as potential energy is concerned. The smaller *N-O* distance in the latter isomer (2.7 Å as compared with 3.0 Å) might presumably contribute to its stability through intramolecular hydrogen bonding, although this is not consistent with the reported OH absorption at 3520 cm^{-1}.[3] Thus, the more likely configuration would seem to be 4(*S*):6a(*S*), as proposed by Ribas' group, but any assignment made on this basis is highly speculative.

In steporphine, the literature reports a triplet at 4.47 ppm, J = 2.5 Hz (in $CDCl_3$), which shifts to 5.86 ppm upon *O*-acetylation,[2] showing that here too the C-4 protons should be pseudoequatorial. In episteporphine and its *O*-acetyl derivative, on the other hand, the corresponding signals appear as "quartets" or rather, doublets of doublets, J = 10, J' = 5.5 Hz, at 4.93 and 6.32 ppm, respectively (in $CDCl_3$), indicating that the C-4 protons should be pseudoaxial.[4] Guinaudeau et al.[4] use these data to propose the 4(*R*):6a(*R*) and 4(*S*):6a(*R*) configurations for steporphine and episteporphine, reasoning "by analogy with cataline". Here again, molecular models do not show any clear conformational preference, and the reported IR spectrum of steporphine (ν_{max} 3360-3500 cm^{-1}) gives no indication of intramolecular hydrogen bonding which could be expected in one of the half-chair conformations, so the relative configurations of these two epimeric bases are also dubious.

On the basis of the PMR spectra of I and II, it can be said that the C-4 proton is pseudoequatorial in 4-hydroxynornantenine and pseudoaxial in its *N,O*-diacetyl derivative, where steric compression of both acetyl groups explains the inversion of the half-chair conformation of ring B. In this case it is obvious that more sophisticated NMR techniques would be required in order to establish the relative configurations at C-4 and C-6a. Even though the chemical shifts of the pseudoequatorial C-4 protons of steporphine and I are nearly identical, the dispersion of δ values for cataline, episteporphine and their acetyl derivatives precludes any reasonable correlation and must await further studies.

As compound II crystallizes well from ethanol, a single-crystal X-ray diffraction analysis was performed on it by Prof. W. H. Watson, of Texas Christian University. This study confirmed the structural assignment, and showed that the absolute configurations are 4(*R*):6a(*S*), as illustrated in the formulae. These configurations are the same as those attributed to cataline,[3] which was used as a reference compound in proposing the configurations of steporphine and episteporphine,[4] but from the foregoing it should be clear that the stereostructures of the 4-hydroxyaporphines have not yet been determined unambiguously, and must still be examined using X-ray diffraction or appropriate spectrometric correlation techniques.

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