185. Total Synthesis of Indole and Dihydroindole Alkaloids. VII[1][2]). The Total Synthesis of Isovelbanamine, Velbanamine, Cleavamine, 18β-Carbomethoxycleavamine and Catharanthine

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(15. V. 75)

Summary. A synthesis of a variety of nine-membered ring intermediates in the cleavamine-velbanamine series is described. The formation of the penultimate intermediate involves a fragmentation reaction in which the cleavamine system is generated from an appropriate rigid pentacyclic *Iboga* alkaloid derivative. Thus dihydrocatharanthinol tosylate (VIII) on reaction with triethylamine in refluxing benzene undergoes fragmentation to the 5,18-*seco*-diene X. This latter substance is then elaborated in various ways to the desired compounds.

In previous studies [3] we were able to complete the total syntheses of a variety of *Iboga* alkaloids and their derivatives. The approach employed initially the synthesis of the appropriate nine-membered ring intermediates of the cleavamine family (for example, I, R = $COOCH_3$) which, after transannular cyclization, convert to pentacyclic *Iboga* systems (II, R = $COOCH_3$). The cleavamine derivatives are furthermore of particular interest in that they represent the indole portion of the bis indole-dihydroindole family of alkaloids exemplified by vinblastine (III) [4] [5], vincristine (IV) [4] [5], leurosidine (V) [6] and leurosine (VI) [7–9], the first two of which are clinically important anti-tumor agents.

In order to provide the required indole units for the laboratory synthesis of these medicinally important agents it was essential to develop a synthetic scheme which would allow functionalization of the 3,4-positions of the cleavamine system. Since the previous investigations [3] did not provide a facile synthetic entry into such systems, a new pathway was required for such an objective.

The approach selected for this purpose involved a fragmentation reaction which, if successful, would generate the nine-membered ring system inherent in cleavamine as well as an enamine group, the latter being useful for introduction of oxygen functionality at the 3,4-positions. The dihydrocatharanthine system readily available from previous studies [3], possessed the essential steric requirements for a fragmentation process (*Scheme 1*) originally studied by *Grob* [10] and subsequently applied in the alkaloid field [11] [12] and it was selected for this study. Catharanthine (II, R = $COOCH_3$, 3,4-double bond) was converted to dihydrocatharanthine (II, R = $COOCH_3$) by catalytic hydrogenation. Lithium aluminum hydride reduction of this product gave dihydrocatharanthinol VII [13], the starting material for our sequence.

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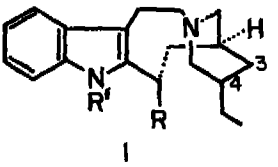
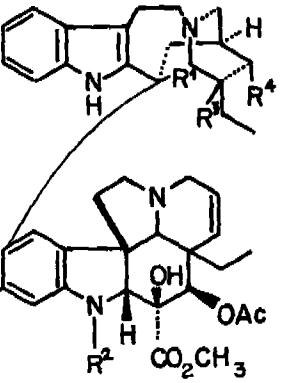
[1]) For a preliminary report on a portion of this work see [1].

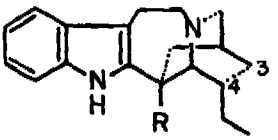
[2]) Part VI s. [2].



I



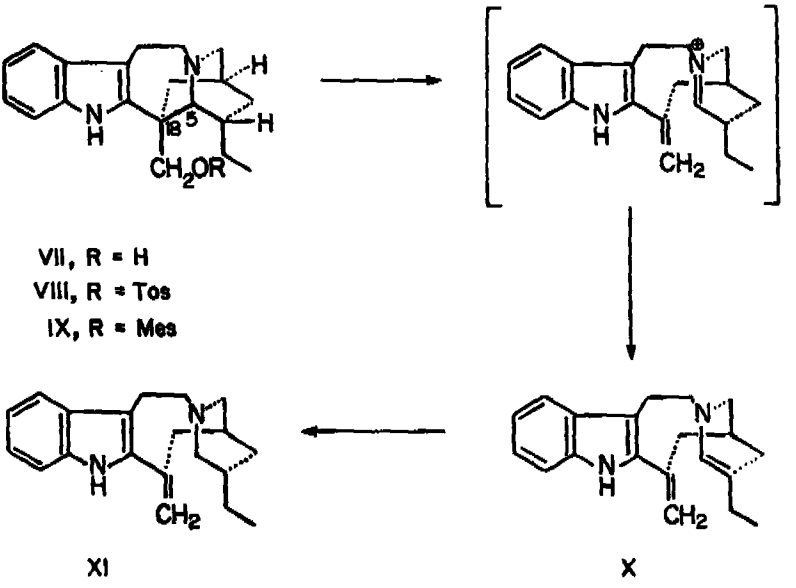
	R^1	R^2	R^3	R^4
III	CO_2CH_3	CH_3	OH	H
IV	CO_2CH_3	CHO	OH	H
V	CO_2CH_3	CH_3	H	OH
VI	CO_2CH_3	CH_3		



II

Treatment of dihydrocatharanthinol with an excess of tosyl chloride in dry pyridine gave the desired tosylate (VIII). The instability associated with this derivative prevented complete characterization although the spectral data taken on the crude material was in accord with the assigned structure.

Scheme 1. *Proposed scheme for ring opening of the dihydrocatharanthine system to the 5,18-seco-diene*



Ring opening of the tosylate occurred rapidly in a warm solution of benzene containing some triethylamine. The change of chromophore from indole to a vinyl-indole system allowed this reaction to be conveniently monitored by UV. spectroscopy. Optimum results were obtained by keeping the solution at 70° for two hours under a dry nitrogen atmosphere. The 5,18-*seco*-diene X was quite unstable in solution when exposed to air and a careful isolation of the product was mandatory. Under optimum conditions the diene could be obtained crystalline and in 62% overall yield based on the starting dihydrocatharanthinol.

Much of our earlier work in this sequence was frustrated by the apparently complex mixtures obtained from this reaction as evidenced by TLC. (both alumina and silica) on the crude product as well as a multitude of products obtained by column chromatography. It turned out, in fact, that the 5,18-*seco*-diene once obtained crystalline and in purified form also gave an extremely complex mixture during the investigation (about eight spots on both alumina and silica) and it became obvious at this point that the material was very unstable to chromatographic procedures.

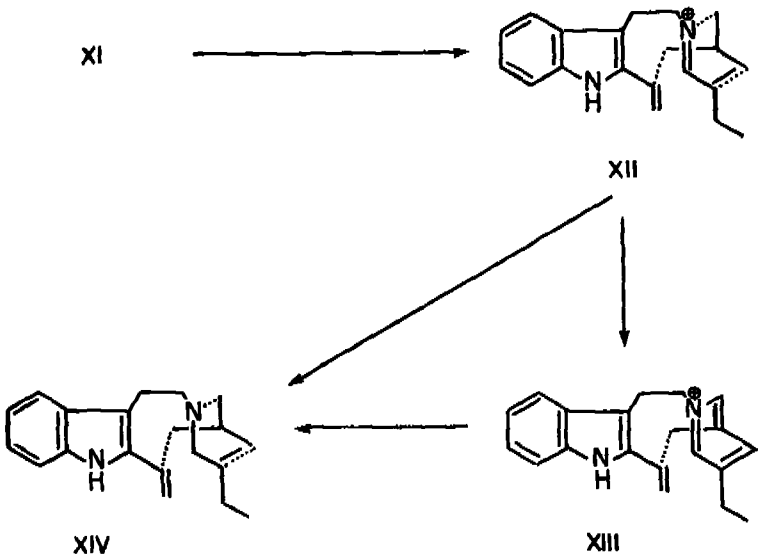
An analytically pure sample, obtained by sublimation, m.p. 136–136.5° was exposed to a detailed spectroscopic analysis. High resolution mass spectrometry gave the correct molecular formula, $C_{20}H_{24}N_2$, for the compound. The enamine system was evident from IR. (1657 cm^{-1}) and NMR. evidence (δ 5.71) while exocyclic olefin was apparent as part of the vinyl-indole chromophore in the UV. (λ_{max} 306 nm), by the absorptions at 1408 and 880 cm^{-1} in the IR., and two singlets at δ 5.25 and 5.11 in the NMR. spectrum.

Reduction of this compound with sodium borohydride in methanol produced the expected exocyclic olefin (XI). The NMR. of this material still showed the protons attributed to the exocyclic olefinic protons as observed in the starting material but the single proton singlet attributed to the enamine system had disappeared. The UV. spectrum also showed the same vinyl indole chromophore. The yield in the overall sequence from dihydrocatharanthinol to the exocyclic olefin XI was optimum (72%) when the intermediate *seco*-diene X was not isolated but immediately reduced directly in the reaction mixture.

The analogous reaction sequence using the mesylate IX instead of tosylate was also studied. The mesylate of dihydrocatharanthinol (IX) formed readily by reacting the starting material with methanesulfonyl chloride in pyridine at 0°. This material could be purified by chromatography although with considerable loss and thus the best yields were obtained by the use of the crude material in the subsequent fragmentation reaction. Ring opening of the mesylate in this case was carried out using potassium *t*-butoxide in *t*-butyl alcohol. The intermediate diene was not isolated from this reaction mixture but borohydride reduction of this mixture gave the exocyclic olefin XI identical to that from the tosylate sequence but in much lower yields (20%). On this basis the tosylate derivative was employed for all subsequent studies.

The above investigations had now provided, in good yield, an enamine grouping in the nine-membered ring system of the cleavamine series. It was now necessary to effect an isomerization of this double bond to the C(3)–C(4) position.

Our first approach to this problem was to attempt to dehydrogenate this tetrahydropyridine system to either a dihydropyridine or the fully aromatic pyridinium salt. Selective reduction of either of these intermediates could provide an entry to the cleavamine system bearing a C(3)–C(4) double bond (see XI → XII → XIII → XIV or XI → XII → XIV). Although aromatization would be the driving force thereby



favouring the formation of the intermediate pyridinium salt XIII, an examination of the molecular models of this intermediate showed it to be severely strained and it was thought that dehydrogenation would not occur to this extent. However, the dihydropyridinium salt XII would be expected to form. Reduction of such a system had been accomplished with sodium borohydride [14] and would lead to the desired diene system.

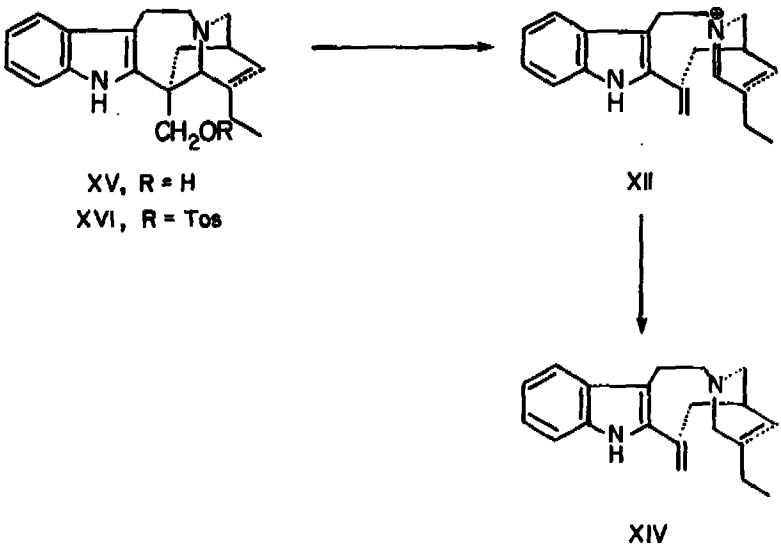
Reaction of the *seco*-diene X with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene at room temperature led to the immediate formation of a dark green precipitate. This material on reduction with sodium borohydride in methanol led to a number of products, a major one being the exocyclic olefin XI. The remaining products showed indole absorption in the UV. spectra instead of the vinyl-indole system which was necessary for our further studies. Dehydrogenation of X with mercuric acetate led to a very complex mixture of products. The UV. spectra of fractions from the chromatography of this mixture also indicated an indole chromophore.

An examination of the model of the desired diene product XIV indicated that it is more difficult for this structure than it is for the olefin XI, to exist in a conformation which would allow the exocyclic double bond to be in the plane of the indole system and hence in conjugation with it. Thus although the olefin XI exhibits the characteristic vinylindole absorption, the diene which could conceivably have the exocyclic double bond in a plane orthogonal to that of the indole moiety, might in such a case exhibit a simple indole absorption [15]. The multitude of products obtained from the dehydrogenation reactions could not therefore be ignored as being

undesired materials just because they exhibit a normal indole absorption in the UV. spectrum.

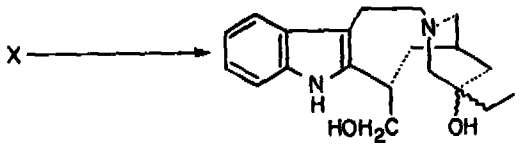
From these initial experiments it became clear that isolation of the diene XIV in reasonable yield from this dehydrogenation-reduction approach might be difficult. It was thought that this task could be simplified considerably if this compound were obtained first *via* a pathway starting with a model substance already containing the desired C(3)–C(4) double bond. If the model sequence could provide the diene, its stability, spectral properties and particularly procedures for its isolation could be studied.

The model substance which appeared ideal for this study was the alkaloid, catharanthine. Ring opening of catharanthinol-O-tosylate (XVI) would give the same intermediate (XII) desired in the dehydrogenation reaction. Reduction of this compound would then give the diene XIV.

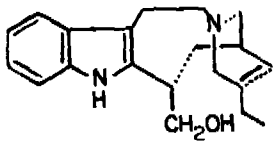


Catharanthinol (XV) obtained by lithium aluminum hydride reduction of catharanthine was tosylated in the usual manner. This compound was subjected to conditions identical to those successfully employed in the case of dihydrocatharanthinol-O-tosylate. The product obtained was not isolated but subjected immediately to sodium borohydride reduction. A complex mixture of products was obtained and all attempts to isolate these materials by chromatographic methods failed to provide any encouraging results.

The above and other studies not detailed here discouraged further work in this direction and thus an alternate study to effect the migration of the double bond in the diene system was initiated. Enamines are subject to electrophilic substitution and addition reactions [16] and in this regard hydroboration [17] appeared the reaction of choice. The anticipated product (XVII) from diborane addition to diene X would be amenable to dehydration (XVIII) and the primary alcohol in the latter could be finally transformed to a carbomethoxy function essential for subsequent studies.



XVII

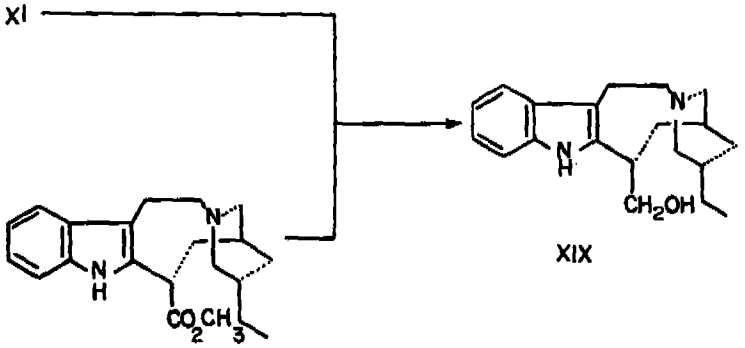


XVIII

In the course of this work and in subsequent hydroboration experiments, it was found that the tertiary nitrogen atom in these compounds could complex with the diborane to form amine-borane adducts. These adducts were stable to chromatographic separation and could be isolated in this manner as crystalline material. Recognition of the amine-borane complexes is readily achieved by IR. spectroscopy (2200–2400 and 1150 cm^{-1}) [18]. A convenient method to convert these complexes to the free bases involved reaction with triethylamine at reflux temperature.

Hydroboration of X, and decomposition of the resultant amine-borane complexes thus formed, provided a product which revealed that addition to both double bonds had occurred. An indole UV. spectrum and the loss of both the enamine and exocyclic methylene protons in the NMR. spectrum were noteworthy features while the mass spectrum with a molecular ion at *m/e* 312 instead of the expected value of 326 gave a clear indication that the product was not the desired diol XVII.

To establish the identity of this compound, the olefin XI was reacted with diborane and after exchange of the amine-borane complexes with triethyl amine, the crystalline product obtained was identical with that isolated from the above study. Reduction of 18β-carbomethoxy-4β-dihydrocleavamine (XX) [14] with lithium



XIX

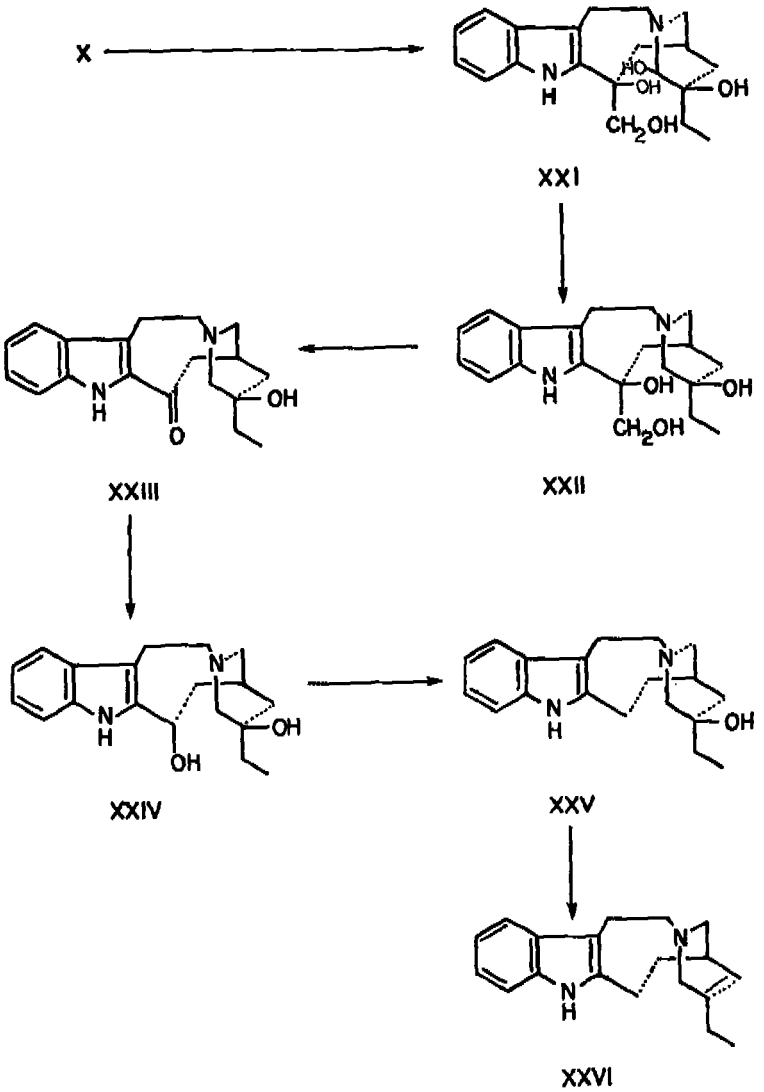
XX

aluminum hydride gave the same alcohol and established beyond doubt that the structure of the alcohol obtained from both the diene X and the olefin XI was 18β-hydroxymethyl-4β-dihydrocleavamine (XIX).

The above results revealed that reduction of the enamine system in X was occurring during the attempted hydroboration. Further studies with varying amounts of diborane were of no success and this approach was abandoned.

Another addition reaction to the enamine system in X involved the reaction of the latter with osmium tetroxide under conditions which do not effect the indole system. This approach proved highly successful and the overall reaction is summarized in *Scheme 2*. Thus the tetrol XXI resulting from the osmylation of X would be

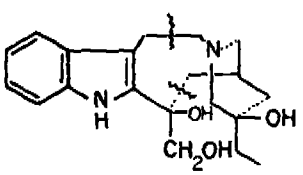
Scheme 2. *Synthesis of isovelbanamine* (XXV) *and cleavamine* (XXVI) *from the diene* (X) via *osmium tetroxide oxidation*



expected to undergo selective reduction to the triol XXII and the latter, *via* periodate cleavage and reduction should provide the diol XXIV. Hydrogenolysis of the 'benzylic' alcohol in this compound would then give XXV which should be either velbanamine or its epimer. Dehydration of this compound would give cleavamine (XXVI).

The osmylation reaction was carried out at dry-ice acetone temperature using exactly two equivalents of osmium tetroxide in a tetrahydrofuran-pyridine solvent system. The major product obtained gave spectral indications of being the correct tetrol. The UV. spectrum showed a typical indole absorption thereby establishing addition of osmium tetroxide to the exocyclic double bond of the vinyl indole system. No molecular ion could be seen in the mass spectrum, the highest peak appearing at *m/e* 342 ($M - 18$) and high resolution mass measurement of this ion established the formula $C_{20}H_{26}N_2O_3$, corresponding not unexpectedly, to a loss of water from the required molecular formula $C_{20}H_{28}N_2O_4$. The NMR. spectrum of this compound was particularly instructive. A one-proton singlet at δ 4.58 was in the expected position for a hydroxy-amine proton. A somewhat broadened singlet at δ 3.64, integrating for two protons and which sharpened considerably on deuterium exchange, could be assigned to the hydroxymethyl function. Deuterium exchange resulted in the loss of at least three protons, other than the indole N–H. Two of these hydroxyl protons appeared as surprisingly sharp singlets at δ 3.42 and δ 2.49.

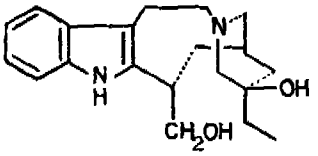
It was expected that the hydroxyl group of the hydroxyl-amine function in XXI would be readily removed with a metal hydride reducing agent. The tetrol was, therefore, treated at room temperature with sodium borohydride in methanol. The resultant compound, formed in essentially quantitative yield, had all the properties expected for the triol XXII. The mass spectrum gave a parent ion at *m/e* 344 and high resolution of this peak established the formula, $C_{20}H_{28}N_2O_3$. One of the important features of this spectrum is the fragment ion at *m/e* 154. By analogy with the mass spectral work done on velbanamine, this ion can be considered to result from the fragmentation shown in structure XXVII [4] [5]. It therefore presented good evidence for the presence of an hydroxyl function in the piperidine portion of the compound. Comparison of the NMR. spectrum of this compound with that of the tetrol showed the loss of the singlet attributed to the hydroxyl-amine proton.



XXVII

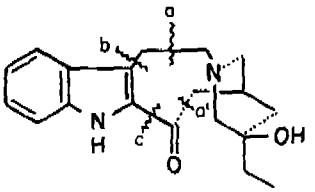
Further reduction of the triol could be achieved when it was treated with lithium aluminum hydride in refluxing tetrahydrofuran. Under these conditions, the 'benzylic' hydroxyl at C(18) (see XXVIII) was lost. Although this reaction was not on the main synthetic pathway, the production of this diol was useful because its NMR. spectrum provided unambiguous evidence for the osmylation of the exocyclic olefin

portion of the starting diene. The NMR. spectrum of XXVIII possessed a quintuplet at δ 4.10 (J = 5 Hz) and a doublet at δ 3.72 (J = 5 Hz), virtually identical to the multiplets observed for 18β-hydroxymethylcleavamine (XVIII) and 18β-hydroxymethyldihydrocleavamine (XIX). It was thus certain that the compound obtained from reduction of the triol XXII was represented by XXVIII.



XXVIII

For the purpose of completing the cleavamine and functionalized cleavamine syntheses it was necessary to remove or alter the C(18)-hydroxymethyl function in the appropriate fashion. The first step in this process was the periodate cleavage of the vicinal diol portion of the triol. The best yield (about 60% based on triol consumed) was obtained when this reaction was carried out in an acetone water solution at 0°. The resultant product XXIII portrayed the spectroscopic features (λ_{max} 317 and 238 nm; 1615 cm^{-1}) characteristic of a 2-acyl indole system[3]). In this instance no difficulty was encountered in obtaining the molecular ion in the mass spectrum. The fragmentation pattern analogous to that shown for the triol namely fissions *a* and *a'* (see XXIX) provide a prominent fragment at *m/e* 154. The indole component corresponding to this fragmentation is seen at *m/e* 157. The alternate fragmentations *b*, *a'* provide *m/e* 143 and 144 while fission *a*, *c* produces the ion observed at *m/e* 130.

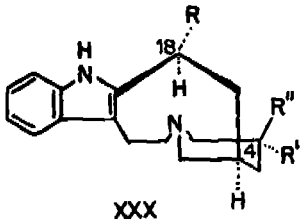


XXIX

Reduction of the ketol to the diol XXIV could be readily achieved by the action of sodium borohydride in methanol at room temperature. On the basis of NMR. spectral data obtained for this compound, the stereochemistry at C(18), one of the three asymmetric centers in this molecule could be assigned. Employing arguments already detailed in the accompanying publication [2] it was clear that the chemical shift observed for the C(18) proton in diol XXIV (δ 5.72) is in accord with the 18β designation for the hydroxyl function and XXIV may be represented in conformational terms by XXX. The configuration at C(4) (R = OH, R'' = CH_2CH_3; R' = OH) becomes available from subsequent studies (see below).

Conversion of the diol to the monohydroxy derivative XXV could be achieved using conditions employed earlier by *Dolby et al.* [20]. The NMR. spectrum of the product showed that the peak assigned to the C(18)-proton in the diol has moved considerably upfield to δ 3.44 and now appeared as a complex multiplet. The remaining OH is seen as a broad, one-proton singlet at δ 1.23 which disappears on

[3]) For a general review see [19].



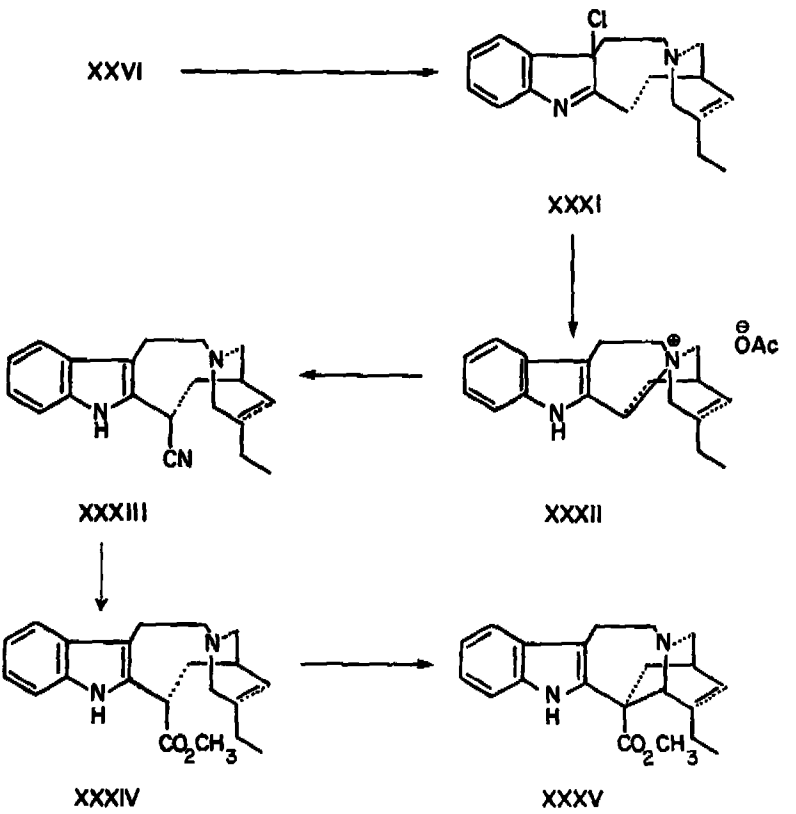
XXX

deuterium exchange. High resolution mass analysis of the parent ion in the mass spectrum established a molecular composition consistent with the assigned formula for the monohydroxy compound. This compound had to be either velbanamine (XXX, R = H; R' = CH_2CH_3; R'' = OH), the monomeric degradation product of vinblastine and vincristine or the epimeric alcohol. TLC. comparison of our compound with an authentic sample of velbanamine obtained by the established procedure from vinblastine [21], showed that these compounds were not the same. The mass spectrum of our compound, which has been named isovelbanamine, was, however, virtually superimposable with the spectrum obtained for velbanamine run under the same conditions and agreed also very well with the published mass spectrum for velbanamine [22]. This result provided strong evidence for the fact that these compounds were epimeric and this situation was proved by the next series of reactions.

It was known that velbanamine undergoes some dehydration to give cleavamine (XXVI) under the acidic conditions used to cleave vinblastine [21]. The acidic medium in this instance would favor an E(1)-elimination process which need not have a particular stereochemical requirement and it was therefore expected that isovelbanamine should dehydrate under the same conditions as velbanamine. Indeed treatment of isovelbanamine with concentrated sulfuric acid at 0° for 2 hours gave cleavamine as identified by a comparison with an authentic sample. Apart from establishing the structure of XXV, this reaction, in a formal sense, also completes a total synthesis of cleavamine since the starting material for this sequence, dihydrocatharanthine, had already been synthesized in our laboratory [3]. Furthermore it was now possible to make absolute stereochemical assignments at all the chiral centers in the various compounds synthesized according to the pathway shown in *Scheme 2*. Thus the 4α-orientation of the hydroxyl group in isovelbanamine (XXV) necessarily requires a similar orientation for the hydroxy-amine hydroxyl group in XXI in view of the well known *cis*-hydroxylation by osmium tetroxide. The absolute configuration at C(2) in cleavamine and velbanamine is *known* from two independent X-ray analyses [23] [24] [5]. Therefore the assignments shown for the various compounds are established in an absolute sense.

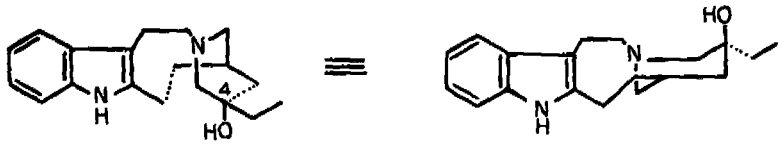
It was now of interest to extend this sequence to the 18β-carbomethoxycleavamine (XXXIV) series since the latter had already been converted, by means of the transannular cyclization reaction, to the alkaloid catharanthine (XXXV) [25]. Furthermore XXXIV would also provide a suitable intermediate for the C(3)–C(4) functionalized cleavamine derivatives required for the bisindole-indole dihydroindole alkaloids (III–VI). The approach employed was a direct adaption of the chemistry developed previously for the introduction of a C(18) carbomethoxy group into the dihydrocleavamine series [3]. A summary of the reactions is provided in *Scheme 3*.

Scheme 3. *Conversion of cleavamine* (XXVI) *to catharanthine* (XXXV)



Oxidation of XXVI with *t*-butyl hypochlorite was carried out at $-15°$ to form the chloroindolenine XXXI. The latter, without isolation, was treated immediately with fused sodium acetate in a solution of glacial acetic acid and acetic anhydride to form the quaternary salt XXXII. Rigorous precautions were taken to exclude water in the system during the preparation of the salt and the subsequent nitrile introduction. The very polar nature of the quaternary salt made it difficult to work with this material and it was found convenient to immediately treat the salt with a large excess of potassium cyanide in refluxing dimethyl formamide. The desired 18β-cyanocleavamine XXXIII exhibited the expected spectral properties. In particular, the characteristic nitrile absorption was observed in the IR. (2240 cm^{-1}) while high resolution mass spectrometry established the correct molecular composition. The NMR. spectrum of this compound showed a one-proton doublet of doublets at δ 5.52 ($J = 2$ and 10 Hz). This multiplet corresponded very closely to one observed in the spectrum of 18β-cyano-4β-dihydrocleavamine (δ 5.45, $J = 2$ and 10 Hz) [3] and was assigned to the C(18)-proton. Alkaline hydrolysis of XXXIII followed by esterification with diazomethane provided 18β-carbomethoxycleavamine (XXXIV) identified by comparison with an authentic sample.

The indole unit obtained from the cleavage of vinblastine (III) and vincristine (IV) [4] [5] is velbanamine (XXXVI) and it was now clearly of interest to extend the



XXXVI

above studies to this system. It was obvious from the above-mentioned conversion of isovelbanamine (XXV) to cleavamine that acidic media which promote carbonium ion formation at C(4) provide an olefinic product through subsequent loss of proton from C(3). We thus turned our attention to S_N2 type reactions even though a tertiary centre is not normally prone to such situations. Our first experiment involved the use of concentrated sodium hydroxide in a water dimethyl sulfoxide solution. Dimethyl sulfoxide was used because it is known to greatly enhance the activity of anions and thus is an excellent solvent for nucleophilic displacement reactions [26]. The driving force for the reaction would be the attainment of a more stable isomer; isovelbanamine has the ethyl substituent in an axial position when the piperidine ring is in a chair conformation, whereas velbanamine has the ethyl group in an equatorial position and also the hydroxyl function in the β-axial position is favourably oriented for hydrogen bonding with the tertiary nitrogen atom (see XXXVI). However, the experiment under a variety of conditions, failed to produce any velbanamine as evidenced by TLC.

In another series of investigations the use of boron-trifluoride etherate was employed under conditions described for cleavage of steroidal ethers [27]. Treatment of isovelbanamine under the prescribed conditions led to the disappearance of starting material as evidenced by TLC. and one major product resulted. Treatment of this product (thought to be an acetate) with lithium aluminum hydride gave, however, isovelbanamine as a major product and no velbanamine.

These preliminary experiments tended to suggest that S_N2 type displacement was unlikely to occur in the desired fashion and we initiated an examination of the alternate approach, that is, reaction conditions which would be expected to generate carbonium ion intermediates. Under the conditions for the conversion of isovelbanamine to cleavamine (concentrated sulfuric acid at 0° for 2 hours), the carbonium ion rapidly loses a proton to provide the olefinic system. We obviously require in the present study non-dehydrating conditions such that the reaction at the carbonium ion centre would instead be nucleophilic attack. We thus treated isovelbanamine with dilute aqueous acid at 0° up to three days and found under these conditions, the compound underwent no change. Also at room temperature no change was observed. However, refluxing this same solution, we obtain, after four hours the first indication on TLC. of the presence of some velbanamine. The proportion of velbanamine increased with time and the reaction was allowed to continue for two days. The resultant product mixture, after chromatographic purification, was shown to contain velbanamine and unreacted isovelbanamine as major components. The synthetic velbanamine thus obtained was identical (mixed m.p., TLC. and IR.) with an authentic sample[4].

[4] We are grateful to Dr. *N. Neuss*, Lilly Research Laboratories, Indianapolis, Indiana, for providing a sample of this substance.

In summary, the above studies have demonstrated that the fragmentation of dihydrocatharanthinol tosylate provides an intermediate which can be elaborated in a variety of compounds in the cleavamine-velbanamine series.

Experimental Part

All details concerning spectral measurement, chromatographic separations, etc. are described in the accompanying publication [2].

Dihydrocatharanthinol O-p-toluenesulfonate (VIII). Dihydrocatharanthinol [13] (1.58 g) was dissolved in dry pyridine (30 ml) and *p*-toluenesulfonyl chloride (4.7 g) was added to this solution. The reaction was allowed to proceed for 10 h at room temperature (RT.). The reaction mixture was then cooled to 0°, ice-cold methylene chloride (50 ml) was added and this solution was washed with 3% sodium hydrogen carbonate solution (3 × 50 ml), keeping the solution at 0° at all times. The methylene chloride/pyridine solution was then taken to dryness using first waterpump pressure and finally high vacuum. Again the solution had to be kept below 0° throughout this procedure. The resulting red gum still containing traces of pyridine, was dissolved in dry benzene (5 ml) and left to crystallize overnight in the refrigerator. The crude tosylate was filtered off to give 1.64 g of light brown crystalline material The mother liquors were taken up in benzene (10 ml) and freeze-dried to give a further 0.65 g of substantially pure tosylate as a reddish amorphous powder. Attempts to recrystallize the crystalline material failed and generally led to less pure tosylate because of decomposition in solution. The crystalline material gave the following data: IR. (KBr): 1355 cm^{-1} and 1173 cm^{-1}. – UV.: 292, 285, 276 (sh) nm.

5,18-seco-Diene X. Dihydrocatharanthinol *o*-tosylate (400 mgs; 0.86 mmol) was dissolved in a solution of dry benzene (15 ml) and triethylamine (0.24 ml; 1.73 mmol). This solution was stirred under a nitrogen atmosphere for 2 h at 70° to effect the displacement. The solution was then cooled to RT. and was filtered *rapidly* through a very short alumina (basic, *Woelm* III) column using pressure. A further portion of benzene (100 ml) was used to wash the column. The combined solutions on removal of solvent under reduced pressure gave a light yellow gum which crystallized on standing to give virtually pure product (155 mg, m.p. 129–135°). This material could be recrystallized from cold benzene, m.p. 130–132°. Sublimation gave an analytically pure sample, m.p. 136–136.5°. – IR. (KBr): 3445 cm^{-1} (indole N–H), 1657 cm^{-1} (C=C, enamine), 1408, 880 (exocyclic methylene). – UV.: 306 (4.16), 235 (sh, 4.34), 340 (sh, 3.40) nm. – NMR.: 0.95 (*t*, 3 H, $-CH_2CH_3$); 5.11 (*s*, 1 H, $R_2C{=}CH_2$); 5.25 (*s*, 1 H, $R_2C{=}CH_2$); 5.71 (br. *s*, 1 H, $R_2N{-}CH{=}CR_2$); 7–7.5 (diffuse, 4 H, aromatic); 7.95 (br. *s*, 1 H, N–H). – MS.: 292, 185, 168, 135, 122, 121, 107. Mol.-Wt.: 292.191.

$C_{20}H_{24}N_2$ (292.194) Calc. C 82.19 H 8.22 N 9.59%; Found C 82.26 H 8.27 N 9.72%.

18-Methylidene-4β-dihydrocleavamine (XI); *concerted sequence from dihydrocatharanthinol O-tosylate.* Dihydrocatharanthinol O-*p*-toluenesulfonate (400 mg, 0.86 mmol) was dissolved in a solution of dry benzene (15 ml) and triethylamine (0.24 ml, 1.73 mmol). This solution was stirred under a nitrogen for 2 h at 70° to effect the displacement. Solvent was removed under reduced pressure and the brown residue dissolved in methanol. Sodium borohydride (200 mg) was added immediately and the reaction mixture stirred for 0.5 h after which, the effervescence had ceased. The solvent was removed and the residue was partitioned between dichloromethane (100 ml) and water (100 ml). The aqueous layer was extracted with additional dichloromethane (2 × 50 ml) and the combined organic extract was dried over anhydrous sodium sulfate and the solvent was removed to give a yellow gum. This material was chromatographed on alumina (100 g). Benzene elution gave the desired 18-methylidene-4β-dihydrocleavamine (182 mg); crystallized from methanol/water, m.p. 90–94°. – UV.: 306 (3.97), 315 (sh, 3.92), 218 (4.16) nm. – NMR.: 0.87 (*t*, 3 H, $-CH_2-CH_3$); 5.07 und 5.21 (2 *s*, 1 H, each, $C{=}CH_2$); 7.0–7.5 (diffuse, 4 H, aromatic); 8.10 (br. *s*, 1 H, N–H). – MS.: 294, 292, 207, 139, 124. Mol.-Wt.: 294.209.

$C_{20}H_{26}N_2$	Calc.	C 81.58	H 8.90	N 9.52%
(294.209)	Found	,, 81.48	,, 8.79	,, 9.50%

Dihydrocatharanthinol O-methanesulfonate (IX). Dihydrocatharanthinol (1.0 g) was dissolved in dry pyridine (10 ml) and to this solution cooled to – 5° was added freshly distilled methanesulfonyl chloride (6 ml). The resulting red solution was stirred at 0° for 20 h. Ice-cold chloroform (100 ml) was then added to the reaction mixture and the resulting solution extracted with water

(3 × 50 ml). The cold chloroform solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide a red gum. Rapid percolation of this material using dichloromethane as eluent, through alumina (IV, 30 g) removed most of the very polar material and gave the crude methanesulfonate ester as a yellow oil. Chromatography on alumina (IV, neutral, 60 g) yielded non-polar impurities (15 mg) in the benzene fractions followed by the desired dihydrocatharanthinol O-methanesulfonate as a yellow unstable foam (UV.: 276, 283, 292 nm). The methanesulfonate was unstable and was used immediately in the subsequent elimination reaction as described below.

18-Methylidene-4β-dihydrocleavamine (XI) *from dihydrocatharanthinol-O-methanesulfonate* (IX). A solution of potassium *t*-butoxide was prepared by dissolving clean potassium (1.2 g) in refluxing *t*-butyl alcohol (50 ml, freshly distilled from sodium). Dihydrocatharanthinol-O-methanesulfonate (350 mg) was dissolved in this solution and the resulting solution refluxed under a nitrogen atmosphere for 50 min. The UV. spectrum of this solution showed a maximum at 304 nm with no indole absorption evident. This solution was made just acidic with glacial acetic acid (2 ml) and an excess of sodium borohydride (600 mg) was added. This solution was refluxed for 3 h. Solvent was removed under reduced pressure, the residue was dissolved in cold water (100 ml) and this mixture was extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated to give a yellow gum (170 mg) which was chromatographed on alumina (IV, neutral, 6 g) using benzene as eluent. The early fractions gave the pure exocyclic olefin XI as a colourless glass (29 mg). This material had identical TLC. and spectral properties to the exocyclic olefin obtained from the reduction of 5,18-*seco*-diene X.

18-Methylidene-4β-dihydrocleavamine (XI): *concerted sequence from dihydrocatharanthinol via methanesulfonate ester.* Dihydrocatharanthinol (1 g) in anhydrous pyridine (9 ml) was treated at – 5° with methanesulfonyl chloride (3 ml). The resulting red solution was kept at 0° for 3 h. The mixture was poured into ice-cold dichloromethane (75 ml) and extracted with water (2 × 50 ml). The organic phase was concentrated to a red crystalline paste. This material was percolated rapidly through alumina (IV, neutral, 30 g) using dichloromethane and the solution on removal of solvent gave a yellow gum. This gum was dissolved in a solution of potassium *t*-butoxide in *t*-butyl alcohol (3.5 g of potassium in 200 ml dry butyl alcohol) and refluxed for 20 min. Solvent was removed under reduced pressure and the residue partitioned between ether and water. The ether extract was dried over anhydrous sodium sulfate and concentrated. The resulting yellow oil was then dissolved in 2-propanol (70 ml) and acetic acid (1 ml) and excess sodium borohydride (2 g) was added. When the effervescence had subsided, solvent was removed, the residue partitioned between ether and water and the organic layer, after drying, concentrated to a yellow gum. This material was chromatographed on alumina (50 g). The early benzene fractions gave pure exocyclic olefin (XI) (180 mg) identical on TLC. and NMR. with the material obtained from the reduction of 5,18-*seco*-diene X.

18β-Hydroxymethylcleavamine (XVIII). 18β-Carbomethoxycleavamine (100 mg) was dissolved in dry tetrahydrofuran and lithium aluminum hydride (50 mg) was added. This mixture was refluxed for 2 h under nitrogen. The reaction product was cooled in an ice-bath and saturated sodium sulfate solution (10 ml) was added dropwise. Water (50 ml) was then added and the mixture extracted with dichloromethane (4 × 25 ml). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed. The product obtained gave the following data: IR. ($CHCl_3$): 3450 cm^{-1} (O—H), 1030 cm^{-1} (C—O). – NMR.: 1.02 (*t*, 3 H, $-CH_2CH_3$); 3.68 (*d*, 2 H, $CH-CH_2OH$); 4.26 (*q*, 1 H, H—C(18)); 5.34 (poorly defined *m*, 1 H, $C=CH-$); 7.0–7.5 (diffuse, 4 H, aromatic); 8.50 (br. *s*, 1 H, N—H). – MS.: 310, 187, 136, 135, 124.

$C_{20}H_{26}N_2O$	Calc.	C 77.38	H 8.44	O 5.15	N 9.03%
(310.441)	Found	,, 77.18	,, 8.72	,, 5.01	,, 8.97%

18β-Hydroxymethyl-4β-dihydrocleavamine (XIX) *from the hydroboration of the 5,18*-seco-*diene* X. The 5,18-*seco*-diene X was prepared from dihydrocatharanthinol O-tosylate (300 mg) and was used as the crude reaction product. After preparation, it was immediately dissolved in a diborane-tetrahydrofuran solution (diborane produced from sodium borohydride (200 mg) and boron-trifluoride etherate (1 ml) in diglyme (25 ml) and passed into tetrahydrofuran (25 ml)). This solution was stirred for 1 h at RT. Aqueous potassium hydroxide solution (2 M) was added until the effervescence had ceased and then hydrogen peroxide (0.5 ml, 30%) was added. The solution

was stirred for 10 min and was then partitioned between dichloromethane (100 ml) and water (100 ml). Further extraction with dichloromethane (2 × 50 ml) and removal of solvent from the combined organic extracts gave the crude product as a yellow gum. This material was chromatographed on alumina (20 g). Elution with benzene/ethyl acetate 8:2 gave the less polar decomposition products in the first three fractions. The following ten fractions contained a mixture of the alcohol- and the amine-boranes of the alcohol. These combined fractions (85 mg) were dissolved in a solution of tetrahydrofuran (25 ml) and triethylamine (1 ml) and refluxed under nitrogen for 2 h. The solvent was removed under reduced pressure and the crude product chromatographed using alumina (III, 10 g). Elution with benzene/ethylacetate 8:2 gave 18β-hydroxymethyl-4β-dihydrocleavamine (47 mg) which crystallized from methanol/water. Sublimed sample m.p., 146.5–147.5°. – IR. (KBr): 3510 cm^{-1} (N—N), 3300 cm^{-1} (O—H), 1045 cm^{-1} (C—O). – UV.: 293 (3.76), 285 (3.84), 275 (sh, 3.72), 221 (4.44) nm. – NMR.: 0.84 (*t*, 3 H, $-CH_2CH_3$); 3.73 (*d*, 2 H, CH—CH_2OH); 4.16 (*qi*, 1 H, H—C(18)); 7.0–7.5 (diffuse, 4 H, aromatic); 8.46 (br. *s*, 1 H, NH). – MS.: 312, 207, 138, 124.

$C_{20}H_{28}N_2O$	Calc.	C 76.91	H 8.98	N 8.98	O 5.13%
(312.457)	Found	,, 77.17	,, 8.88	,, 8.79	,, 5.12%

18β-Hydroxymethyl-4β-dihydrocleavamine (XIX), *from hydroboration of 18-methylidene-4β-dihydrocleavamine* (XI). Dihydrocatharanthinol (200 mg) was converted to 18-methylidene-4β-dihydrocleavamine using the procedure already outlined. The crude product was dissolved in anhydrous tetrahydrofuran (25 ml) and the solution was cooled to 0°. Diborane in tetrahydrofuran (3.0 ml, 2.0 M) was added over a 1 h period. The reaction mixture was then allowed to come to RT. and stirred for an additional 0.5 h. The excess diborane and solvent were removed *in vacuo*. The residue was taken up in tetrahydrofuran (50 ml), aqueous sodium hydroxide (10 drops, 3 M) was added followed by hydrogen peroxide (0.10 ml, 30%) and the resulting solution stirred for 15 min. The reaction mixture was partitioned between water (150 ml) and dichloromethane (100 ml). Further extraction with dichloromethane (2 × 50 ml) and removal of solvent from the combined organic extracts gave the crude product as a yellow gum. This material was chromatographed on alumina (70 g) using ethyl acetate as eluting solvent. The main products were: the desired 18β-hydroxymethyl-4β-dihydrocleavamine (XIX) (22 mg), identical with the material obtained from hydroboration of 5,18-*seco*-diene; amine-borane, A, (Rf 0.7, alumina TLC., ethyl acetate elution, 61 mg) and a second amine-borane, B, (Rf 0.6, 14 mg).

Amine-borane A was dissolved in anhydrous tetrahydrofuran (10 ml) containing triethylamine (0.1 ml) and the solution refluxed for 2 h under nitrogen. Pure 18β-hydroxymethyl-4β-dihydrocleavamine was obtained on taking the reaction solution to dryness and crystallizing the residue from methanol/water.

Amine-borane B was dissolved in anhydrous tetrahydrofuran (2 ml) containing triethylamine (0.05 ml) and the solution was refluxed for 2 h under nitrogen. A mixture of starting amine-borane B and the alcohol was obtained. Separation by preparative layer chromatography gave pure 18β-hydroxymethyl-4β-dihydrocleavamine.

18β-Hydroxymethyl-4β-dihydrocleavamine (XIX) *from reduction of 18β-carbomethoxy-4β-dihydrocleavamine*. 18β-Carbomethoxy-4β-dihydrocleavamine (100 mg) was added to a solution of lithium aluminum hydride (70 mg) in tetrahydrofuran (15 ml) and the reaction mixture was refluxed for 2 h. The mixture was cooled in an ice bath and saturated aqueous sodium sulfate solution (0.5 ml) was added dropwise. Water (100 ml) was then added and this mixture was extracted with dichloromethane (5 × 25 ml). The combined extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The slightly yellow gum could be crystallized from methanol/water (64 mg, m.p. 140–144°). Sublimation gave a white crystalline sample, m.p. 146.5–147.5° identical to the material obtained from the hydroboration of both 5,18-*seco*-diene and 18-methylidene-4β-dihydrocleavamine.

Tetrol XXI. Pure 5,18-*seco*-diene X (300 mg) was dissolved in a solution of anhydrous tetrahydrofuran (18 ml) and dry pyridine (1.8 ml). The reaction was carried out in a long-necked flask and this flask containing the solution was immersed in a dry ice-acetone bath such that 3 or 4 inches of the neck of the flask was also immersed. A solution of osmium tetroxide (522 mg) in anhydrous tetrahydrofuran (5 ml) was then added dropwise over a 1 h period and in such a manner that it ran down the cooled neck of the flask. In this way it was assured that the osmic

acid solution was cooled to the bath temperature when it reached the reaction mixture. Care was taken to keep the system closed to the atmosphere while adding the osmic acid solution to prevent condensation of water into the reaction solution. The reaction mixture was stirred for additional 6 h and was then allowed to come to RT. over a $^1/_2$ h period. It was then poured into a solution of ethanol/dichloromethane 1:1 (50 ml) and hydrogen sulfide was bubbled through this solution with rapid stirring for 10 min. This mixture was filtered through celite and the black residue was washed with an additional amount of ethanol/dichloromethane 1:1 (100 ml). The residue was then suspended in triethylamine (20 ml) and stirred for about 15 h. This mixture was filtered and washed as before. The combined filtrate was taken to dryness and chromatographed on alumina (50 g). Dichloromethane/methanol 99:1 eluted the desired tetrol XXI which crystallized on taking the eluent to dryness (187 mg). This material recrystallized from methanol/water; m.p. 120–123°. – IR. (nujol): 3360, 3510 (sh), 3350 cm^{-1} (OH and NH). – UV.: 293 (3.85), 285 (3.89), 275 (3.82), 228 (4.52) nm. – NMR.: 1.04 (*t*, 3 H, $-CH_2CH_3$); 3.64 (br. *s*, sharpened on D_2O exchange, 2 H, $-CH_2OH$); 4.58 (br. *s*, 1 H, >N–CHOH); 7.0–7.6 (diffuse, 4 H, aromatic); 8.16 (br. *s*, 1 H, N–H). – MS.: 342, 311, 143, 91, no parent ion was observed in this case. High resolution mass spectrometry was performed on the $M^+ - 18$ peak. Mol.-Wt.: 342.192. (Calc. for $C_{20}H_{28}N_2O_3$: 342.194).

$C_{20}H_{28}N_2O_4$	Calc.	C 66.64	H 7.83	O 17.16	N 7.77%
(360.455)	Found	,, 66.42	,, 7.80	,, 17.51	,, 7.82%

Triol XXII. The tetrol XXI (330 mg) was dissolved in methanol (50 ml) and sodium borohydride (200 mg) was added. The solution was stirred at RT. for 1 h. The solvent was removed and the residue was partitioned between dichloromethane (100 ml) and water (100 ml). The aqueous phase was extracted with an additional quantity of dichloromethane (2 × 50 ml) and the combined extract, after drying over anhydrous sodium sulfate, was removed free of solvent. The residue crystallized on trituration with methanol to give pure triol XXII (325 mg). This material could be recrystallized from methanol/water; m.p. 230–235° (decomp.). – IR. (nujol): 3540, 3430 and 3200 cm^{-1} (O–H and N–H). – UV.: 293 (3.87), 285 (3.91), 277 (sh, 3.87), 227 (4.53) nm. – NMR.: 0.90 (*t*, 3 H, $-CH_2CH_3$); 3.78 (*s*, 2 H, $-CH_2OH$); 7.0–7.5 (diffuse, 4 H, aromatic); 8.52 (br. *s*, 1 H, N–H); 9.71 (br. *s*, lost on deuterium exchange, 1 H, O–H). – MS.: 344, 326, 154, 95, 92, 91. Mol.-Wt.: 344.210.

$C_{20}H_{28}N_2O_3$	Calc.	C 69.74	H 8.19	O 13.94	N 8.13%
(344.206)	Found	,, 69.42	,, 8.00	,, 13.71	,, 7.99%

Hydroxy-ketone XXIII. The triol XXII (150 mg) was dissolved in acetone (15 ml), and after dissolution, water (5 ml) was added. This solution was cooled in an ice-water bath and to it was added dropwise an aqueous solution of sodium periodate (90 mg in 10 ml). The solution was stirred for 1.5 h at 0°. The reaction solution was then poured into ice-water (70 ml) and extracted with dichloromethane (3 × 50 ml). The combined extracts were dried over anhydrous sodium sulfate and then the solvent was removed to give a yellow gum. This material was chromatographed on alumina (20 g); dichloromethane/methanol 99:1 elution brought down the desired hydroxy-ketone XXIII (75 mg). Further elution using dichloromethane/methanol 98:2 gave some of the starting triol (15 mg). The hydroxy-ketone could be crystallized from methanol/water to give yellow plates; m.p. 105–109° (dec.). – IR. (nujol): 3430 (N–H), 3100 (O–H), 1615 cm^{-1} (C=O). – UV.: 317 (4.25), 238 (4.16) nm. – NMR.: 0.97 (*t*, 3 H, $-CH_2CH_3$); 2.18 (br. *s*, lost on deuterium exchange, 1 H, O–H); 7.0–7.6 (diffuse, 4 H, aromatic); 9.27 (br. *s*, 1 H, N–H). – MS.: 312, 154, 144, 143, 140. Mol.-Wt.: 312.183.

$C_{19}H_{24}N_2O_2$	Calc.	C 73.04	H 7.74	O 10.24	N 8.97%
(312.184)	Found	,, 72.81	,, 7.52	,, 10.24	,, 8.81%

Diol XXIV. The hydroxy-keton XXIII (93 mg) was dissolved in methanol (20 ml) and the solution cooled in an ice-bath. Sodium borohydride (100 mg) was added; the reaction mixture was allowed to come to RT. and was then stirred for 2 h. The solution was taken to dryness and partitioned between dichloromethane (50 ml) and water (50 ml). The aqueous phase was further extracted with dichloromethane and then the combined organic extracts, after drying over anhydrous sodium sulfate, was taken to dryness. The product crystallized readily from dichloromethane to give the pure diol XXIV (86 mg) m.p. 195–200° (dec.). – IR. (nujol): 3250 and 3360 cm^{-1} (sh) (O–H and N–H). – UV.: 294 (3.83), 286 (3.86), 279 (sh, 3.82), 227 (4.50) nm. – NMR.:

0.92 (*t*, 3 H, $-CH_2CH_3$); 5.72 (*d* × *d*, *J* = 2, 10, 1 H, H–C(18)); 7.0–7.5 (diffuse, 4 H, aromatic); 8.38 (br. *s*, 1 H, NH). – MS.: 314, 173, 154, 144, 142, 140, 130, 124. Mol.-Wt.: 314.199.

$C_{19}H_{26}N_2O_2$	Calc.	C 72.58	H 8.34	O 10.18	N 8.91%
(314.199)	Found	,, 72.25	,, 8.16	,, 10.01	,, 8.90%

Isovelbanamine (XXV). The diol XXIV (100 mg) was dissolved in anhydrous N-methylmorpholine (20 ml), lithium aluminum hydride (100 mg) was added and the resulting mixture was refluxed for 10 h. After this time, it was cooled in an ice-bath and a saturated aqueous sodium sulfate solution (0.5 ml) was added dropwise. Water (60 ml) was added to this mixture and this was then extracted with ethyl acetate (5 × 20 ml). The combined extracts were taken to dryness and the residue chromatographed on alumina (10 g). Dichloromethane elution gave isovelbanamine (XXV) which crystallized from this solvent (42 mg), m.p. 190–194°. – IR. (nujol): 3250 (O–H), 3500 cm^{-1} (N–H). – UV.: 293 (3.88), 286 (3.90), 276 (sh, 3.82), 229 (4.54) nm. – NMR.: 0.87 (*t*, 3 H, $-CH_2CH_3$); 1.23 (br. *s*, disappears on deuterium exchange, 1 H, O–H); 3.44 (complex *m*, 1 H, H–C(18)); 7.0–7.5 (diffuse, 4 H, aromatic); 7.74 (br. *s*, 1 H, N–H). – MS.: 298, 154. Mol.-Wt.: 298.205.

$C_{19}H_{26}N_2O$	Calc.	C 76.47	H 8.78	O 5.36	N 5.39%
(298.205)	Found	,, 76.31	,, 8.70	,, 5.21	,, 9.42%

Cleavamine (XXVI) via *dehydration of isovelbanamine* (XXV). Conc. sulfuric acid (0.5 ml, 36 N) was cooled in an ice-water bath and to this cold acid was added isovelbanamine (XXV) (10 mg). The compound dissolved slowly and the resulting solution was stirred under a dry nitrogen atmosphere for 2 h. This solution was then added dropwise to an ice-cold ammonium hydroxide solution (10 ml, 2 N) and the resulting suspension was extracted with dichloromethane (3 × 5 ml). The combined extracts were filtered rapidly through alumina (1 g) and the eluted material concentrated to give a pale yellow gum (9 mg). This material was chromatographed on alumina (1 g) eluting with benzene to give the desired cleavamine contaminated with some slightly more polar material. Rechromatography on alumina (1 g) eluting with petroleum ether/benzene 1:1 gave pure cleavamine which crystallized from methanol (2.6 mg), m.p. 117–119°. This material had TLC. properties identical to an authentic sample of cleavamine [13] [28] and the IR. spectrum (nujol) was superimposable to that of the authentic sample.

18β-Cyanocleavamine (XXXIII). A solution of cleavamine (250 mg) in dichloromethane (30 ml) and triethylamine (0.15 ml) was cooled in an ice-acetone bath and to it was added dropwise a solution of *t*-butyl hypochlorite in carbon tetrachloride (48 ml of 0.38 M), over the period of 1 h. This reaction solution was then taken to dryness and the residue dissolved in a solution of fused sodium acetate (250 mg) in glacial acetic acid (22.5 ml) and acetic anhydride (2.5 ml). This solution was stirred at RT. for 1 h and then for 2 h at 60°. The solvent was removed under vacuum and the residue dissolved in ethanol and passed *rapidly* through a short column of alumina (20 g as a 1″ column). The eluted material on removal of solvent gave the crude quaternary ammonium salt XXXII as a pale yellow foam. This crude material was dried for 3 h under high vacuum at about 70°. Potassium cyanide (250 mg) dried in a similar manner was added to this residue and dimethylformamide (15 ml) was distilled from over barium oxide into the reaction flask. This reaction mixture was refluxed under a nitrogen atmosphere for 1¾ h. The solvent was removed under reduced pressure and the residue obtained was chromatographed using alumina (*Woelm*, activity III, 15 g). Benzene elution gave the desired product, 18β-cyanocleavamine (XXXIII), which crystallized readily from methanol/water (81.3 mg); m.p. 87–90°. – IR. (nujol): 2240 cm^{-1} (C≡N). – UV.: 293 (3.89), 284 (3.96), 277 (3.93), 225 (4.57) nm. – NMR.: 1.04 (*t*, 3 H, $-CH_2CH_3$); 5.26 (poorly defined *d*, 1 H, CH=C<); 5.52 (*d* × *d*, *J* = 2 and 10, 1 H, H–C(18)); 7.0–7.5 (diffuse, 4 H, aromatic); 8.40 (br. *s*, 1 H, N–H). – MS.: 305, 136, 124. Mol.-Wt.: 305.187.

$C_{20}H_{23}N_3$ (305.189) Calc. C 78.65 H 7.59 N 13.76% Found C 78.42 H 7.44 N 13.51%

18β-Carbomethoxycleavamine (XXXIV) *from 18β-cyanocleavamine* (XXXIII). 18β-Cyanocleavamine (XXXIII) (81 mg) was dissolved in diethylene glycol (2.5 ml) and potassium hydroxide (0.5 g) was added. This mixture was kept at 150° for 9 h. The solution was then cooled in an ice-bath, made slightly acidic with a solution of methanol saturated with hydrochloric acid. A large excess of diazomethane in diethylether was added and the reaction mixture was stirred vigorously for 0.5 h. The solution was allowed to come to RT. and the excess diazomethane was removed using a stream of nitrogen. Water (150 ml) was then added and the solution was extracted with

diethylether (4 × 50 ml). The combined extracts were washed with water (2 × 25 ml), dried over anhydrous sodium sulfate and taken to dryness. The residue was chromatographed on alumina (10 g) and pure 18β-carbomethoxycleavamine (45 mg) was obtained on elution with petroleum ether/benzene 1:1. This material crystallized from methanol, m.p. 122–123°; it had identical properties compared with an authentic sample of 18β-carbomethoxyclcavamine [14] on TLC., and gave a superimposable IR. spectrum.

Velbanamine. Isovelbanamine (XXV) (65 mg) was dissolved in an aqueous sulfuric acid solution (10 ml, 10% v/v) and this solution was refluxed under a nitrogen atmosphere for 2 days. The solution was then cooled to 0° and added dropwise to an ice-cold aqueous ammonium hydroxide solution (20 ml, 5N). The resulting suspension was extracted using dichloromethane (3 × 25 ml) and the combined organic extract was taken to dryness. The residue was chromatographed on alumina (20 g). Dichloromethane elution initially gave velbanamine (17.9 mg) while further elution provide unreacted isovelbanamine (21 mg). The velbanamine crystallized from methanol/water, m.p. 144–146° (authentic velbanamine [28], m.p. 117–134°, recrystallized from methanol/water, m.p. 143–146°). The synthetic velbanamine exhibited identical TLC. properties and had an IR. spectrum (nujol) superimposable to that of the authentic sample.

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REFERENCES

[1] *J. P. Kutney & F. Bylsma*, J. Amer. chem. Soc. *92*, 6090 (1970).
[2] *J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, A. Leutwiler, V. R. Nelson & J. P. de Souza*, Helv. *58*, 1648 (1975).
[3] *J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague & E. Piers*, J. Amer. chem. Soc. *88*, 4756 (1966); ibid. *92*, 1712 (1970).
[4] *N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Buchi & R. Manning*, J. Amer. chem. Soc. *86*, 1440 (1964).
[5] *J. W. Moncrief & W. N. Lipscomb*, J. Amer. chem. Soc. *87*, 4963 (1965).
[6] *N. Neuss, L. L. Huckstep & N. J. Cone*, Tetrahedron Letters *1967*, 811.
[7] *N. Neuss, M. Gorman, N. J. Cone & L. L. Huckstep*, Tetrahedron Letters *1968*, 783.
[8] *D. J. Abraham & N. R. Farnsworth*, J. pharm. Sci. *58*, 694 (1969).
[9] *E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, K. Kunesh & Y. Rolland*, J. Amer. chem. Soc. *95*, 4990 (1973).
[10] *C. A. Grob*, Bull. Soc. chim. France *1960*, 1360.
[11] *M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlitter, R. L. S. Amai, P. Beak, N. V. Bringi & E. Wenkert*, J. Amer. chem. Soc. *84*, 622 (1962).
[12] *U. Renner, K. A. Jaeggi & D. A. Prins*, Tetrahedron Letters *1965*, 3697.
[13] *M. Gorman, N. Neuss & N. J. Cone*, J. Amer. chem. Soc. *87*, 93 (1965).
[14] *J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall & V. R. Nelson*, J. Amer. chem. Soc. *92*, 1704 (1970).
[15] *F. E. Ziegler, J. A. Kloek & P. A. Zoretic*, J. Amer. chem. Soc. *91*, 3242 (1969).
[16] *G. H. Alt*, 'Electrophilic Substitutions and Additions to Enamines' in 'Enamines' A. C. Cook, ed., Marcel Dekker, New York 1969, p. 115.
[17] *J. W. Lewis & A. A. Pearce*, Tetrahedron Letters *1964*, 2039.
[18] *H. C. Brown*, 'Hydroboration' W. A. Benjamin, New York 1969, p. 178.
[19] *J. A. Wiesbach & B. Douglas*, Chemistry & Ind. *1965*, 623; *1966*, 233.
[20] *L. J. Dolby & D. L. Booth*, J. org. Chemistry *30*, 1550 (1965).
[21] *N. Neuss, M. Gorman, H. E. Boaz & N. J. Cone*, J. Amer. chem. Soc. *84*, 1509 (1962).
[22] *K. Biemann*, Lloydia *27*, 397 (1964).
[23] *J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan & N. Camerman*, Chemistry & Ind. *1963*, 648.
[24] *N. Camerman, J. Trotter*, Acta crystallogr. *17*, 384 (1964).
[25] *J. P. Kutney, R. T. Brown, E. Piers & J. R. Hadfield*, J. Amer. chem. Soc. *92*, 1708 (1970).
[26] *J. Miller & A. J. Parker*, J. Amer. chem. Soc. *83*, 117 (1961), and references cited therein.
[27] *C. R. Narayanan & K. N. Iyer*, Tetrahedron Letters *1964*, 759.
[28] *J. P. Kutney, R. T. Brown & E. Piers*, Canad. J. Chemistry *43*, 1545 (1965).