Biomimetic Conversion of Vincoside into Heteroyohimbine Alkaloids

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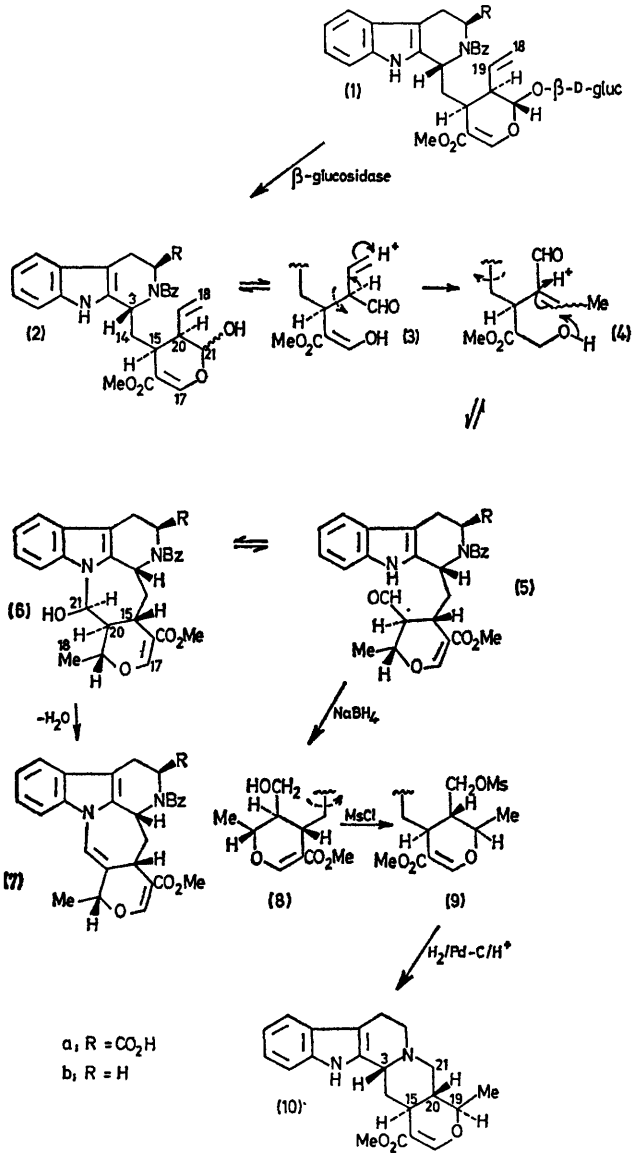
Summary The indole alkaloids 19-epiajmalicine (**11**), 3-iso-19-epiajmalicine (**10**), and their oxindole derivatives, formosanine (**13**) and isoformosanine (**14**) have been synthesised from a vincoside derivative in a biogenetically patterned reaction sequence.

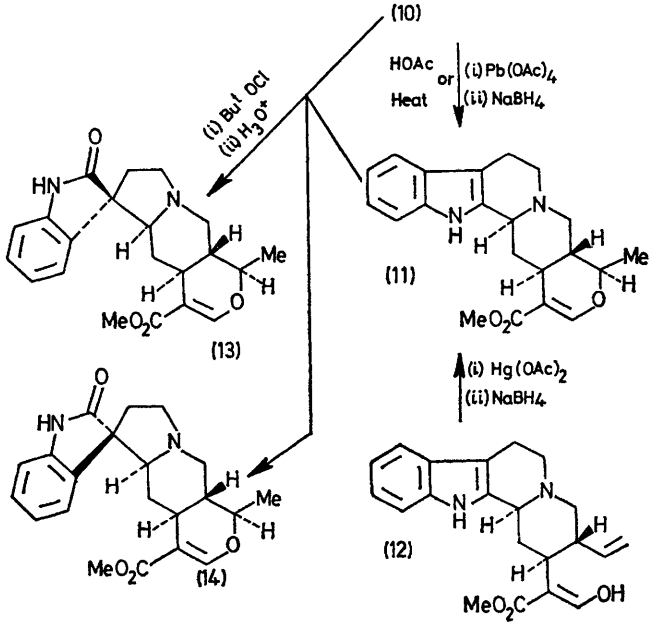
WE have previously reported[1] the biomimetic synthesis of carboxy indole alkaloids of the *Corynanthé* type, and a similar route has recently led to the known tryptamine analogues hirsutine and dihydrocorynantheine.[2] The key intermediate (**1**, 18,19-dihydro) in both cases was obtained

from dihydrosecologanin, which was used to avoid the complication of rearrangements involving the vinyl group of the secologanin derivative (**1**). We now describe the investigation of these rearrangements and their exploitation in a synthesis with implications for the biogenesis of heteroyohimbine alkaloids.



SCHEME 1

Removal of the sugar from 3β,5α-*N*(4)-benzyltetrahydrodeoxycordifoline (**1a**) {methyl ester m.p. 182—186° $[\alpha]_D$ −95° (MeOH)} gave a complex mixture of products, some of which were no longer indolic. Methylation with diazomethane and separation by t.l.c. yielded two major components: one was an indole with the molecular formula expected for the aglycone (**2**, R = CO_2Me) but without the typical rapid base shift in the u.v. spectrum found in the dihydro series; the other had u.v. maxima at 259, 297 and 307 nm typical of an *N*-vinylindole chromophore. Several novel features in their mass and n.m.r. spectra suggested a close relationship which was confirmed when the former was readily converted into the latter by brief treatment with trifluoroacetic acid. These and other data were compatible only with the gross structure (**6a**) for the indole and (**7a**) for the *N*-vinylindole, and their formation from the initially formed aglycone could be rationalised according to Scheme 1. As previously,[1] the *N*-benzyl group played a crucial rôle in preventing attack by N-4 on C-17 to form a vallesiachotamine derivative.



SCHEME 2

At this point it was apparent that the newly formed dihydropyran ring was analogous to that found in ajmalicine and related alkaloids, and the spontaneous rearrangement of the aglycone (**2**) provided an opportunity to duplicate *in vitro* the key steps in the biological transformation of vincoside to the heteroyohimbine alkaloids. Accordingly removal of the sugar from *N*(4)-benzylvincoside (**1b**) {tetraacetate m.p. 195—196° $[\alpha]_D^{25}$ −98° (MeOH)} under carefully controlled conditions yielded as the major product the rearranged aglycone (**6b**), which gave a monoacetate, m.p. 160—162° $[\alpha]_D^{25}$ +130° ($CHCl_3$), and was readily dehydrated into a *N*-vinylindole (**7b**) m.p. 164—167° $[\alpha]_D^{25}$ +268° ($CHCl_3$). Again, the spectral data were in accord with the indicated gross structures, and analysis of the n.m.r. spectrum of (**6b**) showed that 20-H was *cis* to 21-H and *trans* to 19-H. Although it was hoped that sufficient free aldehyde (**5**) would be present in equilibrium with the *N*(1)-cyclised material for the remaining stages to the heteroyohimbine skeleton (**10**) to be achieved in one step as previously,[1] unfortunately under these conditions the seven-membered ring remained intact and only the debenzylated product was obtained.

However, it was noted that prolonged exposure of the aglycone (**6**) to alkali led to the gradual appearance of an ionised β-hydroxyacrylate u.v. chromophore, which was attributed to production of (**4**) *via* (**5**) by a base-catalysed reversal of the formation sequence. Indeed, sodium borohydride in propan-2-ol intercepted (**5**) to give the alcohol

(**8**), together with traces of its C-20 epimer and the *N*-vinylindole. Conversion into the mesylate (**9b**) and subsequent catalytic hydrogenation yielded 3-iso-19-epiajmalicine (**10**) $[\alpha]_D^{25}$ + 76° (MeOH), whose structure was assigned from spectral evidence. In particular the stereochemistry of 3-H(β) and 15-H(β) were shown to be unchanged by c.d., i.r., and n.m.r. data, and from the n.m.r. coupling constant (9·5 Hz) 20-H was *trans*-diaxial to 19-H, whose chemical shift (τ 6·45) consequently established an α-configuration.[3] These deductions were substantiated by t.l.c. and spectral comparison with the synthetic racemate.[4]

In vivo, when vincoside is converted into ajmalicine, the configuration of 3-H is inverted from β to α with retention of hydrogen.[5] Direct epimerisation of isoepiajmalicine in acetic acid[6] afforded a small amount of the 3α-isomer, but an oxidation–reduction sequence[4] was a much more efficient process and gave a good yield of 19-epiajmalicine (**11**) m.p. 181—182° $[\alpha]_D^{25}$ +58° (MeOH), further characterised as the picrolonate salt m.p. 243–244°. Its structure was deduced from c.d., i.r., and n.m.r. data, and confirmed by its identity with a compound obtained by cyclisation of demethylcorynantheine (**12**) (Scheme 2).[7]

Although neither 19-epiajmalicine nor its C-3 epimer has yet been isolated from natural sources, the corresponding oxindole alkaloids, formosanine (**13**) and isoformosanine (**14**) are well known. Both were formed by oxidation[4] of either isomer and identified by direct comparison with authentic material.

Overall the above sequence constitutes a reasonable model for the biosynthesis of heteroyohimbine alkaloids, but obviously not in every detail. One intriguing conclusion is that the stereochemistry generated at C-19 and C-20 is apparently closely dependent on the existing asymmetric centres at C-3 and C-15. Current work involving C-3 epimerisation at earlier stages and blocking groups on N-1 is providing further information on this aspect and will be reported in due course.

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