Electrochemical Synthesis of Anhydrovinblastine

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Electrochemical oxidation of catharanthine in the presence of vindoline performed in MeCN–Et_4NClO_4 at controlled potential yields (16′*S*) and (16′*R*)-anhydrovinblastine (52 and 12%, respectively).

The vinblastine-type alkaloids, in particular vinblastine and vincrystine are currently widely used in chemotherapy. The low concentration of these compounds in the plant material, however, had led to studies on various methods for their syntheses.[1,2] In comparison with vinblastine and vincristine, the *Catharanthus roseus* alkaloids catharanthine and vindoline which are obvious structural units of the dimeric skeleton of the former two, are more easily available so that all the practical synthetic approaches utilize them as starting material for the preparation of the key intermediate anhydrovinblastine.

From most of the published synthetic studies of both vinblastine and vincristine, it can be concluded that two steps are crucial: (*a*) preparation of a suitable intermediate by C(16)–C(21) bond scission in catharanthine, and (*b*) coupling of the catharanthine fragmented intermediate and vinblastine. Although recently published methods[3–6] represent a substantial improvement for the synthesis of the vinblastine bimolecular skeleton, we have examined an alternative, practically one-pot procedure, based on our earlier experience with anodic oxidation transformations of structurally related compounds and model systems. According to our concept, this process presumably involves the following reactions: (*a*) one-electron oxidation of catharanthine and subsequent rearrangement of the intermediate radical cation ($\mathbf{I}_1$) which is further oxidized to the dication ($\mathbf{I}_2$), and (*b*) coupling of the dication ($\mathbf{I}_2$) and vindoline, followed by reduction of the cation **3** to yield the desired anhydrovinblastine.

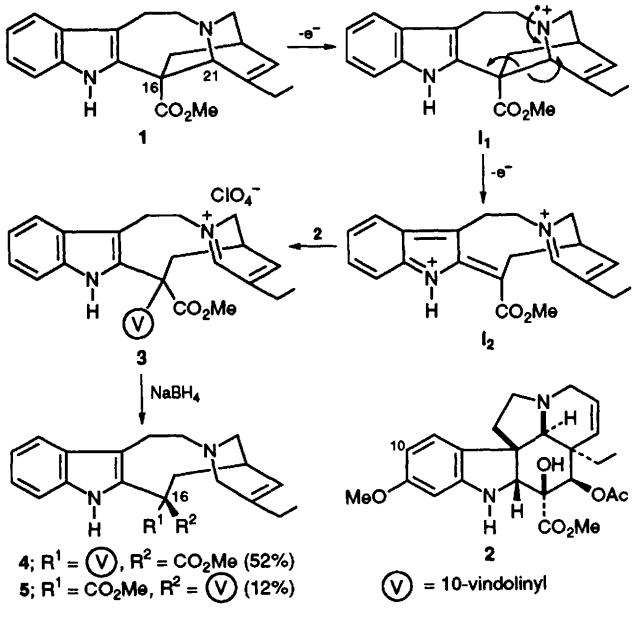
The efficacy of the designed process requires the oxidation of catharanthine **1** to be carried out in presence vindoline **2**; the feasibility of such a scheme depends on the difference between their anodic peak potentials. The experimental limitations, however, imply that this difference must be greater than 120 mV.

In order to establish satisfactory conditions for a controlled potential electrolysis of catharanthine **1**, *i.e.* for C(16)–C(21) bond scission at a potential not affecting **2**, extensive studies by cyclic voltammetry were carried out. It was found that in a non-nucleophile solvent like MeCN, the peak potential difference between **1** and **2** could be optimized at 0.2 V *vs.* standard calomel electrode (SCE) in the presence of 2,6-lutidine (Fig. 1).

As depicted in Scheme 1, controlled potential electrolysis takes place in consecutive steps, allowing the intermediate ($\mathbf{I}_2$) to couple with **2** at C(10). The final step, $NaBH_4$ reduction, is carried out without isolation of **3**, yielding anhydrovinblastine **4** as mixture of natural (16′*S*)- and (16′*R*)-enantiomers in a 4.5:1 ratio. By preparative TLC of the crude reaction mixture, the two enantiomers could be easily separated.

In a typical experiment,[7] **1** (0.137 mmol) and **2** (0.137 mmol) were dissolved in MeCN–0.1 mol l^{-1} Et_4NClO_4 (50 ml) and 2,6-lutidine was added (0.548 mmol). The anodic potential (Pt gauze, 2 × 9 cm) was maintained at 0.6 V *vs.* SCE and the electrolysis continued until 2.2 F mol^{-1} had been transferred. The solution was evaporated to dryness, methanol (10 ml) was added and the precipitated electrolyte filtered off. The obtained clear solution was concentrated to one third of the original volume, $NaBH_4$ (15 mg) was added and, after 30 min, the mixture was diluted with water. Upon drying in air, the crystalline precipitate (105 mg) was purified by preparative TLC (Kieselgel HF 254; EtOAc–MeOH, 9:1) to afford 60 mg of (16′*S*)-anhydrovinblastine (52%), m.p. 207–209 °C, and 14 mg of the (16*R*-enantiomer, 12%), m.p. > 260 °C (lit. m.p.s 208–210 and >260 °C respectively[8]), together with 4.5 mg of unreacted **2**. Spectroscopic data (UV, IR, NMR) are identical with those of authentic samples.

Experiments in nucleophilic solvents yielding different intermediates, also useful for the preparation of vinblastine, are currently underway.



Scheme 1

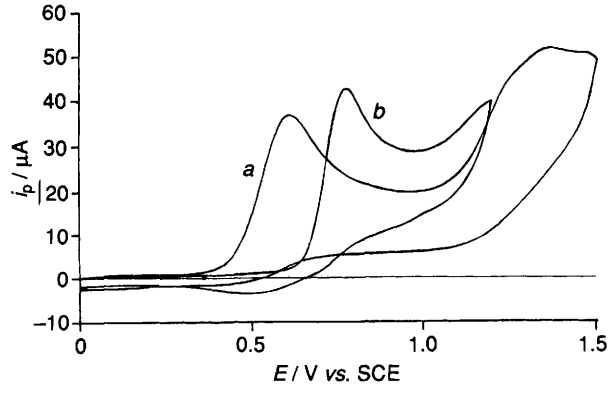


Fig. 1 Cyclic voltammogram of 1 mmol l^{-1} solutions of catharanthine (*a*) and vindoline (*b*) at glassy carbon electrode (A = 0.071 cm^2) in 0.1 mmol l^{-1} Et_4NClO_4–MeCN plus 2,6-lutidine (4 mmol l^{-1}); scan rate 0.1 V s^{-1}

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The authors thank Professor James P. Kutney (The University of British Columbia) for stimulating discussions.

Received, 24th February 1993; Com. 3/01113E

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