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Synthesis of (±)-3-Methoxy-*N*-acetylnornantenine

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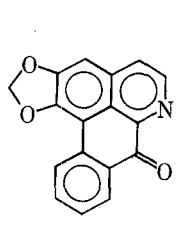
Received July 14, 1975

The heartwood of *Liriodendron tulipifera* has previously yielded two antimicrobial alkaloids, liriodenine (**1**) and dehydroglaucine (**2**),[1] and two nonbasic noraporphine alkaloids, one of which has been identified as (+)-*N*-acetylnornantenine (**3**) by direct comparison with an authentic sample.[2] A structure for the second alkaloid was tentatively assigned as (+)-3-methoxy-*N*-acetylnornantenine (**4**) based on spectroscopic evidence.[2] A total synthesis confirming this assignment has now been achieved.

Decomposition of ω-diazo-3,4-methylenedioxy-6-nitroacetophenone (**5**) in the presence of 2,3,4-trimethoxy-β-phenylethylamine (**6**) and silver oxide afforded the crystalline amide **7**. Compound **7** was smoothly cyclized in the Bishler–Napieralski reaction using phosphorus oxychloride in acetonitrile to the dihydroisoquinoline **8**. Reduction of **8** with sodium borohydride and acetylation with acetyl chloride produced the *N*-acetyl derivative **9**. The NMR spectrum of **9** clearly showed signals for each conformer which is characteristic of hindered rotation in 1-benzyl-1,2,3,4-tetrahydroisoquinolines.[3] Reduction of **9** with zinc dust and sulfuric acid gave **10**, which upon Pschorr cyclization following the method utilized by Weisbach and Douglas[4] gave (±)-3-methoxy-*N*-acetylnornantenine (**4**) which gave TLC, NMR, solution ir, and MS data identical with those of natural (+)-3-methoxy-*N*-acetylnornantenine (**4**).



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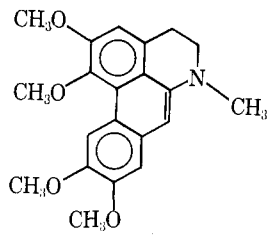

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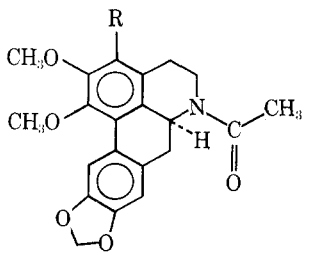
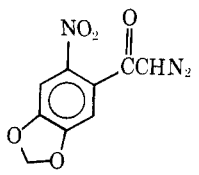


3, R = H
4, R = OCH_3



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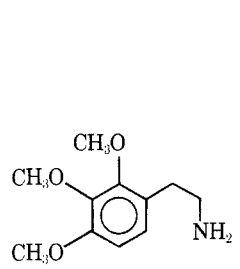

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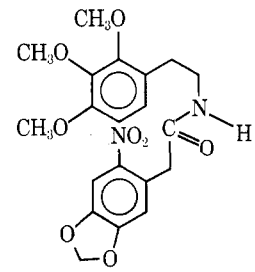

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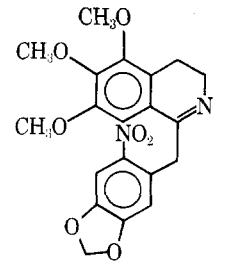

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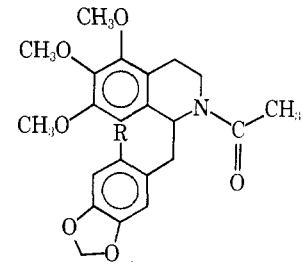

9, R = NO_2
10, R = NH_2

Experimental Section

All melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. The infrared spectra were taken on a Perkin-Elmer 257 or Beckman IR-33 infrared spectrometer. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. NMR spectra were recorded on a Jeol C-60HL spectrometer using deuterated chloroform as solvent and Me_4Si as internal standard, with chemical shifts recorded in δ (ppm) units. Uv spectra were obtained in methanol on a Beckman Acta III spectrophotometer. Mass spectral data were obtained on a Du Pont CEC 492 spectrometer.

***N*-(2,3,4-Trimethoxy-β-phenylethyl)-3′,4′-methylenedioxy-6′-nitrophenylacetamide (7).** To a solution of 7.2 g of ω-diazo-3,4-methylenedioxy-6-nitroacetophenone (**5**)[5] in 75 ml of dry benzene at 60° was added, with stirring, a solution of 7.4 g of 2,3,4-trimethoxy-β-phenylethylamine (liberated from 8.5 g of hydrochloride salt, obtained from Aldrich) in 30 ml of dry benzene and 513 mg of freshly prepared Ag_2O. The suspension was stirred at 60° for 0.5 hr and then an additional 300 mg of Ag_2O was added, followed by 1 hr of refluxing. After cooling, the solution was concentrated under reduced pressure to remove most of the benzene and then dissolved in boiling acetonitrile, filtered through Celite while hot, and evaporated to dryness to leave 10.2 g of amide **7**. Crystallization from acetonitrile gave 9.1 g: mp 181–182°; ir (KBr) 3300 (NH) and 1645 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{22}N_2O_8$; C, 57.40; H, 5.30; N, 6.70. Found: C, 57.33; H, 5.27; N, 6.89.

1-(3′,4′-Methylenedioxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (8).[6] Amide **7** (300 mg) was dissolved in 20 ml of acetonitrile at 60° and with stirring 3 ml of phosphorus oxychloride was added. After 2 hr at 60° the solution was evaporated under reduced pressure to give a red gum which yielded 77 mg of **8** upon crystallization from alcohol, mp 144–145°. Chromatography of the mother liquor on silica gel using benzene–acetone (8:1) as eluent gave an additional 69 mg: NMR ($CDCl_3$) δ 7.43, 6.95, and 6.85 (1 H each, PhH), 5.98 (2 H, s, OCH_2O), 4.30 (2 H, s, $NO_2PhCH_2C{=}N$), 3.87 (3 H, s, OCH_3), 3.80 (6 H, s, OCH_3), 3.55 (2 H, dd, J = 8, 8 Hz, $C{=}NCH_2CH_2$), 2.58 (2 H, dd, J = 8, 8 Hz, $-C{=}NCH_2CH_2$).

Anal. Calcd for $C_{20}H_{20}N_2O_7$; C, 59.98; H, 5.04; N, 6.99. Found: C, 59.72; H, 4.99; N, 6.72.

1-(3',4'-Methylenedioxy-6'-nitrobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (9). Dihydroisoquinoline (8, 1.11 g) was suspended in 150 ml of methanol and with stirring 800 mg of sodium borohydride was added in portions over 30 min. After an additional 1 hr the pH was adjusted to near pH 5 with acetic acid. After removal of all solvent under reduced pressure the residue was dissolved in $CHCl_3$, washed with dilute base and water, dried, and evaporated to dryness to give the tetrahydroisoquinoline as a white solid. This was immediately dissolved in 30 ml of pyridine and treated with 8 ml of acetyl chloride. After 3 hr at room temperature, the solution was treated with dilute base and extracted with $CHCl_3$. The combined organic layers were washed with 2% HCl and then water, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel using benzene–acetone (8:1) as the eluent and afforded a yellow oil which crystallized from methanol to give 840 mg of **9**: mp 159–160°; ir ($CHCl_3$) 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.66 and 7.53 (1 H total, s, PhH), 6.87 and 6.75 (1 H total, s, PhH), 6.63 and 6.57 (1 H total, s, PhH), 6.18 and 6.12 (2 H total, s, OCH_2O), 4.00–3.83 (9 H, OCH_3), 2.02 and 1.62 (3 H total, s, $NCOCH_3$).

Anal. Calcd for $C_{22}H_{24}N_2O_8$; C, 59.44; H, 5.45; N, 6.30. Found: C, 59.13; H, 5.49; N, 6.25.

1-(3',4'-Methylenedioxy-6'-aminobenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (10). A 94-mg sample of **9** was suspended in 50 ml of methanol and with stirring 0.5 g of zinc dust was added slowly followed by 2 ml of 1 *N* H_2SO_4 added dropwise. The suspension was stirred for 30 min at room temperature, filtered, adjusted to pH 8 with NH_3, and then evaporated to dryness. The residue was taken up in $CHCl_3$, washed with water, dried, and evaporated to dryness, leaving a residue which was further purified by chromatography over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 55 mg of **10**: mp 189–190°; ir (KBr) 3440, 3350, 3240 (NH_2), and 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.38; H, 6.31; N, 6.77.

(±)-3-Methoxy-*N*-acetylnornantenine (4). A 56-mg sample of **10** was added to a solution of 0.58 ml of glacial acetic acid and 0.04 ml of concentrated sulfuric acid at 10° and allowed to warm to 20°. A solution of sodium nitrite (11.6 mg in 0.1 ml of H_2O) was added and the solution was stirred at 20° for 50 min. The solution was allowed to warm to room temperature and then 1 mg of sulfamic acid, 0.5 mg of cuprous chloride, and 1.2 ml of acetone were added and the solution refluxed for 30 min. After cooling, the solution was concentrated to about 3 ml, adjusted to pH 8.5 with NH_4OH, and extracted with ether (5 × 10 ml). The combined extracts were dried and evaporated to give a yellow gum which was chromatographed over silica gel. Elution with benzene–acetone (8:1) and crystallization from alcohol gave 7 mg of racemic **4**, mp 174–175°. The synthetic product had the same R_f values in four TLC systems, the same NMR, uv, and mass spectra, and superimposable ir ($CHCl_3$) spectra as that of natural **4**.

Acknowledgment. This work was supported in part by a Faculty Research Grant, University of Mississippi, and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. The authors are grateful to Dr. Stephen Billets, Research Institute of Pharmaceutical Sciences, School of Pharmacy, for determining the mass spectra.

Registry No.—(±)-**4**, 57236-56-3; **5**, 57196-56-2; **6**, 3937-16-4; **7**, 57196-57-3; **8**, 57237-60-2; **9**, 57196-58-4; **10**, 57196-59-5.

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Revision of the Structure of the Bisindole Alkaloid 14',15'-Dihydropycnanthine. A Carbon-13 Nuclear Magnetic Resonance Study[1]

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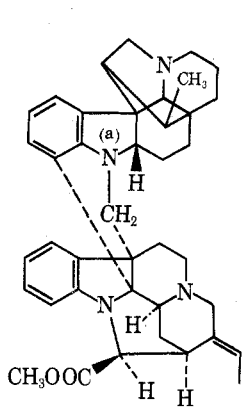
Received July 15, 1975

We wish to describe a ^{13}C nuclear magnetic resonance spectral analysis of the previously reported bisindole alkaloid 14',15'-dihydropycnanthine (1)[2] and present evidence for the necessity of structural revision to **2**.



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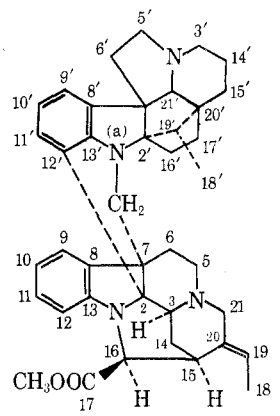

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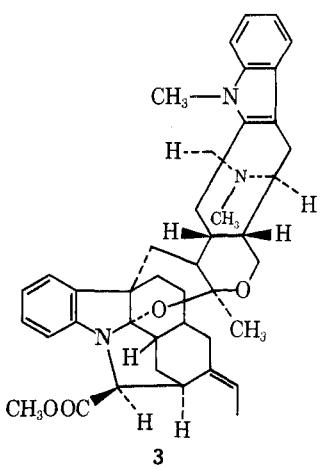

3

From the leaves of *Gonioma malagasy* Mgf. et P. Bt.[3] has been isolated a bisindole alkaloid [mp 247°; $[\alpha]^{22}D$ +243° (*c* 1.4, $CHCl_3$); *m/e* 614] [lit. mp 250°; $[\alpha]^{25}D$ +274 ± 10° (*c* 0.442, $CHCl_3$)] whose spectral characteristics (mass, ^1H NMR, uv, and ir) have indicated that it was identical in every respect with 14',15'-dihydropycnanthine (1) having decarbomethoxy 14',15'-dihydrovindolinine and 2,7-dihydropleiocarpamine moieties.[2,4]

The structure of the decarbomethoxy 14',15'-dihydrovindolinine unit of 14',15-dihydropycnanthine (1) had been