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184. Total Synthesis of Indole and Dihydroindole Alkaloids. VI[1][2]). The Total Synthesis of Some Monomeric Vinca Alkaloids: dl-Vincadine, dl-Vincaminoreine, dl-Vincaminorine, dl-Vincadifformine, dl-Minovine and dl-Vincaminoridine

by **James P. Kutney, Ka Kong Chan, Amedeo Failli, John M. Fromson, Constantine Gletsos, Albert Leutwiler, Vern R. Nelson** and **Joao Pedro de Souza**

Contribution from Department of Chemistry
University of British Columbia, 2075 Wesbrook Place, Vancouver, Canada V6T 1W5

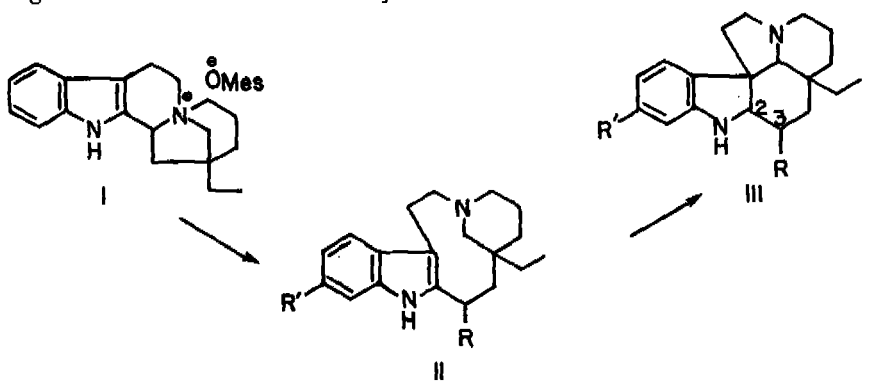
(15. V. 75)

Summary. A synthetic approach to a variety of monomeric *Vinca* alkaloids is described. The sequence involves, among its crucial phases, the generation of appropriate nine-membered ring intermediates which are then elaborated *via* a transannular cyclization approach to the desired natural products.

In a previous publication in this series [2] we described in detail a general synthetic entry into the *Aspidosperma* alkaloid family. Among the various reactions employed in the sequence, perhaps the most crucial steps concern a reductive ring cleavage of an appropriate pentacyclic ammonium system (I) to the tetracyclic nine-membered structure of quebrachamine (II, R = R'= H) and the subsequent cyclization of the latter to the pentacyclic aspidospermidine skeleton (III, R = R'= H). The already demonstrated extension [3] [4] of the cyclization approach to the ester bearing alkaloids, prevalent in a variety of *Vinca* plants[3]) (for example III, R = $COOCH_3$; R'= H; 2,3-double bond)[4]) provided an obvious requirement for the total

[1]) For a preliminary report on a portion of this work, see [1].
[2]) Part V, see [2].
[3]) For a general survey see [5].
[4]) For the sake of clarity and facile comparisons with previous publications, the more recent proposals for numbering and nomenclature of indole alkaloids (*J. Le Men & W. I. Taylor*, Experientia *21*, 508 (1965); *J. Trojanek* and *K. Blaha*, Lloydia *29*, 149 (1966)) have not been adopted in this or succeeding papers.

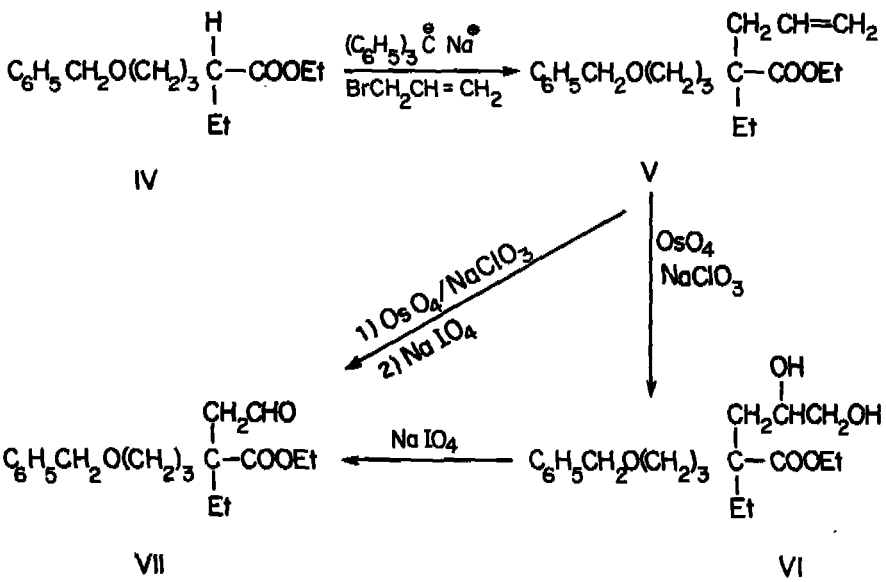
synthesis of nine-membered ring systems possessing the structural features portrayed in II (R = $COOCH_3$; R' = H or OCH_3). The present discussion outlines our detailed investigations which achieve these objectives.



In our earlier investigations [2] [6] the synthesis of the required quaternary systems (I) involved, in the initial stages, the condensation of tryptamine with a substituted succinic ester to provide a succinimide derivative which could then be elaborated to the desired compounds. Unfortunately the yield achieved in the required cyclization of the imide was low and improvements in this sequence were essential if these compounds were to be readily available for the present study.

As an alternative to the above approach a *Pictet-Spengler* reaction [7–9] was envisaged for the conversion of tryptamine to the desired tetracyclic system. An appropriate aldehydo-ester (VII) which would be suitable for this purpose was prepared from ethyl 2-ethyl-5-benzyloxypentanoate (IV), already available from previous studies [2], according to the sequence in *Scheme 1*. It is worthy to note that of

Scheme 1. *Preparation of the aldehydo-ester VII*



the two alternative routes (V → VI → VII and V → VII) employed in converting the allyl derivative V to the aldehydo-ester VII, the one step preparation (V → VII) is superior (overall yield 70% *vs.* 46%).

Having obtained the desired component (VII), condensation of the latter with tryptamine in refluxing glacial acetic acid provided a 90% yield of the tetracyclic lactam (VIII) as a mixture of two inseparable diastereoisomers. The presence of the lactam was evident from the strong carbonyl absorption at 1675 cm^{-1} in the infrared spectrum. The NMR. spectrum was most informative: signals for the α-proton on the indole ring were absent while two almost overlapping triplets at δ 4.79 and 4.76 ($J = 8$ Hz) indicated the presence of a C(3) proton on the lactam ring. The diastereoisomeric nature of this mixture was obvious throughout the whole NMR. spectrum, but for our purposes it was not necessary to try to separate the two racemates at this stage.

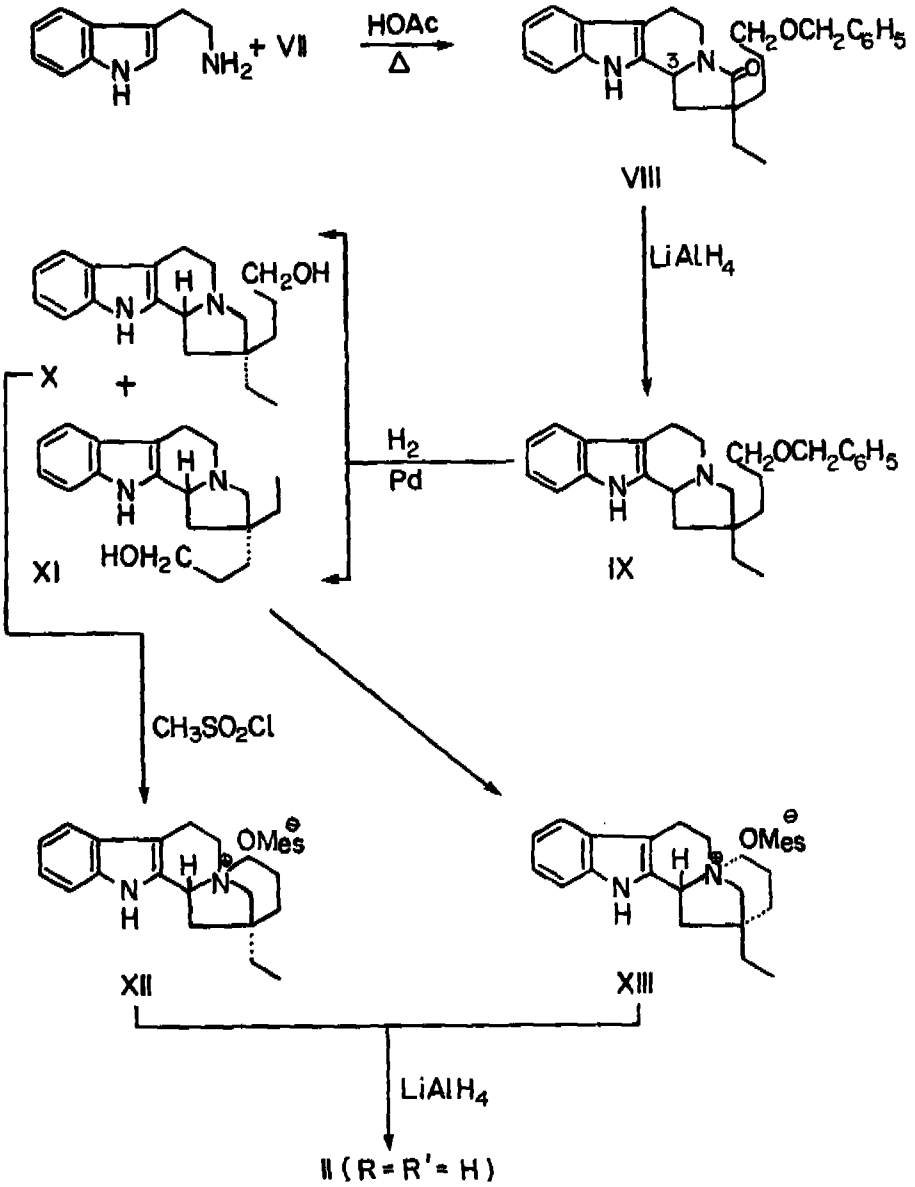
Lithium aluminium hydride reduction of the lactam mixture provided, in high yield (95%) the desired cyclic amine derivative (IX). This product was again a mixture and it was apparent that separation at this stage was going to be extremely difficult. The spectral data obtained was on this isomeric mixture. It was noted that the latter no longer showed a carbonyl absorption in the infrared spectrum. From the NMR. spectrum it was noted that this mixture of epimers was in a 1:1 ratio from the two singlets at δ 4.50 and 4.39 which were almost exactly 1:1 in area (benzylic hydrogens). Further support of the above statement came from the two overlapping triplets for the two methyl groups at δ 0.87 and 0.70 ($J = 7$ Hz), which were also 1:1 in relative intensity. The expected shift to higher field of the two overlapping triplets in the δ 5 region (due to the C(3) proton) was observed as a new triplet at δ 4.12. Mass spectrometry and analysis confirmed the formula $C_{26}H_{32}N_2O$ for this mixture.

The benzyl group of the above mixture was removed by catalytic hydrogenolysis to provide, in 84% yield, a mixture of isomeric alcohols which could now be separated by column chromatography. The identity of these crystalline products with those obtained previously [2] (m.p. 166–167°, alcohol B, XI, and m.p. 168–170°, alcohol D, X) was established in the usual manner. Conversion of *both* compounds to *dl*-quebrachamine (II, R = R′= H) was accomplished in the previously developed manner [2] (*Scheme 2*). This study now provided a vastly improved synthesis of quebrachamine (overall 50% yield from the alcohols X and XI).

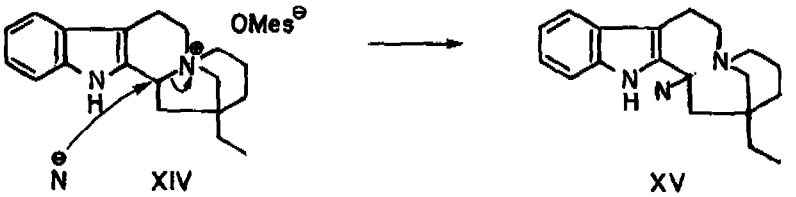
Now that an improved sequence leading to the quebrachamine system was at hand, the next aim was the development of a general and versatile reaction for the introduction of appropriate functionality at C(3) of this system. Success in this direction would provide an entry into the total synthesis of a large number of *Vinca* alkaloids.

For this purpose we considered the use of the quaternary mesylate derivatives (XII and XIII), available in high yield from the above-mentioned alcohols (X and XI), as possible starting materials. We chose to utilize these latter intermediates in a manner such that the formation of the nine-membered ring would occur simultaneously with the introduction of the appropriate function at C(3). A general scheme for this conversion is illustrated (XIV → XV) in which it is noted that attack by a nucleophile ($N^{\ominus}$) takes place at a carbon site adjacent to the quaternary nitrogen

Scheme 2. *Improved synthesis of* dl-*quebrachamine* (II, R = R' = H)

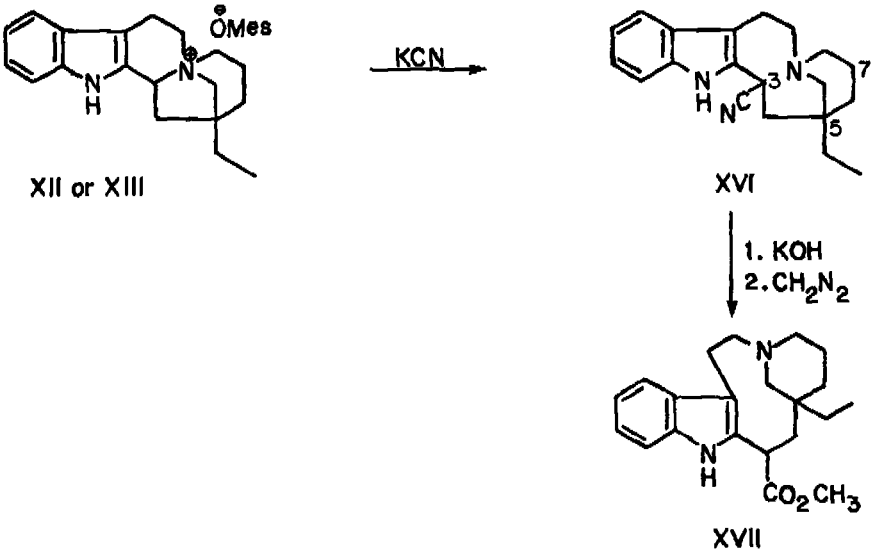


atom of the mesylate. In effect a successful application of the above was performed in the synthesis of quebrachamine from the mesylate as already mentioned, where the nucleophile was hydride anion. In this instance we chose to study the reaction with cyanide ion as nucleophile. When *either* of the mesylates (XII or XIII) were reacted with potassium cyanide in dimethylformamide at 150° a dark gummy product was obtained. Investigation of the product mixture resulting from either mesylate, by means of TLC., showed them to be identical. Chromatography of this crude product gave the two desired isomeric cyanides (cyanide I and cyanide II)



possessing the gross formula (XVI) (*Scheme 3*), another isomeric cyanide (cyanide III) and some starting material. Initial attempts to prepare these desired cyanides failed or gave other products when the reaction was carried out in diethylene glycol. In most of the latter investigations only the starting mesylate could be recovered. A wide variation in the reaction conditions (changes in temperature, time and concentration of reactants) was studied. *Harley-Mason* [10] [11] has also succeeded in applying this type of reaction in other studies and has employed diethylene glycol and potassium cyanide.

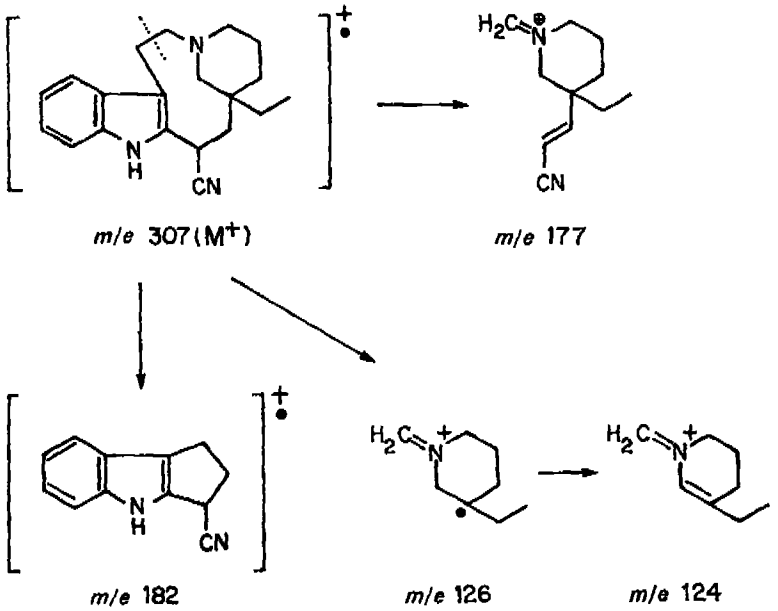
Scheme 3. *Introduction of functional groups at C(3) of the quebrachamine skeleton*



Cyanide I, m.p. 208–210°, exhibited a normal indole UV. spectrum while the IR. spectrum showed the nitrile absorption at 2230 cm^{-1} and the sharp NH vibration at 3360 cm^{-1}. The NMR. spectrum possessed a one-proton quartet at δ 3.92 (-C*H*CN, $J = 2$ and 5 Hz) whereas the MS. of this compound showed a base peak at *m/e* 177 and other significant peaks at 124, 126 and 182. Plausible structures for these fragments are depicted in *Scheme 4* and are in accord with expectation [12] [13].

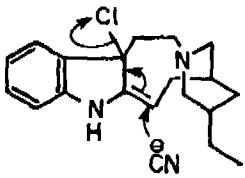
Cyanide II, m.p. 164–168°, also revealed a typical indole UV. spectrum while its IR. (2225 and 3360 cm^{-1}) and NMR. (δ 6.01, C*H*CN, $J = 4$ and 10 Hz) spectra provided support for the nitrile function. Of particular note was the downfield shift of the NMR. signal thereby revealing a different stereochemistry at the nitrile bearing carbon atom. The isomeric nature of cyanide II was confirmed by the fragmentation pattern in the mass spectrometer, which was essentially identical with that obtained for cyanide I.

Scheme 4. *Postulated fragmentation of the isomeric cyanides* (cyanide I and cyanide II)



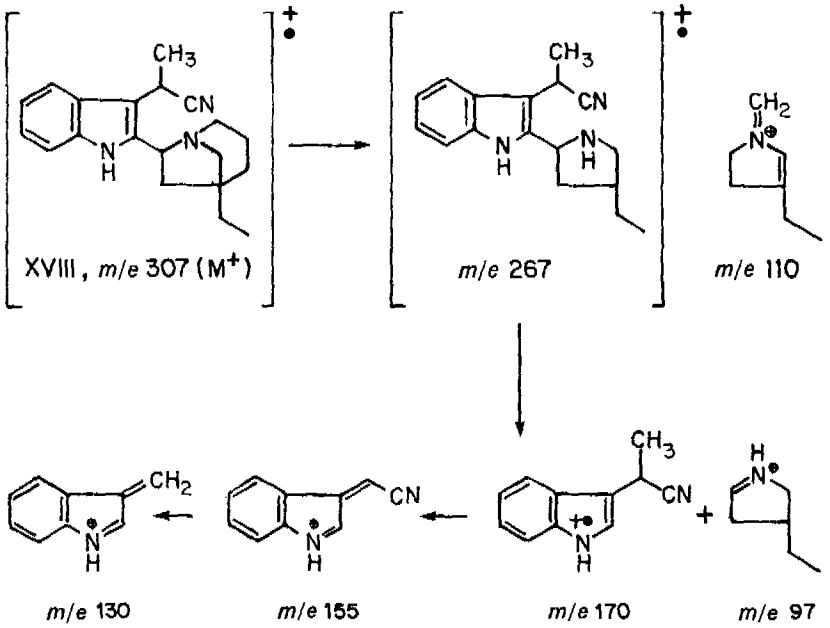
Cyanide III resisted crystallization and was characterized as an amorphous solid. The IR. spectrum showed a pronounced nitrile peak at 2220 cm^{-1}, a strong NH vibration at 3280 cm^{-1} while a typical indole chromophore was seen in the UV. spectrum. The NMR. spectrum was most informative. Two one-proton multiplets at δ 4.50 and 4.12, a methyl triplet at δ 0.83 and the typical indole aromatic proton signals were present. Finally a singlet of two protons at δ 2.58 was apparent. The mass spectrum, with a molecular peak at *m/e* 307, supported the same molecular formula as had been observed in the above-mentioned products. However, a completely different fragmentation pattern was noted. Possible structures for the main fragments of this molecule to which we have assigned structure (XVIII) are shown in *Scheme 5*. The formation of cyanide III can be explained as taking place *via* a *Hofmann*-type elimination and the resulting vinyl indole intermediate (XIX) undergoes cyanide attack to yield XVIII (*Scheme 6*). *Dolby & Gribble* [14] during some investigations on 3-vinylindoles were able to demonstrate a similar reaction and also explained their results in this manner. It seems that potassium cyanide is basic enough to promote such a reaction especially at high temperatures (150°).

It should be noted at this point that another approach to the introduction of a C(3) substituent was considered in view of previous studies in the isomeric nine-

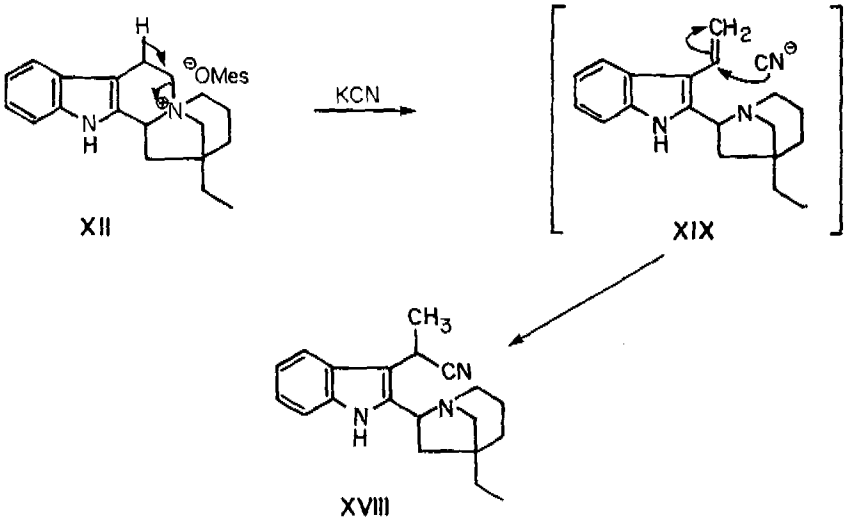


XX

Scheme 5. *Fragmentation of cyanide III in the mass spectrometer*

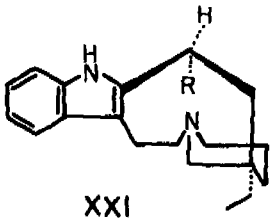


Scheme 6. *Possible mechanism for the formation of cyanide III*

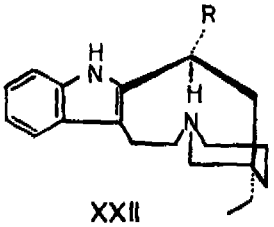


membered ring cleavamine series [15]. The conversion of dihydrocleavamine to its 18-carbomethoxy derivative *via* the chloroindolenine intermediate (XX) suggested an obvious extension to the present study. Unfortunately this approach failed completely when applied to the quebrachamine system.

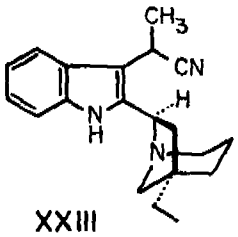
The stereochemistry at C(3) of the isomeric nine-membered ring cyanides I and II could be ascertained by a careful analysis of the low field region in the NMR. spectrum. The significant difference in the chemical shift of the C(3) proton is easily explained by considering several possible conformations for these compounds. Thus in cyanide I (XXI, R = CN) the proton is removed from the lone pair of electrons on the nitrogen atom and thus absorbs in the expected region (δ 3.92) while in cyanide II (XXII, R = CN) the close proximity of this proton to the hetero atom is revealed in a considerable downfield shift (δ 6.01). A similar proposal has been put forth by *Kompis & Mokry* [16] in the structurally related *Vinca* alkaloid series. The most plausible conformational structure for cyanide III (XXIII) is presented for purposes of comparison.



XXI



XXII



XXIII

Alkaline hydrolysis of a mixture of cyanides I and II or either of them separately followed by esterification gave the same reaction products.

Chromatographic purification of the resultant mixture revealed the presence of two isomers in a 2:3 ratio. The more abundant material had the same TLC. properties as an authentic sample of the naturally occurring alkaloid, vincadine[5]). Separation of these two compounds by thick layer chromatography gave crystalline materials which turned dark quickly during the usual handling. For example, attempts at crystallization and/or sublimation were accompanied by extensive decomposition. However both epimers were reasonably stable in the dark and at low temperature (refrigeration).

The major component was subsequently shown to be identical with vincadine (superimposable IR. and mass spectra). The most important features of the NMR. spectrum were a strong methyl singlet at δ 3.72 ($COOCH_3$), a one-proton quartet at δ 3.80 (C_3H, $J_{AB} = 6$ and $J_{AC} = 2$ Hz) and a methyl triplet at δ 0.84. The mass spectrum had significant peaks at *m/e* 124, 138, 210, 215, 281 and 340 (M^+). A rationalization for some of the fragments is presented in *Scheme 7*.

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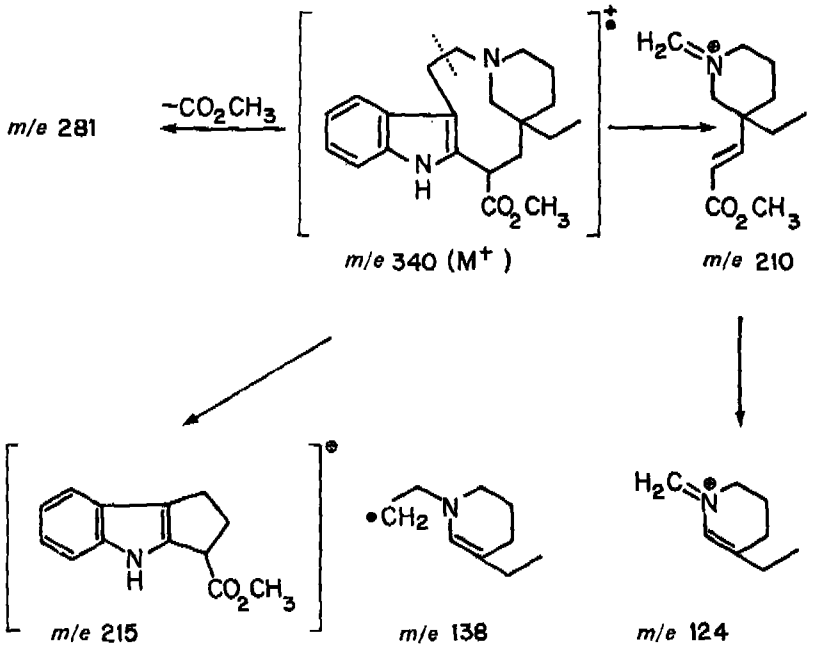
[5]) We are very grateful to Dr. *J. Kompis*, Slovak Academy of Sciences, Bratislava, Czechoslovakia, for a gift of this alkaloid.

Scheme 7. *Postulated fragmentation pattern for vincadine* (XXI, R = $COOCH_3$) *and epivincadine* (XXII, R = $COOCH_3$)



The isomeric nature of the minor component was established by high resolution mass spectrometry, again revealing the formula $C_{21}H_{28}N_2O_2$ while the other spectral data were very similar to that quoted for vincadine. Of particular note were the differences observed in the NMR. spectrum. First of all the C(3) proton signal had shifted from δ 3.80 to 5.59, with coupling constants of 10 and 3 Hz. The simultaneous upfield shift of both methyl groups of the carbomethoxy and ethyl functions to δ 3.65 (singlet) and δ 0.67 (triplet) respectively was evident.

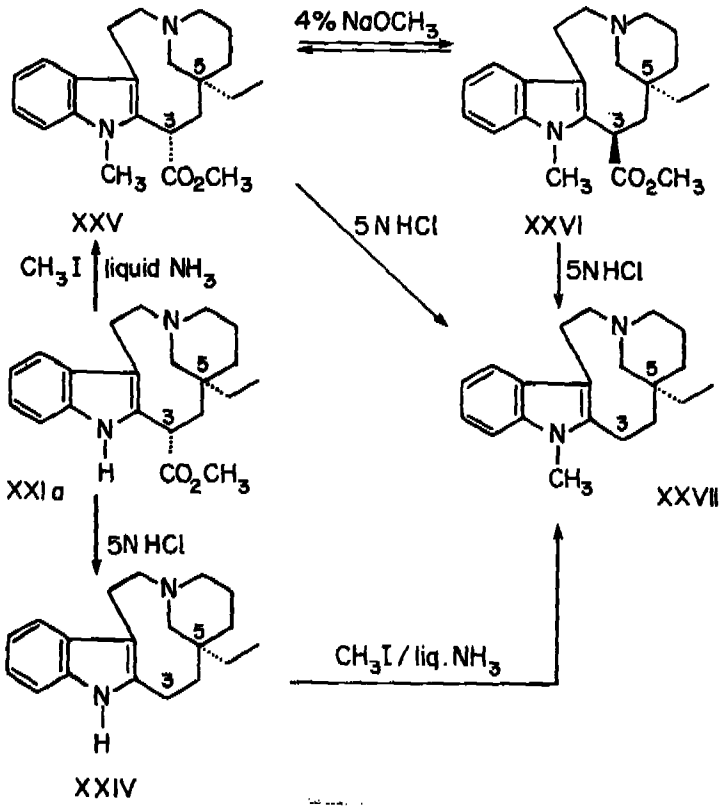
These results are in agreement with expectation in view of factors similar to those previously explained for the case of the epimeric cyanides. Finally, the mass spectrum of this epimer showed the same general fragmentation pattern as that of the major isomer. The small differences in the intensities of these peaks in the spectra of these two epimers, especially the peak at *m/e* 215, reveals the stereochemical difference at C(3) and the data, in general, correlate very well with that of the closely related C(3) epimeric *Vinca* alkaloids, vincaminoreine and vincaminorine [13]. On the basis of the evidence presented above, the major synthetic component was clearly *dl*-vincadine (XXI, R = $COOCH_3$) while the minor isomer was *dl*-epivincadine (XXII, R = $COOCH_3$).

It is pertinent to comment at this point about the stereochemical differences at C(3) already proposed above for the cyanides and esters obtained in the synthetic sequence and to corroborate these proposals with further experimental evidence. First of all, since cyanide I or II reacted separately under the same conditions and gave the *same* mixture of methyl esters it was clear that they were structurally identical except in terms of configuration at C(3). Furthermore, it was obvious that

epimerisation was taking place at C(3) during the basic hydrolysis of the cyanides. When naturally occurring vincadine was treated with sodium methoxide in methanol for $^1/_2$ hour, it also gave a mixture of epimers which was identical with the one obtained from the hydrolysis and esterification of either of the cyanides (TLC. and superimposable IR.). This result established that the natural system behaved in an analogous manner to the synthetic material.

It has been proven that acidic hydrolysis of natural vincadine gives (+)-quebrachamine (XXIV) (*Scheme 8*). Also, vincadine upon N-methylation with methyl iodide in liquid ammonia gives vincaminoreine (XXV) [17]. In the same manner vincaminoreine (XXV) and its epimer vincaminorine (XXVI) by acid hydrolysis are converted to N-methyl (+)-quebrachamine (XXVII) [13]. Finally, vincaminorine

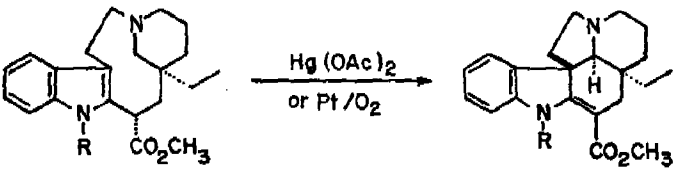
Scheme 8. *Chemical interrelations of some natural alkaloids*



was equilibrated in the presence of sodium methoxide to vincaminoreine. These results indicate that vincadine, vincaminoreine and vincaminorine have the same configuration at C(5). The absolute configuration of (+)-quebrachamine is known from the work of *Schmid* [18] and therefore the configurational assignments, as shown in *Scheme 8*, can be made for these various alkaloids. On this basis vincadine can be represented by the stereoformulae XXI and XXIa while epivincadine is shown as XXII and XXIIa.

Having completed the total synthesis of *dl*-vincadine, the total synthesis of *dl*-vincaminoreine and *dl*-vincaminorine was also in hand, in view of the previously mentioned interconversions, as given in *Scheme 8*.

An entry into the pentacyclic series exemplified by vincadifformine [19] [20] and minovine [16] [21] was now possible by means of the transannular cyclization approach [3] [4]. When vincadine and vincaminoreine were reacted with either mercuric acetate, as before, or oxygen in the presence of a catalyst (5% Pt/C) [22] they provided vincadifformine (XXVIII, R = H) and minovine (XXVIII, R = CH_3) identical in every respect (IR., UV., TLC.) with authentic samples.



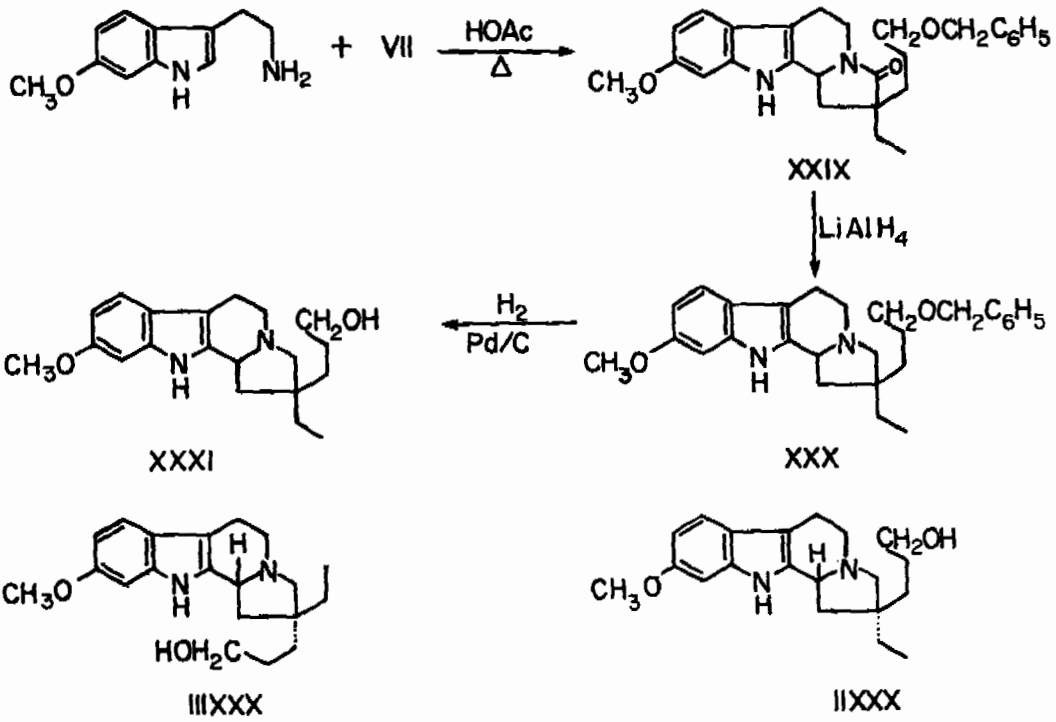
XXVIII

The above studies were now considered in terms of nine-membered ring tetracyclic as well as pentacyclic *Aspidosperma* alkaloids containing oxygen functionality in the aromatic ring. For this purpose 6-methoxytryptamine [23] was selected as the indole unit for condensation with the available aldehydo-ester VII (*Scheme 9*). When the latter was reacted with 6-methoxytryptamine in refluxing glacial acetic acid the tetracyclic lactam XXIX was obtained in 98% yield. This intermediate was a mixture of the two expected diastereoisomers, but no attempts to separate them at this stage were necessary for our purpose. The structure XXIX assigned to this product, was fully substantiated by spectral data.

Hydride reduction of XXIX to XXX and catalytic debenzylation of the latter provided a key intermediate, the tetracyclic amino alcohol of gross structure XXXI in an overall 64% yield. Careful chromatographic purification allowed the separation of two crystalline diastereoisomeric compounds. For the sake of discussion the less polar alcohol is termed alcohol I and the more polar as alcohol II. It is appropriate at this point to discuss the stereochemical differences between these isomers as viewed from analysis of their spectral data. For this purpose, we will adopt a '*cis-trans*' nomenclature as shown in *Scheme 9* to differentiate the two isolated racemic forms. Thus the *cis* isomer is considered to possess the proton at C(3) and the ethyl side chain in a *cis* relationship (XXXII) while *trans* is represented by XXXIII.

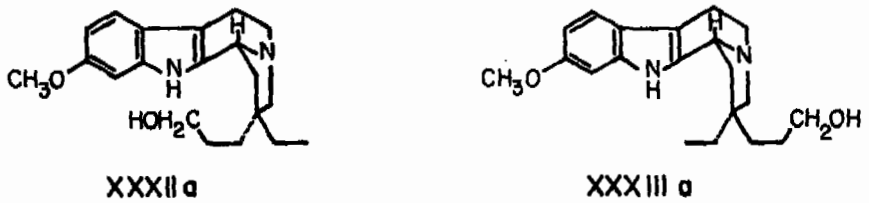
Both alcohol I and II failed to reveal any *Bohlmann* bands in their infrared spectra thereby indicating that the C(3) proton is not *trans* or anti-parallel to the unshared electron pair on the hetero atom [24–28].

Scheme 9. *Preparation of the tetracyclic amino alcohols XXXII and XXXIII*



On this basis the *cis* form may be represented by the conformation XXXIIa while the *trans* isomer is shown as XXXIIIa (*Scheme 10*).

Scheme 10. *Proposed conformations of the isomeric alcohols I* (XXXIIa) *and II* (XXXIIIa)

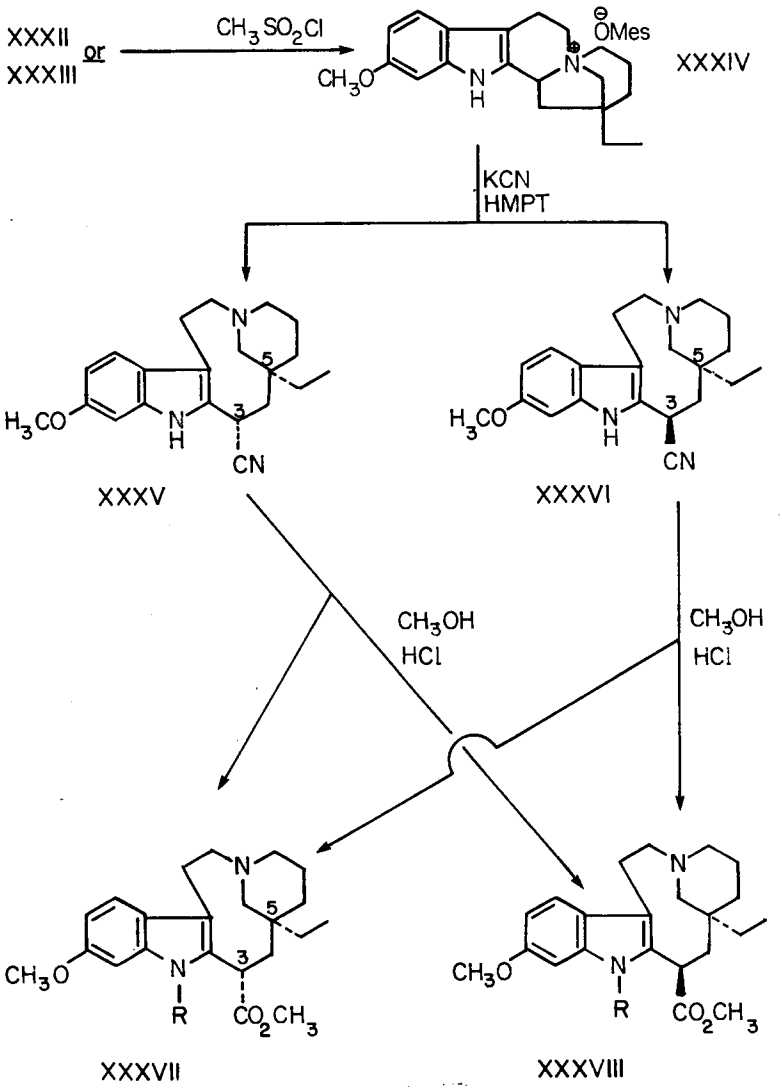


NMR. spectroscopy provides supporting evidence for the above and reveals additional information about the configuration of the amino alcohols. Thus molecular models reveal that when the C(3) proton is *cis* to the nitrogen electron pair, the ethyl side chain of the *trans* isomer (XXXIIIa) will be lying in close proximity to the indole ring. As a result the C(3) proton is deshielded by the nitrogen atom while the ethyl group is shielded and resonates at higher field. Indeed in one of the isomers (alcohol II) the C(3)-proton multiplet occurs at low field δ 4.18 and the methyl triplet at δ 0.72. However in the *cis* case (alcohol I, XXXIIa) the ethyl group is removed from the indole ring but in reasonably close proximity to the nitrogen electrons and to the C(3) proton. As a result, the C(3) proton resonates at δ 4.10 while the methyl

signal is observed at δ 0.86. Support for these assignments is available from the results of other investigations in the alkaloid area [29–32].

Having obtained the required intermediates (XXXII and XXXIII), our next aim was the generation of the nine-membered ring compound bearing the appropriate functional group at C(3), which would provide the basic *Aspidosperma* skeleton. The synthetic approach selected involved ring opening of the quaternary mesylate XXXIV in a manner already previously described (*Scheme 11*). Thus treatment of

Scheme 11. *The synthesis of 16-methoxyvincadine* (XXXVII, R = H), *16-methoxyepivincadine* (XXXVIII, R = H), *and vincaminoridine* (XXXVIII, R = CH_3) *from the isomeric aminoalcohols XXXII and XXXIII*

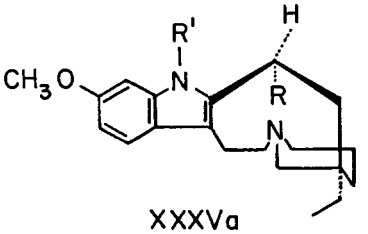


each of the isomeric alcohols with methanesulfonyl chloride in the presence of triethylamine at 0°, provided a quantitative yield of the corresponding mesylates (gross structure XXXIV). These compounds were not completely characterized but utilized directly in the next step of the sequence. When either of the mesylates of alcohol I or alcohol II was treated with potassium cyanide in dimethylformamide at 150°, only a low yield of the desired isomeric cyanides could be obtained. Initial attempts to prepare these cyanides failed or gave other products when the reaction was carried out in solvents such as diethylene glycol, dimethyl sulfoxide and dimethyl acetamide. In most of the cases, starting material was recovered unreacted. A wide variation of reaction conditions (temperature, time, concentration, solvent) was attempted. A summary of these preliminary investigations using 100 mg of the starting material (XXXIV) is given in the Table.

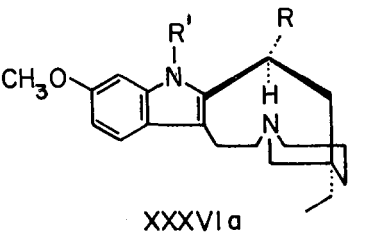
Solvent	Temperature (°C)	Time (h)	mg of CN containing product
DMSO	60	48	3
DMSO	60–100	48	20
DMSO	reflux	48	20
DMF	150	6	26
DMF	reflux	24	20
DMF/10% CH_3OH	reflux	24	15
HMPT	180	24	50

It was clear from these studies that solvent effects play a decisive role. It was known from the previous investigations already described that one of the most serious side reactions in this type of reaction is the ability of the cyanide ion to act as a base, and to perform a *Hofmann* elimination. On this basis it is perhaps not entirely surprising that the best yields are obtained in the highly nucleophilic system, cyanide in hexamethylphosphoramide (HMPT). This latter system was then employed in the preparative scale studies. Purification of the product mixture by high pressure liquid chromatography allowed the isolation of two crystalline cyanides. The isomeric nature of these substances was established by appropriate comparison of analytical and spectroscopic data.

The less polar product designated as 16-methoxycyanide I, revealed in its NMR. spectrum, a quartet at δ 3.88 (J = 10 and 3 Hz) due to the C(3) proton (–C*H*CN) while the more polar substance, 16-methoxycyanide II possessed a quartet at lower field (δ 5.97, J = 10 and 3 Hz). This chemical shift difference is readily interpreted in



XXXVa



XXXVIa

conformational expressions for these substances in the manner already described previously. Thus 16-methoxycyanide I corresponds to XXXV and XXXV a (R = CN; R'= H) while 16-methoxycyanide II is represented by XXXVI and XXXVI a (R = CN; R'= H).

The mass spectral fragmentation patterns of both compounds were essentially identical and in accord with the scheme presented in *Scheme 4* for the previously studied and related series.

Hydrolysis of the nitrile group in the above compounds was achieved in acidic methanol whereupon a direct conversion to the required carbomethoxy group was accomplished. Under these conditions, during which equilibration also occurs, a 3:1 mixture of products was obtained. The major isomer, 16-methoxyvincadine (XXXVII, R = H, δ 3.65, C(3) proton) possesses the same configuration at C(3) as 16-methoxycyanide I, the minor product from the previous step in the sequence, and is therefore assigned the conformational expression XXXV a (R = $COOCH_3$, R'= H) while the minor isomer (XXXVIII, R = H) with a low field signal at δ 5.51 corresponds to XXXVI a (R = $COOCH_3$, R'= H).

The final step in the sequence involved methylation of the indolic nitrogen atom and this was accomplished according to the known procedure [17]. Separation of the resultant mixture by thick layer chromatography afforded two products XXXVII (R = CH_3) or XXXV a (R = $COOH_3$, R'= CH_3, δ 3.80, C(3) proton) and XXXVIII (R = CH_3) or XXXVI a (R = $COOCH_3$, R'= CH_3, δ 6.10, C(3) proton). The latter compound revealed spectral data[6]) identical with that of the alkaloid, vincaminoridine isolated from *Vinca minor* [15].

The above nine-membered ring intermediates XXXVII and XXXVIII (R = CH_3) can be converted *via* the transannular cyclization approach discussed earlier to provide the pentacyclic skeleton corresponding to XXVIII (R = CH_3, methoxy in aromatic ring). The utilization of this intermediate in the total synthesis of vindoline will be presented in a subsequent publication.

Another approach to the total synthesis of *dl*-minovine has been described by *Ziegler* [32]. These authors have also provided a synthesis of the related alkaloid tabersonine [34].

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Experimental Part

Melting points were determined on a *Kofler* block and are uncorrected. UV. spectra (λ_{max} (log ε)) were measured in 95% ethanol or methanol on *Cary* model 11, 14 or 15 spectrophotometers. IR. spectra were recorded on a *Perkin-Elmer* 21 or 137 spectrophotometer. NMR. spectra were taken in deuteriochloroform solution on *Varian* spectrometers, models T-60, HA-100 or XL-100. Line positions are given in the δ scale, with tetramethylsilane as an internal standard. The types of protons, integrated areas, multiplicity and spin coupling constant J (in Hz) are indicated in parentheses. MS. (main peaks, *m/e*) were recorded on an *Atlas* CH-4B or *AEI* MS-902 spectrometer, high resolution measurements being determined on the latter instrument.

Silica gel G and alumina *Woelm* containing 2% by weight of a fluorescent indicator were used for thin-layer chromatoplates (TLC.). As spraying reagent a solution of 1:2 of antimony penta-

[6]) We are grateful to Dr. *I. Kompis*, Slovak Academy of Sciences, Bratislava, Czechoslovakia, for providing us with the IR., NMR., and mass spectra of this alkaloid.

chloride in carbon tetrachloride, or a solution of ceric sulfate in aqueous sulfuric acid were used extensively. Unless otherwise specified column chromatography was performed using either *Woelm* grade silica or neutral alumina, and deactivated as required with the correct amount of water. Distilled solvents were used. High pressure liquid chromatography was performed either on a *Waters* ALC-100 or ALC-202 instrument.

Elemental analyses were performed by Mr. *P. Borda* of the Microanalytical Laboratory, University of British Columbia.

Ethyl α-(γ-benzyloxypropyl)-α-allylbutanoate (*V*). To an ether solution of sodium triphenyl methane (73 ml, 0.26 N, 19 nmol) the ethyl ester IV (5.0 g, 19 mmol) was added and the mixture was stirred for $1^1/_2$ h at room temperature (RT.). The transfer of reagents and the reaction itself was performed under oxygen-free nitrogen and in anhydrous conditions. Allyl bromide (2.3 g, 19 mmol) freshly distilled (b.p. 71°), was added dropwise under efficient stirring and it was left to react for about 20 min more after the addition was completed. The reaction mixture was kept at RT. during the entire period by occasional cooling. By the end of this time the formation of insoluble sodium bromide resulted in a thick cloudy solution. Water (20 ml) was added, the layers separated and extraction with ethyl ether (2 × 20 ml) followed. The combined ether layer was washed with water (2 × 25 ml) and dried over anhydrous magnesium sulfate. Removal of the inorganic agent by filtration and removal of ether under reduced pressure at RT. yielded a yellow viscous oil. To this oil, benzene (10 ml) was added and the solution brought to its boiling point. The triphenyl methane crystallized from the mixture by allowing to stand overnight. Filtration of the triphenyl methane and evaporation of the solvent gave a yellow oil (6.8 g). This oil was chromatographed on silica gel *Woelm* (316 g, activity III). Elution with petroleum ether (30–60°)/benzene 1:1 gave 5,56 g (98%) of a colourless viscous oil. Purification was also possible by vacuum distillation, b.p. 155–160° (bath)/0.2 Torr, to give, in quantitative yield, the desired compound (V). – IR. (liq. film): 1725 *s* (–CO_2Et), 1645 *w* (C=C), 925 *m* (vinyl), 745 *m* and 700 *m* (monosubstituted benzene) cm^{-1}. – UV.: 267.5 (2.15), 263.5 (2.32), 257.5 (2.43), 252 (2.36), 247 (2.28) and 222 (2.81) nm. – NMR. (100 MHz): 0.80 (*t*, *J* = 7, 3 H, CH_3CH_2–) and 1,20 (*t*, *J* = 7, 3 H, –$CO_2CH_2CH_3$); 1.58 (*m*, 6 H, $CH_3CH_2CCH_2CH_2CH_2O$–); 3.40 (*t*, *J* = 6, 2 H, $C_6H_5CH_2OCH_2$–); 4.08 (*q*, *J* = 7, 2 H, $CH_3CH_2O_2C$–); 4.43 (*s*, 2 H, $C_6H_5CH_2O$–); 5.0 (multiplet, 2 H, –CH=CH_2); 6.60 (*m*, 1 H, –CH=CH_2); 7.28 (*s*, 5 H, aromatic). – MS.: 91 (base peak), 139, 156, 167, 197. Mol.-Wt.: 304.204.

$C_{19}H_{28}O_3$ (304.204) Calc. C 74.96 H 9.27% Found C 74.71 H 9.43%

Ethyl α-(γ-benzyloxypropyl)-α-(β,γ-dihydroxypropyl)-butanoate (*VI*). To a solution of the allyl ester V (4.45 g, 14.7 mmol) in tetrahydrofuran (80 ml) a solution of osmium tetroxide (11.7 ml, 0.46 mmol) in tetrahydrofuran was added dropwise with stirring at RT., under a nitrogen atmosphere. After the addition, stirring continued for a further 10 min. To the resultant dark solution, a solution of sodium chlorate (1.84 g, 16.8 mmol) in water (80 ml) was added slowly. The reaction vessel was then placed in a water bath (40–50°) and stirring continued for a further 44 h. The reaction mixture was checked at intervals by TLC., until almost all the starting material had disappeared. The solvent was removed under reduced pressure and water (150 ml) was added. Extraction with ethyl ether (3 × 300 ml) followed. The combined extracts were washed with water (2 × 150 ml) and dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of ether under reduced pressure gave a gray viscous oil (4.81 g). This oil was chromatographed on silica gel *Woelm* (270 g, activity IV). Elution with ethyl ether gave a clear viscous oil (3.47 g, 68.5% yield). A small amount of this oil was dried in a vacuum pistol with phosphorus pentoxide over boiling benzene for 4 h and then for 2 days at RT. – IR. (liq. film): 3400 *s* (2 × OH), 1725 *s* (–CO_2Et), 1645 and 925 (no peaks), 745 *m* and 700 *m* (monosubstituted benzene) cm^{-1}. – UV.: 267 (2.33), 263.5 (2.43), 257.5 (2.51), 252 (2.45), 247 (sh. 2.41) and 218 (3.23) nm. – NMR. (60 MHz): 0.81 (*t*, *J* = 7, 3 H, CH_3CH_2–); 1.24 (*t*, *J* = 7, 3 H, $CH_3CH_2O_2C$–); 3.12 (br. *s*, 2 H, 2 × OH); 3.47 (*t*, *J* = 6, 2 H, –$CH_2OCH_2C_6H_5$); 3.2–4.0 (br. *m*, 3 H, –CHOHCH_2OH); 4.14 (*q*, *J* = 7, 2 H, $CH_3CH_2O_2C$–); 4.50 (*s*, 2 H, $C_6H_5CH_2O$–); 7.32 (*s*, 5 H, aromatic). – Addition of one drop of D_2O caused disappearance of singlet at δ 3.12. – MS.: 91 (base peak), 99, 125, 135, 153, 199, 305. Mol.-Wt.: 338.209.

$C_{19}H_{30}O_5$ (338.210) Calc. C 67.43 H 8.94% Found C 67.34 H 9.05%

Ethyl α-(γ-benzoxypropyl)-α-(α-formylmethyl)-butanoate (VII). To a solution of diol VI (520 mg, 1.53 mmol) in a mixture of tetrahydrofuran (25 ml) and water (25 ml), solid sodium meta-periodate (2.05 g, 5.88 mmol) was added in small portions. The mixture was stirred at RT. under nitrogen for 51 h. At this time only a trace of starting material was present. Water (10 ml) was then added and extraction with ethyl ether (3 × 30 ml) followed. The combined ether extracts were washed with water (2 × 15 ml) and the organic layer dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure afforded a viscous oil (527 mg). The oil was chromatographed on alumina neutral *Woelm* (30 g, activity II). Elution with benzene/ethyl ether 4:1 gave 315 mg (67%) of pure aldehyde (VII). On further elution the starting diol (72 mg) was recovered. For analytical purposes a small amount of this aldehyde was distilled under vacuum (165°/0.1 Torr) to give a colourless viscous oil. – IR. (liq. film): 2750 *w* (CH of CHO), 1722 *vs* (—CO_2Et and CHO), 742 *m* and 705 *m* (monosubstituted benzene) cm^{-1}. – UV.: 267.5 (2.34), 263.5 (2.44), 257.5 (2.51), 252 (2.47), 247 (sh. 2.45), and 220 (3.11) nm. – NMR. (60 MHz): 0.85 (*t*, *J* = 7, 3 H, —CH_2CH_3); 1.23 (*t*, *J* = 7, 3 H, —$CO_2CH_2CH_3$); 2.64 (*d*, *J* = 2, 2 H, —CH_2CHO); 3.45 (*t*, *J* = 6, 2 H, —$CH_2OCH_2C_6H_5$); 4.16 (*q*, *J* = 7, 2 H, —$CO_2CH_2CH_3$); 4.48 (*s*, 2 H, —$OCH_2C_6H_5$); 7.32 (*s*, 5 H, aromatic); 9.78 (*t*, *J* = 2, 1 H, —CHO). – MS.: 91 (base peak), 141, 158, 182 and 199. Mol.-Wt.: 306.181.

$C_{18}H_{26}O_4$ (306.183) Calc. C 70.56 H 8.55% Found C 70.47 H 8.51%

Direct preparation of aldehyde VII. The allyl compound (V) (12.26 g, 40.4 mmol) was dissolved in a mixture of tetrahydrofuran (250 ml, distilled over sodium and lithium aluminum hydride) and water (250 ml). Osmium tetroxide (500 mg, 1.97 mmol) was added under an atmosphere of oxygen-free nitrogen and stirring continued at RT. for 45 min. After this time solid sodium meta-periodate (21.1 g, 60.5 mmol) was added in small portions. Stirring at RT. was continued for 48 h after which time the reaction had ceased. The tetrahydrofuran was removed under reduced pressure and extraction with ethyl ether followed (3 × 200 ml). The combined ether extracts were washed with water (2 × 80 ml). The ether layer dried over anhydrous sodium sulfate and upon filtration and removal of the solvent gave 12.2 g of a crude dark oil. This oil was chromatographed on silica gel *Woelm* (600 g, activity III). Elution with benzene/ethyl ether 19:1 gave 8.62 g of pure aldehyde VII (70%) and with ethyl ether, 1.93 g of the diol (VI) (11%) was recovered. Yield (based on recovered diol): 81.5%. The aldehyde so prepared was identical in every respect with the one prepared by the stepwise procedure.

Cyclic lactam VIII. A solution of tryptamine (2.33 g, 14.6 mmol) and aldehyde (VII) (4.42 g, 14.4 mmol) in glacial acetic acid (20 ml) was refluxed in an oxygen-free nitrogen atmosphere for 1 h. Removal of acetic acid under reduced pressure with gentle heating (~60°) gave a yellow gum. This material chromatographed on alumina neutral *Woelm* (200 g, activity III). Elution with benzene gave 5.23 g (90%) of a yellowish gum. Purification of this material was achieved by high vacuum distillation, b.p. 240°/0.1 Torr to give a yellowish glass. – IR. ($CHCl_3$): 3490 *ms* (—NH), 1675 *vs* (—CON—) cm^{-1}. – UV.: 326 (3.37), 312.5 (3.44), 290 (3.83), 282.5 (3.90), 273 (sh, 3.89), and 224 (4.57) nm. – NMR. (100 MHz): 0.71 and 0.96 (2 *t*, *J* = 7 and 8, 3 H, —CH_2CH_3); 4.33 and 4.45 (2 *s*, 2 H, —$OCH_2C_6H_5$); 4.76 and 4.79 (2 *t*, *J* = 8, 1 H, H—C(3); 7.25 (*m*, 9 H, aromatic); 8.60 and 8.65 (br. overlapping *s*, 1 H, NH). – MS.: 91, 149, 168, 251, and 311 (base peak). Mol.-Wt.: 402.231 (Calc. for $C_{26}H_{30}N_2O_2$: 402.231)

Cyclic amine IX. The cyclic lactam VIII (5.2 g, 12.9 mmol) was dissolved in abs. tetrahydrofuran (300 ml, refluxed over sodium and distilled over lithium aluminum hydride) and lithium aluminum hydride (1.47 g, 38.0 mmol) was added in portions under an oxygen-free nitrogen atmosphere. Stirring and refluxing were continued for $8^1/_2$ h at which time no starting material could be detected by TLC. After cooling to RT. the reaction mixture was treated carefully by the slow addition of water and the mixture was stirred for a further 10 min. The resulting white sludge was filtered through a bed of celite and washed several times with tetrahydrofuran. The filtrate after removal of tetrahydrofuran under reduced pressure was extracted with ethyl ether (3 × 200 ml). The combined ether extracts were washed with water (2 × 80 ml) and dried over magnesium sulfate. Filtration and removal of solvent afforded a yellow viscous oil. This oil was purified by column chromatography on alumina (neutral, *Woelm*, activity II). Elution with benzene/chloroform 7:1 gave 4.76 g (95%) of a mixture of the two expected diastereoisomers. This mixture could also be easily purified by molecular distillation (240°/0.05 Torr) to provide the desired product (IX). – IR. ($CHCl_3$): 3350 *ms*, (—NH) cm^{-1}. – UV.: 291 (3.66), 283 (3.73), 275 (sh. 3.72), and 223

(4.30) nm. – NMR. (100 MHz): 0.70 and 0.87 (2 *t*, J = 7 and 7, 3 H, $-CH_2CH_3$); 4.11 (*t*, J = 6, 1 H, H–C(3)); 4.38 and 4.50 (2 *s*, 2 H, $-CH_2C_6H_5$); 7.25 (*m*, 9 H, aromatic); 7.91 (br. *s*, 1 H, N*H*). – MS.: 91, 149, 184, 260, 297 and 388 (M^+) (base peak). Mol.-Wt.: 388.253.

$C_{26}H_{32}N_2O$ (388.251) Calc. C 80.37 H 8.30 N 7.21% Found C 80.53 H 8.56 N 6.99%

Hydrogenolysis of cyclic amine IX. A solution of cyclic amine IX (4.7 g, 12.1 mmol) in glacial acetic acid (30 ml) was added slowly to a suspension of 10% Pd/C (2.0 g) in glacial acetic acid (100 ml). The catalyst was prehydrogenated until the absorption of hydrogen ceased (about 15 min). The reaction was allowed to proceed at atmospheric pressure and at RT. for 33 h, at which time the absorption of hydrogen had ceased. The mixture was filtered through a bed of celite and the latter was then washed with warm acetic acid (20 ml) and some water. The solution was made basic by slow addition of a saturated solution of sodium carbonate and extracted with methylene chloride (3 × 100 ml). The combined extracts were washed with water (2 × 50 ml) and the organic layer dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a yellow gum (3.6 g). The crude product was chromatographed on an alumina (neutral, *Woelm*, 300 g, activity II) column. Elution with benzene/chloroform 1:1 gave the least polar fraction which was shown to be unreacted starting material (IX) (0.6 g). The desired alcohols were eluted from chloroform/methanol 99:2 to give pure 1.37 g (37%) of alcohol I (less polar), and 1.7 g (46%) of alcohol II, both isolated as a colourless glass.

Alcohol I (XI): It was easily crystallized from methylene chloride, m.p. 166–167°. Comparison of this alcohol I with a crystallized sample of alcohol A obtained previously [2] showed that they were identical (TLC., IR., and NMR. superimposable; mixed m.p., showed no depression).

Alcohol II (X): It was crystallized also from methylene chloride, m.p. 168–170°. Again comparison of this alcohol II with a crystallized sample of alcohol D [2] revealed that they were identical (TLC., IR., and NMR. superimposable; mixed m.p. no depression).

The above alcohols X and XI were converted to *dl*-quebrachamine *via* the mesylates XII and XIII in the manner described previously [2]. In this way *dl*-quebrachamine (II) was available in 50% overall yield from the alcohols.

Cyano compounds XVI. The mesylate derived from alcohol XI, (177 mg, 0.47 mmol) was dissolved in dimethylformamide (10 ml, reagent grade) and pulverised potassium cyanide (130 mg, 2.00 mmol) was added to it. The mixture was refluxed gently in an oxygen-free nitrogen atmosphere for $4^1/_2$ h (160°, oil-bath temperature), with efficient stirring. The reaction was followed carefully by TLC., and IR. After this time the reaction mixture was brought to RT. and aqueous ammonium hydroxide (17 ml, 6N) was added to it under stirring. The basic solution was extracted with warm benzene (3 × 30 ml). The combined benzene extracts were washed with saturated aqueous solution of sodium chloride (2 × 10 ml). The organic layer was dried over anhydrous sodium sulfate, the solids removed by filtration and the solvent removed under reduced pressure to afford a dark gum (112 mg). The aqueous layer was saturated with solid sodium chloride and extracted with chloroform (2 × 30 ml). The organic layer was dried over anhydrous sodium sulfate, filtration and removal of the solvent under reduced pressure gave 21 mg of unreacted mesylate.

The crude reaction product (112 mg) was chromatographed on alumina (neutral *Woelm*, 3.2 g, activity II). Elution with *n*-hexane/benzene 1:1 gave an unidentified product (14 mg, yellow gum). A mixture of cyanide I and II was eluted with benzene (19 mg, white solid), while elution with benzene/ethyl acetate 1:1 gave a mixture of cyanide III (46 mg, yellow gum) containing some cyanide I and II. Further elution with the latter solvent mixture gave 6 mg of an unidentified cyanide (IR. information) and some polar material (41 mg) was also eluted with ethyl acetate.

The fraction containing mainly cyanide III (46 mg) was rechromatographed on silica gel (*Woelm*, 4.6 g, activity IV). Elution with benzene/chloroform 1:1 gave a mixture of cyanide I and II (2 mg), while elution with chloroform afforded pure cyanide III (38 mg).

The fraction containing cyanide I and II (19 mg) was combined with the above (2 mg) and purified by preparative layer chromatography on alumina (*Woelm*) developed with chloroform. The isolated products were cyanide I (9 mg) and cyanide II (12 mg).

Cyanide I (XXI, R = CN): Colourless glass (9 mg, 6%). Crystallization from ethyl ether afforded an analytical sample, m.p. 208–210°. – IR. ($CHCl_3$): 3400 *ms* (NH), 2700–2800 (*Bohlmann* bands), and 2230 (small, –CN) cm^{-1}. – UV.: 292.5 (3.81), 285 (3.85), 278 (sh, 3.82), and 225 (4.47) nm. – NMR. (100 MHz): 0.93 (*t*, J = 7, 3 H, $-CH_2CH_3$); 3.92 (*q*, J_{AB} = 5, J_{AC} = 2, 1 H,

H—C(3); 7.22 (*m*, 4 H, aromatic); 8.20 (br. *s*, 1 H, —N*H*). – MS.: 124, 125, 177 and 307 (M^+). Mol.-Wt.: 307.204 (Calc. for $C_{20}H_{25}N_3$: 307.204).

Cyanide II (*XXII*, *R* = *CN*): Colourless glass (12 mg, 8%). Crystallization from *n*-hexane provided an analytical sample, m.p. 164–168°. IR. ($CHCl_3$): 3370 *ms* (—NH), 2700–2800 (*Bohlmann* bands), and 2225 *m* (—CN) cm^{-1}. – UV.: 293 (3.82), 284 (3.87), 278 (sh, 3.83), and 225 (4.42) nm. – NMR. (100 MHz): 0.66 (*t*, *J* = 7, 3 H, $-CH_2CH_3$); 6.01 (*q*, J_{AB} = 10, J_{AC} = 4, 1 H, H—C(3)); 7.20 (*m*, 4 H, aromatic); 8.20 (br. *s*, 1 H, —N*H*). – MS.: 124, 125, 177 and 307 (M^+). Mol.-Wt.: 307.204 (Calc. for $C_{20}H_{25}N_3$: 307.204).

Cyanide III (*XVIII*): Colourless glass (38 mg, 28%), which resisted crystallization and all data were obtained on the glass. – IR. (neat): 3330 *ms* (—NH) and 2220 *m* (—CN). – UV.: 290 (3.84), 283 (3.90), 275 (sh. 3.89), and 226 (4.35) nm. – NMR. (100): 0.83 (*t*, *J* = 7, 3 H, $-CH_2CH_3$); 2.58 (*s*, 2 H, $-NCH_2C-$); 4.12 and 4.50 (2 *m*, 1 H, each, —C*H*CN and —C*H*—N—); 7.20 (*m*, 4 H, aromatic); 9.06 (br. *s*, 1 H, N*H*). – MS.: 130, 155, 170, 267, and 307 (M^+). Mol.-Wt.: 307.204 (Calc. for $C_{20}H_{25}N_3$: 307.204).

When the mesylate of alcohol X was treated under the same conditions it gave the same mixture of cyanides as above. Separate purification and identification (TLC., IR., NMR. comparison) of each of these products was performed.

dl-*Vincadine and* dl-*epivincadine*. A mixture of cyanides I and II (144) (20 mg, 0.065 mmol) was placed in a small tube and it was dissolved in a solution of 20% potassium hydroxide in distilled diethylene glycol (0.20 ml). The reaction tube was connected to a purified nitrogen trap system, und it was immersed into an oil bath at *ca.* 160°. The evolution of some gas was noted, and the reaction was left on for 12 h. Then the reaction mixture was cooled to RT. and was taken up in methanol (2.0 ml). The diluted solution was cooled to – 10° and neutralized carefully with a saturated solution of hydrogen chloride in methanol. Immediately after neutralization, an ethereal solution of diazomethane was added to the reaction mixture. The resulting solution was allowed to stand at 0° for 15 min and then it was neutralized again. The solution was treated twice more with diazomethane and then the solvent was removed in a stream of nitrogen. The residue was treated with a small amount of aqueous 10% potassium carbonate solution (1 ml) and extracted with ethyl ether (3 × 6 ml). The ether solution was dried over anhydrous sodium sulfate, filtered and the solvent removed to give a gum. Rapid filtration through alumina (neutral *Woelm*, activity II) and elution with benzene/chloroform 1:1 gave 15 mg of a yellow amorphous material.

The above procedure was repeated precisely with pure cyanide I (37 mg, 0.121 mmol) to give 33 mg (81%) of a solid. With pure cyanide II (37 mg, 0.121 mmol) the same process afforded 31 mg (77%) of the same reaction product (TLC., IR., NMR. spectra).

Combination of the above (79 mg) crude reaction products (from three chromatography on silica gel (*Woelm*, developed by benzene/ethyl acetate 1:1) failed to give a good separation. However, silica gel G plates and using benzene/ethyl acetate 4:1 as eluent did provide a separation of the epimeric compounds.

dl-*Vincadine*: Amorphous solid (14 mg, 14.5%). Attempts to crystallize this substance were abandoned when extensive decomposition was noted during the purification. Data were taken on the amorphous solid. – IR. ($CHCl_3$): 3380 (small, —NH) and 1730 *s* (ester) cm^{-1}. – UV.: 292 (3.87), 286 (3.89), and 227 (4.48) nm. – NMR. (100 MHz): 0.84 (*t*, *J* = 7, 3 H, $-CH_2CH_3$); 3.72 (*s*, 3 H, $-CO_2CH_3$); 3.80 (*q*, J_{AB} = 6, J_{AC} = 2, 1 H, H—C(3)); 7.20 (*m*, 4 H, aromatic); 8.96 (br. *s*, 1 H, —N*H*). – MS.: 124, 138, 210, 215, 281 and 340 (M^+). Mol.-Wt.: 340.215 (Calc. for $C_{21}H_{28}N_2O_2$: 340.215).

dl-*Epivincadine*: Amorphous solid (11 mg, 11.5%). Again decomposition occurred during purification so data were taken on the amorphous substance. It was shown to be less polar than natural vincadine on silica gel chromatoplates and benzene/ethyl acetate 1:1 as the developing system. – IR. ($CHCl_3$): 3380 (small, —NH), 1720 *s* (ester) cm^{-1}. – UV.: 293 (3.87), 287 (3.91), and 227 (4.52) nm. – NMR. (100 MHz): 0.67 (*t*, *J* = 7, 3 H, $-CH_2CH_3$); 3.65 (*s*, 3 H, $-CO_2CH_3$); 5.60 (*q*, J_{AB} = 12, J_{AC} = 2, 1 H, C_3—H); 7.20 (*m*, 4 H, aromatic); 8.60 (br. *s*, 1 H, N*H*). – MS.: 124, 210, 281, and 340 (M^+). Mol.-Wt.: 340.215 (Calc. for $C_{21}H_{28}N_2O_2$: 340.215).

Furthermore the synthetic *dl*-vincadine had the same TLC. properties as the natural vincadine kindly provided by Dr. *I. Kompis*. The IR. NMR. and mass spectra of the synthetic and natural samples were identical.

Epimerisation of Vincadine to Epivincadine. To a stirred freshly prepared solution of sodium methoxide in abs. methanol natural vincadine (1 mg) was added. The solution of sodium methoxide was made by addition of 58 mg of freshly cut sodium in abs. methanol (3.5 ml) under a dry nitrogen atmosphere and efficient stirring. After the addition of vincadine, the reaction mixture was refluxed under a dry nitrogen atmosphere for $^1/_2$ h. After cooling to RT. the mixture was treated with ice/water. The mixture was then neutralized by addition of a cold saturated solution of ammonium chloride and extracted with methylene chloride (3 × 5 ml). The combined organic layers were washed with a saturated solution of ammonium chloride (1 × 3 ml) and water (1 × 3 ml) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a colourless semicrystalline material (about 1 mg). TLC. investigation of this reaction mixture with the above mixture of synthetic *dl*-vincadine and *dl*-epivincadine showed them to be identical. Finally the IR. spectra of these two mixtures of natural and synthetic products were superimposable.

11-Methoxy cyclic lactam XXIX. 6-Methoxy triptamine (7 g, 36.8 mmol) and the aldehyde ester VII (15 g, 49 mmol) in glacial acetic acid (25 ml) were refluxed for 1.5 h, under an atmosphere of oxygen-free nitrogen. The acetic acid was removed under reduced pressure to give a yellow residue. Purification on a basic alumina column (*Shawnigan*, 400 g) and elution with petroleum-ether/ethyl acetate 2:3 gave the pure lactam XXIX (16 g, 98%). This product was a mixture of the two expected diastereoisomers but no attempts to separate them at this stage were necessary for our purpose. – IR. (liq. film): 3250 (br., hydrogen bonded NH), 1735 (small) and 1670 *s* (lactam) cm^{-1}. – UV.: 227 (4.12), 264 (sh, 3.73), 272 (sh, 3.72), 295 (3.75), 321 (3.47), 335 (3.39) nm. – NMR. (100 MHz): 0.72 and 0.95 (2 *t*, J = 7 and 7, 3 H, CH_3CH_2—); 3.77 (*s*, 3 H, CH_3O—); 4.34 and 4.45 (2 *s*, 2 H, $C_6H_5CH_2O$—); 4.75 (br. *t*, J = 8, 1 H, H—C(3)); 6.76 (*q*, J_{ortho} = 8, J_{meta} = 2, 1 H, H—C(10)); 6.80 (*s*, 1 H, H—C(12)); 7.25 (*m*, 6 H, aromatic); 8.44 (br. *s*, 1 H, N*H*). – MS.: 91, 149, 188, 263, 341, 432 (M^+). Mol.-Wt.: 432.241.

$C_{27}H_{32}N_2O_3$ (432.241) Calc. C 74.97 H 7.46 N 6.48% Found C 75.21 H 7.51 N 6.52%

11-Methoxy cyclic amine XXX. The lactam XXIX (25 g, 0.51 mol) was dissolved in anhydrous tetrahydrofuran (150 ml, distilled from $LiAlH_4$ and stored over CaH_2) and slowly added with stirring to a solution of $LiAlH_4$ (16 g, 0.420 mol) in anhydrous tetrahydrofuran (450 ml). The reaction was performed under dry conditions and an atmosphere of oxygen-free nitrogen. Refluxing with adequate stirring for 72 h followed. The reaction mixture was cooled to RT. and then in an ice/water-bath. Wet tetrahydrofuran (water/THF 1:3) was added carefully with vigorous stirring to decompose the complex and excess $LiAlH_4$. The white sludge was stirred for 20 min more and it was filtered through a bed of celite. The cake was washed three times with hot tetrahydrofuran. The filtrate was dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a light yellow gum (24.5 g). This gum was chromatographed on a basic alumina column (*Shawnigan*, 400 g). Elution with benzene/ethyl acetate (20–100%) gave the desired product, a pure mixture of the two *dl*-epimers (22 g, 92%). – IR. (neat): no carbonyl absorption. – UV.: 230 (4.18), 263 (3.68), 270 (sh, 3.66), 300 (3.74) nm. – NMR. (100 MHz): 0.70 and 0.84 (2 *t*, J = 7 and 7, 3 H, CH_3CH_2—); 3.74 (*s*, 3 H, CH_3O—); 4.07 (br. *t*, J = 6, 1 H, H—C(3)); 4.35 and 4.47 (2 *s*, 2 H, $C_6H_5CH_2O$—); 6.70 (*q*, J_{ortho} = 8, J_{meta} = 2, 1 H, H—C(10)); 6.75 (*s*, 1 H, H—C(12)); 7.30 (*m*, 6 H, aromatic); 7.96 (br. *s*, 1 H, N*H*). – MS.: 91, 149, 214, 260, 327 and 418 (M^+). Mol.-Wt.: 418.265.

$C_{27}H_{34}N_2O_2$ (418.262) Calc. C 77.47 H 8.19 N 6.69% Found C 77.61 H 8.21 N 6.62%

Debenzylation of the mixture of dl-*epimeric amines XXX.* To the mixture of amines XXX (20 g, 47.8 mmol) dissolved in ethyl alcohol (250 ml) and concentrated hydrochlorid acid (8 ml), 10% Pd/C (2 g) was added. The mixture was stirred and hydrogenated at RT. and 1 atm. pressure for 6.5 h. When no more uptake of hydrogen was noted the reaction was stopped. The catalyst was removed by filtration, through a bed of celite and the cake was washed several times with methanol. The filtrate was concentrated under reduced pressure at RT. and then basified by careful addition of a saturated solution of sodium carbonate. To the resulting basic solution (litmus paper), water (150 ml) was added and extraction with methylene chloride (6 × 100 ml) followed. The combined organic layers were washed with water (2 × 200 ml) and dried over anhydrous sodium sulfate, filtration and removal of the solvent under reduced pressure afforded a yellowish solid (15 g). This material was dissolved in a minimum amount of ethyl acetate. To

the solution was added a few grams of alumina and the ethyl acetate was evaporated off from the slurry. The alumina coated with the same was then transferred to the top of a column filled with alumina (*Shawinigan*, 650 g) in benzene. Gradient elution with ethyl acetate/ethanol 98:2 gave alcohol I (less polar, XXXII) and with ethyl acetate/ethanol 9:1 afforded alcohol II (XXXIII).

11-Methoxy-alcohol I (*XXXII and XXXIIa*): Amorphous solid (3.73 g, 24%). It was crystallized from methylene chloride/*n*-hexane 3:1, washed with cold acetone and recrystallized once more from wet methanol, m.p. 154–155°. – IR. (KBr): absence of strong benzylic bands between 770–689 cm^{-1}. – UV.: 227.5 (4.42), 268 (3.66), 297 (3.73) nm. – NMR. (100 MHz): 0.86 (*t*, 3 H, CH_3CH_2—); 3.45 (*t*, 2 H, —CH_2OH); 3.78 (*s*, 3 H, CH_3O—); 4.10 (*m*, 1 H, H—C(3)); 6.70 (*q*, $J_{meta} = 2$, $J_{ortho} = 9$, 1 H, H—C(10)); 6.78 (*d*, $J_{meta} = 2$, 1 H, H—C(12)); 7.29 (*d*, $J_{ortho} = 9$, 1 H, H—C(9)); 7.72 (br. *s*, 1 H, N*H*). – MS.: 149, 186, 199, 214 and 328 (*M*+). Mol.-Wt.: 328.215.

$C_{20}H_{28}N_2O_2$ (328.215) Calc. C 73.13 H 8.59 N 8.53% Found C 72.89 H 8.69 N 8.60%

11-Methoxy-alcohol II (*XXXIII and XXXIIIa*): Amorphous solid (6.31 g, 40%). Crystallized easier than alcohol I from methylene chloride, m.p. 168–169°. – IR. (KBr): absence of strong benzylic bands between 770–690 cm^{-1} and similar with that of alcohol I. – UV.: 227 (4.50), 269 (3.71), 297 (3.79) nm. – NMR. (100 MHz): 0.72 (*t*, 3 H, CH_3CH_2—); 3.62 (*t*, 2 H, —CH_2OH); 3.77 (*s*, 3 H, CH_3O—); 4.18 (*m*, 1 H, H—C(3)); 6.70 (*q*, $J_{meta} = 2$, $J_{ortho} = 9$, 1 H, H—C(10)); 6.79 (*d*, $J_{meta} = 2$, 1 H, H—C(12)); 7.30 (*d*, $J_{ortho} = 9$, 1 H, H—C(9)); 7.84 (distorted *s*, 1 H, N*H*). – MS.: 199, 214 and 328 (*M*+). Mol.-Wt.: 328.216.

$C_{20}H_{28}N_2O_2$(328.215) Calc. C 73.13 H 8.59 N 8.53% Found C 72.82 H 8.85 N 8.63%

11-Methoxy-mesylates XXXIV. – a) 11-Methoxy-alcohol I (XXXII) (600 mg, 1.82 mmol) was dissolved in a mixture of dry triethylamine (10 ml, distilled over sodium hydroxide) and chloroform (26 ml) and cooled to −10–0° (ice-rock salt bath). Keeping anhydrous conditions, freshly distilled methane sulfonyl chloride (500 mg, 4.37 mmol, distilled over P_2O_5) was added dropwise with efficient stirring. The reaction mixture was allowed to come slowly to RT. and let stand for 44 h. The solvent was removed at RT. and reduced pressure to give a deep red gum. This gum was dissolved in chloroform (20 ml) and extracted with aqueous ammonium hydroxide (4N, 4 × 15 ml) and once with water (15 ml). The combined aqueous layers were washed with a little chloroform (5 ml) and the water was removed under reduced pressure and moderate heating. Any remaining water in the resulting yellow solid was azeotroped several times with dry benzene. The residue was extracted with dry hot chloroform (4 × 10 ml) which dissolved only the mesylate but not the inorganic material. The chloroform solution was filtered and the filtrate was evaporated to dryness under reduced pressure to give the pure mesylate (723 mg, 98%) as a light yellow foam, and it was used for the subsequent steps without further purification. – IR. (neat): 3448 (NH), 1639 (C=C) cm^{-1}. – NMR. (100 MHz): 0.85 (*t*, 3 H, CH_3CH_2—); 3.76 (*s*, 3 H, CH_3O—); 5.05 (*m*, 1 H, H—C(3)); 6.69 (*q*, $J_{meta} = 2$, $J_{ortho} = 8$, 1 H, H—C(10); 7.17 (*d*, $J_{meta} = 2$, 1 H, H—C(12); 7.18 (*d*, $J_{ortho} = 8$, 1 H, H—C(9)).

b) 11-Methoxy-alcohol II (XXXIII) was mesylated exactly as is described above to give the pure mesylate (XXXIV) in quantitative yield. Again this material was used for the next step without further purification. – IR. (neat): 3448 (NH), 1645 (C=C) cm^{-1}. – NMR. (100 MHz): 0.76 (*t*, 3 H, CH_3CH_2—); 3.72 (*s*, 3 H, CH_3O—); 4.92 (*m*, 1 H, H—C(3)); 6.64 (*q*, $J_{meta} = 2$, $J_{ortho} = 8$, 1 H, H—C(10)); 6.97 (*d*, $J_{meta} = 2$, 1 H, H—C(12)); 7.22 (*d*, $J_{ortho} = 8$, 1 H, H—C(9)); 9.16 (*s*, 1 H, N*H*).

16-Methoxy-cyanides XXXV and XXXVI. – a) To a solution of mesylate from alcohol I (450 mg) in dry dimethylformamide (25 ml) pulverized potassium cyanide (330 mg) was added. The reaction was performed in dry nitrogen atmosphere. The reaction mixture was heated at 155° (bath temperature) and stirred for 6 h. The dark reaction mixture was cooled to RT. and 6N aqueous ammonium hydroxide (40 ml) was added to it under stirring. The resulting basic solution was extracted with benzene (5 × 25 ml). The combined benzene extracts were washed with brine (2 × 15 ml). The organic layer was dried over anhydrous sodium sulfate, filtration and removal of the solvent under reduced pressure at RT. gave 190 mg of a brown gum. Chromatography of the crude product on alumina (neutral, *Woelm*, activity III), using benzene as eluent gave 120 mg of a mixture of the epimeric cyanides.

b) To a solution of the mesylate from alcohol II (1.265 g, 3.11 mmol) in dry hexamethylphosphoramide (40 ml), pulverized potassium cyanide (1.170 g, 18 mmol) was added. The resulting mixture was heated at 175° (bath temperature) and stirred for 7.5 h under an atmosphere of oxygen-free nitrogen. The dark reaction mixture was cooled to RT. and aqueous ammonium hydroxide (80 ml, 5N) was added to it with stirring. The resulting basic solution was extracted with ethyl ether (6 × 40 ml). The combined ethereal extracts were washed with water (3 × 15 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure at RT. to afford 600 mg of a yellowish foam.

c) The mesylate from alcohol I (2.276 g, 5.60 mmol) was treated exactly as indicated above to afford 1.000 g of a yellowish foam and checking the reaction products (TLC., IR., NMR. information) it was shown that both mesylates gave the same mixture of epimeric cyanides.

The crude reaction products (600 mg) were chromatographed on an alumina column (40 g, *Woelm*, neutral, activity III). Elution with petroleum ether/benzene 3:2 gave cyanide I (XXXV) and further elution with the same solvent system (1:1) afforded cyanide II (XXXVI).

16-Methoxy-cyanide I (*XXXV and XXXVa*): Amorphous solid (199 mg, 19%). Recrystallized from *n*-hexane/acetone and methylene chloride, m.p. 186–187°. – IR. (KBr): 3346 *s* (NH) and 2252 *m* (—CN) cm^{-1}. – UV.: 227 (4.48), 275 (3.69), 300 (3.81) nm. – NMR. (100 MHz): 0.93 (*t*, J = 7, 3 H, CH_3CH_2—); 3.79 (*s*, 3 H, CH_3O—); 3.88 (*q*, J_{AB} = 4, J_{AC} = 2, 1 H, H—C(3)); 6.73 (*q*, J_{ortho} = 8, J_{meta} = 2, 1 H, H—C(15)); 6.80 (*s*, 1 H, H—C(17)); 7.31 (*d*, J_{ortho} = 8, 1 H, H—C(14)); 8.20 (br. *m*, 1 H, N*H*). – MS.: 124, 126, 177, 212 and 337 (M^+). Mol.-Wt.: 337.218.

$C_{21}H_{27}N_3O$ (337.215) Calc. C 74.74 H 8.07 N 12.45% Found C 74.61 H 8.52 N 12.39%

16-Methoxy-cyanide II (*XXXVI and XXXVIa*): Amorphous solid (320 mg, 30%). Recrystallized from methanol and *n*-hexane, m.p. 191–192°. – IR. (KBr): 3356 *s* (NH), 2232 *m* (—CN) cm^{-1}. – UV.: 226 (4.45), 277 (3.37), 298 (3.83) nm. – NMR. (100 MHz): 0.66 (*t*, J = 7, 3 H, CH_3CH_2—); 3.82 (*s*, 3 H, CH_3O—); 5.97 (*q*, J_{AB} = 10, J_{AC} = 3, 1 H, H—C(3)); 6.77 (*q*, J_{meta} = 2, J_{ortho} = 8, 1 H, H—C(15)); 6.85 (*d*, J_{meta} = 2, 1 H, H—C(17)); 7.36 (*d*, J_{ortho} = 8, 1 H, H—C(14)); 8.06 (br. *s*, 1 H, N*H*). – MS.: 124, 126, 177, 212, 337 (M^+). Mol.-Wt.: 337.216.

$C_{21}H_{27}N_3O$ (337.215) Calc. C 74.74 H 8.07 N 12.45% Found C 74.57 H 8.31 N 12.41%

High Pressure Liquid Chromatography of the Epimeric Cyanides XXXV and XXXVI. Instrument: *Waters'* ALC-202; solvent: petroleum ether (30–60°)/chloroform 1:1; flow rate: 0.6 ml/min column: alumina neutral *Woelm* 6 ft. × 2 mm O.D.; sample load: 10 mg, total; retention time: cyanide I (20 min), cyanide II (29 min).

Epimerization of the Isomeric Cyanides. To a cooled solution (ice-water bath) of the isomeric cyanides (120 mg, 0.356 mmol) in anhydrous methanol, acetyl chloride (0.2 ml) was added under stirring. After 10 min, distilled water (0.1 ml) was added and the reaction mixture was allowed to come slowly to RT. Stirring was continued for 94 h. The solvent was then removed under reduced pressure without heating. The residue was taken up in ether (10 ml) and neutralized with saturated sodium hydrogencarbonate solution, and extracted with ether (3 × 10 ml). The combined organic extracts were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 175 mg of a yellowish solid. Purification of the crude reaction mixture either by column chromatography on alumina neutral *Woelm* (10 g, activity III) using petroleum ether/benzene 1:1 as eluent or high pressure liquid chromatography (*Waters'* ALC 100, petroleum ether/chloroform 3:1, 9 ml/min, alumina neutral *Woelm*, 4 ft × 3/8″ O.D.), afforded 62 mg of cyanide I (XXXV) (15 min) and 12 mg of cyanide II (XXXVI) (35 min).

16-Methoxy-dl-*vincadine* (XXXVII, R = H) *and its Epimer* (XXXVIII, R = H). – a) To a cooled solution of the epimeric cyanides (18 mg) in anhydrous methanol (10 ml), acetyl chloride (7 ml) was added. The reaction mixture was allowed to come slowly to RT. and let stand for 48 h, when distilled water (0.1 ml) was added. After an additional 24 h, the solvent was removed under reduced pressure without heating. The residue was taken up in ether, neutralized with saturated sodium hydrogencarbonate solution, and extracted with ether (3 × 15 ml). The combined organic extracts were dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave 16 mg of a gum. Purification of this crude reaction product by high pressure liquid chromatography (*Waters'* ALC-100, petroleum ether/chloroform 3:1, 9 ml/min, alumina neutral *Woelm* 4 ft. × 3/8″ O.D., 16-methoxy-*dl*-vincadine, 5 min; 16-methoxy-*dl*-epivincadine, 8 min) gave (6 mg) of the desired carbomethoxy derivative in 20% yield.

b) To a solution of 16-methoxy-cyanide II (XXXVI) (280 mg, 0.83 mmol) in anhydrous methanol (20 ml), water (0.2 ml) was added. The solution was cooled (ice/water bath) and saturated with anhydrous hydrogen chloride (20 min). The reaction mixture was then allowed to come slowly to RT. and left standing for 96 h. The solvent was removed under reduced pressure without heating and the residue was taken up in a small volume of dichloromethane and neutralized by the addition of a saturated solution of sodium hydrogencarbonate. The resulting solution was then extracted with methylene chloride (3 × 10 ml). The combined organic layers were dried over sodium sulfate. Filtration and removal of the solvent gave 222 mg of a brown gum.

The above reaction was repeated with a mixture of both cyanides and an identical mixture of diastereoisomeric carbomethoxy derivatives was obtained.

Separation was obtained by preparative layer chromatography on silica gel *Woelm*, developed with a mixture of benzene/ethyl acetate 4:1.

16-Methoxy-dl-*epivincadine* (XXXVIII, R = H): amorphous solid (9%), resisted crystallization, leading to decomposition products. – IR. ($CHCl_3$): 3370 (small, N*H*), 1725 *s* (CO_2CH_3) cm^{-1}. – UV.: 228 (4.43), 278 (3.65), 300 (3.76) nm. – NMR. (100 MHz): 0.64 (*t*, J = 7, 3 H, CH_3CH_2—); 3.62 (*s*, 3 H, CO_2CH_3); 3.77 (*s*, 3 H, CH_3O—); 5.51 (*q*, J_{AB} = 11, J_{AC} = 2, 1 H, H—C(3)); 6.70 (*q*, J_{ortho} = 8, J_{meta} = 2.5, 1 H, H—C(15)); 6.80 (*d*, J_{meta} = 2.5, 1 H, H—C(17)); 7.30 (*d*, 1 H, J_{ortho} = 8, H—C(14)); 8.51 (*s*, 1 H, NH). – MS.: 124, 126, 210, 245, and 370 (M^+). Mol.-Wt.: 370.224 (Calc. for $C_{22}H_{30}N_2O_3$: 370.225).

16-Methoxy dl-*vincadine* (XXXVII, R = H): Amorphous solid (25%) resisted crystallization, leading to decomposition products. It was more polar on silica gel chromatographic plates developed with benzene/ethyl acetate 4:1. – IR. ($CHCl_3$): 3370 *ms* (NH), 1730 *s* (CO_2CH_3) cm^{-1}. – UV.: 228 (4.43), 278 (3.65), 301 (3.76) nm. – NMR. (100 MHz): 0.82 (*t*, 3 H, CH_3CH_2—); 3.65 (*m*, 1 H, H—C(3)); 3.69 (*s*, 3 H, CO_2CH_3); 3.78 (*s*, 3 H, CH_3O—); 6.70 (*q*, J_{ortho} = 8, J_{meta} = 2, 1 H, H—C(15)); 6.79 (*d*, J_{meta} = 2, 1 H, H—C(17)); 7.30 (*d*, J_{ortho} = 8 Hz, 1 H, H—C(14)); 8.84 (br. *s*, N*H*). – MS.: 124, 138, 210, 245 and 370 (M^+). Mol.-Wt.: 370.225 (Calc. for $C_{22}H_{30}N_2O_3$: 370.225).

N_a-Methylation of 16-Methoxy-dl-*vincadine and its Epimer.* Sodium amide (0.25 mmol) was prepared from redistilled liquid ammonia (4–5 ml) and freshly cut sodium metal (5.85 mg, 0.25 mmol). A trace of ferric nitrate was added as a catalyst to the solution of sodium amide in liquid ammonia, kept under highly purified nitrogen and efficient stirring. A solution of epimeric esters (58 mg, 0.15 mmol) in dry tetrahydrofuran (1 ml) was added with a syringe. The dark solution was kept in a dry-ice/acetone bath and stirring continued for 3 min more. Methyl iodide (16 µl, 0.25 mmol) in a few drops of tetrahydrofuran was added with a syringe. The reaction mixture was kept cold and stirred for 25 min more and then the ammonia allowed to evaporate slowly under a stream of nitrogen. The removal of ammonia was enhanced by blowing a stream of warm air around the reaction vessel. The dark residue was taken into a mixture of aqueous ammonium chloride/ethyl ether 1:1 (10 ml) and extracted several times with ethyl ether. The combined organic layers, after washing with water were dried over anhydrous sodium sulfate. Filtration of the inorganic agent and removal of the solvent under reduced pressure at RT. gave 55 mg of a yellow gum. Preparative layer chromatography on silica gel chromatoplates developed with benzene/ethyl acetate 4:1 gave the two N-methylated epimers (62%).

dl-*Vincaminoridine* (XXXVIII, R = CH_3): As an amorphous solid (9 mg). – IR. ($CHCl_3$): No NH absorption and 1735 *s* (CO_2CH_3) cm^{-1}. – UV.: 232 (4.47), 288 (3.78), 299 (3.82) nm. – NMR. (100 MHz): 0.67 (*t*, J = 6, 3 H, CH_3CH_2—); 3.54 (*s*, 3 H, CH_3N); 3.62 (*s*, 3 H, CO_2CH_3); 3.84 (*s*, 3 H, CH_3O—); 6.10 (*q*, J_{AB} = 10, J_{AC} = 2, 1 H, H—C(3)); 6.75 (*q*, J_{ortho} = 8, J_{meta} = 2, 1 H, H—C(17)); 7.35 (*d*, J_{ortho} = 9, 1 H, H—C(14)). – MS.: 124, 210, 259 and 384 (M^+). Mol.-Wt.: 384.240 (Calc. for $C_{23}H_{32}N_2O_3$: 384.241).

dl-*Epivincaminoridine* (XXXVII, R = CH_3): Amorphous solid (32 g). This was the more polar epimer on silica gel chromatoplates developed with benzene/ethyl acetate 4:1. – IR. ($CHCl_3$): No NH absorption and 1725 *s* (CO_2CH_3) cm^{-1}. – UV.: 232 (4.53), 288 (3.78), and 300 (3.81) nm. – NMR. (100 MHz): 0.92 (*t*, J = 7, 3 H, CH_3CH_2—); 3.44 (*s*, 3 H, CH_3N); 3.66 (*s*, 3 H, CO_2CH_3); 6.69 (*d*, J_{meta} = 2, 1 H, H—C(17)); 6.70 (*q*, J_{ortho} = 9, J_{meta} = 2, 1 H, H—C(15)); 7.34 (*d*, J_{ortho} = 9, 1 H, H—C(14)). – MS.: 124, 210, 259 and 384 (M^+). Mol.-Wt.: 384.239 (Calc. for $C_{23}H_{32}N_2O_3$: 384.241).

Epimerization of dl-*Epivincaminoridine to* dl-*Vincaminoridine.* To a stirred freshly prepared solution of sodium methoxide in absolute methanol *dl*-epivincaminoridine (23 mg) was added. The solution of sodium methoxide was made by addition of 14 mg of freshly cut sodium in abs. methanol (12 ml) under a dry nitrogen atmosphere and efficient stirring. After the addition of *dl*-epivincaminoridine the reaction mixture was refluxed under dry nitrogen for 48 h. The cooled solution was concentrated under reduced pressure and the residue taken up in chloroform. Filtration and removal of the solvent gave 32 mg of a yellowish gum. Preparative layer chromatography on silica gel chromatoplates developed with benzene/ethyl acetate 4:1 gave 7.3 mg of *dl*-vincaminoridine and 11.5 mg of *dl*-epivincaminoridine.

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