STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. II.[1] THE SYNTHESIS OF 3',4'-DEHYDROVINBLASTINE, 4'-DEOXOVINBLASTINE AND RELATED ANALOGUES. THE BIOGENETIC APPROACH.

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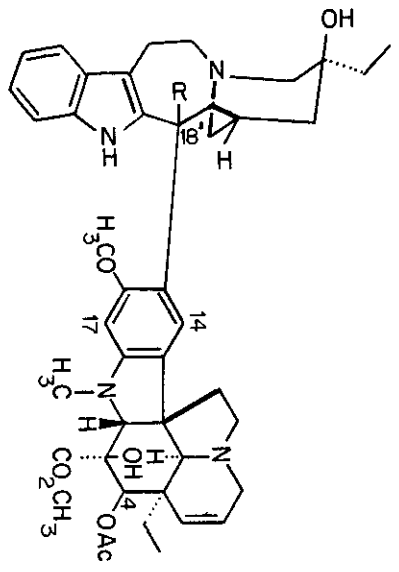
A novel approach to the synthesis of bisindole alkaloids in the vinblastine series has been developed. This approach, which originates from biogenetic considerations is exemplified by the coupling of catharanthine and dihydrocatharanthine N-oxides with vindoline under Polonovski-type fragmentation conditions. The method which provides dimers with natural stereochemistry at $C_{18'}$ represents an exciting entry into this complex family from two readily available alkaloids.

The clinically important anti-tumor agents, vinblastine (I) and vincristine (I, N-formyl instead of N-methyl) represent a series of "dimeric" alkaloids in which the indole (velbanamine-cleavamine) and dihydroindole (vindoline) halves are linked via a carbon-carbon bond involving an aliphatic centre ($C_{18'}$) in the indole unit and an aromatic carbon in the vindoline portion. In devising a laboratory synthesis of

this important family of alkaloids we have shown[1] that such dimeric systems can be obtained in a reaction involving the chloroindolenine derivatives of the appropriate indole unit and vindoline under acidic conditions. More recent studies have revealed that although this method provides considerable versatility and good yields (often 70%) it provides the incorrect stereochemistry at the crucial centre ($C_{18'}$) linking the two units.[2] We describe here a totally different approach which gives the desired dimers with the natural chirality at $C_{18'}$.

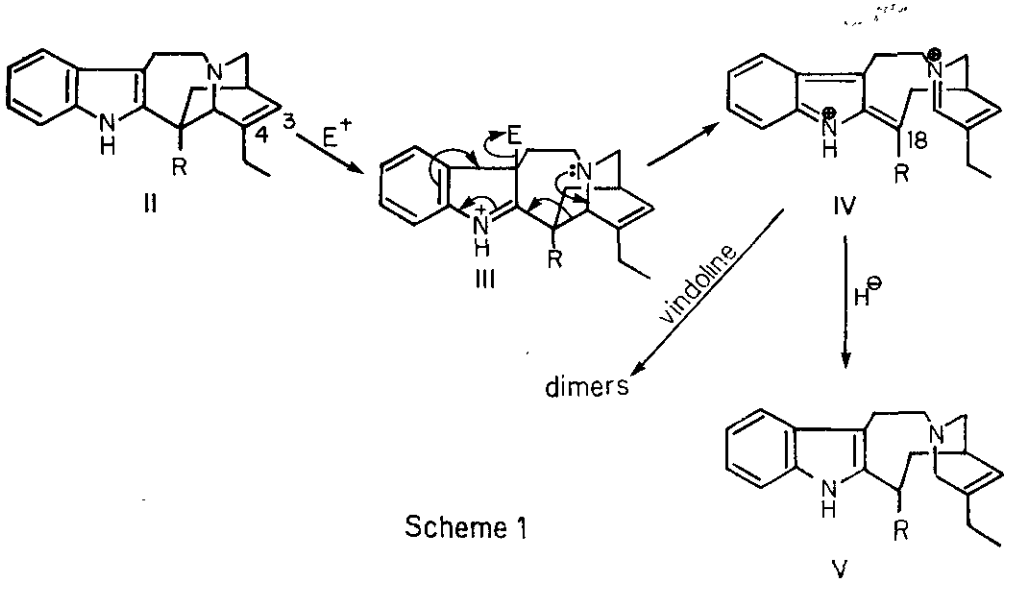
Catharanthus roseus G. Don (Vinca rosea L.) provides a rich source of indole and dihydroindole alkaloids and by now a large number have been isolated and characterized.[3,4] It is of particular interest to note that although the dihydroindole or vindoline unit present in vinblastine occurs as one of the major alkaloids in the plant, the corresponding indole portion has not been isolated even though extensive isolation



I, R = $COOCH_3$

studies have been conducted. On the other hand, one of the other major alkaloids catharanthine (II, R = CO_2Me) is convertible under appropriate laboratory conditions to the nine-membered ring system of the cleavamine-velbanamine series and it is of obvious interest to speculate whether the plant enzymes involved in the biosynthesis of vinblastine are employing a similar fragmentation process. Such biogenetic considerations form the basis of the novel approach described herein.

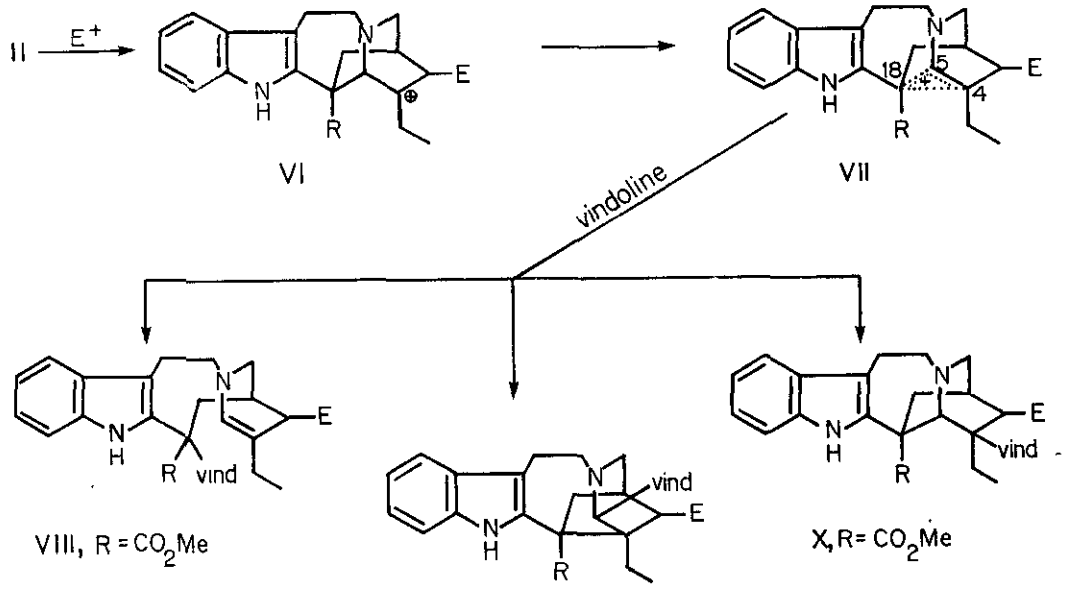
Acid-catalyzed fragmentation of catharanthine has been studied by the Lilly group[5] and in our laboratory.[6,7] More recent refinements in reaction conditions for the fragmentation reaction have allowed us to obtain high yields (about 90%) of cleavamine derivatives. The most plausible rationale for this conversion involves initial electrophilic attack at the β-position of the indole ring and the intermediate III thus formed undergoes the appropriate reactions observed (see Scheme 1, II → III → IV → V).



Scheme 1

From a biogenetic point of view several alternatives for the fragmentation of catharanthine are of interest. The first of these could involve a process fundamentally similar to that portrayed in Scheme 1 wherein oxidative attack at the β-position of the indole ring provides III (E = OH or OOH) and the subsequent intermediate IV reacts with vindoline, acting as a nucleophile, to provide the dimeric substances. Intermediate IV, with respect to the aromatic portion, is essentially identical with that envisaged for the acid-catalyzed coupling reaction of chloroindolenine intermediates with vindoline which as mentioned above, yields the unnatural dimers.[1,2]

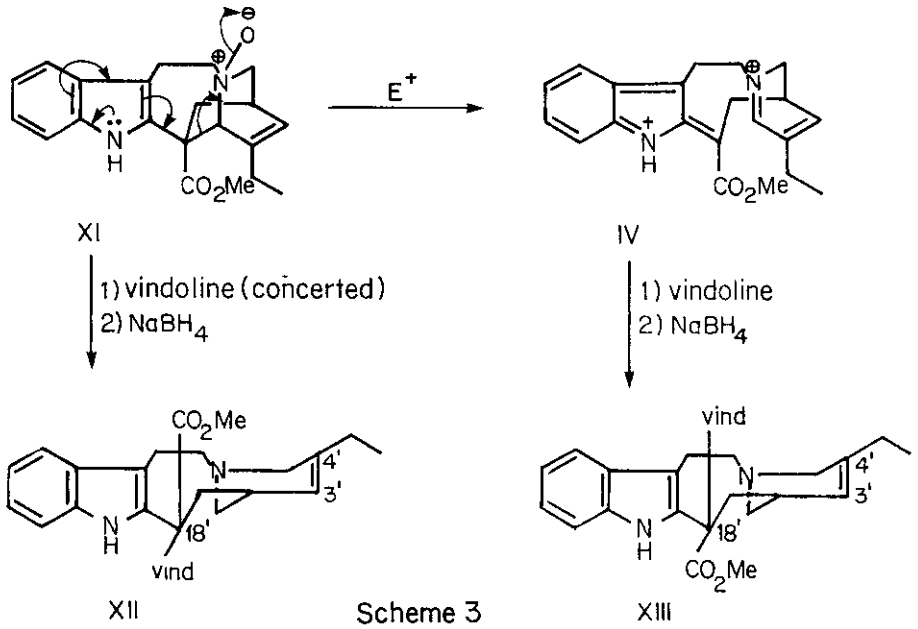
Another fragmentation process (Scheme 2) could be initiated by elctrophilic attack at the 3,4-double bond of catharanthine with subsequent reaction of the ion VI, perhaps via the non-classical ion VII, with vindoline to yield the possible dimers VIII - X. If this fragmentation reaction



Scheme 2

is considered in terms of the bicyclic quinuclidine system in II and comparison is made with the well-studied bicyclo [2.2.2] octyl system,[8] the favored course of reaction would be to provide IX rather than the desired VIII. Studies in this area are underway and will be published at a later time.

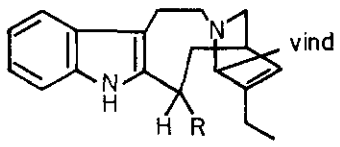
A third and equally plausible alternative involves oxidative attack at the basic nitrogen in II, a process already well known in alkaloid chemistry. Thus conversion of catharanthine to its N-oxide (XI) could, under appropriate conditions, allow a Polonovski-type fragmentation[9] and the intermediate thus formed (Scheme 3) reacts with vindoline to provide the dimeric substances. Thus it should be noted that if initial fragmentation of XI occurs in the expected manner the same intermediate (IV) is generated as shown in Scheme 1 and its subsequent reaction with vindoline would occur to provide dimers with unnatural sterechemistry at C_{18}' as mentioned above.



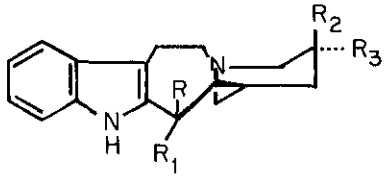
Scheme 3

On the other hand, molecular models reveal that in a concerted process, where vindoline is involved in displacing the C_{18}-C_5 bond in a trans coplanar fashion during the Polonovski fragmentation, the resulting dimers would possess the natural stereochemistry at C_{18}'. In view of the great deal of data available from previous studies[1,2] involving intermediates similar to IV, a systematic evaluation of the approach shown in Scheme 3 was undertaken.

The results obtained in this latter approach are remarkably sensitive to the reaction conditions employed. Thus the composition of the reaction mixture is dependent on temperature, reaction workup and the reagents employed in effecting the reaction. Tables 1 and 2 provide a summary of the various results obtained. A few pertinent comments are in order.



XIV, R = CO_2Me



XV

Experiment 1 provides an indication of results obtained in our initial investigations in 1973.[10] Attempts to isolate catharanthine N-oxide are complicated by its instability and facile conversion to a new product of undetermined structure. The formation of the various N-oxides can be readily determined by reductive methods (H_2, Pt or Zn, HOAc) which

TABLE 1. Coupling of Vindoline with Various N-oxides

Expt.	N-oxide Employed [a]	Coupling Conditions [e]	Dimers Isolated (Yields) [f]
1	catharanthine [b]	HCl, CH_3OH, r.t.	XIV [g] (30)
2	catharanthine [c]	$(CF_3CO)_2O$, -10°C	XII (30) XIII (14)
3	catharanthine [d]	$(CF_3CO)_2O$, -10°C	XII (14) XIII (31)
4	dihydrocatharanthine (II, 3,4-dihydro) [c]	$(CF_3CO)_2O$, -10°C	XV, R = CO_2Me; R_1 = vind; R_2 = CH_2CH_3; R_3 = H. (5) XV, R = CO_2Me; R_1 = vind; R_2 = H; R_3 = CH_2CH_3. (13) XV, R = vind; R_1 = CO_2Me; R_2 = CH_2CH_3; R_3 = H. (14)[h] XV, R = vind; R_1 = CO_2Me; R_3 = CH_2CH_3; R_2 = H.

[a] In all cases, m-chloroperbenzoic acid was employed to prepare N-oxide.

[b] Reaction was performed at room temperature and oxide purified by chromatography. During purification, the N-oxide undergoes conversion to a new product, the structure of which remains undetermined at present.

[c] N-oxide prepared *in situ*.

[d] N-oxide isolated at low temperature.

[e] After coupling in each case the reaction mixture was treated with sodium borohydride prior to isolation of dimers.

[f] Yields quoted are not optimum. For example in related studies yields as high as 55% of XII have been obtained.

[g] Structure assignment based on spectral data only.

[h] Yield quoted on mixture of these dimers with unnatural stereochemistry at $C_{18'}$.

TABLE 2. Characterization Data for Isolated Dimers

Dimer [a]	NMR [b,c]	MS [d]		CD [e] ($\Delta\varepsilon$)	MP
		$C_{46}H_{56}O_8N_4$			
		Requires	Obtained		
XIV	3.94 (s, $C_{17}H$) 2.30-3.00 (m, $C_{14}H$ + aromatic) 5.72 (m, $C_{18}'H$)	792.410	792.412		amorphous
XII	3.89 (s, $C_{17}H$) 3.54 (s, $C_{14}H$)	792.410	792.405	227 nm(+27)	171-173 (dec.)
XIII	3.98 (s, $C_{17}H$) 3.05 (s, $C_{14}H$)	792.410	792.399	224 nm(-31)	amorphous
		$C_{46}H_{58}O_8N_4$			
XV		Requires	Obtained		
R=CO_2Me; R_1=vind; R =CH_2CH_3; R_3=H.	3.87 (s, $C_{17}H$) 3.39 (s, $C_{14}H$)	794.425	794.421	226 nm(+17)	amorphous
XV R=CO_2Me; R_1=vind; R_2=H; R_3=CH_2CH_3.	3.80 (s, $C_{17}H$) 3.42 (s, $C_{14}H$)	794.425	794.422	227 nm(+26)	190-194 (dec.)
XV [f] R=vind; R_1=CO_2Me; R_2=CH_2CH_3; R_3= H.	4.04 (s, $C_{17}H$) 3.05 (s, $C_{14}H$)	794.425	794.419	223 nm(-29)	amorphous

a The UV spectra for all dimers are similar to those already recorded.[1]

b NMR spectra were taken at 100 MHz in $CDCl_3$ solution and data are given in τ values.

c Only the very characteristic aromatic proton signals of the vindoline unit are given. For numbering system, see I.

d Data obtained on AEI MS902 mass spectrometer.

e An extensive CD study on these various dimers has been made in a collaborative investigation involving our group and that of A. I. Scott at Yale University. The results to be published elsewhere reveal that CD data at low wavelengths can be used effectively to predict chirality at C_{18}' in these dimers. Results presented were obtained in methanol solution.

f The dimer isolated here was identical in every respect with that obtained in the chloroindolenine method.[1,2]

regenerate the starting material in essentially quantitative yield. It is of interest that the intermediate (probably IV) formed in this case is attacked at C_5 by the vindoline molecule under the acidic conditions employed.

Experiments 2 and 3 illustrate the rather dramatic changes in the composition of the reaction product mixture when only small changes in reaction conditions are involved. It is clear as already noted (footnote f, Table 1) that higher yields of dimers particularly those bearing the natural stereochemistry at $C_{18'}$ (for example XII) will be obtained after further refinements of the coupling conditions. It should be noted that the structure of dimer XIII has already been established previously[10,2] and therefore the structure of XII follows directly from comparison of the spectral data as shown in Table 2.

Experiment 4 reveals the isolation of four dimers, two of these possessing the natural stereochemistry at $C_{18'}$ while the other two are in isomeric series obtained and characterized previously.[1,2] Within each series, the differences in chirality at $C_{4'}$, the ethyl bearing center, are readily understood in terms of the well-known imine-enamine equilibrium in the Iboga series.[11,12,13] Again comparison of the data in Table 2 with that already recorded for the known dimers (XV)[1,2] provides unambiguous proof of structure for the two new dimers obtained.

In summary, the Polonovski-type fragmentation approach, which arose from biogenetic considerations in this series, provides an exciting

entry into the synthesis of bisindole alkaloids in the vinblastine-vincristine series. Further studies are underway.

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