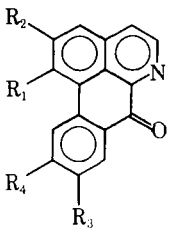
Nonbasic Aporphine Alkaloids from *Liriodendron tulipifera* L.

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

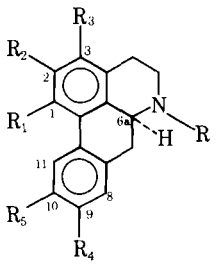
To the Editor:

The heartwood of *Liriodendron tulipifera* L. (Magnoliaceae) had previously yielded the alkaloids liriodenine (I*a*), 1,2,9,10-tetramethoxyoxoaporphine (I*b*), and *d*-glaucine (II*a*) (1–4). Investigation of the nonbasic fraction of the heartwood has led to the isolation of two alkaloids, (+)-*N*-acetylnornantenine (II*b*) and (+)-3-methoxy-*N*-acetylnornantenine (II*e*).

Percolation of the dried ground heartwood[1] 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 2% methanol in chloroform yielded a fraction that was still a mixture as shown by TLC[2]. Rechromatography of this fraction over silica gel G using ether as the eluent yielded the two alkaloids in pure form.



I*a*: $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = H$
I*b*: $R_1 = R_2 = R_3 = R_4 = OCH_3$



II*a*: $R = CH_3$, $R_1 = R_2 = R_4 = R_5 = OCH_3$, $R_3 = H$
II*b*: $R = COCH_3$, $R_1 = R_2 = OCH_3$, $R_3 = H$, $R_4 + R_5 = OCH_2O$
II*c*: $R = R_3 = H$, $R_1 = R_2 = OCH_3$, $R_4 + R_5 = OCH_2O$
II*d*: $R = CH_3$, $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = R_5 = OCH_3$
II*e*: $R = COCH_3$, $R_1 = R_2 = R_3 = OCH_3$, $R_4 + R_5 = OCH_2O$

Alkaloid A had a melting point of 283–284° (alcohol)[3] and $[\alpha]_D^{26}$ + 340° (c 0.50 in $CHCl_3$). It exhibited a parent ion peak at *m/e* 367.1390 corresponding to the formula $C_{21}H_{21}NO_5$ (calculated *m/e* 367.1420), which was also supported by elemental analysis. The UV spectrum [$\lambda_{max}(CH_3OH)$ 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 [ν_{max}(KBr) 1635 cm^{-1}] suggested the presence of a tertiary amide carbonyl. The 60-MHz NMR spectrum ($CDCl_3$) showed three 3H singlets at δ 2.17 (—$NCOCH_3$), 3.60, and 3.82 (—OCH_3), a 2H singlet at δ 5.85 (—OCH_2O—), 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[4] 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-6*a* (6).

These data suggested that Alkaloid A be represented by Structure II*b*. Direct comparison of an authentic sample of (+)-*N*-acetylnornantenine (II*b*)[5] [lit. (7) mp 294°, $[\alpha]_D$ + 349° (c 0.44 in $CHCl_3$)], an alkaloid obtained by acetylation of nornantenine (II*c*), 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)[3], $[\alpha]_D^{26}$ + 271° (c 0.37 in $CHCl_3$)] gave a parent ion peak at *m/e* 397.1527 corresponding to the formula $C_{22}H_{23}NO_6$ (calculated *m/e* 397.1525), which was also supported by elemental analysis. A carbonyl absorption in the IR spectrum [ν_{max}(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 (—OCH_3), a 2H singlet at δ 5.87 (—OCH_2O—), and two 1H singlets at δ 6.63 and 7.77 (Ar—H). Comparison of the NMR spectrum of (+)-*N*-acetylnornantenine (II*b*) with that of Alkaloid B indicated the two alkaloids to be closely related and that Alkaloid B was probably a pentaoxygenated 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-

[1] The plant material was obtained from a tree growing in southern Lafayette County, Miss. The tree was identified by Dr. Maynard W. Quimby; a voucher specimen has been deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi.

[2] TLC analyses were carried out on silica gel-coated plates using ether or acetone–methanol–benzene (1:1:8) as the solvent.

[3] The melting point was determined with a Thomas-Hoover Uni-Melt capillary melting-point apparatus and is not corrected.

[4] Circular dichroism measurements were performed on a Jasco model J-40 automatic recording spectropolarimeter using methanol as solvent.

[5] The authors thank Dr. S. R. Johns of C.S.I.R.O., Melbourne, Australia, for kindly providing an authentic sample for comparison.

pears downfield at δ 7.77 (*cf.*, 7.82 in II*b*) and one of the methoxy groups appears upfield at δ 3.68 (*cf.*, 3.60 in II*b*), a methoxy can be placed at C-1 and a hydrogen at C-11 (5, 10, 11)[6]. The UV spectrum [λ_{max} (CH_3OH) nm (log ϵ): 217 (4.65), 280 (4.08), 307 (4.16), and 313 sh (4.16)] is characteristic of a 1,2,3,9,10-pentaoxygenated aporphine (12, 13) and distinctly different from a 1,2,8,9,10-pentaoxygenated 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-pentaoxygenated 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 II*b*). 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 (5). 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*-acetylnornantenine (II*e*). The absolute stereochemistry at C-6*a* follows by noting the large positive Cotton effect in the circular dichroism spectrum[4] at 243 nm ([θ] = +199,000; 1.80 mg/50 ml), which has been correlated with the *S*-configuration at C-6*a* (6). To our knowledge, these alkaloids (II*b* and II*e*) represent the first two examples of naturally occurring *N*-acetylaporphine alkaloids.

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[6] The NMR spectrum of ocoteine (II*d*) is reported in Ref. 11. It shows $-OCH_2O-$ at C-1,2 as an *AB* quartet and signals for three methoxy groups at δ 3.91, 3.91, and 3.99.

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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.

* National Sciences Foundation Undergraduate Research Participant, 1973.

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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

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 psychotogenic 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