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SYNTHESIS OF ANHYDROVINBLASTINE FROM LEUROSINE

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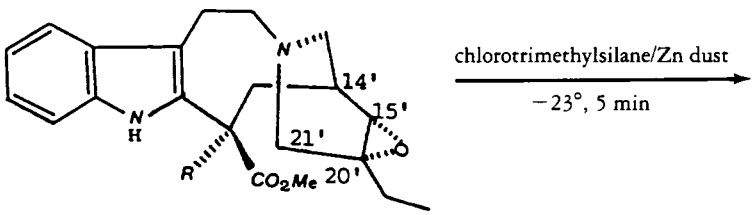
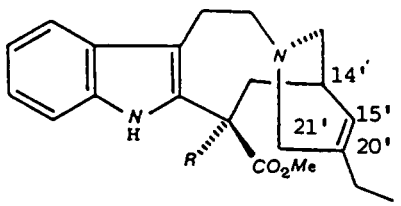
Vinblastine and vincristine are among the most powerful antitumor agents available in medicine for the treatment of a variety of cancers. However, because they could be isolated only in low yields from the leaves of *Catharanthus roseus*, it has been a challenging goal to develop synthetic and semisynthetic approaches to these important molecules. In spite of intensive past efforts by a number of groups, the synthetic approaches developed to these drugs have not been commercialized.

Our earlier efforts as well as those of others in the field have led to the synthesis of dihydrocleavamines (1,2), 16-carbomethoxydihydrocleavamines (3,4), 16-*epi*-anhydrovinblastine (5), and vinblastine (6). Our synthesis of vinblastine was based on a coupling of catharanthine with vindoline by a procedure reported by Potier and co-workers (7,8) and Kutney *et al.* (9), and it resulted in the formation of anhydrovinblastine which was subsequently transformed to vinblastine (10). As a result of our more recent efforts to enhance the isolated yields of vinblastine, we have succeeded in achieving a thirtyfold to sixtyfold increase of yields by an improved isolation procedure (60–120 g/ton, as opposed to the literature yields of 2 g/ton). These pilot plant studies placed in our hands large quantities of the binary alkaloid, leurosine [**1**], which occurs in eightfold to tenfold higher yields than vinblastine in the leaves. We have, therefore, explored various reactions for its conversion to vinblastine. We report here a one-step procedure for the quantitative conversion of leurosine to anhydrovinblastine [**2**]. As anhydrovinblastine has previously been converted by us (6) and Mangeney *et al.* (10) into vinblastine, this constitutes an alternative formal synthetic route to vinblastine.

The procedure (11) involves treatment of leurosine with chlorotrimethylsilane/Zn dust in dry CH_2Cl_2 at $-23°$ for 5 min. The product anhydrovinblastine could be isolated in over 95% yield and was identified by spectroscopic and chromatographic comparison with an authentic sample. Care has to be taken during the isolation process to exclude oxygen during workup, as otherwise a



1 R = 10-vindolinyl



2 R = 10-vindolinyl

facile conversion of anhydrovinblastine to leurosine was observed (12). A mechanism for this reaction has been proposed by other workers (13,14).

EXPERIMENTAL

To a magnetically stirred suspension of activated Zn dust (16.2 mg) in dry CH_2Cl_2 (0.5 ml) containing chlorotrimethylsilane (0.039 ml, 0.308 mmol) at −23° was slowly added a solution of leurosine [**1**] (100 mg, 0.123 mmol) in 0.3 ml dry CH_2Cl_2 at −23°. The reaction mixture was stirred for 5 min and filtered quickly under N_2 and the residue washed with dry CH_2Cl_2 (5 ml). The solution was evaporated on a rotary evaporator (flushed with N_2) to dryness. This afforded anhydrovinblastine [**2**] in 91% yield. The structure of the product was confirmed by direct chromatographic and spectroscopic comparison with an authentic sample.

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