(αR*,2S*,5S*,6S*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2H-pyran-2-glycolamide (Pederamide) 2. Methyl pederate **20** (0.056 g, 0.00023 mol) was dissolved in 5 mL of anhydrous methanol (dried over magnesium ethoxide and distilled), placed in a pressure reaction tube (Fischer-Porter Co.), and cooled to 0 °C. Anhydrous ammonia was bubbled into the solution for 20 min and the tube was then sealed. The reaction mixture was heated at 100 °C for 48 h. After recooling to 0 °C, the tube was cautiously opened and warmed to room temperature. Methanol was removed by evaporation at reduced pressure. Pederamide (0.053 g, single TLC spot) was obtained in quantitative yield. The solid was recrystallized twice from diethyl ether to give a sample showing mp 129–129.5 °C (lit.[11b] mp 128.5–129.5 °C): IR ($CHCl_3$) 3490, 3440, 3370, 2970, 1690, 1655, 1580, 1140, 1105, 1040, 1010, 900 cm^{-1}; NMR ($CDCl_3$) 0.97 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 6 Hz), 2.24 (m, 4 H), 3.29 (s, 3 H), 4.0 (m, 1 H), 4.24 (s, 1 H), 4.78 (d of t, 2 H, J = 10, 2 Hz), 5.9 (bs, 1 H), 6.75 (bs, 1 H) ppm; EIMS, *m/e* (rel intensity) 198 (40), 139 (11), 134 (45), 125 (21), 124 (12), 123 (49), 121 (10), 113 (13), 109 (36), 107 (24), 97 (12), 96 (14), 95 (87), 93 (15), 91 (20), 81 (56), 79 (29), 77 (15), 75 (13), 74 (12), 67 (36), 56 (11), 55 (46), 54 (11), 53 (29), 45 (11), 44 (27), 43 (41), 41 (60); CIMS, *m/e* (rel intensity) 226 (13), 199 (11), 198 (100), 181 (12), 180 (89).

Anal. Calcd for $C_{11}H_{19}O_4N$: C, 57.64; H, 8.30; N, 6.11. Found: C, 57.49; H, 8.36; N, 6.05.

(αR*,2R*,5R*,6R*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2H-pyran-2-glycolamide (*epi*-Pederamide) 26. Methyl *epi*-pederate **25** (0.067 g, 0.00028 mol) was dissolved in 5 mL of anhydrous methanol (dried over magnesium ethoxide and distilled) and was treated with ammonia as described for the synthesis of pederamide **2.** Crude *epi*-pederamide (0.051 g, 81% yield, one TLC spot) was obtained. This solid was recrystallized twice from diethyl ether to give a sample of **26,** mp 131–132 °C: IR ($CHCl_3$) 3510, 3480, 3395, 2970, 1690, 1655, 1580, 1120, 900 cm^{-1}; NMR ($CDCl_3$) 1.03 (d, 3 H, J = 6 Hz), 1.18 (d, 3 H, J = 6 Hz), 2.24 (m, 2 H), 2.28 (d, 1 H, J = 12 Hz), 2.55 (bs, 1 H), 3.35 (s, 3 H), 3.99 (m, 1 H), 4.15 (s, 1 H), 4.8 (d of t, 2 H, J = 12, 2 Hz), 6.12 (bs, 1 H), 6.79 (bs, 1 H) ppm; EIMS, *m/e* (rel intensity) 198 (11), 197 (51), 180 (10), 155 (74), 153 (100), 152 (10), 139 (10), 134 (90), 125 (22), 123 (49), 121 (12), 109 (34), 107 (27), 97 (12), 96 (26), 95 (94), 93 (11), 91 (20), 85 (20), 83 (37), 81 (83), 79 (36), 77 (17), 75 (15), 74 (22), 68 (17), 67 (40), 65 (10), 56 (18), 55 (48), 54 (17), 53 (37), 44 (32), 43 (61), 41 (72); CIMS, *m/e* (rel intensity) 226 (14), 199 (11), 198 (100), 181 (10), 180 (74).

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Total Synthesis of the Yohimbines

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Abstract: A recently introduced scheme of indole alkaloid synthesis has been utilized for the six-step construction of pseudoyohimbine from methyl β-(β-pyridyl)acrylate. Thus the interaction of the *N*-tryptophyl salt of the latter with dimethyl sodiomalonate, followed by acid-catalyzed ring closure, affords an indoloquinolizidine, whose monodecarbomethoxylation and hydrogenation produce a diester, which on base-induced cyclization and hydrogenation leads to the pentacyclic alkaloid. The interconversion of the intermediate tri- and diesters results in formal total syntheses of also the alkaloids yohimbine, β-yohimbine, alloyohimbine, and α-yohimbine. A ^{13}C NMR analysis of all indoloquinolizidines permits their ready conformational analysis.

The yohimbines comprise a group of natural, pentacyclic indole alkaloids containing five chiral centers illustrated by general formula **1,** various stereoisomers of which have been synthesized in the last two decades.[2] In view of the recent introduction of a new method of construction of the indoloquinolizidine unit, a structure moiety common to the yohimbines, and its successful exploitation in the total synthesis of the natural ajmalicinoid bases (**4**)[3,4] the yohimbines appeared to

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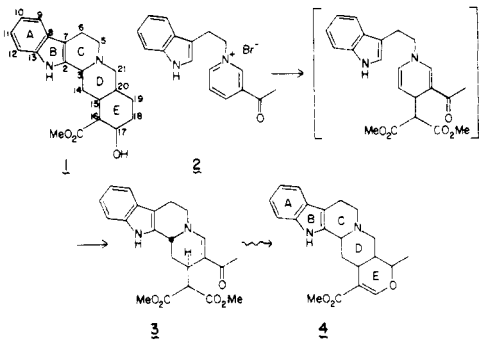
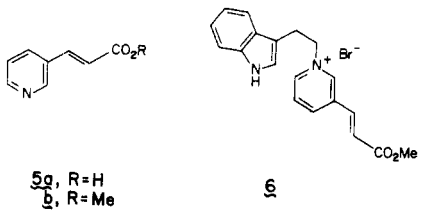


be an ideal goal of synthesis by the same procedure. Hence, a study of yohimbine synthesis was undertaken and the present communication presents the results of this investigation.[5]

The novel indoloquinolizidine synthesis depends on the ability of an *N*-alkyl-β-acylpyridinium salt, e.g., **2,** to accept carbon nucleophiles at its γ-carbon site and of the resultant 1,4-dihydropyridine to undergo acid-catalyzed cyclization at its vicinally unsubstituted α-carbon center, e.g., forming tetracycle **3.** The two-step, one-operation scheme was suited ideally to the synthesis of ajmalicine and related alkaloids (**4**)[3] in view of the nature and proximity of the reactive functional groups introduced in the indoloquinolizidine (**3**) production and their relationship to heterocycle E in the alkaloids. In principle, its adaptation to the synthesis of the yohimbines (**1**) appeared feasible also, since the same functional groups could be envisaged to be useful in the construction of carbocycle E of the latter alkaloids. However, it was decided to vary the scheme without affecting the mechanistic concepts, in order to gain some insight into its possible generality, and to initiate a synthesis by the use of a pyridine nucleus whose β-acyl function has been replaced by a vinylogue thereof.

The pyridinium salt needed as starting material was prepared in the following manner. Nicotinaldehyde was condensed with malonic acid under piperidine catalysis and the azacinnamic acid product (**5a**) esterified with methanol. N-Alkyla-

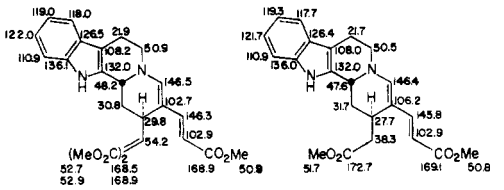


5a, R=H
b, R=Me

6

tion of ester **5b** with tryptophyl bromide yielded the desired pyridinium salt **6.**

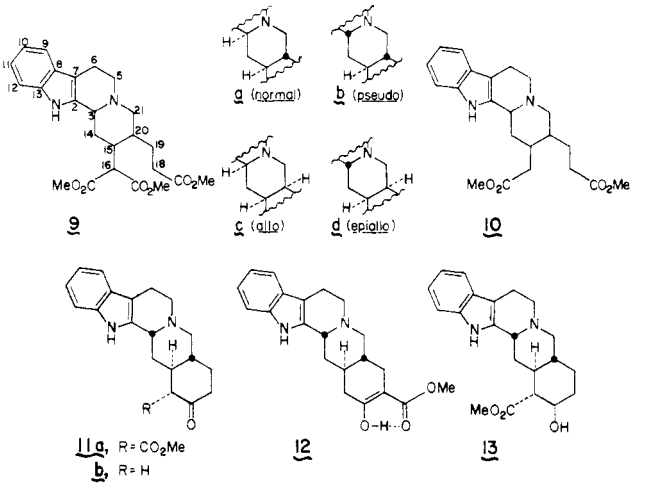
It was hoped that, despite the exposure of five electrophilic sites in compound **6,** the latter's reaction with a carbon nucleophile would follow the behavior of **2** toward such reagents. Indeed, bond formation occurred at the pyridine γ-carbon on reaction of **6** with dimethyl sodiomalonate in 1,2-dimethoxyethane solution. Saturation of a benzene solution of the crude product with hydrogen bromide yielded (two-step total of 18%)[6a] tetracycle **7.** Since only a diester was needed for the later formation of ring E of the yohimbines, one of the carbomethoxy groups of the malonic ester moiety had to be removed at some stage and, hence, as one of the options, the degradation was performed on triester **7.** The customary hydrolysis–decarboxylation procedure was substituted by a demethylation–decarboxylation method, to safeguard the integrity of the dienamine function, and the demethylation was assumed to be restrictable to one ester of the malonate unit on the basis of low rates of nucleophilic displacement at the methyl site of the acrylic ester moiety in view of its inherent stability as a doubly vinylogous urethane and of the second ester of the malonate side chain in the face of the negative charge of the neighboring carboxylate created by the initial demethylation. Iodide-induced demethylation[7] of **7** yielded (82%) diester **8.** In analogy with the structure of the product (**3**) of the earlier indoloquinolizidine synthesis,[3] compounds **7** and **8** represented



7 **8**

single stereoisomers whose relative configuration was ascertained by ^{13}C NMR spectral analysis (carbon shifts listed on the formulas).[3]

Platinum-catalyzed hydrogenation of diene **8** produced diesters **10b** (88%) and **10d** (7%),[6b] whose ^{13}C NMR analysis (vide infra) showed them to possess the pseudo and epiallo configurations, respectively. Dieckmann condensation of diester **10b** over sodium hydride led to pentacyclic esters **11a** (47%) and **12** (40%), whose unwanted isomer was used for obtaining direct chemical evidence regarding the stereochemistry of the pentacycles and their diester precursor. Thus, the hydrolysis and decarboxylation of ester **12** afforded (±)-pseudoyohimbone, a substance known for its configuration **11b.**[3] Platinum-catalyzed hydrogenation[2a,8] of keto ester **11a** gave (±)-pseudoyohimbine (**13**)[2a,c] (72%). This completed a six-step synthesis (**5b** → **6** → **7** → **8** → **10b** → **11a** → **13**) of the racemic form of natural pseudoyohimbine and indicated



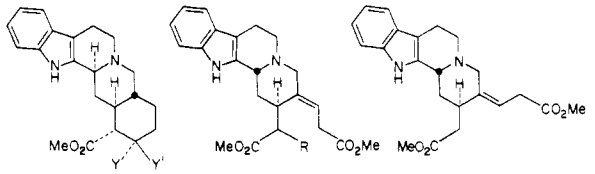
9 **a** (normal) **b** (pseudo) **c** (allo) **d** (epiallo) **10**

11a, R=CO_2Me
b, R=H

12 **13**

that the two-step scheme of indoloquinolizidine synthesis, e.g., **2** → **3**[3] or **6** → **7,** may have wide applicability in alkaloid synthesis.

The decarbomethoxylation–reduction sequence (**7** → **8** → **10b**) for the conversion of dienic triester **7** into saturated diester **10b** could be reversed. Thus platinum-catalyzed hydrogenation of diene **7** produced triesters **9b** (82%) and **9d** (15%) and subsequent iodide-induced, selective demethylation[7] of **9b,** followed by thermal decarboxylation, yielded diester **10b** (67%). Alternatively, the decarbomethoxylation could be accomplished by acid-catalyzed hydrolysis of triester **9b** and decarboxylation, followed by reesterification, although the strenuous conditions led to desired diester **10b** (49%) in accompaniment with its 3-epimer **10a** (14%). This infrequent, but known isomerization[9] could be duplicated more efficiently on **10b,** the latter being transformed into **10a** (56%) on exposure to the acid-induced hydrolysis–esterification scheme. Since diester **10a** has been converted some time ago into (±)-yohimbine (**14a**) and (±)-β-yohimbine (**14b**) by a cyclization–reduction sequence[2b] and the racemates have been resolved,[2b] the present



14 a, Y = OH, Y' = H
b, Y = H, Y' = OH

15 a, R = CO_2Me
b, R = H

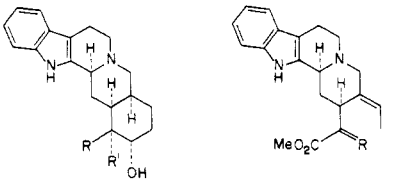
16

synthesis of **10a** constitutes a formal total synthesis of the alkaloids (+)-yohimbine and (−)-β-yohimbine.

As the above discussion of the hydrogenation of the dienes **7** and **8** indicated, the reaction led in over 80% yield to pseudo compounds (**9b** and **10b,** respectively), which, however, were accompanied in less than 15% yield by products of epiallo configuration (**9d** and **10d,** respectively), whose stereochemistry became known by ^{13}C NMR spectral evaluation (vide infra) and by the fact of **10d** having been a diester of established structure.[2g] Since these results suggested that modification of the reaction conditions might affect the product ratio and thus perhaps permit a yield-wise satisfactory access to the yohimbines of allo or epiallo constitution, a broader study of the reduction of the dienes was undertaken. Even the hydrogenations deserved more scrutiny in view of their dissimilar rates. Whereas the hydrogenation of diester **8** was relatively fast and revealed no isolable intermediate on the reaction route, the reduction of triester **7** proved to be slow and on early quenching yielded not only the pseudo and epiallo triesters **9b** (77%) and **9d** (8%), respectively, isolated before, but also the partial reduction product **15a** (13%). Further hydrogenation of the latter led to pseudo (**9b**) and epiallo (**9d**) products in 39% and 59% yields, respectively. These observations revealed that the hydrogenation of diene **7** proceeded at least in part by initial hydrogen 1,4-addition and that the resultant intermediate (**15a**) was responsible to a large extent for the production of an epiallo triester (**9d**). Furthermore, an epiallo compound being the major product of the hydrogenation of olefinic triester **15a** put a premium on the discovery of an efficient production of the latter. Even though no high-yielding procedure was encountered, the reduction of diene **7** with sodium cyanoborohydride in acetic acid solution represented a major improvement over its partial hydrogenation. The new reaction led also to a mixture of **15a, 9b,** and **9d,** but in 46%, 41%, and 11% yields, respectively. Finally, alkaline hydrolysis, decarboxylation, and reesterification transformed triester **9d** into the epiallo diester **10d** (88%). Thus, in contrast to the 7% and 13% yields of the latter by the **8** → **10d** and **7** → **9d** → **10d** reaction sequences, respectively, the **7** → **9d** + **15a** → **9d** → **10d** route produced the desired compound in 35% yield.

Further variations of the type and sequence of reactions in the decarbomethoxylation–reduction scheme failed to improve the yield of epiallo diester (**10d**). Thus, for example, alkaline hydrolysis of triester **15a,** decarboxylation, and reesterification produced diesters **15b** (62%) and **16** (14%), platinum-catalyzed hydrogenation of the former of which led to diesters **10b** (55%) and **10d** (40%), corresponding to a **7** → **15a** → **15b** → **10d** route of 11% yield. Reduction of diene **8** with sodium cyanoborohydride produced diester **10b** (44%) and a difficultly separable mixture (38%) of **15b** and **10d** whose hydrogenation over platinum gave more **10b** (33%) and diester **10d** (43%), equivalent to a **7** → **8** → **15b** → **10d** route of 13% overall yield. The stereochemistry of the olefinic esters **15** and **16** was elucidated by ^{13}C NMR spectral analysis (vide infra).

Ethylenediaminetetraacetic acid mediated mercuric acetate oxidation[10] of epiallo diester **10d** and sodium borohydride reduction of the resultant immonium salt produced the allo diester **10c**[2e] (89%). Since earlier cyclization and reduction have transformed this compound into (±)-alloyohimbine (**17a**)[2e] and (±)-α-yohimbine (**17b**),[2e] the present construction of **10c** constitutes a formal total synthesis of each of these alkaloids.



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

18 a, R = CHOH
b, R = α-H, β-CH(OR')NR''R'''

^{13}C NMR Analysis. Previous ^{13}C NMR data on corynanthoid,[11] yohimboid,[3] and ajmalicinoid[3] alkaloids facilitated the analysis of esters **9** and **10.** In order to complete the isomer series, triesters **9a** and **9c**[2e] were prepared by C(3) epimerization of **9b** and **9d,** respectively, via the oxidation–reduction route of the **10d** → **10c** conversion (vide supra). All carbon shifts are listed in Table I. The configurationally characteristic C(3) and C(6) shift ranges, determined from an analysis of the pentacyclic alkaloids,[3] not only confirmed the stereochemistry assignment of the indoloquinolizidines **9** and **10** but also revealed some of their conformational features. Thus the two carbon shifts of the *normal* esters **9a** and **10a** and allo compounds **9c** and **10c** fit the δ(C-3) = 60 ± 1 ppm and δ(C-6) = 21.5 ± 0.5 ppm spectral constraints of a *trans*-quinolizidine grouping, leaving the two side chains of **9a** and **10a** and the C(15) side chain of **9c** and **10c** in an equatorial disposition. The C(20) substituent of the allo esters is oriented axially, as witnessed by the shielding of C(14) and C(19) induced by a reciprocal γ effect. The epiallo triester **9d** is conformationally dissimilar from the epiallo diester **10d.** Whereas the diester is a *trans*-quinolizidine with an axial C(15) substituent, the latter is bulkier in the triester (**9d**) and thus less inclined to maintaining an axial posture. An alternate conformation for **9d,** overcoming this dilemma, is a *cis*-quinolizidine with equatorial C(15) and axial C(20) side chains. The shift data for the epiallo compounds are in agreement with these conformational requirements. Thus, the δ(C-3) and δ(C-6) values of **9d** fall within the ranges for epiallo systems with cis and trans C/D ring junctures, i.e., 54 ± 1 and 16–22 ppm, respectively, and show a preponderant *cis*-quinolizidine representation in the conformer mixture, whereas the 54.5 ± 0.5 and 21.5 ± 0.5 ppm shifts, respectively, for **10d** reveal this substance to be an epiallo isomer with trans C/D ring juncture. Finally, the pseudo compounds **9b** and **10b,** which would be expected to be *cis*-quinolizidines with two equatorial side chains revealing C(3) and C(6) shifts of 53.5 ± 0.5 and 16.5 ± 0.5 ppm, respectively, show δ values corresponding to those of a mixture of *cis*- and *trans*-quinolizidines. Since a C/D trans pseudo compound holds its two side chains in axial orientations, a highly unlikely conformational state, it can be assumed that the *trans*-quinolizidine form of **9b** and **10b** constrains its ring D to a nonchair conformation.

The shift assignment for olefinic esters **15** and **16,** illustrated in the table, is based on that of the esters **9** and **10** as well as of geissoschizine (**18a**)[12] and geissospermine (**18b**).[12] The C(19)–C(20) double-bond configuration of esters **15** was ascertained readily by shift comparison of **15b** with **16.** The strong shielding of C(15) in diester **15b** and C(21) in **16,** reflecting reciprocal γ effects of C(18) on C(15) in the former and on C(21) in the latter esters, verifies the double-bond stereochemistry portrayed in the formulas. Furthermore, the γ effects being felt through carbon–hydrogen bonds imply that in esters **15** H(15) must be in close proximity to C(18) and hence in an equatorial orientation.

Despite a general structure similarity between esters **15** and alkaloids **18** the conformations of the two systems differ strongly as a consequence of the dissimilarity of the relative

Table I. Carbon Shifts of Esters **9**, **10**, and **15**[a,b]

	9a	9b	9c	9d	10a	10b	10c	10d	15a	15b	16
C(2)	134.0	133.3	134.2	132.7	134.0	133.5	134.6	134.0	133.3	133.6	133.2
C(3)	59.5	54.4	59.9	54.1	59.2	54.2	59.8	54.0	54.6	54.4	54.4
C(5)	52.8	52.2	53.0	51.3	52.8	52.2	53.1	52.7	52.3	52.2	52.2
C(6)	21.6	19.6	21.9	17.8	21.5	19.1	21.6	21.1	21.5	21.3	20.7
C(7)	107.7	107.7	108.1	107.8	107.6	107.8	107.8	107.9	108.3	108.0	108.2
C(8)	127.0	127.0	127.0	127.5	126.9	127.3	127.0	127.1	127.0	126.8	127.0
C(9)	117.8	117.5	117.9	117.7	117.7	117.7	117.8	117.6	117.8	117.7	117.9
C(10)	119.0	118.8	119.1	119.1	119.0	119.1	119.0	118.9	119.0	118.9	119.2
C(11)	121.1	120.7	121.1	121.1	121.0	121.1	120.9	120.9	121.1	120.9	121.3
C(12)	110.7	110.6	110.6	111.1	110.6	110.8	110.6	110.5	110.6	110.5	110.8
C(13)	135.8	135.6	135.7	135.8	135.9	135.7	135.7	135.7	135.8	135.7	135.9
C(14)	31.9	28.3	29.5	27.6	35.7	31.7	31.4	31.5	32.5	33.8	34.2
C(15)	40.8	36.3[c]	40.0	35.2[c]	37.2	32.8	36.4	31.9	34.7	31.2	37.9
C(16)	51.5	52.7	54.4	53.3	37.7	37.1	37.6	33.1	52.7	36.3	37.4
C(18)	31.0	31.4	32.1	32.3	31.9	31.7	32.2	31.2	32.5	32.3	32.7
C(19)	25.6	26.8	20.6	20.8	25.8	26.8	20.7	25.3	121.1	118.4	117.4
C(20)	37.5	35.7[c]	35.1	35.6[c]	39.5	38.9	37.1	38.2	135.0	137.6	137.6
C(21)	60.2	52.2	57.5	48.5	60.0	52.2	57.6	54.8	59.6	59.1	50.9
16-CO	168.2 169.4	168.4 168.7	168.1 168.9	168.2 169.2	173.2[c]	173.2[c]	173.1[c]	173.4[c]	168.0 168.2	172.1	172.3
18-CO	173.4	173.3	173.5	173.4	173.4[c]	173.6[c]	173.8[c]	173.5[c]	171.7	171.7	171.6

[a] In $CDCl_3$ solutions; δ values in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] $\delta(OMe) = 52.3 \pm 0.3$ ppm for the malonate units and 51.4 ± 0.4 ppm for all other esters. [c] Signals in any vertical column may be interchanged.

H(3)/H(15) configurations. Whereas geissoschizine (**18a**) and geissospermine (**18b**) might be expected to be *trans*-quinolizidines with an equatorial C(15) appendage, the latter's strong nonbonded interaction with the methyl group of the neighboring ethylidene unit causes dramatic ring deformation in **18a** and changes to quinolizidine cis ring junctures in both alkaloids.[12] Contrastingly, the H(3)/H(15) trans relationship of esters **15** permits maintenance of a *trans*-quinolizidine structure in the face of an axial C(15) substituent remote from nonbonded interaction with C(18). This conformation is identical with that of the epiallo ester **10d** (vide supra) and is in agreement with the C(3) and C(6) shift ranges characteristic for such spatial orientation. Whereas the absence of nonbonded interaction between C(18) and the C(15) substituent in diester **16**, the double bond isomer holding C(15) and C(18) in a trans relationship, allows conformational equilibrium to be established with the pseudo-like molecular arrangement of a *cis*-quinolizidine with an equatorial C(15) side chain, the carbon shifts of the diester, especially δ(C-6), indicate only a bare trend in this direction.

Experimental Section

Melting points were determined on a Reichert micro hotstage and are uncorrected. Infrared spectra were recorded on Beckman IR-9 and AccuLab 8 spectrophotometers and ultraviolet spectra on a Cary 17 spectrophotometer. Mass spectra were obtained on Finnigan 3300 and CEC 21-110B spectrometers. ^{1}H NMR spectra of deuteriochloroform solutions with Me_4Si as internal standard ($\delta = 0$ ppm) were taken on Varian EM-390 and XL-100-15 spectrometers, while ^{13}C NMR spectra were recorded on the latter instrument operating at 25.2 MHz in the Fourier transform mode. All organic extracts of crude products were washed with water and subsequently saturated brine solution and dried over anhydrous sodium sulfate. Chromatographic separations were accomplished on thick TLC plates coated with Brinkmann HF 254 + 366 silica gel and the developed plates extracted with 4:1 methylene chloride–methanol.

The carbon shifts on formulas **7**, **8**, **19**, **20**, **21**, and **22** are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Asterisked numbers may be interchanged.

β-(β-Pyridyl)acrylic Acid (5a). A solution of 107 g (1.00 mol) of nicotinaldehyde, 240 g (2.30 mol) of malonic acid, and 10 mL of piperidine in 400 mL of pyridine was heated at 90 °C for 1 h and then at 130 °C for 3 h. The mixture was diluted with 2 L of ether. The precipitate was filtered and washed with ether, yielding 144 g (96%) of solid, mp 234–235 °C, whose crystallization from methanol gave acid **5a**, mp 237–237.5 °C: UV (MeOH) λ_{max} 206 (ϵ 12 200), 252 (18 000) nm; ^{1}H NMR (Me_2SO-d_6) δ 6.68 (d, 1, J = 16 Hz, α-H), 7.43 (dd, 1, J = 8, 5 Hz, H-5), 7.63 (d, 1, J = 16 Hz, β-H), 8.13 (dt, 1, J = 8, 2, 2 Hz, H-4), 8.57 (dd, 1, J = 5, 2 Hz, H-6), 8.83 (d, 1, J = 2 Hz, H-2). Anal. ($C_8H_7O_2N$) C, H, N.

Methyl β-(β-Pyridyl)acrylate (5b). A suspension of 30.5 g (0.200 mol) of acid **5a** and 24 mL of concentrated sulfuric acid in 70 mL of methanol was added to 120 mL of dry benzene and the mixture refluxed for 10 h. It then was added to 225 mL of ice–water and neutralized with ammonium hydroxide. The aqueous layer was extracted with ether and the combined ether and benzene solutions washed, dried, and evaporated, leaving 31.7 g (95%) of crystalline product. Crystallization of the latter gave ester **5b**, mp 42 °C: IR ($CHCl_3$) C=O 1714 (s), C=C 1643 (m) cm^{-1}; UV (MeOH) λ_{max} 206 (ϵ 13 300), 257 (18 800) nm; ^{1}H NMR δ 3.82 (s, 3, OMe), 6.48 (d, 1, J = 16 Hz, α-H), 7.29 (dd, 1, J = 8, 5 Hz, H-5), 7.65 (d, 1, J = 16 Hz, β-H), 7.79 (dt, 1, J = 8, 2, 2 Hz, H-4), 8.56 (dd, 1, J = 5, 2 Hz, H-6), 8.70 (d, 1, J = 2 Hz, H-2). Anal. ($C_9H_9O_2N$) C, H, N.

3-(β-Carbomethoxyvinyl)-1-[β-(β-indolyl)ethyl]pyridinium Bromide (6). A mixture of 26.30 g (0.120 mol) of tryptophyl bromide and 19.14 g (0.120 mol) of ester **5b** in 30 mL of methanol was stirred until it was homogeneous. The yellow solution was kept at room temperature for 48 h and the resultant precipitate then filtered. Concentration of the filtrate to a volume of 10 mL under vacuum and the concentrate being kept at room temperature for 24 h resulted in more precipitate. Crystallization of the combined crystalline solids, 44.90 g (98%), from methanol gave salt **6**, mp 195–197 °C: IR (Nujol) NH 3170 (m), C=O 1704 (s), C=C 1640 (m), 1620 (m) cm^{-1}; UV (MeOH) λ_{max} 218 (ϵ 42 000), 256 (16 300), 288 (8500) nm; ^{1}H NMR (Me_2SO-d_6) δ 3.45 (t, 2, J = 7 Hz, benzylic CH_2), 3.78 (s, 3, OMe), 4.92 (t, 2, J = 7 Hz, NCH_2), 6.70 (d, 1, J = 16 Hz, α-H), 6.8–7.6 (m, 4, aromatic Hs), 6.98 (d, 1, J = 16 Hz, β-H), 8.05 (dd, 1, J = 8, 5 Hz, H-5), 8.86 (br d, 1, J = 8 Hz, H-4), 8.97 (br d, 1, J = 5 Hz, H-6), 9.56 (br s, 1, H-2). Anal. ($C_{19}H_{19}O_2N_2Br$) C, H, N, Br.

1,2,6,7-Tetrahydroindolo[2,3-*a*]quinolizines (7 and 8). The salt **6**, 20.0 g, was added to a stirring suspension of 12.0 g (80.0 mmol) of dimethyl sodiomalonate in 250 mL of 1,2-dimethoxyethane and the mixture stirred under nitrogen for 4.5 h. Dry benzene, 300 mL, was added and the stirring continued for 1 h. Thereafter 200 mL of dry benzene, saturated with hydrogen bromide gas, was added slowly over a 0.3-h period, until pH paper indicated pH 4–5, and the stirring continued for 1 h. The resultant precipitate was separated and dissolved in 2 L of methylene chloride and 50 mL of methanol. The combined organic solutions were extracted with sodium bicarbonate solution, washed, dried, and evaporated. The residue, 16.5 g, was

passed through a column of 170 g of deactivated silica gel. Elution with methylene chloride liberated 6.00 g of dimethyl malonate and with 50:1 methylene chloride–methanol, 5.3 g of a solid whose crystallization from methanol yielded 4.20 g (18%) of crystalline triester **7**, mp 220–221 °C: IR (Nujol) NH 3250 (m), C=O 1740 (s), 1726 (s), C=C 1664 (s) cm^{-1}; UV (MeOH) λ_{max} 225 (ϵ 32 300), 284 (5800), 291 (4800), 354 (48 000) nm; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.60, 3.81 (s, 3 each, OMe), 3.69 (d, 1, J = 10 Hz, H-16), 4.78 (dm, 1, J = 12 Hz, H-3), 5.21 (d, 1, J = 15 Hz, H-18), 6.8–7.5 (m, 4, aromatic Hs), 7.16 (d, 1, J = 15 Hz, H-19), 7.17 (s, 1, H-21); *m/e* 438 (M^+, 42%), 407 (16), 308 (21), 307 (base), 306 (16), 305 (25). Anal. ($C_{24}H_{26}O_6N_2$) C, H, N.

A solution of 1.00 g (2.28 mmol) of ester **7** and 480 mg (2.55 mmol) of lithium iodide trihydrate in 5 mL of dimethyl sulfoxide (Me_2SO) was heated at 180 °C for 0.5 h, cooled, and diluted with 15 mL of water. The resultant precipitate was washed with water and dried under vacuum over phosphorus pentoxide. A methylene chloride solution of the solid, 870 mg, was filtered through silica gel. Crystallization of the purified solid, 710 mg (82%), from ether gave diester **8**, mp 209–211 °C: IR (KBr) NH 3290 (m), C=O 1740 (s), 1675 (s), C=C 1580 (s) cm^{-1}; UV (MeOH) λ_{max} 222 (ϵ 38 100), 282 (9400), 289 (5400), 354 (43 600) nm; ^1H NMR δ 3.67, 3.73 (s, 3 each, OMe), 4.56 (dm, 1, J = 12 Hz, H-3), 5.41 (d, 1, J = 15 Hz, H-18), 6.58 (s, 1, H-21), 6.9–7.6 (m, 4, aromatic Hs), 7.22 (d, 1, J = 15 Hz, H-19); *m/e* 380 (M^+, 47%), 308 (21), 307 (base), 305 (26), 247 (26), 137 (26). Anal. ($C_{22}H_{24}O_4N_2$) C, H, N.

Reductions of Olefins 7, 8, 15a, and 15b. A mixture of 180 mg (0.41 mmol) of triester **7** and 100 mg of platinum oxide in 10 mL of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 24 h, at which time hydrogen uptake had ceased. The mixture was filtered, the catalyst washed with acetic acid and the combined filtrate and washings neutralized with ammonium hydroxide and extracted with methylene chloride. The extract was washed, dried, and evaporated. Thick-layer chromatography of the residue, 180 mg, and two plate developments with 4:1 benzene–acetone led to 148 mg (82%) of a fast-moving solid whose crystallization from methanol yielded pseudo triester **9b**, mp 159–160 °C: IR ($CHCl_3$) NH 3500 (w), C=O 1741 (s) cm^{-1}; ^1H NMR δ 3.62, 3.75, 3.78 (s, 3 each, OMe), 3.5–4.0 (m, 2, H-3, H-16), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 442 (M^+, base), 441 (66%), 312 (31), 311 (55), 170 (28). Exact mass: *m/e* 442.2088 (calcd for $C_{24}H_{30}O_6N_2$: 442.2104).

Crystallization of the slower moving solid, 27 mg (15%), from methanol gave epiallo triester **9d**, mp 69–70 °C: IR (KBr) NH 3410 (m), C=O 1735 (s), 1713 (s), C=C 1623 (w) cm^{-1}; ^1H NMR δ 3.48 (d, 1, J = 11 Hz, H-16), 3.65, 3.65, 3.76 (s, 3 each, OMe), 4.21 (m, 1, H-3), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 442 (M^+, 83%), 441 (86), 311 (95), 184 (98), 170 (base), 169 (86), 156 (62). Anal. ($C_{24}H_{30}O_6N_2$) C, H, N.

A mixture of 400 mg (0.91 mmol) of triester **7** and 80 mg of platinum oxide in 10 mL of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 3.5 h. Workup and chromatography as above led to 308 mg (77%) of pseudo compound **9b** and 31 mg (8%) of epiallo ester **9d.** The chromatographically fastest moving solid, 51 mg (13%), was crystallized from methanol yielding triester **15a,** mp 88–90 °C: IR ($CHCl_3$) NH 3485 (w), C=O 1740 (s), C=C 1650 (w), 1600 (w) cm^{-1}; ^1H NMR δ 3.61, 3.63, 3.80 (s, 3 each, OMe), 4.00 (d, 1, J = 12 Hz, H-16), 5.69 (t, 1, J = 7 Hz, H-19), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 440 (M^+, 8%), 309 (34), 185 (68), 170 (97), 169 (base), 156 (68), 144 (68). Exact mass: *m/e* 440.1940 (calcd for $C_{24}H_{28}O_6N_2$: 440.1947).

A mixture of 100 mg (0.26 mmol) of diester **8** and 15 mg of platinum oxide in 3 mL of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 5 h. Workup and chromatography as above afforded 7 mg (7%) of fast-moving solid whose crystallization from methanol gave epiallo diester **10d,** mp 169–170 °C (lit.[2g] mp 152–153 °C): IR (KBr) NH 3342 (s), C=O 1732 (s), 1712 (s), C=C 1623 (w) cm^{-1}; ^1H NMR δ 3.65, 3.72 (s, 3 each, OMe), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 384 (M^+, 21%), 383 (25), 184 (25), 170 (30), 169 (33), 156 (21), 43 (base). The slower moving, air-sensitive, amorphous solid, pseudo diester **10b,** 88 mg (88%) [IR (KBr) NH 3400 (m), C=O 1740 (s), 1715 (s), C=C 1630 (w) cm^{-1}; ^1H NMR δ 3.58, 3.67 (s, 3 each, OMe), 3.91 (m, 1, H-3), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 384 (M^+, base), 383 (92%)] was converted into a salt. Crystallization from methanol yielded **10b** hydrochloride, mp 234–235.5 °C. Anal. ($C_{22}H_{29}O_4N_2Cl$) C, H, N, Cl.

Sodium cyanoborohydride, 600 mg (9.55 mmol), was added slowly over a 10-min period to a stirring suspension of 2.00 g (4.57 mmol) of triester **7** in 38 mL of glacial acetic acid at room temperature and the stirring continued for 0.5 h. The mixture was neutralized with ammonium hydroxide, diluted with water, and extracted with methylene chloride. The extract was washed, dried, and evaporated. Thick-layer chromatography of the residue, 2.05 g, and plate development with 4:1 benzene–acetone led to 920 mg (46%) of olefinic triester **15a,** 815 mg (41%) of pseudo triester **9b,** and 215 mg (11%) of epiallo triester **9d,** spectrally and by mp and mmp identical with like samples described above.

Sodium cyanoborohydride, 110 mg (1.78 mmol), was added in portions over a 10-min period to a stirring solution of 253 mg (0.67 mmol) of diester **8** in 5 mL of glacial acetic acid at room temperature and the stirring kept up for 10 min. Workup as above led to 95 mg (38%) of a fast-moving, foamy 3:2 **15b–10d** mixture (by ^1H NMR spectral analysis), unfortunately homogeneous on TLC with a variety of solvent systems, and 110 mg (44%) of pseudo diester **10b,** identical with above sample by TLC and spectra. Hydrogenation of 95 mg of the **15b–10d** mixture over 25 mg of platinum oxide in 2 mL of glacial acetic acid at room temperature and atmospheric pressure for 10 h and workup as above yielded 41 mg (43%) of epiallo diester **10d** and 31 mg (33%) of pseudo diester **10b,** spectrally and by TLC identical with like samples above.

A mixture of 390 mg (0.89 mmol) of triester **15a** and 80 mg of platinum oxide in 10 mL of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 12 h. Workup and chromatography as above led first to 151 mg (39%) of pseudo triester **9b** and then to 230 mg (59%) of epiallo triester **9d,** identical with above like samples by mp, mmp, and spectra.

A mixture of 40 mg (0.10 mmol) of diester **15b** (vide infra) and 10 mg of platinum oxide in 2 mL of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 10 h. Workup and chromatography as above yielded first 16 mg (40%) of epiallo diester **10d** and then 22 mg (55%) of pseudo diester **10b,** spectrally and by TLC identical with above like samples.

Decarbomethoxylations. A solution of 200 mg (0.45 mmol) of triester **9b** and 86 mg (0.46 mmol) of lithium iodide trihydrate in 2 mL of Me_2SO was heated at 180 °C for 0.5 h, cooled, diluted with 10 mL of water, and extracted with methylene chloride. The extract was washed, dried, and evaporated and the residue, 180 mg, filtered through silica gel, yielding 116 mg (67%) of pseudo diester **10b.**

A solution of 125 mg (0.28 mmol) of triester **9d** and 52 mg (0.28 mmol) of lithium iodide trihydrate in 2 mL of Me_2SO was heated at 180 °C for 0.5 h. Workup as in the **9b** → **10b** conversion (vide supra) led to 55 mg (51%) of epiallo diester **10d.**

A solution of 150 mg (0.34 mmol) of triester **9d** and 1.0 g (17.8 mmol) of potassium hydroxide in 2 mL of water and 8 mL of ethanol was refluxed under nitrogen for 8 h and then evaporated under vacuum. The residue was diluted with 3 mL of water and the solution acidified to pH 6 with 3% hydrochloric acid solution and refluxed for 8 h. After removal of the solvent under vacuum, the residue was treated with methanolic hydrogen chloride, prepared from 3 mL of acetyl chloride and 25 mL of methanol, at room temperature for 12 h. After evaporation of the solution under vacuum, the residue was treated with sodium bicarbonate solution and extracted with methylene chloride. The extract was washed, dried, and evaporated, yielding 115 mg (88%) of crystalline epiallo diester **10d.**

A solution of 224 mg (0.51 mmol) of triester **15a** and 0.50 g (8.93 mmol) of potassium hydroxide in 1 mL of water and 4 mL of ethanol was refluxed under nitrogen for 8 h and then evaporated under vacuum. Enough 3% hydrochloric acid solution was added to the residue to achieve pH 6 and the mixture refluxed for 10 h and then evaporated under vacuum. Methanolic hydrogen chloride, 23 mL of 9%, was added to the residue and the solution kept at room temperature for 15 h and then evaporated. Sodium bicarbonate solution was added to the residue and the mixture extracted with methylene chloride. The extract was washed, dried, and evaporated. Thick-layer chromatography of the residue, 190 mg, and two plate developments with 4:1 benzene–acetone led to 121 mg (62%) of a fast-moving solid whose crystallization from methanol afforded diester **15b,** mp 157–158 °C: IR (KBr) NH 3400 (s), C=O 1740 (s), 1725 (s), C=C 1630 (w), 1600 (w) cm^{-1}; ^1H NMR δ 3.66, 3.70 (s, 3 each, OMe), 5.58 (t, 1, J = 7 Hz, H-19), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 382 (M^+, 31%), 381 (30), 309 (60), 170 (87), 169 (74), 156 (43), 44 (base). Anal. ($C_{22}H_{26}O_4N_2$) C, H, N.

Crystallization of the slower moving solid, 27 mg (14%), from methanol gave diester **16,** mp 143–146 °C: IR (KBr) NH 3360 (m), C=O 1745 (s), 1720 (s) cm^{-1}; ^1H NMR δ 3.68, 3.70 (s, 3 each, OMe), 5.53 (t, 1, J = 7 Hz, H-19), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 382 (M^+, 20%), 381 (15), 309 (20), 170 (48), 156 (49), 154 (33), 144 (50), 54 (base). Anal. ($C_{22}H_{26}O_4N_2$) C, H, N.

The slowest moving solid could not be induced to crystallize from methanol and may be a C(20) epimer mixture of the α,β-unsaturated ester isomer of diesters **15b** and **16,** i.e., 18,19-dehydro-**10b** and 18,19-dehydro-**10d**: IR (KBr) NH 3360 (m), C=O 1720 (s), 1705 (s), C=C 1650 (m), 1625 (w) cm^{-1}; ^1H NMR δ 3.69, 3.71 (s, 3 each, OMe), 5.86 (d, 1, J = 16 Hz, H-18), 6.63 (dd, 1, J = 16, 8 Hz, H-19), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 382 (M^+, 68%), 381 (71), 309 (21), 283 (27), 184 (27), 170 (53), 169 (67), 156 (base).

A solution of 450 mg (1.02 mmol) of triester **9b** in 10 mL of a 2:1 mixture of 18% hydrochloric and glacial acetic acids was refluxed under nitrogen for 1.5 h and then evaporated. A mixture of the residue and 20 mL of dry methanol, saturated with dry hydrogen chloride gas, was kept at room temperature for 12 h and then evaporated. A methylene chloride solution of the residue was treated with sodium bicarbonate solution, washed, dried, and evaporated. Thick-layer chromatography of the residue and plate development with 4:1 benzene–acetone gave 50 mg (14% based on recovered starting material) of a solid whose crystallization from ligroin gave crystalline *normal* diester **10a,** mp 153–155 °C (lit.[2b] mp 155–156 °C): IR (KBr) NH 3375 (s), C=O 1735 (s), 1718 (s), C=C 1600 (w) cm^{-1}; ^1H NMR δ 3.67, 3.71 (s, 3 each, OMe), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 384 (M^+, 44), 383 (53), 309 (42), 184 (42), 170 (base), 169 (84), 156 (73); then 50 mg of starting triester **9b** and, finally, 170 mg (49% based on recovered starting material) of pseudo diester **10b.**

C(3) Epimerizations. A mixture of 201 mg (0.45 mmol) of triester **9b,** 255 mg (0.80 mmol) of mercuric acetate and 300 mg (0.81 mmol) of disodium ethylenediaminetetraacetate (EDTA) in 10 mL of glacial acetic acid was heated at 120 °C under nitrogen for 3 h. The resultant precipitate was filtered and washed with acetic acid. The combined filtrate and washings were evaporated under vacuum and the residue dissolved in 10 mL of methanol. Sodium borohydride, 300 mg (7.89 mmol), was added in portions over a 15-min period to the solution at 0 °C and the mixture acidified with glacial acetic acid and evaporated under vacuum. Aqueous sodium bicarbonate, 10 mL, was added to the residue and the mixture extracted with methylene chloride. The extract was washed, dried, and evaporated. Thick-layer chromatography of the residue, 172 mg, and plate development with 4:1 benzene–acetone gave 65 mg (40% based on recovered starting material) of a fast-moving solid whose crystallization from methanol yielded *normal* triester **9a,** mp 197–199 °C: IR (KBr) NH 3392 (s), C=O 1740 (s), 1733 (s), 1717 (s), C=C 1630 (w), 1600 (w) cm^{-1}; ^1H NMR δ 3.69, 3.69, 3.76 (s, 3 each, OMe), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 442 (M^+, 89%), 441 (base), 311 (66), 309 (31), 283 (29), 169 (34), 156 (26), 144 (25). Anal. ($C_{24}H_{30}O_6N_2$) C, H, N.

A slower moving solid, 42 mg, was an uncharacterized mixture and the slowest moving solid, 38 mg, starting triester **9b.**

A mixture of 75 mg (0.17 mmol) of triester **9d,** 101 mg (0.32 mmol) of mercuric acetate, and 120 mg (0.32 mmol) of Na_2EDTA in 3 mL of glacial acetic acid was heated at 120 °C under nitrogen for 2 h. Workup as above gave a residue whose methanol solution, 10 mL, was treated with 150 mg (3.98 mmol) of sodium borohydride in portions over a 15-min period at 0 °C. Workup as above gave 75 mg of a residue whose thick-layer chromatography as above yielded 58 mg (91% based on recovered starting material) of fast-moving, amorphous solid allo triester **9c:** IR (KBr) NH 3375 (m), C=O 1751 (s), 1730 (s), 1725 (s), C=C 1623 (w) cm^{-1}; ^1H NMR δ 3.65, 3.76, 3.80 (s, 3 each, OMe), 3.50 (d, 1, J = 11 Hz, H-16), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 442 (M^+, 92%), 441 (base), 311 (50), 309 (29), 283 (26), 184 (39), 170 (49), 169 (58), 156 (36); which resisted crystallization from methanol; **9c** hydrochloride, mp 203–206 °C (lit.[2e] mp 205–207 °C), crystallized from methanol. The slower moving solid, 11 mg, proved to be starting triester **9d.**

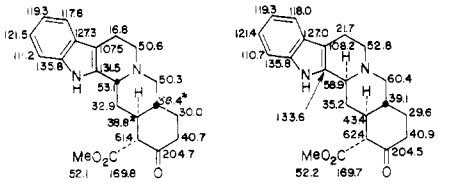
A solution of 110 mg (0.29 mmol) of diester **10b** in 5 mL of a 2:1 mixture of 18% hydrochloric and glacial acetic acids was refluxed under nitrogen for 24 h and then evaporated under vacuum. A solution of the residue in 20 mL of methanol saturated with hydrogen chloride gas was kept at room temperature for 12 h and then evaporated. Aqueous sodium bicarbonate, 5 mL, was added to the residue and the mixture stirred and extracted with methylene chloride. The extract was washed, dried, and evaporated. Thick-layer chromatography and plate development as above yielded first 45 mg (56% based on recovery of starting material) of *normal* diester **10a** and secondly 30 mg of starting diester **10b.**

A mixture of 90 mg (0.23 mmol) of diester **10d,** 120 mg (0.38 mmol) of mercuric acetate, and 145 mg (0.39 mmol) of Na_2EDTA in 10 mL of 5% aqueous acetic acid was refluxed gently under nitrogen for 4 h. Workup as above gave a residue whose methanol solution, 15 mL, was treated with 150 mg (3.98 mmol) of sodium borohydride in portions over a 0.5-h period at 0 °C and then evaporated. A solution of the residue in 20 mL of dry methanol saturated with hydrogen chloride gas was kept at room temperature for 10 h and then evaporated. Workup as above and thick-layer chromatography of the crude product, 110 mg, and plate development as above led to 76 mg (89% based on recovered starting material) of fast-moving solid whose crystallization from acetone yielded allo diester **10c,** mp 165–166 °C (lit.[2e] mp 204 °C): IR (KBr) NH 3380 (s), C=O 1735 (s), 1710 (s), C=C 1628 (w) cm^{-1}; ^1H NMR δ 3.65, 3.72 (s, 3 each, OMe), 7.0–7.6 (m, 4, aromatic Hs); *m/e* 384 (M^+, 72%), 383 (base), 169 (28), 156 (19), 144 (20); **10d** hydrochloride, mp 258–261 °C (lit.[2e] mp 261–262 °C), crystallized from methanol. The slower moving solid, 5 mg, was starting diester **10d.**

(±)-Pseudoyohimbinone (11a). A mixture of 310 mg (0.81 mmol) of diester **10b** and 30 mg (1.25 mmol) of sodium hydride (from an oil suspension, washed with hexane) in 5 mL of tetrahydrofuran (THF) was stirred at 50 °C under argon for 1.5 h (the reaction progress being monitored by TLC, developed with 4:1 ether–methanol), then neutralized with glacial acetic acid and filtered through anhydrous magnesium sulfate. The latter was washed with THF, and the combined washings and filtrate were evaporated. Thick-layer chromatography of the residue, 280 mg, plate development with 4:1 ether–methanol and fraction extraction with 3:1 methylene chloride–methanol led to 20 mg of starting diester **10b** as fastest moving solid and to 105 mg (40% based on recovered starting material) of slower moving solid whose crystallization yielded enol ester **12,** mp 223–225 °C: IR ($CHCl_3$) OH 3660 (w), NH 3462 (m), C=O 1735 (s), 1720 (s), 1710 (s), C=C 1655 (s), 1615 (s) cm^{-1}; ^1H NMR δ 3.67 (s, 3, OMe), 4.60 (br s, 1, H-3), 6.9–7.6 (m, 4, aromatic Hs); *m/e* 352 (M^+, 6%), 184 (21), 170 (23), 169 (34), 156 (23), 44 (base). Exact mass: *m/e* 352.1784 (calcd for $C_{21}H_{24}O_3N_2$: 352.1787).

Crystallization of the slowest moving solid, 125 mg (47% based on recovered starting material), from methanol afforded crystalline (±)-pseudoyohimbinone (**11a**), mp 227–228.5 °C: IR ($CHCl_3$) NH 3479 (m), C=O 1739 (s), 1715 (s), C=C 1650 (w), 1600 (w) cm^{-1}; ^1H NMR δ 3.87 (s, 3, OMe), 4.53 (br s, 1, H-3), 6.9–7.5 (m, 4, aromatic Hs); *m/e* 352 (M^+, 27%), 351 (29), 184 (43), 170 (58), 169 (92), 156 (68), 44 (base). Exact mass: *m/e* 352.1793 (calcd for $C_{21}H_{24}O_3N_2$: 352.1787).

The carbon shifts of pseudoyohimbinone (**11a**) and its C(3) epimer, yohimbinone,[3] are presented on formulas **19** and **20,** respectively.

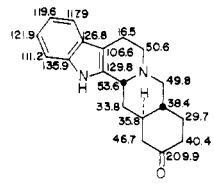


19 **20**

(±)-Pseudoyohimbone (11b). A solution of 50 mg (0.14 mmol) of ester **12** and 125 mg (2.23 mmol) of potassium hydroxide in 0.5 mL of water and 1.5 mL of ethanol was refluxed under nitrogen for 2 h and then acidified to pH 5 with 3% hydrochloric acid and refluxed for 0.5 h. The mixture was evaporated under vacuum and a methylene chloride solution of the residue treated with 5% sodium bicarbonate solution, washed, dried, and evaporated. A methylene chloride solution of the residue, 40 mg, was filtered through a short silica column and evaporated. Crystallization of the residual solid, 15 mg, from ether–chloroform yielded (±)-pseudoyohimbone (**11b**), mp 247–249.5 °C (lit.[3] mp 249–251 °C).

The carbon shifts of pseudoyohimbone (**11b**)[3] and pseudoyohimbine (**13**)[3] (vide infra) are listed on formulas **21** and **22,** respectively.

(±)-Pseudoyohimbine (13). A mixture of 65 mg (0.18 mmol) of keto ester **11a,** 0.2 mL of concentrated hydrochloric acid, 1 mL of glacial acetic acid, and 15 mg of platinum oxide in 11 mL of methanol was hydrogenated at room temperature and atmospheric pressure for 24



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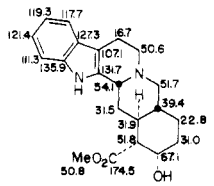

22

h. More catalyst, 10 mg, was added and the hydrogenation continued for another 24 h. The catalyst was filtered and washed with methanol and the combined washings and filtrate evaporated. The residue was taken up in 20 mL of methylene chloride and the solution treated with 5 mL of 5% sodium bicarbonate solution, washed, dried, and evaporated. A methylene chloride solution of the residue, 55 mg, was chromatographed on 3 g of silica gel. Elution with 100:1 ether–methanol gave 47 mg (72%) of solid, a single spot on TLC with various solvent systems, whose crystallization from methanol yielded (±)-pseudoyohimbine (**13**), mp 249–251 °C dec (lit. mp[1a] 252–256 °C, charring at 250 °C; mp[1c] 248–251 °C).

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Kinetics and Mechanisms of Carbon Monoxide Dissociation from Chelated Heme–CO Complexes. Models for Hemoprotein Reactions[1a]

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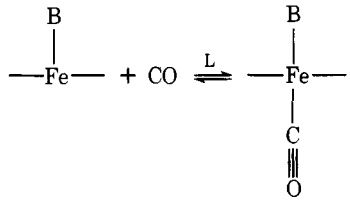
Abstract: Rates of carbon monoxide dissociation from a series of chelated heme compounds have been measured. Unstrained chelated hemes, having attached proximal bases, remain five coordinated and therefore react reversibly with carbon monoxide by a simple one-step mechanism. Both the rates and activation enthalpies of dissociation are similar to those of fully ligated (R-state) hemoglobin, indicating that chelated protoheme accurately models hemoglobin in its R state. This leads to the conclusion that the iron–carbon–oxygen bending observed in carboxyhemoglobin does not appreciably affect the CO off rates or affinities. Variations in side-chain electron donation or in proximal basicity cause no appreciable change in the CO dissociation rate. Solvent polarity is also without substantial effect. However, introducing steric strain in the proximal base chelating arm causes the mechanism of dissociation to change from direct dissociation to base elimination.

Although carbon monoxide is not a natural substrate in biological systems, its interaction with metalloproteins has been widely studied.[2-6] This interest in carbon monoxide derives from its strong binding to those metalloproteins which bind or utilize oxygen, and its consequent ability to interfere with or inhibit their function. In those hemoproteins which contain a five-coordinated ferrous ion, CO binding constants vary greatly: $L \simeq 10^5\ M^{-1}$ for cytochrome P-450[7] to $L \simeq 7 \times 10^8\ M^{-1}$ for hemoglobin.[2b,8] This wide variation in binding constants as well as some variation in the spectroscopic properties of the carbon monoxide complexes has made carbon monoxide binding an important tool in the characterization of hemoproteins.



(1)

To understand the structure–reactivity relationships developed in natural and reconstituted hemoproteins[3-5] similar structure–reactivity relationships in simple five-coordinated hemes which resemble the hemoprotein active sites are required. To fill this need we have prepared a number of chelated

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