CHEMISTRY OF SOME DIMERIC INDOLE ALKALOIDS

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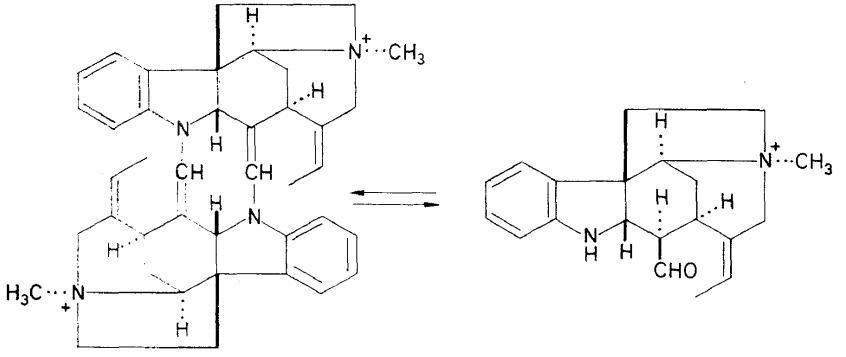
The intensive interest in bisindole alkaloids witnessed within the last few years can be traced back to work on the constituents of calabash-curare which led to the isolation and characterization of alkaloids with fascinating chemistry and useful pharmacological activities[1, 2]. *C*-Dihydrotoxiferin (I) was the first of these dimeric indole alkaloids to be elucidated structually[3-5]. It represents a self-condensation product of hemidihydrotoxiferine (II) and in aqueous acidic media monomer and dimer do exist in equilibrium.

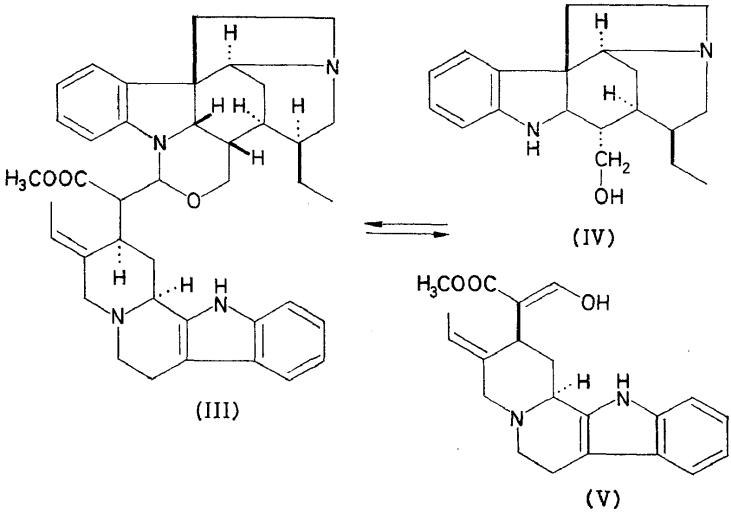


(I) (II)

A second type of bisindole alkaloid is represented by geissospermine (III)[6, 7], an aminoacetal resulting from the union of the aldehyde geissoschizine (V) with the aminoalcohol geissoschizoline (IV). Cleavage and recombination reactions in this series are analogous to those observed with *C*-dihydrotoxiferine (I) and alkaloids of the geissospermine type are consequently also available by synthesis[8].

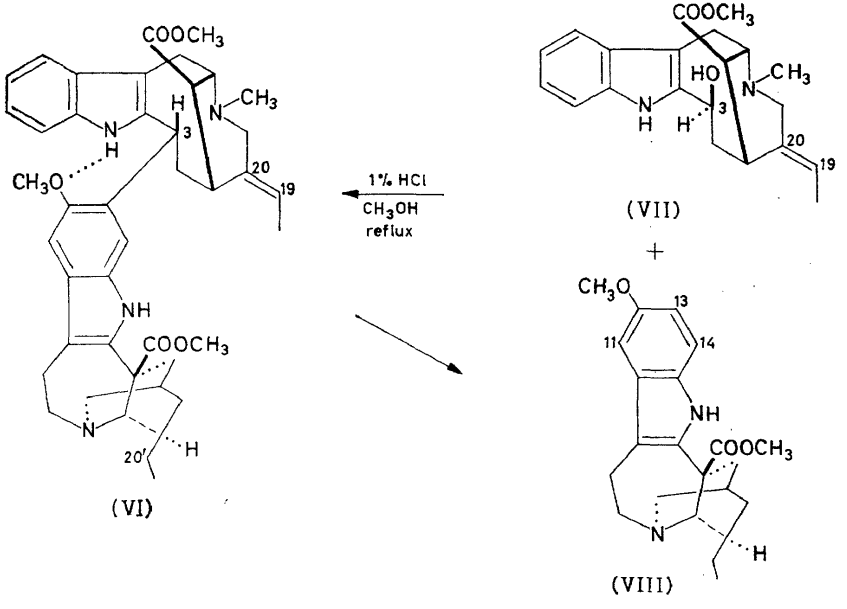
Certain species of plants belonging to the tribe of *Tabernaemontaninae* elaborate a third type of bisindole alkaloids characterized structurally by the presence of a single bond between the two monomeric moieties. An insight into the chemical architecture of these bases came from a study of voacamine (VI) first isolated from *Voacanga africana*[9, 10]. Preliminary structural work[11] led to the suggestion that voacangine[12] (VIII) might be a moiety of the voacamine (VI) molecule and this was subsequently established by acid-catalysed cleavage of the "dimer" which does indeed afford voacangine (VIII)[13]. Attempts to isolate products derived from the unknown half

of the molecule failed. The base-catalysed epimerization of voacamine (VI) to epi-voacamine parallels that of vobasine[14] and it was tentatively proposed that the latter alkaloid is related to a biogenetic precursor of voacamine (VI)[15]. The structure of voacamine (VI) was established in our laboratory in 1963[16] and mass spectrometric studies carried out by Biemann at M. I. T.



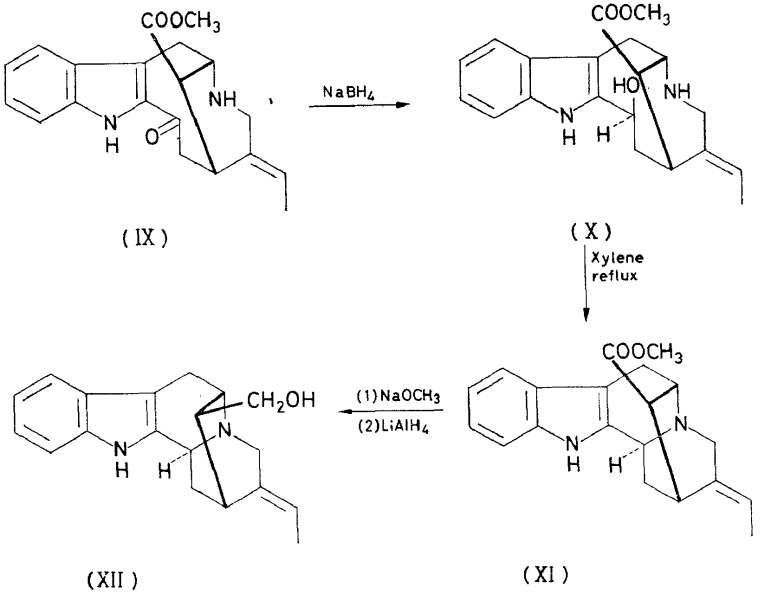
(III) (IV) (V)

and elsewhere[17] are not in conflict with the proposal. At the time our findings were published in preliminary form[16] the absolute configurations of the two monomers were unknown but chemical evidence on this point has been secured since then and will be discussed briefly.



(VI) (VII) + (VIII)

Reduction of perivine (IX)[18] (des-*N*-methylvobasine) with sodium borohydride yields the anticipated alcohol (X) which in boiling xylene cyclizes to the pentacyclic ester (XI)†. This ester is smoothly isomerized with sodium methoxide to the more stable epimer which on reduction with lithium aluminum hydride is converted to normacusine-B (XII)[19] of known absolute configuration. This conclusion is already allowed for in all formulae presented in this lecture.

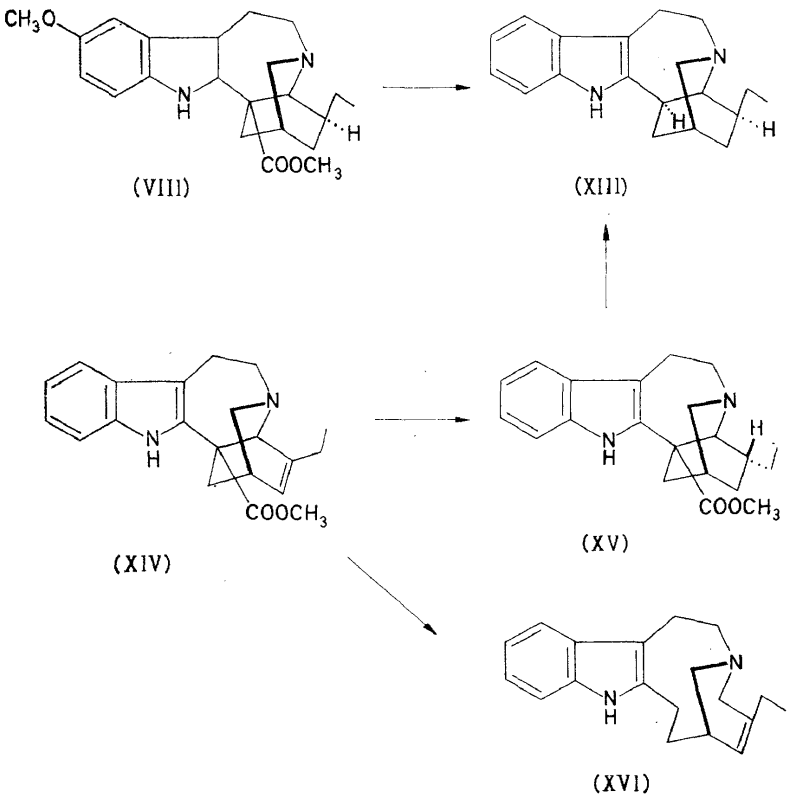


The absolute configuration of voacangine (VIII) follows from its relationship with cleavamine (XVI) whose absolute stereochemistry was determined by the X-ray method[20]. Reductive decarbomethoxylation of catharanthine (XIV) using tin and hydrochloric acid gives cleavamine (XVI)[21]. Secondly, catalytic hydrogenation of catharanthine (XIV) furnishes epi-coronaridine (XV) which on exposure to hot hydrochloric acid is transformed to a mixture of epi-ibogamine and ibogamine (XIII)[21]. Furthermore, voacangine (VIII) on heating in acid media suffers ready decarbomethoxylation[22] to ibogaine and the latter substance has now been converted to ibogamine (XIII) by standard procedures. These transformations correlate cleavamine (XVI) with voacangine (VIII) and the absolute configuration of the voacanga alkaloids is that already pictured in the formulae[23]. The remaining question of stereochemical detail in voacamine (VI) concerns the geometry at C_3 and although no unambiguous evidence is available a fairly convincing argument will be presented later.

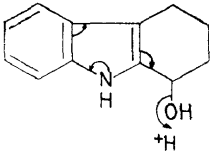
We now turn to a discussion of the partial syntheses of dihydrovoacamine and of voacamine. To effect these syntheses it is necessary to condense voacangine (VIII) with a suitable derivative of vobasine and a Mannich

† *Note added in proof:* This cyclization can also be effected in hot acetic acid (M. Gorman, private communication).

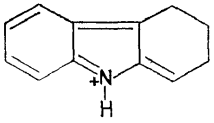
type condensation seemed ideally suited. It had been noted previously that 1-hydroxy-1,2,3,4-tetrahydrocarbazole (XVII) in the presence of acid undergoes a rapid self-condensation to the dimer (XX)[24]. The first bond forming process obviously involves nucleophilic attack of the indole nitrogen atom on the iminium salt (XVIII) to yield the alcohol (XIX). An intramolecular counterpart of this process completes the formation of the dimer (XX). This indicated that vobasinol (VII) might serve as a precursor in the planned synthesis of voacamine (VI) and the question of whether or not an activated benzene ring could replace the nitrogen atom of an indole



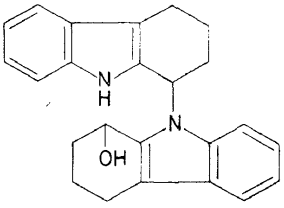
as nucleophile was answered as follows. Condensation of 6-hydroxy-1,2,3,4-tetrahydrocarbazole (XXI) with formaldehyde and piperidine yields the adduct (XXII). Similarly, an equimolar mixture of the two isomeric hydroxytetrahydrocarbazoles (XVII and XXI) on exposure to acid produces the condensation product (XXV). The n.m.r. spectrum of the tetradeutero analogue of (XXV) from Ar-tetradeuteroalcohol (XVII) demonstrates that condensation has taken place again at C_5. Molecular models however indicate that substitution on C_{11} in voacangine (VIII) leads to a highly crowded intermediate suggesting that Mannich condensation might indeed take the desired course.



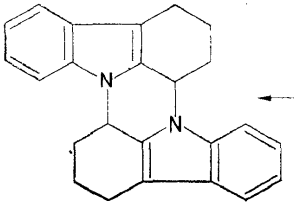
(XVII)



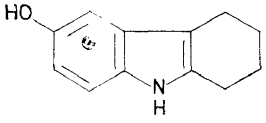
(XVIII)



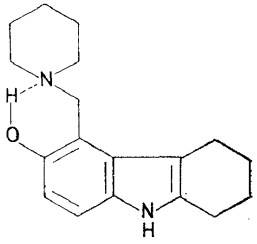
(XIX)



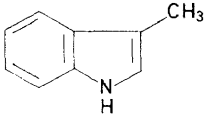
(XX)



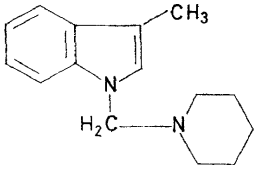
(XXI)



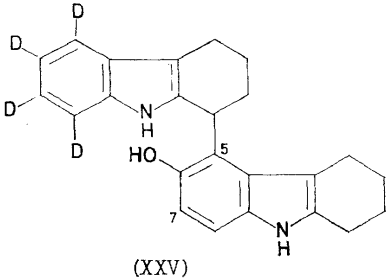
(XXII)



(XXIII)

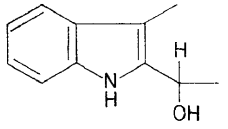


(XXIV)

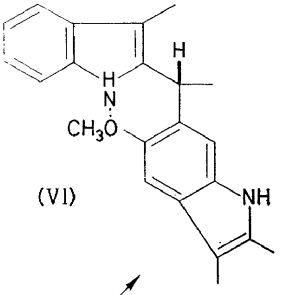


(XXV)

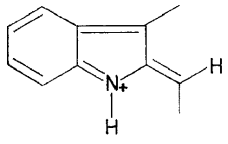
In practice, condensation of equimolar amounts of dregaminol (19,20-dihydro-VII) and voacangine (VIII) in 1 per cent HCl-CH_3OH (1 h, reflux) gives 50 per cent of dihydrovoacamine[16] (19,20-dihydro-VI) and analogous condensation using vobasinol (VII) furnishes voacamine (VI) in similar yield[29]. The n.m.r. spectrum of deuterated dihydrovoacamine prepared from voacangine (VIII) and Ar-tetradeuterodregaminol shows two one-proton singlets in the aromatic region and substitution has thus occurred at C_{13}. Because the combination of the monomers proceeds under such mild conditions it was necessary to ascertain whether or not voacamine (VI) is formed from its progenitors in the course of isolation from natural sources. When a mixture of voacangine (VIII) and vobasinol (VII) is processed in the manner recommended for the isolation of voacamine (VI)



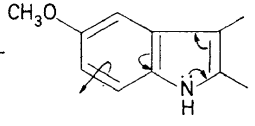
(VII)



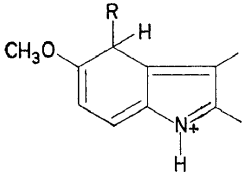
(VI)



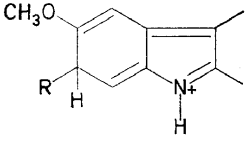
(XXVI)



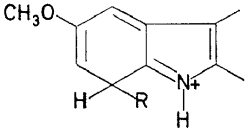
(XXVII)



(XXVIII)



(XXIX)



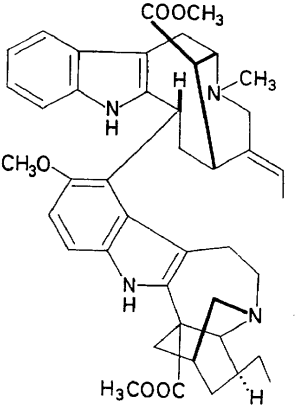
(XXX)

from plant material the latter alkaloid is not detectable and the monomers are recovered unchanged.

Before leaving this subject it is of interest to compare the relative stabilities of the three formally possible intermediates resulting from the addition of a 5-methoxyindole (XXVII) to an iminium salt (XXVI). Electronically isomer (XXVIII) appears most stable because the oxygen atom of the methoxy group and the positively charged nitrogen atom are fully conjugated. Condensation with voacangine (VIII) does not appear to follow this course because, as already mentioned, it leads to a very crowded intermediate. The second ion (XXIX) still exhibits considerable conjugation and is actually involved in both cleavage and condensation reactions. Dreiding molecular models of the iminium salt (XXVI) derived from vobasinol (VII) reveal shielding of one face of the chromophore by the carbomethoxy group and it is suggested that the nucleophile adds from the opposite side dictating the configuration at C_3 indicated in formula (VI). In the third Mannich intermediate (XXX) electron delocalization between oxygen and nitrogen is no longer possible and the absence of products derived from it is not surprising. It should also be recalled that condensation of 3-methylindole (XXIII) with formaldehyde and piperidine yields *N*-piperidinomethyl-3-methylindole (XXIV).

Voacorine[25] a second bisindole alkaloid of *Voacanga africana* gives voacristine[26, 27] on hydrolysis[28] and was previously postulated to be 20′-hydroxyvoacamine. This hypothesis has now been confirmed by a partial synthesis from vobasinol (VII) and voacristine as well as by mass spectrometry[17].

After our studies on voacamine (VI) were complete the structures of

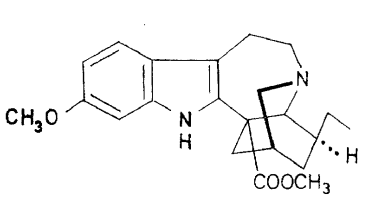


(XXXI)

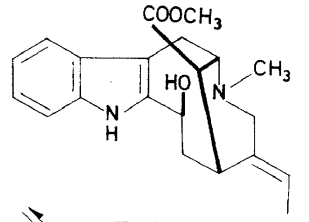
three isomeric alkaloids were announced[29]. Voacamidine (XXXI) isolated from *Voacanga africana* on treatment with 2N hydrochloric acid is cleaved partly to voacangine (VIII) and isomerized partly to voacamine (VI). The latter alkaloid consequently is the more stable of the two bisindoles and this situation is consonant with our previous discussion.

The question as to why voacamidine (XXXI) is not produced in the partial synthesis of voacamine (VI) cannot be answered at present†.

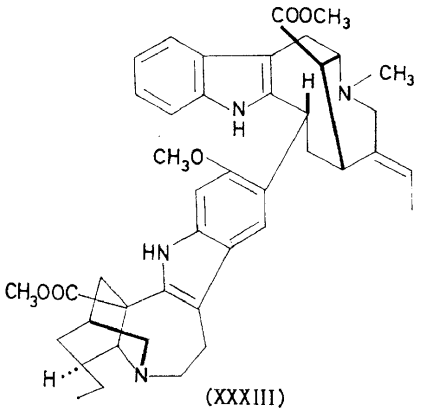
Condurine (XXXIV) and conoduramine (XXXIII) on acid-catalysed cleavage are converted to isovoacangine (XXXII) which co-occurs with the two bisindole alkaloids in *Conopharyngia durissima*. The structures are confirmed by partial syntheses from isovoacangine (XXXII) and vobasinol



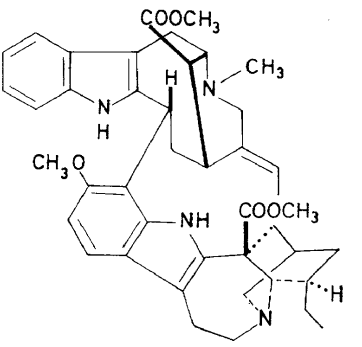
(XXXII)



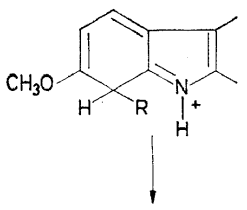
(VII)



(XXXIII)

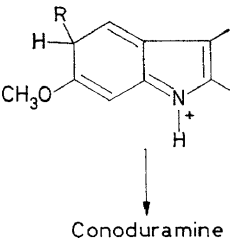


(XXXIV)



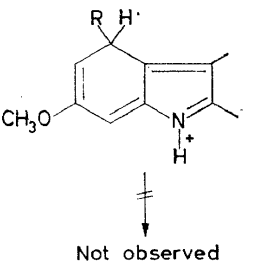
Conodurine

(XXXV)



Conoduramine

(XXXVI)



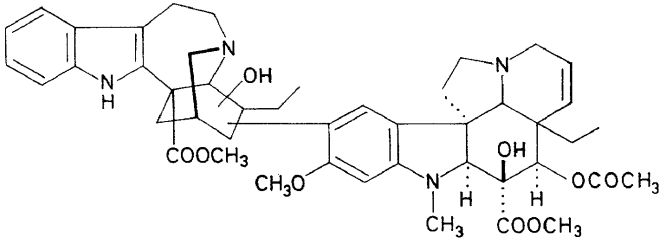
Not observed

(XXXVII)

(VII)[29]. The two "dimers" are formed from the two intermediates (XXXV) and (XXXVI). Again, no products seem to originate from the electronically unfavourable ion (XXXVII).

† *Note added in proof:* A re-examination of the partial synthesis of voacamine has led to the isolation of minor quantities of voacamidine.

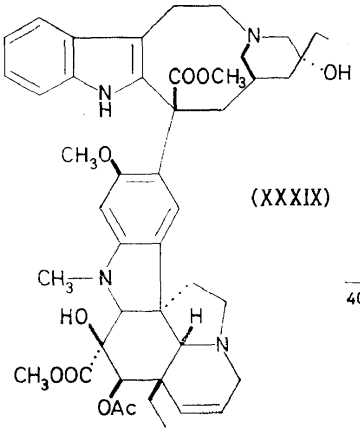
The literature describes the isolation of a number of bisindole alkaloids from *Vinca rosea*. Two of these, namely vinblastine and vincristine are therapeutically useful antitumour alkaloids. Their chemistry is being studied intensively at Eli Lilly and Company. Vincristine is des-*N*(a)-methyl-*N*(a)-formyl vinblastine and cleavage of vinblastine in the presence of tin-metal and aqueous hydrochloric acid affords desacetylvindoline[31] and velbanamine (XLII)[32]. The detailed structure of velbanamine (XLII) remained unknown until recently but early spectral studies[32] indicated a tetracyclic framework and it was assumed, correctly, that velbanamine is a hydroxydihydrocleavamine. The site of attachment of the indole moiety to the vindoline portion was revealed by n.m.r. studies and the additional carbomethoxy group present in the "dimer" but missing in velbanamine (XLII) was proposed to be located on the carbon atom adjacent to the α-position of the indole ring. Mainly on the basis of these facts a part structure (XXXVIII) was suggested for vinblastine[52].



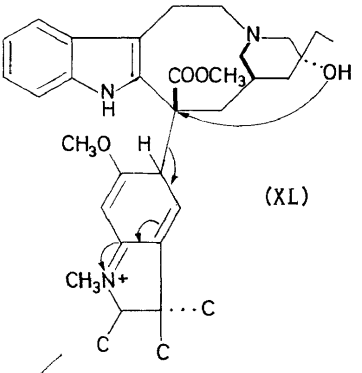
(XXXVIII)

The acid-promoted cleavage of vinblastine suggested to us a structural relationship to voacamine and subsequent work carried out in collaboration with the group at Eli Lilly and Company fully confirmed this suspicion[33, 34]. Structure (XXXIX) explains the chemical and spectroscopic behaviour of the alkaloid. For example, it provides a rationale for the hitherto puzzling appearance of tetracyclic cleavage products and also the hydrolytic fragmentation reaction is now understood easily. In the presence of reducing agents the intermediate cation (XLIII) is reduced to carbomethoxyvelbanamine which subsequently suffers the familiar acid-catalysed decarbomethoxylation to give velbanamine (XLII). Cleavage of vinblastine (XXXIX) in boiling 40 per cent sulphuric acid without added reducing agent affords the amino-acid (XLI) which retains the original carboxy function of the indole moiety. The commonly observed decarboxylation is prohibited in this instance because the crucial intermediate would violate Bredt's rule. Formation of the fragment (XLI) can be understood if the intermediate (XL) undergoes the neighbouring group reaction indicated. Deuterium labelling experiments demonstrate that the hydroxyl substituent occupies identical positions in both vinblastine (XXXIX) and its degradation product velbanamine (XLII). A high resolution mass spectrum of velbanamine agrees only with formula (XLII) and the configuration of the hydroxy group is dictated by the structure of the cyclic ether (XLI). The molecular compositions of voacamine (VI) and vinblastine (XXXIX) were determined by Biemann and his co-workers using mass spectrometry. The

spectra were most puzzling until it was realized that these high molecular weight aminoesters of low volatility undergo intermolecular methyl transfer when samples are vaporized into the ion source. The resulting methine derived from voacamine (VI) is fourteen mass units heavier than the original alkaloid and the spectrum of vinblastine (XXXIX) contains peaks at $M + 14$ as well as at $M + 28$[34]. It should be mentioned that structural work on these alkaloids is most frustrating without mass spectrometric measurements and to illustrate I only have to point out that



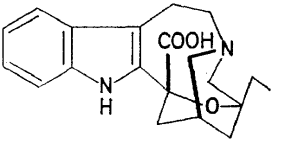
(XXXIX)



(XL)

40 % H_2SO_4

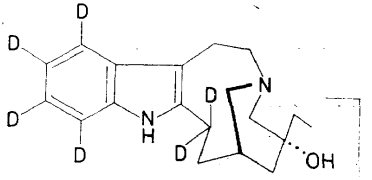
Desacetylvindoline +



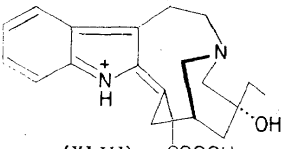
(XLI)

(XXXIX)

$HCl; H_2O$
$SnCl_2$; Sn
or $DCl; D_2O$
etc.



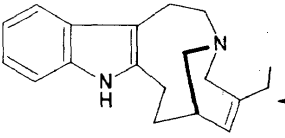
(XLII)



(XLIII) $COOCH_3$

H^+

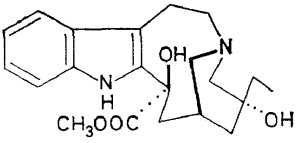
+



(XVI)

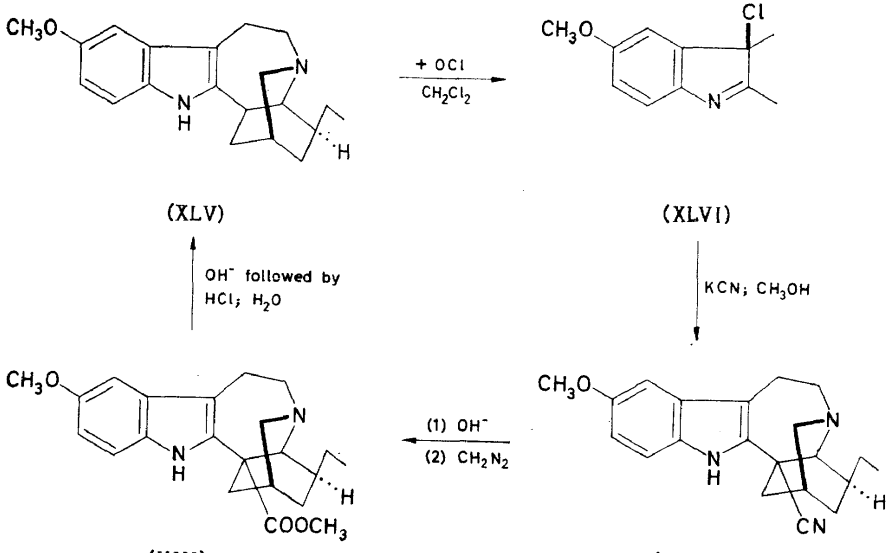
combustion analyses previously led to incorrect molecular formulae for *all seven* alkaloids of the voacamine type.

Investigations on a partial synthesis of vinblastine (XXXIX) are not complete but the route which is being pursued will be outlined briefly. To duplicate the approach used in the partial synthesis of voacamine (VI) a precursor (XLIV) has to be prepared. In principle it could be synthesized



(XLIV)

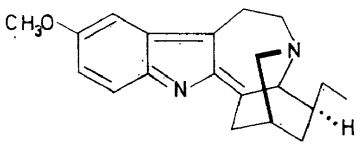
from velbanamine (XLII) and a method for the introduction of the carbomethoxy group was tested using the more easily available alkaloid ibogaine (XLV). Treatment with t-butylhypochlorite in methylene chloride solution produces the 3-chloroindolenine (XLVI)[35, 36] which is not isolated in a pure state but which does exhibit the anticipated ultraviolet spectrum



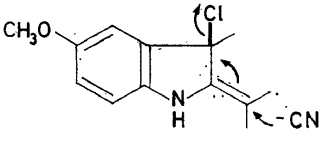
($\lambda_{max.}^{iso\text{-}octane}$ 227, 278 mμ). In aqueous methanol the chloride combines with potassium cyanide to yield a mixture of isomeric nitriles. One of these has $\gamma_{max.}^{CHCl_3}$ 3450, 2220 cm^{-1}; $\lambda_{max.}^{EtOH}$ 213, 282, 295 mμ (ϵ 34500, 9620, 7820). Its properties are in agreement with structure (XLVII) and on saponification with potassium hydroxide in diethylene glycol at 140° followed by methylation with diazomethane it is converted to voacangine (VIII).

The mechanism of the chloride–nitrile change requires comment because

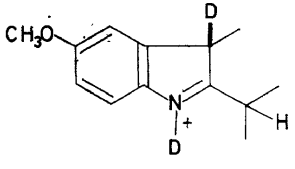
the intermediacy of the imine (XLVIII) is improbable. In its planar form it represents an extremely strained molecule. One possibility is that the indolenine (XLVI) is in equilibrium with the corresponding enamine (XLIX) which undergoes an S_N2' type displacement reaction. A remote analogy is provided by the acid-catalysed hydrogen–deuterium exchange in ibogaine (XLV). After crystallization from alcohol the resulting product (L) contains four deuterium atoms. Three of these are located on the aromatic ring (n.m.r. evidence) and the mass spectrum suggests that the fourth is attached as shown in (L). Deuterium incorporation can be rationalized by the sequence (LI → LII → LIII → L). These suggestions imply that the chloroenamine (XLIX) exhibits electrophilic properties while the enamine (LII) displays commonly accepted nucleophilic character.



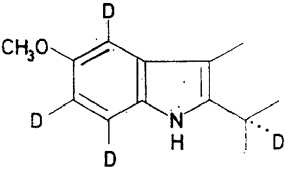
(XLVIII)



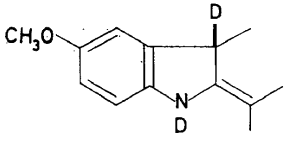
(XLIX)



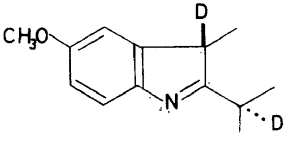
(LI)



(L)

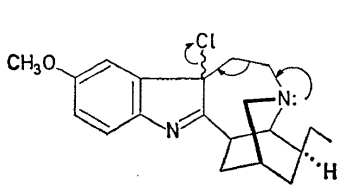


(LII)

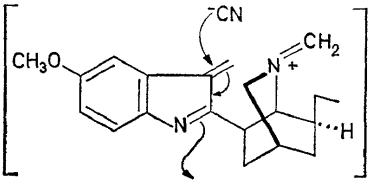


(LIII)

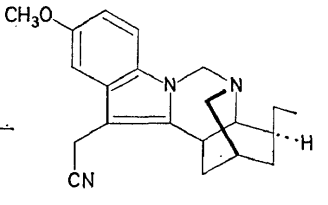
The second nitrile mentioned earlier represents a minor product when metathesis is performed at low temperatures but at elevated temperatures it becomes the major product. Its absorption in the ultraviolet region is typical of indoles but the lack of infrared absorption in the 3400 cm^{-1} region demands an *N-a* substituted structure. During exposure of this nitrile to methanolic hydrochloric acid a methyl ester is formed whose n.m.r. spectrum agrees with structure (LVI). The original nitrile consequently is represented by (LV). Further evidence in favour of these formulae



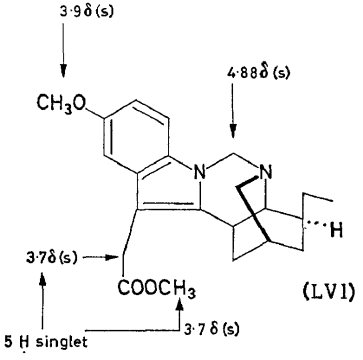
(XLVI)



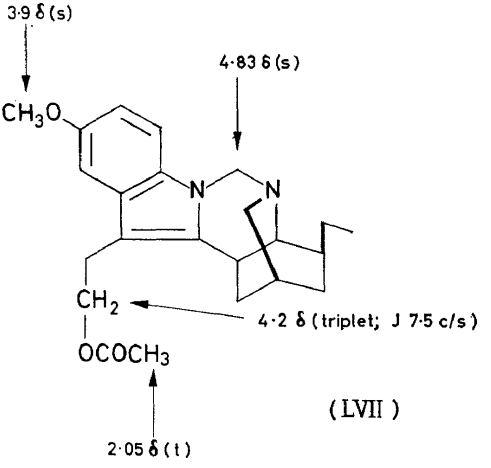
(LIV)



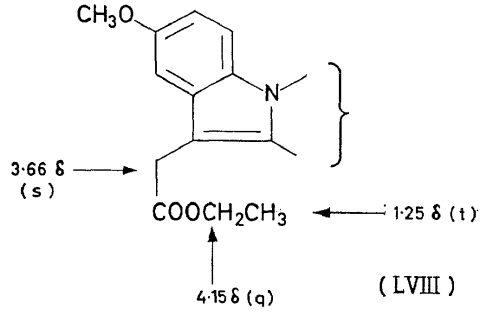
(LV)



(LVI)



(LVII)



(LVIII)

is provided by the spectral properties of the corresponding ethyl ester (LVIII) and the acetate (LVII). We are currently attempting to use this method for the introduction of a carbomethoxy group into indole alkaloids to prepare an intermediate useful in a synthesis of vinblastine (XXXIX).

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