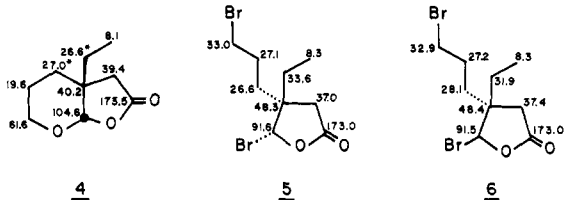
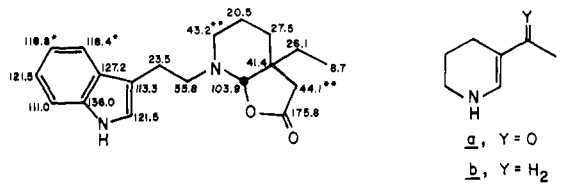


4 5 6

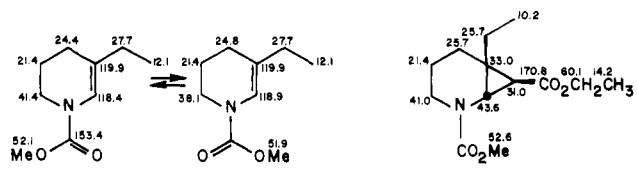


7

a, Y = O
b, Y = H_2

8

with methyl chlorocarbonate (tetrahydrofuran, triethylamine, 4 h) yielded (94%) of enamide **2b** (~4:1 **9a–9b** mixture in

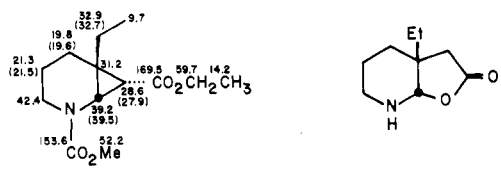


a b

9

10

deuteriochloroform solution): IR (neat) 5.87 μ; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3, J = 7 Hz), 1.8–2.2 (m, 6), 3.54 (m, 2), 3.73 (s, 3), 6.60 (s, 1). Decomposition of ethyl diazoacetate in the latter over copper bronze (~135 °C) gave (95%) esters **3b,** bp 93–95 °C (0.008 Torr), in an ~2:1 exo (**10**) to endo (**11**) ratio. Exo: IR (neat) 5.81, 5.86 μ; ^{1}H NMR ($CDCl_3$) δ 0.88,



11

12

1.26 (t, 3 each, J = 7 Hz), 1.3–2.9 (m, 9), 3.35 (d, 1, J = 4 Hz), 3.70 (s, 3), 4.15 (q, 2, J = 7 Hz). Endo:[9] IR (neat) 5.81, 5.86 μ; ^{1}H NMR ($CDCl_3$) δ 0.97, 1.24 (t, 3 each, J = 7 Hz), 1.9–2.2 (m, 7), 2.93, 3.00 (d each, total 1, J = 6 Hz), 3.1–3.4 (m, 2), 3.67 (s, 3), 4.05 (q, 2, J = 7 Hz). Alkaline hydrolysis (aqueous potassium hydroxide, diethylene glycol, 100 °C, 12 h) of **3b** produced (88%) lactone **12** (mp 72 °C; IR ($CHCl_3$) 2.94, 5.74 μ; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3, J = 7 Hz), 1.2–1.8 (m, 4), 1.81 (q, 2, J = 7 Hz), 2.2–3.0 (m, 5), 5.12 (s, 1)) whose exposure to tryptophyl bromide (benzene, 30% sodium hydroxide, triethylbenzylammonium chloride, 35 °C, 6 h) led (60%) to lactone **7.**

Thermolysis (250 °C, 0.01 Torr, 0.5 h) of lactone **7** yielded (60%) (±)-eburnamonine (**1**), mp 200–201 °C (lit.[3] mp 200–202 °C) (spectrally identical with an authentic sample), completing two short syntheses of the alkaloid.

Acknowledgment. The authors are indebted to the U.S. Public Health Service for support of this work.

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(2) An early stage implies the replacement of an enol system by an enamine derivative. Since enamines themselves misbehave in the cyclopropanation step (E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.*, **94,** 8084 (1972); E. Wenkert, C. A. McPherson, E. L. Sanchez, and R. L. Webb, *Synth. Commun.*, **3,** 255 (1973)), an enamide was needed as starting material (cf. E. Wenkert, M. E. Alonso, H. E. Gottlieb, E. L. Sanchez, R. Pellicciari, and P. Cogolli, *J. Org. Chem.*, **42,** 3945 (1977), and references cited therein; cf. also W. J. Welstead, Jr., H. F. Stauffer, Jr., and L. F. Sancilio, *J. Med. Chem.*, **17,** 544 (1974)).
(3) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87,** 1580 (1965). For syntheses of vincamine and other eburnamonine-like alkaloids see the following recent publications and references cited therein: C. Szántay, L. Szabó, and G. Kalaus, *Tetrahedron,* **33,** 1803 (1977); W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, *Helv. Chim. Acta,* **60,** 1801 (1977).
(4) E. Wenkert, B. L. Buckwalter, and S. S. Sathe, *Synth. Commun.*, **3,** 261 (1973).
(5) The numbers on the formulas represent carbon shifts in parts per million downfield from Me_4Si; δ (Me_4Si) = δ ($CDCl_3$) + 76.9 ppm. Asterisked numbers may be interchanged.
(6) A sensitive solid whose melting point could not be observed because of thermal decomposition.
(7) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33,** 747 (1968).
(8) Cf. E. Leete and L. Marion, *Can. J. Chem.*, **31,** 775 (1953); T. Nugrady and T. W. Doyle, *ibid.*, **42,** 485 (1964).
(9) The carbon shifts denoted in parenthesis on formula **11** refer to the minor urethane rotamer.
(10) Public Health Service postdoctoral fellowship holder, 1974–1976.

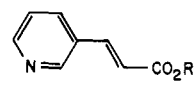
Ernest Wenkert,* Tomáš Hudlický
H. D. Hollis Showalter[10]
Department of Chemistry, Rice University
Houston, Texas 77001
Received March 20, 1978

A Short Route to Pseudoyohimbine and Yohimbine

Sir:

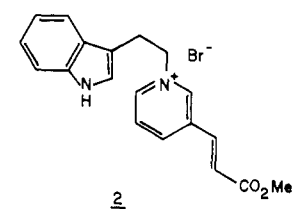
Recently a short, new route of synthesis of the indoloquinolizidine skeleton characteristic of many indole alkaloids was introduced and applied to the total synthesis of a variety of ajmalicinoid bases.[1] The new method consists of γ-alkylation of *N*-alkyl-β-acylpyridinium salts with carbon nucleophiles, acid-induced cyclization of the resultant 1,4-dihydropyridine product, and further elaboration of the thus-formed indoloquinolizideine. To test the generality of the reaction scheme, a study of similar reactions emanating from a β-acylpyridine vinylogue was undertaken and, as shown below, turned into total syntheses of pseudoyohimbine and yohimbine.

Condensation of nicotinaldehyde with malonic acid in pyridine solution in the presence of piperidine yielded (96%) β-(β-pyridyl)acrylic acid (**1a**), mp 237–237.5 °C, whose es-



a, R = H
b, R = Me

1



2

terification with methanolic sulfuric acid gave (95%) its ester **1b,** mp 41–42 °C. Alkylation of the latter with tryptophyl bromide[1] afforded (98%) the salt **2,** mp 195–197 °C.

Interaction of **2** with the sodio salt of dimethyl malonate in monoglyme, followed by treatment of the mixture with a saturated benzene solution of hydrogen bromide, yielded (10%) tetracycle **3a:**[2] mp 220–221 °C; IR (Nujol) 3247, 1739, 1727, 1664 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.58, 3.60, 3.81 (each s, 3), 4.78 (dm, 1, J = 11 Hz), 5.21 (d, 1, J = 15 Hz), 6.8–7.5 (m, 6). Exposure of the latter to lithium iodide trihydrate in Me_2SO[3] at 180 °C for 0.5 h led (82%) to diester **3b** (mp 209–211 °C; IR (KBr) 3290, 1740, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67, 3.73 (each s, 3), 4.56 (dm, 1, J = 12 Hz), 5.41 (d, 1, J = 15 Hz), 6.58 (s, 1), 6.9–7.6 (m, 5)) whose hydrogenation (platinum, glacial acetic acid, atmospheric pressure, room temperature, 5 h) produced (96%) diester **4a**[2] (hydrochloride mp 234–235.5 °C; IR ($CHCl_3$) 3497, 1730 cm^{-1}; ^{1}H

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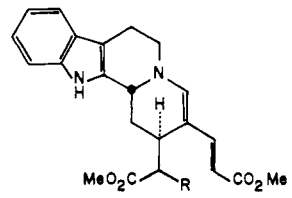
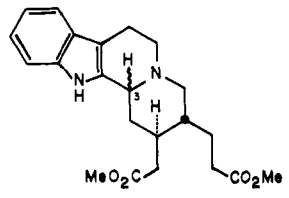


a, R = CO_2Me
b, R = H

3

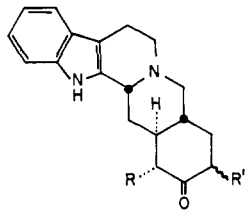


a, H(3β)
b, H(3α)

4

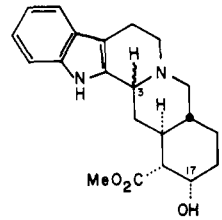
NMR ($CDCl_3$) δ 3.58, 3.67 (each s, 3), 3.91 (br s, 1), 6.9–7.5 (m, 4)).

Treatment of **4a** with sodium hydride in tetrahydrofuran (50 °C, 1.5 h) gave (44 and 36%, respectively) keto esters **5a**[2] (mp 227–228.5 °C; IR ($CHCl_3$) 3460, 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3), 4.53 (br s, 1), 6.9–7.5 (m, 4)) and **5b**[2] (mp 223–225 °C; IR ($CHCl_3$) 3465, 1720, 1655, 1615



a, R = CO_2Me, R' = H
b, R = H, R' = CO_2Me
c, R = R' = H

5



a, H(3β)
b, H(3α)

6

cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3), 4.60 (br s, 1), 6.9–7.6 (m, 4)). Alkaline hydrolysis and acid-induced decarboxylation of the latter afforded (±)-pseudoyohimbone (**5c**), mp 247–250 °C (lit.[1] mp 249–251 °C) (spectra identical with those of authentic sample), confirming the stereochemistry of all precursors. Hydrogenation of **5a** (platinum, 1:1 methanol–acetic acid, 1 drop of 36% hydrochloric acid, atmospheric pressure, room temperature, 48 h) yielded (72%) (±)-pseudoyohimbine (**6a**),[2,4,5] mp 249–251 °C dec (lit. mp[4] 252–256 °C, charring at 250 °C; mp[5] 248–251 °C) (spectra identical with those of an authentic specimen).

Hydrolysis of diester **4a** in refluxing 2:1 18% hydrochloric–acetic acids (24 h), followed by esterification with methanolic hydrogen chloride, led to the recovery (27%) of starting ester and the formation (41%) of isomer **4b:** mp 153–155 °C (lit.[6] mp 152–154 °C); IR (KBr) 3375, 1735, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67, 3.71 (each s, 3), 7.0–7.8 (m, 4). In view of the previous conversion of the latter into (+)-yohimbine (**6b**)[6] and (−)-β-yohimbine (17-*iso*-**6b**),[6] this constitutes a formal total synthesis of these alkaloids also.[5]

Acknowledgment. The authors are indebted to the U.S. Public Health Service for support of this work.

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(2) The stereochemistry is based on a ^{13}C NMR analysis (R. L. Stephens, unpublished observations).
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(8) NATO fellowship holder during 1975–1976.

Ernest Wenkert,* Gerhard Kunesch,[8] Kazuhiko Orito
Wayne A. Temple, Jhillu S. Yadav
Department of Chemistry, Rice University
Houston Texas 77001
Received March 20, 1978

Structure of Mildiomycin, a New Antifungal Nucleoside Antibiotic

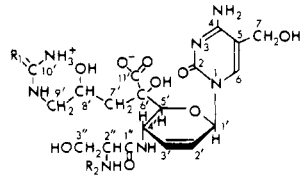
Sir:

A new nucleoside antibiotic, mildiomycin, was isolated from the culture filtrate of *Streptoverticillium rimofaciens* B-98891 in our laboratories.[1] It shows strong activity against powdery mildews on various plants[1a] and remarkably low toxicity in mammals and fishes.[1b] This paper deals with the structural elucidation of mildiomycin carried out on the basis of chemical degradations and spectral evidence as shown in Chart I.

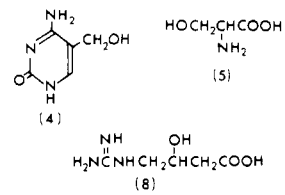
Mildiomycin (**1**)[1b] is a water-soluble, basic antibiotic: $C_{19}H_{30}N_8O_9 \cdot H_2O$; mp >300 °C dec; $[\alpha]^{23}_D$ +100°;[2] pK_a' = 2.8 (-COO^-), 4.2 (3-NH^+=), 7.2 (2″-NH_3^+), and >12 (guanidine); ν 1650 (-CONH-) and 1000–1150 (-C-O-) cm^{-1};[3] λ (pH 7) 271 nm (ε 8720) and λ (0.1 N HCl) 280 nm (ε 13 100); positive with Sakaguchi, Greig–Leaback and ninhydrin reactions. Because **1** is noncrystallizable, hygroscopic and nonvolatile, determination of the molecular formula of **1** was based on two crystalline derivatives, 2″-*N*-monobenzoate **2** ($C_{19}H_{30}N_8O_9 \cdot C_7H_4O \cdot 2H_2O$ (benzoyl chloride/5% $NaHCO_3$), mp >300 °C, $[\alpha]^{27}_D$ +92.5° ($AcOH-H_2O$ (2:8)) and 2′,3′-dihydromildiomycin (**3**, $C_{19}H_{32}N_8O_9 \cdot H_2O$ (PtO_2/water), mp >300 °C, $[\alpha]^{22}_D$ ±0°). The ^{13}C NMR spectra of **1** and **3** also support the molecular formula as shown in Table I.

On acidic hydrolysis (2 N HCl, reflux, 2 h), **1** gave 5-hydroxymethylcytosine (**4**) and L-serine (**5**), which were identified with the authentic samples. The ^{13}C NMR signals of **1**

Chart I



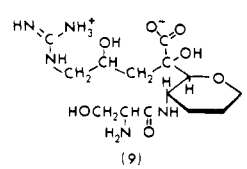
(1): R_1=NH, R_2=H (Mildiomycin)
(2): R_1=NH, R_2=Bz
(3): 2′,3′-Dihydro derivative of (1)
(6): R_1=O, R_2=H, Not ionized
(7): Formic acid salt of (1)



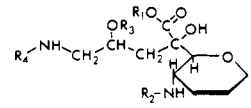
(4)

(5)

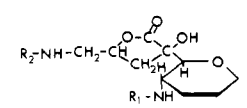
(8)



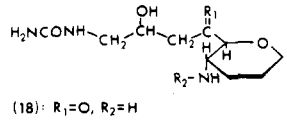
(9)



(13): R_{1-3}=H, R_4=C(=NH)NH_2·HCl
(14): R_{1-3}=H, R_4=C(=NH)NH_2
(15): R_{1-3}=H, R_4=$CONH_2$
(16): R_1=H, R_{2-3}=Ac, R_4=CONHAc
(17): R_1=CH_3, R_{2-3}=Ac, R_4=CONHAc



(10): R_1=COCH(NHBz)CH_2OH, R_2=$CONH_2$
(11): R_1=COCH(NHBz)CH_2OAc, R_2=CONHAc
(12): R_1=H·HCl, R_2=C(=NH)NH_2·HCl



(18): R_1=O, R_2=H
(19): R_1=H,OH, R_2=Ac

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