Tetrahedron Letters,Vol.24,No.24,pp 2497-2500,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS AND ABSOLUTE STEREOCHEMISTRY OF (-)-VINCATINE

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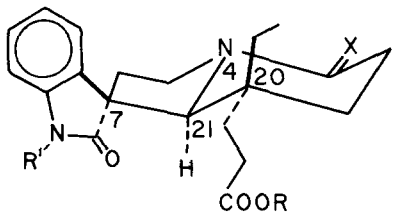
Abstract : The alkaloid (-)-vincatine (I) has been synthesised by resolution of the intermediate acid III and its absolute stereochemistry suggested from CD data.

The alkaloid vincatine (I)[1], isolated from Vinca minor is the only indole alkaloid so far reported, to possess the 2,16-seco-Aspidosperma skeleton. The relative stereochemistry of the racemic alkaloid has been recently established by syntheses of all the four possible stereoisomers[2]. Herein we report the synthesis of (-)-vincatine and determination of its absolute stereochemistry from the CD data.

Alkaline hydrolysis of the ester (±)-II[3], the starting material for our synthesis of (±)-vincatine, yielded the acid (±)-III[4], m.p. 268°, the optical resolution of which could be efficiently done by crystallisation of the brucine salt to yield first the salt of (+)-III, m.p. 258-60° (from alcohol), $[\alpha]_D$-16.7° (c 1.1, MeOH) and then the salt of (-)-III, m.p. 168-70°(from benzene), $[\alpha]_D$-18.6° (c 1.0, MeOH). Regeneration of the acids followed by crystallisation yielded the enantiomerically pure (+)-III and (-)-III in 39% and 36% yields respectively from (±)-III. Diazomethane treatment of the acids yielded the corresponding methyl esters (+)-II and (-)-II.

The synthetic route to (-)-vincatine (I) from (-)-II was parallel to that used for the racemic base[2]. Methylation (MeI/NaH/DMF) of (-)-II yielded (-)-IV as a glass, which was converted (P_4S_{10}, pyridine, reflux) to the



I R = R' = Me, X = H_2

II R = Me, R' = H, X = O

III R = R' = H, X = O

IV R = R' = Me, X = O

V R = R' = Me, X = S

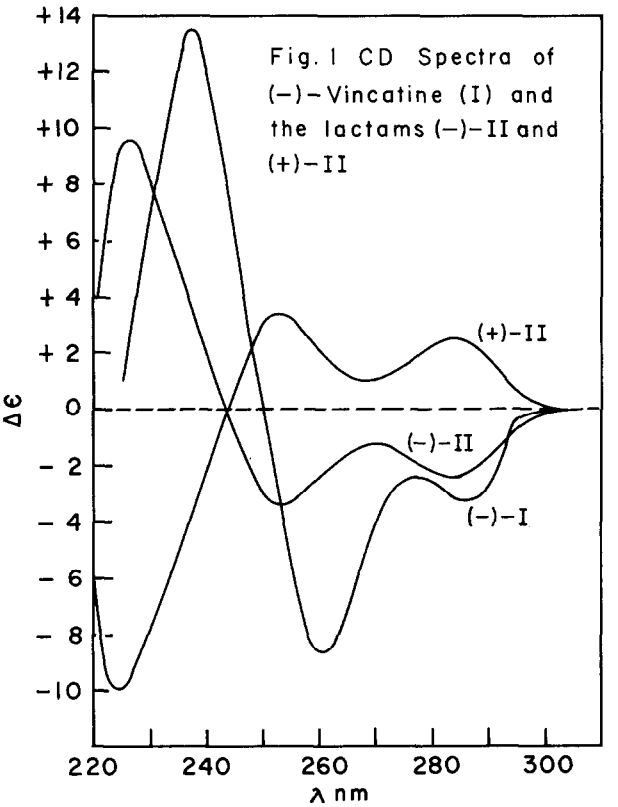


Table 1. Selected physical data of (−)-vincatine and the intermediate lactams

Compound	m.p. (°C)	$[\alpha]_D$ (in MeOH)	CD (in MeOH) : λ nm (Δε)
(−)-I*	110-12	−11.7° (c 0.8)	287(−3.22), 260(−8.51), 238(+13.60)
(−)-II	186-88	−13.9° (c 1.3)	284(−2.52), 252(−3.43), 227(+ 9.61)
(+)-II	184-86	+12.0° (c 1.2)	284(+2.50), 252(+3.43), 225(−10.02)
(−)-III	246-48	−23.9° (c 1.2)	286(−2.23), 254(−2.84), 228(+ 8.34)
(+)-III	246-48	+23.3° (c 1.2)	285(+2.21), 253(+2.87), 226(− 8.86)
(−)-IV	Amorph.	−28.5° (c 0.9)	287(−2.62), 257(−5.41), 228(+13.27)
(−)-V	170-72	−176.7° (c 1.0)	345(−0.42), 286 sh (−7.94), 266(−19.64), 226 (+18.39)

* CD in THF, $[\alpha]_D$ in chloroform. Lit.[1] m.p. 110-12°, $[\alpha]_D$ −13.5° (solvent and conc. not specified). The isomerisation[2] of vincatine in MeOH solution was found to be too fast for recording the optical properties in this solvent.

thiolactam (-)-V. Raney nickel desulphurisation of (-)-V in THF under carefully controlled conditions yielded (-)-vincatine as well crystalline needles (from hexane-ether). An authentic sample of natural vincatine was not available for comparison but the identity of the synthetic sample was established by comparison of the IR, UV and NMR spectra with those of (±)-vincatine[5].

The CD spectra of (-)-I, (-)-II, (-)-III and (-)-IV were similar with three Cotton effects in the 220-300 nm region (Fig. 1 and Table 1)[6] and as expected the spectra of the enantiomers were virtually mirror images. The CD spectrum of (-)-V, however, was qualitatively different due to the strong negative Cotton effect of the thiolactam chromophore at 268 nm. A comparison of the CD data of vincatine with those of known oxindoles[7-10] indicated that the absolute stereochemistry of (-)-vincatine at N-4, C-7 and C-21 correspond to those of isoformosanine, isomitraphylline and isocarapanaubine. We, therefore, suggest that structure I with 4R, 7S, 20R, 21S configuration is the complete representation of (-)-vincatine. The C-20 stereochemistry of (-)-vincatine would then correspond to that of (+)-vincadiffornine[11,12] from which probably it is biogenetically derived.

Acknowledgement : The authors thank Drs. A.K. Chakravarty, N.P. Sahu, B.C. Pal and Mr. P.P. Ghosh Dastidar for the NMR and CD spectra and the Director, Indian Institute of Chemical Biology and CSIR, New Delhi for Research Fellowships to S.R. and P.K.C.

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4. All compounds described here were fully characterised from analytical/ spectral data and in case of optically active compounds by comparison with the corresponding racemic compound.

5. There was an inadvertant mistake in the ^{13}C chemical shifts of C-3 and C-5 of vincatine reported in our earlier publication (Ref. 2, Table 2). The correct values are : δ 53.8(C-3) and 55.2(C-5).

6. Another Cotton effect around 200 nm could not be accurately measured due to instrumental difficulties.

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(Received in UK 21 March 1983)