Antitumour Alkaloids of the Vinblastine-type: is Leurosine an Artefact?

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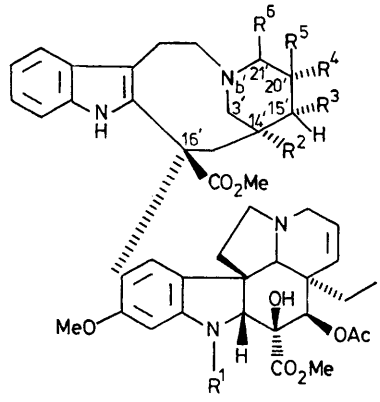
Summary The $\Delta^{15'(20')}$ double bond of anhydrovinblastine (**1**) is oxidized by various oxidants, in particular by air, to give the corresponding epoxide leurosine (**5**); the question of leurosine (**5**) being an artefact is discussed.

OUR discovery[1] of the first method for the synthesis of bis-indoles of the vinblastine group [*e.g.* anhydrovinblastine (**1**), formed by coupling between catharanthine (**9**) and vindoline (**10**)] has allowed the development of approaches[2–7] to the synthesis of the important antitumour

natural products: vinblastine (**2**), vincristine (**3**), leurosidine (**4**), leurosine (**5**), vincadioline (**6**),[8] and leurocolombine (**7**).[9]

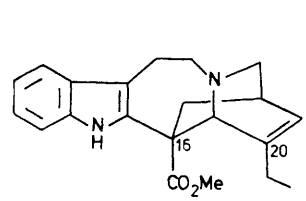
These compounds can result directly (pathway A) from appropriate modifications of the tetrahydropyridine ring of precursors such as (**1**) or (**8**);[2,4] in another pathway (B) vindoline (**10**) is coupled with catharanthine derivatives containing oxygen functionalities at C-15 and/or C-20.[3,4,6,7]



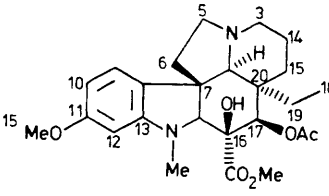
	R^1	R^2	R^3	R^4	R^5	R^6
(**1**)	Me	H	$\Delta^{15'(20')}$		Et	H
(**2**)	Me	H	H	Et	OH	H
(**3**)	CHO	H	H	Et	OH	H
(**4**)	Me	H	H	OH	Et	H
(**5**)	Me	H	–O–		Et	H
(**6**)	Me	H	OH	Et	OH	H
(**7**)	Me	OH	H	Et	OH	H
(**8**)	Me	H	H	Et	$\Delta^{20'(21')}$	

Using pathway (A) in the synthesis of leurosine (**5**) from (**1**), we have now observed that epoxidation can be achieved not only using peroxy-acids or hydroperoxides but also reagents such as lead tetra-acetate.†‡ Even these reagents may not be necessary; the epoxidation of (**1**) can be achieved using air oxygen and when anhydrovinblastine (**1**) is not stored under an inert atmosphere (nitrogen or argon), it is transformed directly into leurosine (**5**). This transformation is even faster when (**1**) is in solution in, *e.g.*, chloroform or acetone and in presence of adsorbants such as silica or alumina.‡ Yields (not optimized) are *ca.* 40% after 72 h at room temperature.[10]

We are studying this unusual reactivity of the $\Delta^{15'(20')}$ double bond of (**1**) in relation to the formation of other products. It could explain the absence of any anhydrovinblastine (**1**) isolated from the various species of *Catharanthus* examined so far; the ready conversion of (**1**) into (**5**) raises the question of whether or not leurosine (**5**) is an artefact. However, even if a significant part of the leurosine (**5**) isolated from various *Catharanthus* species is of natural origin, it is likely that some could well be formed by air oxidation during the extraction procedure.



(9)



(10)

The absence so far of the isolation from *Catharanthus* species of catharanthine derivatives bearing oxygen functions at C-15 or C-20 should be emphasized. It seems likely therefore that the biosynthesis of 'dimeric' indole alkaloids of the vinblastine group follows pathway (A) rather than (B) and that the oxidative modifications take place at the later stages in the biosynthesis.

We thank the Eli Lilly Laboratories for a sample of leurosine.

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† The indolic chromophore is not affected in this reaction; details will be reported elsewhere.

‡ The C-16′ epimer of (**1**) reacts similarly leading to the corresponding epoxide.

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[10] A small amount of catharine, one of the products of fragmentation of the tetrahydropyridine ring, is also formed; *cf.* R. Z. Andriamialisoa, N. Langlois, P. Potier, A. Chiaroni, and C. Riche, *Tetrahedron*, in the press.