Tetrahedron Vol. 37, No 23, pp 4017 to 4025, 1981
Printed in Great Britain.

0040-4020/81/234017-09$02.00/0
Pergamon Press Ltd

TOTAL SYNTHESES OF EBURNAMONINE, QUEBRACHAMINE, VINCADINE AND EPIVINCADINE

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(*Received in U.S.A.* 13 *May* 1981)

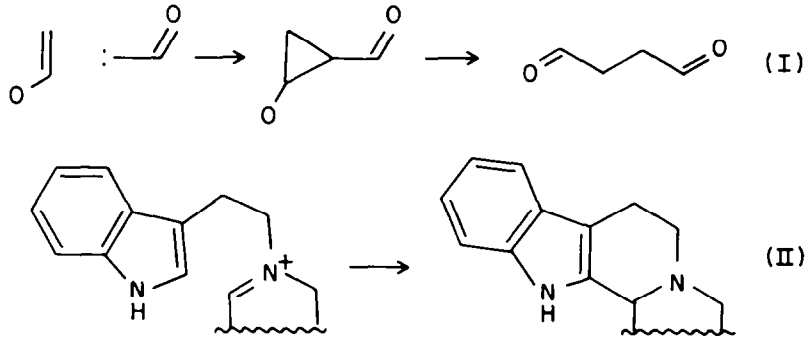
Abstract—Syntheses of the alkaloids eburnamonine and quebrachamine are presented in which the non-tryptamine portion of the skeleta is constructed by the β-oxycyclopropylcarboxylate preparation-fragmentation route. A similar reaction scheme is utilized for the synthesis of the alkaloids vincadine and epivincadine.

For some time the two-step reaction sequence leading to γ-diketo substances, involving the copper-catalyzed interaction of enol derivatives with α-diazocarbonyl compounds and acid-induced ring cleavage of the resultant β-oxycyclopropylcarbonyl substances (Scheme I), has formed the basis for syntheses of cyclopentanoid terpenes and structurally related compounds.[2] In an effort to broaden the scope of the concept for general natural product synthesis its applicability in alkaloid chemistry became of interest. Since the intermediacy of a 1,4-diketo system thus assumed prime importance, its facile incorporation into an alkaloid skeleton became a necessity. This requirement appeared satisfied in part by the tetrahydrocarboline moiety of certain indole alkaloids whose traditional route of preparation encompasses in its last step the ready cyclization of an immonium salt, i.e. a marked carbonyl group (Scheme II). The presence of another keto function in a γ relationship to the latter thus would be the sole remaining prerequisite for a successful indole alkaloid synthesis via the β-oxycyclopropylcarbonyl route (Scheme I).

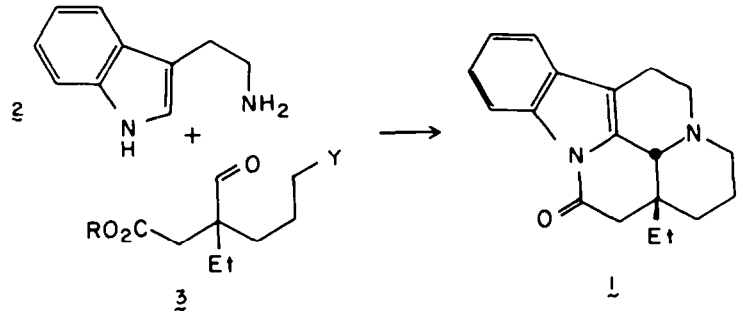
Eburnamonine synthesis.[3] The tetrahydrocarboline-containing alkaloid eburnamonine (**1**) was chosen as the initial goal, since the application of the above concepts to its synthesis suggested a simple interaction of tryptamine (**2**) with the γ-dicarbonyl system **3** for the ultimate reaction sequence.

Scheme I forming the underlying concept, the aldehydo acid derivative **3** could be envisaged as originating from an interaction of diazoacetic ester with an aldehyde enol derivative, e.g. the dihydropyran **4**, followed by acid hydrolysis. In anticipation of the present investigation and a related study[4] many of the necessary experiments had been accomplished already.[5] Thus the starting enol ether (**4**) had been prepared by a route similar to Scheme I. Furthermore, β-ethyldihydropyran (**4**) had been converted already into the β-oxycyclopropylcarboxylate **5**,[5] whose acid hydrolysis now transformed it into lactone **6**.[6]

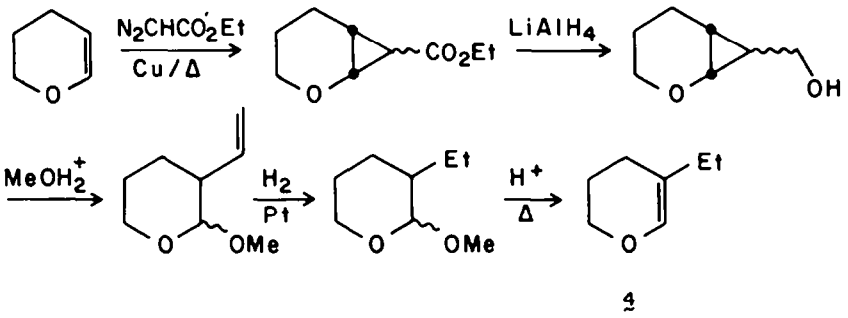
Even though lactol ether **6** was in the same oxidation state as the theoretical intermediate **3** and represented the latter in masked form, its three functional groups were not considered reactive enough to accommodate

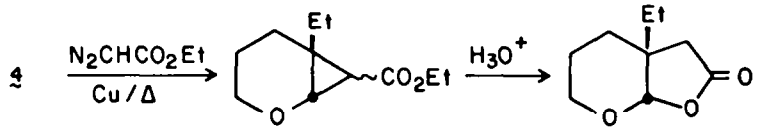


Scheme I.



Scheme II.

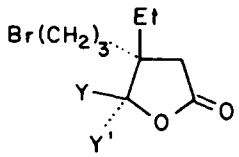




facile interaction with tryptamine (2). Hence the tetrahydropyran ring was ruptured by the reaction of **6** with boron tribromide and the resultant, humidity-sensitive dibromide isomers **7a** and **b** (the former predominating, as indicated by ^{13}C NMR spectroscopy[3a]) partially hydrolysed in acid, yielding lactol **7c** (or **7d**). This material, a masked form of **3** (R = H, Y = Br), readily alkylated tryptamine, producing the carbinolamine lactone **8**[6] by presumably the following pathway.

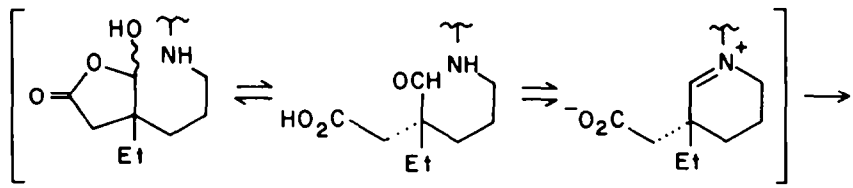
Heating of lactone **8**, thus inducing equilibration with its immonium carboxylate precursor, transformed the compound into (±)-eburnamonine (**1**).[7]

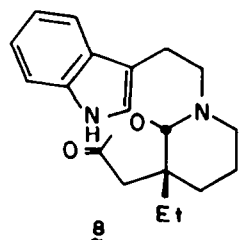
Quebrachamine synthesis.[3b] The close biosynthetic relationship between the Vinca alkaloids, such as eburnamonine (**1**), and the Aspidosperma bases, e.g. quebrachamine (**9a**), leads to structure similarities among sets of members of the two families. For example, quebrachamine (**9a**) differs structurally from eburnamonine (**1**), aside from oxidation level, only by the points of attachment of their tryptamine (**2**) and C_9 (**3**) units. In view of the ease of construction of the C_9 moiety **6** and its facile utilization in the above eburnamonine synthesis the lactone or its relatives could be envisaged serving as intermediates en route also to the Aspidosperma bases.



7g, Y = H, Y' = Br
b, Y = Br, Y' = H
c, Y = H, Y' = OH
d, Y = OH, Y' = H

4 + **7c** (or **7d**) ⟶





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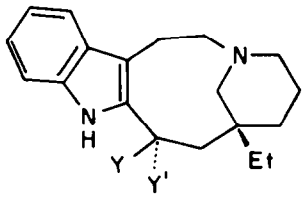
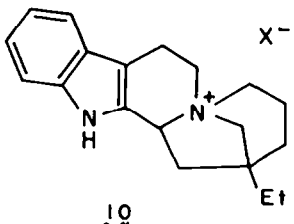


9a , Y = Y' = H
b , Y = H, Y' = CO_2Me
c , Y = CO_2Me, Y' = H



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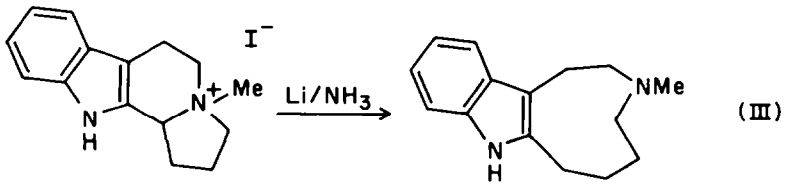
Hence the synthesis of quebrachamine (**9a**), emanating from intermediates in the eburnamonine synthesis, was undertaken.

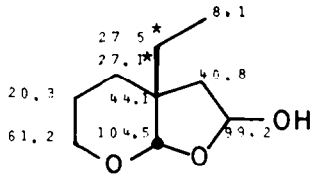
A model study for the construction of the indoloazacyclononane unit (eqn III),[8] a major challenge in a quebrachamine synthesis, had laid the groundwork some time ago for a reaction sequence whose ultimate stage would require the reduction of a quaternary ammonium salt of type **10**. The route of synthesis thus merely awaited an innovative scheme for the preparation of the requisite C_9 unit to envelope the tryptamine residue.[9] The γ-diketo route of natural product synthesis now offered such an opportunity.

Bicycle **6** with the CO group in oxidation level of an aldehyde was needed as starting material. It could be prepared in the form of hemiacetals **11a** and **b** by the reduction of the lactone with diisobutylaluminum hydride or in the form of enol ether **13** by the Fetizon oxidation of alcohol **12** (obtained earlier from a reduction of ester **5** with LAH[5]), in analogy with the general oxidative conversion of β-oxycyclopropylcarbinols into 2-oxy-2,3-dihydrofurans.[11] Acid-catalyzed condensation of the masked aldehyde in either hemiacetal (**11**) or enol ether (**13**) forms with tryptamine produced a mixture of isomeric carbinolamine ethers (**14a** and **b**), whose reduction with sodium cyanoborohydride led to alcohols **15a** and **b**.

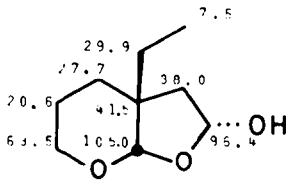
Since the alcohols are diastereomers of each other, their precursors must possess the same relative stereochemistry at the benzylic aminomethine and quaternary



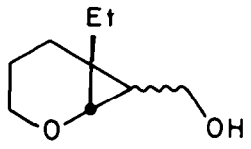
(III)



11a



11b



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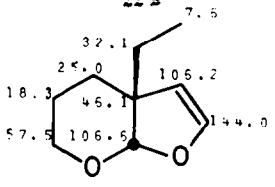

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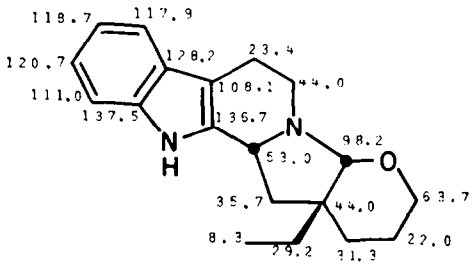
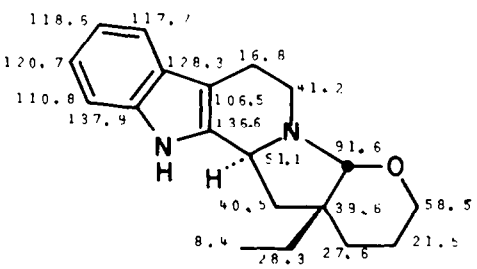
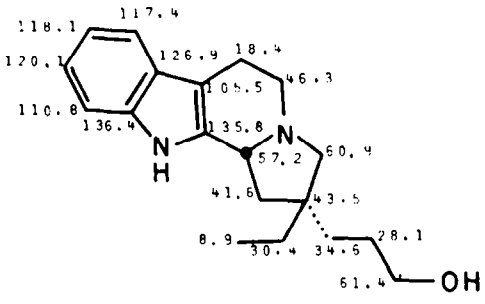


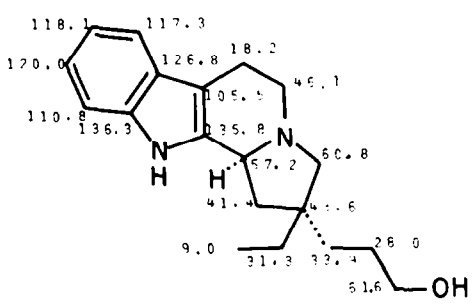
14a



14b



15a



15b

carbon centers. If it be assumed that the acid-catalyzed condensation leading to compounds **14a** and **b** permitted equilibration at the carbinolamine ether sites and the stable configuration is a *cis* pyrrolidine-tetrahydropyran arrangement, the ethers must have the stereochemistry depicted in **14a** and **b** and conformations **16a** and **b**, respectively. On this basis the ^{13}C NMR data can distinguish the two isomers from each other. The conformation of the indoloquinolizidine unit of the yohimboid and related alkaloids has been shown to be reflected by the benzylic methylene shift, i.e. 21.5 ± 0.5 and 16.5 ± 0.5 ppm for *trans* and *cis* cases, respectively.[12] Thus the strong shielding (16.8 ppm) of the benzyl carbon of the indoloindolizidine **14b** is indicative of a γ effect exerted by the oxymethine, a phenomenon requiring this substituent to be axial to the piperidine ring and the oxymethine hydrogen to be oriented toward the benzyl site. These constraints restrict isomer **14b** to the configuration indicated on the formula. The γ effect is shown reciprocally by the shielding (91.6 ppm) of the oxymethine (when compared with its δ value in **14a**).

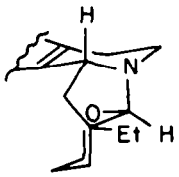
Whereas the benzyl carbon resonance of 23.4 ppm might suggest the indoloindolizidine **14a** to be a *trans* system (see conformation **17**), the oxymethylene shifts of **14a** and **b** reveal this stereochemical pattern not to be present. Even though the indolizidine nitrogen would be expected to exert a γ effect on the oxymethylene of both **14a** amd **b**, were their conformations **17** and **16b**, respectively, only the oxymethylene of **14b** is shielded (58.5 ppm). Thus **14a** also must contain a *cis*-indoloindolizidine skeleton, but one with a different nitrogen disposition toward the tetrahydropyran ring. This is consistent with conformation **16a**, a structure in which despite the axial orientation of the oxymethine toward the piperidine moiety no γ effect is exerted on the benzyl carbon. In fact, the latter is deshielded even with respect to the same site in yohimboid alkaloids of the *trans*-indoloquinolizidine type, indicative of the deshielding δ effect by the oxygen.

In view of the above analysis the preparation of alcohols **15a** and **b** from carbinolamine ethers **14a** and **b**, respectively, settles the stereochemistry of the alcohols. As the benzyl carbon shifts of the latter (18.4 and 18.2 ppm, respectively) indicate, the alcohols are conformer mixtures of *cis*- and *trans*-indoloindolizidines in solution, making their *a priori* stereochemical analysis impossible.[13] Had the compounds been conformationally unique, the carbon shifts of the neopentyl methylenes of their sidechains would have revealed the relative orientation of the sidechains and hence the relative configuration of the alcohols.

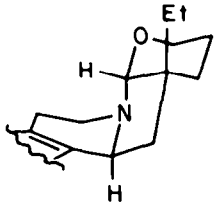
The alcohols (**15a** and **b**), prepared earlier by another reaction scheme,[14] had been converted into their methanesulfonates, whose intramolecular cyclization had yielded salts **18a** (Y = Ms) and **b** (Y = Ms).[14] Reduction of these salts with sodium in liquid ammonia or lithium aluminum hydride had led previous workers to (±)-quebrachamine (**9a**),[10c,14] through this tie-up thus completing the present alkaloid synthesis.

The ^{13}C NMR analysis of the salts as perchlorates (**18a** and **b**, Y = ClO_4),[15] prepared by the mesylation procedure for the present study, permits an unambiguous assignment of stereochemistry. In **18a** the indole ring is *endo* to the azabicyclo[3.2.1]octane system, causing the indole α carbon to be in strong non-bonded interaction with the aminomethylene of the 3-carbon bridge. This γ effect shields reciprocally both carbon centers. Furthermore, the conformation of the piperidine ring fused to the indole moiety is different in the two salts, the orientation in **18b**[16] causing the benzyl methylene to be within a non-bonded interaction distance of the one-carbon bridge of the azabicyclooctane species. The resultant γ effect leads to shielding of the two centers in salt **18b**. These considerations limit the stereochemistry of the salts as depicted on the formulas, in accord with prediction based on their relationship with the carbinolamine ether precursors (**14a** and **b**).[17-19]

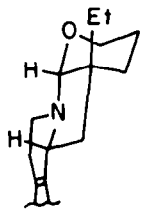
Syntheses of vincadine and epivincadine. In view of vincadine and epivincadine being carbomethoxyquebrachamines **9b** and **9c**, respectively, it appeared



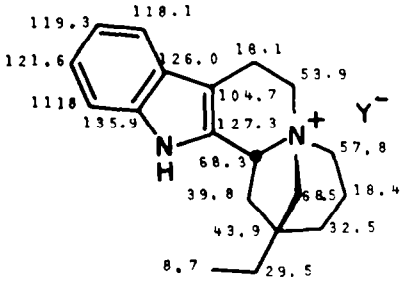
16a



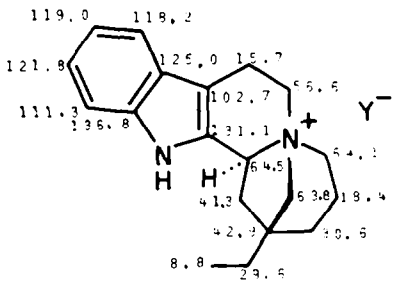
16b



17



18a

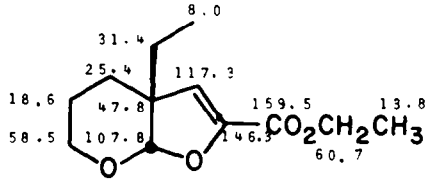


18b

reasonable to assume that their facile construction could be based on the above quebrachamine synthesis. For this purpose carbomethoxy derivatives of bicycle **11** or **13** were needed as starting materials. The recent discovery of the one-step formation of 5-alkoxy-4,5-dihydrofuroic esters on copper-catalyzed interaction of diazopyruvic esters with enol ethers made this task easy.[11] Thus a reaction of ethyl diazopyruvate and dihydropyran **4** over copper yielded ester **19**, whose acid hydrolysis, followed by diazomethane treatment, gave the masked α-ketoester isomers **20**. In analogy with the behavior of the hemiacetals **11** (*vide supra*) an acid-catalyzed condensation of esters **20** with tryptamine led to the carbinolamine ether esters **21a** and **b**.

The same arguments used to differentiate the stereochemistry of the carbinolamine ethers **14a** and **b** are applicable to the pair of esters **21**, thus establishing the relative configuration of the two isomers and all substances derived from them. Reduction of the carbinolamine ethers with sodium cyanoborohydride yielded hydroxyesters **22a** and **b**, whose methanesulfonylation and intramolecular displacement led to the quaternary ammonium salts **23a** and **b**.

As indicated by the benzylic methylene shift of *ca* 15 ppm, the presence of the carbomethoxy group in alcohols **22a** and **b** forces the indoloindolizidine nucleus to assume a *cis* configuration. Thus in contrast to the case of the alcohols **15a** and **b**, whose mixed in-



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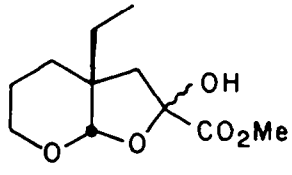

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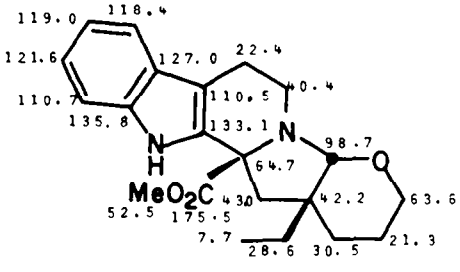
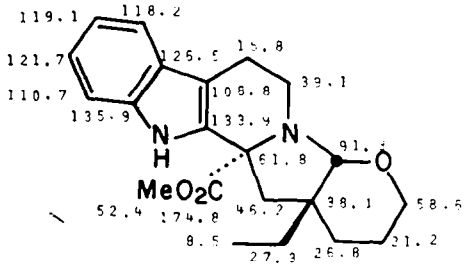
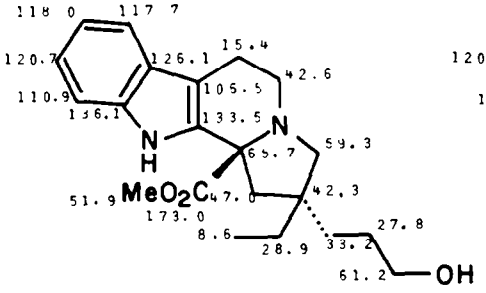


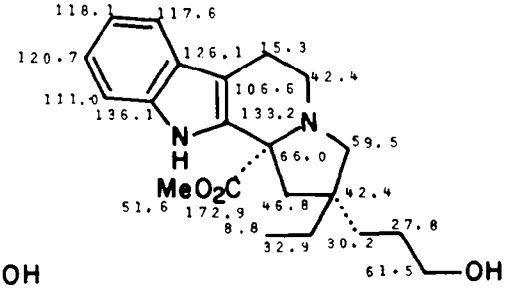
21a



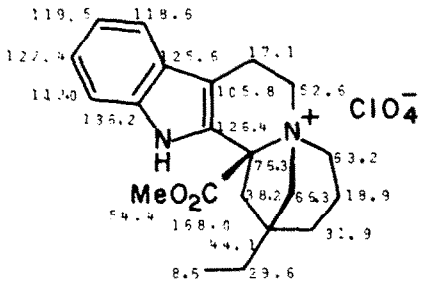
21b



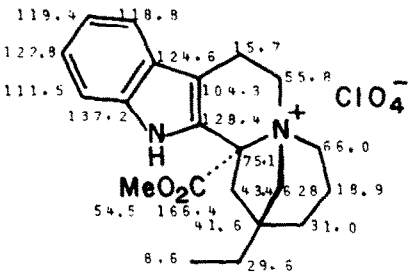
22a



22b



23a



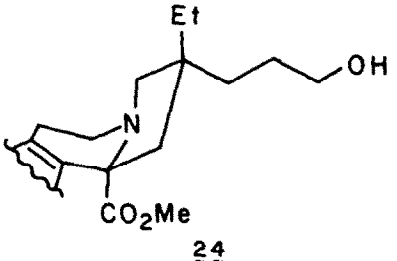
23b

doloindolizidine configuration prevented an *a priori* stereochemical analysis (*vide supra*), the carbomethoxy derivatives **22a** and **b** are amenable to full stereostructure determination. The locked *cis*-indolizidine conformation causes one of the sidechains to be axially oriented toward its pyrrolidine ring and consequently in non-bonded 1,3-diaxial interaction with the nitrogen electron pair (see conformational representation **24** for **22b**). The resultant γ effect by the nitrogen on the ring-attached methylene of the axial sidechain produces shielding of this methylene. Hence a comparison of the resonances of the neopentyl sidechain carbons in isomer **22a** with the shifts of like sites in **22b** reveals the stereochemistry of these centers and shows them to be in accord with the relative configurations depicted in the formulas.

For ease of intramolecular nitrogen quaternization the nitrogen electron pair and the oxypropyl sidechain must be oriented 1,3-diaxially toward each other. This reaction constraint is satisfied by the methanesulfonate of alcohol **22b** (see conformation **24**), but the derivative of isomer **22a** requires ring inversion into the less stable *trans*-indolizidine form before salt formation can take place. Thus it was not surprising that mesylation of hydroxyester **22a** yielded a sulfonate, which only on heating was transformed into a salt, whereas derivatization of alcohol **22b** led to a salt rapidly. These observations are in agreement with the stereochemistry indicated for the hydroxyesters **22a** and **b** and the salts derived therefrom, **23a** and **b**, respectively. An independent ^{13}C NMR analysis of the salts by the procedure developed for the decarbomethoxy counterparts **18a** and **b** (*vide supra*) confirms the stereochemical conclusions. The introduction of a carbomethoxy group attenuates the shift differences between the isomers.

Hydrolysis of each ester (**23a** or **b**), reduction of the resultant acid salt with lithium in liquid ammonia[8] and reesterification produced (±)-vincadine (**9b**) and (±)-epivincadine (**9c**).[20]

Summary. The syntheses of the four alkaloids, eburnamonine (**1**), quebrachamine (**9a**), vincadine (**9b**) and epivincadine (**9c**) now establishes the β-oxycyclopropylcarbonyl preparation-fragmentation route (Scheme I) or its equivalent as a viable procedure for alkaloid synthesis.



24

EXPERIMENTAL

M.ps were determined on a Reichert micro hotstage and are uncorrected. IR spectra were recorded on a Beckmann IR-9 spectrophotometer and mass spectra on Finnigan 3300 and CEC 21-110B spectrometers. ^1H NMR spectra of $CDCl_3$ solutions with TMS 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. The carbon shifts are downfield from TMS; $\delta(TMS) = \delta(CDCl_3) + 76.9$ ppm.

3 - *Carboxymethyl* - 3 - *ethyl* - 2 - *hydroxytetrahydropyran lactone* (**6**). A soln of **5** (5.00 g) and 100 ml 10% H_2SO_4 aq in 50 ml dioxane was refluxed for 15 hr. The dioxane was removed by evaporation under vacuum and the residue saturated with NaCl and extracted exhaustively with ether. The extract was washed with a sat NaCl aq and $NaHCO_3$ aq, dried ($MgSO_4$) and evaporated. Distillation of the residue yielded 4.00 g (93%) of colorless, liquid lactone **6**: b.p. 82–84° (0.2 Torr); IR (neat) C=O 5.58 (s) μ; ^1H NMR δ 0.92 (t, 3, J = 7 Hz, Me), 1.3–1.8 (m, 6, methylenes), 2.36 (s, 2, CH_2CO), 3.5–4.0 (m, 2, OCH_2), 5.28 (s, 1, OCH); *m/e* 126 (M^+, 13%), 97 (93), 96 (base), 81 (93), 70 (30), 55 (53). (Found: C, 63.56; H, 8.50. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29%).

γ - *Bromo* - β - (γ - *bromopropyl* -)β - *ethyl* - γ - *butyrolactone* (**7a** *and* **b**). A soln of **6** (5.00 g) and BBr_3 (1 M in CH_2Cl_2, 85.5 ml) in 40 ml freshly distilled CH_2Cl_2 was stirred at room temp for 14 hr. It then was poured into a cold sat $NaHCO_3$ aq and the mixture stirred for 15 min. The organic layer was separated and the aqueous soln extracted with CH_2Cl_2. The combined organic solns were washed with NaCl aq, dried (Na_2CO_3) and evaporated. Chromatography of the residual oil on silica gel and elution with benzene yielded 5.75 g of light orange oil, whose distillation gave 5.23 g (71%) of colorless, viscous, liquid dibromolactones **7a** and **b**: b.p. 122–124° (0.007 Torr); IR (neat) C=O 5.52 (s) μ; ^1H NMR δ 0.93, 0.96 (t, total 3, J = 7 Hz, Me), 1.4–2.1 (m, 6, methylenes), 2.41, 2.46 (s, total 2, CH_2CO), 3.2–3.6 (m, 2, $BrCH_2$), 6.30, 6.31 (s, total 1, BrCHO); *m/e* 233–235 (M^+, 52%), 176–178 (base), 95–97 (21), 80–82 (52). (Found: C, 34.70; H, 4.54. Calcd. for $C_9H_{14}O_2Br_2$: C, 34.42; H, 4.49%).

3 - *Carboxymethyl* - 3 - *ethyl* - 2 - *hydroxy* - 1 - (β - *indolylethyl* -) *piperidine lactone* (**8**).[21] A mixture of 1.10 g of lactone **7a–b** and 5 ml HCl soln in 3 ml dioxane was stirred at 80° for 20 hr. It then was saturated with NaCl and extracted with ether. The extract was washed with sat NaCl aq, dried (Na_2CO_3) and evaporated, leaving 465 mg (53%) of **7c** (or **7d**): ^1H NMR δ 0.90 (t, 3, J = 7 Hz, Me), 1.1–2.0 (m, 6, methylenes), 2.33 (s, 2, CH_2CO), 3.6–4.0 (m, 2, $BrCh_2$), 5.28 (s, 1, OCH).

A mixture of tryptamine hydrochloride (700 mg), the lactol (700 mg) and dry Linde 3 Å molecular sieves (for water absorption) in 1 ml thoroughly dried DMSO was stirred at 55° under N_2 for 12 hr. The red mixture then was poured into water and

extracted with ether. The extract was washed with water, dried (Na_2CO_3) and evaporated. Preparative tlc of the residue on silica gel and development with EtOAc yielded 1.35 g (78%) of solid lactone **8**:[22] IR ($CHCl_3$) NH 2.90 (m), C=O 5.74 (s) μ; ^{1}H NMR δ 0.78 (t, 3, J = 7 Hz, Me), 1.2–1.8 (m, 6, methylenes), 2.1–3.1 [m, 8, $COCH_2$, benzyl H_2, $(NCH_2)_2$], 5.06 (s, 1, NCH), 6.9–7.5 (m, 5, aromatic Hs), 8.36 (s, 1, NH); *m/e* 312 (M^+, 18%), 239 (40), 218 (10), 182 (base), 138 (72). (Found: *m/e* 312.1843. Calcd. for $C_{19}H_{24}O_2N_2$: *m/e* 312.1838).

(±)-*Eburnamonine* (**1**). Pyrolysis of a sample of lactone **8** in a Kugelrohr apparatus at 250° (0.01 Torr) for 0.5 hr led to a distillate which crystallized spontaneously, giving a 60% yield of pure (±) **1**: m.p., m.m.p. 200° (lit.[7b] m.p. 200–202°); IR, UV and ^{1}H NMR spectra identical with those of an authentic sample.[7b]

Hemiacetals **11**. Diisobutylaluminum hydride (1.60 mmol in toluene) was added dropwise over a 5 min period to a stirring soln of **6** (243 mg; 1.43 mmol) in 5 ml dry ether at −78° under N_2. After 1 hr the mixture was warmed and 1 M HCl (10 ml) added. The mixture was extracted with ether and the extract washed with sat $NaHCO_3$aq, dried (Na_2SO_4) and evaporated. Short-path vacuum distillation of the residue, 246 mg (99%) of pure (by tlc) liquid, yielded a *ca.* 1:1 mixture of **11a** and **b**: IR (neat) OH 2.93 (m) μ; ^{1}H NMR δ 0.83, 0.84 (t, total 3, J = 7 Hz, Me), 1.0–2.1 (m, 8, methylenes), 3.3–3.7 (m, 2, OCH_2), 4.66 (s, 1, OCHOR), 4.98 (s, 1, OCHOH); ^{13}C NMR δ values on formulas **11a**[16] and **b**; *m/e* 171 (M^+-1, 2%), 154 (13), 149 (48), 108 (58), 97 (60), 69 (38), 55 (56), 43 (59), 41 (base). (Found: C, 63.03; H, 9.13. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36%).

Dihydrofuran **13**. A mixture of $AgCO_3$ (37.5 g) and Celite (0.57 g/mmol of oxidizing agent) in 500 ml benzene was refluxed under N_2 in the absence of light, while 100 ml solvent was removed by a Dean–Stark trap. Alcohol **12**, 2.00 g, was added and the mixture refluxed for another 2.5 hr. The hot mixture was filtered and the residue washed thoroughly with hot benzene. Evaporation of the combined filtrate and washings left an oil, whose distillation yielded 1.70 g (86%) of colorless, liquid enol ether **13**: IR (neat) C=C 6.20 (m) μ; ^{1}H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.9 (m, 6, methylenes), 3.3–4.1 (m, 2 OCH_2), 4.74 (d, 1, J = 3 HZ, olefinic H), 5.33 (s, 1, OCHO), 6.40 (d, 1, J = 3 Hz, olefinic OCH); ^{13}C NMR δ values on formula **13**; *m/e* 154 (M^+, 19%), 125 (base), 97 (54), 95 (52), 83 (57), 67 (41). (Found: C, 70.17; H, 9.22. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15%).

Carbinolamine ethers **14a** *and* **b**. A mixture of **13** (2.17 g) and tryptamine hydrochloride (3.60 g) in 20 ml 10% aqueous AcOH was stirred for 7 hr. NaOAc (752 mg) was added to the red mixture and stirring continued for 40 hr. After basification with 10% Na_2CO_3aq the mixture was extracted with CH_2Cl_2 and the extract dried (Na_2SO_4), passed through a short, deactivated alumina column (for the removal of excess tryptamine) and evaporated. Chromatography of the residue on alumina (activity V) and elution with 1:1 hexane–CH_2Cl_2 yielded 2.81 g (67%) of solid, thermally labile, air-sensitive, acid-sensitive carbinolamine ethers **14a** and **b** in three fractions (the second being a 157 mg mixture of the two substances). Fraction 1, 1.39 g (33%), was pure **14a**: IR ($CHCl_3$) NH 2.88 (m), C=C 6.18 (m), μ; ^{1}H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.2–1.8 (m, 8, methylenes), 2.5–3.8 (m, 6, OCH_2, NCH_2, benzyl CH_2), 4.20 (s, 1, OCHN), 4.40 (t, 1, J = 7 Hz, NCH), 7.0–7.6 (m, 4, aromatic Hs); ^{13}C NMR δ (acetone-d_6)[23] values are on formula **14a**. (Found: *m/e* 296.1883. Calc. for $C_{19}H_{24}ON_2$: *m/e* 296.1888).

Fraction 3, 1.26 g (30%), was pure **14b**: IR ($CHCl_3$) NH 2.88 (m), C=C 6.18 (m), 6.27 (m) μ; ^{1}H NMR δ (acetone-d_6) 0.78 (t, 3, J = 7 Hz, Me), 1.0–3.4 (m, 14, methylenes), 4.27 (s, 1, OCHN), 4.63 (t, 1, J = 7 Hz, NCH), 6.9–7.5 (m, 4, aromatic Hs); ^{13}C NMR δ (acetone-d_6)[23] values are on formula **14b**. (Found: *m/e* 296.1880. Calcd. for $C_{19}H_{24}ON_2$: *m/e* 296.1888).

Alcohols **15a** *and* **b**. A mixture of **14a** (345 mg) and sodium cyanoborohydride (73 mg) in 5 ml 50% aqueous AcOH was stirred for 10 min. It was made basic with 10% Na_2CO_3aq and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Chromatography on alumina (grade V) and elution with EtOAc yielded 276 mg (79%) of **15a**; m.p. 169–169.5° (from EtOAc) (lit.[14] m.p. 166–167°); IR (KBr) OH, NH 2.99 (w), 3.00 (m) μ: ^{1}H NMR δ (DMSO-d_6) 0.84 (t, 3, J = 7 Hz, Me), 1.1–2.2 (m, 8, methylenes), 2.3–3.2 [m, 6, $(NCH_2)_2$, benzyl CH_2], 3.30 (m, 2, OCH_2), 3.96 (t, 1, J = 7 Hz, NCH), 6.7–7.5 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **15a**. (Found: *m/e* 298.2040. Calcd. for $C_{19}H_{26}ON_2$: *m/e* 298.2045).

The same treatment and work-up for ether **14b** gave a 93% yield of **15b**: m.p. 169–170° (from CH_2Cl_2) (lit.[14] m.p. 168–170°); IR (KBr) OH, NH 2.94 (w), 3.07 (m) μ; ^{1}H NMR δ (DMSO-d_6) 0.71 (t, 3, J = 7 Hz, Me), 1.0–2.2 (m, 8, methylenes), 2.3–3.3 [m, 6, $(NCH_2)_2$, benzyl CH_2], 3.45 (m, 2, OCH_2), 3.98 (t, 1, J = 7 Hz, NCH), 6.8–7.5 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **15b**. (Found: *m/e* 298.2040. Calcd. for $C_{19}H_{26}ON_2$: *m/e* 298.2045).

A mixture of **11** (467 mg) and tryptamine hydrochloride (800 mg) in 5 ml 10% aqueous AcOH was stirred under N_2 for 7 hr. NaOAc, 150 mg, was added and stirring continued for 40 hr. The mixture was made basic with 10% Na_2CO_3aq and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), passed through a short column of alumina (grade V) and evaporated. A mixture of the residue and sodium cyanoborohydride (210 mg) in 10 ml 10% aqueous AcOH was stirred for 10 min, then made basic with 10% Na_2CO_3aq and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), passed through 15 g of alumina (grade V) and evaporated, yielding 750 mg (93%) of a foamy, *ca.* 1:1 mixture of pure **15a** and **b**. The two alcohols were separated by crystallization of **15a** from EtOAc and partitioning the mother liquor by the above chromatographic procedure.

Dihydrofuran ester **19**. A soln of ethyl diazopyruvate (3.77 g) in **4** (10 ml) and CH_2Cl_2 (2 ml) was added slowly (*ca* 1 drop/3 sec) to a stirring mixture of freshly prepared copper bronze (0.60 g) in **4** (5.00 g) kept at 95° under N_2. Heating was continued for 0.5 hr and the then cooled mixture filtered. Distillation of the filtrate at 60 Torr led to the recovery of starting dihydropyan. Finally, Kugelrohr distillation (*ca.* 90°/0.2 Torr) of the distillation residue yielded colorless, liquid ester **19** (5.00 g; 83%): IR (neat) C=O 5.75 (s), C=C 6.10 (m) μ; ^{1}H NMR δ 0.90 (t, 3, J = 7 Hz, Me of Et), 1.33 (t, 3, J = 7 Hz. Me of OEt), 1.0–2.2 (m, 6, methylenes), 3.71 (m, 2, OCH_2), 4.25 (q, 2, J = 7 Hz, OCH_2 of Et), 5.48 (s, 1, OCH), 5.78 (s, 1, olefinic H); ^{13}C NMR δ values on formula **19**; *m/e* 226 (M^+, 0.9%), 169 (3), 153 (4), 141 (3), 125 (73), 29 (base). (Found: C, 63.47; H, 7.87. Calcd. for $C_{12}H_{18}O_4$; C, 63.70; H, 8.02%).

Esters **20**. Ester **19**, 4.50 g, was added dropwise to fluoroboric acid (50 ml of conc acid in 30 ml water) and the mixture stirred at room temp for 50 hr. It then was saturated with NaCl and extracted exhaustively with CH_2Cl_2. The organic soln was extracted with 10% Na_2CO_3aq and the extract acidified with conc HCl. The aqueous soln was extracted with CH_2Cl_2 and the extract dried (Na_2SO_4) and evaporated. The residual organic acid, 3.20 g (74%), crystallized in the refrigerator. Diazomethane, liberated from Diazald (5.0 g), was distilled into an ice-cold soln of the acid in 75 ml ether up to the point of persistence of a yellow color. The excess diazomethane was evaporated under a slow stream of N_2. The soln then was dried (Na_2SO_4) and evaporated, yielding 3.37 g (99%) of a liquid 3:2 ester **20** isomer mixture: IR (neat) OH 2.93 (m), C=O 5.74 (s) μ; ^{1}H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.0–2.5 (m, 8, methylenes), 3.40 (m, 2, OCH_2), 3.80, 3.82 (s, 3 total, OMe), 4.93, 5.04 (s, 1 total, OCH); ^{13}C NMR δ major (minor) isomer OCH_2 61.7 (61.5), pyran β-CH_2 20.5 (20.2), pyran γ-CH_2 26.5 (26.6), pyran β-C 41.1 (42.1), OCH 107.0 (106.0), Me of Et 8.3 (8.3), CH_2 of Et 27.8 (28.0), CO 171.1 (170.2), CO α-C 100.0 (99.8), CO β-CH_2 42.8 (41.9), OMe 52.8 (52.8); *m/e* 230 (M^+, 0.5%), 125 (3), 97 (45), 96 (40), 95 (35), 83 (74), 69 (65), 67 (95), 57 (83), 55 (base). (Found: *m/e* 230.1148. Calcd. for $C_{11}H_{18}O_5$: *m/e* 230.1154).

Carbinolamine ether esters **21a** *and* **b**. A soln of 2 drops of glacial AcOH in 5 ml dry MeOH was added to a soln of **20** (3.40 g) and tryptamine (3.50 g) in 125 ml CH_2Cl_2 and the mixture stirred at room temp for 72 hr. Solid Na_2CO_3 (0.20 g), was added and the solvent evaporated. Chromatography of the residue on silica gel and elution with 2:1 hexane-EtOAc yielded 4.00 g (76%) of a partially crystalline mixture of esters **21a** and **b**. Separation of the solid and crystallization from hexane–EtOAc gave crystalline **21a**: m.p. 187–188°; IR (KBr) NH 2.97 (s), C=O 5.88 (s) μ; ^{1}H NMR δ 0.83 (t, 3, J = 7 Hz, Me), 0.9–3.7 (m, 14, methylenes), 3.70 (s, 3, OMe), 4.31 (s, 1, OCHN), 6.9–7.6 (m, 4, aromatic Hs);

^{13}C NMR δ values on formula **21a**; *m/e* 354 (M^+, 1%), 295 (39), 15 (base). (Found: C, 70.87; H, 7.65; N, 7.71. Calcd. for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.39; N, 7.90%).

Chromatography of the mother liquor as before and crystallization of the resultant solid from hexane yielded crystalline **21b**: m.p. 92–94°; IR (KBr) NH 2.97 (s), C=O 5.88 (s) μ; ^{1}H NMR δ 0.75 (t, 3, J = 7 Hz, Me), 1.0–3.7 (m, 14, methylenes), 3.75 (s, 3, OMe), 4.32 (s, 1, OCHN), 6.9–7.6 (m, 4, aromatic Hs); ^{13}C NMR δ values on formula **21b**; *m/e* 354 (M^+, 1%), 295 (23), 15 (base). (Found: *m/e* 354.1940. Calcd. for $C_{21}H_{26}O_3N_2$: *m/e* 354.1943).

Hydroxyesters **22a** *and* **b**. Sodium cyanoborohydride (700 mg) and 3 ml glacial AcOH was added to a soln of **21a** (2.50 g) in 60 ml MeOH and the mixture stirred for 15 min. The solvent was evaporated, sat $NaHCO_3$aq (40 ml) added to the residue and the mixture extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel and elution with EtOAc yielded amorphous **22a** (2.00 g; 80%): IR (KBr) NH 2.94 (s), C=O 5.81 (s) μ; ^{1}H NMR δ 0.83 (t, 3, J = 7 Hz), 0.9–3.1 (m, 14, methylenes), 3.2–3.6 (m, 2, OCH_2), 3.70 (s, 3, OMe), 7.0–7.6 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **22a**; *m/e* 356 (M^+, 1%), 355 (2), 298 (30), 297 (base), 237 (21), 223 (29), 208 (69), 154 (19). (Found: *m/e* 356.2097. Calcd. for $C_{21}H_{28}O_3N_2$: *m/e* 356.2100).

The same reduction of **21b** provided a 90% yield of oily **22b**: IR (neat) NH 2.94 (s), C=O 5.78 (s) μ; ^{1}H NMR δ 0.69 (t, 3, J = 7 Hz, Me), 1.0–3.7 (m, 16, methylenes), 3.73 (s, 3, OMe), 6.9–7.6 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **22b**; *m/e* 356 (M^+, 0.5%), 355 (1), 297 (36), 208 (22), 15 (base). (Found: *m/e* 356.2094. Calcd. for $C_{21}H_{28}O_3N_2$: *m/e* 356.2100).

Vincadine (**9b**) *and epivincadine* (**9c**). A soln of **22a** (149 mg) in 3 ml dry CH_2Cl_2 at 0° was treated with dry triethylamine (54 mg) and then 60 mg methanesulfonyl chloride and the mixture stirred at 0° for 15 min and then at room temp for 45 min. A 10% Na_2CO_3 (15 ml) was added and the aqueous phase extracted exhaustively with CH_2Cl_2. The combined organic solns were dried (Na_2SO_4). Evaporation of the solvent yielded only **22a** mesylate (171 mg; 94%) pure by tlc on silica gel: IR (KBr) NH 2.94 (s), C=O 5.76 (s) μ; ^{1}H NMR δ 0.83 (t, 3, J = 7 Hz, Me), 1.0–3.4 (m, 14, methylenes), 2.70 (s, 3, $MeSO_3$), 3.70 (s, 3, OMe), 3.96 (t, J = 6 Hz, OCH_2), 7.0–7.5 (m, 4, aromatic Hs). A soln of the latter in 5 ml 1,2-dimethoxyethane was refluxed for 18 hr and the solvent then evaporated. A MeOH soln of the residue was passed through an ion exchange column, holding 18 g perchlorate-activated Dowex 1-X2 resin. Evaporation of the MeOH eluates yielded 138 mg (80%) of colorless, glassy, non-crystallizable perchlorate **23a**: IR ($CHCl_3$) NH 3.16 (m), C=O 5.75 (s) μ: ^{1}H NMR δ (acetone-d_6) 0.93 (t, 3, J = 7 Hz, Me), 1.0–4.5 (m, 16, methylenes), 3.61 (s, 3, OMe), 6.8–7.7 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **23a**.

A mixture of salt **23a** (35 mg) and KOH (5 mg) in 6 ml MeOH was stirred at room temp for 20 hr. The solvent was evaporated and the residue dried under vacuum and suspended in 3 ml THF. Ammonia was condensed in the reaction flask until a volume of 7 ml was reached and excess metallic Li then introduced. After *ca* 2 min the mixture was dark blue and after another 2 min the reduction was quenched by the addition of NH_4Cl (200 mg) and 4 ml MeOH. The ammonia was allowed to evaporate and the mixture was filtered. The filtrate was treated with diazomethane (from 3.0 g of Diazald) in 10 ml ether. After 1 hr the soln was evaporated and the residue mixed with 10 ml water and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Preparative tlc of the residue, 32 mg, on silica gel and development with 2:1 hexane–EtOAc led to amorphous (±)-**9c** (18 mg; 66%): tlc behavior and IR and mass spectra identical with those of an authentic sample and literature data,[10a] and amorphous (±) **9b** (2 mg; 7%): tlc behavior and IR and mass spectra identical with those of an authentic sample and the literature report.[10a,24]

A soln of **22b** (100 mg) in 2 ml dry CH_2Cl_2 at 0° was treated with dry Et_3N (36 mg) and then methanesulfonyl chloride (40 mg) and the mixture stirred at 0° for 15 min and then at room temp for 45 min. A 10% Na_2CO_3aq (10 ml) was added and the aqueous phase extracted exhaustively with CH_2Cl_2. The combined organic solns were dried (Na_2SO_4) and evaporated. A MeOH soln of the residual salt (by tlc behavior) was passed through an ion exchange column (18 g of perchlorate-laden Dowex 1-X2 resin) and the eluates evaporated, yielding colorless, glassy, non-crystallizable perchlorate **23b** (90 mg, 73%): IR (KBr) NH 2.92 (m), C=O 5.75 (s) μ; ^{1}H NMR δ 0.70 (t, 3, J = 7 Hz, Me), 1.0–4.5 (m, 16, methylenes), 3.91 (s, 3, OMe), 6.9–7.8 (m, 4, aromatic Hs); ^{13}C NMR δ[15] values on formula **23b**.

Li–ammonia reduction of salt **23b** by the above procedure gave a 70% yield of a 10:1 mixture of (±)-epivincadine (**9c**) and (±)-vincadine (**9b**). The compounds were separated and identified as above.

Acknowledgements—The authors are indebted to the U.S. Public Health Service for support of this work and to Dr. Bela Zsadon for samples of vincadine and epivincadine.

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[13]A previous stereochemistry assignment[14] based on IR C–H stretching vibrations and aminomethine and methyl hydrogen shifts is invalid in view of the complexity of the conformer mixtures. Whereas the downfield position of the aminomethine hydrogen NMR signal and the absence of an IR absorption band for the same hydrogen, characteristic of *trans*-indoloquinolizidines, is indicative of a trend toward a *cis*-indoloindolizidine conformation for the alcohols, the data are compatible with either this conformation or a conformer mixture. In the absence of any information regarding the rotamer population preferences of the alcohol sidechains and the orientation of the methyl group *vis-a-vis* the distant indole nucleus the methyl hydrogen shift is of no stereochemically diagnostic value.

[14]J. P. Kutney, N. Abdurahman, C. Gletsos, P. Le Quesne, E. Piers and I. Vlattas, *J. Am. Chem. Soc.* **92**, 1727 (1970).

[15]In DMSO-d_6 solution; δ(TMS) = δ(DMSO-d_6) + 39.5 ppm.

[16]Starred δ values on the formula may be interchanged.

[17]In **18b** the *exo* indole moiety has its π face oriented toward the quaternary bridgehead carbon site causing the Me group in one

of the Et rotamers to be within the anisotropic shielding zone of the aromatic nucleus. This fact, added to the observation of dissimilar methyl hydrogen shifts for the two salts (1.04 and 0.71 ppm), has permitted an earlier stereochemical differentiation of the salts by ^{1}H NMR spectroscopy.[3c]

[18]Reduction of the salts with Li in liquid ammonia according to an earlier procedure[8] yielded (±)-**9a**.

[19]For previous syntheses of quebrachamine see [a]G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.* **85**, 2872 (1963); [b]M. E. Kuehne and C. Bayha, *Tetrahedron Letters* 1311 (1966); [c]F. E. Ziegler, J. A. Kloek and P. A. Zoretic, *J. Am. Chem. Soc.* **91**, 2342 (1969); [d]V. S. Giri, E. Ali and S. C. Pakrashi, *J. Heterocyclic Chem.* **17**, 1133 (1980); and Refs. 14, 10*a*, 10*b*, 3*a*, 10*c* and 3*b*.

[20]For a previous synthesis of vincadine and epivincadine see Ref 10*a*.

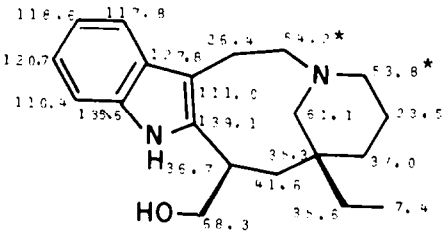
[21]The **7c** (or **7d**) → **8** → **1** conversions were executed by T. Hudlický (Ph.D. dissertation, Rice University (1978)).

[22]The melting point, *ca.* 114°, is only approximate in view of the ready, thermal conversion of lactone **8** into **1**.

[23]δ(TMS) = δ(acetone-d_6) + 29.2 ppm.

[24]Whereas reductions of the salts **23a** and **b** themselves (i.e. without prior hydrolysis and subsequent esterification) with lithium, calcium or magnesium on short reaction times (typically, quenching after 2 sec) afforded the alkaloids, their yields varied widely and reaction reproducibility was poor. On most occasions the major product was the alcohol derived from epivincadine.[25]

[25]Some time ago a ^{13}C NMR spectral study of a large number of quebrachamine-like substances had shown that due to serious conformation differences vincadine and epivincadine possess dramatically different carbon shifts.[26] Since their shift patterns were characteristic of their derivatives also and since the shift data on the alcohol derived from vincadine on lithium aluminum hydride reduction were on record, comparison of the carbon shifts of the product of overreduction of salts **23a** and **b** (see shifts for a $CDCl_3$ solution on formula **i**[16]) with the previous data shows the alcohol to possess an epivincadine-like structure.



i

[26]E. Wenkert, E. W. Hagaman, N. Kunesch, N. Wang and B. Zsadon, *Helv. Chim. Acta* **59**, 2711 (1976).