Stereochemistry of Strictosidine

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Summary The complete stereochemistry of strictosidine has been established by chemical correlation with antirhine; a second correlation *via* strictosamide confirms the α-C-3 configuration† and demonstrates the β-C-3 stereochemistry of vincoside.

PREVIOUSLY we reported the isolation, structural elucidation,[1] and biosynthesis[2] of strictosidine (**1**). We now summarise our investigations which establish its complete stereochemistry.

TABLE 1

Physical constants related to C-3-*stereochemistry*

Compound	$[\alpha]_D$ ($CHCl_3$)	τ (3-H) ($CDCl_3$)	Compound	$[\alpha]_D$ ($CHCl_3$)	τ (3-H) ($CDCl_3$)
(**4**)	+220	5·56	(**27a**)	− 38	5·90
(**6**)	−180	5·76	(**33a**)	+ 45	above 6·2†
(**5**)	+ 23	5·42	(**32**)	+ 53	above 6·2†
(**7**)	− 20	5·60	(**30**)	− 21	5·58
(**9**)	− 68	5·44	(**28**		5·53
(**11**)	− 82	5·48	(**29**)		5·48
(**8**)	− 31	5·56	(**34a**)	− 49	6·10
(**13**)		5·70	(**39a**)	+ 12	above 6·2†
(**15a**)	− 10	5·75	(**36a**)	− 117	5·68
(**16a**)	− 49	5·65	(**38a**)	− 8·5	above 6·2†
(**17a**)	+ 27	above 6·2†	(**37a**)	− 39	
(**18a**)	+ 20	above 6·2†	(**35a**)	− 27·5	5·8

* Compounds of the 3α-series are characterised by τ (3-H) < 6·2 and the absence of strong Bohlmann bands whereas the 3β-series show strong Bohlmann bands and τ (3-H) > 6·2.
† Strong Bohlmann i.r. bands ($CHCl_3$).

On mild hydrolysis strictosidine (**1**) yields vallesiachotamine (**4**) and isovallesiachotamine (**6**), whose configurations within the C-15 substituent are assigned on the basis of n.m.r. evidence. The major isomer (**4**) possesses the lower field ethylidene proton (τ 3·32) which is sterically prevented from long-range coupling with 15-H. In contrast, (**6**) has the lower field ethylidene methyl (τ 7·83) homoallylically coupled to 15-H (*J* 1·0 Hz).

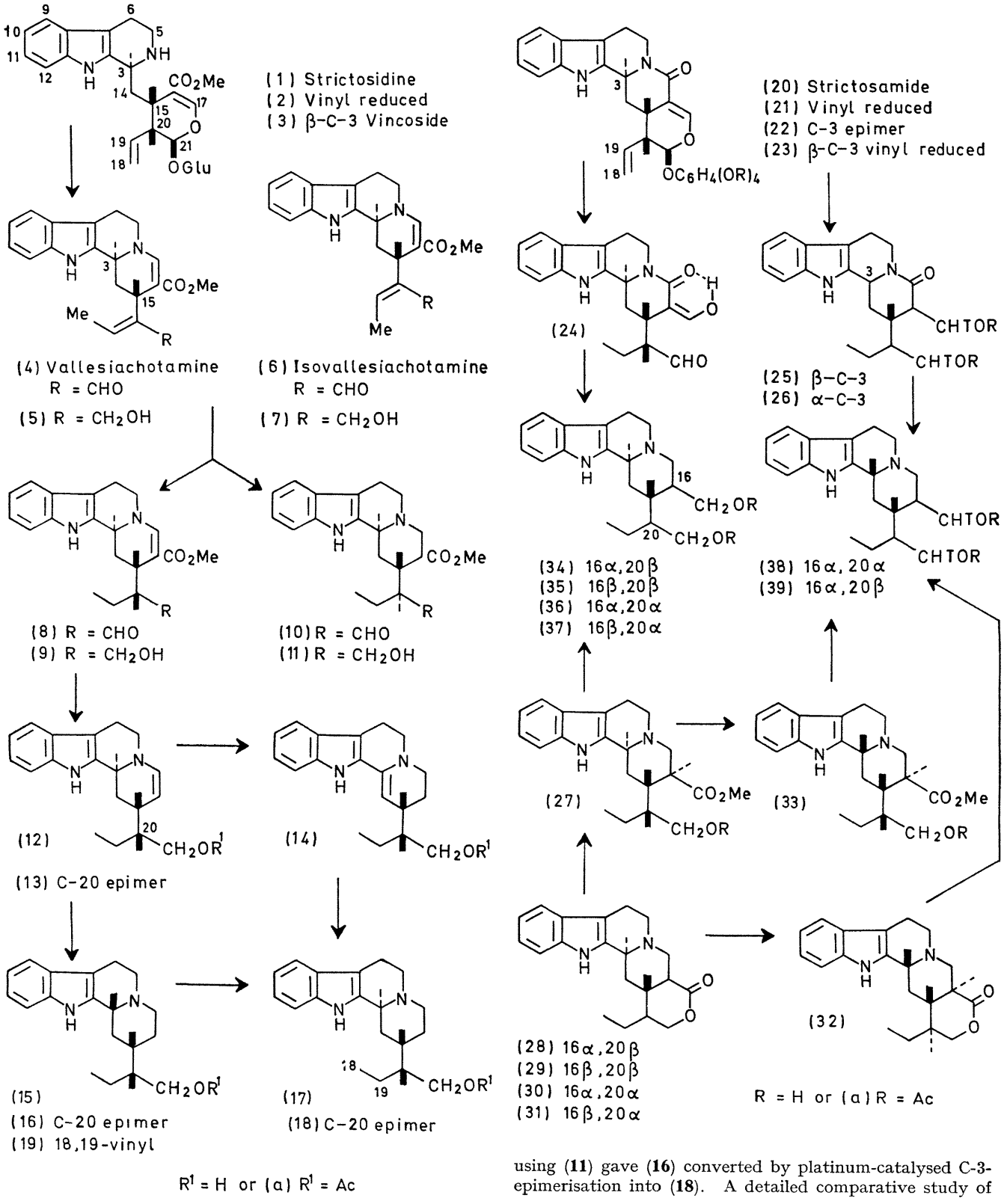
Sodium borohydride reduction gave the corresponding alcohols, dihydrovallesiachotamine (**5**)[6] and dihydroisovallesiachotamine (**7**) each of which, on catalytic hydrogenation, produced tetrahydrovallesiachotamines (**9**) and (**11**). Controlled hydrolysis of dihydrostrictosidine (**2**) gave a quantitative yield of 19,20-dihydrovallesiachotamine (**8**) which on reduction produced tetrahydrovallesiachotamine (**9**) exclusively. The isomeric aldehyde (**10**), obtained by base catalysed equilibration, was similarly reduced to 20-*epi*-tetrahydrovallesiachotamine (**11**).

These correlations demonstrate the common C-20 configuration of strictosidine (**1**) and tetrahydrovallesiachotamine (**9**) and firmly establish the identical ring stereochemistry of the vallesiachotamines (**4**)—(**11**). Detailed examination of the n.m.r. spectra of such derivatives revealed their common ring D conformation which is best interpreted[6] in terms of a *trans*-relationship between 3-H and 15-H. In view of the ready incorporation of loganin[2] and the postulated mechanism for the formation of vallesiachotamine[1] this stereochemical feature strongly favoured structure (**1**) for absolute configuration of strictosidine. This hypothesis was tested by correlation of tetrahydrovallesiachotamine (**9**) with dihydroantirhine (**15**)[7,8] which had just become available[5] through our isolation of antirhine (**19**) (rhazinine)[9] m.p. 106° $[\alpha]_D$ −1·8° ($CHCl_3$), from *Rhazya stricta*.

Mild basic hydrolysis of (**9**) followed by controlled acid-catalysed decarboxylation gave the enamine (**12**) which was isomerised to (**14**) λ_{max} (EtOH) 348 (H^+), 310 (OH^-) nm,

† In this and the following communication, all indolic compounds are numbered in accordance with the scheme devised by J. LeMen and W. I. Taylor, *Experientia*, 1965, **21**, 508.

under more vigorous acid conditions. Borohydride reduction of the thermodynamically less stable enamine (**12**) afforded dihydroantirhine (**15**) exclusively, whereas (**14**) similarly gave only the thermodynamically more stable 3-iso-dihydroantirhine (**17**). Repetition of the degradation using (**11**) gave (**16**) converted by platinum-catalysed C-3-epimerisation into (**18**). A detailed comparative study of



the isomeric indoloquinolizidines (**15**)—(**18**) and their acetates (a) by n.m r.[10,11], i.r ,[12] t.l.c.,[13] $[\alpha]_D$[14], and equilibration studies[14] rigorously confirmed their assigned structures.

Although the correlation left little doubt concerning the stereochemistry of the vallesiachotamines it was conceivable that C-3-epimerisation occurred during their formation from strictosidine (**1**). Fortunately a second indolic glycoside, strictosamide (**20**) $[\alpha]_D$ −77° (MeOH) had been isolated from *R. stricta*[4] which facilitated investigation of this possibility. The natural occurrence of strictosamide (**20**) is questionable as it is formed from strictosidine (**1**) under a variety of basic conditions.[4,5] Catalytic hydrogenation of (**20**) gave 18,19-dihydrostrictosamide (**21**), $[\alpha]_D$ −102° (MeOH), whose tetra-acetate (**21a**) is characterised by an anomalous high field acetate signal (τ 8·78) which is absent from the corresponding vincoside derivative (**23a**).‡ Hydrolysis of (**21**) with β-D-glucosidase yielded the aglycone (**24**), (C-21H, τ 0·43, d, J 3 Hz), reduced by sodium borohydride to a mixture of diols (**26**). Lithium aluminium hydride reduction gave the hexahydrovallesiachotamine diols (**34**) 84%, (**35**) 10%, and (**36**) 6% whose structures were assigned by partial synthesis.

Reduction of tetrahydrovallesiachotamine (**9**) with sodium borohydride in acetic acid[6] gave the lactones (**28**) 93% and (**29**) 7%. The minor lactone (**29**) was reduced directly with lithium aluminium hydride to diol (**35**) whereas the methyl ester (**27**) prepared from (**28**) was converted into its C-3-epimer (**33**) by platinum-catalysed isomerisation and the diols (**34**) and (**39**) prepared. Similarly 20-*epi*-tetrahydrovallesiachotamine (**11**) was initially reduced to lactones (**30**) 97% and (**31**) 3% and the former converted into lactone (**32**) and diols (**36**) and (**38**).

Examination of the diols (**34**)—(**39**), their acetates (a) and indoloquinolizidine precursors by the criteria[10–14] used to establish C-3-configurations left no doubt that the diols (**34**)—(**36**) obtained from strictosamide (**20**) belonged to the α-series.

When these results were first presented[3] it was apparent that the stereochemistry deduced for strictosidine (**1**) corresponded to that assigned to vincoside[15] whereas the physical properties were much more comparable with those of isovincoside. Direct comparison of strictosidine (**1**) and isovincoside confirmed their identity.

Clearly our correlations could only be in error if C-3-epimerisations were occurring at some stage and although this was considered unlikely since the strictosidine (**1**) transformation products belonged to the thermodynamically less stable series it was necessary to similarly degrade a compound of the vincoside series to substantiate our claims. The limited amount of vincoside lactam (**22**) available (0·5 mg) precluded a conventional correlation and hence a tritium label was introduced during the reduction of the aglycone to diols (**25**) and (**26**). The sequence was performed in parallel starting with strictosamide (**20**) and vincoside lactam (**22**) under identical conditions and finally the diols (**34**), (**36**), (**38**), and (**39**) were added to each series and assayed for radioactivity. The results (Table 2) clearly demonstrate that no C-3-epimerisations occurred during the course of the correlation.

TABLE 2

Dilution analysis experiment

Precursor:—	Strictosamide (**20**)	Vincoside lactam (**21**)
Added diol	Relative specific activities	
(**34**) and (**34a**)	178*	<2
(**36**) and (**36a**)	26*	<5
(**36**) and (**38a**)	<6	28*
(**39**) and (**39a**)	<9	141*

* Constant activity.

In view of the confirmation‡ of the surprising preferential incorporation of vincoside (**3**) into the indole alkaloids of known α-C-3-configuration further support for our correlations was sought by studying the stereochemistry of 5-carboxy-strictosidine[16] whilst Battersby and his co-workers[17] investigated the structure of ipecoside by *X*-ray analysis. Subsequently Brown and his co-workers[18] isolated vincoside lactam (**22**) from *Adina rubescens* and carried out an independent correlation.

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