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FOUR NEW *N*-ACETYLNORAPORPHINE ALKALOIDS FROM *LIRIODENDRON TULIPIFERA*

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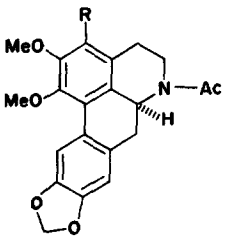
Key Word Index—*Liriodendron tulipifera*; Magnoliaceae; isolation; heartwood; *N*-acetylnoraporphine alkaloids.

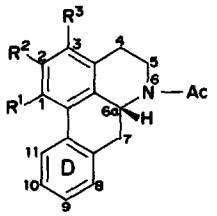
Abstract—Four new naturally occurring *N*-acetylnoraporphine alkaloids were obtained from the heartwood of *Liriodendron tulipifera*; (−)-*N*-acetylanonaine, (−)-*N*-acetylnornuciferine, (−)-*N*-acetylasimilobine, and (−)-tuliferoline. Structure determination was accomplished by physical and chemical methods.

INTRODUCTION

The systematic study of the nonbasic fractions of alkaloid bearing plants has received almost no attention to date with the exception of some alkaloidal amides being reported from peyote [1, 2]. A study of the heartwood of *Liriodendron tulipifera* L. has revealed the presence of two *N*-acetylnoraporphine alkaloids, (+)-*N*-acetylnornantenine (**1**) and (+)-3-methoxy-*N*-acetylnornantenine (**2**) [3, 4].* Subsequent studies, herein reported, have revealed the presence of four additional naturally occurring nonbasic alkaloids, (−)-*N*-acetylanonaine (**3**), (−)-*N*-acetylnornuciferine (**4**), (−)-*N*-acetylasimilobine (**5**), and (−)-tuliferoline (**6**).



(**1**) R = H
(**2**) R = OMe



(**3**) $R^1 = R^2 = OCH_2O$, $R^3 = H$
(**4**) $R^1 = R^2 = OMe$, $R^3 = H$
(**5**) $R^1 = OMe$, $R^2 = OH$, $R^3 = H$
(**6**) $R^1 = R^2 = R^3 = OMe$
(**7**) $R^1 = OMe$, $R^2 = OAc$, $R^3 = H$

RESULTS AND DISCUSSION

An ethanolic extract of the heartwood was partitioned between ether and 2N HCl. Chromatography of the ether soluble residue on silicic acid yielded fractions that were still mixtures. These were further purified by chromatography over silica gel to yield the four new alkaloids.

(−)-*N*-Acetylanonaine (**3**), mp 229–230°, showed an IR band at 1640 cm^{-1} and high resolution MS established the formula as $C_{19}H_{17}O_3N$. The UV spectrum was consistent with a 1,2-dioxygenated aporphine [5]. The NMR spectrum indicated a 1-proton multiplet centered near δ 8.2 (C-11), 1-proton singlet at δ 6.87 (C-3), a pair of 1-proton doublets at δ 6.20 (J 1.8 Hz) and δ 6.08 (J 1.8 Hz) (OCH_2O), and a 3-proton singlet at δ 2.23 (NCOMe). The above data suggested a 1,2-methylenedioxy-*N*-acetylnoraporphine alkaloid and were consistent with those reported for (−)-*N*-acetylanonaine, an acetylation product of anonaine [6]. A direct comparison with an authentic sample confirmed the identity of **3** as (−)-*N*-acetylanonaine.

(−)-*N*-Acetylnornuciferine (**4**), mp 229–230°, had an IR band at 1630 cm^{-1} and a 3-proton singlet at δ 2.17 in the NMR spectrum which are indicative of an *N*-acetyl group. High resolution MS established the formula as $C_{20}H_{21}NO_3$ and the UV spectrum was similar to that of **3**. The NMR spectrum of **4** indicated two 3-proton singlets at δ3.60 and δ3.82 (OMe), but no signals for a methylenedioxy group; otherwise, the spectrum was similar to that of **3**. These data suggested that **4** was a 1,2-dimethoxy-*N*-acetylnoraporphine and comparison with an authentic sample of (±)-*N*-acetylnornuciferine [7] confirmed the identity. The absolute stereochemistry at C-6a follows from the CD spectrum which shows a large negative cotton effect at 245 nm indicating the R-configuration [3, 8].

(−)-*N*-Acetylasimilobine (**5**), mp 280–282°, had IR bands at 3200 and 1630 cm^{-1}. Elemental analysis and high resolution MS established the formula as $C_{19}H_{19}O_3N$. The UV spectrum was similar to **3** and **4** except a bathochromic shift was noted upon addition of base. The NMR spectrum revealed the presence of one methoxyl group as a singlet at δ 3.57, an exchangeable 1-proton singlet at δ 5.97 (OH); otherwise, the spectrum was similar to that of **4**. These data suggest a 1,2-dioxygenated-*N*-acetylnoraporphine with the pheno-

* A total synthesis of (±)-3-methoxy-*N*-acetylnornantenine has been achieved confirming the structure proposed in reference 3; see Hufford, C. D. and Morgan, J. M. (1976) *J. Org. Chem.* **41**, 375.

lic group at C-2†. The acetate of **5** was prepared and compared with an authentic sample of *O,N*-diacetylasimilobine (**7**) [10]. The two samples were indistinguishable on TLC and gave superimposable IR spectra and no mmp depression. Thus, **5** is (−)-*N*-acetylasimilobine.

The fourth alkaloid for which the name (−)-tuliferoline (**6**) has been proposed had mp 145–146° and a molecular formula of $C_{21}H_{23}O_4N$ as established from elemental analysis and high resolution MS. An IR band at 1640 cm^{-1}, a 3-proton singlet at δ 2.22 in the NMR spectrum, and the UV spectrum were consistent with an *N*-acetylated noraporphine alkaloid. Additional features of the NMR spectrum include a 1-proton multiplet (C-11) near δ 8.5 and a 3-proton multiplet near δ 7.4 (C-8,9,10) which is characteristic for unsubstituted D rings as shown from the NMR spectra of **3**, **4**, and **5**. The absence of any signals for the C-3 proton and the presence of three methoxyl signals at δ 4.05, 3.98, and 3.82 suggests that tuliferoline can be represented as a 1,2,3-trimethoxy-*N*-acetylnoraporphine alkaloid. A negative cotton effect at 238 nm indicates the R-configuration at C-6a [3, 8] and thus the structure represented by **6** is proposed for (−)-tuliferoline.

The *N*-acetylnoraporphines thus far isolated follow the general rule that aporphines with unsubstituted D rings are levorotatory while those with substituents at C-1,2 (and 3) 9,10 are dextrorotatory [11].

EXPERIMENTAL

Mp's are uncorrected. UV spectra were determined in MeOH; NMR spectra were recorded at 60 MHz using TMS as internal standard; chemical shift values are reported in δ (ppm) units. Elemental analyses were performed by Scandinavian Microanalytical Laboratory. CD measurements were performed on a JASCO J-40 recording spectropolarimeter.

Isolation of alkaloids **3**–**6**. The air-dried ground heartwood of *Liriodendron tulipifera*† (11.2 kg) was Soxhlet extracted with EtOH and yielded 311.4 g of residue after evaporation of solvent at red pres and at 40°. The alcohol-soluble residue (311.4 g) was redissolved in 650 ml 95% EtOH and then 1.3 l 2N HCl was added. The alcohol was then evaporated and the remaining suspension extracted 4× with 1.3 l Et_2O. Combined Et_2O layers were evaporated to yield 59.6 g of residue. The 59.6 g of Et_2O-soluble residue was dissolved in $CHCl_3$ and chromatographed over silicic acid (1 kg) using $CHCl_3$ and increasing amounts of MeOH in $CHCl_3$ as eluent. The fractions (200 ml) were monitored by TLC using Si gel G coated plates with either Me_2CO–MeOH–C_6H_6 (1:1:8) or Et_2O as solvent. After elution with 3 l $CHCl_3$ a fraction was obtained (1.5 g) that yielded (−)-*N*-acetylanonaine (**3**) upon crystallization from alcohol. Recrystallization from alcohol gave 55 mg of **3**: mp 229–230°, $[\alpha]_D^{25}$ − 356° ($CHCl_3$; *c* 0.49); UV: λ_{max} (log ϵ), 217(4.24), 269(4.12), 312(3.49); IR (KBr) ν_{max}: 1640 cm^{-1}; CD: $[\theta]_{273}$ +30,600, $[\theta]_{251}$ 0, $[\theta]_{230}$ −168,700 (MeOH; *c* 0.001834); NMR ($CDCl_3$): δ 8.18 (1 H, *m*, C-11), 7.37 (3 H, *m*, C-8,9,10), 6.87 (1 H, *s*, C-3), 6.20 and 6.08 (1 H ea., *d*, *J* 1.8 Hz, OCH_2O) and 2.23 (3H, *s*,$NCOCH_3$); MS: *m/e* 307.120 (M^+, $C_{19}H_{17}NO_3$ requires 307.121). A direct comparison of **3** with an authentic sample of (−)-*N*-acetylanonaine, an acetylation product of (−)-anonaine [6], showed the 2 samples to be indistinguishable (TLC, mp, mmp, superimposable IR spectra). After elution with an additional 1 l $CHCl_3$ a 3.1 g fraction was obtained that was further purified by chromatography over 150 g specially prepared Si gel G (Merck) [4, 12] using Et_2O as eluent. After 640 ml of eluent had been collected a fraction (2.16 g) was obtained that upon crystallization from MeOH gave 782 mg of **4**: mp 229–230°; $[\alpha]_D^{25}$ −406° ($CHCl_3$; *c* 0.65); UV: λ_{max} (log ϵ) 211(4.09), 268(3.78), 300*sh*(3.10); IR (KBr) ν_{max}: 1630 cm^{-1}; CD: $[\theta]_{310}$ −6900, $[\theta]_{297}$ 0, $[\theta]_{272}$ +39,400, $[\theta]_{248}$ 0, $[\theta]_{235}$ −212200 (MeOH; *c* 0.001674); NMR($CDCl_3$): δ 8.43(1H, *m*, C-11), 7.42(3H, *m*, C-8,9,10), 6.82(1H, *s*, C-3), 3.97(3H, *s*, OCH_3 at C-2), 3.73(3H, *s*, OCH_3 at C-1) and 2.27(3H, *s*, $NCOCH_3$); MS: *m/e* 323.151 (M^+, $C_{20}H_{21}NO_3$ requires 323.152). A direct comparison of **4** with an authentic sample of (±)-*N*-acetylnornuciferine (**4**) [7] indicated they had the same R_f value in two TLC systems and superimposable IR spectra. Elution with another 2 l $CHCl_3$ yielded a 5.22 g fraction that was further purified by chromatography over 200 g Si gel G (as before) using Et_2O as eluent. After a total of 750 ml of eluent had been collected a 1.7 g fraction was obtained that yielded 1.128 g of **6** upon crystallization from C_6H_6–hexane. Recrystallization from alcohol–hexane gave 754 mg **6**: mp 145–146°; $[\alpha]_D^{25}$ −330° ($CHCl_3$; *c* 0.83); UV: λ_{max} (log ϵ) 224(4.06), 273(4.10); IR (KBr) ν_{max}: 1642 cm^{-1}; CD: $[\theta]_{277}$ +46,800, $[\theta]_{251}$ 0, $[\theta]_{238}$ −300,900, $[\theta]_{224}$ 0, $[\theta]_{219}$ +105,100 (MeOH; *c* 0.004868); NMR($CDCl_3$): δ 8.52(1H, *m*, C-11), 7.40(3H, *m*, C-8,9,10), 4.05(3H, *s*, OCH_3), 3.98(3H, *s*, OCH_3), 3.82(3H, *s*, OCH_3), 2.27(3H, *s*, NCOMe); MS: *m/e* 353.162 (M^+, $C_{21}H_{23}NO_4$ requires 353.163). (Found: C,71.11; H, 6.55; N, 4.52. Calc. for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 4.53%). An additional quantity (958 mg) of **4** was also obtained after **6** had eluted. Continued elution with 2 l of $CHCl_3$ and 3 l. of 1% MeOH in $CHCl_3$ yielded no alkaloid fractions. Elution with 2 l. 2% MeOH yielded a 5.22 g fraction that was a mixture of **1** and **2** as shown by TLC and a 8.30 g fraction that was mostly lirioresinol-β-dimethyl ether [4]. Continued elution with 5 l 4% MeOH gave a 4.52 g fraction that was further purified by chromatography over 200 g of Si gel G (as before) using Et_2O as eluent. After elution with 750 ml of Et_2O an 892 mg fraction was obtained that gave 470 mg of **5** from $CHCl_3$. Recrystallization from $CHCl_3$–MeOH gave 389 mg of **5**: mp 280–282°; $[\alpha]_D^{25}$ −405° (pyridinc; *c* 0.595); IR (KBr) ν_{max}: 3100 and 1630 cm^{-1}; CD: $[\theta]_{312}$ −7,000, $[\theta]_{297}$ 0, $[\theta]_{272}$ +45,700, $[\theta]_{249}$ 0, $[\theta]_{235}$ −232,900 (MeOH; *c* 0.002163); NMR ($CDCl_3$): δ 8.53(1H, *m*, C-11), 7.43(3H, *m*, C-8,9,10), 6.90(1H, *s*, C-3), 6.10(1H, *s*, OH, lost in D_2O), 3.65(3H, *s*, OCH_3) and 2.27(3H, *s*, $NCOCH_3$); MS: *m/e* 309.134 (M^+, $C_{19}H_{19}O_3N$ requires 309.136). (Found: C, 73.67; H, 6.29; N, 3.96. Calc. for $C_{19}H_{19}O_3N$: C, 73.75; H, 6.19; N, 3.97). Acetylation of **5** with Ac_2O Py gave O,N-*Diacetylasimilobine* (**7**), crystals from benzene-hexane, mp 143–144°; IR (KBr) ν_{max}: 1770 and 1630 cm^{-1}. A direct comparison of **7** with *O,N*-diacetylasimilobine [10] showed the two samples to be indistinguishable (TLC, mp, mmp, superimposable IR spectra).

* The assignment of the phenolic group at C-2 was based upon the fact that a methoxyl group located at C-1 will consistently appear at higher field than one located at C-2 [9].

† A large tree was cut in the fall of 1973 in southern Lafayette County, Mississippi. The tree was identified by Dr. Maynard W. Quimby and a voucher specimen has been deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi. The heartwood used in this study represents a different collection than used previously and the isolation procedure has been modified slightly.

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