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One Pot Electrochemical Synthesis of 10,10'-Bisvindoline by an Oxidation-Reduction Sequence

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Abstract: Anodic oxidation of vindoline, **1**, at the controlled potential of Pt-electrode (E=1.1 V vs. SCE) followed by the reduction (E=0.0 V vs. SCE) of the formed intermediate **2a** gave 10,10'-bisvindoline, **2**, in 60% yield.

Aspidosperma alkaloid vindoline, **1**, is with catharanthine the direct precursor of the antitumor alkaloids of *Catharanthus roseus* like vinblastine and vincristine.[1] Vindoline has served as a useful model compound for elaborating biochemical mechanisms by which nitrogen heterocycles are converted into other molecules.[2] The investigation of the vindoline oxidation with the bacterium *Sterptomices griseus* [3] and chemical oxidizing agents [4] revaeled that the N-4 position is susceptible to oxidation resulting in the formation of the 3',14-dimeric product.[5]

This paper reports the efficient synthesis of 10,10'-bisvindoline, **2**, from vindoline, **1**, using the particular advantage of electrochemical methodology in the control of the electrode potential. The functionalization of vindoline at position 10 is of potential interest due to fact that vindoline is coupled with catharanthine by the electrochemical oxidation to yield anhydrovinblastine.[6] The abilty to functionalize vindoline at position 10 may open up an alternative route to anhydrovinblastine. It is also possible that 10,10'-bisvindoline, **2**, is one of the natural alkaloids of *Catharnthus roseus* which has not been identified. Cyclic voltammetry of vindoline, **1**, exhibits two anodic waves at 0.83 and 1.03 V (Fig.1a). The first peak corresponds to the oxidation of the amine moiety at position N-4, and the second peak presumably to the oxidation of the indoline moiety in **1**. Notably, the results of the chemical oxidations of vindoline suggest that the oxidation is initiated at the tertiary amine moiety. By adding TFA, the oxidation of the amine moiety was prevented and second wave increased (Fig.1b). Sweep reversal from the anodic to the cathodic side caused the appearance of the reduction peak at 0.58 V corresponding to the reduction of the dication **2a** to **2**, which is then oxidized in the repeated anodic sweep at 0.72 V (Fig.1c).

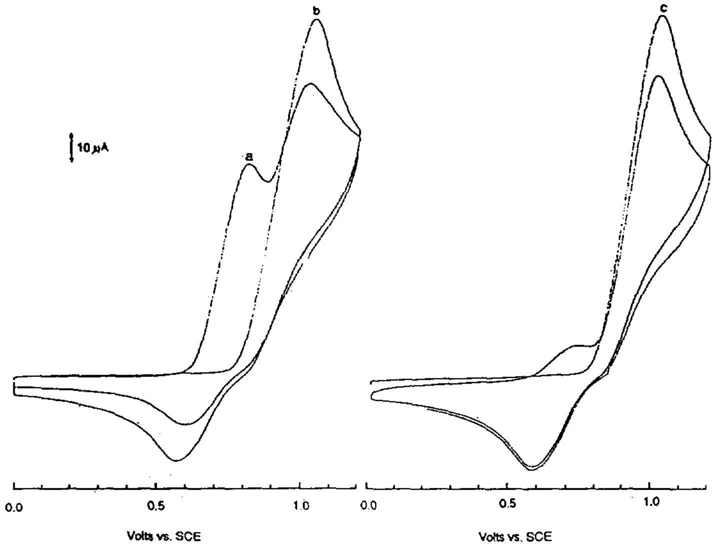
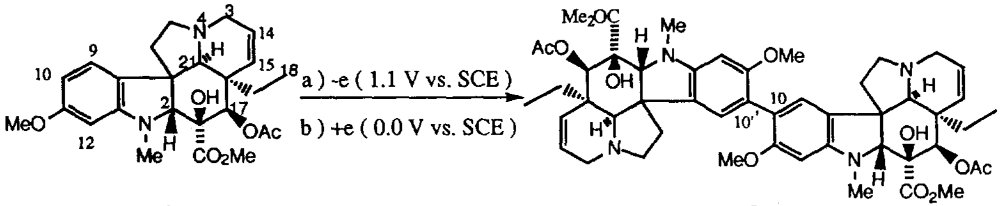


Fig.1. Cyclic voltammogram of **1** in CH_3CN-0.1 M $LiClO_4$ at GCE; v=100 mV/s
a) **1** (4 mM), b) **1** plus TFA (1 equiv.), c) same as (b)

The synthesis of 10,10'-bisvindoline, **2**, was performed in divided cell in CH_3CN-0.1 M $LiClO_4$ with the addition of TFA in the anodic compartment by using Pt-anode (3x5 cm) and graphite cathode.[7] The controlled potential anodic oxidation at 1.1 V (2F/mol) followed by the controlled potential cathodic reduction at 0.0 V (1F/mol) resulted in the formation of **2** which was isolated in 60% yield as a major product together with two minor products whose structure has not been yet identified.

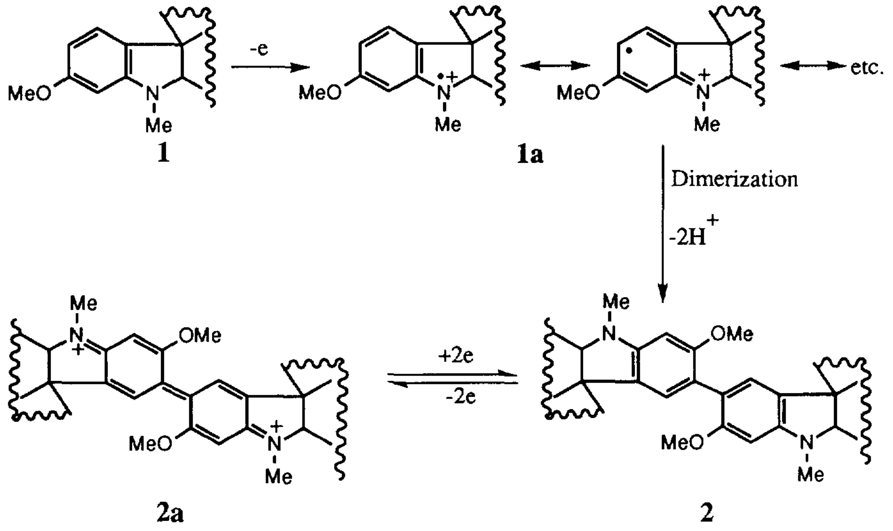


1 **2**

The structure of **2** was supported by UV, IR, NMR, and mass spectral analysis. High resolution EIMS showed a strong $M^{\cdot+}$ at m/z 910.4357 corresponding to the formula $C_{50}H_{62}N_4O_{12}$ (Calcd. 910.4364). Most proton signals in the ^{1}H NMR spectrum of **2** were directly comparable to those of vindoline, **1**.[8]

However, aromatic proton signals at 6.25 ppm for H-10 in **1** were absent in the spectrum of **2** indicating the position of the coupling. The product **2** showed two singlets in the aromatic region at 6.79 (H-9 and H-9') and 6.14 (H-12 and H-12') ppm, respectively.

The oxidation-reduction process can be explained according to the following Scheme. Vindoline, **1**, is oxidized to radical cation **1a** which dimerized to **2**. Since the oxidation potential of **2** is lower than the applied potential (E=1.1 V) , 10,10'-bisvindoline, **2**, is further oxidized to the intrmediate dication **2a**. The brown solution of **2a** is reduced to the olive colored solution of **2** by adjusting the reduction potential to 0.0V.



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7. In a typical procedure, vindoline (56 mg) and TFA (10 μL) are disolved in 30 mL of CH_3CN-0.1 M $LiClO_4$ anolyte solution. The anodic potential was maintained at 1.1 V vs. SCE and electrolysis was discontinued until 2F/mol were passed. The potential was then adjusted at 0.0 V vs. SCE and the reduction was carried out until 1F/mol was passed. After evaporation the resulting residue was suspended in 5% $NaHCO_3$ solution and extracted with EtOAc. The combined organic phases were dried and evaporated. Colomn chromatography (silica gel, EtOAc/ MeOH, 3:1) gave the major product **2**, which was further purified by preparative TLC afording 30 mg of **2** (60% yield): mp 191° C, dec.; R_f 0.52 (EtOAc/MeOH); UV (log ε) 223 (4.33), 276 (4.05), 319 (4.02); IR (KBr) 2961, 2929, 2874, 2860, 1737, 1616, 1436, 1384, 1266, 1189, 1135, 1171, 1135, 1121, 1097, 1076, 801 cm^{-1}; EIMS (relative intensity) 910 (20), 850 (4), 750 (5), 643 (7), 577 (9), 523 (14), 368 (100), 313 (50), 239 (55), 236 (62), 211 (25), 135 (47), 95 (66), 83 (77); 500 MHz ^{1}H NMR ($CDCl_3$) 6.79 (s, 2H, H-9 and H-9'), 6.14 (s, 2H, H-12 and H-12'), 5.85 (ddd, J=10, 3.5, 1.5 Hz, 2H, H-14 and H-14'), 5.50 (s, 2H, H-17 and H-17'), 5.25 (d, J=10 Hz, 2H, H-15 and H-15'), 3.78 (s, 6H, 2xCH_3O), 3.75 (s, 2H, H-2 and H-2'), 3.72 (s, 6H, 2xCH_3O), 2.76 (s, 6H, 2xCH_3-N), 2.65 (s, 2H, H-21 and H-21'), 2.19 (s, 6H, 2xCH_3CO), 0.51 (t, J=7 Hz, 6H, H-18 and H-18') ppm.
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