'One-pot' Biomimetic Synthesis of 19β-Heteroyohimbine Alkaloids

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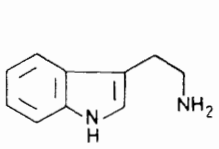
Summary Tryptamine and secologanin have been converted into akuammigine (**7b**), tetrahydroalstonine (**7a**), and ajmalicine (**7c**), in a highly regio- and stereo-selective sequence of reactions which duplicates the *in vivo* process; strictosidine (**6a**) is a precursor for 3α-alkaloids and vincoside (**6b**) for 3β.

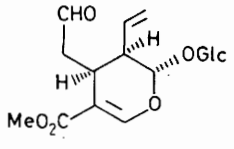
IN previous communications[1-3] we have described the conversion of secologanin into pentacyclic indole alkaloids *via* *N*-benzylvincoside and other unnatural derivatives. We now report the synthesis of three heteroyohimbines, akuammigine (**7b**), tetrahydroalstonine (**7a**), and ajmalicine (**7c**), in a 'one pot' process which requires only the natural substrates tryptamine (**1**) and secologanin (**2**). The mild conditions and the high degree of regio- and stereo-selectivity lead us to believe that it duplicates the biogenetic sequence in all essential details.

Equimolar quantities of secologanin and tryptamine in

pH 5 phosphate–citrate buffer together with β-glucosidase and an excess of $NaBH_3CN$ were incubated at 37 °C overnight. Extraction with chloroform afforded mainly one compound which was chromatographed on silica, to give pure 2,3-secoakuammigine (**5**), $[\alpha]_D^{25}$ −30° ($CHCl_3$), in *ca.* 30% yield. It was identified from u.v., i.r., n.m.r., and mass spectroscopic data and by conversion into a mixture of akuammigine (**7b**) and tetrahydroalstonine (**7a**) by Hg(OAc)$_2$–$NaBH_4$ treatment.[4] The 2,3-seco-alkaloid was formed by hydride reduction of the imine (**3**) to (**4a**) and sugar cleavage to the aglycone (**4b**) which underwent rearrangement and reduction to (**5**). No appreciable amounts of pentacyclic alkaloids had been obtained because cyclisation of (**3**) to vincoside (**6b**) and strictosidine (**6a**) was too slow to compete with hydride reduction.



(1)



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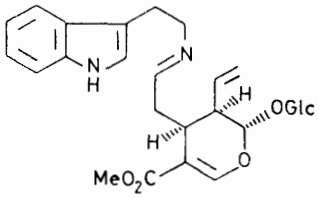

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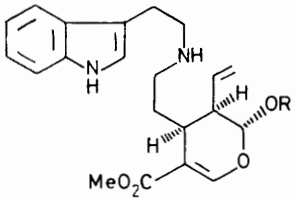
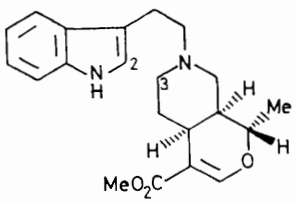


(4)

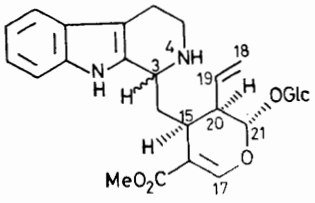
a; R = Glc
b; R = H

Consequently the tryptamine and secologanin were allowed to condense in pH 4 buffer for 48 h before the pH was adjusted to 5 and the β-glucosidase and $NaBH_3CN$ were added as before. After 18 h at 37 °C extraction with chloroform afforded indolic products in *ca.* 70% yield (allowing for recovered tryptamine). Separation by preparative t.l.c. gave 2,3-secoakuammigine, akuammigine, and tetrahydroalstonine in the proportions of 3:3:1 together with a small amount of ajmalicine, which were identified by direct comparison (mixed m.p., t.l.c., i.r., n.m.r.) with authentic samples. No other stereoisomers could be detected.

The most striking feature of the products (**5**) and (**7a**—**c**) is that they all have the same 19β(*S*) chirality, which can be rationalised by the initially formed dienamine (**9**) undergoing stereospecific conversion into the conjugated immonium compound (**10**) with an *E* configuration of the ethylidene group. Certainly this geometric arrangement is always found in naturally occurring alkaloids, and could arise by intramolecular protonation by the enol (Scheme). Owing to constraints imposed by the C-18 methyl group and the α-orientation of H-15, subsequent Michael addition of the enolate can only occur from the upper (β) face in (**10**), resulting in a β-orientation for H-19 in the 20,21-dehydro-intermediate (**11**).[5] Since ajmalicine is only a minor product under these reaction conditions, (**11**) must then be

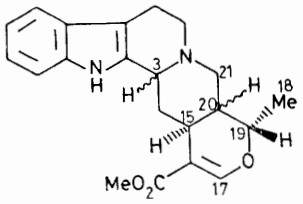


(5)



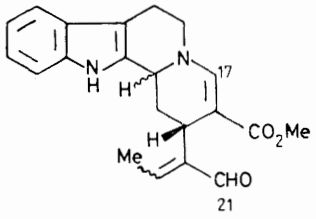
(6)

3-H
a; α
b; β



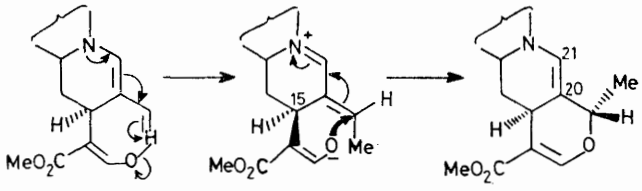
(7)

3-H 20-H
a; α α
b; β α
c; α β

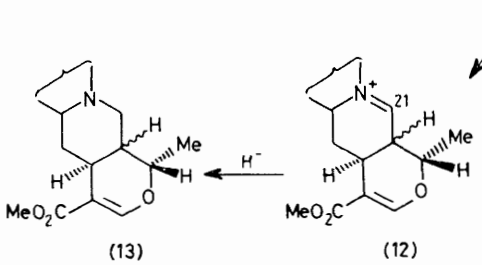


(8)

protonated chiefly from the α-side to give (**12**), reduced by hydride addition at C-21 to (**13**). In accordance with biosynthetic results,[6] we have previously established[3] that a β 3-H can readily be inverted to α with retention of hydrogen by a mechanism involving C-3–N-4 cleavage in a dehydrospecies such as (**10**) or (**11**). It is thus certain that (**7a**) and (**7c**) can be derived from vincoside (**6b**) but strictosidine (**6a**) could not be excluded as a precursor. In the reaction of strictosidine alone under the same conditions, tetrahydroalstonine was indeed obtained, but no akuammigine. Hence no epimerisation is required, strictosidine acting as a precursor for 3α alkaloids and vincoside for the 3β series. In view of these rather surprising results, the relative roles of vicoside and strictosine in biosynthesis[6] should be re-examined.



(9) (10) (11)



(13) (12)

SCHEME.

In the absence of a reducing agent removal of the sugar from (**6a** or **b**) results in the eventual formation of vallesiachotamine isomers (**8**) with N-4–C-17 bonds which are thermodynamically more stable than the compounds formed by addition of N-4 to the C-21 aldehydes. Since relatively little vallesiachotamine was obtained in the present experiments, the alkaloids with N-4–C-21 bonds result from hydride trapping of the kinetically favoured intermediates. At the same time reduction prevents any equilibration of (**11**) with (**9**) which could eventually give a *Z* configuration of the ethylidene and H-19 α as in 19-epi-ajmalicine.[1] A comparable process dependent on the availability of NADH may well operate *in vivo* since the 19β-alkaloids such as tetrahydoalstonine and ajmalicine are certainly the most common.

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