Nonbasic Aporphine Alkaloids from Liriodendron tulipifera L.

Keyphrases: 1 Liriodendron tulipifera L.—alkaloids identified in the heartwood 2 Aporphine alkaloids (nonbasic) — isolated and identified from L. tulipifera 3 Structure elucidation — N-acetylaporphine alkaloids by IR, UV, NMR, and circular dichroism

To the Editor:

The heartwood of Liriodendron tulipifera L. (Magnoliaceae) had previously yielded the alkaloids liriiodidine (Ia), 1,2,9,10-tetramethoxyoxoaporphine (IIb), and d-glaucine (IIa) (1-4). Investigation of the nonbasic fraction of the heartwood has led to the isolation of two alkaloids, (+)-N-acetylnornantenine (IIb) and (+)-3-methoxy-N-acetylnornantenine (IIe).

Percolation of the dried ground heartwood with alcohol followed by evaporation of the solvent left a dark residue which was partitioned between ether and 2% aqueous citric acid. The ether solution was evaporated and then chromatographed over silicic acid using chloroform and increasing amounts of methanol in chloroform as the eluent. Elution with 13% methanol in chloroform yielded the two alkaloids in pure form.

Alkaloid A had a melting point of 283-284° (alcohol) and [α]D 364° (c 0.50 in CHCl3). It exhibited a parent ion peak at m/e 367.1390 corresponding to the formula C21H21N05 (calculated m/e 367.1420), which was also supported by elemental analysis. The UV spectrum [λmax(CH3OH) nm (log ε): 215 (4.61), 281 (4.04), and 307 (4.12)] was indicative of an aporphine substituted at C-1,2,9,10 (5); the IR spectrum [νmax (KBr) 1685 cm⁻¹] suggested the presence of a tertiary amide carbonyl. The 60-MHz NMR spectrum (CDCl3) showed three 3H singlets at δ 2.17 (-NCOCH3), 3.60, and 3.82 (-OCH20), a 2H singlet at δ 5.85 (-OCH2O-), and three 1H singlets at δ 6.48, 6.62, and 7.82 (Ar-H). The presence of a 2H singlet for the methylenedioxy hydrogens required that the two methoxy groups be placed at C-1 and C-2 and the methylenedioxy group at C-9,10 since the hydrogens of a methylenedioxy group at C-1,2 will be split into two doublets (5). This assignment is also supported by the fact that one methoxy group appears at higher field (δ 3.60) than the other and thus must be located at C-1 (5). The circular dichroism spectrum showed a large positive Cotton effect at 241 nm ([θ] +198,000; 1.90 mg/50 ml), which has been correlated with the S-configuration at C-6α (6).

These data suggested that Alkaloid A be represented by Structure IIb. Direct comparison of an authentic sample of (+)-N-acetylnornantenine (IIb) [lit. (7) mp 294°, [α]D + 349° (c 0.44 in CHCl3)], an alkaloid obtained by acetylation of nornantenine (IIc), with Alkaloid A showed them to be identical in all respects (melting point, mixed melting point, TLC, IR, UV, and circular dichroism). A synthesis of (+)-N-acetylnornantenine has also been reported (8).

Alkaloid B [mp 216-217° (alcohol), [α]D 364° (c 0.37 in CHCl3)] gave a parent ion peak at m/e 397.1527 corresponding to the formula C22H23N06 (calculated m/e 397.1525), which was also supported by elemental analysis. A carbonyl absorption in the IR spectrum [νmax(KBr) 1638 cm⁻¹] along with a 3H singlet at δ 2.20 in the NMR spectrum suggested the presence of an N-acetyl group. Other features of the NMR spectrum included three 3H singlets at δ 3.68, 3.83, and 3.90 (-OCH3), a 2H singlet at δ 5.87 (-OCH2O-), and two 1H singlets at δ 6.63 and 7.77 (Ar-H). Comparison of the NMR spectrum of (+)-N-acetylnornantenine (IIb) with that of Alkaloid B indicated the two alkaloids to be closely related and that Alkaloid B was probably a pentaoygenated aporphine with three methoxy groups and a methylenedioxy group. Since positions 1 and 2 are always substituted in naturally occurring aporphine alkaloids (5, 9) and one of the aromatic hydrogens ap-
pears downfield at δ 7.77 (cf., 7.82 in IIb) and one of the methoxy groups appears upfield at δ 3.68 (cf., 3.60 in IIb), a methoxy can be placed at C-1 and a hydrogen at C-11 (5, 10, 11). The UV spectrum [λ_max (CH₂OH) nm (log ε)] shows 271 (4.65), 280 (4.08), 307 (4.18), and 313 sh (4.16) characteristic of a 1,2,3,9,10-penta-oxygenated aporphine (12, 13). The methylenedioxy group at C-2,3 or C-9,10, the methoxy groups at C-2,3 and 313 sh (4.16) is characteristic of a 1,2,3,9,10-penta-oxygenated aporphine (10). Thus, the only substitution pattern for Alkaloid B that is consistent with both the UV and NMR spectra (singlets for the two aromatic hydrogens) is a C-1,2,3,9,10-penta-oxygenated aporphine with a C-1 methoxy group.

The methylenedioxy group could be located at C-2,3 or C-9,10. The location of the methylenedioxy group at C-9,10 and the methoxy groups at C-2 and C-3 is preferred since a 2H singlet at δ 5.87 is observed for the methylenedioxy protons in Alkaloid B (cf., 5.85 in IIb). The protons of a methylenedioxy group located at C-2,3 form an AB quartet (14) just as they do when located at C-1,2. Additional evidence for this oxygenation pattern comes from observing the chemical shifts of the methoxy resonances. When methoxy groups are located at C-9 and C-10, they usually appear as overlapping signals near δ 3.9 (5, 11); but when methoxy groups are located at C-1,2, and 3, they appear as discrete signals (14) as observed in the NMR spectrum of Alkaloid B.

Based on this evidence, we propose that Alkaloid B be represented as (+)-3-methoxy-N-acetylornartanine (IIe). The absolute stereochemistry at C-6a follows by noting the large positive Cotton effect in the circular dichroism spectrum at 243 nm ([α] = +199,000; 1.80 mg/50 ml), which has been correlated with the S-configuration at C-6a (6). To our knowledge, these alkaloids (IIb and IIe) represent the first two examples of naturally occurring N-acetylporphine alkaloids.


To the Editor:

Currently, there is renewed and active interest in elucidating the biochemical etiology of schizophrenia (1). Based on a hypothesis put forth by Osmond and Smythies (2) that an aberration in the metabolism of catecholamines could produce an endogenous psychotogen structurally related to mescaline, several investigators proposed various derivatives of phenethylamine as potential endogenous toxins responsible for psychosis (1, 3-5). Shulgin et al. (4) recently carried out a detailed analysis of structure–activity relationships among 40 phenethylamine derivatives and proposed 2-hydroxy-4,5-dimethoxyphenethanolamine (I) as a potential endogenous psychotogen. However, no report has appeared on the synthesis and psychogenic evaluation of I.

In continuing investigations on peyote and related alkaloids (6, 7), the authors extended the work to the study of I and its methylenedioxy analog (II). The synthesis of racemates of I and II is reported here.

Synthesis and Psychotropic Activity of 2-Hydroxy-4,5-dimethoxyphenethanolamine, a Potential Endogenous Psychotogen, and Its Methylenedioxy Analog

Keyphrases: 2-Hydroxy-4,5-dimethoxyphenethanolamine and methylenedioxy analog—synthesis and psychotropic activity, potential endogenous psychotogen, Phenethylamine derivatives—synthesis and psychotropic activity of 2-hydroxy-4,5-dimethoxyphenethanolamine, role in schizophrenia, Schizophrenia—synthesis and psychotropic activity of 2-hydroxy-4,5-dimethoxyphenethanolamine, a potential endogenous psychotogen

Received February 11, 1974. Accepted for publication May 10, 1974.

Supported in part by the Committee on Faculty Research, University of Mississippi, and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

* To whom inquiries should be directed.

Vol. 63, No. 8, August 1974 / 1339

---

6 The NMR spectrum of ocoteine (IId) is reported in Ref. 11. It shows —OCH₂— at C-1,2 as an AB quartet and signals for three methoxy groups at δ 3.91, 3.91, and 3.99.

---

Charles D. Hufford*
Mary Jo Funderburk*
Department of Pharmacognosy
School of Pharmacy
University of Mississippi
University, MS 38677

---