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Mechanistic Aspects of the Formation of Anhydrovinblastine by Potier-Polonovski Oxidative Coupling of Catharanthine and Vindoline. Spectroscopic Observation and Chemical Reactions of Intermediates

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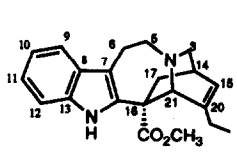
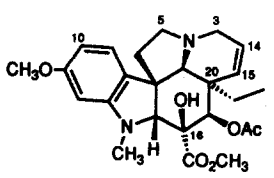
Abstract

The fragmentation-coupling of catharanthine and vindoline by trifluoroacetic anhydride has been carried out under conditions which allow observation of intermediates and comparison of reactivity by low temperature NMR. These studies have confirmed or revealed the following facets of the mechanism of the reaction: (1) fragmentation of an intermediate derived from catharanthine-N-oxide which otherwise is stable at -40°C occurs rapidly on addition of vindoline; (2) other bases including tri-*n*-butylamine, N,N-dimethyl-3-methoxyaniline, N,N-dimethyl-2-(2,4-dimethoxyphenyl)ethylamine and 10-trifluoroacetyl-vindoline also accelerate fragmentation; (3) the stereoselectivity of coupling is controlled in part by the different rates of reaction of vindoline with separate precursors of anhydrovinblastine and 16'-epi-anhydrovinblastine; (4) N_a-methylcatharanthine-N_b-oxide undergoes fragmentation in a manner analogous to catharanthine-N-oxide but there is an observable intermediate which can not be detected in the latter case; (5) the rate of fragmentation of N_a-methylcatharanthine-N_b-oxide is also subject to some acceleration by base; (6) several products formed from the final fragmentation intermediate have been identified. These observations are consistent with the previous representation of the fragmentation-coupling mechanism but contribute new details.

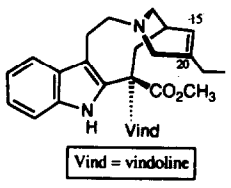
In the early 1970's Potier and co-workers discovered the stereoselective coupling of catharanthine-N-oxide (1) with vindoline which is mediated by trifluoroacetic anhydride (TFAA).[1] Kutney and his group also studied this reaction extensively.[2] While there have been significant advances following other approaches[3,4,5], this oxidative fragmentation remains an important means for the generation of precursors of the dimeric *vinca* alkaloids.[6] The general outline of the mechanism which is summarized in Scheme 1 involves an antiperiplanar fragmentation of the C16-C21 bond in the trifluoroacetylated intermediate **A**. The stereoselectivity of the coupling reaction is temperature dependent with the 16'-*S* isomer being the primary product below -40°C while at 25°C, mainly the 16'-*R* isomer is formed. This facet of the reaction can be interpreted in terms of a conformational transformation between fragmented intermediates **B** and **B'**, which in turn lead to **C**, and **C'** the precursors, respectively, of anhydrovinblastine (AVLB) and its C16'-*R*-epimer (16'-epi-AVLB). The conformation **B'** is assumed to be more stable, while **B** can be trapped at low temperatures prior to its relaxation to **B'**.[1,2] As Potier has pointed out, however,[1c] this mechanistic interpretation is not necessarily unique and some specific complexation of vindoline and catharanthine-N-oxide might offer an alternative explanation.



Catharanthine



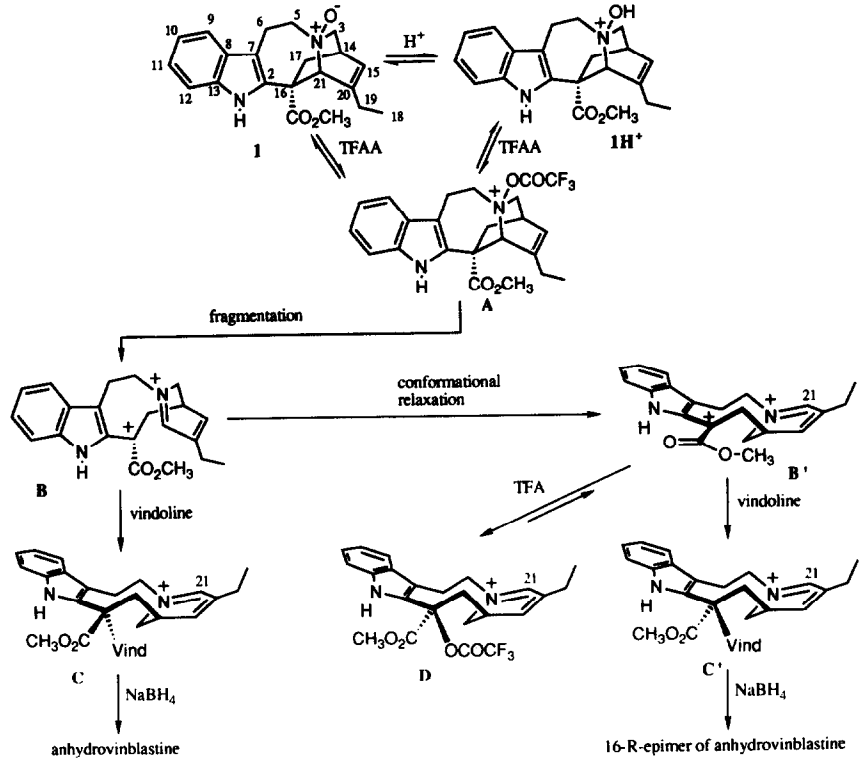
Vindoline



Anhydrovinblastine

We have synthesized several analogs of catharanthine[7] and have begun study of the oxidative fragmentation of these compounds in the presence of vindoline. To provide a mechanistic basis for this work we studied the catharanthine-N-oxide/vindoline coupling process by low temperature NMR and have observed certain intermediates. We have noted effects of added acid and base on the fragmentation-coupling reaction and have explored the possible role of electron transfer steps in the coupling process. We have also examined some chemical transformations of the fragmented intermediates.

Scheme 1



Results

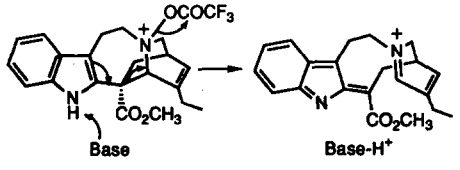
A. Fragmentation of Catharanthine-N-Oxide in the Absence of Vindoline.

Catharanthine was oxidized by *m*-chloroperoxybenzoic acid (MCPBA) as described by Langlois *et al.* taking precaution to avoid sigmatropic rearrangement.[1b] The oxide could be used as the resulting *m*-chlorobenzoate salt ($1H^+$ $MCBA^-$) or as the purified neutral amine oxide without major differences. Figure 1 shows a progression of ^{1}H-NMR spectra leading from **A** to a fragmented species assigned structure **D**. It is noteworthy that very little **D** is formed below -30°C. At -30°C the spectrum begins to convert to **D**. After 1.5 h at -20°C, the spectrum is predominantly **D**. No signals attributable to the intermediates **B** or **B'** are detectable. The ^{1}H-NMR spectrum of **A**, the material generated immediately upon addition of TFAA, strongly resembles that of both **1** and its conjugate acid $1H^+$ but certain peaks undergo significant shifts. The ^{1}H-NMR assignments for **1**, $1H^+$ and **A** are given in Table I.

The proton spectrum of **D** was assigned on the basis of observed chemical shifts supplemented by proton-proton decoupling. A noteworthy feature of the spectrum is the signal at 8.95 ppm assigned to the imine proton at C21. The ^{13}C-NMR data for **D** are given in Table II. The ^{13}C-NMR spectrum was assigned by application of ^{1}H-^{13}C correlations. An especially significant signal is that at 84.2 ppm assigned to C16. We have drawn two structural conclusions from these spectral data: (1) the indole ring is essentially unperturbed in both **A** and **D**; (2) C16 in **D** is not a "carbocation" but instead has a substituent, presumably a trifluoroacetoxy group, bound to it.

An important mechanistic point also is revealed by these spectroscopic studies. The conversion of **A** to **D** under these conditions occurs more slowly than fragmentation and coupling occurs in the presence of vindoline. Thus irreversible unimolecular fragmentation of **A** cannot be the rate-determining step in the fragmentation-coupling. This is consistent with Potier's[1b] and Kutney's[2b] description of the coupling reaction as "concerted."

We considered two possible mechanisms by which vindoline might induce fragmentation of **A**. One is by base catalysis.



The second is by an electron-transfer (ET) mechanism. Some precedent can be cited for an ET mechanism for an N-trifluoroacetoxyammonium ion.[8] We have presented evidence that the aminium radical cation derived from catharanthine undergoes C16-C21 fragmentation.[9]

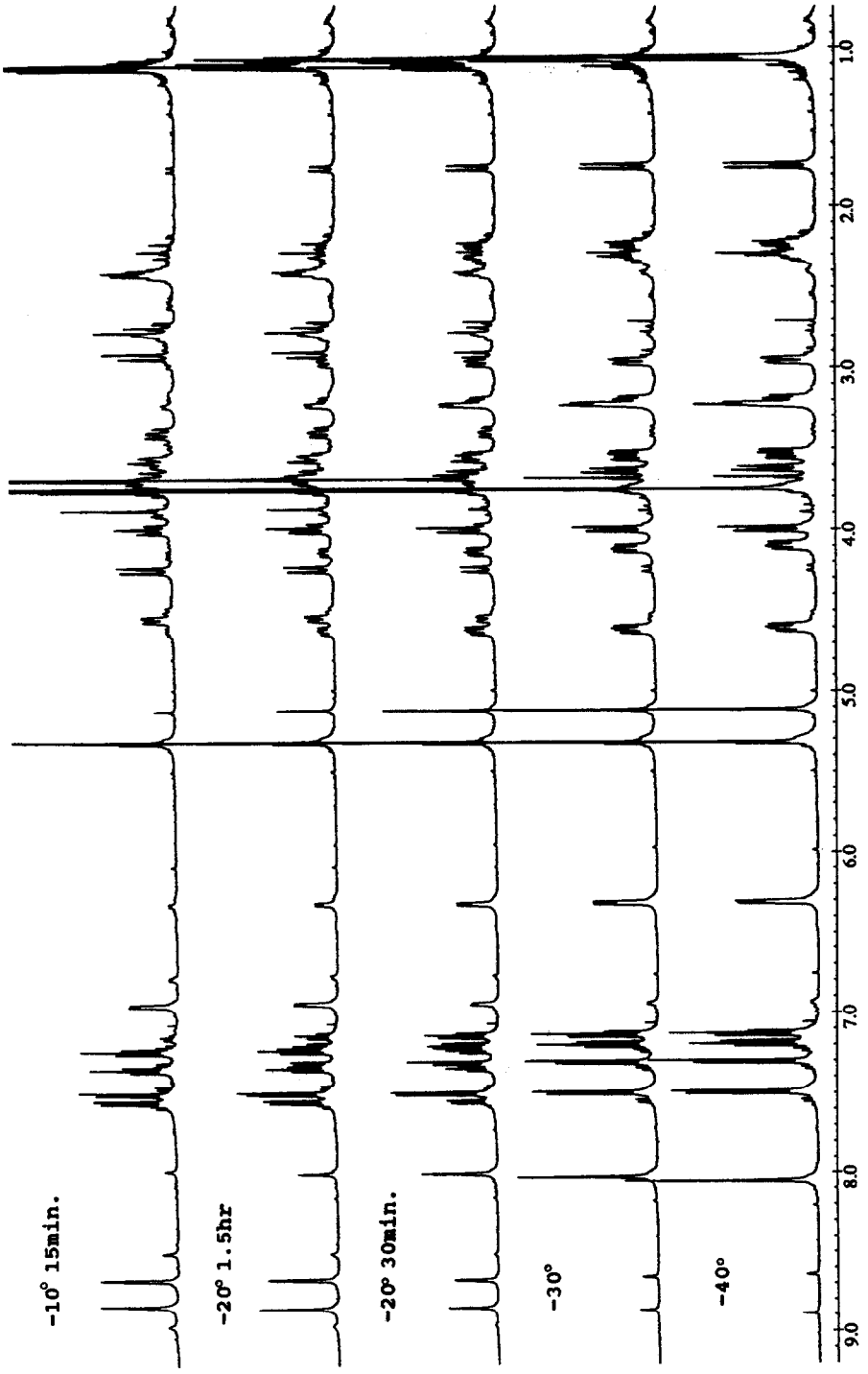


Figure 1. ^{1}H-NMR spectral changes corresponding to transformation of **A** to **D** in CD_2Cl_2.

Table I. Spectra Assignment for Reactants, Intermediates and Product

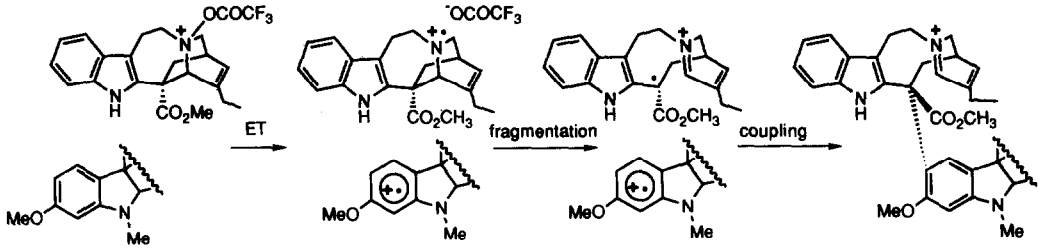
	3	5	6	9	10	11	12	14	15	17	18	19	21	OCH_3	NCH_3
1	3.78d 3.44dm J_{gem}=12	4.27dd 3.95dd J_{gem}=13	3.51dd 3.04dd[c] J_{gem}=17	7.50d	7.13t[d]	7.18t[d]	7.28d	3.0m[c]	6.14d J=6	1.61d c J_{gem}=14	1.12t	2.23m 2.58m	4.75s	3.74	-
1H^{+a}	3.96d 3.84d J_{gem}=13	4.84dd 4.21dd J_{gem}=14	3.59 3.11 J_{gem}=18	7.47[d]	7.13t[d]	7.19t[d]	~7.3[c]	3.0m	6.18d	1.67d 2.94dm J_{gem}=14	1.10t	2.22m 2.53m	5.06s	3.76	-
A[a]	4.81d 3.61d J_{gem}=12	4.59dd 4.11dd J_{gem}=14	3.53dd 3.21dd J_{gem}=18	7.50d	7.13t[d]	7.19t[d]	7.31d	3.24m	6.32d	1.71d 2.96d J_{gem}=14	1.06t	2.23m 2.30m	5.12s	3.78	-
A[b]	3.63d 3.97d J_{gem}=12	5.08dd 5.62dd J_{gem}=13	3.53dd 3.20[c] J_{gem}=16	7.489	7.12t[d]	7.18t[d]	7.30d	c	6.29 J=6	1.73d 2.95dm J_{gem}=14	1.06t	2.20m 2.30m	5.11s	3.74s	-
D[a]	3.61dm 4.29d J_{gem}=13	4.68dm 3.93t J_{gem}=13	3.43dd 3.70dm J_{gem}=16	7.56d	7.27t	7.38t	7.47d	2.73m	6.88d J=6	2.83dd 2.94d	1.15t	2.43q	8.67s	3.75s	-
D[b]	3.57dt 4.26d J_{gem}=14	4.54dm 4.01t J_{gem}=13	3.40tm c J=13	7.54d	7.24t[d]	7.34t[d]	7.49d	2.79m[c]	6.94d J=6	2.74dd 2.93d J_{gem}=14	1.14t	2.43q	8.63s	3.71s	-
N-Me-1[a]	c	4.48dd	c	7.53d	7.14t	7.25[c]	7.25[c]	3.05[c]	6.18d				4.94s		
N-Me-1H^{+a}	4.0 ABq	5.29m c	c	7.50d	c	c	c	3.1[c]	6.29d J=6	1.72d c J_{gem}=14	1.11t	2.06m 2.48m	5.24s		
N-Me-A[b]	3.72d 3.95d J_{gem}=13	4.86dd 3.84t J_{gem}=14	3.25dd c	7.51d	7.13t	c	c	3.33m	6.38d J=7	1.76d 3.11dm	1.07t	2.05m 2.27		3.63	
N-Me-D[b]	4.17d J=14	4.62dd J=12,3	c	7.55d	c	c	c	2.77m	6.72d	2.84dd	1.13t	2.43q	8.72s	3.73	3.91
E[b]	4.12d 4.03 J_{gem}=16	4.9m 4.2m	3.5m c					c	6.37d J=5	2.94d 3.02dd J_{gem}=16	0.53t J=7	2.67m 2.50m	6.45s	3.71	3.81

a) in $CDCl_3$; b) in CD_2Cl_2; c) part of unresolved multiplet; d) assignments may be interchanged.

Table II. Carbon-13 Spectral Data

	2	3	5	6	7	8	9	10	11	12	
Cath	137.0	53.7	50.0	22.0	111.2	129.5	118.7	119.9	124.2	111.0	
1	134.6	74.4	~77[a]	19.5	111.9	127.0	118.0	120.0	122.5	111.0	
1H$^+$	134.6	73.1[b]	75.2	19.1	110.5	126.8	118.0	120.4	123.2	111.2	
D	137.8	52.5	63.0	25.6	110.7	126.4	118.2	121.2	125.0	111.7	
H	136.5	53.3[c]	51.1[c]	27.0[d]	108.1	126.7	118.4	120.9	123.8	111.9	
	13	14	15	16	17	18	19	20	21	C=O	OCH_3
Cath	135.6	31.3	124.2	56.0	39.0	26.8	11.3	149.8	62.4	174.7	52.9
1	133.8	29.9	124.0	50.8	31.6	28.9	10.2	145.8	74.1	171.7	53.3
1H$^+$	132.2	29.3	126.7	50.4	31.1	27.4	10.2	143.9	71.1[b]	170.1	53.7
D	134.9	28.6	145.4	84.2	28.0	25.7	12.5	e	167.0	166.0	59.8
H	133.1	31.7[b]	144.0	38.0	33.1[b]	25.7[d]	12.5	e	169.0	173.0	59.9

a) overlaps solvent; b,c,d) assignments can be interchanged; e) not assigned.



To explore these two possibilities we examined the effect of both bases and potential electron donors on the rate of fragmentation of **A**.

B. Fragmentation in the Presence of Vindoline.

The initial experiments involved efforts to follow the **1** + vindoline → **C** transformation in NMR tubes. The results were inconclusive and there was considerable variation between individual experiments. We attribute this difficulty to variability in mixing and thermal effects upon transfer of TFAA by syringe. Reproducible results were achieved by doing the mixing in small flasks at -55°C, ±5°C and making rapid transfers to NMR tubes with cold syringes. Under these conditions initial spectra could be recorded within 15-30 min of mixing, during which time the temperature of the solution was kept below -40°C.

Two parallel experiments were done in which the order of addition of vindoline and TFAA was reversed. Solutions of **1** in CD_2Cl_2 at -40°C were treated either in the "normal"

way by adding TFAA after the vindoline or in an inverted order, by adding vindoline 5 min or 20 min after TFAA had been added. These solutions gave rise to series of peaks at 2.42(q), 6.23(s), 5.95(s) and 6.75(d) which were attributed to the coupled intermediate C. Reduction of these solutions with $NaBH_4$, followed by isolation of the crude product mixture confirmed the formation of anhydrovinblastine (AVLB). While accurate yield data have not been obtained, we estimate yields of about of 30% under these conditions, as compared to 60-70% under optimal preparative conditions.[1,2,6] Unreacted vindoline is the other major component of the reaction mixture. The alternate orders of addition produce comparable amounts of coupling product as determined by comparison of the NMR spectra. The result that the order of addition of vindoline is not critical is consistent with the conclusion that vindoline induces the fragmentation of **A**. A role for base-catalysis was further implicated when the vindoline was premixed with 3 eq of TFA. No fragmentation of **A** was observed at -40°C upon addition of the vindoline salt.

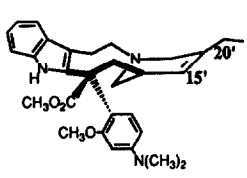
Experiments which provide information on the stereoselectivity of the coupling with vindoline were also done. The series of peaks associated with the intermediates C and C' were used to monitor the course of coupling. After reductive workup, the amount of AVLB and 16'epi-AVLB could also be estimated from characteristic NMR peaks. In agreement with Potier's and Kutney's results, solutions quenched at -40°C by $NaBH_4$ gave AVLB with only traces of the 16'-*R* epimer. When such solutions were brought to 0°C prior to quench, the proportion of epi-AVLB increased to about one-third. When the fragmentation of **A** → **D** was allowed to proceed to completion prior to addition of vindoline, the dominant coupling product was 16'-epi-AVLB (~3:1). These results are entirely consistent with the earlier results but provide an additional fact. The rate of formation of C must exceed that for C' so that the AVLB and epi-AVLB precursors are formed sequentially. Thus quenching the coupling reaction at -40°C, minimizes the amount of epi-AVLB formed at least in part because **B'** does not couple with vindoline at this temperature. At a higher temperature **D** reacts with vindoline and primarily C' is formed. Thus under any given set of conditions the major factors in stereoselectivity are the ratio of the fragmented intermediate B which is trapped before it is converted to B'and D and the extent to which B' and/or D react with vindoline.

C. Effect of Other Bases and Acids on Fragmentation

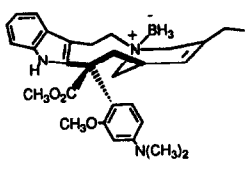
When tri-*n*-butylamine is added to a solution of **A** below -40°C there is immediate formation of **D**. Similarly, when 10-trifluoroacetylvindoline,[2a] which can act as a base but cannot undergo normal coupling, is used in place of vindoline the formation of **D** occurs rapidly at -40°C.

In an effort to mimic the fragmentation-coupling observed with vindoline N,N-dimethyl-2,4-dimethoxyphenylethylamine (**DMPA**) was prepared. When it was mixed with **1** and TFAA added, immediate fragmentation was observed and **D** is formed as the major product detectable by NMR. There was no evidence of formation of a coupled product at -40°C. With N,N-dimethyl-3-methoxyaniline (**DMA**) fragmentation occurred at -40°C and was accompanied by

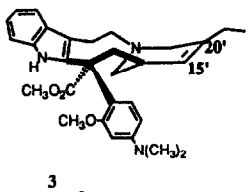
coupling as evidenced by the appearance of new peaks in the NMR at 8.51 and 6.8 ppm. Reductive quench led to the isolation of a coupled product 2 and the corresponding borane adduct 2-BH_3. When fragmentation to D was permitted to come to completion at 0°C prior to addition of DMA a different coupling product 3 was isolated. Compound 2 was assigned the 16'-*S* configuration and 3 was assigned at the 16'-*R* epimer. The stereochemical assignments are based upon comparison with ^{1}H-NMR spectral data for AVLB and its 16'-*R* epimer and data reported by Schill *et al.*[3c] for compounds in which the upper (velbanamine) portion of the structure is saturated at C15-C20 and lacks the C20 ethyl substituent. The spectrum of the borane adduct 2-BH_3 was also compared with that of the borane adduct of AVLB.[11] The following features of the spectra appear to be correlated with stereochemistry. (a) The 9'-H is distinctly downfield in the 16'-*S* series as compared to the 16'-*R* series; (b) The indole NH is farther downfield in the 16'-*R* series than in the 16'-*S* series; (c) The 16'-CO_2CH_3 methyl and aromatic methoxy signals are somewhat more widely spaced in the 16'-*S* series (Table III). There are also qualitative similarities in the aliphatic portions of the spectra. These stereochemical assignments lead to the conclusion that DMA exhibits the same temperature-dependent stereoselectivity as vindoline, with the 16'-*S* isomer being formed preferentially at -40°C.



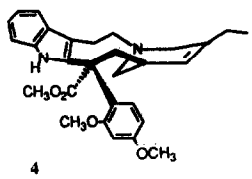
2
44A[3c] 15',20' dihydrodesethyl



2-BH_3



3
44B[3c] 15',20' dihydrodesethyl



4

Acid has an inhibitory effect on the rate of conversion of **A** → **D**. Thus when 3 equiv. of TFA was included in reaction mixtures of 1 and TFAA, conversion of **A** → **D** occurred very slowly even at 0°C. The preparation and transfer of TFAA in such a way as to completely avoid contamination by TFA was challenging, in our experience. (See the Experimental Section for our procedures). Several runs were inadvertently retarded by contamination of TFAA by TFA. Such runs typically showed a strong signal due to carboxylic protons near 13 ppm. Even in "good" runs, a significant carboxylic proton peak was observed although the stoichiometric reaction of 1 with TFAA generates no TFA.

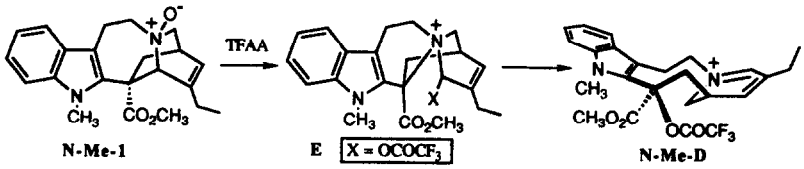
If indole nitrogen deprotonation is a key step in the fragmentation of **A** an N-substituted indole would be expected to behave differently. To test this idea we synthesized N_a-methylcatharanthine,[11] which has not previously been studied in the Potier-Polonovski fragmentation. We anticipated that the N_a-methyl-N_b-oxide **N-Me-1** might fragment more slowly than 1, and be insensitive to the influence of base catalysis. When **N-Me-A** was generated in the presence of tri-n-butylamine or N,N-dimethyl-3-methoxyaniline, the rate

Table III. Comparison of ^{1}H-NMR Peak Positions

Proton	AVLB[a]	44A[b]	2	AVLB-BH_3[a]	2-BH_3	epiAVLB	44B[b]	3	4
1'-NH	8.05	8.25	8.25	8.06	8.31	9.07	9.07	9.06	9.04
9'	7.53	7.48	7.48	7.65	7.67	7.39	7.34	7.37	7.39
9	6.62	6.86	6.84	6.45	6.75	6.97	7.31	7.30	7.32
12'				7.09		7.23	7.22	7.24	7.26
10'	7.14	7.19-7.02	7.3-7.0	7.12-7.16	7.30-7.08	7.00	7.07	7.1	7.12
11'						7.10	6.98	7.0	7.01
8	-	6.29	6.3	-	6.27	-	6.29	6.25	-
12	6.13	6.18	6.19	6.10	6.17	6.00	6.18	6.17	-
3'	3.31ß			3.96ß	3.97ß				
	2.58α			2.46α	2.5α				
21'	3.52ß			3.48α	3.5α				
	3.28α			3.23ß	3.25ß				
16'-CO_2CH_3[c]	3.62	3.59	3.60	3.62	3.62	3.76	3.75	3.78	3.74
									3.78
11-OCH_3[c]	3.82	3.81	3.82	3.81	3.85	3.90	3.88	3.89	3.87

a. Ref. 10; b. Ref. 3c; c. The assignment of the methoxy peaks has been made unambiguously only in the case of AVLB. The other assignments are made by analogy.

of reaction was somewhat slower than that of **A**. However, the amines did appear to accelerate fragmentation relative to comparable solutions without amines. An intermediate species was observed and assigned structure **E**. This intermediate subsequently was converted to **N-Me-D**. The corresponding spectral changes are shown in Figure 2. Thus the N-methylation of 1 does not entirely remove the sensitivity of the reaction to base, but it does diminish it. This indicates base must also be involved in the formation of **N-Me-A**, either by effecting the **N-Me-1** ⇌ **N-Me-1H$^+$** equilibrium or by catalyzing trifluoroacetylation of **N-Me-1**. Amine oxides are comparable in basicity to tertiary amines[12] and O-protonation would be expected to retard acylation. Thus bases may influence the rate of trifluoroacetylation by affecting the **N-Me-1** ⇌ **N-Me-1H$^+$** equilibrium. This mechanism may also contribute to the effect of bases on the reactivity of 1.



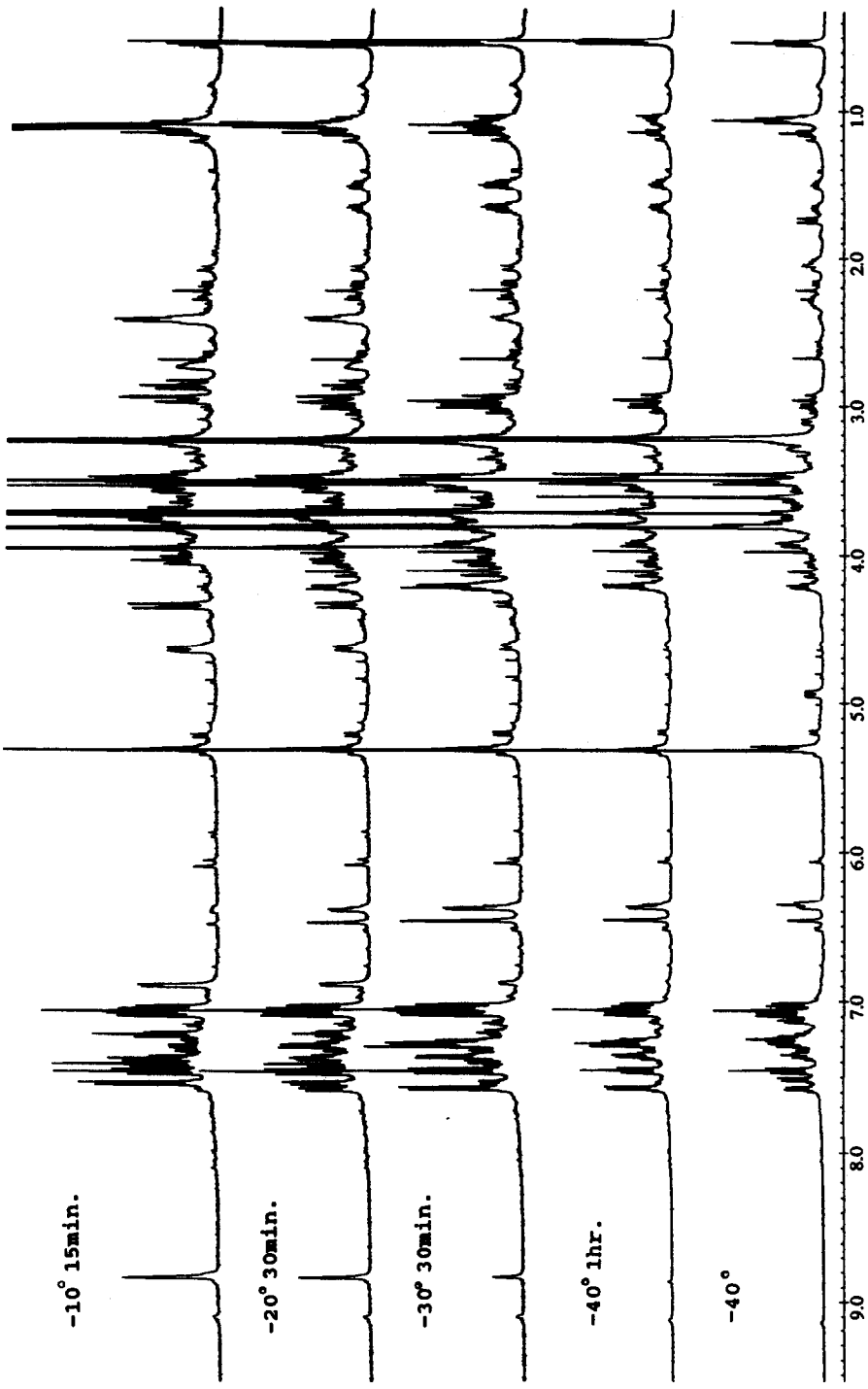


Figure 2. ^{1}H-NMR spectral changes corresponding to transformation of **N-Me-A** to **E** to **N-Me-D** in CD_2Cl_2 in the presence of one equivalent of DMA. Initial spectrum represents ~ 50% conversion to E_t

D. Reactions in the Presence of Potential Electron Donor

To investigate the possibility of the ET mechanisms we examined the behavior of several aromatic compounds which bracket vindoline in oxidation potential. These compounds were used in place of vindoline under the normal conditions for coupling. The behavior of tetramethoxybenzene (**TMB**) was most informative. It induced no fragmentation of **A** over a period of three hours at -40°C. However it was partially oxidized to the radical cation in the solution. An EPR signal due to the **TMB** radical cation[13] was detectable and the **TMB** signals disappeared from the ^{1}H-NMR spectrum, presumably due to exchange broadening. Thus, although **TMB** is partially oxidized to the radical cation under the conditions of the experiment, the occurrence of this process has no effect on the fragmentation of **A**, which remains stable at -40°C. N,N,N,N-Tetramethylphenylenediamine (**TMPD**) was also oxidized to the radical cation (Wurster ion) as indicated by the intense color generated, but in this case fragmentation of **A** also occurred, because **TMPD** can act as a base. 1,3-Dimethoxybenzene (**DMB**) had no effect on **A** at -40°C. When a solution containing **A** and **DMB** was warmed to 0°C coupling occurred as revealed by the appearance of new signals at 7.0, 6.9, 6.43 and 6.38 ppm due to alkylation of the **DMB** ring by **D**. Reduction of the reaction mixture followed by workup and chromatographic purification lead to isolation of the coupling product **4**. Since this occurs via the relaxed intermediate **D** it would be expected to have the 16'-*R* configuration. The close correspondence of the ^{1}H-NMR spectra of **3** and **4** support this stereochemical assignment (Table III).

E. Chemical Transformations of A and D.

We have investigated the reactivity of the intermediates **A** and **D** under a number of other conditions in order to confirm the structural conclusions based on spectroscopy.

Adding $NaBH_4$ to solutions of **A** at -40°C led to the recovery of catharanthine as the major (>85%) product. Use of $NaBH_3CN$ returned mainly the N-oxide **1**. These observations confirm the conclusion from the spectroscopic data that the *iboga* skeleton remains intact in the intermediate **A** at -40°C.

In connection with related studies we have examined the products from reaction of **D** with the base DABCO followed by treatment with $NaBH_4$.[14] The major product is the cyclo-

Table IV. Redox Potentials

	E_{PA}[a]	E^b
N,N-dimethyl-2,4-dimethoxyphenylethylamine (**DMPA**)	0.80	
N,N-dimethyl-3-methoxyaniline (**DMA**)	0.67	0.51
Vindoline	0.70,0.98	0.55,0.85
Catharanthine	0.53,1.2	0.41
1,2,4,5-tetramethoxybenzene (**TMB**)	0.68	
N,N,N',N'-tetramethylphenylenediamine (**TMPD**)	0.15,0.72	

[a] In volts referenced to SCE. The anodic peak potential was measured in degassed dry acetonitrile with ferrocene as internal reference

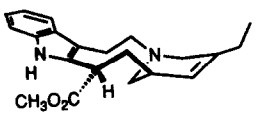
[b] Oxidation potentials measured by Haque in 9:1 acetonitrile relative to Ag/Ag^+ (0.01M) at pH ≈11.5; I. U. Haque, *J. Chem. Soc. Pak.*, **11**, 232 (1989).

propane 5. Formation of 5 is believed to occur via F, the conjugate base of D. Treatment of D with TMSCN/$LiClO_4$ generates 21-cyanocatharanthine 6 in 74% yield. Mangeney *et al.* had observed formation of this product in competition with other products by treatment of the 1-TFAA reaction mixture with methanolic KCN. A mechanism involving cyanide ion addition at C21, N4 cyclization at C16 and Stevens' rearrangement accounts for the formation of 6.[15]

Treatment of a solution of D with triethylsilane for 1 h at 0°C, followed by TMSCN/$LiClO_4$ gave 21-cyano-16-carbomethoxycleavamine (7) a compound which we have recently characterized by ^1H and ^{13}C-NMR spectra and by X-ray crystallography.[9] The ^1H and ^{13}C-NMR spectra of the reaction solution were recorded after the reaction with triethylsilane but prior to addition of the TMSCN. While the ^1H spectrum was too broad to be informative, the ^{13}C spectrum showed that a nearly pure material was present at that point. The spectrum is consistent with this being H and the assignments are given in Table II.

Treatment of solutions of D with $NaBH_4$ or $NaBD_4$ gave rather complex product mixtures. Not all the components could be identified. However among those which were are 16α-carbomethoxycleavamine (8),[16] 16-hydroxy-16-carbomethoxycleavamine (9) and a 7-trifluoroacetoxy derivative of 16-carbomethoxycleavamine (10). The 7-hydroxyindolenine derived from catharanthine (11) was also observed. The material balance was low and the product composition was very sensitive to the exact experimental procedure.

The structural assignment of 8 was based on the general similarity of the ^1H-NMR spectrum to that of the definitively characterized compound 7. In particular a doublet, J=11, at 5.16 is indicative of a proton at C16. This peak, as well as one of the peaks of the AB doublet at 3.07, 3.16, disappears in the dideuterio compound isolated when $NaBD_4$ is used as the reducing agent. The ^{13}C-NMR spectrum is in excellent agreement with the data reported for the α-carbomethoxy stereoisomer.[16c] The 16-hydroxy derivative 9 also shows a generally similar ^1H-NMR spectrum and the aromatic region is characteristic of an indole ring. The structural assignment of 10 is somewhat more tentative. The ^1H-NMR indicates that the ring is part of an anilinoacrylate chromophore.[17] The molecular weight (MS) reveals the incorporation of a trifluoroacetoxy group. The 7-hydroxyindolenine of catharanthine has not been reported before, although hydroxyindolenines have often been obtained from oxidation of other *iboga* alkaloids.[18] The observed ^{13}C resonance of the C7 carbon (88.2 ppm) is in good agreement with reported values for other hydroxyindolenines, and the aromatic signals are similar to those of the hydroxyindolenine of heyneanine.[19]



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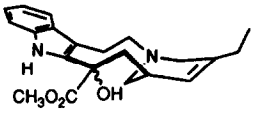

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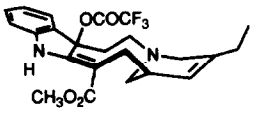

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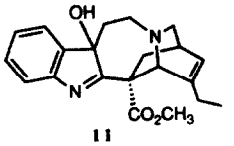


11

Discussion

The initial studies of the group at Gif-sur-Yvette established the temperature dependence of the stereoselectivity of the vindoline-catharanthine-N-oxide fragmentative

coupling.[1b] The studies of the Vancouver group added much detail on solvent effects and other factors which affected both yield and stereoselectivity.[2a] The resulting mechanistic outline (summarized in Scheme 1) has served to describe the fragmentative coupling for the past 15 years. It emphasized the anti-periplanar relationship of the C16-C21 bond to the N-oxide and the C15-C20 double bond as crucial structural features for efficient fragmentation.[1c,2b]

Our experiments with the bases tri-*n*-butylamine, 10-trifluoroacetylvindoline, **DMA** and **DMPA** provide compelling evidence that the fragmentation of **A** is accelerated by base. Deprotonation of the indole nitrogen represents a reasonable and precedented[20] mechanistic pathway for this catalysis. Base catalysis provides an explanation for the observation that vindoline induces the fragmentation of **A**, which is otherwise stable for a few hours at -40°C. However the fragmentation of N_a-methylcatharanthine-N_b-oxide is also accelerated by base, indicating that there must be a second aspect of base catalysis. We suggest that bases affect the reaction both at the trifluoroacetylation and fragmentation stages. No support was found for an alternative mechanistic possibility involving electron-transfer. 1,2,4,5-Tetramethoxybenzene, which should be similar in electron donor capacity to vindoline, does not induce fragmentation of **A** at -40°C, even though it is partially oxidized to a radical cation by other components of the reaction mixture.

The recognition that proton-transfer can accelerate the fragmentation of **A** provides a possible basis for the observed stereoselectivity at low temperature. The reaction may proceed through a hydrogen-bonded species in which the base is maintained in close contact with the fragmented intermediate. When this base is sufficiently reactive for aromatic substitution to occur, coupling may occur faster than dissociation and conformational relaxation. If the base is incapable of capturing the initial intermediate, conformational relaxation to **B'** and formation of **D** occurs. Our results show that **D** can then react, but at a slower rate, to form 16'-*R* coupling products.

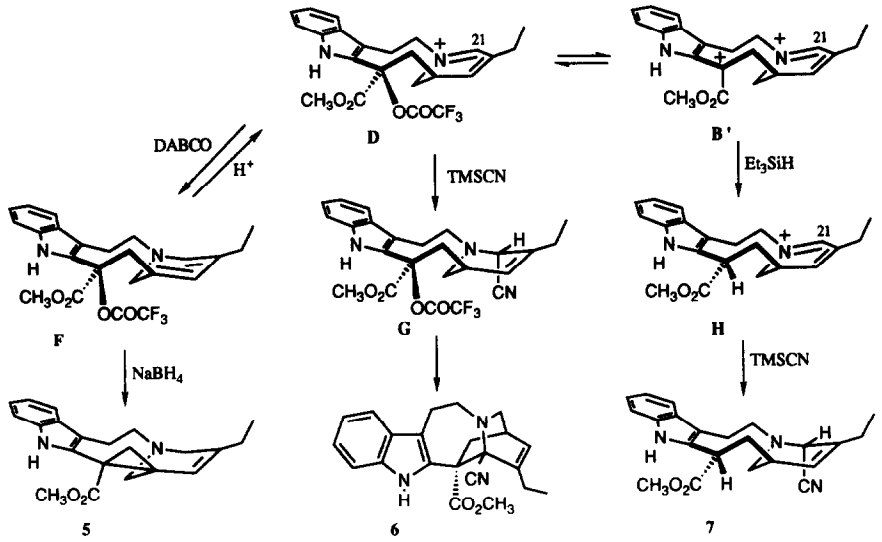
Our spectroscopic and chemical studies on the nature of the intermediate **D** formed at -20°C to 0°C also provide some new information on the structure and reactivity of this species. Because both the ^{1}H- and ^{13}C-NMR aromatic signals are indicative of an indole nucleus we believe a substituent, presumably trifluoroacetate, must be bound at C16. The chemical shift of the C16 signal in the ^{13}C NMR is consistent with this formulation. It is quite likely that an equilibrium between species **D** and the corresponding cation **B'** exists (*vide infra*).

The structural formulation is also consistent with the chemical behavior observed for **D**. The deprotonation at C14 by DABCO can lead to the neutral dihydropyridine **F** and then to the cyclopropane **5**.[14] The formation of 21-cyanocatharanthine is also consistent with this formulation of **D**.[14,15] The behavior of **D** on exposure to triethylsilane is especially revealing. The ^{13}C-NMR spectrum observed after reaction with the silane is consistent with structure **H** (Table II), which could arise from reduction of **D** at C16 through carbocation **B'**. The susceptibility of **D** to reduction by triethylsilane indicates the existence of an

equilibrium between D and the C-16 "carbocation" B'. The conjugated dihydropyridinium system in B' is not readily reduced by triethylsilane, but addition of TMSCN results in addition of cyanide ion and formation of 7.

The array of products from $NaBH_4$ (or $NaBD_4$) reduction of D is less informative but is, at least, not inconsistent with the formulation in Scheme 2. Thus 16-carbomethoxycleavamine 8 can result from D by reduction at both C16 and C21. 16-Hydroxy-16-carbomethoxycleavamine 9 can arise by borohydride attack on the trifluoroacetoxy group in D. Hydroxyindolenines such as 11 are well-known oxidation products of related *iboga* alkaloids.[18] Compound 11 might be formed by N → C7 rearrangement of the trifluoroacetoxy group followed by subsequent reduction at the trifluoroacetyl group. The detection of 10 is suggestive of this reaction path. However, because none of these products is formed in high yield, it is not certain that they are derived from the dominant path.

Scheme 2



Experimental Section

Procedures for Low Temperature NMR Experiments.

Approx. 15 mg of 1 or its MCBA salt was dissolved in 0.5 mL CD_2Cl_2 which had been cooled and briefly degassed with argon before being transferred by syringe to a dry side arm flask (0°C) under argon. If the additional reactant to be added was a liquid (e.g. 1,3-dimethoxybenzene, tri-*n*-butylamine) a total of 1.0 mL CD_2Cl_2 was used to dissolve the N-oxide and the liquid was added neat to the flask at 0°C. If the additional reactant was a solid (e.g. vindoline, tetramethoxybenzene) it was dissolved in 0.5 mL CD_2Cl_2 and added to the flask at 0°C. The flask was then cooled to -60°C and cold TFAA (distilled from P_2O_5

immediately before use) was added rapidly from a syringe. One-half of the solution (~0.4 mL) was removed using a cold gas-tight syringe and rapidly transferred to a cold (-68°C) NMR tube kept under argon. In the absence of additional reactants the spectrum observed at this point was that of **A**. Warming or delay during the transfer led to observation of contamination by the **D** spectrum. The remaining half of the reaction was stirred at ~ -50°C for a total of 3 h and then transferred to an NMR tube as above. Spectra were recorded at appropriate time intervals. After all the spectra had been taken, each cold NMR tube was quickly emptied into a cold (-40°C) solution of reducing agent (excess $NaBH_4/C_2H_5OH$ or excess $NaBD_4/CH_3OD$). The tubes were not rinsed. After allowing the mixture to warm to room temperature for 5 min, acetone (1 mL) was added to destroy remaining reducing agent. Aqueous 20% Na_2CO_3 was added and the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated and examined by NMR.

(a) Comparison of Normal and Inverse Modes of Addition of Vindoline

Two duplicate experiments were run starting with $1H^+$ $MCBA^-$. One tube in each experiment was prepared in the normal way by adding vindoline (1.0 eq) prior to the TFAA. In the inverse addition tubes the TFAA was added at -60°C, and the tube was then held at -50°C for 5 min or 20 min before vindoline was added. The progress of fragmentation/coupling was determined at 1 h and at 3 h after mixing. The extent of coupling as determined by the appearance of the **C** peaks was similar for either mode of addition. AVLB was identified by its characteristic peaks in the crude product obtained after $NaBH_4$ reduction.

(b) Comparison of -40°C and 0°C Quench of Coupling Reactions.

-40°C Quench. Two identical runs were carried out with 1 and $1H^+$ MCBA salt. One eq of vindoline was added to each solution and then each solution was cooled to -60°C and treated with 6 eq of TFAA. The progress of coupling was checked after about 0.5 and 3 h and formation of **C** was confirmed. The solutions were then quenched as described for the normal procedure. The product was isolated by extraction and shown by NMR to contain primarily vindoline and AVLB. 16'-epi-AVLB constituted less than 10% of the coupled product. No major differences in extent of coupling was noted between the solution containing MCBA and the one in which it was absent.

0°C Quench. The experiment was conducted similarly except that the reaction solution was brought to 0°C and held there one h prior to quench. Under these conditions the ratio of epi-AVLB increased to about 25% of the coupled product.

(c) Addition of Vindoline after Conversion to D.

A solution of 1 in $CDCl_3$ was treated with TFAA and fragmentation to **D** was allowed to come to completion. The TFA salt of vindoline was then added. A coupling reaction leading to peaks at 0.43, 5.43 and 6.00 ppm ensued. These peaks are attributed to **C'**. After coupling was complete, reduction gave epi-AVLB and AVLB in the ratio of 3:1.

(d) Effect of Trifluoroacetic Acid.

The normal experimental conditions described in (a) were repeated both for 1 and its

MCBA salt except that the vindoline was pre-mixed at -60°C with 3 eq of TFA. The spectra were recorded a few minutes after mixing and after 3 h at -50°C. No evidence of either fragmentation (appearance of D) or coupling (appearance of C) was observed. The reaction samples were quenched in the usual way and returned vindoline and catharanthine.

(e) Effect of tri-*n*-butylamine and 10-trifluoroacetylvindoline.

A solution of $1H^+$ $MCBA^-$ salt was prepared in the standard manner. In two separate experiments 1 and 2 eq of tri-*n*-butylamine were included. TFAA was then added. In both experiments the spectrum recorded at -40°C within a few minutes showed **A** had undergone complete fragmentation to **D**. The **D** spectrum remained stable for 3 h at -40°C but deteriorated at 0°C. A similar result was observed when 10-trifluoroacetylvindoline was used in place of tri-*n*-butylamine.

Reduction of Solutions of A Prior to Fragmentation.

(a) $NaBH_4$. A solution of **A** was prepared at -40°C in the usual way. Quenching with $NaBH_4$ returned catharanthine.

b) $NaBH_3CN$. A solution of **A** was prepared at -40°C in the usual way. Quenching with $NaBH_3CN$ lead to recovery of pure 1 (NMR).

Preparation of N_a-Methylcatharanthine-N_b-oxide (N-Me-1).

Catharanthine (100 mg, 0.3 mmol) was added to a suspension of hexane-washed NaH (7 mg) in THF (2 mL) at 0°C. The solution was heated for 5 min to complete evolution of H_2 and then cooled to 0°C. Methyl iodide (19 μL, 0.3 mmol) was added at 0°C. The solution was stirred at 25°C for 1 h. The solvent was removed and the product extracted and separated from unreacted catharanthine by preparative layer chromatography on silica (R_f=0.3, 1:1 hexane/ethyl acetate). ^{1}H-NMR ($CDCl_3$) 300 MHz: 1.08 (J=7), 3H; 1.70 dd (J=12,2), 1H; 1.90-2.05 m, 1H; 2.2-2.35 m, 1H; 2.48 d (J=8), 1H; 2.72 m, 1H; 2.85-2.95 m, 2H; 3.0 dt (J=14,2), 1H; 3.05-3.13 m, 2H; 3.30 ddd (J=18,13,5), 1H; 3.48 s, 3H; 3.58 s, 3H; 3.72 dt (J=12,2), 1H; 4.49 s, 1H; 6.02 bd, (J=6), 1H; 7.1-7.15 m, 1H; 7.2-7.25 m, 2H; 7.57 d (J=8), 1H.

Fragmentation of N-Me-1

The experiments were conducted as described for 1 using tri-*n*-butylamine and **DMA** as added bases.

Reaction of 1 and N,N-Dimethyl-3-methoxyaniline (DMA).

(a) Addition of DMA at -50°C. A solution of $1H^+$ MCBA salt in CH_2Cl_2 (2 mL) was prepared from catharanthine (30 mg, 0.0889 mmol) and MCBPA (1 eq) at 0°C. After stirring for 1 h the solution was cooled to -50°C. **DMA** (1 eq) and TFAA (6 eq) were added successively. The solution, which had a deep orange color, was stirred for 3 h at -40 – -50°C. The reaction solution was then poured into ethanol containing $NaBH_4$ at -40°C . After 5 min, acetone was added and the reaction mixture was partitioned between CH_2Cl_2 and 10% Na_2CO_3 solution. The crude product was subjected to preparative layer chromatography (0.5 mm silica) using 2:1 ethyl acetate/hexane for elution. The product 2 (R_f=.35) was obtained in 9% yield. ^{1}H-NMR

($CDCl_3$) 300 MHz: 1.0 t, 3H; 1.95 q, 2H; 2.45 d (J=5), 1H; 2.65 m, 3H; 3.0 s, 6H; 3.0-3.6 m, 7H; 3.60 s, 3H; 3.85 s, 3H; 5.54 bd, 1H; 6.19 dd (J=9, 1), 1H; 6.25 d (J=1) 1H; 6.83 d (J=9) 1H; 7.0-7.3 m, 3H; 7.49 d (J=8), 1H; 8.25 s, 1H. CIMS m/z: 488 (30%), 197 (100%), 170 (55%), 99 (100%), 72 (30%). The borane adduct 2-BH_3 had an R_f of 0.8 and was isolated in 7% yield. ^{1}H-NMR ($CDCl_3$) 300 MHz: 1.00 t (J=7.5), 3H; 1.75 m (BH_3); 2.0 q (J=7.5), 2H; 2.5 dt (J=13.5), 1H; 2.95 s, 6H; 3.94-2.9 m, 7H; 3.25 d (J=16.5), 1H; 3.5 d (J=16.5), 1H; 3.62 s, 3H; 3.85 s, 3H; 3.97 d (J=13.5), 1H; 5.51 d (J=6), 1H; 6.17 dd (J=9, 2), 1H; 6.27 d (J=2), 1H; 6.75 d (J=9), 1H; 7.08-7.30 m, 3H; 7.67 d (J=7.5) 1H; 8.31 s, 1H. CIMS m/z: 502 (2%), 500 (3%), 488 (25%), 87 (100%).

(b) **Addition of DMA at 0°C.** The solution of $1H^+$ MCBA was prepared as described above. TFAA (6 eq) was then added at -50°C and the solution allowed to warm to 0°C over 20 min. The **DMA** (2 eq) was then added. The reaction mixture was allowed to stir at 0°C for 30 min and then poured into $NaBH_4/C_2H_5OH$ and worked up as described above. The major product 3 (R_f=0.5) was obtained in 11% yield. ^{1}H-NMR ($CDCl_3$) 300 MHz: 1.05 t (J=9), 3H; 2.0 q (J=9), 2H; 2.3 d (J=16.5), 1H; 2.65 d (J=13.5), 1H; 2.87 s, 6H; 2.85-3.35 m, ~8H; 3.79 s, 3H; 3.90 s, 3H; 5.63 d (J=5), 1H; 6.18 d (J=2), 1H; 6.25 dd (J=9,2), 1H; 7.0 t (J=9), 1H; 7.10 t (J=9), 1H; 7.24 d (J=9), 1H; 7.39 d (J=9), 1H; 9.05 s, 1H. CIMS m/z 488 (60%), 337 (20%); 121 (70%), 84 (70%).

Reaction of 1 and 1,3-Dimethoxybenzene (DMB).

Catharanthine (30 mg, 0.089 mmol) in dry $CDCl_3$ (2 mL) was oxidized by MCPBA by the usual procedure and then cooled to -40°C. **DMB** (2 eq) and triethylamine (1 eq) were added, followed by TFAA (6 eq). The reaction solution was allowed to warm to 0°C for 30 min and kept at 0°C for 1.5 h. A ^{1}H-NMR spectrum was recorded at this point. The remainder of the reaction solution was reduced using $NaBH_4$/EtOH and the product was isolated in the usual way. The major product 4 was isolated by PTLC (0.5 mm, silica 2:1 ethyl acetate/hexane, R_f=0.5). ^{1}H-NMR ($CDCl_3$) 300 MHz: 1.05 t (J=7.5), 3H; 2.00 q (J=7.5), 2H; 3.8-2.1 overlapping multiplets, 11H; 3.74 s, 3H; 3.78 s, 3H; 3.78 s, 3H; 5.63 d (J=7.5), 1H; 6.41 d (J=2), 1H; 6.43 dd (J=10.5,2) 1H; 7.01 t (J=7.5), 1H; 7.12 t (J=7.5), 1H; 7.26 d (J=7.5), 1H; 7.32 d (J=10.5), 1H; 7.39 d (J=7.5), 1H; 9.05 s, 1H. HRMS 474.251984; calculated for C_{29} $H_{34}N_2O_4$: 474.25186.

Reactions of 1 in the Presence of other Aromatic Compounds.

(a) N,N,N',N'-Tetramethylphenylenediamine (TMPD). One eq of **TMPD** was added prior to addition of TFAA. On addition of TFAA (3 eq) fragmentation proceeded rapidly and was complete after 1 h at -40°C. The D spectrum was stable at -20°C but some additional peaks appeared at 0°C. No attempt was made to identify the products of $NaBD_4$ quench.

(b) 1,2,4,5-Tetramethoxybenzene (TMB). A solution of 1H+ $MCBA^-$ and 1 eq of **TMB** was treated with TFAA at -60°C. The spectrum recorded within a few minutes showed only the A peaks. No **TMB** peaks were evident. After 3 h at -40°C a weak D spectrum was evident but the spectrum remained primarily that of **A**. An ESR recorded on this solution provided a signal consistent with that of the reported signal of the $TMB^{+\cdot}$ radical cation.[13]

(c) N,N-Dimethyl-2,4-dimethoxyphenylethylamine (DMPA). Duplicate reactions were run with 1 and $1H^+$ $MCPBA^-$ with 1 eq of DMPA. Immediate fragmentation to D occurred on addition of TFAA (6 eq) at -50°C. There was no evidence of coupling and the solution was stable for 3 h at -40°C. The spectrum became more complex at 0°C but the products at this point were not investigated.

Characterization of Products from the Fragmented Intermediate D.

(a) 21-Cyanocatharanthine (6) by Treatment with DABCO and TMSCN/$LiClO_4$.

Pure 1 was prepared from 50 mg (0.15 mmol) of catharanthine and *p*-nitroperoxybenzoic acid (85%, 35 mg) in CH_2Cl_2 (5 mL). The CH_2Cl_2 layer was washed with aq. Na_2CO_3 (5 mL), dried and concentrated to give the neutralized N-oxide. The N-oxide was dissolved in $CHCl_3$ (3 mL) and cooled to -60°C. Freshly distilled TFAA was added (75 μL, 0.56 mmol). The reaction mixture was maintained at -45 to -40°C for 1 h and at ~0°C for 3 h. A solution of TMSCN (100 μL, 80 mmol) and $LiClO_4$ (2 mg) in CH_2Cl_2 (2 mL) was transferred into the reaction mixture at 0°C. After being stirred at 0°C for 0.5 h and at room temperature for 1 h, the solvent was removed under reduced pressure. The residue was partitioned between 10% Na_2CO_3 and CH_2Cl_2. The residue from the CH_2Cl_2 layer was purified (silica, ethyl acetate/hexane 3:7→1:1) to give 6 (42 mg, 74%), which was identified by comparison with a previously characterized sample.[14]

(b) 16α-Carbomethoxy-21α-cyanocleavamine by Treatment with Triethylsilane followed by TMSCN/$LiClO_4$. To 1 (55 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) at -60°C was added TFAA (75 μL, 0.53 mmol) and the mixture was maintained at -45 to -40°C for 1 h and subsequently at -10 to 0°C for 3 h. Neat triethylsilane (75 μL, 0.47 mmol) was then added to the reaction mixture at 0°C. After 1 h at room temperature the volatile material was removed under high vacuum (10^{-3}-10^{-4} mmol Hg). A ^{13}C NMR of the residue showed a spectrum of the fragmented iminium salt H (>90% pure by ^{13}C NMR). The iminium salt was redissolved in CH_2Cl_2 (1 mL) at 0°C. A solution of TMSCN (80 μL, 0.6 mmol) and $LiClO_4$ (5 mg) in CH_2Cl_2 (1 mL) at 0°C was added and the mixture was stirred at 0°C for 15 min and at room temperature for 1 h. The solvent was removed under reduced pressure. The ^1H NMR of the crude reaction mixture showed nearly pure 7 in about 75% yield. The ^1H NMR spectrum and the TLC behavior were identical with the sample prepared earlier by photochemical cleavage of catharanthine.[9]

Products from $NaBH_4$ and $NaBD_4$ Quench of Intermediate D. A number of experiments were conducted under various conditions. Material balance was poor in all cases. Following the conditions for preparation of D, TFAA (3 eq) was added to 1 at -60°C. The solution was then held at -40°C for 1 h and 0°C for 3 h Quench with $NaBD_4$ in CH_3OD gave modest amounts of 16-carbomethoxycleavamine-16,21-d_2 (8). Similar experiments which included an aqueous bicarbonate wash in the workup also provided small amounts of 16-carbomethoxy-16-hydroxycleavamine-21-d (9). In one such experiment the 7-hydroxyindolenine derivative (11) of catharanthine was also isolated. In an experiment in which the conversion of A → D was allowed to proceed for 3 h at -22°C a 16-carbomethoxy-7-trifluoroacetoxy-$\Delta^{2,16}$ derivative (10) of cleavamine was isolated.

Spectroscopic Data

(a) 16-Carbomethoxycleavamine 8: ^{1}H NMR ($CDCl_3$) 300 MHz: 1.07 t (J=3), 3H; 2.03-2.10 m, 3H; 2.18 bm, 1H; 2.28-2.42 m, 4H; 2.72 dt (J=14,2), 1H; 2.82-2.90 m, 2H; 3.07, 3.16 ABq (J_{gem}=15), 2H; 3.65s, 3; 5.16 d (J=11), 1H; 5.28 bd (J=4), 1H; 7.08 t (J=8), 1H; 7.15 t (J=8), 1H; 7.32 d (J=8), 1H; 7.50 d (J=8), 1H; 8.55 bs, 1H. ^{13}C NMR ($CDCl_3$): 13.1; 26.8; 28.1; 35.1; 38.7; 39.1 52.5; 53.5; 54.2; 55.7; 111.0; 112.1; 118.7; 119.4; 1211.9; 122.2; 128.4; 135.0; 136.1; 141.9; 176.2; CIMS m/z: 338.

(b) 16-Carbomethoxy-16-hydroxycleavamine-21-d_1 9: ^{1}H NMR ($CDCl_3$) 300 MHZ: 1.02 t (J=7), 3H; 1.9-2.1 m, 2H; 2.18 dd (J=12,3), 1H; 2.27 d (J=14), 1H; 2.42 bm, 1H; 2.47 d (J=12), 1H; 2.5-2.63 m, 2H; 2.83 dm (J=15), 1H; 2.98 d (J=14), 1H; 3.12 bs, 1H; 3.58 td (J=14,6), 1H; 3.81 s, 3H; 5.45 bd (J=5), 1H; 7.10 t (J=8), 1H; 7.18 t (J=8), 1H; 7.33 d (J=8), 1H; 7.52 d (J=8), 1H; 8.86 bs, 1H; 10.20 s, 1H. CIMS m/z: 356.

(c) 16-Carbomethoxy-7-trifluoroacetoxy-$\Delta^{2,16}$-cleavamine-21-d_1 10: ^{1}H NMR ($CDCl_3$) 300 MHz: 1.03 t; 2.25-2.35 m; 2.40 dd (J=14, 4); 2.5-2.65 m; 3.0 dm (J=15); 3.52 dd (J=15,12); 3.67 s, 3.98 s; 5.27 s; 5.90 d (J=5); 6.56 d (J=8); 6.79 t (J=8); 7.17 t (J=8); 7.19 d (J=8). CIMS m/z 452.

(d) Catharanthine 7-Hydroxyindolenine (11) ^{1}H-NMR ($CDCl_3$) 300 MHZ: 1.03 t (J=7), 3H; 1.85-2.05 m, 2H; 2.05-2.15 m, 2H; 2.20-2.35 m, 1H; 2.6-2.8 m, 3H; 2.93 dt (J=13,2), 1H; 3.05 dq (J=15,1), 1H; 3.64 s, 3H; 3.65-3.75 m, 1H; 3.83 ddd (J=15,13,2), 1H; 4.58 s, 1H; 5.93 bd, (J=6), 1H; 7.24 t (J=8), 1H; 7.30-7.38 m, 2H; 7.47 d (J=8), 1H. ^{13}C-NMR ($CDCl_3$): 11.2, 27.0, 31.6, 33.7, 40.0, 47.1, 47.6, 53.3, 58.0, 59.9, 88.2, 121.4, 122.0, 123.7, 127.3, 130.1, 141.9, 149.0, 152.2, 172.3, 189.7. CIMS m/z: 353.

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References

1) (a) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F.; *Fr. Brev.* 7443221 (31.12) **1974**; (b) Langlois, N.; Gueritte, F. Langlois Y.; Potier, P.; *J. Am. Chem. Soc.*, **1976**, 98, 7017; (c) Potier, P.; *J. Nat. Prod.*, **1980**, 43, 72.

2) (a) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutami, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S.; *Helv. Chim. Acta*, **1976**, 59, 2858; (b) Kutney, J. P.; *Lloydia*, **1977**, 40, 107; (c) Kutney, J. P.; *Nat. Prod. Rep.*, **1990**, 7, 85.

3) (a) Schill, G.; Löwer, H.; Priester, C. U.; Windhövel, U. F.; Fritz, H. *Tetrahedron*, **1987**, 43, 3729; (b) Schill, G.; Priester, C. U.; Windhövel, U. F.; Fritz, H. *Tetrahedron*, **1987**, 43, 3747; (c) Schill, G.; Priester, C. U.; Windhövel U. F.; Fritz, H. *Tetrahedron*, **1987**, 43, 3765.

4) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G.; *J. Org. Chem.*, **1991**, 56, 513.

5) Magnus, P.; Stamford, A., Ladlow, M.; *J. Am. Chem. Soc.*, **1990**, 112, 8210.

6) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M., Boulet, C. A.; *Heterocycles*, **1988**, 27, 1845.

7) Sundberg, R. J.; Bloom, J. D.; *J. Org. Chem.*, **1981**, 46, 4836; Sundberg, R. J., Amat, M.; Fernando, A. M.; *J. Org. Chem.*, **1987**, 52, 3151; Sundberg, R. J.; Cherney, R. J.; *J. Org. Chem.*, **1990**, 55, 6028; Sundberg, R. J.; Gadamasetti, K. G.; *Tetrahedron*, **1991**, 47, 5673.

8) For example N-methylpyrrole induces a radical decomposition of perfluoroacyl peroxides: Yoshida, M.; Yoshida, T.; Kobayashi, M.; Kamigata, N.; *J. Chem. Soc., Perkin Trans. I*, **1989**, 909.

9) Sundberg, R. J.; Desos, P.; Gadamasetti, K. G.; Sabat, M.; *Tetrahedron Lett.*, **1991**, 32, 3035.

10) Szántay, C. Jr.; Balázes, M.; Bölcskei, H.; Szántay, C. *Tetrahedron*, **1991**, 47, 1265.

11) Shafiee, A.; Ahond, A.; Bui, A.-M.; Langlois, Y.; Riche, C.; Potier, P.; *Tetrahedron Lett.*, **1976**, 921. We synthesized the compound by an alternative route as described in the Experimental Section.

12) Pawlak, Z.; Wawrzynów, A.; *J. Chem. Soc., Faraday Trans. 1*, **1983**, 79, 1523.

13) Fairhurst, S. A.; Smith, I. M.; Sutcliffe, L. H.; Taylor, S. M.; *Org. Mag. Resonance*, **1982**, 18, 231.

14) Sundberg, R. J.; Hunt, P. J.; Desos, P.; Gadamasetti, K. G.; *J. Org. Chem.*, **1991**, 56, 1689.

15) Mangeney, P.; Langlois, N.; Leroy, C.; Riche, C.; Langlois, Y.; *J. Org. Chem.*, **1982**, 47, 4261.

16) a) Brown, R. T.; Hill, J. S.; Smith, G. F.; Stapleford, K. S. J.; *Tetrahedron*, **1971**, 27, 5217; b) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; *Heterocycles*, **1981**, 15, 245; c) Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.; Zsadon, B.; *Helv. Chim. Aacta*, **1976**, 59, 2711.

17) Kuehne, M. E.; Earley, W. G.; *Tetrahedron*, **1983**, 39, 3707; Gadamasetti, K. G.; Ph.D. Thesis, University of Vermont, 1987, p A46.

18) Rastogi, K.; Kapil, R. S.; Popli, S. P.; *Heterocycles*, **1983**, 20, 2001; Ouannes, C.; Thal, C.; *Tetrahedron Lett.*, **1981**, 22, 951; Wenkert, E.; Gottlieb, H. E.; *Heterocycles*, **1977**, 7, 753; Hwang, B.; Weisbach, J. A.; Douglas, B.; Raffauf, R.; Cava, M. P.; Bessho, K.; *J. Org. Chem.*, **1969**, 34, 412; Schnoes, H. K.; Thomas, D. W.; Aksornvitaya, R.; Schleigh, W. R.; Kupchan, S. M.; *J. Org. Chem.*, **1968**, 33, 1225; Thomas, D. W.; Biemann, K.; *Tetrahedron*, **1968**, 24, 4223; Guise, G. B.; Ritchie, E.; Taylor, W. C.; *Aust. J. Chem.*, **1965**, 18, 1279.

19) Ladhar, F.; Ghorbel, N.; Damak, M.; *J. Soc. Chim. Tunis.*, **1981**, 5, 45; Wenkert, E.; Hagaman, E. W.; Wang, N.; Kunesch, N.; *Heterocycles*, **1979**, 12, 1439.

20) The base-catalyzed elimination-addition mechanism for substitution of gramine derivatives provides an analogy: Snyder, H. R.; Eliel, E. L.; *J. Am. Chem. Soc.*, **1948**, 70, 1857; Albright, J. D.; Snyder, H. R.; *J. Am. Chem. Soc.*, **1959**, 81, 2239; Russell, H. F.; Waller, E. J.; Ducharme, N. R., II; *J. Org. Chem.*, **1991**, 56, 871.