Rearrangement of Catharanthine. 5.† 21-Cyanocatharanthine

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21-Cyanocatharanthine (11) and 15-cyano-16-(methoxycarbonyl)-16-methoxy-15-cyano-Δ^{20}-cleavamines 12 and 13 were prepared in two steps from catharanthine (1). In a study directed toward a new hemisynthetic route to vinblastine (6), the 21-cyanocatharanthine (11) was shown to undergo C_6–C_5 bond rupture as the sole fragmentation pathway under modified Polonovski conditions. When the reaction was carried out in the presence of vindoline (4), the rearranged dimeric product 29 was isolated.

Catharanthine (1) is a major alkaloidal constituent of the Madagascan periwinkle, *Catharanthus roseus* (G. Don, Apocynaceae), and undergoes a number of fragmentation reactions (Scheme I).

The fragmentation in acidic media of the C_{21}–C_{16} bond, studied by Gorman, Neuss, et al.,[1] led after reduction to 16(*S*)- and 16(*R*)-(methoxycarbonyl)cleavamines (**2a** and **2b**). The reverse fragmentation (C_{16}–C_{21}) of catharanthine N_b-oxide (**3**) induced by trifluoroacetic anhydride (TFAA; modified Polonovski reaction[2]) in the presence of vindoline (**4**) allowed us to prepare by hemisynthesis anhydrovinblastine (**5**)[3] and the main antitumor alkaloids of the vinblastine (**6**) group.[4]

Under classical Polonovski conditions[5] (acetic anhydride), catharanthine N_b-oxide (**3**) gave rise to a completely different fragmentation pathway and provided products derived from C_5–C_6 bond fission, like compound **7**.[6]

Lastly, two fragmentations of the C_{21}–N_b bond are noteworthy. The first arises via a [2,3] sigmatropic rearrangement of the N_b-oxide **3** to afford isoxazolidine (**8**). The second involves a decarboxylative fragmentation of catharanthinic acid and gives rise to 16-demethoxycarbonyl)catharanthine (**9**) through the intermediacy of the diene **10**[8] (Scheme I).

We report herein a new rearrangement of catharanthine N_b-oxide (**3**) leading principally to 21-cyanocatharanthine (**11**) and the details of a study concerning the reactivity of this compound.

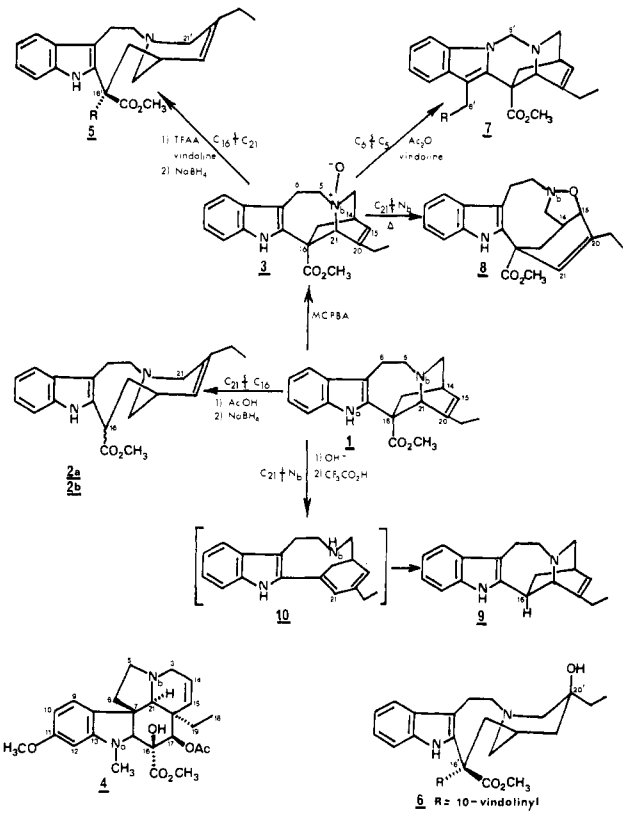
The Polonovski reaction is known to evolve in quite different fashions according to, inter alia, the nucleophilic species involved in the reaction.[6,9] Thus, in connection with our work oriented toward the hemisynthesis of vinblastine (**6**),[10] we decided to study the behavior of catharanthine N_b-oxide (**3**) in the presence of trifluoroacetic anhydride and cyanide ion.

Catharanthine N_b-oxide (**3**), when first treated by trifluoroacetic anhydride and, after evaporation of the excess reagent in vacuo, by a saturated solution of potassium cyanide in methanol, led to three indolic products.

The major product was assigned structure **11** on the basis of its spectral properties. The mass spectrum exhibited a molecular ion at m/z 361 while the IR spectrum revealed a cyano absorption at 2230 cm^{-1}. Comparison of the ^1H NMR spectrum of compound **11** with that of catharanthine (**1**) indicated the absence of a signal for $C_{21}H$. In addition, the ^{13}C NMR spectrum exhibited two signals of quaternary carbons at 64.5 and 60.8 ppm.

Compounds **12** and **13** exhibited identical molecular ions ($M^{+\cdot}$ at m/z 393) and similar fragmentation patterns in their mass spectra. In each case the base peak at m/z 160 localized the position of the cyano group on the piperidine portion of the molecule. The ^1H NMR spectrum of compound **12** showed two methoxy signals at 3.64 and 3.45

Scheme I



ppm, whereas the corresponding signals in the ^1H NMR spectrum of compound **13** appeared at 3.99 and 2.94 ppm. These data suggested that compounds **12** and **13** were epimeric at C_{16}.[11] The stereochemistry at C_{16} and C_{15} was ultimately established by a single-crystal X-ray analysis of compound **12**. The complete molecular structure is given in Figure 1.

If the reaction mixture (catharanthine N_b-oxide (**3**),

† For the preceding paper in the series, see ref 6b.

(1) M. Gorman, N. Neuss, and N. J. Cone, *J. Am. Chem. Soc.*, **87**, 93 (1965).
(2) P. Potier, *J. Nat. Prod.*, **43**, 72 (1980).
(3) N. Langlois, F. Gueritte, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, **98**, 7017 (1976).
(4) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, **101**, 2243 (1979), and references therein.
(5) M. Polonovski and M. Polonovski, *Bull. Soc. Chim. Fr.*, 1190 (1927).
(6) (a) N. Langlois, F. Gueritte, Y. Langlois, and P. Potier, *Tetrahedron Lett.*, 1487 (1976); (b) R. Z. Andriamialisoa, N. Langlois, Y. Langlois, P. Potier, and P. Bladon, *Can. J. Chem.*, **57**, 2572 (1979).
(7) Y. Langlois, F. Gueritte, R. Z. Andriamialisoa, N. Langlois, P. Potier, A. Chiaroni, and C. Riche, *Tetrahedron*, **32**, 945 (1976).
(8) P. Mangeney and Y. Langlois, *Tetrahedron Lett.*, 3015 (1978).
(9) P. Mangeney, *Tetrahedron*, **34**, 1359 (1978).
(10) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Org. Chem.*, **44**, 3765 (1979).
(11) Examination of CD curves of compounds **12** and **13** did not allow us to attribute the configuration at C_{16}.

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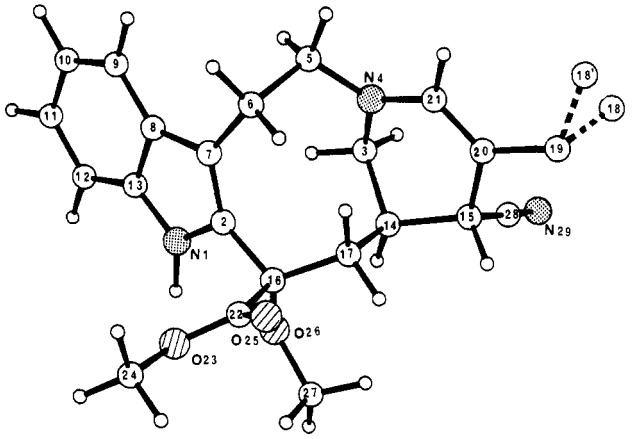
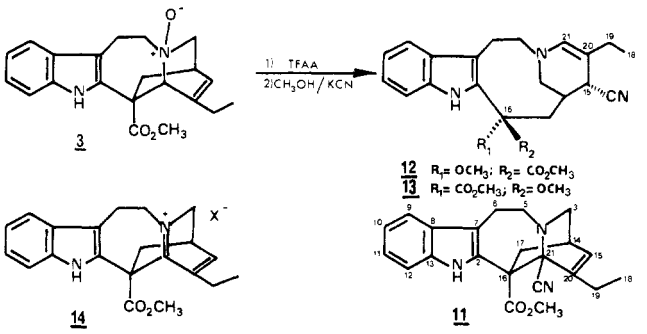


Figure 1. Complete molecular structure for **12**.

Scheme II



TFAA, CH_2Cl_2) was treated, after removal of the excess TFAA in vacuo, first with methanol alone and then with methanolic KCN, cleavamine derivatives **12** and **13** could be prepared to the complete exclusion of compound **11**.

This last experiment led us to propose a mechanism for the formation of compounds **11–13**.

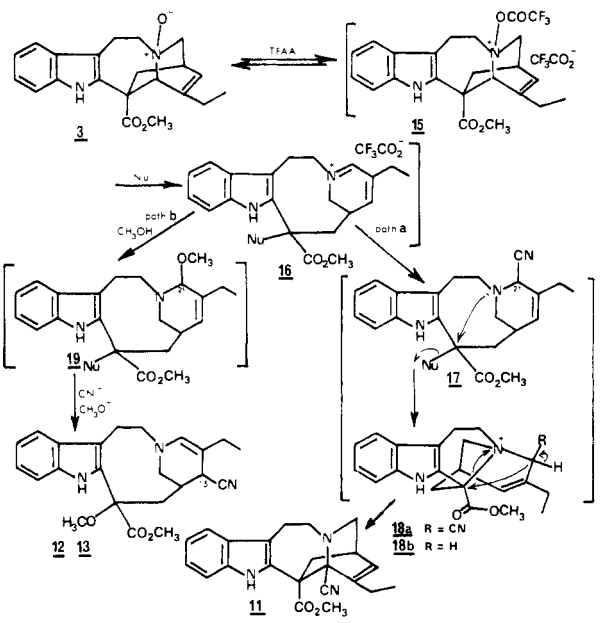
In the case of 21-cyanocatharanthine (**11**), although examples of such bridgehead intermediates have been reported,[12] the formation of the immonium salt **14** (Scheme II) seems unlikely. The addition of cyanide ion at C_{21} in conjugated immonium **16** could lead via the quaternary ammonium salt **18a** (R = CN) and Stevens rearrangement to the 21-cyanocatharanthine (**11**; path a, Scheme III). Furthermore, the formation of a quaternary ammonium salt, **18b** (R = H), has been observed during the coupling reaction of catharanthine N_b-oxide (**3**) with vindoline (**4**).[13]

The formation of compounds **12** and **13** appears to be the result of competition between cyanide and methoxide ions for the highly electrophilic conjugated immonium salt **16**. Intermediate **19**, the product of addition of methoxide ion at C_{21}, could be transformed by an S_N2' process to cleavamine-like compounds **12** and **13** bearing a cyano substituent at C_{15}.

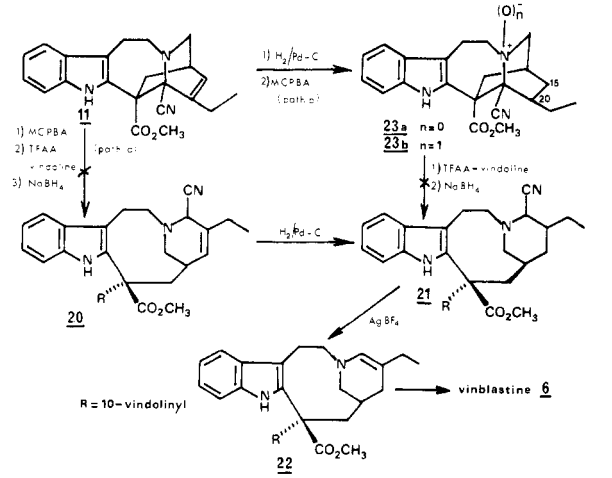
This hypothesis is consistent with the fact that the formation of 21-cyanocatharanthine (**11**) was not observed in the second experiment when the reaction medium was exposed to methanol prior to treatment by potassium cyanide. In that case only path b (Scheme III) was operative.

21-Cyanocatharanthine (**11**), easily obtained from catharanthine (**1**), might in principle serve as a precursor of enamine **22**, whose transformation to vinblastine (**6**) is known.[4] Two paths were envisioned for the conversion

Scheme III



Scheme IV



of **11** into enamine **22** and are outlined in Scheme IV. Compound **11** or its dihydroderivative **23a** might be used to prepare intermediates **20** or **21**, respectively, via a classical coupling reaction. The latter compound upon elimination of HCN would afford enamine **22** (Scheme IV).

Thus, 21-cyanocatharanthine (**11**) was treated with *m*-chloroperbenzoic acid (MCPA, 1.25 equiv); however, this reaction at temperatures as low as −30 °C failed to afford the N_b-oxide **24** but led rather to a rearranged product, **27a**, whose structure was assigned on the basis of its high-field ^1H NMR spectrum. Double-resonance experiments allowed the identification of all protons in the molecule (see Experimental Section).

The formation of nitrone **27a** can be rationalized by a [2,3] sigmatropic rearrangement of the intermediate *N*-oxide **24**[7] followed by overoxidation of the isoxazolidine **25**, leading to compound **27a** via the unstable isoxazolidine N_b-oxide **26**[14] (Scheme V). Indeed, in a related oxidation rearrangement sequence isoxazolidine **8** led to the corresponding nitrone **27b**.

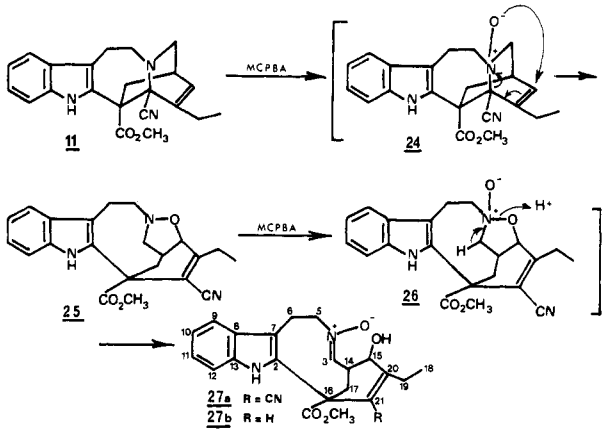
Nitrone formation could be suppressed if the oxidation steps were carried out at −70 °C. Exposure of 21-cyano-

(12) (a) K. J. Shea and S. Wise, *J. Am. Chem. Soc.*, **100**, 6519 (1978); (b) H. O. House, W. A. Kleschick, and E. J. Zaiko, *J. Org. Chem.*, **43**, 3653 (1978); (c) K. J. Shea, *Tetrahedron*, **36**, 1683 (1980).

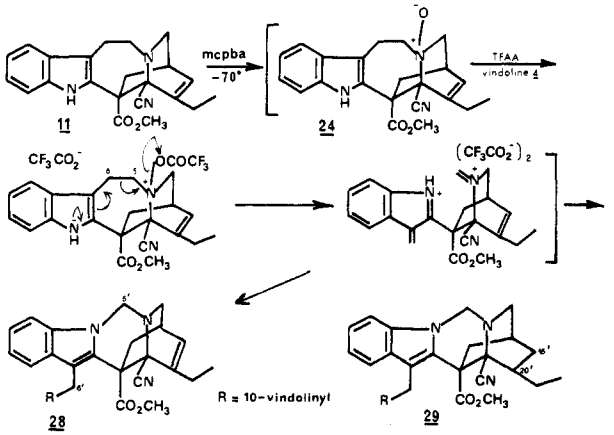
(13) P. Mangeney, et al., to be submitted for publication.

(14) (a) J. J. Tufariello and G. B. Mullen, *J. Am. Chem. Soc.*, **100**, 3638 (1978); (b) N. A. Lebel, M. E. Post, and D. Hwang, *J. Org. Chem.*, **44**, 1819 (1979).

Scheme V



Scheme VI



catharanthine (11) to *m*-chloroperbenzoic acid at −70 °C in the presence of vindoline (4)[15] followed by the addition of TFAA led to the formation of coupling product **28** (Scheme VI). In sharp contrast to what we observed with catharanthine (1),[3] the modified Polonovski reaction induced only C_5–C_6 fragmentation.

The feasibility of using path b (Scheme IV) to prepare the enamine **22** was in turn examined. 21-Cyanocatharanthine (**11**) led by hydrogenation to 21-cyano-15,20-dihydrocatharanthine (**23a**), whose corresponding *N*-oxide **23b** was stable at −10 °C. In the presence of vindoline (**4**) and TFAA, this compound led only to the coupling product **29** (Scheme VI).

The additional steric hindrance engendered by cyanide at C_{21} cannot completely explain the totally unlike orientation of the fragmentation reaction in comparison with catharanthine (**1**). In addition, the more or less strict antiperiplanarity of the N_b–O and C_5–C_6 bonds could well be a factor in the orientation toward either C_5–C_6 or C_{16}–C_{21} fragmentation reactions. The preferential orientation toward the C_5–C_6 fragmentation has already been observed with other catharanthine derivatives.[17]

Other studies directed toward the unequivocal synthesis of $\Delta^{20'}$-anhydrovinblastine (**22**) are currently under investigation in our laboratory.

Experimental Section

Melting points were taken on a Kofler apparatus. Optical rotations were measured (g/100 mL of solvent) on a Perkin-Elmer 141 MC, infrared spectra (cm^{-1}, $CHCl_3$) on a Perkin-Elmer 257, ultraviolet spectra [EtOH; λ_{max}, nm (ϵ)] on a Bausch and Lomb Spectronic 505, and CD curves [EtOH; λ_{max}, nm ($\Delta\epsilon$)] on a Roussel-Jouan Dichrograph II. ^1H NMR spectra were obtained ($CDCl_3$; Me_4Si, δ 0) from Varian T 60 and IEF 240- and 400-MHz[18] spectrometers (chemical shifts are given as δ values, and coupling constants, J, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively). ^{13}C NMR spectra (data given as δ values) were recorded on a Brucker HX 90 E apparatus. Mass spectra were measured on an AEI MS9 and MS50. Preparative layer chromatography (preparative TLC) was performed with Kieselgel HF 254 (Merck).

Preparation of Compounds 11–13. To a stirred solution of catharanthine N_b-oxide (**3**;[3] 400 mg, 1.1 mmol) in dry CH_2Cl_2 (5 mL) was added under argon at −78 °C TFAA (0.4 mL, 2.77 mmol). After 0.5 h, the reaction medium was evaporated in vacuo, and the residue was dissolved in a saturated solution of KCN in anhydrous methanol (5 mL). This solution was stirred for 12 h at 20 °C, poured into brine, and then extracted with $CHCl_3$. After drying with Na_2SO_4, filtration, and evaporation of the organic layer, the residue was purified by preparative TLC (eluent ether/hexane/methanol, 80:15:5); compounds **11** (75 mg, 17%), **12** (58 mg, 13%), and **13** (192 mg, 51%) were isolated.

Compound 11: mp 108 °C (EtOH); $[\alpha]^{20}_D$ −41° (*c* 1.07, EtOH); IR 3400, 2950, 2230, 1730, 1650; UV 228 (15 200), 286 (6800), 292 (6100); CD 285 (−), 238 (+), 200 (+); MS, *m/z* 361 (M^+), 334, 229, 214, 201, 160, 154, 147; NMR (240 MHz) 7.65 (s, 1 H, N_aH), 7.5–7.0 (m, 4 H, H aromatic); 6.00 (d, 1 H, $J_{14,15}$ = 6, C_{15} H), 3.84 (s, 3 H, C_{16} CO_2CH_3), 1.08 (t, 3 H, $J_{18,19}$ = 8, $C_{18}H_3$); ^{13}C NMR ($CDCl_3$) 171.8 (CO), 145.2 (C_{20}), 134.0 (C_{13}), 132.9 (C_2), 129.9 (C_8), 124.5 (C_{15}), 122.1 (C_{11}), 119.8 (C_{10}), 118.5 (C_9), 117.4 (C≡N), 111.8 (C_7), 110.9 (C_{12}), 64.5 (C_{21}), 60.8 (C_{16}), 52.9 (OCH_3), 49.5 (C_3 + C_5), 36.6 (C_{17}), 29.0 (C_{14}), 25.5 (C_{19}), 20.2 (C_6), 10.9 (C_{18}).

Compound 12: mp 132 °C (EtOH); $[\alpha]^{20}_D$ + 147° (*c* 1.03, EtOH; IR 3400, 2950, 2220, 1730, 1650; UV 228 (16 500), 286 (6800), 292 (6600); CD 285 (+), 232 (−), 214 (+); MS, (relative intensity) *m/z* 393 (M^+), 378, 334, 232, 214, 160 (100); NMR (240 MHz), 8.8 (s, 1 H, N_aH), 7.5–7.0 (m, 4 H, H aromatic), 5.95 (s, 1 H, C_{21} H), 3.64 (s, 3 H, $C_{16}CO_2CH_3$), 3.45 (s, 3 H, $C_{16}OCH_3$), 1.10 (t, 3 H, $C_{18}H_3$); ^{13}C NMR ($CDCl_3$) 172.4 (CO); 134.6 and 132.2 (C_{13} and C_2), 133.8 (C_{21}), 129.4 (C_8), 122.9 (C_{10}); 122.5 (C_{20}), 119.4 and 118.3 (C_9 and C_{11}), 111.2 (C_7 and C_{12}), 98.8 (C≡N), 80.6 (C_{16}), 53.7 (C_5), 52.8 and 51.7 (CO_2CH_3 and OCH_3), 44.4 (C_3), 34.9 and 28.6 (C_{15} and C_{14}), 30.6 (C_{17}), 27.4 and 26.5 (C_{19} and C_6), 13.5 (C_{18}).

Structural analysis for 12: system orthorhombic; space group $P2_12_12_1$; a = 8.358 (3), b = 13.540 (5), c = 21.445 (8) Å; Z = 4; μ (Cu Kα) = 5.1 cm^{-1}; d_c = 1.22 g cm^{-3}. Intensity data were measured on a Philips PW1100 diffractometer by using graphite-monochromated Cu Kα radiation (λ = 1.5418 Å) and the (ω–2θ) scan-technique up to θ = 65°. Of the 2193 measured reflections, 1226 were considered as observed [$I > 3\sigma(I)$; $\sigma(I)$ derived from counting statistics]. The structure was solved by direct methods and refined by least-squares methods with anisotropic thermal parameters for nonhydrogen atoms. A molecule of ethanol was found from the difference Fourier map. Its oxygen atom occupied two different positions and is hydrogen bonded to N1 and N(C≡N) according to the following scheme: N1-H···OH···N(C≡N) [distances: 2.98 and 2.71 Å (first site) and 3.30 and 3.10 Å, respectively]. The ethyl chain is also disordered, occuping two positions with an approximate relative weight of 0.5. Hydrogen atoms were located on the difference Fourier maps. They were replaced geometrically (d_{C-H} = 1.08 Å) and assigned the equivalent isotropic thermal parameters of the attached atom. The final R factor is 0.072. Calculations were performed on a CII-HB Mini6 computer, with the main programs being SHELX[19]

(15) Nitrogen N_b of vindoline (**4**) is protected against oxidative reagents by a hydrogen bond with an alcoholic function of C_{16}: L. Diatta, Y. Langlois, N. Langlois, and P. Potier, *Bull. Soc. Chim. Fr.*, 671 (1975).
(16) C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, 8, 535 (1969).
(17) (a) R. Z. Andriamialisoa, Y. Langlois, N. Langlois, and P. Potier, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **284**, 751 (1977); (b) Y. Honma and Y. Ban, *Heterocycles*, **6**, 291 (1977); (c) J. P. Kutney, A. V. Joshua, and P. H. Liao, *Ibid.* **6**, 297 (1977); (d) Y. Honma and Y. Ban, *Tetrahedron Lett.*, 155 (1978).
(18) (a) S. K. Kan, P. Gonord, C. Duret, J. Salset, and C, Vibet, *Rev. Sci. Instrum.*, **44**, 1725 (1973); (b) M. Lounasmaa and S. K. Kan, *Tetrahedron*, **36**, 1607 (1980).

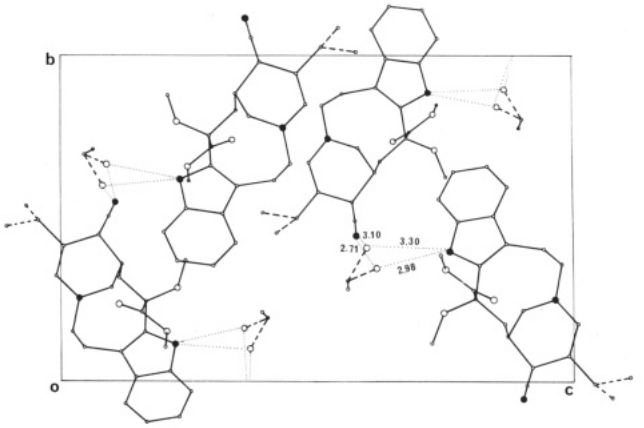


Figure 2. Oyz projection showing the hydrogen-bonding scheme. The disordered ethyl chain and ethanol molecule are indicated by dotted lines. Distances are in angstroms.

and DEVIN.[20] Computer drawings were done with ORTEP[21] (see Figure 2).

Compound 13: mp 114 °C (EtOH); $[\alpha]^{20}_D$ + 72° (*c* 0.88, EtOH); IR 3400, 2950, 2230, 1730, 1650; UV 226, 266, 288, 295 (neutral), 226, 275, 288, 295 (acidic); CD 250 (+), 215 (−); MS, *m/z* (relative intensity) 393 ($M^{+\cdot}$), 378, 334, 232, 214, 160 (100); ^{1}H NMR (240 MHz) 8.8 (s, 1 H, N_aH), 7.5–7.0 (m, 4 H, H aromatic), 5.95 (s, 1 H, $C_{21}H$), 3.99 (s, 3 H, $C_{16}CO_2CH_3$), 2.94 (s, 3 H, $C_{16}OCH_3$), 1.03 (t, 3 H, $C_{18}H_3$).

Preparation of Compounds 12 and 13 (by reaction of CH_3OH followed by addition of KCN). Catharanthine N_b-oxide (**3**; 200 mg, 0.57 mmol) in solution in dry CH_2Cl_2 (2.5 mL) was treated at −78 °C for 0.5 h by TFAA (0.2 mL, 1.38 mmol). After evaporation of the solvent, the residue was dissolved in CH_3OH (5 mL), stirred at room temperature under argon for 1 h, and then saturated with KCN. After the usual workup and purification by preparative TLC (eluent ether/hexane/methanol, 80:15:5), **12** (42 mg, 19%) and **13** (35 mg, 16%) were isolated.

Preparation of Compound 27a. MCPBA (8.6 mg, 0.05 mmol) in dry CH_2Cl_2 (2.5 mL) was added at 30 °C to a stirred solution of 21-cyanocatharanthine (**11**; 15 mg, 0.04 mmol) in CH_2Cl_2 (2.5 mL) under argon. After 10 min the reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 (0.5 mL) and then extracted with $CHCl_3$. After the usual workup and preparative TLC (eluent $CHCl_3/CH_3OH$), the compound **27a** was obtained: 9.7 mg (61%); IR 3400, 2950, 2200, 1730, 1605; UV 228, 288, 296, 306; MS, *m/z* 393 ($M^{+\cdot}$), 378, 364, 187, 156, 139, 110; NMR (400 MHz) 9.57 (s, 1 H, N_aH), 7.43–7.1 (m, 4 H, H aromatic), 6.88 (d, 1 H, $J_{15,OH}$ = 12, $C_{15}OH$), 5 .68 (s, 1 H, C_3H), 4.35 (dd, 1 H, $J_{OH,15}$ = 12 $J_{14,15}$ = 5, $C_{15}H$), 3.95 (dd, 1 H, $J_{5,5'}$ = 11, $J_{5,6}$ = 4, C_5H), 3.90 (s, 3 H, $C_{16}CO_2CH_3$), 3.5 (dd, 1 H, $J_{6,6'}$ = 15, $J_{5,6}$ = 4, C_6H), 3.37 (dd, 1 H, $J_{5,5'}$ = 11, $C_{5'}H$), 3.2 (m, 1 H, $C_{14}H$), 3.06 (m, 1 H, $C_{6'}H$), 2.9 (m, 2 H, $C_{19}H_2$), 2.7 (ABX system, 2 H, $J_{17,17'}$ = 8, $J_{14,17}$ = 4, $C_{17}H_2$), 1.22 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); ^{13}C NMR ($CDCl_3$) 174.4 (CO), 169.3 (C_{20}), 138.5 (C_3), 135.8 and 134.8 (C_2 and C_{13}), 127.5 (C_8), 123.9, 110.4, and 118.2 (C_{10}, C_{11}, and C_9), 117.3 (C≡N), 112.3 (C_7), 111.4 (C_{12}), 101.5 (C_{21}), 68.2 (C_5), 67.1 (C_{15}), 54.2 (OCH_3), 50.5 (C_{16}), 45.2 (C_{17}), 41.6 (C_{14}), 26.1 and 25.8 (C_{19} and C_6), 12.6 (C_{18}).

Preparation of Compound 27b. MCPBA (19 mg, 0.11 mmol) was added to a stirred solution of isoxazolidine (**8**; 35 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) under argon at 0 °C. After 20 min at 0 °C, the reaction medium was poured into a saturated aqueous solution of Na_2CO_3 (2 mL) and extracted with $CHCl_3$. After a standard workup, pure nitrone **27b** was isolated in quantitative yield: IR 3200, 2950, 1730, 1600; UV (EtOH) 226, 279 (sh), 285, 294; MS, *m/z* (relative intensity) 368 ($M^{+\cdot}$), 339, 187 (100), 186, 170, 169, 156, 144, 143, 130; ^{1}H NMR (400 MHz) 8.47 (s, 1 H, N_aH), 7.46 and 7.32 (2 d, 2 H, *J* = 8, C_9H and $C_{12}H$), 7.23 and 7.13 (2 dd, 2 H, *J* = *J'* = 8, $C_{10}H$ and $C_{11}H$), 7.16 (d, 1 H, $J_{15,OH}$ = 11, disappeared by D_2O exchange, OH), 5.78 and 5.55 (2 br s, 2 H, C_3H and $C_{21}H$), 4.35 (br dd, 1 H, $J_{15,OH}$ = 11, $J_{14,15}$ = 3, $C_{15}H$), 3.94 (dd, 1 H, $J_{5,5'}$ = 11.5, $J_{5,6}$ = 4, $J_{5,6'}$ = 2, C_5H), 3.77 (s, 3 H, CO_2CH_3), 3.35 and 3.32 (2 H, 2 m, $C_{5'}H$ and C_6H), 3.22 (m, 1 H, $C_{14}H$), 3.18 (m, 1 H, $C_{6'}H$), 2.82 (dd, 1 H, $J_{17,17'}$ = 14, $J_{17,14}$ = 3, $C_{17}H$), 2.59 (br dd, 1 H, $J_{17,17'}$ = 14, $J_{17',14}$ = 3.5, $C_{17'}H$), 2.51 and 2.42 (2 m, 2 H, $J_{19,19'}$ = 15, $C_{19}H_2$), 1.13 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$).

Preparation of Compound 28. To a stirred solution of 21-cyanocatharanthine (**11**; 50 mg, 0.14 mmol) and vindoline (**4**; 70 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) under argon was added at −70 °C MCPBA (24 mg, 0.14 mmol). After 10 min, TFAA (0.07 mL, 0.48 mmol) was added to the reaction medium and the solution stirred at 0 °C for 1 h under argon. After evaporation of the solvent, the residue was dissolved in CH_3OH (2 mL) and reduced by $NaBH_4$. A standard workup and preparative TLC (eluent $CHCl_3/CH_3OH$, 95:5) afforded compound **28**: 8 mg (7%); IR 3300, 2950, 1740, 1620; UV 221, 232, 266, 294, 304; MS, *m/z* 815, 788, 733, 756, 730, 656, 548, 469, 308, 282, 200, 188, 135, 122, 121; NMR (400 MHz) 7.35–6.97 (m, 4 H, H aromatic), 6.58 and 6.07 (2 s, 2 H, C_9H and $C_{12}H$), 6.25 (d, 1 H, $J_{14',15'}$ = 7, $C_{15'}H$), 5.75 (dd, 1 H, $J_{14,15}$ = 9.5, $J_{3,14}$ = 3.5, $C_{14}H$), 5.53 and 5.13 (AB system, 2 H, J_{AB} = 13, C_6H_2), 5.37 (s, 1 H, $C_{17}H$), 5.28 (d, 1 H, $J_{14,15}$ = 9.5, $C_{15}H$), 3.85, 3.77, 3.58 (3 s, 9 H, $C_{11}OCH_3$, $C_{16}CO_2CH_3$ and $C_{16'}CO_2CH_3$), 2.67 (s, 3 H, N_aCH_3), 2.03 (s, 3 H, $OCOCH_3$), 1.12 and 0.22 (2 t, 6 H, *J* = 7, $C_{18'}H_3$ and $C_{18}H_3$).

Preparation of Compound 23a. 21-Cyanocatharanthine (**11**; 120 mg, 0.33 mmol) in solution in EtOH (10 mL) was hydrogenated (PtO_2, 50 mg) for 5 days at room temperature. After filtration of the catalyst and evaporation of the solvent, the residue was purified by preparative TLC ($CHCl_3/CH_3OH$, 95:5) to afford compound **23a**: 98 mg (82%); IR 3460, 2910, 2220, 1720, 1450; UV 228, 286, 292; MS, *m/z* 363, 334, 304, 214, 154, 149; ^{1}H NMR (60 MHz) 7.5 (s, 1 H, N_aH), 7.4–6.8 (m, 4 H, H aromatic), 3.8 (s, 3 H, $C_{16}CO_2CH_3$), 1.0 (t, 3 H, $C_{18}H_3$).

Preparation of Compound 23b. MCPBA (45 mg, 0.26 mmol) in CH_2Cl_2 (15 mL) was added at −10 °C to a stirred solution of 15,20-dihydro-21-cyanocatharanthine (**23a**; 80 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) under argon. After 10 min, the reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 and extracted by $CHCl_3$. A standard workup afforded pure 15,20-dihydro-21-cyanocatharanthine N_b-oxide (**23b**): 78 mg (93%); IR 3400, 2950, 2200, 1730, 1460; UV 228, 286, 292; MS, *m/z* 379, 362, 333, 144, 130; ^{1}H NMR (60 MHz) 9.1 (s, 1 H, N_aH), 7.5–6.9 (m, 4 H, H aromatic), 3.7 (s, 3 H, $C_{16}CO_2CH_3$), 1.1 (t, 3 H, $C_{18}H_3$).

Preparation of Compound 29 (One Pot Experiment). A solution of 15,20-dihydro-21-cyanocatharanthine (**23a**; 60 mg, 0.16 mmol) under argon in CH_2Cl_2 (1 mL) was treated for 10 min at −10 °C by *m*-chloroperbenzoic acid (30 mg, 0.18 mmol). When the formation of the N_b-oxide was complete, vindoline (**4**; 73 mg, 0.16 mmol) and TFAA (0.07 mL, 0.48 mmol) were added sequentially, and the reaction mixture was stirred for 1 h. After evaporation of the solvent, the residue was dissolved in CH_3OH (2 mL) and reduced by $NaBH_4$. A standard workup and preparative TLC (eluent ether/hexane/CH_3OH, 80:15:5) afforded compound **29**: 8 mg (6%); IR 3300, 2950, 1740; UV 221, 232, 266, 294, 304; MS, *m/z* 817, 774, 758, 741, 658, 577, 550, 282, 142, 141, 135; ^{1}H NMR (400 MHz), 7.3–7.1 (m, 4 H, H aromatic), 6.5 and 6.1 (2 s, 2 H, C_9H and $C_{12}H$), 5.57 (dd, 1 H, $J_{14,15}$ = 9.5, $J_{3,14}$ = 3.5, $C_{14}H$), 5.55 and 4.95 (AB system, 2 H, *J* = 13, C_6H_2), 3.87, 3.77, and 3.60 (3 s, 9 H, $C_{11}OCH_3$, $C_{16}CO_2CH_3$, $C_{16'}CO_2CH_3$), 2.67 (s, 3 H, N_aCH_3), 2.03 (s, 3 H, $OCOCH_3$), 0.97 and 0.19 (2 t, 6 H, *J* = 7, $C_{18}H_3$, $C_{18'}H_3$).

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Supplementary Material Available: Tables of thermal parameters, bond distances and angles, and atomic coordinates for **12** (4 pages). Ordering information is given on any current masthead page.

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