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ON THE C-16 CONFIGURATION OF SITSIRIKINE

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Abstract:- The indole alkaloid sitsirikine has been synthesised by a biomimetic conversion of strictosidine and its C-16 configuration established as R by cyclisation to a 16,17-dihydroheteroyohimbine.

The structure assigned from chemical and spectral data to the indole alkaloid sitsirikine (4) from Vinca rosea (syn. Catharanthus roseus) was established by a correlation with corynantheine (1) via the corresponding 18,19-dihydro-derivatives.[1] Acid-catalysed cleavage of the enol ether in dihydrocorynantheine and subsequent $NaBH_4$ reduction of the aldehyde afforded dihydrositsirikine (3), together with a smaller amount of its C-16 epimer, as shown by reduction of both with $LiAlH_4$ to a common diol (5). This sequence also determined the absolute configuration at every chiral centre with the obvious exception of C-16. From our biomimetic conversion of strictosidine (2) we obtained mainly tetrahydroalstonine,[2] but two minor products (ca.8%) were sitsirikine m.p. 206-9° $[\alpha]_D^{25}$ -58° (MeOH) and 16-episitsirikine m.p. 205-7° $[\alpha]_D^{25}$ -22°. Their identities were established by direct comparison (mixed m.p., t.l.c., spectra) with natural sitsirikine and the pair of 16-epimers (4a, b) derived from corynantheine by cleavage and reduction as above. Again, catalytic hydrogenation afforded the two dihydro-epimers (3) and $LiAlH_4$ reduction to a common diol showed that they differed only at C-16.

Recently Zenk et al.[3] assigned the C-16 configurations of sitsirikine and its epimer from the relative positions in the p.m.r. spectra of the C-17 methylene protons, which were attributed to doublets (J=6Hz) at τ 6.06 for the former and 6.32 for the latter. This apparent difference in chemical shift was ascribed to differing interactions between the CH_2OH and vinyl groups in 15-16 rotamers of the two epimers, from which unjustified assumptions were made about the C-16 chirality. It is not clear on what basis such correlations could be made, but in any event they are not tenable since no appreciable chemical shift difference between the C-17 proton pairs of the two epimers actually exists. Examination of the 300 MHz p.m.r. spectra with appropriate decoupling experiments reveals the C-17 methylene group in both as an ABX system: H-17a and H-17b appear as pairs of doublets at τ 6.03 (J=11, 8 Hz) and 6.24 (J=11, 6.5 Hz) respectively in sitsirikine, and at 6.08 (J=11, 8 Hz) and 6.29 (J=11, 3.5 Hz) in 16-episitsirikine. Furthermore, the vinyl group per se has no marked shielding or deshielding effect, as the corresponding H-17 signals are at τ 6.05/6.06 and 6.30/6.33 for the dihydrositsirikine epimers. Hence the purported assignments of C-16 chirality were invalid, and an unambiguous solution was required.

Our approach has been to restrict rotation about the 15-16 bond by ring formation so that the relative orientations of H-15 and H-16 could then be determined from their mutual coupling constant. Oxymercuration

TABLE.

300 MHz NMR Spectra in $CDCl_3$

	Cyclositsirikine.			16-Epicyclositsirikine.			
Proton	τ	Multiplicity	J/Hz (coupled proton)	Proton	τ	Multiplicity	J/Hz (coupled proton)
NH	2.26	s		NH	2.24	s	
3	6.67	d + fc	10(14β),~3(14α),~1(6α),~1(6β)	3	6.61	d + fc	10(14β),~3(14α),~1(6α),~1(6β)
5α	7.38	td	12(6β),12(5β), 3.5(6α)	5α	7.31	td	12(5β), 11(6β), 4.5(6α)
5β	~6.95	m	12(5α),~5(6β),~2(6α)	5β	6.84	m	12(5α),~5(6β),~2(6α)
6α	7.30	d + fc	14(6β), 3.5(5α),~2(5β),~1(3)	6α	7.23	d + fc	15(6β), 4.5(5α),~2(5β),~1(3)
6β	~7.0	m	14(6α), 12(5α), 5(5β),~1(3)	6β	~7.0	m	15(6α), 11(5α),~5(5β),~1(3)
9 - 12	2.5 - 3.0			9 - 12	2.5 - 3.0		
14α	7.90	m	14(14β), 3(15),~3(3)	14α	~7.9	m	14(14β), 3(15),~3(3)
14β	8.66	q	14(14α), 11(15), 10(3)	14β	8.62	q	14(14α), 11(15), 10(3)
15	8.18	qd	11(14β), 11(20), 11(16), 3(14α)	15	8.22	m	11(20), 11(14β), 4.5(16), 3(14α)
16	7.47	td	11(15), 11(17α), 4.5(17β)	16	7.41	m	4.5(15), 3(17α),~1(17β)
17α	6.46	t	11(17β), 11(16)	17α	6.23	dd	12(17β), 3(16)
17β	5.88	dd	11(17α), 4.5(16)	17β	5.64	dd	12(17α),~1(16)
18-Me	8.80	d	7(19)	18-Me	8.70	d	7(19)
19	6.75	m	10(20), 7(18)	19	6.78	m	10(20), 7(18)
20	~8.5	m	11(21α), 11(15), 10(19), 3.5(21β)	20	8.37	m	11(21α), 11(15), 10(19), 4.5(21β)
21α	7.90	t	11(21β), 11(20)	21α	~7.9	t	11(21β), 11(20)
21β	~7.0	dd	11(21α), 3.5(20)	21β	~6.9	dd	11(21α), 4.5(20)
CO_2Me	6.28	s		CO_2Me	6.29	s	

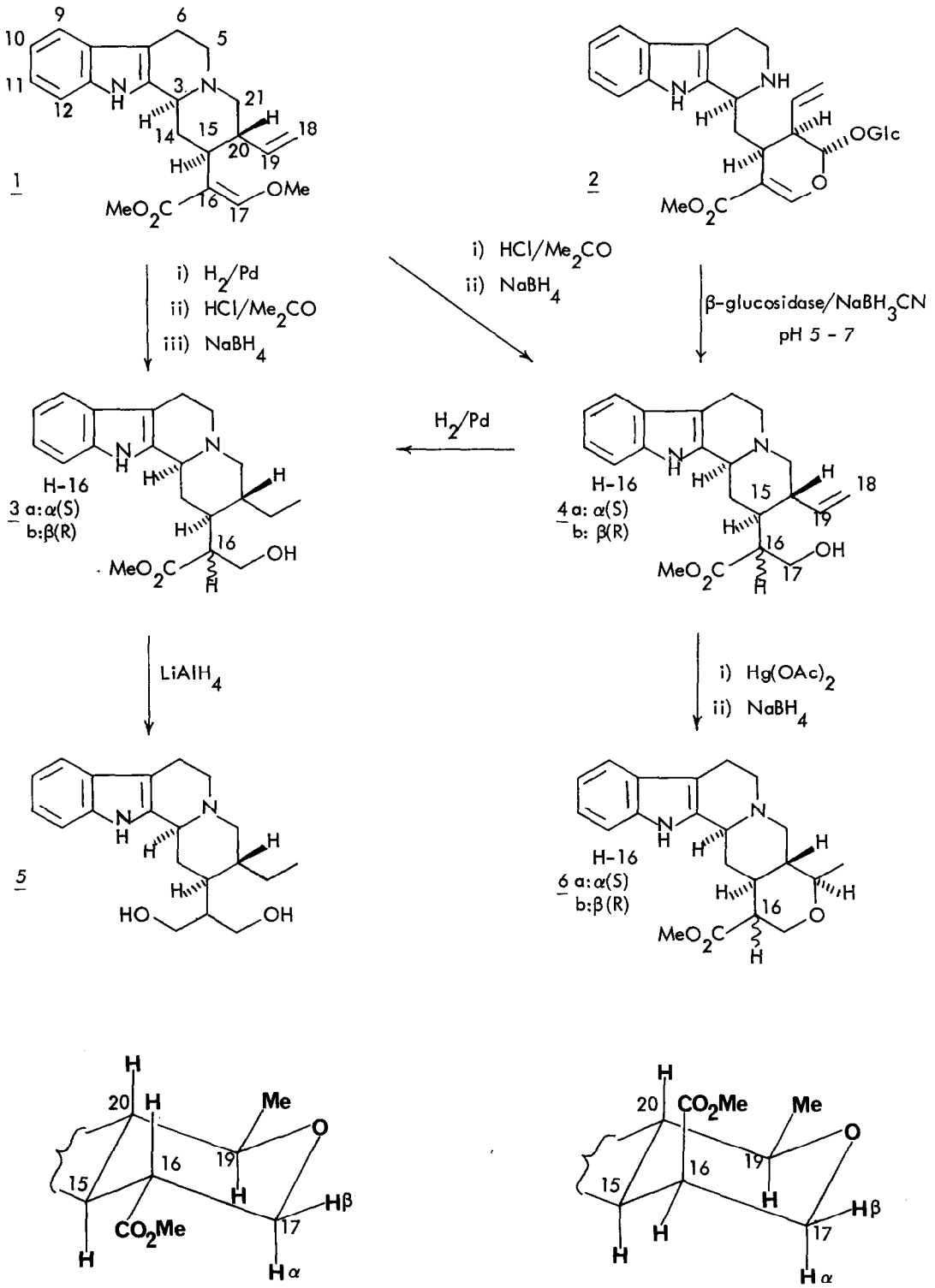

Fig.I (6b)

Fig.II (6a)

of the vinyl group in sitsirikine with $Hg(OAc)_2$ in AcOH overnight and subsequent reduction with $NaBH_4$ yielded one major isomeric product m.p. 208-9° $[\alpha]_D^{25}$ + 68° (MeOH), whose c.d. spectrum showed that H-3 was unchanged. Its mass spectral fragmentation differed considerably from that of sitsirikine: in particular, the intense peak at m/e 249 due to loss of MeO_2CCHCH_2OH was no longer present and the molecular ion was now the base peak. Moreover, it could not be acetylated, as anticipated for the desired cyclositsirikine (6). This structure was confirmed by a detailed analysis with decoupling of the p.m.r. spectrum which allowed assignment of every proton and relative stereochemical centre (see Table). Most importantly, H-16 was located at τ 7.47 as a triplet of doublets due to two large trans-diaxial couplings with H-15 and H-17α and a small a-e coupling with H-17β, and thus has the axial β-configuration indicated in Figure I. This is in accord with structure (6b) for cyclositsirikine and hence (4b) for sitsirikine.

However, since the carbomethoxy group in (6b) is in the more stable equatorial orientation, H-16 might have been inverted at some stage. This possibility could be discounted when cyclisation of 16-episitsirikine in the same manner gave a different isomer $[\alpha]_D^{25}$ -87° (MeOH) which was shown to be 16-epicyclositsirikine (6a). In particular, the p.m.r. spectrum (see Table) had H-16 at τ 7.41 with small couplings - e-a to H-15 and H-17α, and e-e to H-17β - in accordance with Figure II. Finally, treatment of (6a) with NaOMe in refluxing MeOH epimerised H-16 and converted it to cyclositsirikine (6b).

We have thus established that the chirality at C-16 is R in natural sitsirikine and the complete structure is (4b), whereas 16-episitsirikine is (4a).

It is of interest to note that both cyclisations generate the same configuration at C-19 with the methyl group in the preferred equatorial orientation and the stable trans-trans H-15, 20, 19 stereochemistry of 16,17-dihydro-19-epiajmalicine. The only natural 16,17-dihydroheteroyohimbine is herbaceine[4] in which the methyl and carbomethoxy groups are both axial, but there seems no reason why other analogues should not be isolated.

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