Configuration at C-3 in Vincoside

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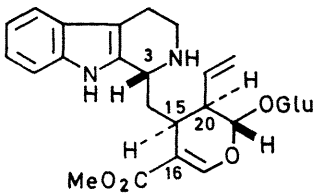
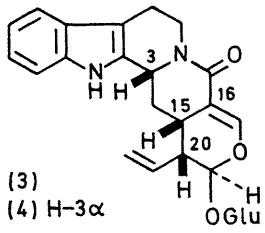
Summary The absolute stereochemistry at C-3 and C-15 in vincoside (**1**) has been established by a chemical correlation with corynantheine (**11**).

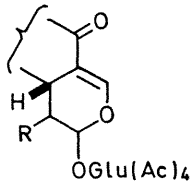
PURSUING our investigations[1] on the constituents of *Adina* spp. we isolated from *Adina rubescens* a neutral indolic glucoside, $C_{26}H_{30}O_8N_2$, m.p. 201—204° $[\alpha]_D^{25}$ −104°. Comparison of our physical constants and spectral data with those reported for a lactam obtained from vincoside by Battersby and his co-workers[2] suggested that the compounds could be identical. This was confirmed by direct comparison with authentic vincoside lactam synthesised from tryptamine and secologanin according to the published procedure.[2]



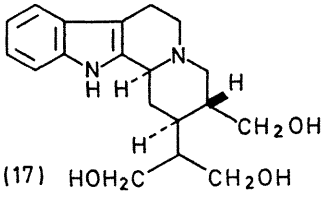
(1)
(2) H-3α



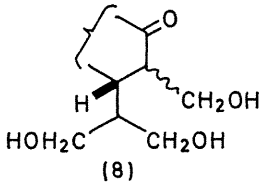
(3)
(4) H-3α



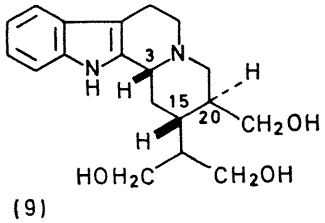
(5) R = CH(OH)CH$_2$OH
(6) R = CHO
(7) R = CH$_2$OH



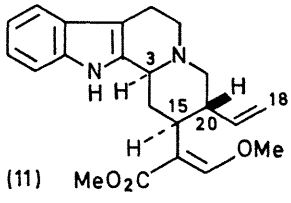
(17)



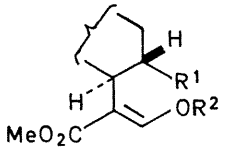
(8)



(9)
(10) H-20β



(11)



(12) R^1 = CH(OH)CH$_2$OH, R^2 = Me
(13) R^1 = CHO, R^2 = Me
(14) R^1 = CH$_2$OH, R^2 = Me
(15) R^1 = CH$_2$OAc, R^2 = Me
(16) R^1 = CH$_2$OAc, R^2 = H

Condensation of tryptamine and secologanin gives two diastereoisomers, vincoside (**1**) or (**2**) and strictosidine (isovincoside) (**2**) or (**1**), which can readily be converted into the corresponding lactams, vincoside lactam (**3**) or (**4**) and strictosamide (isovincoside lactam) (**4**) or (**3**).[2,4] From these partial syntheses it follows that, since the absolute stereochemistry of secologanin is established,[3] the configuration at every asymmetric centre in vincoside and strictosidine is known except C-3. From a comparison of molecular rotation differences in vincoside and ipecoside derivatives, it was deduced that vincoside had the 3α (**2**) and strictosidine the 3β (**1**) orientation.[2] This conclusion was apparently in agreement with biosynthetic results since vincoside was a precursor for Corynanthe-type alkaloids possessing a 3α configuration whereas strictosidine (isovincoside) was not, and furthermore the hydrogen at C-3 was not lost during these transformations.[2,5] However, other work on strictosidine led to the opposite conclusion.[6]

In order to resolve this discrepancy we proposed to determine the configuration at C-3 (and incidentally at C-15) in vincoside by converting the lactam into a triol (**9**) which could be compared directly with the enantiomeric triol (**17**) derived from an alkaloid of known absolute stereochemistry, corynantheine (**11**).[7] Our scheme envisaged that if vincoside were 3β the triol (**9**) would be obtained directly, and if 3α then an additional oxidation–reduction sequence[7] would achieve epimerisation to the desired triol (**9**).

In the event, treatment of vincoside lactam tetra-acetate with osmium tetroxide afforded two diastereoisomeric diols (**5**), both of which were cleaved with sodium periodate to an aldehyde (**6**), $[\alpha]_D^{25}$ −56°; subsequent reduction with sodium borohydride gave an alcohol (**7**) $[\alpha]_D^{25}$ −51°.† Zemplen deacetylation, followed by cleavage of the sugar unit with β-glucosidase afforded the aglycone, which was reduced with sodium borohydride to two triol lactams (**8**); further reduction with lithium aluminium hydride in dioxan gave two isomeric bases that were readily separated. The major product (66%) was a crystalline triol, $C_{19}H_{26}O_3N_2$, m.p. 240—242°, which yielded a triacetate, $[\alpha]_D^{25}$ +9°; the minor product (34%) was amorphous but gave a crystalline triacetate, m.p. 199—200°. Both triacetates showed strong Bohlmann bands in their i.r. spectra between 2740 and 2850 cm^{-1}, indicating that H-3 and H-15 had a *cis*-relationship. More importantly, the o.r.d. curves of both displayed a similar negative Cotton effect between 298 and 244 nm which constituted strong evidence for a 3β configuration.[8] It was concluded that the two triols were the 18-norcorynane derivative (**9**) and its C-20 epimer (**10**), since protonation of the position corresponding to C-20 could occur from either side during the reduction of the aglycone to the triol lactams (**8**).

Corynantheine (**11**) was hydroxylated with osmium tetroxide to a mixture of two glycols (**12**), which were cleaved with sodium periodate to an aldehyde (**13**), subsequently reduced by sodium borohydride to an alcohol (**14**). There was no indication of epimerisation occurring

† All new compounds were fully characterised by appropriate analytical and spectral data.

during this sequence and hence the β configuration of C-20 was presumably retained. The alcohol was then protected by formation of the acetate (**15**) $[\alpha]_D^{25}$ −10° to prevent acetal formation during the cleavage of the enol ether, and treatment with dry HCl in acetone yielded the required enol (**16**). The final transformations were achieved in one step by reduction with sodium borohydride in methanol to afford 3α,15α,20β,18-norcorynan-17,19,22-triol (**17**), m.p. 240—242°. This triol was the enantiomer of the major triol derived from vincoside; the m.p. and t.l.c. behaviour in several systems were identical and the i.r. and n.m.r. spectra were superimposable. A similar correspondence was shown by the triacetates, the only difference being in their enantiomeric o.r.d. curves which displayed Cotton effects of opposite sign. Thus the triacetate derived from corynantheine showed extrema at 244 and 298 nm with an amplitude difference of +6,300°, whereas that from vincoside had an amplitude difference of −6,600°. Hence the major triol obtained from vincoside must be 3β,15β,20α,18-norcorynan-17,19,22-triol (**9**) and the minor the 20β epimer (**10**).

This correlation establishes the absolute configuration at C-3 in vincoside as β. The remote possibility that inversion of C-3 could have taken place, even under the mild conditions employed, was excluded by taking strictosamide through a parallel reaction sequence and showing that the intermediates always differed from the isomeric vincoside derivatives. In particular both triacetates from strictosamide exhibited positive Cotton effects in the 240—300 nm region, in accordance with a 3α configuration.[8] Therefore the correct stereochemistry for vincoside is (**1**). It follows that strictosidine is the 3α epimer (**2**).

One further consequence is that since the absolute stereochemistry of vincoside has been correlated with that of ipecoside[2] then the configuration of the corresponding C-5 in ipecoside is now β rather than α.[9] Independent results leading to the same conclusions are reported in the accompanying Communications by Smith and Battersby and their co-workers.[10,11]

An intriguing outcome is why the biogenesis of Corynanthe (and Ipecacuanha) alkaloids involves the inversion of the C-3 (C-5) centre with retention of hydrogen[12] when the compound with the 'correct' stereochemistry is available.

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