in and evaporated with aqueous trifluoracetic acid (90%, 2 × 10 mL) followed by coevaporation with water (2 × 10 mL) to give a syrup that was purified on a silica gel column (ethyl acetate–methanol–water 85:10:5) to give 0.19 g (97%) of the product **12**: $[\alpha]_D$ +15.0° (*c* 1.6, water); ^{1}H NMR (D_2O, 80 °C) δ 4.73 (dd, 2 H, H-1 H-1′), 1.33 (d, 6 H, $J_{5,6} \approx J_{5,6}$ = 5.6 Hz, H-6, H-6′); ^{13}C NMR (D_2O) 101.8 ($J_{C1,H1}$ = 170.6 Hz, C-1), 98.4 ($J_{C1',H1'}$ = 159.7 Hz, C-1′), 78.7 (C-3), 73.8, 73.4, 73.1 (3 C, C-3′, C-5′, C-4′), 72.1 (C-4), 71.6 (C-2), 69.3 (C-2′), 68.5 (C-5), 55.9 (OMe), 18.0, 17.9 (2 C, C-6′, C-6). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.98; H, 7.60.

Methyl 2-*O*-(β-L-Rhamnopyranosyl)-α-L-rhamnopyranoside (13). Compound **9** (0.22 g, 0.3 mmol) was dissolved in methanol (25 mL) containing a catalytic amount of sodium methoxide and left at room temperature for 2 h. The reaction mixture was neutralized with Rexyn 101(H^+) and evaporated to a syrup that was taken up in aqueous acetic acid (80%, 25 mL) and hydrogenated at 70 psi of H_2 overnight. The reaction was filtered through Celite 505 (Baker), evaporated, and purified on a silica gel column (ethyl acetate–methanol–water, 7:2:1) to give 85 mg (81%) of **13**: $[\alpha]_D$ +37.4° (*c* 1.4, water); ^{1}H NMR (D_2O, 80 °C) δ 4.78 (d, 1-H, $J_{1,2}$ = 1.7 Hz, H-1′), 4.69 (d, 1 H, $J_{1,2}$ = 0.9 Hz, H-1); ^{13}C NMR (D_2O) 99.7 (2 C, $^1J_{C1,H1}$ = 161.5, $^1J_{C1',H-1'}$ = 170.5 Hz, C-1, C-1′). 78.6 (C-2), 73.7 (2 C, C-3, C-3′), 73.5 (C-5′), 73.1 (C-4′), 72.1 (C-4), 70.8 (C-2′), 69.7 (C-5), 56.0 (OMe), 17.9, 17.7 (2 C, C-6′ and C-6). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.94; H, 7.56.

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Registry No. **1**, 14917-55-6; **2**, 76209-07-9; **3**, 76209-08-0; **4**, 14133-63-2; **5**, 79681-50-8; **6**, 69558-07-2; **7**, 76209-09-1; **8**, 79681-51-9; **9**, 79681-52-0; **10**, 79681-53-1; **11**, 74517-07-0; **12**, 79681-54-2; **13**, 79681-55-3; 1-ethoxycyclohexene, 1122-84-5; benzoylchloride, 98-88-4; dibromomethyl methyl ether, 3492-44-2; trimethyl orthobenzoate, 707-07-3; 3,4-di-*O*-benzyl-β-L-rhamnopyranose 1,2-(methyl orthoacetate), 72657-01-3; methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside, 71715-59-8; 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride, 72599-87-2.

20′-Deethylanhydrovinblastine

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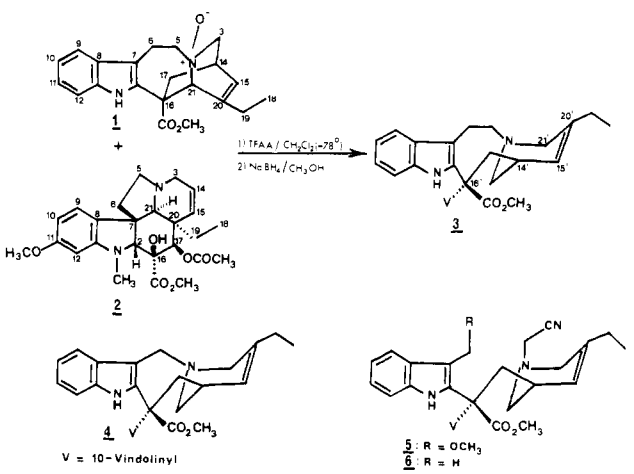
Racemic 20-deethylcatharanthine of synthetic origin has been coupled with vindoline by the fragmentative coupling method via the amine oxide. After reduction in methanol (16′*S*,14′*R*)-20′-deethylanhydrovinblastine is formed, accompanied by two methanol adducts, 15′-methoxy-20′-deethyl-15′,20′-dihydroanhydrovinblastine, which are epimeric at $C_{16'}$ and $C_{14'}$. If this step is performed in tetrahydrofuran, the yield of 20′-deethylanhydrovinblastine is increased and an equal yield of the 16′*R*,14′*S* epimer is obtained.

The discovery in our laboratory of a coupling reaction between catharanthine *N*-oxide (**1**) and vindoline (**2**) induced by a Polonovski fragmentation[1] has resulted in the preparation of anhydrovinblastine (**3**)[2] (Scheme I) and the main antitumor alkaloids extracted from the Madagascan periwinkle *Catharanthus roseus*.[3] In addition, derivatives **4**, **5**, and **6**,[4,5] having a modified skeleton, were synthesized. Some of them have shown interesting antitumor activities against leukemia L1210 and P-388 in mice and are currently under clinical evaluation.

The efficient total synthesis of (±)-20-deethylcatharanthine (**7**) by Sundberg and Bloom[6,7] prompted us to investigate the fragmentation reaction with the corresponding N_b-oxide **8** in the presence of vindoline (**2**). Besides comparing the behavior of (±)-20-deethylcatharanthine N_b-oxide (**8**) and catharanthine N_b-oxide (**1**),

Scheme I



(1) A. Cave, C. Kan-Fan, P. Potier, and J. LeMen, *Tetrahedron*, **23**, 4681 (1967).

(2) N. Langlois, F. Guéritte, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, **98**, 7017 (1976), and references therein.

(3) (a) N. Langlois and P. Potier, *Tetrahedron Lett.*, 1099 (1976); (b) Y. Langlois, N. Langlois, P. Mangeney, and P. Potier, *ibid.*, 3948 (1976); (c) N. Langlois and P. Potier, *J. Chem. Soc., Chem. Commun.*, 102 (1978); (d) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, **101**, 2243 (1979).

(4) P. Mangeney, R. Z. Andriamialisoa, J. Y. Lallemand, N. Langlois, and P. Potier, *Tetrahedron*, **35**, 2175 (1979).

(5) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Org. Chem.*, **44**, 3765 (1979).

(6) (a) R. J. Sundberg and J. D. Bloom, *Tetrahedron Lett.*, 5157 (1978); (b) R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, **45**, 3382 (1980).

(7) C. Marazano, J. L. Fourrey, and B. C. Das, *J. Chem. Soc., Chem. Commun.* 37 (1981).

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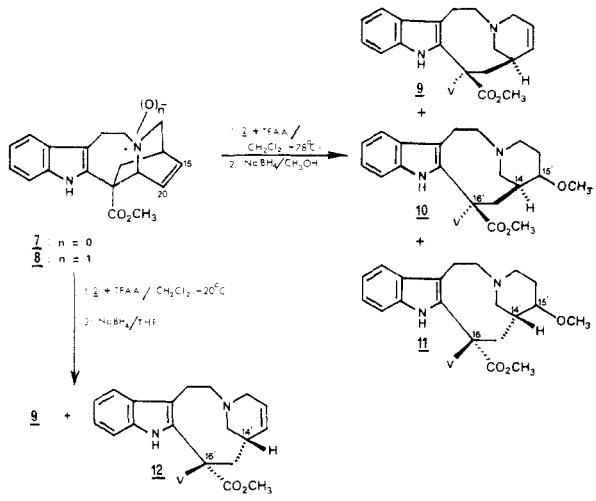
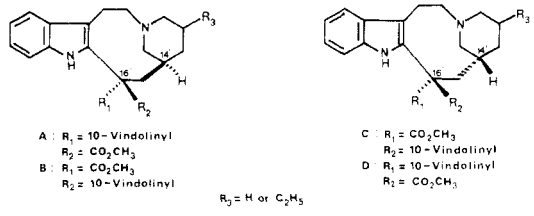
Scheme II



with respect to the coupling reaction this experiment could give rise to additional knowledge of the structural parameters which are necessary for antitumor activity by introducing a modification in the ibogane part of the molecule. Furthermore, this coupling reaction could theoretically lead to four diastereoisomers A, B, C, and D (R_3 = H), and if these compounds were easily separable, a resolution of the racemic synthetic indole could be avoided in the preparation of vinblastine-type compounds. Finally, it would



be interesting to evaluate the amount of asymmetric induction from vindoline (2). Such an enantiodifferentiation has been already observed during the coupling reaction between vindoline (2) and (±)-eburnamenine.[8] However, the coupling reaction of the chloroindolenine derived from (±)-vincadifformine with vindoline (2) led to equal amounts of dimeric diastereoisomers.[9]

(±)-20-Deethylcatharanthine N_b-oxide (8) was prepared by action of *m*-chloroperoxybenzoic acid on the corresponding free amine 7. In contrast with other N_b-oxides derivatives in this series,[10] compound 8 seemed to be as stable as catharanthine N_b-oxide 1 at 0 °C and did not give rise to spontaneous [2,3] sigmatropic rearrangement.[11]

The N_b-oxide 8 submitted to the Polonovski–Potier reaction conditions (trifluoroacetic anhydride, methylene chloride) at −78 °C gave rise, after sodium borohydride reduction in methanol, to three dimeric compounds **9**, **10**, and **11** isolated in poor yield after preparative TLC (Scheme II).

All these compounds exhibit the characteristic indole–dihydroindole UV chromophore. The mass spectrum of the compound **9** shows a molecular peak $M^{+\cdot}$ at m/z 764 and fragments characteristic of dimers of the vinblastine type. In the NMR spectrum (400 MHz),[12] four ethylenic protons (C_{14}-H, C_{15}-H, $C_{15'}$-H, and $C_{20'}$-H) are located between 5 and 6 ppm; in addition, the chemical shifts of protons C_{12}-H, C_9-H, and C_{18}-H (respectively at 6.11, 6.49, and 0.79 ppm) indicate a "natural" configuration (*S*) at $C_{16'}$. As the CD curves of the four possible diastereoisomers, A, B, C, and D, (R_3 = C_2H_5) are already known,[13,14] the CD spectrum is a very good tool with which allows the configuration at $C_{16'}$ and $C_{14'}$ to be established. The examination of the curve of **9** gave conclusive evidence of the 16′*S*,14′*R* configurations (type A, R_3 = H) and the structure of 20′-deethylanhydrovinblastine (**9**) can be easily deduced.

The mass spectra of the other dimeric compounds **10** and **11** are very similar and show a molecular peak at m/z 796. In their ^{1}H NMR spectra[12] one can note a signal corresponding to an additional methoxyl group and the lack of ethylenic protons arising from the tetrahydropiperidine ring of the ibogane part of the molecule. The CD curves of **10** and **9** are the same (type A), while the curve of **11** is similar to those of vincovaline[13] and of two dimeric compounds **14** and **15** resulting from the coupling of coronaridine N_b-oxide (**13**; antipodal series of catharanthine) with vindoline (**2**), indicating compound **11** is a diastereoisomer of type C. These spectral data allow the

assigment of the structure of the compound **10** as 15′-methoxy-20′-deethyl-15′,20′-dihydroanhydrovinblastine, the structure of **11** being epimeric both at $C_{16'}$ and $C_{14'}$. The formation of dimeric compounds **10** and **11** can be easily rationalized by a 1,4 addition of a methoxy anion on to $C_{15'}$ of the conjugated immonium salt intermediates, followed by reduction with sodium borohydride of the resulting enamine. It is evident since the dimeric compounds **9**, **10**, and **11** are obtained in poor yield (2.7%, 3.6%, and 5.2%, respectively) that the fragmentative coupling of 20-deethylcatharanthine N_b-oxide **8** is much less efficient than for catharanthine N_b-oxide (**1**) which led to anhydrovinblastine (**3**) in 50–60% yield under the same conditions.

Other experiments were undertaken both to improve the yield and to suppress the side reaction leading to 15′-methoxy derivatives **10** and **11**. The best results were obtained when the Polonovski–Potier reaction was performed at −20 °C followed by reduction of the resulting conjugated immonium salt with sodium borohydride in THF. After the reaction mixture boiled for 1 h in ethanol, in order to hydrolyze amine–boranes, two dimeric compounds were isolated in 16% yield each. One is 20′-deethylanhydrovinblastine (**9**). The spectral data of the other permit us to assign the diastereoisomeric structure **12** (16′*R*,14′*S*, type C; R_3 = H).

It is worthy of note that dimeric compounds corresponding to "unnatural" configurations 16′*R*,14′*R* (type B) and 16′*S*,14′*S* (type D) were not isolated even when the coupling experiment was performed at −20 °C. In the case of catharanthine N_b-oxide **1**, this temperature was critical to avoid the formation of 16′-epianhydrovinblastine

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(9) D. Royer, Thèse de Doctorat ès Sciences Pharmaceutiques, Reims, 1980.
(10) P. Mangeney, Y. Langlois, and colleagues, manuscript submitted for publication.
(11) Y. Langlois, F. Guéritte, R. Z. Andriamialisoa, N. Langlois, P. Potier, A. Chiaroni, and C. Riche, *Tetrahedron*, **32**, 945 (1976).
(12) Laboratory-built 400-MHz high-resolution spectrometer; see M. Lounasmaa and S. K. Kan, *Tetrahedron*, **36**, 1607 (1980).
(13) R. Z. Andriamialisoa, N. Langlois, and P. Potier, *Tetrahedron Lett.*, 2849 (1976).
(14) R. Z. Andriamialisoa, Thèse de Doctorat ès Sciences Physiques, Orsay, 1978.

(16'R,14'R, type B, $R_3 = C_2H_5$). Finally, no asymmetric induction from the vindoline could be detected as the dimeric compounds **9** and **12** were isolated in the same yield.

From a biogenetic point of view, this observation can be compared with the fact that the two series of dimeric compounds type A and type C that are isolated from *Catharanthus* species[13] probably arise from a common biogenetic pathway with antipodal pentacyclic ibogane alkaloids as precursors, although definitive proof of this point is lacking.

Interactions between compounds **9** and **12** and their receptor, tubulin,[15] have been tested in comparisom with vinblastine. Compound **9** showed an I_{50}[16] = 6×10^{-6} M (vinblastine, $I_{50} = 2 \times 10^{-6}$ M) and S_{50}[16] = 4×10^{-5} M (vinblastine, $S_{50} = 3 \times 10^{-5}$ M), while compound **12** was inactive.

These in vitro experiments must be completed by in vivo tests using L1210 and P-388 leukemias.

Experimental Section

Infrared spectra (ν cm^{-1}, $CHCl_3$) were recorded 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, $\delta = 0$ ppm) on an IEF_{400} spectrometer (coupling constants, J, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively). Mass spectra were measured on an MS 50. Preparative layer chromatography (preparative TLC) was performed with Kieselgel HF 254 (Merck).

(±)-Deethylcatharanthine N_b-Oxide. *m*-Chloroperoxybenzoic acid (17 mg, 0.1 mmol) in CH_2Cl_2 (2.4 mL) was added at 0 °C to a stirred solution of (±)-20-deethylcatharanthine (**7** (20.0 mg, 0.065 mmol) under argon. After 10 min, the reaction mixture was poured into a saturated solution of Na_2CO_3 and the N_b-oxide was extracted with CH_2Cl_2 (90%): UV 223, 274, 283, 292; mass spectrum, m/z 324 ($M^{+\cdot}$), 307, 265, 226, 220, 218, 204, 194, 167; ^1H NMR 7.88 (1 H, N_a-H), 7.5–7.0 (4 H, aromatic), 6.57 (m, 2 H, C_{15}-H and C_{20}-H), 5.0 (1 H, d, $J_{20,21} = 5$, C_{21}-H), 3.74 (3 H, CO_2CH_3).

Coupling of (±)-Deethylcatharanthine N_b-Oxide with Vindoline at −78 °C. Trifluoroacetic anhydride (24 μL, 0.15 mmol) was added to a stirred solution of (±)-deethylcatharanthine N_b-oxide (**8**, 15.5 mg, 0.048 mmol) and vindoline (**2**; 24.8 mg, 0.054 mmol) in 0.3 mL of dichloromethane under argon at −78 °C. After 1 h, excess solvent and TFAA were distilled off in vacuo. The residue was dissolved in MeOH (1 mL) and excess $NaBH_4$ was added at 0 °C. After 30 min, the reaction mixture was poured into H_2O and extracted with $CHCl_3$. Preparative TLC ($CHCl_3$–MeOH, 9:1) of the residue afforded **9** (1.0 mg 2.7%), **10** (1.4 mg, 3.6%), and **11** (2.0 mg, 5.2%).

Compound 9: IR 1740, 1615; UV 218, 261, 288, 296; CD: 214 (−), 225 (+), 259 (+), 304 (+); mass spectrum 764, 733, 605, 497, 282, 136, 135, 122, 121, 107; ^1H NMR 8.05 (1 H, C_{16}-OH), 7.88 (1 H, N_a-H, 7.5–7.0 (aromatic), 6.49 (1 H, s, C_9-H), 6.11 (1 H, s, C_{12}-H), 5.89 (3 H, C_{14}-H, C_{15}-H, and C_{20}-H), 5.43 (1 H, s, C_{17}-H), 5.29 (1 H, C_{15}-H), 3.83 (3 H, s), 3.80 (3 H, s), 3.65 (3 H, s, C_{11}-OCH_3, C_{16}-CO_2CH_3, and $C_{16'}$-CO_2CH_3), 2.74 (3 H, s, N_a-CH_3), 2.11 (3 H, s, $OCOCH_3$), 0.79 (3 H, t, $J_{18,19} = 7$, C_{18}-H).

Compound 10: UV 218, 263, 288, 296; CD 214 (−), 227 (+), 260 (+); mass spectrum, 796, 765, 737, 637, 529, 469, 341, 282, 135, 122, 121, 107; ^1H NMR 7.98 (1 H, N_a-H), 7.5–7.0 (aromatic), 6.48 (1 H, s, C_9-H), 6.07 (1 H, s, C_{12}-H), 5.84 (1 H, dd, $J_{14,15} = 9.4$ and $J_{3,14} = 4$, C_{14}-H), 5.41 (1 H, s, C_{17}-H), 5.3 (1 H, d, $J_{14,15} = 9.4$, C_{15}-H), 3.79 (3 H, s), 3.77 (3 H, s), 3.63 (3 H, s, C_{11}-OCH_3, C_{16}-CO_2CH_3, and $C_{16'}$-CO_2CH_3), 3.08 (3 H, s, OCH_3), 2.69 (3 H, s, N_a-CH_3), 2.10 (3 H, s, $OCOCH_3$), 0.79 (3 H, t, $J_{18,19} = 7$, C_{18}-H).

Compound 11: UV 222, 258, 292, 297; CD 222 (−), 258 (+), 304 (−); mass spectrum, 796, 765, 737, 637, 529, 469, 341, 282, 135, 122, 121, 107.

Coupling of (±)-Deethylcatharanthine N_b-Oxide with Vindoline at −20 °C. Trifluoroacetic anhydride (0.2 mmol) was added to a stirred solution of **8** (0.06 mmol) and **2** (0.063 mmol) in 0.3 mL of CH_2Cl_2 under argon at −20 °C. After 1 h excess solvent and TFAA were distilled off in vacuo. The residue was dissolved in THF (1 mL), excess $NaBH_4$ was added at 0 °C, and the mixture was stirred at 0 °C for 1 h. After the usual workup, the residue was dissolved in EtOH and the solution was heated under reflux for 1 h. The residue was purified by preparative TLC ($CHCl_3$–MeOH, 90:10) and gave 20'-deethylanhydrovinblastine (**9**, 16%) and compound **12** (16%).

Dimeric compound 12: IR 1740, 1615; UV 220, 257, 288, 296; CD 223 (−), 260 (+), 306 (−); mass spectrum, 764, 733, 705, 605, 497, 282, 135, 122, 121, 107; ^1H NMR 8.07 (1 H, N_a-H), 7.5–7.0 (aromatic), 6.67 (1 H, s), 6.15 (1 H, s, C_9-H and C_{12}-H), 5.79 (3 H, m, C_{14}-H, $C_{15'}$-H, and $C_{20'}$-H), 5.46 (1 H, s, C_{17}-H), 5.23 (1 H, $J_{14,15} = 9.4$, C_{15}-H),3.81 (3 H, s), 3.80 (3 H, s), 3.56 (3 H, s, C_{11}-OCH_3, C_{16}-CO_2CH_3, and $C_{16'}$-CO_2CH_3), 2.73 (3 H, s, N_a-CH_3), 2.07 (3 H, s, $OCOCH_3$), 0.37 (3 H, t, $J_{18,19} = 7$, C_{18}-H).

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Registry No. **2**, 2182-14-1; **7**, 74194-98-2; **8**, 79681-29-1; **9**, 79703-87-0; **10**, 79703-88-1; **11**, 79733-72-5; **12**, 79733-73-6.

(15) F. Zavala, D. Guénard, and P. Potier, *Experientia*, **34**, 1498 (1978).

(16) I_{50}, concentration inducting 50% of the rate of inhibition of polymerization of tubulin. S_{50}, concentration inducing 50% of the maximum of spiralization of tubulin.

Photochemical Studies.[1] On the Photofragmentation of Substituted 1,2-Dihydrophthalic Anhydrides

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The irradiation-induced transformations of 4,5-diphenyl-1,2-dihydrophthalic anhydride (**2b**) as well as those of the 3,6-dimethyl-4,5-diphenyl and 3,4,5,6-tetraphenyl derivatives (**2c,d**) are elaborated. All undergo photofragmentation, viz., CO + CO_2 ejection to give aromatic hydrocarbons, while only **2b** also closes electrocyclically to the bicyclo[2.2.0]hex-5-ene product **5**. The quantum yields for fragmentation are indicative in this respect. The rearrangement accompanying the fragmentation of **2d** to give 1,2,3,5-tetraphenylbenzene (**11**) was shown to occur via a triplet excited state, populated by benzene sensitization.

We had discovered,[2] while working on the photodecarbonylation of substituted norbornen-7-ones (**1**), that the resulting 1,2-dihydrophthalic anhydrides (**2**) undergo a surprisingly facile extrusion of CO and CO_2 to give the

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