(XII) which showed one spot on tlc (silica gel, 1:9 ethyl acetate–chloroform) and gave $[\alpha]^{24}D$ +3° (ethanol); λ_{max} 250, 278, 296 mμ (log ε 4.09, 3.47, 3.39, respectively); $\nu_{max}^{CCl_4}$ 1725 ($COOCH_3$), 1660 ($NC(=O)CH_3$), 1595 (aromatic C=C) cm^{-1}; nmr τ 2.75–3.20 (diffuse, 4 H, aromatic), 6.42 (singlet, 3 H, $COOCH_3$), 7.86 (singlet, 3 H, $NC(=O)CH_3$), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91. Found: C, 72.57; H, 8.10.

Epimerization of 7α-Ethyl-5-desethyldihydrovincadifformine (Dihydropseudovincadifformine) (IX). To a solution of compound IX (200 mg, 0.6 mmol) in methanol (2 ml) containing sodium methoxide (60 mg) was added saturated methanolic magnesium methoxide (2 ml). The resulting solution was sealed in a glass tube and heated at 100° for 5 hr. The cooled solution was poured into water (20 ml) and extracted immediately with ether (4 × 20 ml). The combined ether extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residual amorphous powder (165 mg, 83%) was identical with 7α-ethyl-5-desethylisodihydrovincadifformine (isodihydropseudovincadifformine) (X), as shown by thin layer chromatography and infrared spectra.

Mercuric Acetate Oxidation of 18β-Carbomethoxycleavamine (XVIII). A solution of compound XVIII (500 mg, 1.5 mmol) and mercuric acetate (1.8 g, 5.7 mmol) in glacial acetic acid (60 ml) was stirred at room temperature under an atmosphere of nitrogen for 75 min. The precipitated mercurous acetate (1.13 g) was filtered off and the filtrate was treated with hydrogen sulfide gas. The resulting mixture was filtered through Celite, the filtrate was evaporated under reduced pressure at room temperature, and the residue was treated with aqueous ammonia (55 ml). The aqueous alkaline mixture was extracted with dichloromethane (3 × 50 ml), the combined extracts were washed once with water, and then dried over anhydrous sodium sulfate. Evaporation of the solvent produced a light brown oily residue (465 mg), which was subjected to column chromatography on alumina (Woelm, activity III, 50 g).

(a) 6,7-Dehydro-7-ethyl-5-desethylvincadifformine (6,7-Dehydropseudovincadifformine) (XX). Elution with petroleum ether (bp 30–60°)–benzene (2:1) (50 ml) afforded a colorless oil (31 mg), which rapidly decomposed in the presence of air to an intensely violet colored gum. The latter was not characterized. Further elution with the same solvent mixture (120 ml) provided 145 mg (29%) of compound XX as an amorphous solid: λ_{max} 222, 298, 327 mμ (log ε 4.09, 4.10, 4.22, respectively); λ_{min} 258, 307 mμ (log ε 3.19, 4.06, respectively); $\nu_{max}^{CHCl_3}$ 3340 (NH), 1660 ($COOCH_3$), 1600 (C=C) cm^{-1}; nmr (100 MHz) τ 1.06 (singlet, 1 H, NH), 2.70–3.36 (diffuse, 4 H, aromatic), 4.57 (multiplet, 1 H, olefinic H), 6.33 (singlet, 3 H, $COOCH_3$), 8.00 (quartet, 2 H, CH_2CH_3), and 9.00 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33; O, 9.51; mol wt 336. Found: C, 74.82; H, 7.21; N, 8.18; O, 9.46; mol wt 336 (high-resolution mass spectrometry).

Hydrogenation (room temperature and atmospheric pressure) of the above amorphous material in ethyl acetate over 10% palladium on charcoal afforded an amorphous product which was shown by infrared spectrum and tlc (silica gel, 1:9 ethyl acetate–chloroform) to be identical with 7α-ethyl-5-desethylvincadifformine (pseudovincadifformine) (V).

(b) Catharanthine (XIX). Further elution in the above column chromatography with petroleum ether (bp 30–60°)–benzene (1:1) afforded 29 mg of a crystalline material which, after recrystallization from methanol (25 mg, 5%), showed mp 56–59°. This material was shown to be identical with catharanthine (XIX) by direct comparison (mp and mmp 56–59°, infrared spectrum) with an authentic sample.

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Total Synthesis of Indole and Dihydroindole Alkaloids. IV.[1,2] The Total Synthesis of *dl*-Dihydrocleavamine, *dl*-Carbomethoxydihydrocleavamine, *dl*-Coronaridine, *dl*-Dihydrocatharanthine, and *dl*-Ibogamine. A General Entry into the Iboga and Vinca Alkaloids

James P. Kutney, Walter J. Cretney, Philip Le Quesne, Bruce McKague, and Edward Piers

Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, Canada. *Received April 7, 1969*

Abstract: The total synthesis of *dl*-dihydrocleavamine, *dl*-carbomethoxydihydrocleavamine, *dl*-coronaridine, *dl*-dihydrocatharanthine, and *dl*-ibogamine is described. The sequence utilizes in its penultimate step a reductive cleavage reaction to generate the nine-membered ring system of the cleavamine molecule.

The general utility of appropriate nine-membered ring intermediates of the cleavamine and quebrachamine series in the partial synthesis of various members of the Aspidosperma, Vinca, and Iboga alkaloids has been demonstrated in previous publications.[2] It was, therefore, clear that the completion of laboratory syntheses of these intermediates would similarly complete the total syntheses of these various alkaloids. It is the purpose of this publication to describe our successful sequence to several relatives of the cleavamine family.

The stereochemical problems associated with the syntheses of such molecules are often considerable, but in this instance these are simplified markedly by the fact that the transannular cyclization process is completely stereospecific. As we have shown previously,[2,3]

(1) For a preliminary report on a portion of this work, see J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, 88, 4756 (1966).

(2) Part III. J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *ibid.*, 92, 1708 (1970).

(3) Part I. J. P. Kutney, E. Piers, and R. T. Brown, *ibid.*, 92, 1700 (1970).

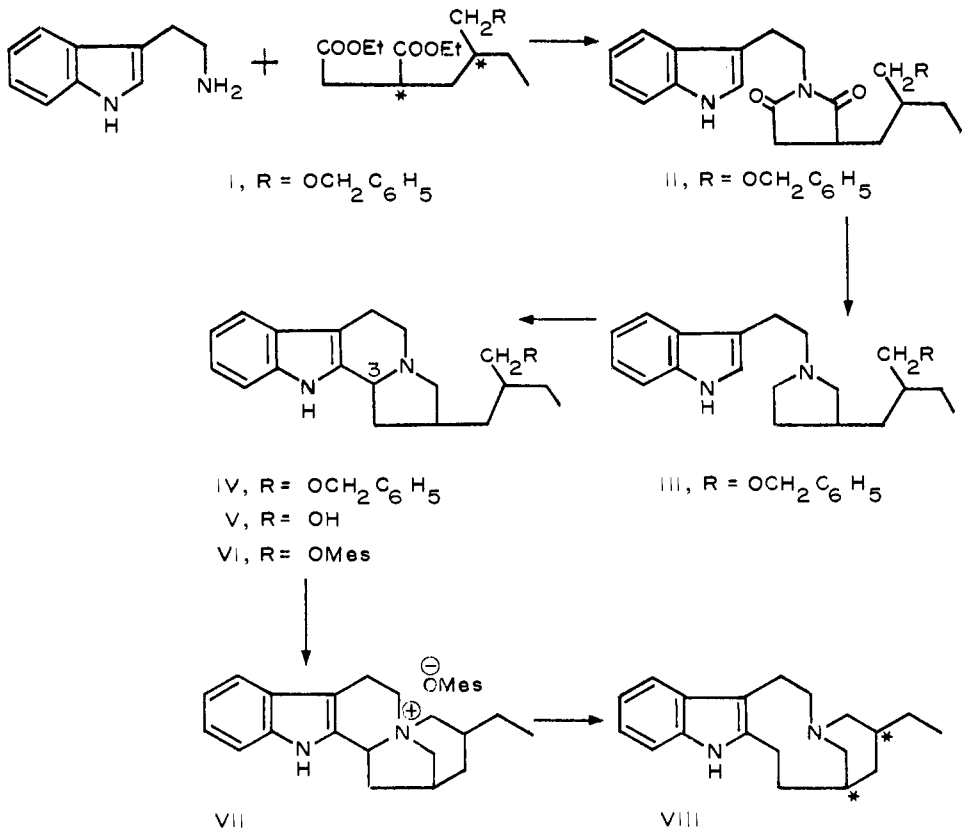

Figure 1. Outline of synthetic sequence leading to *dl*-dihydrocleavamine.

the asymmetric center at C_2 in the cleavamine series (corresponding to C_5 in Aspidosperma numbering system) and C_5 in quebrachamine completely controls the steric course of this cyclization. Thus, it was unnecessary in our initial investigations to give serious consideration to the stereochemistry at the various stages of the sequence. As will be shown later, the final achievement of the total synthesis of the cleavamine derivatives, for which the stereochemistry is established by X-ray analysis, also provides directly the stereochemistry of the various intermediates used in the synthetic pathway. For the sake of clarity, we will first consider the chemistry involved in the synthesis and then return to the stereochemical question in the later portion of this paper.

In our initial considerations regarding the possible synthetic pathways to the desired nine-membered ring intermediates, it was attractive to devise a sequence which was completely general to *both* the cleavamine and quebrachamine series. Several schemes were postulated, the first involving ring closures of the acyloin or Dieckmann type to afford the ring system, while a second sequence involved a reductive cleavage of a particular bond common to five- and six-membered rings in the appropriate intermediate. It is this latter sequence which we would like to discuss presently and which is shown in Figure 1.

The ultimate success of this sequence centers on the formation of the nine-membered ring by a reductive cleavage process. Such a cleavage of carbon–nitrogen bonds in quaternary ammonium salts is a well-known reaction and the investigation by the Wenkert group[4] is particularly relevant to the present work. Other groups have also shown its utility in the alkaloid field.[5-8]

The synthesis of the desired succinic ester necessary for the first step of the sequence is presented in Figure 2. Diethyl ethylmalonate was reduced to 2-ethyl-1,3-propanediol[9] and the latter was converted to the monobenzyl ether (X) in a straightforward manner.[10] The infrared spectrum of this compound possessed an absorption band at 3300 cm^{-1} (OH) and characteristic aromatic C–H out-of-plane bending modes at 695 and 740 cm^{-1} (also present in all other benzyl ethers reported subsequently). The nmr spectrum showed a five-proton singlet at τ 2.7 for the aromatic protons and a two-proton singlet at τ 5.5 for the benzyl methylene protons. These two singlets were also very characteristic for all the subsequent compounds containing the benzyl ether moiety.

It was a distinctive feature of the compounds examined in this synthetic sequence that they all possessed extremely informative nmr spectra, so some emphasis will be placed on these data during the discussion.

The ether–alcohol (X) was converted to the chloride (XI) by treatment with thionyl chloride in N,N-dimethylaniline[11] and the alkylation of diethyl malonate with this compound using sodium ethoxide as base[12] provided diethyl 3-benzyloxy-2-ethylpropylmalonate

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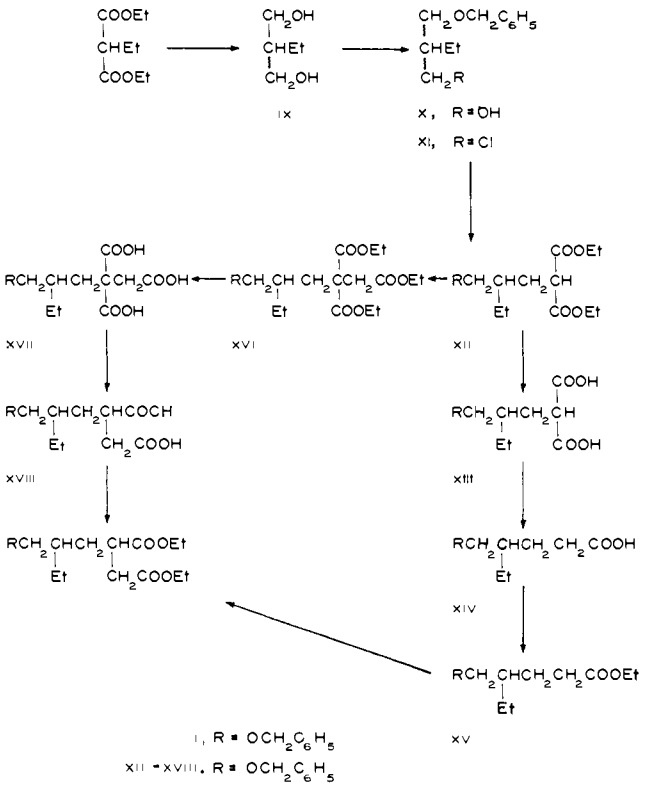

Figure 2. Synthesis of succinic ester derivative (I).

(XII). The reaction was sluggish and consistent recoveries of 50% of unreacted halide were observed. This was easily separable from the much higher boiling alkylated malonic ester (XII) and an overall yield of 89% was thereby attained in the reaction.

Initially, the route from this malonic ester to the substituted succinic ester (I) was considered *via* the sequence XII → XV as indicated in Figure 2.

Indeed, the synthesis of this compound by first converting it to the substituted ester XV and then alkylating with ethyl iodoacetate was successful. However, the alternate route *via* the triester (XVI) to be discussed later was anticipated to proceed in better yield and this was subsequently verified.

Thus, hydrolysis of the substituted malonic ester (XII) with aqueous potassium hydroxide,[12] provided the corresponding malonic acid (XIII) as a viscous oil. This compound could not be induced to crystallize, but the spectral data were in accord with the assigned structure. Smooth decarboxylation of the latter to the monoacid (XIV) was effected by heating this compound for 5 hr at 120°.[12] The resultant viscous oil was esterified without purification by treatment with ethanol and sulfuric acid to provide the substituted ester XV.

When ethyl iodoacetate was added immediately to the enolate of the ester XV, the reaction was virtually instantaneous, and sodium iodide precipitated.[13] Analysis of the crude reaction product (thin layer and gas chromatography) clearly indicated the presence of a new minor compound, but the major component was still the starting ester. The new product was separated and purified by column chromatography on alumina, followed by distillation to provide a low yield of the succinic ester (I). Gas chromatography effected further purification of a small quantity of this material for analytical and spectral data.

The diester (I) possessed an absorption band in the carbonyl region of the infrared spectrum at 1730 cm^{-1} and the two familiar aromatic bands. The nmr spectrum was very informative. The benzyl ether was apparent from the five-proton singlet at τ 2.7 and the two-proton singlet at τ 5.5. Two almost superimposable quartets which appeared at τ 5.85, integrating for four protons and combined with a triplet centered at τ 8.75, indicated the presence of two ethyl ester groups. The methylene protons on the carbon adjacent to the oxygen of the benzyloxy function appear as a two-proton multiplet at τ 6.6, and the three protons on the carbon atoms α to the carboethoxy groups appear in the region of τ 7.0–7.6.

Although the synthesis of the desired succinic ester had been achieved, the low yield in the alkylation technique necessitated an investigation of an alternate route *via* the triester, XVI.

The alkylation of the malonic ester (XII) with ethyl bromoacetate using sodium ethoxide as base[14] provided a fair yield of the triester (XVI), along with a good recovery of starting material. The use of sodium in ether[15] in place of sodium ethoxide, however, provided an improved yield (60%) of the triester, as well as some recovered malonic ester (30%). A good separation of the higher boiling triester from the starting material could be achieved by fractional distillation.

The triester (XVI) was hydrolyzed with potassium hydroxide[16] to the corresponding triacid (XVII), obtained as a noncrystalline viscous oil. Nmr data on the latter indicated complete removal of the ethyl ester groups and a broad three-proton signal now appeared in the expected region (τ −0.4) for the carboxyl hydrogen atoms.

Decarboxylation of the above triacid to the succinic acid derivative (XVIII) followed by esterification of the resultant brown viscous acid provided the desired succinic ester (I) in an overall yield of 78% from the triester.

When the succinic ester from either of the described synthetic routes was subjected to careful gas chromatographic analysis, an interesting phenomenon was observed. An analytically pure sample appeared almost as one peak except for the presence of a slight shoulder when examined on an SE 30 (20%) column at 260°. This shoulder became more pronounced at 245°, while examination using a FFAP (20%) column showed the presence of two peaks at 265° more effectively and this was much more pronounced at 245°. Collection and reinjection of this material produced the same peak ratios indicating that the compound was not being altered by the gas chromatographic procedure. While this material satisfied all the necessary criteria to support the structure (I) and appeared as one compound by thin layer chromatography, the presence of two diastereoisomers was expected, since the compound possessed two asymmetric centers. Since these asymmetric centers would ultimately appear at the two asymmetric centers of dihydrocleavamine (I and VIII, Fig-

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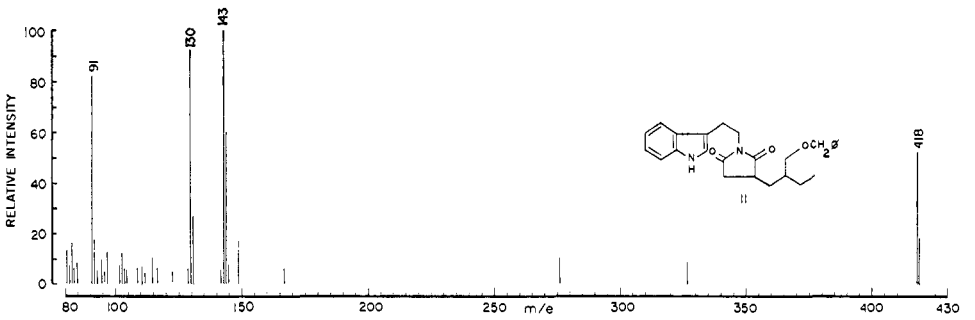


Figure 3. Mass spectrum of succinimide derivative (II).

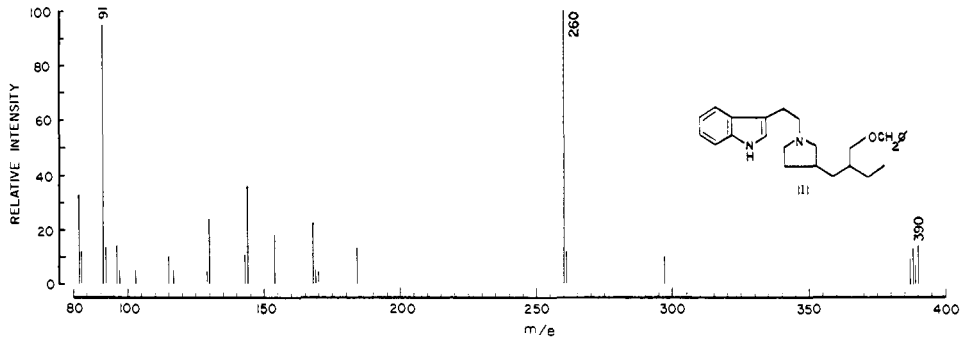
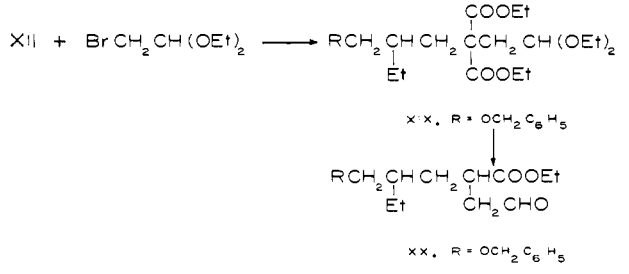


Figure 4. Mass spectrum of benzyl ether (III).

ure 1, indicated by the asterisks), their demonstration in the succinic esters should be reflected by the synthesis of the two known[17] isomeric dihydrocleavamines (as will be shown later).

Because of the high degree of success in the synthesis of the succinic ester (I) *via* the triester (XVI), a brief attempt was made at an analogous synthesis of the aldehydo ester (XX) *via* alkylation of the malonic ester (XII) with bromoacetaldehyde diethyl acetal. The expected product (XIX) could possibly then be decarboxylated and the aldehyde group regenerated.

The condensation of aldehydo esters with tryptamine is a well known and valuable synthetic route. Its importance lies in the fact that the aldehyde group reacts preferentially before the ester group with the tryptamine, and can, therefore, be used to direct the position of the alkyl side chain in the resultant lactam. Several



recent examples are available from synthetic work in the Hunteria and Aspidosperma alkaloids.[18,19]

Unfortunately, bromoacetaldehyde diethyl acetal failed to react with the malonic ester under the conditions found successful for the alkylation with ethyl bromoacetate. This acetal is apparently relatively inert,[20,21] and this made it unsuitable as an alkylating agent in this case.

We, therefore, proceeded to the condensation of the succinic ester (I) with tryptamine as initially outlined in Figure 1. The resulting imide (II), obtained in 77% yield, lent itself to a straightforward structural analysis due to the presence of certain very characteristic spectroscopic features. The compound possessed a typical indole absorption in the ultraviolet region while in the infrared spectrum, there appeared sharp bands at 1755 (medium intensity) and 1685 cm^{-1} (strong), which are characteristic of a five-membered ring imide.[22] The nmr spectrum exhibited a one-proton singlet at τ 1.9 (NH) and a nine-proton multiplet centered at τ 2.7 due to the aromatic protons of the benzene rings. The α proton on the heterocyclic ring of the indole moiety appeared as a one-proton doublet at τ 3.0.

The mass spectrum of the succinimide (Figure 3) provided further structural evidence. The molecular ion peak was indicated as being the desired value of 418 and the spectrum was dominated by peaks at *m/e* 143, 130, and 91. The peaks at *m/e* 143 and 130 are the characteristic indole fragments of the type XXI and XXII, respectively, and commonly observed in many simple indole alkaloids.[23] The peak at *m/e* 91 is undoubtedly due to the cleavage of the benzyl group.

The imide (II) was reduced to the tertiary amine (III) in high yield. The mass spectrum of this compound (Figure 4) was dominated by a very intense peak at *m/e* 260 which could be attributed to the simple and ex-

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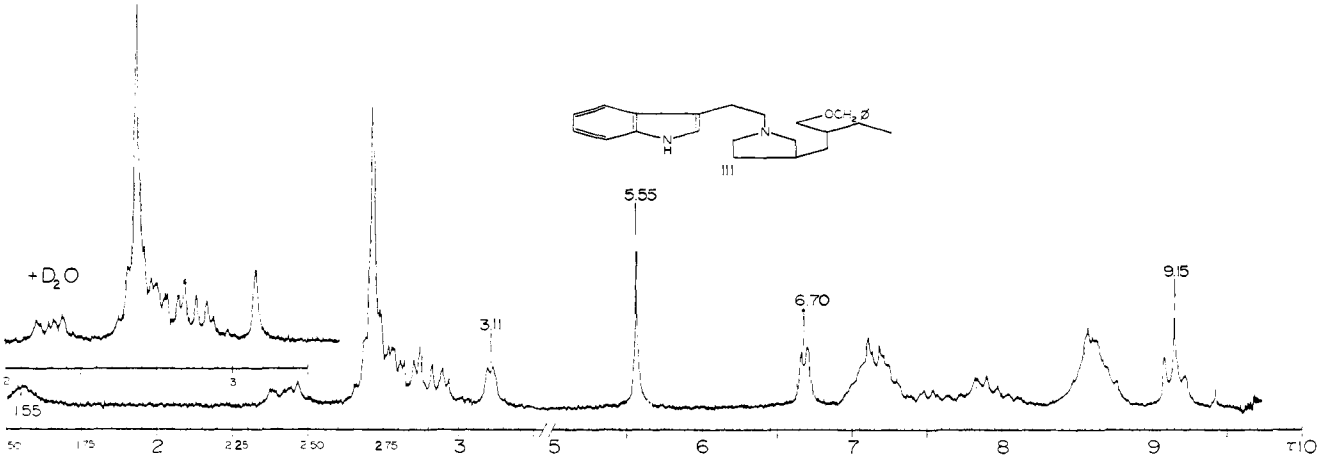
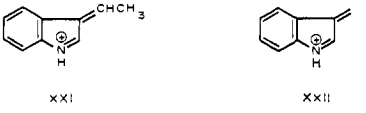


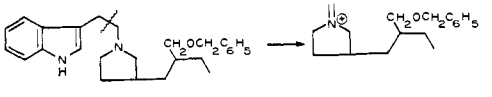
Figure 5. Nmr spectrum of benzyl ether (III).

pected fragmentation of the parent molecule to the ion XXIII. The presence of the benzyl ether was again indicated, as in the imide, by a strong peak at *m/e* 91.



XXI XXII

It now became important to locate accurately in the nmr spectrum the chemical shift of the proton on the carbon atom α to the nitrogen of the indole ring. Its presence or absence in the reaction products obtained from the attempted cyclization of III to IV would be a measure of the success of this reaction. Fortunately, this proton is usually located at slightly higher field than



III XXIII

the other aromatic protons of the indole ring, as shown by the analysis of simple indoles and tryptamines.[24,25] These studies have demonstrated that this proton usually appears in the range of τ 3.0–3.4, depending on concentration[26] and is coupled to the proton on the indole nitrogen atom.

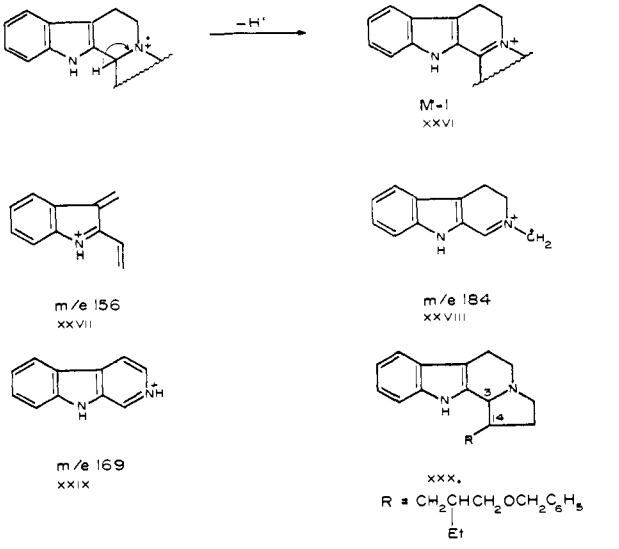
Indeed, examination of the nmr spectrum of this amine taken at 100 MHz (Figure 5) showed that this proton was located as a doublet at τ 3.11. As shown, addition of deuterium oxide caused this doublet to collapse to a singlet demonstrating the coupling mentioned above.

The next step in the proposed scheme (Figure 1) required cyclization of the amine III to provide the tetracyclic amine IV. Of several alternatives, mercuric acetate was the oxidant chosen for this purpose. The conversion of tertiary amines to iminium salts by means of this reagent had received considerable attention in our laboratory, as mentioned in previous publications in this series, as well as elsewhere.[27] Preliminary investigations indicated that a convenient method of following the reaction was through further oxidation of the already cyclized product (IV) to the salt XXIV. This compound provided a characteristic chromophore which

XXIV, R = $OCH_2C_6H_5$ XXV, R = $OCH_2C_6H_5$

absorbed at 352 mμ in the ultraviolet region[27] and the appearance of this absorption was an indication of the extent of cyclization. The addition of dilute sodium hydroxide to a solution of the oxidation product (XXIV) caused a disappearance of the absorption maximum at 352 mμ and the appearance of two new maxima at 310 and 322 mμ. This spectral alteration is indicative of an imine–enamine shift (XXIV → XXV) and has been observed in similar compounds.[28] Subsequent reduction of XXIV with sodium borohydride then leads to the desired product (IV).

The reaction of amine III with mercuric acetate provided an overall 37% yield of cyclized products. A total of four compounds designated A, B, C, and C′, on the basis of their R_f values, were obtained in pure



(24) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, 82, 2184 (1960).
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(26) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *Chem. Ind.* (London), 151 (1964).
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(28) R. N. Schut and T. J. Leipzig, *J. Heterocycl. Chem.*, 3, 101 (1966).

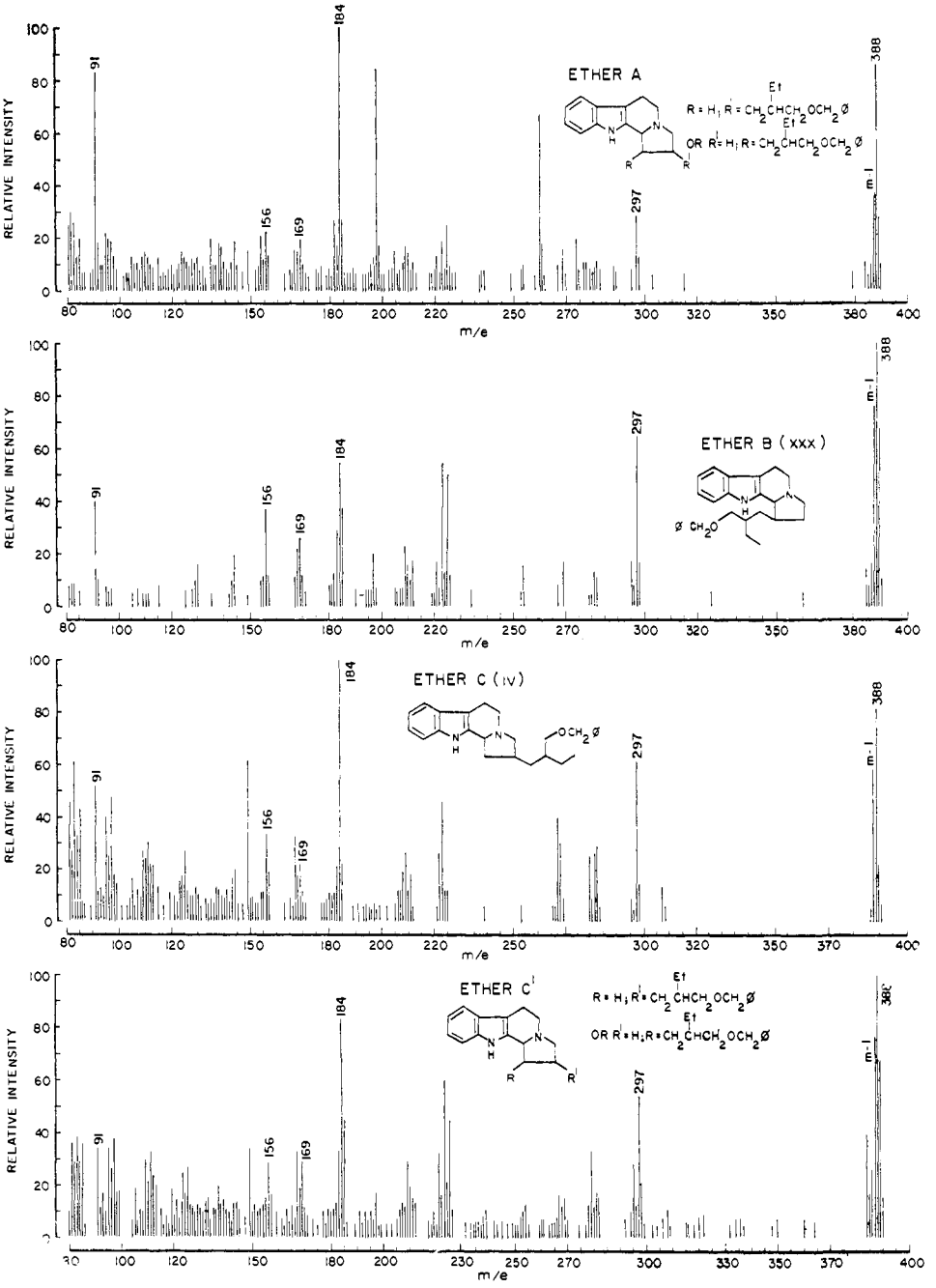


Figure 6. Mass spectra of the isomeric cyclic benzyl ethers.

form by a combination of careful chromatographic separations. A fifth very minor component (D) could not be separated in pure form.

The mass spectra of the four pure components (Figure 6) were very similar and much different from that observed for the uncyclized amine (III). A number of peaks present in their fragmentation patterns are also present in the spectra of indole alkaloids of the tetrahydro-β-carboline type,[23] as for example, ajmalicine and yohimbine. A strong M − 1 peak, which appeared in the spectra of all four compounds, also appears in these alkaloid spectra and has been demonstrated as partially arising from the ion XXVI. A series of significant peaks then appeared at *m/e* 156, 169, and 184, which have been shown, in the case of the alkaloids mentioned, to arise from the indole portion of the molecule (XXVII–XXIX). The presence of the benzyl ether moiety was indicated by the presence of peaks at *m/e* 297 (M − 91) and *m/e* 91.

While these mass spectrometric results established that the cyclization had in fact occurred to produce a mixture of isomeric products, there remained the question of the location of the benzyloxypropyl side chain on the five-membered ring. Although it has not been mentioned previously, it is obvious that there are three possible iminium products in the mercuric acetate oxidation of III. Of these alternatives, two could be considered as possibly cyclizing to the indole nucleus. A third iminium salt in which the double bond was exocyclic to the five-membered ring was unlikely to cyclize, since it would lead to an unfavorable four-membered ring system. Therefore, of the two possible

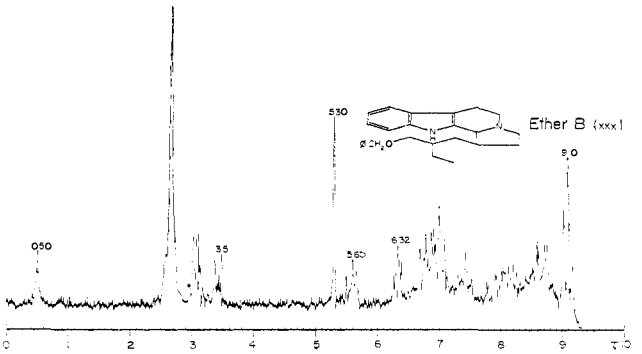


Figure 7. Nmr spectrum of undesired benzyl ether.

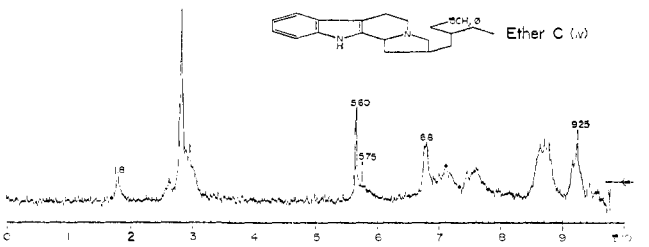


Figure 8. Nmr spectrum of desired cyclic benzyl ether.

cyclization products derivable from this reaction (IV and XXX), only one (IV) would ultimately lead to a dihydrocleavamine. It had been also anticipated that the increased steric effects created by the proximity of the side chain to the indole portion of the molecule might minimize or preclude the formation of isomer XXX.

The two major cyclized benzyl ethers (B and C) were examined extensively by nmr spectroscopy and the spectra obtained are shown in Figures 7 and 8, respectively. Radical differences were immediately apparent in the spectra of these two compounds, the most outstanding of which was the aromatic region. Ether C, which was obtained in slightly greater amount than ether B in this reaction, exhibited a nine-proton multiplet in the region τ 2.5–3.1 (see Figure 8). The characteristic one-proton doublet at τ 3.11 in the uncyclized amine due to the α proton on the indole nucleus was now absent. By contrast, some of the aromatic peaks in the nmr spectrum of ether B (Figure 7) were located at higher field, in the region τ 3.0–3.5. The reason for for this dramatic upfield shift in the aromatic region of the nmr spectrum of ether B became apparent upon examination of other features of the two spectra. The proton on the nitrogen atom of the indole nucleus was located at τ 0.50 in the spectrum of ether B, while in ether C it appeared in the more normal position at τ 1.80. The methylene protons of the benzyloxy group were located as two-proton singlets at τ 5.30 and 5.60 in the spectra of ethers B and C, respectively. The downfield shift of the benzyloxy methylene protons in the spectrum of ether B relative to ether C revealed the most important feature of these spectra. A doublet was present at τ 5.60 in the spectrum of ether B which integrated for approximately one proton. The spectrum of ether C possessed a broad multiplet integrating for approximately one proton in the region τ 5.7. This was partially obscured, however, by the methylene singlet of the benzyloxy group. Nmr studies[27,29] of indole alkaloids of the tetrahydro-β-carboline type have shown that the C_3 proton may be located as low as τ 5.5, depending on the conformation of the molecule, although in another instance it is reported as a multiplet in the region τ 5.8–6.0.[4]

While the desired cyclized benzyl ether C (IV) was expected to exhibit a one-proton multiplet for the proton at C_3, the undesired cyclization product (XXX) was expected to show a doublet, one of the protons at C_{14} now having been replaced by the benzyloxypropyl side chain. It appeared, therefore, on the basis of this nmr spectral data, that the undesirable cyclization product XXX was in fact being obtained, although in somewhat lower yield than the desired product IV. The upfield shift of the aromatic protons of the indole nucleus as well as the observed differences for the protons already mentioned in the spectrum of ether B may be attributed to the proximity of the benzyloxy group. Molecular models of the compound XXX show that the benzene ring of the benzyloxy group may be easily located directly beneath the indole nucleus.

The difficulties associated with the separation of the above benzyl ethers caused us to consider the removal of the benzyl ether group in the compounds of the original reaction mixture and hence separate the resultant alcohols. Catalytic hydrogenolysis[30,31] accomplished this goal and chromatographic separation provided a much more facile isolation of five compounds.

The major alcohol, designated C, was shown from subsequent experiments to possess the desired cyclic structure and thereby the most pertinent spectral characteristics are discussed presently. The mass spectrum (Figure 9) possessed significant peaks at M − 1 (*m/e* 297), *m/e* 184, 170, 169, and 156, also observed in the mass spectra of the benzyl ethers. However, the strong peak at *m/e* 91 observed in the spectra of the benzyl ethers was lacking. The nmr spectrum also indicated that the benzyl group had been removed as the aromatic region now consisted of a four-proton multiplet centered at τ 2.85 and the two-proton singlet of the benzyloxy methylene group originally observed in the region τ 5.3–5.7 had disappeared. The removal of this latter signal in the nmr spectrum now clearly revealed a broad one-proton multiplet at τ 5.78 ascribed to the C_3 proton.

The alcohol C was established as being derived from the ether C in a separate experiment. A small quantity of ether C was purified by the chromatographic procedures described earlier and hydrogenolyzed under the identical conditions. The resultant alcohol obtained was shown by thin layer chromatography to be identical with alcohol C obtained from the hydrogenolysis of the ether mixture, and different from all other isomeric alcohols obtained.

The alcohol designated B was formed in slightly less quantity than alcohol C and was suspected as having been derived from ether B. The fragmentation pattern in the mass spectrum (Figure 9) was similar to that of

(29) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, 83, 4816 (1961).

(30) H. Meerwein in Houben-Weyl, "Methoden der Organischen Chemie," Vol. VI/3, Georg Thieme Verlag, Stuttgart, Germany, 1965, p 169.

(31) W. H. Hartung and R. Simonoff, *Org. Reactions*, 7, 269 (1953).

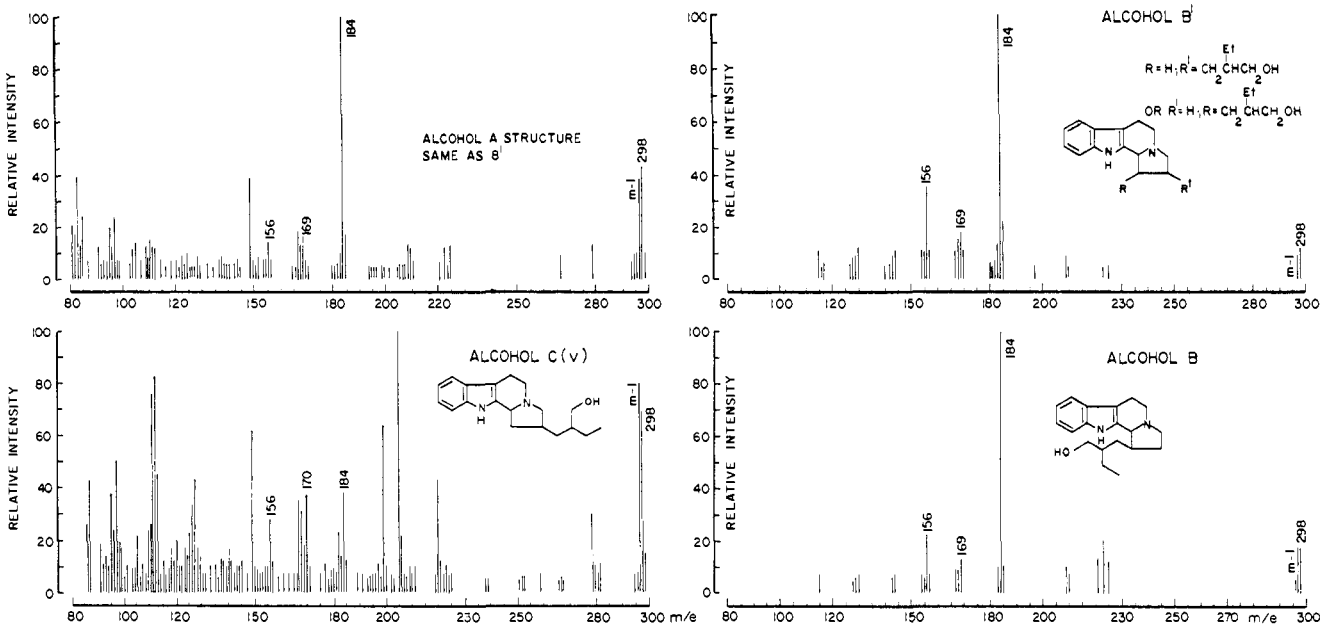


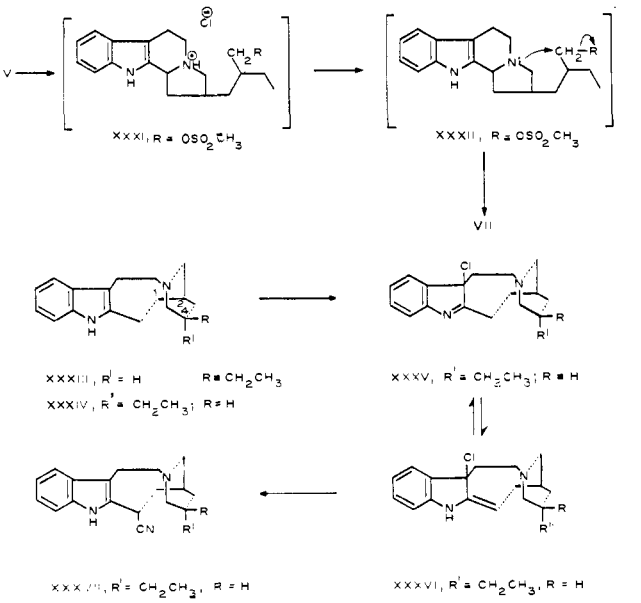
Figure 9. Mass spectra of the isomeric amino alcohols.

alcohol C while the nmr spectrum displayed a four-proton multiplet in the region τ 2.5–3.15 and no longer possessed the two-proton singlet of the benzyloxy methylene group at τ 5.3. The removal of the benzyl group was thus seen to be accompanied by a downfield shift of the protons which were located at τ 3.15–3.5 in benzyl ether. This shift is, therefore, in accord with the earlier suggestion that the protons of the indole nucleus were shielded to some extent by the benzyloxy group. An isolated one-proton *doublet* was present at τ 6.72, which was ascribed to the C_8 proton of the undesired cyclized amino alcohol. The nmr spectrum of this compound, therefore, supported the earlier proposal that cyclization was occurring during the mercuric acetate reaction to provide both the desired cyclization product (IV) and the undesired product (XXX).

The remaining two isomeric amino alcohols which were obtained pure were also indicated as possessing the molecular formula, $C_{19}H_{26}N_2O$. Their mass spectra (Figure 9) were essentially the same as that of the alcohols B and C, and both exhibited normal indole ultraviolet absorption. Insufficient quantities of these isomers were obtained in a pure state for detailed nmr analysis.

The conversion of the alcohol C (V) to the quaternary salt (VII) desired for ring cleavage was now examined. Treatment of this compound with methanesulfonyl chloride in pyridine at 0° provided an ether insoluble material, possibly the salt XXXI, which was treated with ammonia to ensure the presence of the free base (XXXII). Upon standing for a period of a few days, the latter converted to the quaternary salt (VII). Reduction of VII with sodium in liquid ammonia[4] provided three compounds, two of which were identical in their behavior with the authentic samples of the known 4α (XXXIII) and 4β (XXXIV) dihydrocleavamines.

We turn now to a brief discussion of some of the stereochemical aspects of the synthetic sequence. As mentioned at the beginning of this publication, a serious consideration of the stereochemistry at the individual stages of the synthesis was unnecessary. The stereochemistry, including the absolute configuration, of 4α- and 4β-dihydrocleavamine is known from our previous work[2,3] to be as shown in XXXIII and XXXIV,



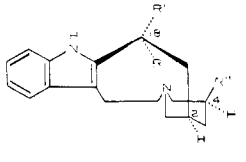
respectively. From the sequence outlined in Figure 1, it is obvious that C_2 and C_4, the two asymmetric centers present in the above cleavamine derivatives (asterisked positions in VIII), are derived directly from the two asymmetric centers of the succinate ester (I, see asterisked positions). Therefore, the appropriate stereochemistry in the latter compound, as well as in the imide (II) and the amine (III), is completely defined. The subsequent conversion of III to a mixture of the desired tetracyclic benzyl ethers (IV), and in turn transformation of the latter to the alcohols (V), can be also elaborated in a stereochemical sense. Thus, the major alcohol, designated as alcohol C in the above discussion, must not only possess the gross structure, V, but must bear the required stereochemistry at the two relevant

asymmetric centers in order to provide eventually 4α- and 4β-dihydrocleavamine. The only point of uncertainty in these compounds, and obviously in the quaternary salt (VII), is C_3, since its asymmetry is destroyed in the final step of the synthesis.

In order to complete the total synthesis of the Iboga alkaloid system, it was necessary to introduce a carbomethoxy group into the dihydrocleavamine molecule, and thereby complete a laboratory synthesis of a carbomethoxydihydrocleavamine derivative. For this purpose, 4β-dihydrocleavamine was oxidized with *t*-butyl hypochlorite[32] in the hope that the chloroindolenine (XXXV) would be obtained. The product obtained from this reaction was a viscous oil, which, even after chromatographic purification, failed to crystallize. However, the data obtained on this compound were in complete support for the desired structure (XXXV). The molecular formula, $C_{19}H_{25}N_2Cl$, was established by high-resolution mass spectrometry, and the presence of the chlorine atom was noted by the appropriate peaks due to ^{37}Cl, as well as ^{35}Cl. The loss of the halogen atom was facile as noted by the base peak at *m/e* 281 (M − Cl). The characteristic cleavamine fragmentation as typified by peaks at *m/e* 138 and 124 was also observed. Further support for the chloroindolenine chromophore was provided by the ultraviolet spectrum (λ_{max} 227.5, 260 (broad), 303 mμ) which was completely different from the normal indole absorption. Finally, reduction of the chloroindolenine with lithium aluminum hydride yielded 4β-dihydrocleavamine. This result eliminated any usual or unexpected rearrangement during the oxidation reaction.

The conversion of chloroindolenine XXXV to the appropriate eighteen-substituted dihydrocleavamine derivative was investigated in some detail in order to obtain the optimum experimental conditions. Initially XXXV was allowed to react at room temperature with potassium cyanide in a mixture of methanol–water–ether. Under these circumstances, a complex mixture resulted from which an 18-cyano-4β-dihydrocleavamine (XXXVII) and 18α-methoxy-4β-dihydrocleavamine (XXXVIII) were isolated in low yield. The stereochemistry at C_{18} in the latter substance could be readily assigned by virtue of the methoxyl resonance at τ 6.80 in the nmr spectrum.[33]

Reaction of XXXV with hydrogen cyanide in an anhydrous methanolic solution provided the 18α-methoxy derivative (XXXVIII, 24% yield) and the 18β-methoxy isomer (XXXIX, 10% yield).



XXXVIII, R = OCH_3; R' = H; R'' = CH_2CH_3
XXXIX, R = H; R' = OCH_3; R'' = CH_2CH_3
XL, R = H; R' = OH; R'' = CH_2CH_3
XLI, R = H; R' = CN; R'' = CH_2CH_3
XLII, R = H; R' = $COOCH_3$; R'' = CH_2CH_3

In another series of experiments, the chloroindolenine was treated with a mixture of anhydrous sodium acetate in glacial acetic acid. It was hoped that the expected 18-acetoxy derivative would allow subsequent displacement of the C-18 substituent by cyanide ion. Indeed, inspection of the reaction mixture, after various reaction times, revealed that these compounds were being formed, but they were extremely unstable and a pure sample could not be obtained. An attempt to achieve some purification by chromatography on alumina resulted in the formation of a new compound. This compound, mp 202–205°, had the molecular formula $C_{19}H_{26}N_2O$, as shown by high-resolution mass spectrometry, and exhibited an ultraviolet spectrum which was typical for the indole chromophore. The nmr spectrum was completely consistent with the structure 18β-hydroxy-4β-dihydrocleavamine (XL). It was thus clear that either facile hydrolysis or displacement of the acetoxy function was occurring during the chromatographic process.

It was observed that the compound believed to be an 18-acetoxy-4β-dihydrocleavamine, on the basis of the spectral properties of a partially purified sample, had reached a maximum concentration in the reaction mixture after 30 min at 60° as shown by thin layer chromatography. After 2 hr at 60°, there remained in the reaction product only a very polar material having saltlike characteristics. Indeed, the properties of this material were reminiscent of those observed previously for the quaternary ammonium salts encountered in the syntheses of quebrachamine[34] and dihydrocleavamine.[1] When this polar material was allowed to react with potassium cyanide in dimethylformamide, a new product, mp 150–152°, was obtained in 24% yield. Spectral and chromatographic comparisons established this substance to be identical with 18β-cyano-4β-dihydrocleavamine (XLI) prepared previously *via* procedures already discussed. This sequence which provided the desired cyano compounds in considerably higher yield was used for all subsequent preparations.

The final step of the synthetic pathway involved the reaction of 18β-cyano-4β-dihydrocleavamine (XLI) with potassium hydroxide in diethylene glycol and esterification of the resulting acid with diazomethane. The product, after chromatographic purification (58% yield), was crystalline and was shown to be identical in every respect with an authentic sample of 18β-carbomethoxy-4β-dihydrocleavamine (XLII).

The total synthesis of *dl*-coronaridine and *dl*-dihydrocatharanthine was now complete in view of the previous results.[2] Since the conversion of coronaridine to ibogamine has also been accomplished,[35] this work also completes a total synthesis of ibogamine.

Various total syntheses of Iboga alkaloids have now been achieved by completely different routes.[36]

After our synthesis of 4α- and 4β-dihydrocleavamines and the corresponding carbomethoxy dihydro-

(32) G. Büchi and R. E. Manning, *J. Amer. Chem. Soc.*, 88, 2532 (1966).

(33) Part II. J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and V. R. Nelson, *ibid.*, **92**, 1704 (1970).

(34) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *ibid.*, 88, 3656 (1966). See also Part V of this series.

(35) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *ibid.*, 82, 1142 (1960).

(36) (a) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, 87, 2073 (1965); 88, 3099 (1966); (b) S. I. Sallay, *ibid.*, 89, 6762 (1967); (c) W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *ibid.*, 90, 1650 (1968); (d) Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, *Tetrahedron Lett.*, 3383 (1968); (e) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 947 (1968); (f) M. Ikezaki, T. Wakamatsu, and Y. Ban, *ibid.*, 88 (1969).

cleavamine had been published, a second synthesis of the two isomeric dihydrocleavamines appeared.[37]

Finally it should be noted that the recent investigations in the quebrachamine series[38] eliminate the troublesome mercuric acetate cyclization and thereby provide a markedly improved synthetic sequence. The obvious application of this modification to the present dihydrocleavamine synthesis allows a similar improvement.

Experimental Section[39]

3-Benzyloxy-2-ethylpropanol (X). Freshly cut sodium metal (1.06 g, 0.046 mol) was added in small pieces to a hot (115–120°) stirred solution of 2-ethyl-1,3-propanediol[9] (14.4 g, 0.138 mol) in dry xylene (6 ml). After all the sodium had reacted, benzyl chloride (6.5 g, 0.051 mol) was added dropwise, the temperature of the reaction mixture being maintained as above. The resulting mixture was stirred at 120° for 1 hr, cooled, and filtered to remove the precipitated sodium chloride (2.69 g). The filtrate was concentrated under reduced pressure and the resulting viscous yellow oil was distilled under nitrogen through a spiral tantalum distillation column (5 mm × 33 cm), equipped with a heating jacket. After a forerun of xylene, unreacted 2-ethyl-1,3-propanediol (9.1 g), bp 102–108° (2 mm), was obtained, followed by 3-benzyloxy-2-ethylpropanol (X) (6.88 g, 77%), bp 130–133° (2 mm): ν_{max}^{film} 3300 (OH), 740, 695 (aromatic) cm^{-1}; nmr τ 2.70 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 6.25–6.75 (diffuse, 4 H, $C_6H_5CH_2O$-CH_2 and $HOCH_2$), 7.20 (singlet, 1 H, OH), 8.00–8.90 (diffuse, 3 H, $CHCH_2$-CH_3), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.01; H, 9.58; O, 16.60.

3-Benzyloxy-2-ethylpropyl Chloride (XI). To a stirred mixture of 3-benzyloxy-2-ethylpropanol (X) (29.0 g, 0.150 mol) and N,N-dimethylaniline (20.0 g, 0.165 mol) was added, dropwise, freshly distilled thionyl chloride (18.5 g, 0.155 mol). During the addition, the temperature of the reaction mixture was maintained below 45° by external cooling with an ice bath. After complete addition of the thionyl chloride, the reaction mixture was stirred at 45° for 30 min and then poured into dilute hydrochloric acid contained in a separatory funnel. The resultant mixture was extracted thoroughly with chloroform. The extract was washed once with dilute hydrochloric acid, several times with cold water, and then dried over anhydrous sodium sulfate. Evaporation of the chloroform afforded a pale yellow oil which, upon distillation under reduced pressure, gave 21.0 g (66%) of 3-benzyloxy-2-ethylpropyl chloride (XI) as a clear colorless oil, bp 88–90° (0.3 mm): ν_{max}^{film} 735, 695 (aromatic) cm^{-1}; nmr τ 2.70 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 6.25–6.60 (two doublets, 4 H, $C_6H_5CH_2O$-CH_2 and $ClCH_2$), 7.90–8.80 (diffuse, 3 H, $CHCH_2CH_3$), and 9.10 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{12}H_{17}OCl$: C, 67.75; H, 8.06. Found: C, 67.39; H, 8.10.

Diethyl 3-Benzyloxy-2-ethylpropylmalonate (XII). To a solution of sodium ethoxide (from 3.68 g, 0.16 mol, of sodium metal) in absolute ethanol (75 ml) was added, over a period of 10 min, 37 g (0.23 mol) of diethyl malonate. The resulting solution was heated to reflux and 3-benzyloxy-2-ethylpropyl chloride (XI) (32.5 g, 0.153 mol) was added dropwise over a period of 3 hr. After the mixture had been refluxed for a further 30 hr, most of the ethanol was removed by distillation. The resulting mixture of sodium chloride and oil was cooled and poured into cold water containing 10 ml of glacial acetic acid. The layers were separated and the aqueous layer was extracted thrice with ether. The separated oil and the ether extracts were combined, washed once with water, twice with 10% sodium bicarbonate solution, once with saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. Removal of the solvent gave a viscous yellow oil which, upon distillation under reduced pressure afforded, in the initial fractions, unreacted diethyl malonate, then unreacted 3-benzyloxy-2-ethylpropyl chloride (XI) (16.8 g, 52% recovery), and finally the desired diethyl 3-benzyloxy-2-ethylpropyl malonate (XII) (22 g, 89% based on unrecovered starting material) as a pale yellow oil, bp 155–160° (9.3 mm): ν_{max}^{film} 1735 (COOEt), 690, 735 (aromatic) cm^{-1}; nmr τ 2.65 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 5.80 (quartet, 4 H, OCH_2CH_3), 6.25–6.67 (diffuse, 3 H, $C_6H_5CH_2OCH$ and $CH(COOEt)_2$), 8.05 (unresolved multiplet, 2 H, CH_2CH-$(COOEt)_2$), 8.80 (triplet, 6 H, OCH_2CH_3), and 9.15 (triplet, 3 H, $CHCH_2CH_3$).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.17; H, 8.50.

Ethyl 4-Benzyloxymethylhexanoate (XV). To a cold stirred solution of potassium hydroxide (5.9 g, 13.5 mmol) in a mixture of water (9 ml) and ethanol (1 ml) was added, over a period of 90 min, diethyl 3-benzyloxy-2-ethylpropyl malonate (XII) (9.0 g, 26.8 mmol). The resulting mixture was stirred with cooling in an ice bath for 4 hr and then allowed to stand at room temperature overnight. The yellow solution was extracted twice with ether, cooled in an ice bath, diluted with water (10 ml) and ether (20 ml), and then made strongly acidic (to Congo red paper) by careful addition of concentrated hydrochloric acid. The layers were separated and the acidic aqueous layer was extracted twice with ether. The combined ether extracts were washed twice with water, once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent provided an extremely viscous oil which could not be induced to crystallize, but which showed spectral properties consistent with the structure 3-benzyloxy-2-ethylpropyl malonic acid (XIII): ν_{max}^{film} 3500–2400, 1710 (COOH) cm^{-1}; nmr τ 0.97 (broad singlet, 2 H, COO*H*), 2.61 (singlet, 5 H, aromatic), 5.49 (singlet, 2 H, $C_6H_5CH_2O$), and 9.11 (triplet, 3 H, CH_2CH_3).

The crude malonic acid (XIII) (approximately 7.5 g) was heated in an oil bath at 120° for 5 hr. The resulting crude 4-benzyloxymethylhexanoic acid (XIV) was a light brown viscous oil, and was not purified further: ν_{max}^{film} 1710 (COOH) cm^{-1}; nmr τ −0.60 (broad singlet, 1 H, COO*H*), 2.65 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 6.60 (doublet, 2 H, $C_6H_5CH_2OCH_2$), 7.63 (multiplet, 2 H, CH_2COOH), and 9.11 (triplet, 3 H, CH_2CH_3).

The crude hexanoic acid (XIV) (approximately 5 g) was dissolved in anhydrous ethanol (20 ml) containing concentrated sulfuric acid (1 ml) and the resulting solution was refluxed for 90 min. After the solution was cooled, it was poured into ice-cold water and the resulting mixture was extracted twice with ether. The combined ether extracts were washed successively with water, 5% aqueous sodium bicarbonate, and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. Removal of the ether gave a residual yellow oil which, upon distillation under reduced pressure afforded 5.3 g (75%, from the malonic ester XII) of ether 4-benzyloxymethylhexanoate (XV) as a clear colorless oil, bp 122–128° (0.6 mm): ν_{max}^{film} 1730 (COOEt), 735, 695 (aromatic) cm^{-1}; nmr τ 2.67 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 5.85 (quartet, 2 H, OCH_2CH_3), 6.64 (broad doublet, 2 H, $C_6H_5CH_2$-OCH_2), 7.69 (multiplet, 2 H, CH_2COOEt), 8.75 (triplet, 3 H, OCH_2CH_3), and 9.10 (triplet, 3 H, CH-CH_2CH_3).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; O, 18.16. Found: C, 62.34; H, 9.27; O, 18.54.

Diethyl 2-(2-Benzyloxymethylbutyl)-2-carbethoxysuccinate (XVI). Freshly cut sodium metal (1.71 g, 0.075 mol) was added to dry xylene in a round-bottomed three-necked flask equipped with an external stirring motor. The xylene was heated until the sodium melted and the stirrer was turned on and off a number of times in order to disperse the sodium as a fine sand. The xylene was allowed to cool to room temperature and a large portion was decanted. Anhydrous ether was added and decanted from the sodium dispersion a few times to remove the remaining xylene. Finally, the sodium sand was covered with anhydrous ether (100 ml). Diethyl 3-benzyloxy-2-ethylpropylmalonate (XII) (25 g, 0.075 mol) was added and the mixture was refluxed for 3 hr, at which time evolution of hydrogen had ceased and all the sodium metal had disappeared. Redistilled ethyl bromoacetate (12.7 g, 0.076 mol) was added dropwise to the cooled pale green solution of the malonate salt and the resulting solution was stirred at room temperature for 30 min and then refluxed for 1 hr. The reaction mixture was poured into cold water containing a small amount of acetic acid, and the resulting mixture was extracted thrice with ether. The combined extracts were washed once with water and dried over anhydrous sodium sulfate. Removal of the ether afforded a yellow viscous oil which was distilled under reduced pressure. The first fraction (14.5 g, bp 140–190° (0.2 mm)) consisted of a mixture of starting malonic ester (XII) and the desired triester diethyl 2-(2-benzyloxymethylbutyl)-2-carbethoxysuccinate (XVI). Nmr spectroscopy revealed that the ratio of triester to malonic ester was approximately 2:1. The second distillation fraction (10.9 g, bp 190–

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(38) J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *J. Amer. Chem. Soc.*, 90, 3891 (1968).

(39) For general information, see ref 3.

200° (9.2 mm)) consisted of pure triester. Redistillation of the lower boiling fraction provided an additional amount of the desired triester, giving an overall yield of 78%, based on unrecovered starting material: ν_{max}^{film} 1730 (COOEt), 695, 730 (aromatic) cm^{-1}; nmr τ 2.69 (singlet, 5 H, aromatic), 5.55 (singlet, $C_6H_5CH_2O$), 5.85 (multiplet, 6 H, OCH_2CH_3), 6.72 (doublet, 2 H, $C_6H_5CH_2OCH_2$), 6.97 (singlet, 2 H, CH_2COOEt), 7.90 (multiplet, 2 H, $CHCH_2C(COOEt)_2$), 8.75, 8.80 (two triplets, 9 H, OCH_2CH_3), and 9.17 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.06; H, 7.95.

Diethyl 2-(2-Benzyloxymethylbutyl)succinate (I). (a) From Ethyl 4-Benzyloxymethylhexanoate (XV). An ether solution of 0.22 *N* triphenylmethyl sodium (86.5 ml, 19 mmol) was quickly run into a round-bottomed flask that had been thoroughly flushed with dry nitrogen. Ethyl 4-benzyloxymethylhexanoate (XV) (5.0 g, 19 mmol) was immediately added and the resulting solution was stirred for 2 min. Ethyl iodoacetate (4.05 g, 19 mmol) was added dropwise and the resulting mixture was stirred for 30 min at room temperature. After addition of glacial acetic acid (2.5 ml) to remove any excess base, the mixture was filtered to remove sodium iodide and the filtrate was dried over anhydrous sodium sulfate. The ether was evaporated and the residual light brown oil was chromatographed on alumina (750 g). Elution with petroleum ether (bp 30–60°)–benzene (4:1) gave triphenylmethane. Further elution with petroleum ether–benzene (2:1 and 1:1) gave unreacted starting ester (2.5 g), contaminated with a small amount of triphenylcarbinol. A mixture of unreacted starting material and product (1.6 g), again contaminated with a small amount of triphenylcarbinol, was then eluted with benzene. Since the triphenylcarbinol crystallized from the later mixture, the esters were separated from the alcohol by means of a pipet and then rechromatographed on alumina (96 g). Careful elution with petroleum ether–benzene (3:1) provided starting material in the initial fractions, followed by the desired product. Further purification by vacuum distillation (130–180°, bath temperature, (0.1 mm)) yielded the desired succinic ester (I) (380 mg) as a clear colorless oil. Preparative gas–liquid chromatography (10 ft × 1/4 in. stainless steel column, 20% SE30 in 60–80 mesh Chromosorb W, column temperature 230°, helium flow rate 90 ml/min) provided an analytical sample: ν_{max}^{film} 1730 (COOEt), 735, 690 (aromatic) cm^{-1}; nmr τ 2.70 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 5.62–6.08 (two quartets, 4 H, OCH_2CH_3), 6.60 (multiplet, 2 H, $C_6H_5CH_2OCH_2$), 7.00–7.20 (diffuse, 1 H, CHCOOEt), 7.24–7.60 (diffuse, 2 H, CH_2COOEt), 8.75 (triplet, 6 H, OCH_2CH_3), and 9.10 (triplet, 3 H, $CHCH_2CH_3$).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.79.

(b) From Diethyl 2-(2-Benzyloxymethylbutyl)-2-carbethoxysuccinate (XVI). A solution of the triester (XVI) (11.5 g, 27.3 mmol) in 95% ethanol (20 ml) containing potassium hydroxide (4.94 g, 90 mmol) was refluxed for 5 hr. After most of the alcohol had been removed by distillation, the residue was taken up in water and the resulting solution was extracted twice with ether. The aqueous solution was cooled in an ice bath and made strongly acidic (to Congo red paper) by careful addition of concentrated hydrochloric acid. The resulting mixture was extracted twice with ether. The combined ether extracts were washed twice with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave a very viscous light brown oil which could not be induced to crystallize. This material, 2-(2-benzyloxymethylbutyl)-2-carboxysuccinic acid (XVII), showed the following spectral characteristics: ν_{max}^{film} 1715 (COOH) cm^{-1}; nmr τ −0.4 (broad singlet, 3 H, COOH), 2.69 (singlet, 5 H, aromatic), 5.55 (singlet, 2 H, $C_6H_5CH_2O$), 6.69 (broad doublet, 2 H, $C_6H_5CH_2OCH_2$), 6.86 (broad singlet, 2 H, CH_2COOH), 8.02 (broad signal, 2 H, $CHCH_2C(COOH)_2$), and 9.20 (triplet, 3 H, CH_2CH_3).

The crude tricarboxylic acid (XVII) obtained above (approximately 9 g) was heated at 165–170° for a period of 3 hr. The resulting crude material was refluxed with a 20% aqueous solution of potassium hydroxide to remove any anhydride (2–3 hr or until a clear solution was obtained). The aqueous solution was then cooled to 0° (ice bath), made strongly acidic (to Congo red paper) by careful addition of concentrated hydrochloric acid, and extracted three times with ether. The combined extracts were washed twice with water, dried over anhydrous sodium sulfate, and evaporated to provide crude 2-(2-benzyloxymethylbutyl)succinic acid (XVIII) as a viscous oil: ν_{max}^{film} 1700 (COOH), 740, 695 (aromatic) cm^{-1}; nmr τ 1.05 (broad singlet, 2 H, COOH), 2.70 (singlet, 5 H, aromatic), 5.50 (singlet, 2 H, $C_6H_5CH_2O$), 6.60 (broad signal, 2 H, $C_6H_5CH_2OCH_2$), 7.00–7.55 (diffuse, 3 H, CH_2COOH and CHCOOH), and 9.13 (triplet, 3 H, CH_2CH_3).

The above crude succinic acid (XVIII) (approximately 7 g) was dissolved in absolute ethanol (20 ml) containing concentrated sulfuric acid (1 ml). The resulting solution was refluxed for 90 min, cooled, and poured into ice-cold water. The mixture was extracted twice with ether, the combined ether extracts were washed twice with water, once with 5% aqueous sodium bicarbonate, once with water, and then dried over anhydrous sodium sulfate. Evaporation of the ether provided a light yellow oil which was distilled under reduced pressure (bath temperature 135–165° (0.5 mm)) to afford 7.44 g (78% from the tricarboxylic ester XVI) of pure diethyl 2-(2-benzyloxymethylbutyl)succinate (I) as a clear colorless oil. Spectral and gas–liquid chromatographic properties of this material were identical with those of the compound obtained by the alternative route as described in (a) above.

N-[β-(3-Indolyl)ethyl]-3-(2-benzyloxymethylbutyl)succinimide (II). Tryptamine (3.1 g, 19.4 mmol), tryptamine hydrochloride (150 mg), and diethyl 2-(2-benzyloxymethylbutyl)succinate (I) (2.2 g, 6.3 mmol) were added to freshly distilled 2-(2-ethoxyethoxy)-ethanol (30 ml, bp 190–200°) and the resulting solution was refluxed under an atmosphere of nitrogen for 50 hr. The mixture was cooled to room temperature, taken up in ether, and washed three times with water, five times with 10% acetic acid, and three times with water. The green ethereal solution was dried over anhydrous sodium sulfate and then evaporated to yield a dark brown gum (approximately 3.1 g). This material was chromatographed on alumina (175 g) and the desired imide (II) was eluted with benzene and benzene–ether (4:1) as a light brown gum (2.02 g). A small quantity of this material was distilled under reduced pressure to provide an analytical sample as a light brown glass, bp 260–270° (bath temperature, (0.005 mm)): ν_{max}^{Nujol} 3320 (NH), 1755 (medium), 1685 (strong) (imide), 740, 695 (aromatic) cm^{-1}; λ_{max} 222, 283 mμ (log ε 4.57, 3.79, respectively); nmr τ 1.90 (broad signal, 1 H, NH), 2.22–2.90 (diffuse, 9 H, aromatic), 3.00 (doublet, 1 H, α proton of indole), 5.55 (singlet, 2 H, $C_6H_5CH_2O$), 6.20 (triplet, 2 H, CH_2N), 6.65 (unresolved multiplet, 2 H, $C_6H_5CH_2OCH_2$), and 9.15 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.81; H, 7.40; N, 6.52.

N-[β-(3-Indolyl)ethyl]-3-(2-benzyloxymethylbutyl)pyrrolidine (III). The imide (II) (925 mg, 2.21 mmol) in dry tetrahydrofuran (25 ml) was added to a stirred suspension of lithium aluminum hydride (250 mg, 6.60 mmol) in dry tetrahydrofuran (25 ml) and the resulting mixture was refluxed with stirring, under dry nitrogen, for 8.5 hr. The reaction mixture was cooled in cold water and the excess lithium aluminum hydride was destroyed by careful addition of cold, wet tetrahydrofuran. The mixture was allowed to warm to room temperature and then filtered through Celite to remove the inorganic salts. The salts were washed well with hot tetrahydrofuran and the combined filtrate and washings were dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude amine (925 mg) as a pale yellow oil, which was subjected to column chromatography on alumina (50 g). Elution with benzene and benzene–ether (4:1) provided the pure amine (III) (815 mg, 95%) as a very pale yellow gum which gradually darkened upon standing. Vacuum distillation of a small quantity provided an analytical sample, bp 240–250° (bath temperature, (0.005 mm)) as a clear colorless glass: ν_{max}^{film} 3350 (NH), 735 and 695 (aromatic) cm^{-1}; λ_{max} 222, 283 mμ (log ε 4.56, 3.80, respectively); nmr (100 MHz), τ 1.55 (broad singlet, 1 H, NH), 2.20–2.85 (diffuse, 9 H, aromatic), 3.11 (doublet, 1 H, α proton of indole, collapses to a singlet upon addition of D_2O), 5.55 (singlet, 2 H, $C_6H_5CH_2O$), 6.70 (doublet, 2 H, $C_6H_5CH_2OCH_2$), and 9.15 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{26}H_{34}N_2O$: C, 79.95; H, 8.78; N, 7.17; mol wt 390.267. Found: C, 80.02; H, 8.82; N, 7.35; mol wt 390.267 (high-resolution mass spectrometry).

Mercuric Acetate Oxidation of Amine III. A solution of mercuric acetate (3.40 g, 10.7 mmol) and the amine (III) (500 mg, 1.28 mmol) in anhydrous methanol (260 ml) containing glacial acetic acid (7.5 ml) was refluxed for 4.5 hr under highly purified nitrogen. The reaction was followed by periodically treating an aliquot of the mixture with hydrogen sulfide gas and observing the development of the 353-mμ absorption peak of the supernatant liquid. The resultant greenish yellow mixture was allowed to cool and then filtered through a sintered glass disk (medium porosity) into a three-necked round-bottomed flask, to remove the precipitated mercurous acetate (1.18 g, 1.8 mmol). While a flow of purified nitrogen was continuously passed through one neck of the flask, the filtrate was warmed to approximately 50°, and then hydrogen

sulfide gas was bubbled into the solution for 15 min in order to destroy the mercury complexes. The resultant precipitate of mercury sulfides was removed by filtration, under an atmosphere of nitrogen, through another sintered glass disk as described above, except that Celite was used as a filter aid and high vacuum (oil pump) was employed to aid filtration.

It is important to emphasize that optimum yields in this reaction were obtained only if the entire operation described above was conducted under an inert atmosphere. For this purpose, an apparatus consisting of a series of three-necked flasks interconnected by bent adaptors, which already contained the sintered glass disks, was used. In this manner, addition of reagents, filtration, etc., could be conveniently carried out under an atmosphere of purified nitrogen.

Sodium borohydride (2.2 g) was immediately added to the filtrate and the resulting solution was stirred under nitrogen for 4 hr, after which time the absorption peak at 353 mμ had completely disappeared. The solution was then concentrated to approximately 20 ml and partitioned between chloroform and water. The aqueous layer was extracted twice more with chloroform. The combined extracts were washed twice with water, twice with 5% sodium hydroxide solution, twice with water, and dried over anhydrous sodium sulfate. The chloroform was evaporated to yield a brown gum (430 mg) which was chromatographed on alumina (20 g). Elution with benzene–ether (4:1 and 1:1) removed, in addition to uncyclized starting material, a mixture of the cyclized benzyl ethers of increasing polarity and these were designated A, B, C, C′ (C and C′ were indistinguishable by tlc on alumina) and D (total weight = 175 mg). Initially a mixture of isomers A and B was obtained, followed by mixtures of isomers B, C, C′, and a small amount of uncyclized material. Elution with methanol yielded an additional mixture of isomers C, C′, and D, along with some polar material (total 160 mg). Rechromatography of the latter gave an additional amount of isomers C, C′, and D (35 mg). The total weight of the cyclized product was 210 mg (yield 37%, based on an estimate by tlc of 20% uncyclized material being present). This total mixture was used for the preparation of the corresponding alcohols. Small quantities of pure benzyl ethers were obtained by preparative tlc (see below) of the partially separated mixtures obtained by column chromatography, as described above.

A mixture (16 mg) of one of the minor isomers (A) and one of the major isomers (B) was spotted on a thin layer chromatoplate (alumina, 20 × 20 cm, 0.3 mm thickness) and developed in benzene–ethyl acetate (2.5:1). The developed plate was examined under ultraviolet light while still wet, and the bands corresponding to isomers A and B were scraped off and extracted separately with methanol. The extracts were filtered through a sintered glass disk, and the filtrates were evaporated to dryness. The resultant residues taken up in anhydrous ether and removed from any alumina by means of a pipet. Evaporation of the ether solutions provided pure isomer A (3 mg) as a mixture of crystals and gum and pure isomer B (XXX) (9 mg) as a pale green glass: isomer A, λ_{max} 226, 274 (sh), 283, 291 mμ.

Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21; mol wt 388.251. Found: C, 79.95; H, 8.10; N, 7.15; mol wt 388.251 (high-resolution mass spectrometry).

Isomer B showed the following characteristics: ν_{max}^{film} 3240 (NH), 740 and 695 (aromatic) cm^{-1}; λ_{max} 226, 275 (sh), 283, 291 mμ; nmr (100 MHz) τ 0.50 (singlet, 1 H, N*H*), 2.5–3.5 (diffuse, aromatic), 5.30 (singlet, 2 H, $C_6H_5CH_2O$), 5.60 (broad doublet, approximately 1 H, C-3H), 6.32 (quartet, $C_6H_5CH_2OCH_2$), and 9.10 (triplet, CH_2CH_3).

Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21; mol wt 388.251. Found: C, 80.10; H, 8.25; N, 7.11, mol wt 388.252 (high-resolution mass spectrometry).

The fractions as obtained in the above column chromatography and which appeared initially to be a pure ether C were found by tlc on silica gel (methanol) to contain another minor isomer designated as C′. A mixture of these two isomers (30 mg) was separated by preparative tlc on silica gel (20 × 20 cm, 0.3 mm, methanol). The bands were separated as described above to provide the pure major isomer C (IV) (13 mg) as a clear pale green glass and pure isomer C′ (3 mg) as a clear pale green glass.

Isomer C exhibited the following characteristics: ν_{max}^{film} 330 (NH), 740 and 695 (aromatic) cm^{-1}; λ_{max} 225, 273 (sh), 282, 290 mμ; nmr (100 MHz) τ 1.80 (singlet, 1 H, NH), 2.5–3.1 (diffuse, 9 H, aromatic), 5.60 (singlet, 2 H, $C_6H_5CH_2O$), 5.75 (broad multiplet, 1 H, C_3–H), 6.8 (doublet, C_6H_5–CH_2OCH_2), and 9.25 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21; mol wt 388.251. Found: C, 80.12; H, 8.35; N, 7.01; mol wt 388.252 (high-resolution mass spectrometry).

Isomer C′ showed: λ_{max} 225, 275 (sh), 282.5, 290.5 mμ.

Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.37; H, 8.30; N, 7.21; mol wt 388.251. Found: C, 79.98; H, 8.19; N, 7.25; mol wt 388.251 (high-resolution mass spectrometry).

Hydrogenolysis of the Mixture of Cyclized Benzyl Ethers. A mixture of the benzyl ethers (235 mg) obtained as described above and palladium (235 mg, 10% on charcoal) in glacial acetic acid (25 ml) was stirred under an atmosphere of hydrogen for 3.5 hr, after which time the uptake of hydrogen had essentially ceased (approximately 80% of the theoretical amount consumed). The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residual gum was taken up in chloroform, and the resulting solution was washed with 5% sodium hydroxide solution, twice with water, and dried over anhydrous sodium sulfate. Evaporation of the chloroform yielded a pale orange gum (165 mg), which, by tlc (alumina, ethyl acetate, antimony pentachloride in carbon tetrachloride, 1:1, as spray reagent), showed the presence of unreacted benzyl ethers as well as a mixture of more polar green spots and one polar brown spot. The crude product was chromatographed on alumina (10 g). Elution with benzene–ethyl ether (1:1) removed the unreacted benzyl ethers (65 mg, 28% recovery). Ether–methanol (99:1) removed a mixture of the alcohols designated A and B (21 mg) and ether–methanol (98:2) removed a mixture of alcohols B and B′ (5 mg). Continued elution with ether–methanol (98:2 and 95:5) removed a further mixture of alcohols (B, B′) and the uncyclized amino alcohol (49 mg). The uncyclized amino alcohol was identical by tlc with that prepared by hydrogenolysis of a small amount of uncyclized benzyl ether. Elution with ether–methanol (95:5 to 9:1) then removed the major pure cyclized alcohol C (26 mg) as an amorphous white solid while elution with ether–methanol (4:1) removed residual alcohol C (6 mg). Although a very minor alcohol designated D was observed in tlc of the crude product as being more polar than C, this material was not recovered from the column. The total weight of the amino alcohols (107 mg) represented an 83% yield. Rechromatography of the mixture of cyclized alcohols B, B′, and the uncyclized amino alcohol afforded complete separation of these cyclized alcohols from the uncyclized alcohol.

Alcohol C (V) exhibited the following: $\nu_{max}^{CHCl_3}$ 3500, 3350, 3150 (NH and OH) cm^{-1}; λ_{max} 225, 273 (sh), 282, 290 mμ; nmr (100 MHz) τ 0.40 (NH), 2.5–3.0 (diffuse, 4 H, aromatic), 5.78 (multiplet, 1 H, C-3H), 6.61 (broad singlet, CH_2OH), and 9.18 (distorted triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.205. Found: C, 76.31; H, 8.62; N, 9.25; mol wt 298.203 (high-resolution mass spectrometry).

Preparative tlc of a mixture of alcohols A and B (30 mg) on silica gel (20 × 20 cm, 0.3 mm, methanol) was performed. The bands removed from the plate were extracted with methanol and filtered. Evaporation of the filtrate provided residues which were taken up in chloroform to remove any silica gel and the solvent evaporated again to yield pure alcohol A (9 mg) and pure alcohol B (16 mg), both as white amorphous solids. Preparative tlc on a mixture of alcohols B and B′ (11 mg) using the same conditions provided an additional quantity of pure alcohol B (5 mg) and pure alcohol B′ (2 mg) as amorphous solids.

Alcohol A showed: λ_{max} 226, 273 (sh), 282.5, 290.5 mμ.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.205. Found: C, 76.21; H, 8.51; N, 9.30; mol wt 298.205 (high-resolution mass spectrometry).

Alcohol B exhibited the following: $\nu_{max}^{CHCl_3}$ 3400, 3330, 3200 (NH and OH) cm^{-1}; λ_{max} 226, 274 (sh), 283, 291 mμ; nmr (100 MHz) τ 2.50–3.15 (diffuse, approximately 4 H, aromatic), 5.72 (doublet, 1 H, C-3H), and 9.15 (triplet, CH_2CH_3).

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.205. Found: C, 76.12; H, 8.70; N, 9.40; mol wt 298.205 (high-resolution mass spectrometry).

Alcohol B′ showed: λ_{max} 226, 274 (sh), 282.5, 290.5 mμ.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.205. Found: C, 76.35; H, 8.60; mol wt 298.204 (high-resolution mass spectrometry).

Hydrogenolysis of Cyclized Benzyl Ether C (IV). The ether C (IV) (8 mg) obtained pure by preparative tlc as described earlier was treated with palladium catalyst according to the procedure used above for the isomeric mixture. The product obtained (5 mg) was identical by tlc (alumina, ethyl acetate; silica gel, methanol) with alcohol C isolated from the hydrogenolysis of the mixture of ethers and different from the isomeric alcohols A, B, and B′.

Mesylation of Alcohol C (V). A number of experiments with varying amounts of alcohol C were performed. Only one typical experiment is reported.

A solution of alcohol C (V) (43 mg) in dry pyridine (0.3 ml, distilled from potassium hydroxide) was cooled in an ice bath and added to ice-cold methanesulfonyl chloride (120 mg) in a small test tube. The resultant light orange solution was allowed to stand in a refrigerator for 16 hr after which time the solution was dark red. Most of the pyridine was evaporated under a stream of nitrogen with the aid of slight warming and the last traces finally removed on an oil pump. The gummy red residue was washed twice with anhydrous ether, treated with water (0.5 ml) which appeared to partially dissolve the product, and washed twice further with benzene. Ammonium hydroxide (1 ml, 6 *N*) was added and the aqueous mixture was extracted thoroughly with chloroform (until the color of the extract was only pale yellow). The resultant dark red chloroform was dried quickly over anhydrous sodium sulfate and evaporated to provide a dark red gum (60 mg). Tlc (alumina, ethyl acetate, antimony pentachloride spray) showed the complete absence of the starting alcohol (R_f 0.25–0.30) and the presence of a less polar green spot (compound VI) (R_f 0.70), as well as a green spot on the base line (compound VII); λ_{max} 226, 282, 289 mμ (shoulder at 273 distorted, probably due to presence of pyridine). This product was allowed to stand in a vacuum desiccator for 4 days, after which time it was very hygroscopic and tlc indicated a considerable increase in intensity of the base line spot relative to the spot which was less polar than the starting alcohol. Refluxing the material in chloroform for a few minutes did not noticeably alter the relative quantities of these two spots so this material was used for the following reduction.

Reduction of the Quaternary Mesylate (VII). The mesylate (30 mg), obtained as described above, was placed in a round-bottomed three-necked flask equipped with a Dry Ice trap and an ammonia inlet. (This operation was carried out as rapidly as possible because the amorphous mesylate turned gummy very quickly.) Ammonia (5 ml) was run into the flask and sodium (50 mg) added to the suspension. The resulting blue solution was stirred for 20 min, then quenched with ammonium chloride. The ammonia was allowed to evaporate and the residue partitioned between chloroform and water. The layers were separated and the chloroform layer washed three times with water and dried over anhydrous sodium sulfate. Evaporation of the chloroform provided a brown residue (20 mg). Chromatography of this material on alumina (1.0 g) and elution with benzene removed the major product (8 mg) which, by tlc on silica gel (chloroform–ethyl acetate, 1:1, antimony pentachloride), contained both 4α- and 4β-dihydrocleavamine, as well as a third component which had an R_f value intermediate between the two cleavamine derivatives.

The above procedure was repeated on the remaining mesylate (28 mg) to yield an additional identical mixture (7 mg). The combined products (15 mg) were chromatographed on neutral alumina (10 g, Woelm). Elution with ether yielded pure 4α-dihydrocleavamine (XXXIII) (1 mg) which was identical with an authentic sample (mass spectrometry, tlc on several systems—silica gel, chloroform–ethyl acetate, 1:1, antimony pentachloride and 1% ceric ammonium sulfate in 85% phosphoric acid as spray reagents; alumina, petroleum ether–benzene, 4:1, same spray reagents, as well as infrared comparison as noted below). Continued elution with ether removed a mixture of the three compounds (8 mg) which was then further purified.

Preparative tlc on silica gel (20 × 20 cm, 0.3 mm, chloroform–ethyl acetate, 1:1) was performed on this mixture. As the bands corresponding to 4β-dihydrocleavamine and the unknown compound occurring between the two dihydrocleavamines overlapped extensively, only the very top portion of the desired band was removed and extracted with methanol. Extraction, with chloroform, of the residue obtained by removal of the methanol, gave, after evaporation of the solvent, pure 4β-dihydrocleavamine (XXXIV) (1 mg) which was identical with an authentic sample (mass spectrometry, tlc in several systems—silica gel, chloroform–ethyl acetate, 1:1, alumina, petroleum ether–benzene, 4:1, using sprays mentioned above).

In larger scale experiments both dihydrocleavamine isomers were obtained in sufficient quantities for further comparisons. Thus, 4α-dihydrocleavamine, obtained as an amorphous solid, showed an infrared spectrum superimposable with that of an authentic sample,[17] while 4β-dihydrocleavamine, obtained crystalline, mp 136–138°, was also identical (infrared and mmp 136–138°) with the authentic compound.[17]

Oxidation of 4β-Dihydrocleavamine with *t*-Butyl Hypochlorite. A solution of 0.50 *M* *t*-butyl hypochlorite (7.1 ml, 0.36 mmol) in carbon tetrachloride was added over a period of 30 min to a solution of 4β-dihydrocleavamine (100 mg, 0.36 mmol) and triethylamine (0.07 ml) in methylene chloride (13.3 ml) cooled in an ice–acetone bath. After the addition was complete, the solution was stirred for a further 15 min at the temperature of the ice–acetone bath. The orange colored solution was then diluted with an equal volume of benzene and rapidly percolated through a column of alumina (1.5 g). The bulk of the solvent was removed at room temperature in a rotary evaporator and then the last traces were removed *in vacuo* to provide the chloroindolenine XXXV as a pale yellow oil (101 mg): $\lambda_{max}^{isooctane}$ 227, 260 (broad), 303 (broad) mμ (log ε 4.31, 3.55, 3.42, respectively); $\nu_{max}^{CHCl_3}$ 2770 (Bohlmann band), 1600 and 1560 cm^{-1} (indolenine C=N); nmr (100 MHz) τ 2.5–3.1 (diffuse, 4 H, aromatic protons), 8.79 (approximately quartet, 2 H, CH_2–CH_3), and 9.14 (triplet, 3 H, CH_2–CH_3); mass spectrum, main peaks, *m/e* 318, 316, 281, 138, and 124.

Anal. Calcd for $C_{19}H_{25}N_2Cl$: C, 72.01; H, 7.95; N, 9.15; mol wt 316.171. Found: C, 72.11; H, 7.82; N, 9.21; mol wt 316.172 (high-resolution mass spectrometry).

Lithium Aluminum Hydride Reduction of Chloroindolenine (XXXV). Lithium aluminum hydride powder (5 mg) was added slowly while stirring to a solution of the above chloroindolenine (23 mg) in anhydrous diethyl ether (20 ml). After 15 min, ethyl acetate (saturated with water) was added until gas evolution ceased. The mixture was then filtered and the filtrate dried and evaporated to give a gummy residue (21 mg) which was chromatographed on alumina (2 g). Elution with 1:1 petroleum ether (bp 30–60°)–benzene provided 12.5 mg of a crystalline material, which on recrystallization from methanol gave 4β-dihydrocleavamine, mp 136–138°, identical with an authentic sample as shown by mp and mmp 136–138°, comparison ir, and tlc (alumina, benzene and silica gel, chloroform).

Reaction of Chloroindolenine (XXXV) with Potassium Cyanide. A solution of the chloroindolenine (XXXV, 559 mg), potassium cyanide (1.22 g), methanol (15.5 ml), water (1.67 ml), and diethyl ether (3.34 ml) was stirred under a nitrogen atmosphere for 48 hr at room temperature. An aqueous potassium carbonate solution (10%, 25 ml) was then added and the solution extracted with methylene chloride (three 25-ml portions). The combined extracts were dried and evaporated to give a glassy residue (491 mg). This residue was chromatographed on alumina (50 g). Elution with benzene provided 118 mg of a mixture of compounds called group A. Tlc (alumina, benzene) showed one major spot which was blue in color with a pink fringe at R_f 0.5. Silica gel chromatoplates (1:1 chloroform–ethyl acetate) showed two major spots: one pink in color at R_f 0.9 and the other grey-blue at R_f 0.1; λ_{max} 294, 285, 278 (sh), 225 (indicative of indole chromophore); $\nu_{max}^{CHCl_3}$ 3410 (NH), 2220 (nitrile group) cm^{-1}.

Further elution in the above chromatography with methylene chloride (vol %, from 12 to 30) in benzene provided 140 mg over 42 fractions of a mixture of compounds called group B. Alumina chromatoplates (3:1 benzene–ethyl acetate) of early fractions of mixture showed one green-brown spot at R_f 0.5 and chromatoplates of late fractions of mixture showed one red-brown spot at R_f 0.5. Silica gel chromatoplates (1:1 chloroform–ethyl acetate) showed one brown spot at R_f 0.5; λ_{max} 290, 282, 278, 273; $\nu_{max}^{CHCl_3}$ 3400 (NH), 2220 (very strong, indicating a conjugated nitrile group) cm^{-1}. Nmr spectra of select fractions indicated the spectra were composed of signals from three compounds—one with distinguishing signals at τ (approximate) 6.63 (singlet), 5.41 (singlet), 1.63 (singlet, exchangeable proton); another with distinguishing signals at τ (approximate) 6.35 (singlet), 1.45 (singlet, exchangeable proton); the third with distinguishing τ (approximate) 6.6 (singlet).

Group A was chromatographed on silica gel (10 g) Elution with 3:1 benzene–chloroform provided a series of fractions which contained 36 mg of a mixture of compounds that was initially thought to be one compound, but freshly activated silica gel chromatoplates (chloroform) showed two overlapping spots at R_f 0.3. Preparative tlc (freshly activated silica gel, chloroform) provided a sample of both components of the mixture, each of which contained about 10% of the other component as an impurity. The partially purified sample having the larger R_f value had λ_{max} 293, 240, and 210 mμ; ν_{max} 3300 and 2220 (both very weak and probably from contaminant), 1613 and 1595 (indolenine C=N?) cm^{-1}; nmr (100 MHz) τ 9.12 (triplet, 3 H, CH_2CH_3), 5.98 (singlet, exchangeable proton, 1 H, O*H* or N*H*), and 2.8–3.5 (diffuse, 4 H, aromatic protons). Further purification was attempted without success.

The partially purified sample having the smaller R_f value had λ_{max} 293.5, 284.5, 272 (sh), 225 mμ; ν_{max} 3300 (NH), 2670 (Bohlmann band), 2220 (CN) cm^{-1}; nmr (100 MHz) τ 9.10 (triplet, 3 H, CH_2CH_3), 4.58 (doublet, 1 H, C-18 proton), 2.45–3.0 (diffuse, 4 H, aromatic protons), and 1.47 (singlet, 1 H, NH). The sample

was subjected to rigorous purification by preparative tlc. Freshly activated silica gel plates (5 × 20 cm, 0.25 mm thickness) were used and chloroform was used as the transporting solvent. The desired band was scraped off and eluted with ethyl acetate to provide a sample of 18β-cyano-4β-dihydrocleavamine (XLI, 10 mg): mass spectrum, main peaks, *m/e* 307 (molecular ion), 138, and 124.

Anal. Calcd for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67; mol wt 307.205. Found: C, 78.01; H, 8.10; N, 13.37; mol wt 307.205 (high-resolution mass spectrometry).

Further elution in the above chromatography with 2% triethylamine in acetone provided 40 mg of 18α-methoxy-4β-dihydrocleavamine (XXXVIII) as a glass which became crystalline in form on standing. Recrystallization of this compound from methanol provided a sample with mp 126–127°: λ_{max} 292, 284, 277 (sh), 225 mμ (log ε 3.86, 3.90, 3.86, 4.49, respectively); ν_{max} 3280 (NH), 2780 (Bohlmann band), 1070 (COMe) cm^{-1}; nmr (100 MHz) τ 1.63 (singlet, 1 H, N*H*), 2.45–3.2 (diffuse, 4 H, aromatic protons), 5.47 (pair of doublets, 1 H, C-18 protons), 6.80 (singlet, 3 H, COOC*H*$_3$), and 9.46 (triplet, 3 H, CH_2CH_3); mass spectrum; main peaks, *m/e* 312, 281, 280, 187, 182, 138, and 124.

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97; mol wt 312.220. Found: C, 76.51; H, 9.12; N, 8.82; mol wt 312.220 (high-resolution mass spectrometry).

18β-Carbomethoxy-4β-dihydrocleavamine (XLII) *via* Treatment of Group A with Methanolic Hydrochloric Acid. A solution of group A (113 mg) in anhydrous saturated methanolic hydrochloric acid (35 ml) was heated under reflux for 30 min, let stand overnight at room temperature, and heated again under reflux for 4.5 hr. After the reaction solution had been evaporated almost to dryness, it was partitioned between diethyl ether and an aqueous solution of sodium carbonate. The organic layer was separated, washed with water, and dried. Removal of the solvent provided a gummy residue (92 mg) which was chromatographed on alumina (4 g). Elution with benzene provided a mixture (30 mg) which contained 18β-carbomethoxy-4β-dihydrocleavamine as a major component. This mixture was rechromatographed on alumina (2.5 g). Elution with benzene provided several fractions containing 18β-carbomethoxy-4β-dihydrocleavamine. One of these fractions (3.3 mg) showed only one spot when subjected to an investigation on alumina chromatoplates (3:1 benzene–chloroform, 3:1 benzene–ethyl acetate). Further investigation by tlc (silica gel, 1:1 chloroform–ethyl acetate) showed that it was a mixture of several compounds. Purification by preparative tlc using a silica gel plate (5 × 20 cm, 0.25 mm thickness) and the above solvent system provided 18β-carbomethoxy-4β-dihydrocleavamine (0.7 mg) as shown by tlc comparison and identical mass spectra with an authentic sample (see below for further characterization).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: mol wt 340.215. Found: 340.212 (high-resolution mass spectrometry).

18β-Carbomethoxy-4β-dihydrocleavamine (XLII) *via* Treatment of Group B with Potassium Hydroxide and Diazomethane. A sample of group B (10.0 mg) was dissolved in a 20% solution (0.1 ml) of potassium hydroxide in diethylene glycol and heated at 150° for 8.5 hr under nitrogen atmosphere. The solution was then allowed to cool to room temperature and diluted with methanol (0.2 ml). This methanolic solution was cooled in an ice–water bath and treated with a saturated solution of hydrogen chloride in methanol until it had become slightly acidic as shown by indicator paper. An ethereal solution (1 ml) of diazomethane (~20 mg) was added immediately and the resulting mixture was allowed to stand in an ice–water bath for 15 min. In the same manner as above, the mixture was reacidified and treatment with excess diazomethane two more times before the ether, methanol, and excess diazomethane were removed with the aid of a nitrogen stream and a warm water bath. The residue obtained was shaken with an aqueous 10% solution of potassium carbonate (1 ml) and extracted with diethyl ether (three 5-ml portions). After the ethereal extract had been dried, the ether was removed to provide a viscous material (14.5 mg) containing diethylene glycol which was chromatographed on alumina (2 g). Elution with 4:1 petroleum ether (bp 30–60°)–benzene provided 18β-carbomethoxy-4β-dihydrocleavamine (3.1 mg) which upon recrystallization from methanol had a mp of 145–148° and was found to be identical with an authentic sample as shown by mp and mmp 145–148°, comparison ir and tlc (alumina, 3:1 benzene–chloroform and silica gel, 1:1 chloroform–ethyl acetate).

Reaction of Chloroindolenine (XXXV) with Hydrogen Cyanide. An anhydrous methanolic solution (19.5 ml) containing 1.5% hydrogen chloride was added slowly with stirring to a mixture of the chloroindolenine (229 mg) and potassium cyanide (378 mg) in a flask which had been fitted with an efficient condenser and was cooled in an ice–water bath. Escaping hydrogen cyanide gas was passed into an aqueous potassium hydroxide solution and the entire experiment was carried out in an efficient fume hood. After the addition of the methanolic hydrogen chloride had been completed, the resulting solution was refluxed for 3 hr under a nitrogen atmosphere. Then the reaction solution was cooled in an ice–water bath and solid sodium carbonate was added until the solution was neutral to indicator paper. The solution was diluted with water (29.5 ml), made quite basic by the addition of sodium carbonate, and extracted with methylene chloride (five 20-ml portions). The methylene chloride solution was dried and rotary evaporated to yield a glassy residue (219 mg). The major portion (196 mg) of this residue was chromatographed on alumina (20 g). Elution with 3:1 petroleum ether (bp 30–60°)–benzene provided a mixture (79 mg) of two compounds. A portion (62 mg) of this mixture was chromatographed on silica gel (6 g). Elution with 1:1 chloroform–ethyl acetate provided a compound (15 mg) which immediately crystallized on trituration with methanol. Recrystallization of this compound from methanol–diethyl ether provided a sample, mp 175–178°, of 18β-methoxy-4β-dihydrocleavamine (XXXIX): λ_{max} 294, 286, 279 (sh), 227 (log ε 3.85, 3.91, 3.87, 4.48, respectively); ν_{max} 3250 (NH), 2780 (Bohlmann band), 1075 cm^{-1} (COMe); nmr (100 MHz) τ 1.70 (singlet, 1 H, N*H*), 2.44–3.06 (diffuse, 4 H, aromatic protons), 4.76 (pair of doublets, 1 H, C-18 proton), 6.86 (singlet, 3 H, COOC*H*$_3$), and 9.11 (triplet, 3 H, CH_2CH_3); mass spectrum: main peaks, *m/e* 312, 281, 280, 187, 182, 138, 126, and 124.

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97; mol wt 312.220. Found: C, 77.01; H, 9.13; N, 8.80; mol wt 312.221 (high-resolution mass spectrometry).

Elution in the above chromatography with 2% triethylamine in acetone provided a compound (37 mg) which slowly crystallized on standing. Recrystallization of this compound from methanol provided a sample with mp 126–127°, which was identical (mp and mmp 126–127°, nmr, ir, tlc) with authentic 18α-methoxy-4β-dihydrocleavamine (XXXVIII).

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 77.15; H, 9.28; N, 8.75.

Preparation of Quaternary Acetate Salt. A solution of the chloroindolenine XXXV (101 mg) in a glacial acetic acid solution (6.5 ml), which contained 10% fused sodium acetate by weight, was heated at 60° for 2 hr under a nitrogen atmosphere. The reaction solution was then poured into a mixture of 15 *N* ammonium hydroxide (8 ml) and methylene chloride (26 ml) with rapid stirring. The organic phase was separated and saved and the aqueous phase was made strongly basic by the addition of 15 *N* ammonium hydroxide, saturated with ammonium acetate, and extracted with methylene chloride (three 10-ml portions). The methylene chloride extracts were then combined and dried. Removal of the solvent provided 93 mg of a white powder. Tlc (alumina, 3:1 ethyl acetate–ethanol) showed two overlapping green colored spots at R_f 0.2. This material was used directly for the synthesis of 18β-cyano-4β-dihydrocleavamine (XLI) as described below.

An Attempt to Prepare an 18-Acetoxy-4β-dihydrocleavamine. A solution of the chloroindolenine XXXV (367.5 mg) in a glacial acetic acid solution (23.3 ml), which contained 10% fused sodium acetate by weight, was heated at 60° for 30 min under a nitrogen atmosphere. Then, the reaction solution was immediately poured into a rapidly stirred mixture of 15 *N* ammonium hydroxide (30 ml) and methylene chloride (93 ml) which was maintained at low temperature in an ice–acetone bath. The organic phase was separated and saved. A further portion of methylene chloride (46.5 ml) was added to the aqueous phase and while the mixture was being rapidly stirred at the temperature of the ice–acetone bath, the weakly basic aqueous phase was made strongly basic by the addition of 15 *N* ammonium hydroxide. The organic phase was separated and combined with the previously separated organic phase. The combined solution was dried and rotary evaporated to give a gummy residue (416 mg) which was chromatographed almost immediately on silica gel (20 g). Elution with ethyl acetate provided 67 mg of material over several fractions. Each fraction was shown to contain the chloroindolenine XXXV and another compound(s) believed to be an 18-acetoxy-4β-dihydrocleavamine. The spectral properties of the purest fractions were determined: λ_{max} 292 (sh), 284, 278 (sh), 226 (slightly distorted indole spectrum); $\nu_{max}^{CHCl_3}$ 3300 (indole NH), 1720 (ester C=O) cm^{-1}; nmr (100 MHz) τ 1.72 (singlet, NH), 2.5–3.2 (diffuse, aromatic protons), 3.97 (pair of doublets, C-18 proton), 7.96 (singlet, CH_3COO), and 9.15 (triplet, CH_2CH_3) (signals which could be attributed to an acetoxy-4β-dihydrocleavamine).

Further elution in the above chromatography with 3% triethyl-

amine in ethyl acetate gave a further 116 mg of material consisting mainly of the chloroindolenine XXXV and the compound(s) believed to be an 18-acetoxy-4β-dihydrocleavamine. Finally, the column was washed with 5% acetic acid in methanol and 1:1 methanol–water. The washings were combined, rotary evaporated to give a residue which was treated with a saturated aqueous ammonium acetate solution (10 ml) containing ammonium hydroxide, and extracted with methylene chloride (three 25-ml portions). The combined extracts were dried and evaporated to provide 164 mg of a mixture of compounds which consisted mainly of the quaternary salt as shown by tlc.

A mixture (65.5 mg) containing the alleged 18-acetoxy-4β-dihydrocleavamine from the chromatography above was chromatographed on alumina (6 g). Elution with 1:1 petroleum ether (bp 30–60°)–benzene gave 27 mg of a mixture which was shown by tlc to contain the chloroindolenine XXXV as the major component. Elution with 1:1 benzene–ethyl acetate gave 14.3 mg of 18β-hydroxy-4β-dihydrocleavamine (XL). Recrystallization from methanol provided a sample, mp 202–205°: λ_{max} 292, 284, 278 (sh), 226 mμ (log ε 3.86, 3.91, 3.87, 4.50, respectively); ν_{max} 3200 (broad, NH and OH), 2700 (Bohlmann band) cm^{-1}; nmr (100 MHz) τ 1.42 (broad singlet, 1 H, OH), 2.19 (singlet, 1 H, N*H*), 2.5–3.15 (diffuse, 4 H, aromatic protons), 4.77 (unresolved multiplet becoming a doublet after treatment of nmr sample with D_2O, 1 H, C-18 proton), and 9.17 (triplet, 3 H, CH_2CH_3); mass spectrum, main peaks, *m/e* 298, 281, 280, 173, 168, 138, and 124.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39; mol wt 298.205. Found: C, 76.31; H, 8.60; N, 9.31; mol wt 298.205 (high-resolution mass spectrometry).

Reduction of Quaternary Acetate Salt with Lithium Aluminum Hydride. A mixture (25 mg) of salt and lithium aluminum hydride (101 mg) was allowed to react in refluxing N-methylmorpholine (10 ml) under a dry, oxygen-free nitrogen atmosphere. Aliquots (approximately 0.5 ml) were taken periodically. Each aliquot was treated with ethyl acetate (saturated with water) until gas evolution ceased. The mixture was filtered and the residue washed with methylene chloride (approximately 2 ml). The filtrate and washings were combined, dried, and evaporated with the aid of a nitrogen stream and a hot-water bath. The residue was examined by tlc (alumina, 3:1 benzene–chloroform and 3:1 ethyl acetate–ethanol, and silica gel, chloroform). After 1 hr, the presence of 4β-dihydrocleavamine was detected. After 4.5 hr, the chromatoplates on development showed a major spot which corresponded in color and R_f value to a spot from an authentic sample of 4β-dihydrocleavamine.

18β-Cyano-4β-dihydrocleavamine (XLI). The quaternary ammonium salt (73.3 mg) was allowed to react with potassium cyanide (56 mg) in refluxing dimethylformamide (9 ml) for 1.7 hr under a nitrogen atmosphere. The solvent was then removed by distillation at reduced pressure. The residue obtained was treated with 6 *N* ammonium hydroxide (1 ml) and the aqueous mixture was extracted with methylene chloride (three 5-ml portions). The extract was then dried and the solvent removed to provide a gummy residue (64.4 mg). The residue was then chromatographed on silica gel (7 g). Elution with 1:1 benzene–chloroform provided 15.7 mg of 18β-cyano-4β-dihydrocleavamine (XLI) which gave crystals from methanol with mp 150–152°: λ_{max} 294, 285, 277, 226 mμ (log ε 3.86, 3.93, 3.89, 4.44, respectively); ν_{max} 3300 (NH), 2760 (Bohlmann band, 2220 (CN) cm^{-1}; nmr (100 MHz) τ 1.72 (singlet, 1 H, N*H*), 2.48–3.04 (diffuse, 4 H, aromatic protons), 4.58 (pair of doublets, 1 H, C-18 protons), and 9.10 (triplet, 3 H, CH_2CH_3), mass spectrum, main peaks, *m/e* 307, 281, 280, 182, 177, 138, and 124.

Anal. Calcd for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67; mol wt 307.205. Found: C, 77.98; H, 8.05; N, 13.43; mol wt 307.205 (high-resolution mass spectrometry).

18β-Carbomethoxy-4β-dihydrocleavamine (XLII) from 18β-Cyano-4β-dihydrocleavamine (XLI). A solution of 18β-cyano-4β-dihydrocleavamine (5.21 mg) in a solution (0.05 ml) of diethylene glycol containing 20% KOH by weight was heated at 150° for 9 hr under a nitrogen atmosphere. Then, the solution was allowed to cool to room temperature and diluted with methanol (0.1 ml). While this new solution was kept cool in an ice–water bath, a saturated solution of methanolic hydrochloric acid was added to it until it had become slightly acidic to test with indicator paper. A solution (0.5 ml, approximate concentration 20 mg/ml) of diazomethane in ether was immediately added and the resulting mixture was allowed to stand in an ice–water bath for 15 min. In the same manner as above, the reaction mixture was reacidified and treated with excess diazomethane two more times before the ether, methanol, and excess diazomethane were removed with the aid of a nitrogen stream and a warm water bath. The residue obtained was shaken with an aqueous 10% potassium carbonate solution and extracted with diethyl ether. After the ethereal extract had been dried, the ether was removed to provide a viscous material (23 mg) which was mainly diethylene glycol. This material was chromatographed on alumina (1 g). Elution with 4:1 petroleum ether (bp 30–60°)–benzene provided 18β-carbomethoxy-4β-dihydrocleavamine (2.97 mg). Recrystallization provided a sample, mp 146–148°, which was identical with an authentic sample of 18β-carbomethoxy-4β-dihydrocleavamine as shown by mp and mmp 146–148°, comparison ir, and tlc (alumina, 3:1 benzene–chloroform and silica gel, 1:1 chloroform–ethyl acetate).

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