isopropylpentyl)triphenylphosphonium bromide, 71436-81-2; (3-tetrahydropyranyloxypropyl)triphenylphosphonium bromide, 70665-02-0; isohexyltriphenylphosphonium bromide, 70240-41-4; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; (3-tetrahydropyranyloxypropylidene)triphenylphosphorane, 71436-82-3; [3-(2-methyl-1,3-dioxolan-2-yl)propylidene]triphenylphosphorane, 3054-93-1; (4-methylpentylidene)triphenylphosphorane, 54517-55-4; 3-methylbutylidenetriphenylphosphorane, 39110-24-2; methoxymethylidenetriphenylphosphorane, 20763-19-3; 4-isopropyltetrahydropyran, 66760-31-4; 3-isopropyl-1,5-pentanedioic acid, 4165-99-5; 3-isopropyl-1,5-pentanediol, 61898-54-2; 1-acetoxy-5-bromo-3-isopropylpentane, 66760-27-8; 1-bromo-3-ethylpentan-4-one, 66760-26-7; 3-bromo-1-propanol tetrahydropyranyl ether, 33821-94-2; pregnenolone, 145-13-1; 3-bromo-1-propanol, 627-18-9; dihydropyran, 110-87-2; triphenylphosphine, 603-35-0; 2-acetylbutyrolactone, 517-23-7; 2-acetyl-2-ethylbutyrolactone, 31770-00-0; cyanoacetamide, 107-91-5; 2-methylpropanal, 78-84-2; methyltriphenylphosphonium iodide, 2065-66-9.

A New Class of Antitumor Compounds: 5′-Nor and 5′,6′-Seco Derivatives of Vinblastine-Type Alkaloids

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The reaction medium obtained after applying the modified Polonovski reaction to the N_b-oxide of anhydrovinblastine (3) led mainly to seco C_5–C_6 derivatives after treatment with various nucleophiles. In the presence of cyanide ion, a minor product formed by nucleophilic attack onto the conjugated immonium salt 7 was also isolated. On the other hand, 20′-deoxyleurosidine N_b-oxide (20) led only to seco C_5–C_6 derivatives.

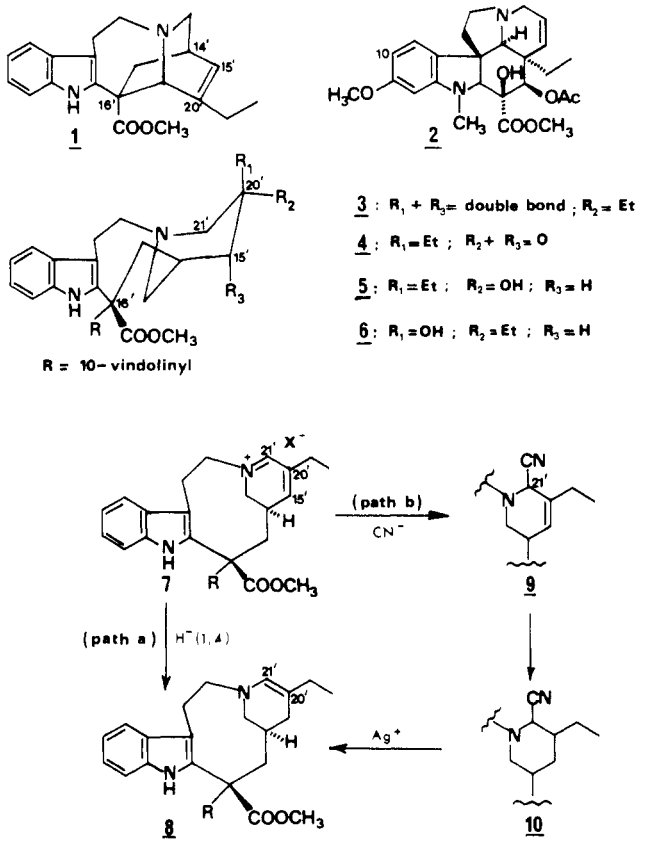
The discovery in our laboratory[1] of a coupling reaction, based on the modified Polonovski reaction[2] and leading to $\Delta^{15'(20')}$-20′-deoxyvinblastine (anhydrovinblastine, 3) from catharanthine (1) and vindoline (2), has stimulated a considerable amount of work aimed at the partial synthesis of leurosine (4),[3] leurosidine (5),[4] and vinblastine (6),[5] the main antitumor alkaloids extracted from various *Catharanthus* species.

The most fruitful approach for the preparation of these complex alkaloids took advantage of several stereoelectronic factors for the direct functionalization of carbon $C_{20'}$ and/or $C_{15'}$ of anhydrovinblastine (3) or other intermediates formed during the coupling reaction.

The conjugated immonium salt 7[6] appeared to be an interesting intermediate which could lead to $\Delta^{20'}$-20′-deoxyvinblastine (8)[7] either by a 1,4 reduction (path a, Scheme I) or by addition of cyanide ion at $C_{21'}$, followed by reduction of the remaining $C_{15'}$–$C_{20'}$ double bond and treatment with silver ion (path b, Scheme I).

The modified Polonovski reaction also appeared to be well suited for the preparation of the conjugated immonium salt 7 using anhydrovinblastine N_b-oxide (11) as the starting material. One of the two allylic protons at $C_{21'}$ would be regioselectively eliminated, giving rise to the desired conjugated immonium salt 7 via the trifluoroacetoxyammonium salt 12 (Scheme II).

Scheme I



Anhydrovinblastine N_b-oxide 11 was exposed to modified Polonovski reaction conditions (TFAA–CH_2Cl_2) and treated after evaporation with several reagents known to allow 1,4 reduction, such as formic acid in pyridine[8] or potassium formate in the presence of 18-crown-6.[9] All of

(1) (a) P. Potier, N. Langlois, Y. Langlois, and F. Gueritte, *J. Chem. Soc., Chem. Commun.*, 670 (1975); (b) N. Langlois, F. Gueritte, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, **98**, 7017 (1976).

(2) P. Potier, *Rev. Latinoamer. Quim.*, **9**, 47 (1978), and references therein.

(3) (a) Y. Langlois, N. Langlois, P. Mangeney, and P. Potier, *Tetrahedron Lett.*, 3945 (1976); (b) N. Langlois and P. Potier, *J. Chem. Soc., Chem. Commun.*, 102 (1978); (c) J. P. Kutney, J. Balsevitch, G. H. Bokelman, T. Hibino, I. Itoh, and A. H. Ratcliffe, *Heterocycles*, **4**, 997 (1976).

(4) N. Langlois and P. Potier, *Tetrahedron Lett.*, 1099 (1976).

(5) (a) A. U. Rahman, A. Basha, and M. Ghazala, *Tetrahedron Lett.*, 2351 (1976); (b) P. Mangeney, R. Zo Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Am. Chem. Soc.*, in press.

(6) Obviously, this conjugated immonium salt 7 can be obtained directly from the coupling reaction between vindoline (2) and catharanthine *N*-oxide, but in this case it is always contaminated with unreacted vindoline and other byproducts.

(7) A procedure for the preparation of the enamine 8 has been described (see ref 5b).

(8) L. R. Gizzi and M. M. Joullié, *Tetrahedron Lett.*, 3117 (1969).

(9) Y. Ohnishi and S. Tamimoto, *Tetrahedron Lett.*, 1909 (1977).

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6.11 (s, 1 H, $C_{12'}$–H), 5.84 (dd, $J_{14,15}$ = 10 and $J_{3,11}$ = 4.5, C_{14}–H), 5.44 (1 H, $C_{15'}$–H), 5.41 (s, 1 H, $C_{17'}$–H), 5.27 (d, 1 H, $J_{14,15}$ = 10, C_{15}–H), 4.51 (m, 2 H), 4.32 and 3.98 (2d, 2 H, N_b–CH), 3.84, 3.78, and 3.69 (3 s, 9 H, C_{11}–OCH_3, C_{16}–CO_2CH_3, and $C_{16'}$–CO_2CH_3), 2.62 (s, 3 H, N_a–CH_3), 2.09 (s, 3 H, $OCOCH_3$), 1.06 and 0.64 (2 t, $J_{18,19}$ = 7, 6 H, C_{18}–H_3 and $C_{18'}$–H_3).

Preparation of Compounds 13a and 15. Anhydrovinblastine N_b-oxide (145 mg, 0.18 mmol) in solution in dry CH_2Cl_2 was treated for 1 h at 0 °C and under argon by trifluoroacetic anhydride (TFAA) (0.12 mL, 0.83 mmol). After evaporation of the solvent without heating, the residue was dissolved in a saturated solution of KCN in anhydrous methanol (4 mL). This solution was stirred for 2 h at 20 °C and poured into brine, and then extracted with $CHCl_3$. After the usual workup and purification by preparative TLC (eluant, $CHCl_3$–MeOH, 93:7), compounds **13a** (48 mg, 32%) and **15** (82 mg, 54%) were isolated.

Compound 13a: IR 3460, 2960, 2230, 1740, 1650, 1610; UV 220 (36 500), 263 (14 300), 284 (9000), 292 (8300); MS *m/e* 817 ($M^{+\cdot}$), 758, 658, 282, 160, 135, 122, 121; NMR (240 MHz) 8.0 (s, 1 H, N_a–H), 7.55 (d, J = 7.5, 2 H, H aromatic indolic), 6.70 and 6.57 (2 s, 2 H, C_9–H and C_{12}–H), 5.93 (s, 1 H, $C_{21'}$–H), 5.89 (m, 1 H, C_{14}–H), 5.50 (s, 1 H, $C_{17'}$–H), 5.30 (d, $J_{14,15}$ = 9.5, 1 H, C_{15}–H), 3.80 and 3.60 (2 s, 9 H, C_{11}–OCH_3, C_{16}–CO_2CH_3, and $C_{16'}$–CO_2CH_3), 2.79 (s, 3 H, N–CH_3), 2.09 (s, 3 H, $OCOCH_3$), 1.08 and 0.86 (2 t, 6 H, C_{18}–H_3 and $C_{18'}$–H_3).

Compound 15: $[\alpha]^{20}_D$ +7° (*c* 0.6, EtOH); IR 3410, 2960, 1740, 1620; UV 222 (37 000), 264 (11 200), 296 (8000), 318 sh (5600); MS *m/e* 863 ($M^{+\cdot}$ + 14), 849 ($M^{+\cdot}$), 819, 817, 790, 658, C_{16}–CO_2CH_3), 598, 379, 282, 258, 244, 222, 161, 135, 122, 121, 107; NMR (240 MHz) 7.61 and 7.37 (d, J = 7 and d, J = 7.5, 2 H, H aromatic indolic), 7.14 (m, 2 H, H aromatic indolic), 7.12 and 5.97 (2 s, 2 H, C_9–H and $C_{12'}$–H), 5.91 (dd, $J_{14,15}$ = 9.5, $J_{3,14}$ = 3.5, 1 H, C_{14}–H), 5.58 (s, 1 H, $C_{17'}$–H), 5.40 (d, $J_{14,15}$ = 9.5, 1 H, C_{15}–H), 4.87 (m, 1 H, $C_{15'}$–H), 4.29 and 4.19 (2 d, $J_{6'a,6'b}$ = 12, 2 H, $C_{6'}$–H_2), 3.75, 3.61, and 3.36 (3 s, 9 H, C_{11}–OCH_3, C_{16}–CO_2CH_3, and $C_{16'}$–CO_2CH_3), 3.07 (s, 3 H, CH_2–OCH_3), 0.84 and 0.76 (2 t, 6 H, C_{18}–H_3 and $C_{18'}$–H_3).

Preparation of Compound 16. Anhydrovinblastine *N*-oxide (**11**) (98 mg, 0.12 mmol) in solution in dry CH_2Cl_2 (0.9 mL) was treated for 1 h at 0 °C and under argon by TFAA (0.08 mL, 0.5 mmol). After evaporation of the solvent without heating, the residue was dissolved in CH_3OH (2 mL) and reduced by $NaBH_3CN$ (7 mg) for 30 min. After treatment as above, the residue is purified by preparative TLC (eluant, $CHCl_3$–MeOH, 90:10). Anhydrovinblastine **3**[1b] (24 mg, 24%), compound **16** (33 mg, 35%), and small amounts of compound **18** (7 mg, 7%) were isolated.

Compound 16: $[\alpha]^{20}_D$ +19° (*c* 0.5, EtOH); IR 3460, 2960, 1740, 1610; UV 218 (13 000), 263 (5980), 288 (4700), 296 (4700); CD 248 (+), 215 (+), 200 (–); MS *m/e* 808, 794 ($M^{+\cdot}$), 735, 657, 635, 598, 527, 282, 188, 152, 135, 122; NMR (240 MHz) 7.41 and 7.29 (2 d, J = 7.5, 2 H, H aromatic indolic), 7.06 (m, 2 H, H aromatic indolic), 6.90 and 6.00 (2 s, 2 H, C_9–H and C_{12}–H), 5.85 (dd, $J_{14,15}$ = 9.5 and $J_{3,14}$ = 3.5, 1 H, C_{14}–H), 5.46 (s, 1 H, $C_{17'}$–H), 5.32 (d, $J_{14,15}$ = 9.5, 1 H, C_{15}–H), 4.90 (s, broad, 1 H, $C_{15'}$–H), 3.76, 3.61, and 3.53 (s, 9 H, C_{11}–OCH_3, $C_{16}CO_2CH_3$, and $C_{16'}CO_2CH_3$), 2.66 (s, 3 H, N_a–CH_3), 2.24 (s, 3 H, N_b–CH_3), 2.08 (s, 3 H, $OCOCH_3$), 1.95 (s, 3 H, $C_{7'}$–CH_3), 0.87 and 0.63 (2 t, $J_{18,19}$ = 7.5, 6 H, $C_{18'}$–H_3 and C_{18}–H_3).

Preparation of Compound 17. Anhydrovinblastine N_b-oxide was treated as in the preparation of compound **16** and reduced by an excess of sodium borohydride in CH_3OH. After purification by preparative TLC ($CHCl_3$–MeOH, 90:10), compound **17** (30%), anhydrovinblastine (**3**) (25%), and compound **18** (7%) were isolated.

Compound 17: $[\alpha]^{20}_D$ –7.3° (*c* 0.6, EtOH); IR 3405, 2950, 1745, 1620; UV 220 (37 100), 263 (11 400), 284 (9100), 292 (8500), 314 (5700); CD 257 (+), 215 (+), 200 (–); MS *m/e* 838, 824 ($M^{+\cdot}$), 808, 794, 793, 792, 748, 734, 656, 598 (100%), 336, 282, 152, 135, 122; NMR (240 MHz) 7.41 and 7.29 (2 d, J = 7.5, 2 H, H aromatic indolic), 7.03 (m, 2 H, H aromatic indolic), 6.98 and 6.00 (2 s, 2 H, C_9–H and C_{12}–H), 5.90 (dd, $J_{14,15}$ = 9.5 and $J_{3,14}$ = 3.5, 1 H, C_{14}–H), 5.54 (s, 1 H, $C_{17'}$–H), 5.40 (d, $J_{14,15}$ = 9.5, 1 H, C_{15}–H), 5.02 (s, broad, 1 H, $C_{15'}$–H), 4.39 (dd, $J_{6'a,6'b}$ = 11, 2 H, $C_{6'}$–H_2), 3.75, 3.62, and 3.48 (3 s, 9 H, C_{11}–OCH_3, C_{16}–CO_2CH_3, and $C_{16'}$–CO_2CH_3), 3.10 (s, 3 H, $C_{6'}$–OCH_3), 2.71 (s, 3 H, N_a–CH_3), 2.38 (s, 3 H, N_b–CH_3), 2.16 (s, 3 H, $OCOCH_3$), 0.98 and 0.85 (2 t, $J_{18,19}$ = 7.5, 6 H, $C_{18'}$–H_3 and C_{18}–H_3).

Preparation of Compound 16 from Compound 15. To a stirred solution of compound **15** (12 mg, 0.014 mmol) in solution in CH_3OH was added trifluoroacetic acid (0.02 mL), and the resulting mixture was treated by sodium cyanoborohydride (4 mg, 0.065 mmol) under stirring in argon atmosphere at room temperature. After 1 h, this reaction mixture was poured in aqueous sodium carbonate solution and extracted by $CHCl_3$. Compound **16** (10 mg, 90%) was obtained after the usual treatment.

Preparation of Deoxy-VLB-B N_b-Oxide (20). To a stirred solution of deoxy-VLB-B (45 mg, 0.056 mmol) in dry CH_2Cl_2 (1 mL) was added at 0 °C *p*-nitroperbenzoic acid (13 mg, 0.07 mmol). After 10 min, the reaction medium was poured in a saturated aqueous solution of Na_2CO_3 (1 mL) and extracted by $CHCl_3$. After the usual treatment and preparative TLC (eluant, $CHCl_3$–MeOH, 90:10) pure deoxy-VLB-B *N*-oxide (38 mg, 83%) was isolated: UV 228, 268, 286, 296, 312; MS *m/e* 822, 808, 794, 792, 612, 610, 468, 282, 138, 135 (100%), 124, 122, 121; NMR (60 MHz) 9.5 (s, 1 H, C_{18}–OH), 7.9 (s broad, 1 H, $N_{a'}$–H), 7.3–6.8 (m, 4 H aromatics), 6.3 and 6.0 (2 s, 2 H, C_9–H and C_{12}–H), 5.6 (m, 1 H, C_{14}–H), 5.3 (s + m, 2 H, C_{17}–H and C_{15}–H), 3.7 and 3.5 (2 s, 9 H, OCH_3, C_{16}–CO_2CH_3 and $C_{16'}$–CO_2CH_3), 2.7 (s, 3 H, N_a–CH_3), 2.0 (s, 3 H, $OCOCH_3$), 0.8 (m, 6 H, C_{18}–H_3 and $C_{18'}$–H_3).

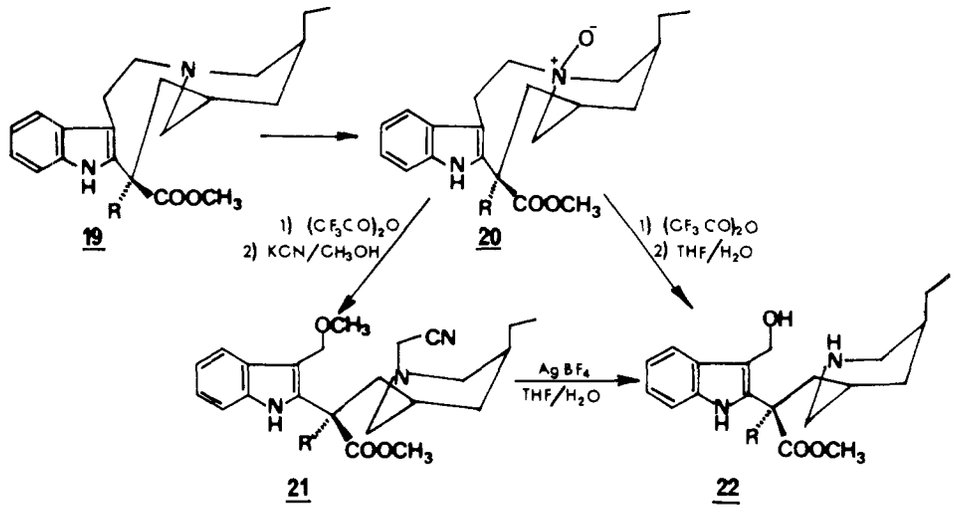
Preparation of Compound 21. Deoxy-VLB-B N_b-oxide (37 mg, 0.045 mmol) in solution in dry CH_2Cl_2 (0.6 mL) was treated, at 0 °C under argon, with TFAA (0.03 mL, 0.21 mmol). After 1 h, the reaction medium was evaporated in vacuo and dissolved in anhydrous methanol (2.5 mL). KCN (25 mg) was added to the solution at 0 °C. After 30 min, the reaction medium was poured into water and extracted by $CHCl_3$. After the usual treatment, the residue (38 mg) was purified by preparative TLC ($CHCl_3$–MeOH, 93:7) and gave compound **21** (19 mg, 51%): IR 3300, 2950, 2300, 1740; UV 220 (58 000), 264 (11 800), 284 (9900), 295 (9100), 315 (sh 6000); CD 295 (–3.8), 285 (–3.8), 255 (+15.2), 228 (+9.5), 205 (–22.8); NMR (60 MHz) 9.8 (s broad, $N_{a'}$–H or OH), 7.2–7.0 (m, 5 H, aromatic), 6.0 (s, 1 H, C_9–H or C_{12}–H), 5.5 (s, 1 H, $C_{17'}$–H), 5.4 (s, 1 H, C_{15}–H), 4.2 (s broad, 2 H, $C_{5'}$–H or $C_{6'}$–H), 3.8, 3.65, 3.45, 3.05 (4 s, 12 H, OCH_3, C_{16}–CO_2CH_3, $C_{16'}$–CO_2CH_3, $C_{6'}$–OCH_3), 2.65 (s, 3 H, N_a–CH_3), 2.05 (s, 3 H, $OCOCH_3$), 0.65 (m, 6 H, C_{18}–H_3 and $C_{18'}$–H_3); MS *m/e* 851 ($M^{+\cdot}$), 821, 819, 690, 660, 282 (100%), 222, 163 (100%), 138 (100%), 136, 135 (100%), 124, 122, 121.

Preparation of Compound 22. To a stirred solution of deoxy-VLB-B N_b-oxide (70 mg, 0.09 mmol) in dry CH_2Cl_2 (0.67 mL) was added under argon at 0 °C TFAA (0.065 mL, 0.45 mmol). After 1 h, the reaction medium was evaporated in vacuo and the residue was dissolved in THF (5 mL). An aqueous solution of sodium carbonate (40 g/L, 0.012 mL) was added and the resulting mixture was stirred overnight at room temperature. After extraction by $CHCl_3$ and the usual treatment, the residue was purified by preparative TLC ($CHCl_3$–MeOH), 90:10) and gave compound **22** (16 mg, 23%): IR 3400, 2950, 1740; UV 222 (50 000), 265 (14 000), 285 (12 000), 292 (11 200), 310 (sh 7000); CD 295 (–4.0), 287 (–4.0), 260 (+18.3), 225 (+16.6), 215 (–18.0); MS *m/e* 810, 796, 794, 764, 750, 738, 736, 598, 577, 522, 480, 282, 144, 138 (100%), 135 (100%), 125, 124 (100%), 122, 121; NMR (250 MHz) 8.70 (s, 1 H, $N_{a'}$–H or OH), 7.55–7.0 (m, 4 H, aromatic), 7.02 and 5.97 (2 s, 2 H, C_9–H and C_{12}–H), 5.91 (m, 1 H, C_{14}–H), 5.49 (s, 1 H, $C_{17'}$–H), 5.34 (d, $J_{14,15}$ = 7.5, 1 H, C_{15}–H), 4.28 (s broad, 2 H, $C_{6'}$–H), 3.79, 3.66, 3.42 (3 s, 9 H, OCH_3, C_{16}–CO_2CH_3, $C_{16'}$–CO_2CH_3), 2.70 (s, 3 H, N_a–CH_3), 2.12 (s, 3 H, $OCOCH_3$), 0.70 and 0.52 (2 t, 6 H, J = 7, C_{18}–H_3 and $C_{18'}$–H_3).

Preparation of Compound 22 from Compound 21. To a stirred solution of compound **21** (16 mg, 0.019 mmol) in anhydrous THF (1 mL) under argon, $AgBF_4$ (7 mg, 0.034 mmol) was added. After 15 min at room temperature, a solution of CF_3CO_2H (0.02 mL) in water (0.5 mL) was added. The reaction mixture was poured into aqueous sodium carbonate solution and extracted by $CHCl_3$ after 30 min. Usual treatment furnished, after preparative TLC ($CHCl_3$–MeOH, 90:10), a compound (8 mg, 54%) identical (R_f, IR, NMR, MS) with compound **22**.

Registry No. **3**, 38390-45-3; **11**, 60332-19-6; **13a**, 71425-87-1; **15**, 71411-43-3; **16**, 71486-23-2; **17**, 71434-97-4; **18**, 71486-22-1; **19**, 21631-00-5; **20**, 70420-76-7; **21**, 71434-96-3; **22**, 71434-95-2.

Scheme IV



The easy preparation of this new class of seco $C_{5'}$–$C_{6'}$ analogues of vinblastine prompted us to investigate nucleophiles other than cyanide ion and to check the behavior of other substrates related to anhydrovinblastine (3).

The reaction medium resulting from the modified Polonovski reaction on compound 11 was treated either with sodium cyanoborohydride in methanol, or with an excess of sodium borohydride in methanol, or with a mixture of water and tetrahydrofuran. From the common diimmonium salt intermediate 14, compounds 16, 17, and 18 were respectively isolated (Scheme III).

In the ^1H NMR spectrum of compound 16 ($M^{+\cdot}$ m/e 794), no AB system is detected but two methyl groups at 2.25 and 1.96 ppm, attributed respectively to an N_b-methyl and a skatole type methyl, are observed.

Compound 17 ($M^{+\cdot}$ m/e 824) shows in its ^1H NMR spectrum a signal at 2.38 ppm corresponding to a N_b-methyl and a signal at 3.10 ppm corresponding to an additional methoxyl.

Formation of compounds 16 and 17 could be easily rationalized if one takes into account the difference of pH of each reaction medium. Because the addition of methanol is reversible in an acidic medium,[13] the sodium cyanoborohydride reduction of 14 ultimately leads to compound 16. On the contrary, during reduction with excess sodium borohydride, the reaction medium is basic and compound 17 is stable. This compound was in turn transformed into compound 16 by simple treatment with sodium cyanoborohydride in acidic medium (Scheme II).

The structural analysis and the formation of the compound 18, 5′-noranhydrovinblastine, will be discussed in a forthcoming paper.

In the case of deoxy-VLB-B[1b,14] (20′-deoxyleurosidine, 19), having no double bond at C_{15}–$C_{20'}$, fragmentation of the tryptamine chain was the only reaction observed. Thus, deoxy-VLB-B N_b-oxide (20) treated by trifluoroacetic anhydride in dichloromethane and, after evaporation, with a solution of potassium cyanide in methanol gave rise to compound 21 (yield, 50%) (Scheme IV). Structural assignments were made in comparison with compounds 15 and 17.

If the Polonovski reaction medium is treated with a water–tetrahydrofuran mixture in the presence of sodium bicarbonate, compound 22 is isolated (yield, 80%) (Scheme IV). The compound 21 was also treated with silver tetrafluoroborate in tetrahydrofuran[15] and gave rise, after decyanation and loss of formaldehyde, to compound 22. This observation fits the structure attributed on the basis of spectral analysis.

The formation of compound 22, which we were unable to transform into 5′-nordeoxy-VLB-B (analogous to compound 18, Scheme III) showed that the behavior of anhydrovinblastine and deoxy-VLB-B derivatives is rather different.[16]

This fragmentation reaction was applied to other bis indole alkaloids[11] like leurosine (4) and vinblastine (6) and gave rise to a new class of analogues of vinblastine whose antitumor properties are currently under investigation.

Experimental Section

Melting points were taken on a Kofler apparatus, optical rotations measured ($CHCl_3$ solution, g/100 mL) on a Perkin-Elmer 141 MC, infrared spectra (ν 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 ppm) from Varian T 60 or IEF 240[17] and CAMECA 250-MHz spectrometers (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 AEI MS9 and MS 50. Preparative layer chromatography (preparative TLC) is performed with Kieselgel HF 254 (Merck).

Anhydrovinblastine N_b-Oxide (11). *m*-Chloroperbenzoic acid (86 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C to a stirred solution of anhydrovinblastine (3) (340 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) under argon. After 10 min, the reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 (3 mL), extracted by $CHCl_3$ (50 mL), and washed three times with brine (5 mL). After drying with sodium sulfate and filtration, the chloroform extract was evaporated under reduced pressure. Pure anhydrovinblastine N_b-oxide (11) was obtained (346 mg, 100%): UV 268, 289, 299, 310; MS m/e 822, 820, 808 ($M^{+\cdot}$), 806, 792, 733, 669, 631, 610, 282, 136, 135, 122, 121 (100%); NMR (240 MHz) 9.80 (s, 1 H, C_{16}–OH), 8.19 (s, 1 H, N_a–H), 7.70 (d, 1 H, J = 7.5, H aromatic indolic), 7.14 (m, 2 H, H aromatic), 6.43 (s, 1 H, C_9–H),

(13) Traces of trifluoroacetic acid and anhydride always remained after vacuum evaporation of the Polonovski's reaction medium.

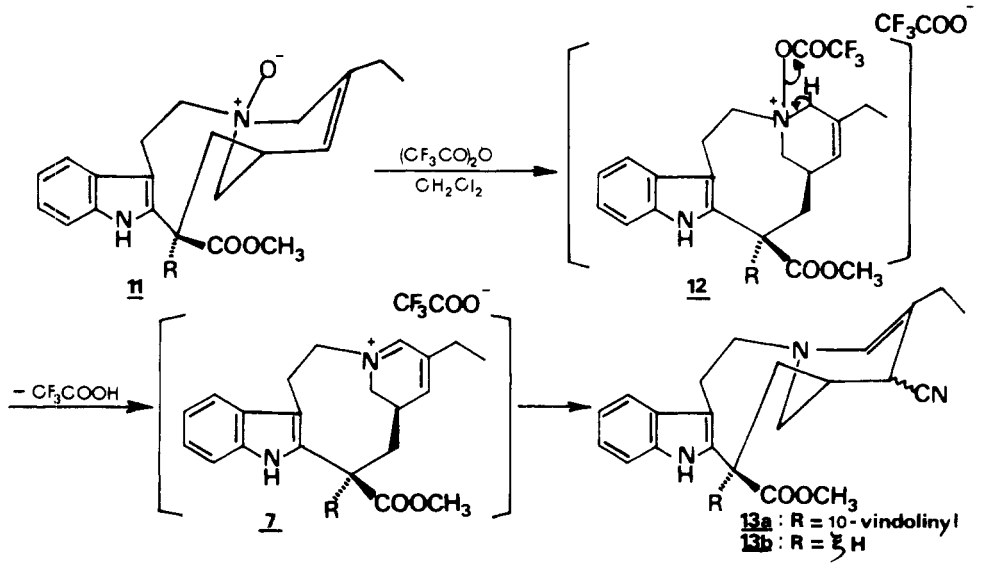
(14) N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Lett.*, 783 (1968).

(15) We thank Dr. R. T. Brown (University of Manchester) for experimental data concerning his paper: R. T. Brown and J. Leonard. *Tetrahedron Lett.*, 4251 (1978).

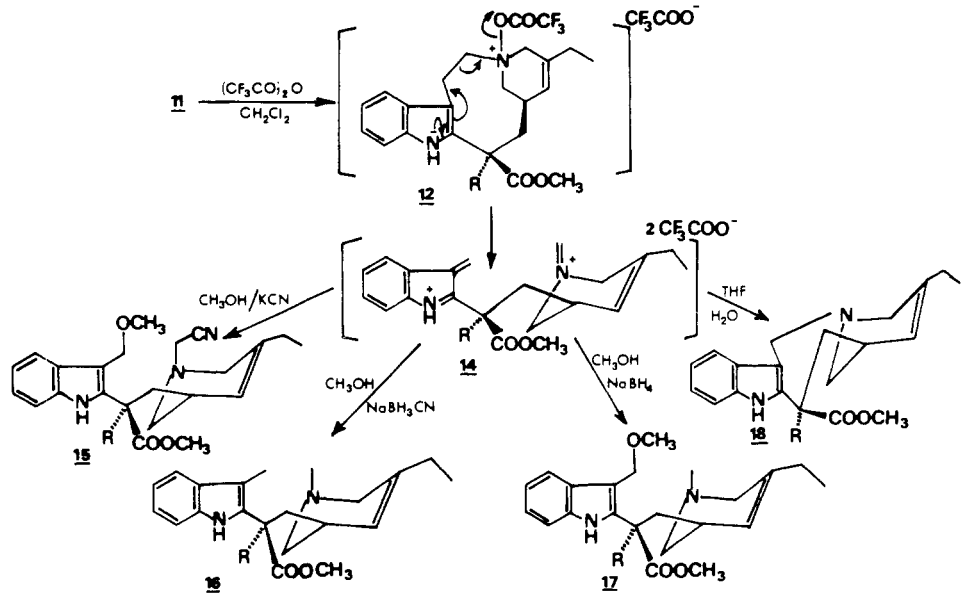
(16) Probably due to steric hindrance of ethyl side chain on $C_{20'}$. Further experiments are necessary to ascertain this point.

(17) S. Kan, P. Gonord, C. Duret, J. Salset, and C. Vibet, *Rev. Sci. Instrum.*, 44, 1725 (1973).

Scheme II



Scheme III



these reactions were unsuccessful.

The possibility of using cyanide ions (path b, Scheme I) was in turn investigated. The reaction medium obtained from the modified Polonovski reaction on anhydrovinblastine N_b-oxide (11) is treated after evaporation with a saturated methanolic solution of potassium cyanide.

The minor product (yield, 32%) shows an odd molecular weight: $M^+ \cdot$ m/e 817. A singlet of one proton appears in its ^1H NMR spectrum at 5.93 ppm. In the IR spectrum of this compound, a strong band appears at 1650 cm^{-1}, consistent with an enamine. Comparison of the spectral data of this compound with those of the cleavamine derivative **13b**[11] are in accordance with the structure **13a** for this compound (Scheme II).

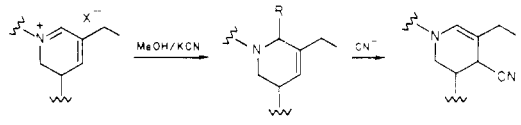
The mass spectrum of the major product (yield, 54%), isolated after chromatography, indicates the addition of a cyanide ion: $M^+ \cdot$ m/e 849. The ^1H NMR spectrum exhibits a broad singlet at 4.87 ppm, assigned to $C_{15'}$-H, with a strong chemical shift toward high field, in comparison with the same proton in anhydrovinblastine (3) (5.4 ppm). In addition, the ^1H NMR spectrum shows an AB system at 4.24 ppm (J = 12 Hz) and an additional signal corresponding to a methoxyl at 3.07 ppm. All of these observations and other spectral data can be reconciled with structure **15** for this compound[10] (Scheme III).

In contrast with the regioselectivity generally observed in the case of tetrahydropyridines,[2] the modified Polonovski reaction applied to anhydrovinblastine N_b-oxide (11) did not lead only to the conjugated immonium salt **7**, but mainly to a fragmentation reaction of the tryptamine side chain. On the other hand, attack of cyanide ion onto the conjugated immonium salt **7** did not lead to a 1,2-addition product (i.e., 21'-cyano derivative **9**) but rather to a 1,4-addition product (i.e., 15'-cyano derivative **13a**). The formation of this compound results most probably from a SN' substitution.[12]

(10) Position of methoxy and cyano groups was attributed in comparison with compounds **16** and **17** (see later).

(11) To be published.

(12) Other experiments on catharanthine showed that 1,2 addition was followed by SN' substitution by cyanide ions (to be published):



R = MeO or CN