SYNTHESIS AND STEREOCHEMISTRY OF (±)-VINCATINE

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Abstract - The structure and relative stereochemistry of vincatine, an alkaloid isolated from Vinca minor, have been established as 4B by synthesis of all the four possible stereoisomers of (±)-vincatine. ^{13}C-Nmr spectra of the alkaloid and its synthetic intermediates are discussed.

In the preceding communication[1] we have reported the synthesis of the stereoisomeric tetracyclic lactams 1A-1D, by condensation of 2-hydroxytryptamine with dimethyl 4-ethyl-4-formylpimelate. It has also been observed that although the δ-lactam functions of 1A-1D or their N-methyl derivatives, 2A-2D could be selectively reduced by treatment with phosphorus oxychloride followed by sodium borohydride, the resulting amines underwent stereochemical equilibration. Herein, we report the reduction of 2A-2D by an alternative method which permitted the synthesis of (±)-vincatine[2] without isomerisation. The ^{13}C-nmr data used for the assignment of the stereochemistry of all the isomers are also discussed.

Thiolation of the lactams 2A-2D with P_2S_5 in refluxing pyridine (8 h) yielded the corresponding thiolactams 3A (mp 138-140°C), 3B (mp 146-148°C), 3C (mp 206-208°C) and 3D (mp 218-220°C) in excellent yields[3]. The compounds 3A-3D could be smoothly desulphurised with Raney Ni, but the resulting amines were found to undergo very facile stereochemical equilibration. Stirring of a solution of lactam 3A or 3B in tetrahydrofuran in the presence of Raney Ni (75 min, r.t.), immediate filtration and removal of solvent at ambient temperature furnished the corresponding amines 4A [mp 110-112°; $\nu_{max.}$ (Nujol) : 1740, 1710 cm^{-1}; $\lambda_{max.}$ (MeOH) (log ε) : 213 (4.58), 254 (4.09), 282 (3.43) nm; m/z (rel. int.) : 370 (M^+, 100), 339 (12), 297 (26), 215 (16), 211 (16), 182 (54), 173 (20), 124 (55)] and 4B [mp 110-112°C; $\nu_{max.}$ (Nujol) : 1735, 1710 cm^{-1}; uv and ms almost identical with 4A] in pure form. Even under this condition the products from 3C and 3D were isomerised to some extent and as such the amines 4C and 4D could not be obtained in complete stereochemical purity. We were unable to resolve the four amines by tlc or hplc, nevertheless, they could be

differentiated by the chemical shifts of the CH_3CH_2- and the $COOCH_3$ groups in the pmr spectra (Table 1). The shielding of the C-CH_3 group in 4B and 4D and of the OCH_3 group in 4A and 4C can be explained as due to anisotropy of the aromatic ring. It may be pointed out that the effect is more pronounced in the amines than in the lactams[1], because these substituents are more close to the aromatic ring in the former than in the latter.

Table 1. ^1H Chemical shifts (δ ppm) in $CDCl_3$ of (±)-vincatine and its isomers

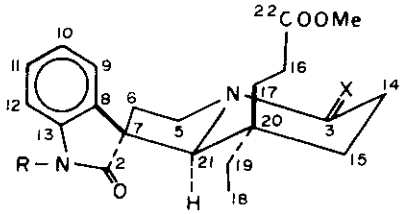
Comp.	CH_2CH_3	N-CH_3	OCH_3	Comp.	CH_2CH_3	N-CH_3	OCH_3
4A	0.73	3.22	3.55	4C	0.68	3.22	3.47
4B	0.51	3.19	3.63	4D	0.45	3.23	3.61

Refluxing of any of the isomers 4A-4D in chloroform (2 h) yielded an almost 1:1 mixture of 4A and 4B. The same mixture was also obtained by equilibration in pyridine, confirming that 4A and 4B possess the thermodynamically more stable anti configuration[4]. Isomerisation with 10% aqueous acetic acid yielded a more complex mixture of all the four isomers.

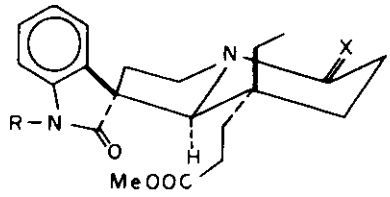
Now, a comparison of the 100 MHz pmr spectra[5] of the isomers with that of vincatine established the structure of the natural product to be 4B. In view of the facile isomerisation discussed above, the isolation of one of the isomers from a plant in pure form is surprising unless it was fractionally crystallised from a mixture of the two thermodynamically more stable isomers.

^{13}C-Nmr spectra : The ^{13}C-nmr spectral data of the lactams 1A-1D, their N-methyl derivatives 2A-2D, the thiolactams 3A, 3D, 5B, 5C, vincatine (4B) and its isomer 4A are given in Table 2. The assignment of all the carbons except the methylene carbons C-14, C-15, C-16, C-17 and C-19 could be made from the multiplicities in the off resonance decoupled spectra and the chemical shifts. From the spectra of model tetracyclic oxindoles, Wenkert et al.[6] observed that the chemical shifts of C-7, C-9 and C-21 are dependant on the stereochemistry at the spiro carbon atom. The chemical shifts of C-9 around δ125 ppm in all the isomers A and B clearly indicated their anti configuration at C-7. In the isomers C and D, on the other hand, this signal was observed around δ122 ppm consistent with their syn configuration. The expected difference in the chemical shift of C-21 in the two

series was however not observed, presumably due to the presence of two substituents at C-20. Small but consistent chemical shift differences were also observed for C-2, C-3, C-5, C-6, C-7, C-8 and C-13 in the syn and the anti series.



A



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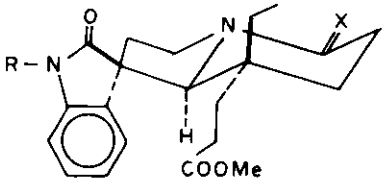
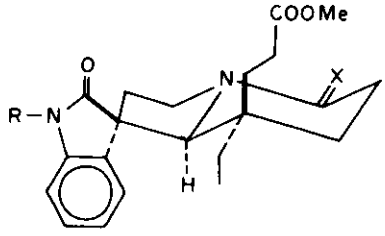


C



D

1, R = H X = O 2, R = Me X = O 3, R = Me X = S
4, R = Me X = H_2 5, R = H X = S

Of the five methylene carbons, C-14, C-15, C-16, C-17 and C-19, the signals for three were observed in the narrow range of δ 27.6 - 28.5 in all the lactams 1A-1D and 2A-2D. These three signals could be assigned to C-14, C-15, and C-16, because one of them (C-14) was deshielded in the thiolactams and shielded in the amines 4A and 4B, the second one (C-15) was shielded in the amines 4A and 4B and the other (C-16) was not affected by thiolation or reduction of the C-3 carbonyl group. As expected, C-20 and C-7 stereochemistry were found to have no significant influence on the chemical shifts of these three carbons. Of the other two methylene signals one was shielded and the other deshielded in the isomers B and C with respect to A and D. The shielded signal must be assigned to axial C-19 and the deshielded one to equatorial C-17 in the isomers B and C. Thus, the stereochemistry

Table 2. ^{13}C Chemical shifts (100 MHz, $CDCl_3$) of vincatine and intermediate lactams

CARBON NO.	1A	1B	1C	1D	2A	2B	2C	2D	3A	3D	5B	5C	4A	4B
2	178.3	178.2	180.0	179.9	176.0	175.8	177.0	177.1	175.1	176.5	177.7	179.4	179.6	179.4
3	169.6	169.6	169.0	168.8	169.2	169.2	168.5	168.4	197.1	195.9	197.7	196.6	53.7	51.2
5	43.7	43.9	44.1	43.9	43.3	44.0	44.0	43.8	51.2	51.7	51.7	51.9	54.9	53.8
6	36.0	36.0	35.1	35.3	35.9	35.7	35.0	34.8	35.1	33.9	35.3	34.6	36.7	36.5
7	55.8	55.7	54.7	54.7	55.1	55.3	54.2	54.1	55.2	54.3	56.0	55.0	55.4	55.1
8	130.7	130.8	128.9	129.0	130.3	130.0	128.3	128.9	129.6	129.2	130.2	129.3	133.9	134.0
9	125.2	125.1	122.2	122.2	124.8	125.0	121.9	122.2	124.8	122.3	125.1	122.8	127.1	126.9
10	122.4	122.2	122.0	122.0	122.6	122.5	122.5	122.2	122.8	122.3	122.6	122.3	121.9	121.8
11	128.5	128.3	128.9	128.8	128.5	128.5	128.3	128.3	128.8	127.7	128.8	128.4	127.5	127.5
12	110.7	110.7	110.5	110.0	108.7	108.7	108.5	108.3	108.9	108.4	110.8	110.7	107.7	107.8
13	140.1	140.1	141.0	141.0	142.4	142.3	143.2	143.3	142.4	143.3	139.6	140.4	142.4	142.4
14	28.5	28.4	28.2	28.7	28.4	28.4	28.2	28.5	37.5	37.5	37.6	37.7	21.4	21.4
15	27.9	27.8	27.9	27.9	27.6	27.8	28.0	27.9	27.9	27.9	27.7	28.1	31.4	31.2
16	28.2	27.8	27.9	28.2	28.3	28.1	28.0	28.1	28.1	28.0	27.8	28.1	29.6	28.0
17	28.2	30.2	29.6	28.2	28.3	30.1	29.7	28.2	28.2	28.3	30.3	29.9	29.9	30.9
18	7.6	7.5	7.6	7.5	7.6	7.5	7.6	7.5	7.5	7.5	7.4	7.6	7.8	7.9
19	28.5	25.1	23.2	26.4	28.5	24.9	23.4	26.4	28.7	26.7	25.7	23.8	29.3	26.3
20	38.0	38.2	38.0	38.0	37.8	38.2	38.2	37.8	37.9	38.0	38.2	38.6	39.2	39.3
21	69.4	69.0	69.7	69.7	69.5	69.4	70.2	69.6	71.7	71.9	71.6	72.8	77.3	76.7
22	173.4	173.8	173.1	173.5	173.2	173.7	173.0	173.4	172.9	173.3	173.7	172.9	174.3	174.4
OMe	51.5	51.5	51.4	51.5	51.5	51.5	51.4	51.6	51.5	51.5	51.5	51.7	51.2	51.2
NMe	-	-	-	-	26.5	26.5	26.2	26.1	26.6	26.2	-	-	26.3	26.3

at C-20 for all the lactams were unambiguously settled. Some of the assignments of the methylene carbons are obviously exchangeable, but it does not affect the orientations assigned to C-17 and C-19 in the two series of compounds.

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