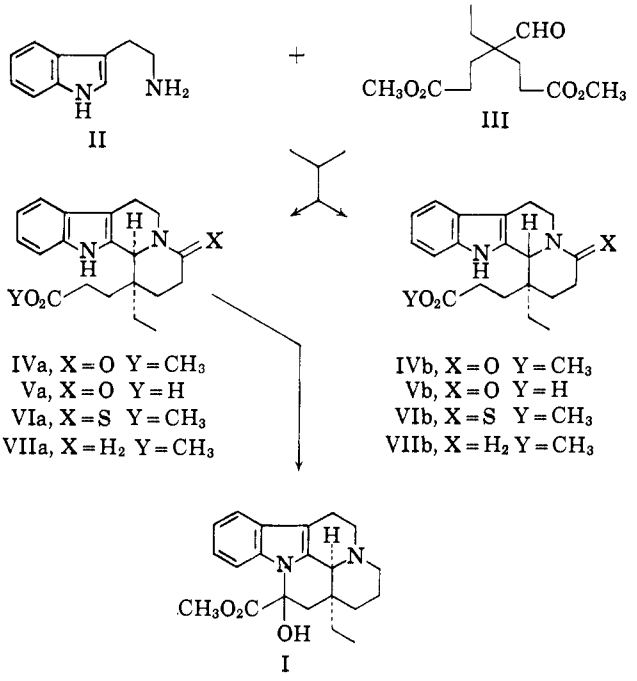
The Total Synthesis of Vincamine

Sir:

Vincamine, the antihypertensive and sedative[1] major alkaloid of *Vinca minor* L. (Apocyanaceae) was first isolated and characterized by Schlittler.[2] Recent degradative experiments[3-8] have established structure I for this compound, with the stereochemistry of the D–E ring junction related to the previously synthesized alkaloid eburnamonine.[9,10] The synthesis of vincamine has now been accomplished starting from tryptamine (II), which was condensed with dimethyl 3-ethyl-3-formylpimelate (III), b.p. 108–109° (0.03 mm.). *Anal.* Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.88; H, 8.20. The latter was readily obtained by exhaustive alkylation of the pyrrolidine enamine of butyraldehyde[11] with methyl acrylate, followed by hydrolysis (45% yield).



The key intermediate lactam ester IVa and its epimer IVb were isolated as a crystalline mixture (53% yield), m.p. 160–182°. *Anal.* Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.17; H, 7.39; N, 7.90. Found: C, 70.89; H, 7.46; N, 7.59. This was accompanied by a mixture of crystalline lactam acids Va and Vb (37% yield), m.p. 226–240°. *Anal.* Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.56; H, 7.12; N, 8.16. Hydrolysis of the lactam esters IVa and IVb with aqueous sodium bicarbonate furnished the lactam acids Va and Vb (quantitative yield), which could be converted back to the methyl esters with diazomethane (quantitative yield). Reaction of the mixture of epimeric lactam esters IVa and IVb with phosphorus pentasulfide gave the individual epimeric thiolactam esters VIa (29% yield), m.p. 163–164°, and VIb (29% yield), m.p. 144–145°, which were readily separated by column chromatography on neutral alumina. *Anal.* Calcd. for $C_{21}H_{26}N_2O_2S$ (VIa): C, 68.07; H, 7.07; N, 7.56; S, 8.66. Found: C, 67.84; H, 6.95; N, 7.38; S, 8.94. *Anal.* Calcd. for $C_{21}H_{26}N_2O_2S$ (VIb): C, 68.07; H, 7.07; N, 7.56; S, 8.66. Found: C, 68.05; H, 7.09; N, 7.42; S, 8.77. Desulfurization of the thiolactams with Raney nickel furnished the amino esters VIIa (54% yield), m.p. 149–150°, and VIIb (54% yield), m.p. 144–145°. *Anal.* Calcd. for $C_{21}H_{28}N_2O_2$ (VIIa): C, 74.09; H, 8.29. Found: C, 74.13; H, 8.32. *Anal.* Calcd. for $C_{21}H_{28}N_2O_2$ (VIIb): C, 74.09; H, 8.29. Found: C, 74.20; H, 8.40.

Alternatively, the epimeric mixture of thiolactams could be converted to a mixture of amino esters and this then separated by column chromatography on neutral alumina. By either route one obtained the epimeric compounds in equal amounts. Mercuric acetate oxidation of either amino ester VIIa or VIIb to a didehydro immonium salt with ultraviolet absorption at 250 and 359 mμ and reduction of the immonium salt with sodium borohydride gave a mixture of amino esters VIIa and VIIb. Thus a path is provided for complete conversion of intermediates to either of the epimeric series.

Oxidation of the more rapidly eluted amino ester VIIa with *p*-nitrosodimethylaniline and triphenylmethylsodium, followed by carefully controlled acid treatment, furnished *dl*-vincamine (I, 3% yield), which was identified by comparison with an authentic sample of natural vincamine by exact matching of t.l.c. retention times in multiple adsorption and solvent systems and by infrared solution spectra.

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Studies on the Azidoazomethine–Tetrazole Equilibrium[1]

Sir:

Treatment of 5-aminotetrazole with acetylacetone[2a] and reaction of 4,6-dimethyl-2-hydrazinopyrimidine with nitrous acid[2b,c] have been reported to give the same product, 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine (IA).[3]

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