Partial Synthesis of Vinblastine-type Alkaloids

By PIERRE POTIER*, NICOLE LANGLOIS, YVES LANGLOIS, and FRANÇOISE GUÉRITTE
(*Institut de Chimie des Substances Naturelles du C.N.R.S., 91190-Gif s/Yvette, France*)

Summary Application of a modification of Polonovski's reaction facilitates partial synthesis of vinblastine-type alkaloids.

SEVERAL antitumour alkaloids have been isolated from *Catharanthus roseus*,[1] two of them, vinblastin (**1**) and vincristine (**2**) being widely used clinically. Attempts[2–8] to synthesize these compounds have not yet been successful;† and although compounds possessing the 'non-natural' configuration at C(16')[3,5,8] have been obtained, they have shown no significant antitumour activity.

All attempts so far have consisted of coupling vindoline (**3**) with a *seco*-16,21-catharanthine derivative, *i.e.* 16-carbomethoxycleavamine (**4**), obtained by reductive cleavage of catharanthine (**5**). However, since in Nature vinblastine-type alkaloids could well be formed through a direct coupling of vindoline (**3**) with a suitable catharanthine (or 20-hydroxycatharanthine) derivative rather than with a *seco*-16,21 compound, we have now devised a new partial synthesis of these dimeric indole alkaloids having a 'natural' configuration at C(16').

TABLE 1

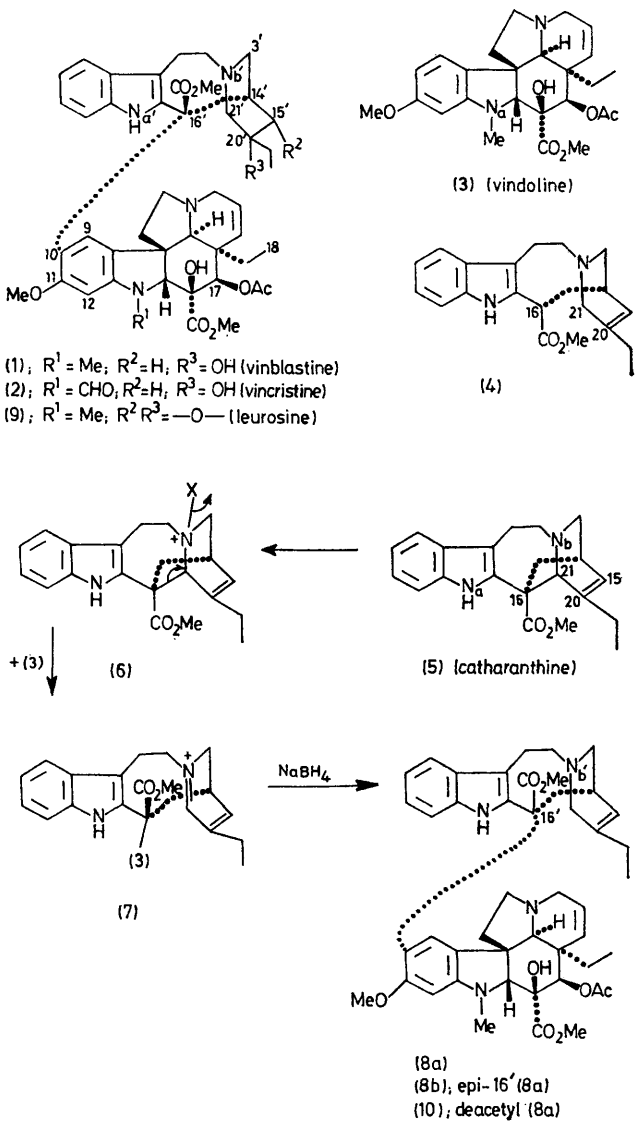
δ ($CDCl_3$)	(**1**)	(**8a**)	(**8b**)	(**9**)	(**10**)
C(12)-H	6·12	6·03	5·92	6·11	6·02
C(9)-H	6·62	6·52	6·85	6·59	6·50
C(18)-H	0·89	0·81	0·60	0·80	0·93

When a derivative of catharanthine such as (**6**), (where X is a convenient leaving group) reacts with vindoline (**3**) an intermediate immonium ion (**7**) is obtained, reduction of which leads to compound (**8**). [(**3**) + (**6**) → (**7**) → (**8**)]. For example, the N_b-oxide of catharanthine undergoes a fragmentation reaction when treated with trifluoroacetic anhydride[9] to give (**6**, X = $OCOCF_3$), and when this reaction is carried out with vindoline (**3**) *in situ*, two dimeric indole alkaloids are obtained after reduction with $NaBH_4$, (**8a**) (30—40%), m.p. 216—218° (decomp.), $[\alpha]_D$ + 19°, ($CHCl_3$) and (**8b**), hydrobromide m.p. >260° (decomp.); $[\alpha]_D$ − 86°, ($CHCl_3$). The yields and relative proportions of these two compounds depend upon experimental conditions; this, and inspection of molecular models

TABLE 2

c.d.(EtOH)	(**1**)	(**8a**)	(**8b**)	(**10**)
λ/nm	254	258	258	260
Δ ε	+10·5	+13·3	−13·2	+12·0
λ/nm			280	
Δ ε			+3·2	
λ/nm	302	305	309	304
Δ ε	+4·8	+6·4	+8·0	+4·8

suggest that they are formed by two different mechanisms, either concerted or non-concerted; spectral data are in full agreement with the planar structure (**8**), the nature of the junction between the two monomeric units being established by ^1H n.m.r. spectra[10] [absence of a signal between 4 and 5 p.p.m. eliminates the possibility of a substitution of one of the carbon atoms α to N_b of catharanthine (**5**) by vindoline (**3**)]. Moreover, C(12)-H and C(9)-H appear as singlets in (**8a**) or (**8b**) suggesting that vindoline is itself substituted on C(10). Comparison of δ values of C(9)-H, C(12)-H, and C(18)-H of (**8a**) and (**8b**) with those of the corresponding protons in vinblastine (**1**) and leurosine (**9**) (Table 1) indicates the similarity between these two natural compounds and (**8a**).[5]



A corresponding similarity is noted between (**8a**) [but not (**8b**)] and vinblastine when the circular dichroism curves are compared (Table 2); this simple spectroscopic method is

† Recently, Prof. J. P. Kutney, University of British Columbia, Vancouver, has kindly informed us of a successful approach to this problem.

of high diagnostic value and its use in this area does not seem to have been previously reported.

Reaction of vindoline (**3**) with the chloroindolenine of (**4**)[6] leads to a dimeric compound having a 'non-natural' configuration at C(16′), identical in all respects, with (**8b**); no trace of (**8a**) is obtained under these conditions.

A chemical correlation has also been carried out. Vinblastine (**1**) treated with H_2SO_4 at 0° undergoes a dehydration ($\Delta^{15'(20')}$) and deacetylation reaction [on -O-C(17)] leading to compound (**10**) identical with the deacetylation product [on -O-C(17)] of (**8a**). This fully confirms the 'natural' 16′ configuration of our synthetic material.

The same reaction scheme has been successfully applied to the partial syntheses of other dimeric indole alkaloids. Dihydro-15,20*S*-catharanthine, coronaridine,[11] allocatharanthine and dihydro-15,20-allocatharanthine,[12] have been coupled with dihydro-indoles such as vindoline or its derivatives and dihydro-2,16 methoxy-11 tabersonine and its N_a-methyl derivative.

We thank the Ligue Nationale Française contre le Cancer for a grant to F.G.; Dr. P. Bladon for high resolution mass spectrometry; Dr. S. K. Kan and his co-workers and M. Z. Andriamialisoa for 240 MHz n.m.r. spectrometry; and Rhône-Poulenc S.A. and Eli-Lilly Laboratories for comparison samples.

(*Received*, 11*th June* 1975; *Com.* 664.)

[1] R. L. Noble, *Lloydia*, 1964, **27**, 280.
[2] M. Gorman and E. C. Kornfeld, Fr. P. 1.435519, 1966; G. Büchi and R. E. Manning, *J. Amer. Chem. Soc.*, 1966, **88**, 2532; J. Harley-Mason and A. U. Rahman, *Chem. Comm.*, 1967, 1048.
[3] N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Letters*, 1968, 783.
[4] J. P. Kutney, J. Beck, F. Bylsma, and W. J. Cretney, *J. Amer. Chem. Soc.*, 1968, **90**, 4504.
[5] F. Bylsma, Ph.D. Thesis, Vancouver, 1970.
[6] A. U. Rahman, *Pakistan J. Sci. Ind. Res.*, 1971, **14** (6), 487.
[7] P. Rasoanaivo, 'Thèse de Doctorat de 3ème Cycle,' Orsay, 1973.
[8] J. P. Kutney, personal communication.
[9] A. Ahond, Ad. Cavé, C. Kan-Fan, H. P. Husson, J. de Rostolan and P. Potier, *J. Amer. Chem. Soc.*, 1968, **90**, 5622; A. Ahond, Ad. Cavé, C. Kan-Fan, Y. Langlois and P. Potier, *Chem. Comm.*, 1970, 517.
[10] M. D. Sauzade and S. K. Kan, *Adv. electronics and electron physics*, 1973, **34**, 1; S. K. Kan, P. Gonord, C. Duret, J. Salset, and C. Vibet, *Rev. Sci. Instr.*, 1973, **44**, 1725.
[11] I. Blaha, Z. Koblicova, and J. Trojanek, *Coll. Czech. Chem. Comm.*, 1974, **39**, 2258.
[12] M. Muquet, N. Kunesch, and J. Poisson, *Tetrahedron*, 1972, **28**, 1363.
[13] C. Kan-Fan, B. C. Das, P. Potier, J. Le Men and P. Boiteau, *Ann. pharm. fran.*, 1968, **26**, 577.