Total Synthesis of Indole and Dihydroindole Alkaloids. V.[1,2] The Total Synthesis of *dl*-Quebrachamine and *dl*-Aspidospermidine. A General Entry into the Aspidosperma Alkaloids

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Abstract: The total synthesis of *dl*-quebrachamine and *dl*-aspidospermidine is described. The synthetic sequence parallels the pathway employed for the total synthesis of the dihydrocleavamine skeleton in which the nine-membered ring system is generated in the final step *via* a reductive cleavage reaction.

The previous publication in this series[2] has described in detail a total synthesis of the *dl*-dihydrocleavamines and the carbomethoxy derivative *via* a sequence which, in its initial stages, involves the condensation of tryptamine with an appropriately substituted succinic ester. We would now like to present a laboratory synthesis of the Aspidosperma alkaloid, *dl*-quebrachamine (XXII) employing a fundamentally similar pathway.

Quebrachamine (XXII) is structurally isomeric with dihydrocleavamine and possesses an ethyl group at C_5 rather than at C_7 (Aspidosperma alkaloid numbering). Clearly, a synthesis of the suitably modified succinic ester (VIII), followed by an analogous sequence of reactions to those already discussed previously,[2] should complete the total synthesis of this alkaloid.

The synthetic scheme which provides the desired ester (VIII) is outlined in Figure 1. As before,[2] no discussion of stereochemistry at the individual steps of the sequence will be given presently, but is deferred to the latter portion of this publication.

γ-Benzyloxypropanol (I) was prepared[3] in 65% yield by condensing the monosodium salt of propane-1,3-diol with benzyl chloride. The treatment of this compound with thionyl chloride gave 1-chloro-3-benzyloxypropane[4] in 80% yield, and this compound on alkylation with diethyl ethylmalonate yielded diethyl γ-benzyloxypropylethylmalonate (III) in 47% yield. The most characteristic features of the nmr spectrum of III are, a five-proton singlet at τ 2.75 due to the aromatic protons, a two-proton singlet at τ 5.56 due to the benzyl methylene, and a two-proton triplet at τ 6.58 arising from the propyl methylene adjacent to the ether oxygen atom. These resonances are due to the benzyloxypropyl group, and their presence in the spectra of subsequent compounds quickly revealed whether this protecting group was still intact.

Hydrolysis of the substituted malonic ester (III) with potassium hydroxide gave the crystalline γ-benzyloxypropylethylmalonic acid (IV) which exhibited in the nmr spectrum a new sharp singlet at τ −1.50 assignable to the two carboxylic acid protons. In addition, the monoester derivative (V) was clearly present in the mother liquors from the crystallization of IV.

γ-Benzyloxypropylethylmalonic acid was smoothly decarboxylated at 160° to provide 2-(γ-benzyloxypropyl)butanoic acid (VI), which without further purification, was converted to the ester VII. The latter, on alkylation with α-bromoethyl acetate in the presence of triphenylmethylsodium provided the desired succinate derivative (VIII) in 40% yield. The purity of this compound was most conveniently assessed by vapor phase chromatography, the succinate (VIII) having a longer retention time (3 times that of the monoester, VII). The nmr spectrum of VIII showed a new sharp two-proton singlet at τ 7.40 due to the methylene protons (CCH_2COOEt). The two ester groups were not magnetically equivalent giving rise to two quartets and two triplets at τ 5.92 and 8.82, respectively.

Attempts to prepare VIII using the methylsulfinyl carbanion[5] as the base resulted in the total recovery of the starting material (VII).

Having the required succinate derivative at hand, we next considered its condensation with tryptamine. Indeed, we were able to obtain the imide (IX) by refluxing a mixture of tryptamine and the succinate ester (VIII) in diethylene glycol monoethyl ether. The imide exhibited characteristic[6] infrared bands at 1760 (weak) and 1690 (strong) cm^{-1} and its mass spectrum (Figure 2) demonstrated the facile fragmentation of the molecule into the characteristic indole and succinimide fragments. In addition to the normal signals for the benzyloxypropyl group, the nmr spectrum showed a one-proton doublet at τ 3.60 due to the α proton on the indole nucleus,[7] two triplets at τ 6.18 and 7.00 arising from the ethylene bridge, and a two-proton singlet at τ 7.60 due to the methylene of the succinimide moiety.

The next step in the sequence involved the cyclization of the succinimide ring onto the α position of the indole nucleus. For this purpose, the Bischler–Napieralski reaction was first considered. Following the experimental conditions described by Morrison,[8] the cycliza-

(1) For a preliminary report on a portion of this work, see J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Amer. Chem. Soc.*, 88, 3656 (1966).
(2) Part IV. J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, 92, 1712 (1970).
(3) L. Smith and J. Spring, *ibid.*, 65, 1271 (1943).
(4) G. Bennett and A. L. Hock, *J. Chem. Soc.*, 128, 472 (1927).
(5) E. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 87, 1345 (1965).
(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.
(7) L. Cohen, J. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, 82, 2184 (1960). See also ref 25 and 26 in paper IV (ref 2).

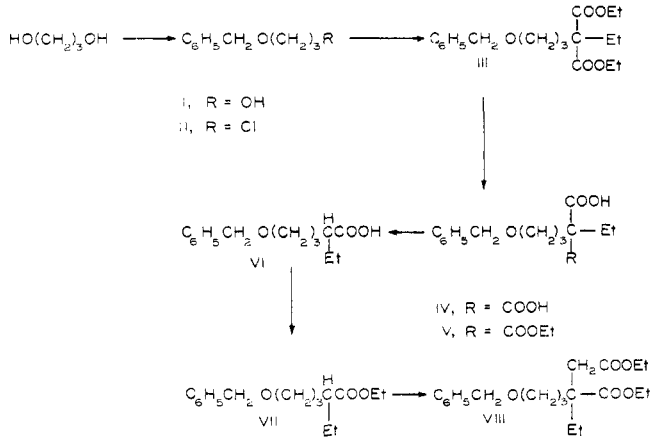


Figure 1. Synthesis of succinic ester derivative, VIII.

In a concurrent investigation, the γ-chloropropyl analog of the imide (XI), which would not be expected to undergo elimination under Bischler–Napieralski conditions, was employed. The chloro compound was cyclized under the same conditions to provide the desired intermediate (XII) in 18% yield. This compound was smoothly reduced with platinum oxide in acetic acid to the chlorolactam (XIII). However, reduction of this lactam with lithium aluminum hydride was accompanied by the hydrogenolysis of the chlorine group. Since this reaction product (XIV) no longer possessed any functionality in the propyl side chain, it too was impractical for our synthesis.

With these experimental facts in hand, we considered the cyclization of the imide (IX) using milder conditions (shorter reaction time and lower temperature). The

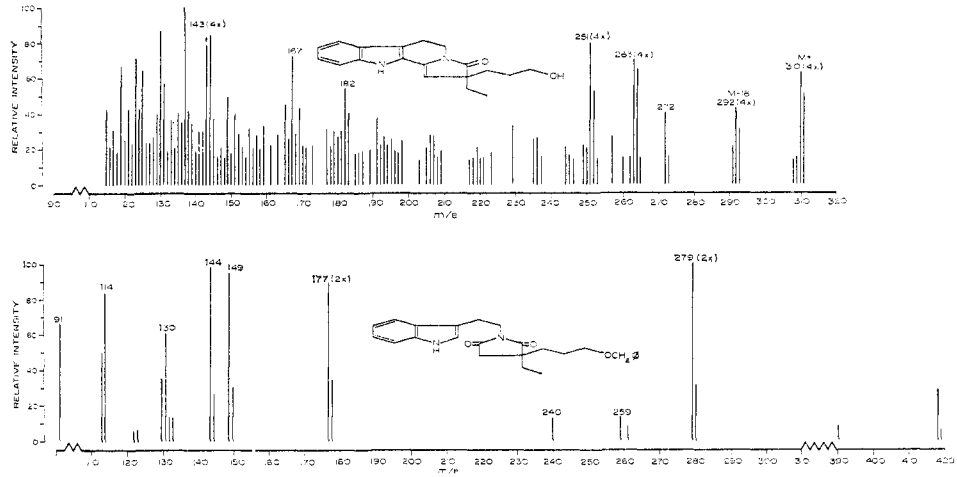
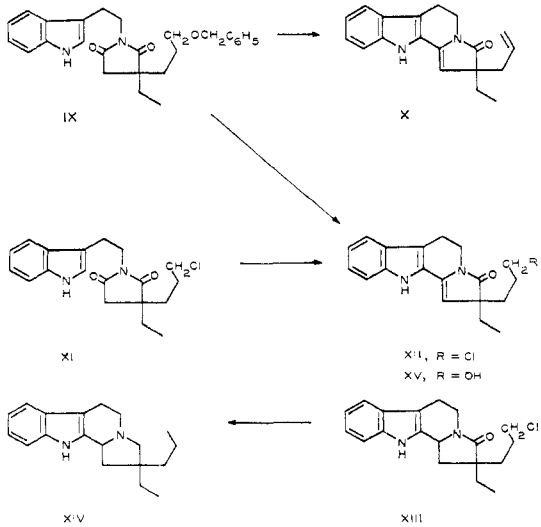


Figure 2. Mass spectra of succinimide derivative (IX) and unsaturated lactam (XV).

tion of the imide (IX) to provide the expected unsaturated lactam was accompanied by the loss of the benzyloxy group to give a terminal double bond. This



product (X), which was obtained in poor yield (5%), would require subsequent hydration of this double bond to regenerate the desired side chain, and for this reason, this approach was abandoned.

(8) G. Morrison, W. Cetenka, and J. Shavel, Jr., *J. Org. Chem.*, **29**, 2771 (1964).

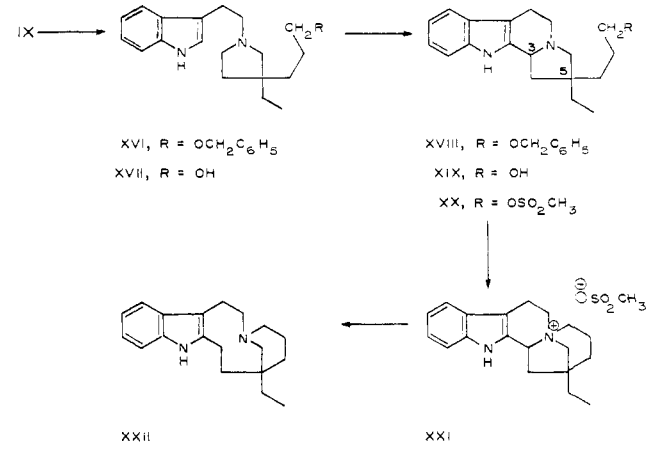


Figure 3. Outline of synthetic sequence leading to *dl*-quebrachamine.

resultant amorphous yellow solid (10% yield) exhibited an ultraviolet spectrum which was in perfect agreement with that reported[8] for an analogous compound. The mass spectrum (Figure 2) had a molecular ion peak (*m/e* 310) which corresponds to the molecular formula, $C_{19}H_{22}N_2O_2$, and a strong peak at M − 18 corresponding to the loss of water. These spectral properties are in agreement with the structure (XV) which now possesses the suitably functionalized propyl side chain. Addi-

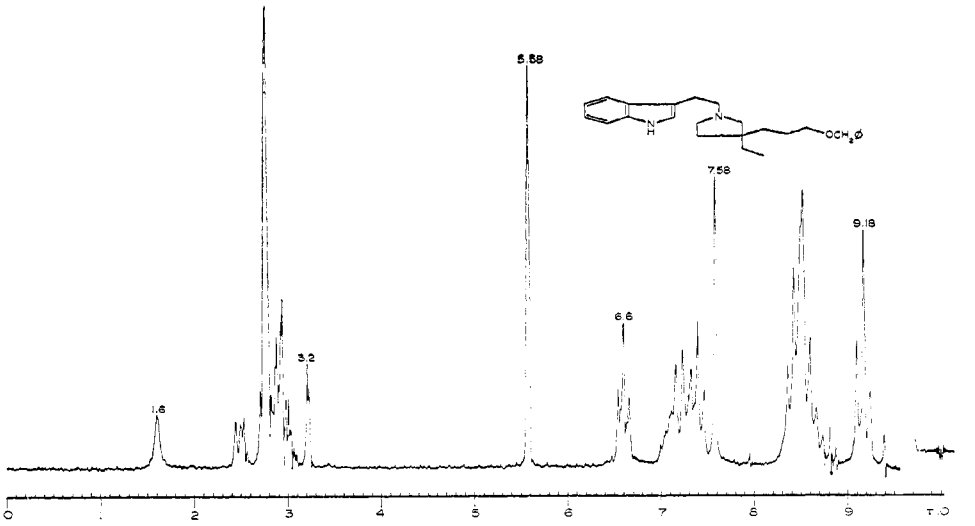


Figure 4. Nmr spectrum of benzyl ether (XVI).

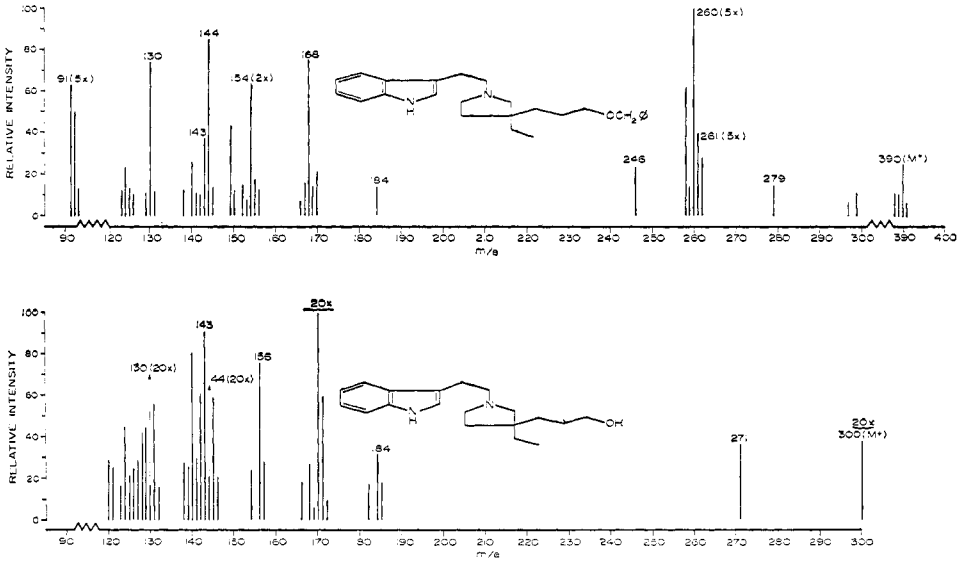
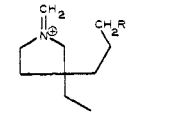


Figure 5. Mass spectra of benzyl ether (XVI) and amino alcohol (XVII).

tional data in support of this structure were difficult to obtain due to its susceptibility to air oxidation. For this reason, the crude cyclization product was hydrogenated using platinum oxide in acetic acid. The ultraviolet spectrum of this crude hydrogenation product, being that of a typical indole, indicated that the double bond of the lactam ring had been saturated. A complete separation of the products of hydrogenation was, however, unsuccessful and the low yields of these reactions caused us to consider an alternate route to the formation of the indolopyrrocoline system (Figure 3).

The imide (IX) was reduced with lithium aluminum hydride under mild conditions to provide a product which on the basis of its spectral data, particularly nmr (Figure 4) and mass spectrometry, could be readily assigned the structure XVI. In particular, the mass spectrum (Figure 5) revealed the expected fragmentation to provide the base peak at *m/e* 260 due to the stable ion (XXIII). The peaks at *m/e* 144, 143, and 130 are due to the typical fragments found in the mass spectra of indole alkaloids of the tetrahydrocarboline type[9] and discussed previously.[2] The peak at *m/e* 91 originates from the benzyl group.



XXIII, R = $OCH_2C_6H_5$

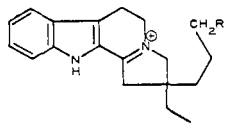
XXIV, R = OH

During the reduction of the imide, it was noted that treatment with lithium aluminum hydride under vigorous conditions led to hydrogenolysis of the benzyl group and the product was the amino alcohol XVII (see Figure 5).

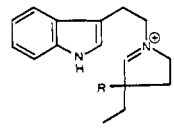
The benzyl ether amine (XVI) was now oxidized with excess mercuric acetate in a similar manner to that described previously.[2] The course of the cyclization was again followed spectroscopically by observing the characteristic absorption (λ_{max} 352 mμ) for the new chromophore in XXV. Subsequent sodium boro-

(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964.

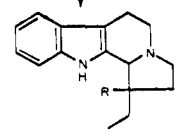
hydride reduction of the latter provided the tetracyclic amine (XVIII).



XXV, R = $OCH_2C_6H_5$



XXVI, R = $(CH_2)_3OCH_2C_6H_5$



XXVII, R = $(CH_2)_3OCH_2C_6H_5$

XXXI, R = $(CH_2)_3OH$

Although there are three directions in which the oxidation can occur, only the two endocyclic iminium ions would lead to cyclized products. One would expect the cyclization of the iminium salt (XXVI) to occur to a lesser extent, since it would give rise to the sterically less favored structure (XXVII).

A great deal of difficulty was encountered in the attempted separation of the crude mixture of stereoisomeric components resulting from the cyclization reaction. In fact, we were not successful in achieving complete resolution of this mixture, and the spectral data quoted were obtained on a mixture of components. The ultraviolet spectrum exhibited a normal indole absorption, while the nmr spectrum showed that the benzyloxy group was still present and that the doublet at τ 3.20 due to the α proton on the indole ring was absent. This latter result indicated that the mixture did not contain any uncyclized material. The mass spectrum indicated the highest peak at *m/e* 388, which would be the expected mass for the desired cyclic system as shown in XVIII. The most diagnostic peaks in the mass spectrum were found at *m/e* 184, 170, 169, and 156. These four peaks, as already mentioned previously, are characteristic of a tetrahydro-β-carboline system,[2,9] and could, thus, only arise from compounds having a cyclic structure.

Although the above experimental problem was not completely overcome, we felt that it would not be necessary to separate the expected cyclic products, since (a) the asymmetric center at C_3 (see XVIII) would be destroyed in the final ring opening reaction to give quebrachamine and (b) the asymmetric center at C_5 merely determines which optical isomer of quebrachamine is formed, as quebrachamine possesses only one asymmetric center.

Indeed, the above spectral data provide no more than strong suggestive evidence for the presence of several cyclic products, but conclusive results came forth from our subsequent debenzylation experiments where we were able to isolate four isomeric alcohols (see later).

In our initial investigations, the benzyl group was removed by brief treatment with boron tribromide[10] to provide a solid amorphous mixture of cyclized amino alcohols. It was on this mixture that we first investigated the later steps of the sequence as indicated below.

When the above mixture was treated with methanesulfonyl chloride in pyridine or triethylamine at 0°, the initially formed mesylate ester (XX) proceeded to quaternize spontaneously to provide a water soluble salt as an amorphous powder.

The ultimate step of the synthesis involved the reductive ring cleavage of the above mentioned quaternary salt. Reaction of the latter with sodium and liquid ammonia[2] or lithium aluminum hydride in N-methyl morpholine (see later) provided the desired *dl*-quebrachamine (XXII) which was identical in all respects with the natural material.

The formation of quebrachamine verifies, in retrospect, that at least one of the isomeric benzyl ether amines has the desired structure (XVIII), and also that the amino alcohol and the quaternary salt arising from XVIII must possess the structures XIX and XXI, respectively.

Although the synthesis of *dl*-quebrachamine was formally completed, it was clearly desirable to obtain some further information on the later steps of the sequence. For this purpose, we first reinvestigated the debenzylation experiments in the hope that a separation of the cyclized components could be achieved at the alcohol stage.

Another debenzylation technique was considered since it might possibly lead to a less complex mixture of products. Catalytic hydrogenolysis using palladium on charcoal in glacial acetic acid[11,12] was attempted, and indeed, gave purer products. By careful column chromatography, we were able to separate four alcohols, referred to as A, B, C, and D in order of increasing polarity. Two of these compounds (alcohols A and C) were obtained as gums, while alcohols B and D were crystalline. The yields of these alcohols were 10, 11, 17, and 14%, respectively (total 52%).

These four compounds all showed identical indole ultraviolet absorption spectra, while the mass spectra (Figure 6) all contained a molecular ion peak at *m/e* 298 and peaks at 297, 184, 170, 169, and 156. These latter four fragments have been observed in the mass spectra of the benzyl ether amines and their significance has already been discussed. High-resolution mass spectrometry established that these amino alcohols each possessed the molecular formula, $C_{19}H_{26}N_2O$.

The nmr spectra indicated that the benzyl group had been removed and also that these compounds *all* lacked the absorption due to the α proton on the indole nucleus. Interesting differences in several pertinent regions of the nmr spectra were noted for these isomers and it is appropriate to first discuss some of these results for the two crystalline amino alcohols (B and D), since they possess the correct cyclic system (see later). In particular, the regions involving the C_3 proton and the ethyl group provide information about the relative stereochemistry of these alcohols. It was observed that both B and D possess triplets for C_3H (τ 5.86 and 5.78, respectively) as well as the expected methyl triplets at high field (τ 9.15 and 9.30). The chemical shift of the C_3 proton in related indole alka-

(10) R. D. Yossefyeh and Y. Mazur, *Chem. Ind.* (London), 690 (1963).

(11) H. Meerwein, Houben-Weyl, "Methoden der Organischen Chemie," Vol. 6, 1965, p 169.

(12) R. Adams, *Org. Reactions*, 7, 269 (1953).

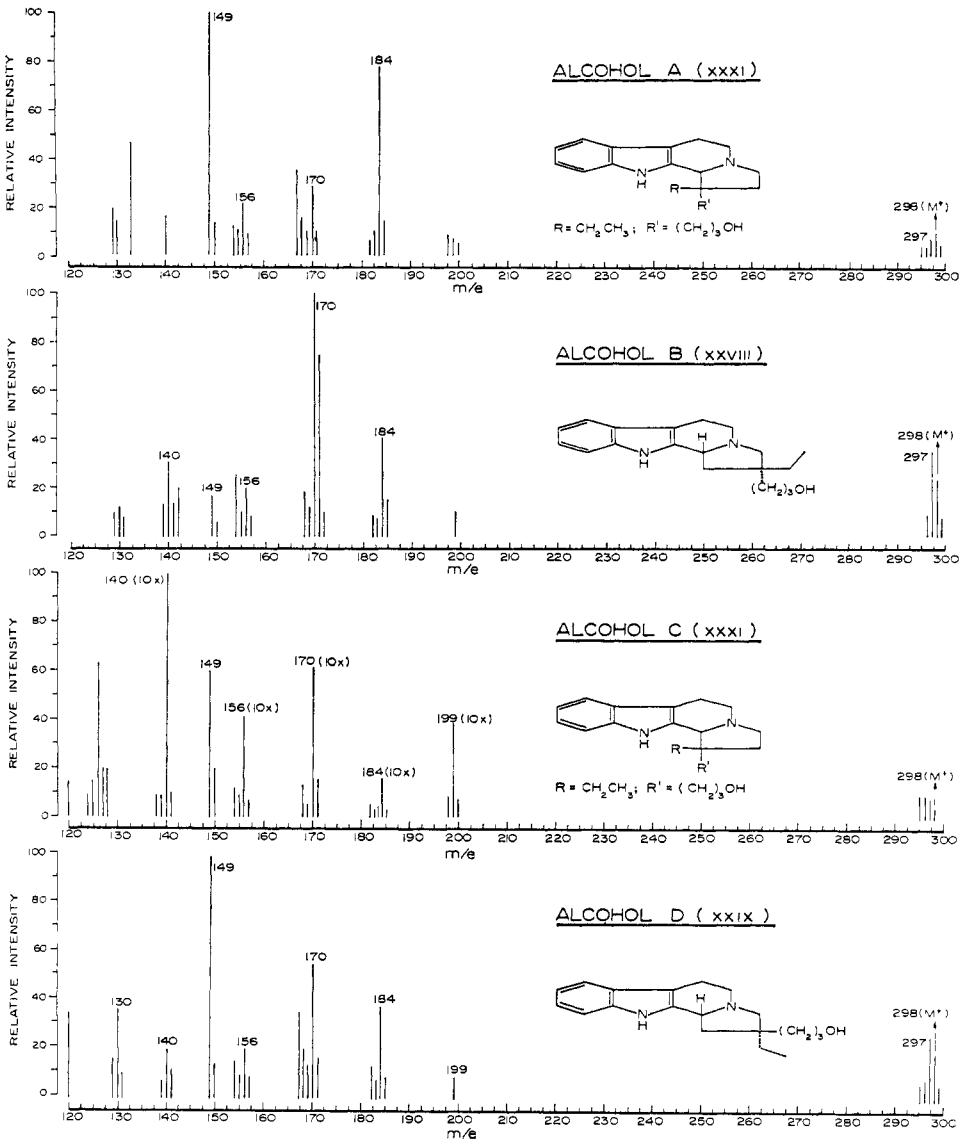
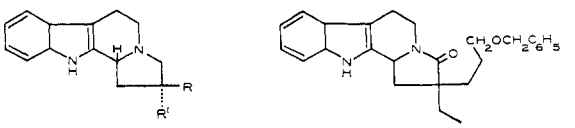


Figure 6. Mass spectra of the isomeric amino alcohols.

loids has been studied in several laboratories[13–16] and it has been shown that this signal generally appears below τ 6.0 when this proton is oriented *cis* to the lone pair of electrons on the nitrogen atom, whereas a higher field signal is observed if a *trans* relationship prevails. On this basis, it is clear that both amino alcohols B and D possess the C_3 proton in a *cis* relationship to the electrons on the basic nitrogen atom. This relationship is further confirmed by ir spectroscopy since neither of these compounds exhibit the well-known Bohlmann bands[17–19] which appear when hydrogen atoms on a carbon atom adjacent to a nitrogen are *trans* to the unshared electrons of this heteroatom. It was, therefore, clear that the only difference which exists between these two alcohols relates to the relative orientation of the side chains with respect to C_3H. Here again, nmr spectroscopy was useful, since alcohol B possesses the methyl triplet of the ethyl group at τ 9.15, while D shows this signal at τ 9.30. Other workers have commented on the relative effect of N electrons on alkyl groups which are situated in a 1,3 relationship to this heteroatom and have found differences in the degree of resolution and chemical shifts.[16,20] On this basis, we were able to assign the structures, including stereochemistry, to alcohols B and D as shown in XXVIII and XXIX, respectively.

The correctness of the above structures for these alcohols was established in two independent investiga-



XXVIII, R = CH_2CH_3; R' = $(CH_2)_3OH$
XXIX, R = $(CH_2)_3OH$; R' = CH_2CH_3

XXX

(13) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961).
(14) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961).
(15) E. Wenkert and B. Wickberg, *ibid.*, **87**, 1580 (1965).
(16) W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, **23**, 365 (1967).
(17) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(18) E. Wenkert and D. Roy Chaudhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956).
(19) W. E. Rosen, *Tetrahedron Lett.*, 481 (1961).
(20) T. M. Moynehen, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

tions. In one series of experiments, each of the pure alcohols was treated with methanesulfonyl chloride in triethylamine to provide essentially quantitative yields of the corresponding quaternary mesylates (gross structure, XXI). Each of these quaternary salts was then cleaved reductively, as before, and in both instances, *identical* crystalline products were obtained. Comparison with an authentic sample of quebrachamine (XXII) established the identity of the synthetic material. The overall yield of the latter product from both reactions was 18%.

A subsequent reinvestigation of the reductive cleavage of the mesylates, *i.e.*, XXI → XXII, utilizing lithium aluminum hydride in refluxing N-methyl morpholine, provided *dl*-quebrachamine in a markedly improved yield (overall 51% from the alcohols B and D).

A separate study was undertaken in the hope of improving the above synthetic pathway. In particular, it would be highly desirable to eliminate the troublesome mercuric acetate oxidative cyclization to the amino alcohols A–D. Indeed, such a sequence has been recently reported[21] and provides a vastly improved synthesis of *dl*-quebrachamine. Its relevance to the present discussion lies in the fact that it provides an independent structure proof for alcohols B and D. It will be noted from this sequence that the synthesis of the tetracyclic lactam (XXX) is unambiguous. Subsequent reduction of the latter and removal of the benzyl ether function provided two products which were identical in all respects with alcohols B and D.

As already mentioned above, the two remaining amino alcohols (designated A and C) isolated along with B and D revealed spectral data which established their isomeric nature. It was clear that these compounds possess the gross structure XXXI, but the nmr data were not sufficiently instructive to allow any definite stereochemical assignments. The C_3 proton signal appeared at τ 5.90 in A, while in C it overlapped with the protons of the primary alcohol function (near τ 6.2). On the other hand, both triplets due to the methyl protons of the ethyl side chain resonated at nearly identical positions (τ 9.12 in A; 9.16 in C). Whether the upfield shift of the C_3 proton signal in C is due to a *trans* orientation of this proton with the electrons on the nitrogen atom or else due to some effect created by the side chain is difficult to ascertain.

The completion of the quebrachamine synthesis *via* a pathway which parallels that of the dihydrocleavamine scheme[2] establishes the generality of this approach for the synthesis of nine-membered ring intermediates. Its potential in the total synthesis of a whole series of Vinca alkaloids is now apparent[21] and will be the subject of future publications.

Experimental Section[22]

γ-Benzyloxypropanol (I). Sodium (50 g, 2.18 g-atom) was added in small portions to a hot (115–120°), vigorously stirred solution of trimethylene glycol (500 g, 6.6 mol) in dry xylene (200 ml). After all the sodium had dissolved, benzyl chloride (300 g, 2.38 mol) was slowly added with stirring to the hot (120°) solution over a period of 2 hr. The reaction mixture was heated for an additional 1 hr and then cooled to room temperature. The precipitated sodium chloride was removed by filtration and washed with benzene. The combined filtrate and washings were concentrated under reduced pressure to provide a clear liquid (600 g), which was fractionated through a 1-ft Vigreux column. After a forerun of trimethylene glycol (345 g), bp 80–85° (2 mm), the γ-benzyloxypropanol (243 g, 65%) distilled as a clear colorless oil, bp 95–100° (1–2 mm) (lit.[23] 145–150° (13 mm)); nmr 2.76 (singlet, 5 H, aromatic), 5.59 (singlet, 1 H, O*H*), 5.65 (singlet, 2 H, $C_6H_5CH_2O$), 6.35 (triplet, 2 H, CH_2-OH), 6.51 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), and 8.21 (quintet, 2 H, $OCH_2CH_2CH_2OH$).

Benzyl γ-Chloropropyl Ether (II). Thionyl chloride (190 g, 1.5 mol) was added to a mixture of γ-benzyloxypropanol (234 g, 1.4 mol) and dimethylaniline (200 g) at such a rate as to keep the temperature below 60°. After completing the addition, which took 3 hr, the reaction was allowed to proceed for an additional hour. The mixture was then poured into hydrochloric acid (10%, 500 ml) and extracted with chloroform. The chloroform extract was washed with water, sodium bicarbonate solution, and with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting dark oil was distilled through a 1-ft Vigreux column to provide the desired material (200 g, 80%) as a colorless oil, bp 95–100° (1 mm) (lit.[24] 129° (16 mm)); nmr 2.72 (singlet, 5 H, aromatic), 5.72 (singlet, 2 H, $C_6H_5CH_2O$), 6.57 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), 6.65 (triplet, 2H, CH_2CH_2Cl), and 8.30 (quintet, 2 H, $CH_2CH_2CH_2Cl$).

Diethyl γ-Benzyloxypropylethylmalonate (III). To a solution of sodium ethoxide (70 g, 1 mol) in absolute ethanol (500 ml) was added diethyl ethylmalonate (190 g, 1 mol). The solution was heated to reflux and benzyl γ-chloropropyl ether (185 g, 1 mol) added over a period of 0.5 hr. Refluxing was continued for 10 hr and the reaction mixture was then stirred at room temperature for a further 10 hr. Most of the ethanol was removed by distillation and water added to dissolve the inorganic salts. The layers were acidified with glacial acetic acid and separated. The aqueous layer was extracted with ether. The oil and ether extracts were combined, washed with water, sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude liquid (320 g) was distilled to give the desired material (163 g, 46%) as a clear colorless oil, bp 140–150° (0.1 mm); ν_{max}^{neat} 1721 ($COOCH_2CH_3$) cm^{-1}; nmr 2.75 (singlet, 5 H, aromatic), 5.56 (singlet, 2 H, C_6H_5-CH_2O), 5.86 (quartet, 4 H, 2 × OCH_2CH_3), 6.58 (triplet, 2 H, $C_6H_5CH_2OCH_2$), 8.00 (multiplet, 6 H, $OCH_2CH_2CH_2CCH_2CH_3$), 8.82 (triplet, 6 H, 2 × OCH_2CH_3), and 9.20 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39; O, 23.78 Found: C, 67.75; H, 8.31; O, 23.94.

γ-Benzyloxypropylethylmalonic Acid (IV). A mixture of intermediate III (163 g, 0.5 mol), potassium hydroxide (108 g), water (200 ml), and ethanol (50 ml) was warmed to 40° for 10 hr and then allowed to stir for a further 10 hr at room temperature. The alkaline solution was extracted with ether to remove any starting material (5.0 g). The aqueous layer was acidified with concentrated hydrochloric acid using Congo red as indicator and the oil that separated was collected. The aqueous layer was extracted with ether and the combined ether extracts and oil were washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting oil was diluted with warm ether, and hexane added until the solution was opalescent. Upon cooling, the desired acid (IV) separated as a white crystalline solid (70 g, 50%), mp 117–120°; ν_{max}^{KBr} 1742, 1698 (COOH) cm^{-1}; nmr −1.5 (singlet, 2 H, 2 × COO*H*), 2.70 (singlet, 5 H, aromatic), 5.47 (singlet, 2 H, C_6H_5-CH_2O), 6.50 (triplet, 2 H, $C_6H_5CH_2OCH_2$), 7.8–8.8 (multiplet, 6 H, $OCH_2CH_2CH_2CCH_2CH_3$), and 9.12 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.14; H, 7.12; O, 28.62.

Examination of the mother liquors by thin layer chromatography (silica, chloroform) indicated the presence of another compound in addition to the foregoing diacid (IV). The nmr spectrum showed the presence of an ethyl ester function (quartet at τ 5.95 and triplet at τ 8.85) and a carboxylic acid proton (singlet at τ −1.6). The structure (V) was assigned on this basis and was confirmed by decarboxylation to yield ethyl 2-(γ-benzyloxypropyl)butanoate (VII), see experiment b below.

2-(γ-Benzyloxypropyl)butanoic Acid (VI). Ethyl γ-benzyloxypropylmalonic acid (67 g, 0.25 mol) was heated at 160°. The

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evolution of carbon dioxide ceased after 6 hr. The product, a yellow viscous oil (54 g) was used for subsequent reaction without further purification: ν_{max}^{film} 1704 (COOH) cm^{-1}; nmr −1.6 (singlet, 1 H, COO*H*), 2.71 (singlet, 5 H, aromatic), 5.55 (singlet, 2 H, $C_6H_5CH_2O$), 6.56 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), 7.65 (multiplet, 1 H, $CHCO_2H$), 8.45 (multiplet, 6 H, $OCH_2CH_2CH_2CCH_3CH$), and 9.11 (triplet, 3 H, CH_2CH_3).

Ethyl 2-(γ-Benzyloxypropyl)butanoate (VII). (a) A solution of 2-(γ-benzyloxypropyl)butanoic acid (VI) (54 g, 0.23 mol) in absolute ethanol (1 l.) and concentrated sulfuric acid (8 ml) was refluxed for 10 hr. Part of the ethanol (800 ml) was removed by distillation and the rest of the reaction mixture was poured into ice water. The resulting mixture was extracted with ether. The ether extract was washed with water, 5% sodium carbonate solution, and with water again, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting liquid was distilled under reduced pressure, to afford the desired material (50 g, 81%) as a clear oil, bp 135° (1.5 mm): gas chromatography, performed on a Wilkins Aerograph Autoprep, Model A-700, using a 20% SE 30 analytical column (60–80 Chrom W, 10 ft × 1/4 in. column temperature 260, helium flow rate 100 ml/min), retention time 5 min; ν_{max}^{film} 1724 ($COOCH_2CH_3$) cm^{-1}; nmr 2.75 (singlet, 5 H, aromatic), 5.58 (singlet, 2 H, $C_6H_5CH_2O$), 5.95 (quartet, 2 H, OCH_2CH_3), 6.61 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), 7.75 (multiplet, 1 H, $CHCOOC_2H_5$), 8.40 (multiplet, 6 H, $OCH_2CH_2CH_2CCH_2CH_3$), 8.85 (triplet, 3 H, OCH_2CH_3), and 9.15 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; O, 18.16. Found: C, 73.16; H, 8.99; O, 17.85.

(b) The mother liquors (60 g) obtained from the crystallization of the diacid (IV) were decarboxylated as described above. The crude product, by thin layer chromatography (silica, chloroform), contained a highly polar component and a nonpolar component whose R_f value was identical with that of VII. Without further purification the crude product was esterified by the above procedure. The final product of reaction (40 g) was identical in all respects with VII.

Ethyl α-(γ-Benzyloxypropyl)-α-ethylsuccinate (VIII). (a) Using Triphenylmethylsodium. An ethereal solution (200 ml, 0.485 mol) of triphenylmethylsodium was added to a 500-ml flask which had been filled with nitrogen and fitted with a dropping funnel containing the monoester VII. The monoester was added over a period of 15 min and the solution allowed to stir at room temperature for 1.5 hr. Ethyl bromoacetate (12.8 g, 0.0485 mol) was slowly added through the dropping funnel at such a rate as to keep the ether from refluxing. After the addition was completed (15 min), the mixture was stirred for 30 min at room temperature. The reaction mixture was then treated with water (100 ml) and the ether layer collected, washed with fresh water, dried over anhydrous magnesium sulfate, and concentrated. The resulting oil was diluted with a small quantity of benzene and allowed to stand until most of the triphenylmethane has crystallized. The triphenylmethane was removed by filtration and the filtrate chromatographed through alumina (1100 g). The triphenylmethane which remained in the filtrate was eluted with petroleum ether (65–110°), while the unreacted starting monoester (VII) was eluted with benzene–petroleum ether (65–110°) (1:1) (7.8 g). The desired succinate derivative (VIII) was eluted with benzene as a yellow oil, which was subsequently purified by molecular distillation (2.80 g, 42%, based on unrecovered starting material) to provide a clear viscous oil, bp 180–200° (0.1 mm): gas chromatography, performed on a Wilkins Aerograph Autoprep, Model A-700, using a 20% SE 30 analytical column (60–80 Chrom W, 10 ft × 1/4 in. column temperature 260, helium flow rate 100 ml/min), retention time 15 min; ν_{max}^{film} 1724 ($COOCH_2CH_3$) cm^{-1}; nmr 2.72 (singlet, 5 H, aromatic), 5.56 (singlet, 2 H, $C_6H_5CH_2O$), 5.92 (octet, 4 H, 2 × OCH_2CH_3), 6.60 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), 7.4 (singlet, 2 H, CH_2COOEt), 8.32 (multiplet, 6 H, $OCH_2CH_2CCH_2CH_3$), 8.82 (sextet, 6 H, 2 × CH_2CH_3), and 9.18 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.47; H, 8.55; O, 22.99.

(b) Using Methylsulfinyl Carbanion. Sodium hydride (1.0 g, 0.20 mol, 50% mineral oil dispersion, Metal Hydrides, Inc.) was placed in a two-necked flask and washed thrice with dry petroleum ether and decanted to remove the mineral oil. Dimethyl sulfoxide (distilled from calcium hydride, bp 64° (4 mm)) was added and the mixture heated to 70–75° until the evolution of hydrogen ceased.

The monoester (5.28 g, 0.02 mol) (VII) and a small amount of triphenylmethane as indicator were dissolved in anhydrous ether (250 ml) and placed in a three-necked flask fitted with a nitrogen inlet, drying tube, and a syringe cap. The methyl sulfinyl carbanion was introduced into this mixture through the syringe cap using a hypodermic syringe until the red color of triphenylmethylsodium persisted. Ethyl bromoacetate (3.24 g, 0.02 mol) was added over a period of 15 min and the mixture stirred for a further 15 min. After this time, a thick precipitate had formed. The reaction mixture was then poured into water and the ether layer separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product contained a quantitative yield of unreacted monoester (VII).

N-[β-(3-Indolyl)ethyl]-α-(γ-benzyloxypropyl)-α-ethylsuccinimide (IX). A suspension of tryptamine hydrochloride (6.1 g, 0.0312 mol) in a mixture of water (100 ml) and ether (200 ml) was basified with 10% sodium hydroxide solution. The ether extract, which contained the free base, was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. A solution of the succinate derivative (2.5 g, 0.00715 mol) and tryptamine hydrochloride (152 mg) in freshly distilled 2-(2-ethoxyethoxy-ethanol) (75 ml) was added to the tryptamine residue. The mixture was heated to reflux and 10 ml of the solvent was distilled to remove the last traces of water. Refluxing was continued for 48 hr under an atmosphere of purified nitrogen. After cooling, the reaction mixture was poured into water and the aqueous solution extracted with ether. The ether extract was washed with water, 10% acetic acid solution, water, 5% sodium bicarbonate solution, and finally with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude reaction product, a dark brown oil (4.1 g), was purified by chromatography on alumina (300 g). The desired imide (IX) was eluted with benzene–chloroform (1:1) as a clear slightly brown gum (2.5 g, 86%). An analytical sample was prepared by molecular distillation (290° (0.05 mm)): ν_{max}^{film} 3325 (NH), 1760 (weak) and 1690 (strong) (imide), 750 and 700 (aromatic) cm^{-1}; λ_{max} 224, 275 (sh), 282, 290 mμ (log ε 4.23, 3.64, respectively); nmr 1.48 (broad singlet, 1 H, N*H*), 2.70 (multiplet, 9 H, aromatic), 3.06 (doublet, 1 H, α proton of the indole), 5.60 (singlet, 2 H, $C_6H_5CH_2O$), 6.13 (triplet, 2 H, CH_2CH_2N), 6.66 (triplet, 2 H, $C_6H_5CH_2OCH_2CH$), 7.00 (triplet, 2 H, CH_2CH_2N), 7.60 (singlet, 2 H, CH_2CN), 8.55 (multiplet, 6 H, $OCH_2CH_2CH_2CCH_2CH_3$), and 9.26 (triplet, 3 H, CH_2CH_3); mass spectrum, main peaks, *m/e* 144, 143, 130, and 91; mol wt 418.

Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.01; N, 6.69. Found: C, 74.45; H, 7.17; N, 7.07.

Bischler–Napieralski Cyclization of Imide (IX). A solution of the imide (118 mg) in dry toluene (75 ml) was placed in a three-necked flask fitted with a nitrogen inlet and condenser. The toluene was heated to reflux and approximately 10 ml distilled to remove the last traces of moisture. With a steady stream of nitrogen passing through the apparatus, phosphorus pentoxide (approximately 0.9 g) was added in three equal portions over a period of 45 min. After refluxing for a further 30 min, the reaction was cooled to room temperature and the toluene decanted. The brown precipitate was treated with ice–water and then made strongly alkaline with concentrated potassium hydroxide. The basic solution was extracted with chloroform and the chloroform extract washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford a brown gum (49 mg). Purification by chromatography on alumina provided a yellow amorphous solid (15 mg). Further purification by tlc (alumina, chloroform) afforded a yellow amorphous solid (10 mg), to which we assigned structure XV: λ_{max} 224, 313, 326 mμ, λ_{max}^{HC} 395 mμ; mass spectrum, main peaks, *m/e* 282 (M − 18), 263, 251, 143, and 130; mol wt 310.

N-[β-(3-Indolyl)ethyl-3-(γ-hydroxylpropyl)]-3-ethylpyrrolidine (XVII). To a solution of the imide (110 mg, 0.262 mmol) in dry tetrahydrofuran (20 ml) was added lithium aluminum hydride (400 mg) and the resulting mixture was refluxed for 10 hr and then allowed to stand at room temperature for 12 hr. The excess lithium aluminum hydride was destroyed by addition of moist tetrahydrofuran, the solid hydroxide salts were removed by filtration and the residue was washed with fresh tetrahydrofuran. The combined filtrate and washings were poured into water and the resulting mixture was extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue (90 mg) was chromatographed on alumina (10 g). The desired material was eluted with benzene–chloroform (1:4) as a clear greenish gum (64 mg, 82%). An analytical sample was prepared by molecular distillation (220° (0.1 mm)): ν_{max}^{film} 3222 (OH), 750 (aromatic) cm^{-1}; λ_{max} 221, 274 (sh), 282, 290 mμ (log ε 4.30, 3.56, 3.59, 3.53, respec-

tively); nmr (100 MHz) 1.75 (broad singlet, 1 H, N*H*), 2.70 (multiplet, 4 H, aromatic), 3.05 (doublet, 1 H, α proton on indole nucleus) 6.40 (triplet, 2 H, CH_2CH_2OH), 6.60 (broad singlet, 1 H, CH_2OH—disappears on treatment with D_2O), 7.35 (multiplet, 8 H, $CH_2CH_2N(CH_2)_2$), 8.52 (multiplet, 8 H, $CH_2(C(CH_2CH_3)CH_2CH_2CH_2OH)$), and 9.16 (triplet, 3 H, CH_2CH_3); mass spectrum, main peaks, *m/e* 170 (base peak), 156, 144, and 130; mol wt 300.

Anal. Calcd for $C_{19}H_{28}N_2O$: C, 76.00; H, 9.33; N, 9.33. Found: C, 75.96; H, 9.34; N, 9.29.

N-[β-(3-Indolyl)ethyl-3-(γ-benzyloxypropyl)]-3-ethylpyrrolidine (XVI). To a solution of the imide (4.5 g, 11 mmol) in dry tetrahydrofuran (500 ml) was added lithium aluminum hydride (4.6 g, 120 mmol) and the resulting mixture was stirred at room temperature for 12 hr and then refluxed for 4 hr. The reaction mixture was worked up as described above. The crude reaction product (4.5 g) was purified by chromatography on alumina (300 g). The desired benzyl ether amine (XVI) was eluted with benzene–chloroform (9:1) as a light brown viscous oil (3.50 g, 81%). The analytical sample was prepared by molecular distillation 280° (0.05 mm): ν_{max}^{film} 3200 (NH), 740 and 695 (aromatic) cm^{-1}; λ_{max} 224, 275 (sh), 282, 290 mμ (log ε 4.27, 3.63, 3.66, 3.61, respectively); nmr (100 MHz) 1.6 (broad singlet, 1 H, NH), 2.68 (multiplet, 8 H, aromatic), 3.22 (doublet, 1 H, α proton on indole nucleus), 5.58 (singlet, 2 H, $C_6H_5CH_2O$), 6.50 (triplet, 2 H, $C_6H_5CH_2OCH_2CH_2$), 7.25 (multiplet, 6 H, $CH_2CH_2NCH_2$–CH_2), 7.59 (singlet, 2 H, NCH_2C), 8.50 (multiplet, 8 H, $-CH_2C(CH_2CH_2)CH_2CH_3$), and 9.20 (triplet, 3 H, CH_2CH_3); mass spectrum, base peak *m/e* 260, strong *m/e* 91.

Anal. Calcd for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17; mol wt 390.267. Found: C, 79.76; H, 8.97; N, 7.02; mol wt 390.269 (mass spectrometry).

Mercuric Acetate Oxidation of Benzyl Ether Amine (XVI). To stirred absolute methanol (500 ml) in a well-dried apparatus, a solution of benzyl ether amine (XVI) (920 mg, 2.3 mmol) in 10 ml of absolute methanol was added. This and the following procedure were performed under highly purified nitrogen, dried by passing through traps of concentrated sulfuric acid and Drierite. Glacial acetic acid (15 ml) was added slowly to the stirred solution. To this mixture solid mercuric acetate (6.0 g, 18.8 mmol) was added in small portions and the reaction mixture was left at room temperature overnight. Then the reaction mixture was refluxed and the progress of the reaction followed by removing small aliquots of the reaction mixture, bubbling hydrogen sulfide through as described later, and observing the development of the strong uv absorption at 3.53 mμ. The reaction mixture was allowed to come to room temperature and the yellowish crystalline mercurous acetate (2.35 g, 4.5 mmol) was filtered off under vacuum through a bed of Celite on a sintered glass disk in a nitrogen atmosphere. The light greenish solution was immersed in a bath of hot water (about 50°) and immediately hydrogen sulfide was bubbled through for about 10 min to destroy the mercury complex. By checking, the completion of the precipitation of black mercuric sulfides was ensured. Then the solution was left to come to room temperature and the precipitate of mercuric sulfide was allowed to settle down. Filtration under vacuum followed through a bed of Celite. Evaporation of the solvent under reduced pressure at moderate temperature gave a reddish oily residue. This residue was processed immediately to the next reaction step without delay. It was dissolved in methanol (300 ml) and a large excess of solid sodium borohydride (7.1 g, 0.187 mmol) was added slowly with sufficient stirring. By the end of the addition, the strong absorption at 353 mμ had disappeared. The reaction mixture was left for 2 hr at room temperature and then the methanol was removed under vacuum with gentle heating. The resultant greenish sludge was taken in water (50 ml) and was extracted with chloroform (3 × 150 ml). The combined chloroform extracts were washed with water (1 × 50 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave a brown gum (754 mg). Complete separation of all the products of the reaction by alumina was not successful. Chromatography on alumina (Shawinigan, 45 g, activity II, III) gave a mixture of the cyclic products (XVIII and XXVII) by elution with benzene–chloroform (1:1). This mixture (341 mg, brown gum, 38%) and the starting material (XVI) had very similar R_f values on thin layer chromatoplates (alumina, ethyl acetate–chloroform, 3:1). No further attempt to separate these components at this time was made.

Spectral data of this mixture were as follows: ν_{max}^{film} 3400 (NH), 740 and 700 (aromatic) cm^{-1}; λ_{max} 224, 275 (sh), 283, 291 mμ; nmr 1.94 (broad singlet, 1 H, NH), 2.75 (multiplet, 9 H, aromatic), 5.53 (two overlapping singlets, 2 H, $C_6H_5CH_2O$), 6.30 (multiplet, 1 H, C-3 proton), 6.55 (collapsed triplet, 2 H, $C_6H_5CH_2OCH_2$), and 9.15 (triplet, 3 H, CH_3CH_2); mass spectrum, main peaks, *m/e* 198, 184, 170, 169, 156, 154, and 140. Molecular distillation of a sample of this mixture for purposes of elemental analysis was unsuccessful, leading to extensive decomposition as was shown by tlc and ultraviolet spectra.

Debenzylation of the Cyclized Benzyl Ether Amines. (a) Using Boron Tribromide. A mixture of the cyclized benzyl ether amines obtained as described above (90 mg) was dissolved in dichloromethane (5 ml) and the solution cooled to 0°. Boron tribromide (10 drops) was added slowly, the temperature being held at 0°. The reaction was stirred vigorously for 10 min and then poured into 20% potassium hydroxide solution (15 ml). The resulting mixture was thoroughly extracted with dichloromethane. The dichloromethane extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide a yellow-green solid (50 mg) which, according to tlc (alumina, chloroform–methanol 20:1), was a mixture of products: λ_{max} 225, 283, 292 mμ; nmr 2.80 (multiplet, aromatic, no α proton absorption at 3.10), and 9.20 (triplet, CH_2CH_3). A small sample of this mixture was separated by tlc on alumina to provide a pure sample of the major component (see later): mass spectrum, main peaks, *m/e* 184, 170, 169, and 156.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.204. Found: C, 76.21; H, 8.52; N, 9.27; mol wt 298.204 (high-resolution mass spectrometry).

(b) By Catalytic Hydrogenolysis. To a mixture of cyclized benzyl ether amines (242 mg, 0.25 mmol), glacial acetic acid (15 ml) and 10% palladium on charcoal (242 mg) were added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure with continuous stirring. The uptake of hydrogen was measured. When the uptake of hydrogen ceased (about 25 hr) the reaction was stopped. The catalyst was removed by filtration through Celite and washed with warm acetic acid and warm water. The clear yellowish filtrate was neutralized with 40% aqueous sodium carbonate. The resulting solution was extracted with chloroform and the extract dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude alcohols as greenish brown gum (160 mg).

The crude product was purified by column chromatography on alumina (8.5 g, Shawinigan, activity II, III). The chromatography provided four pure alcohols designated as A, B, C, and D, in order of increasing polarity. Alcohols A and B were eluted with benzene–chloroform–methanol (99:1).

Alcohol A (XXXI), 18 mg, 10%, as a greenish glass, exhibited the following characteristics: ν_{max}^{film} 3250 (OH), 740 (aromatic) cm^{-1}; λ_{max} 227, 275 (sh), 283, 290 mμ; nmr (100 MHz) 1.20 (broad singlet, 1 H, N*H*), 2.85 (multiplet, 4 H, aromatic), 5.90 (multiplet, 1 H, C-3 proton), 6.58 (triplet, J = 6 Hz, 2 H, CH_2OH), and 9.12 (triplet, J = 7 Hz, 3 H, CH_2CH_3), mass spectrum, main peaks, *m/e* 297 (M − 1), 184, 170, and 156.

Anal. Calcd for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.204. Found: C, 76.07; H, 8.61; N, 9.20; mol wt 298.204 (high-resolution mass spectrometry).

Alcohol B (XXVIII), 20 mg, 11%, mp 166–167° (crystallized from methylene chloride) showed the following characteristics: $\nu_{max}^{CHCl_3}$ 3440 (NH), 3280 (OH) cm^{-1}; λ_{max} 291, 283, 275 (sh), 227 mμ (log ε 3.92, 4.01, 3.97, 4.54, respectively); nmr (100 MHz) 1.99 (broad singlet, 1 H, N*H*), 2.78 (multiplet, 4 H, aromatic), 5.86 (triplet, J = 6 Hz, 1 H, C-3 proton), 6.55 (triplet, J = 6 Hz, 2 H, CH_2OH), and 9.15 (triplet, J = 7 Hz, 3 H, CH_2CH_3); mass spectrum, main peaks, *m/e* 297 (M − 1), 184, 170, and 156.

Anal. Calcd for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.204. Found: C, 76.19; H, 8.92; N, 9.28; mol wt 298.204 (high-resolution mass spectrometry).

Alcohol C (XXXI), 32 mg, 17%, as a greenish glass, exhibited the following: ν_{max}^{film} 3230 (OH), 745 (aromatic) cm^{-1}; λ_{max} 223, 274 (sh), 283, 291 mμ; nmr (100 MHz) 1.90 (broad singlet, 1 H, N*H*), 2.75 (multiplet, 4 H, aromatic), 6.51 (triplet, J = 6 Hz, 2 H, CH_2OH), 8.04 (singlet, 2 H, NCH_2C), and 9.16 (triplet, J = 7 Hz, 3 H, CH_2CH_3), mass spectrum, main peaks, *m/e* 297 (M − 1), 199, 170, 156, and 140.

Anal. Calcd for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.204. Found: C, 76.72; H, 8.54; N, 9.19; mol wt 298.204 (high-resolution mass spectrometry).

Alcohol D (XXIX), 25 mg, 14%, mp 168–170° (crystallized from methylene chloride), showed: $\nu_{max}^{CHCl_3}$ 3390 (NH), 3240 (OH) cm^{-1}; λ_{max} 291, 283, 275 (sh), 227 mμ (log ε 3.39, 3.96, 3.95, 4.52, respectively); nmr (100 MHz) 1.70 (broad singlet, 1 H, N*H*), 2.75 (multiplet, 4 H, aromatic), 5.78 (triplet, J = 6 Hz, 1 H, C-3 proton), 6.38

(collapsed triplet, 2 H, CH_2OH), and 9.30 (triplet, J = 7 Hz, 3 H, CH_2CH_3); mass spectrum, main peaks, *m/e* 297 (M − 1), 184, 170, and 156.

Anal. Calcd for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.204. Found: C, 76.81; H, 8.93; N, 9.15; mol wt 298.204 (high-resolution mass spectrometry).

Mesylation of Alcohols B and D. **(a) Alcohol B** (XXVIII) (206 mg, 0.69 mmol) was dissolved in a mixture of dry triethylamine (2.5 ml) and chloroform (5.0 ml). The reaction mixture was cooled at −10 to −0° (ice–rock salt bath) and freshly distilled methanesulfonyl chloride (approximately 500 mg, 4.37 mmol) was added dropwise with efficient stirring. The resulting mixture was allowed to come slowly to room temperature (moisture was excluded). After 42 hr the solvent was removed under reduced pressure and the resulting deep red solid was dissolved in chloroform and extracted several times with aqueous 4 *N* ammonium hydroxide. The basic solution was concentrated under reduced pressure with gentle heating (water bath) to give a yellow gum. Traces of water were removed from the gum by virtue of several azeotropic distillations with benzene. The resulting solid was treated with warm chloroform several times. The combined chloroform extracts, after removal of the solvent under reduced pressure, gave an amorphous yellowish compound. This substance was the desired mesylate of alcohol A (XXI, 260 mg) and formed in essentially quantitative yield. This substance was usually used directly for the next step. However, fast column chromatography on alumina (neutral Woelm, activity II), followed by elution with chloroform–methanol (3:1), can be used if necessary. It was not important for our purpose to completely characterize this compound.

(b) Alcohol D (XXIX) was mesylated exactly as above to give an amorphous yellowish material. Here again, the yield was essentially quantitative.

Preparation of *dl*-Quebrachamine (XXII). The reductive cleavage of the quaternary mesylate was studied under a variety of conditions. The initial investigations involving alkali metals in liquid ammonia were abandoned when it was found that hydride reduction provided markedly higher yields. A few typical experiments are recorded here.

(a) Using Sodium in Liquid Ammonia. The quaternary salt (XXI) obtained directly from a mixture of the amino alcohols (100 mg) as mentioned above was dissolved in anhydrous ethanol (2 ml) and transferred to a three-necked flask fitted with a Dry Ice condenser and an ammonia outlet. After condensing approximately 30 ml of liquid ammonia into the flask, small quantities (50 mg each) of freshly cut sodium were added until after the final addition the blue color persisted for 20 min. Ammonium chloride was added and the ammonia allowed to evaporate. The residue was treated with water and extracted with ether. The ether extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue, a light green gum (32 mg) was chromatographed on alumina (Woelm, activity I, 3 g). *dl*-Quebrachamine (15 mg, 18%—based on mixture of cyclized amino alcohols) was eluted with dichloromethane–ether 20:1. The ir, nmr, and mass spectra of this material were identical with those of natural (−)-quebrachamine.

(b) Using Lithium Aluminum Hydride. The mesylate of alcohol B (130 mg, 0.345 mmol) was taken in N-methylmorpholine (50 ml, distilled over lithium aluminum hydride) and lithium aluminum hydride (390 mg, 10.3 mmol) was added in small portions to it under efficient stirring. The entire reaction was performed under oxygen-free nitrogen. The mesylate which was almost insoluble in this solvent formed during the reflux period (11 hr). The reaction mixture was cooled to room temperature and the excess of lithium aluminum hydride was decomposed carefully by slow addition of water in excess with vigorous stirring. The resulting gray sludge was stirred for a further 15 min and then filtered through a bed of Celite. The solid on the funnel was washed several times with warm chloroform and discarded. The filtrate was taken in some water (20 ml) and the organic layer was separated. The aqueous layer was washed with chloroform and the combined organic layers were washed with water. The chloroform layer was dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure to give a viscous colorless oil. This material was chromatographed on alumina (50 g, neutral Woelm, activity I). Elution with benzene–chloroform (1:1) gave 50 mg of a colorless viscous oil which solidified upon standing in a desiccator. Pure *dl*-quebrachamine (50% yield) was obtained by crystallization from wet methanol (mp 141–144°).

(c) The mesylate of alcohol D was also converted to quebrachamine following the above reaction procedure. Similar comparison confirmed the identity of the purified reaction product. The yield was 51%.

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Failure Sequences in the Solid Phase Synthesis of Polypeptides

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Abstract: Failure sequences occur during solid phase synthesis of polypeptides. The number of these failure sequences can be considerably decreased by acetylation of the amino groups which do not react or by the use of specially prepared, resin-coated glass beads.

One of the limitations of Merrifield's[1-3] solid phase approach to the synthesis of peptides and proteins is the possibility of creating failure sequences, which cannot be separated or even analytically distinguished from the desired sequence. Theoretically the number of failure peptides increases exponentially with increasing chain length. Only 100% yield in every coupling step could prevent the formation of failure sequences.

We can distinguish between the truncated sequences, in which amino acids are missing from the amino end, and the failure sequences, in which amino acids are missing from within the chain. If a truncated sequence cannot couple in later steps, no failure sequences are

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