Conversion of Secologanin into *Corynanthé*-type Alkaloids

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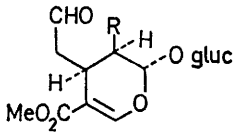
Summary Indole alkaloids of the *Corynanthé* type have been synthesised from secologanin *via* 3β-hexahydrodeoxycordifoline, the major steps corresponding to a possible biosynthetic sequence.

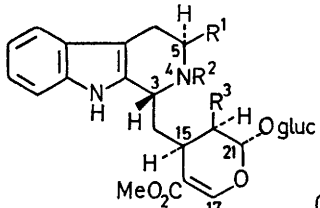
THE biogenetic sources of monoterpenoid indole alkaloids are firmly identified as secologanin (**1a**) and tryptamine, their 3β-condensation product, vincoside (**2a**) being the active precursor to the exclusion of the 3α-isomer, strictosidine (isovincoside), at least in the plant species examined so far.[1] The next stage involves conversion into the *Corynanthé* skeleton, presumably by removal of the sugar, cyclisation of N-4 to C-21 and reduction. Intriguingly, this applies to alkaloids with 3α-configuration where a stereochemical inversion occurs with retention of hydrogen - A further point of interest is that *in vitro* N-4 apparently prefers to bond to either C-22 or C-17[2,3] and not to C-21, so some form of selective control must be exercised. To obtain further information on these aspects we have carried out an analogous conversion, duplicating as closely as practicable the essential stages in a likely biosynthetic sequence. For the tryptophan series 3β,5α-tetrahydrodeoxycordifoline (**2b**) corresponds exactly to vincoside, and initially we have used a derivative of the former with the secondary objective of synthesising a model compound to support the *Corynanthé* structure recently proposed for adirubine (**7a**).[4]

As anticipated, the only isolable product after removal of the sugar from 3β-hexahydrodeoxycordifoline (**2c**) with β-glucosidase was the vallesiachotamine derivative (**3b**), and the 3α-epimer likewise gave (**3a**). Condensation of *N*(b)-benzyl-L-tryptophan with dihydrosecologanin (**1b**) in acetic acid afforded exclusively 3β,5α-*N*(4)-benzylhexahydrodeoxycordifoline (**2d**) $[\alpha]_D^{22}$ — 41° (MeOH), the benzyl group

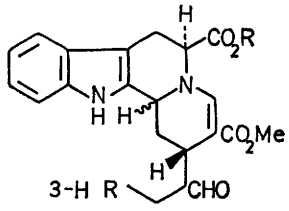
preventing premature reaction of N-4 at this and subsequent stages. Cleavage by β-glucosidase gave a mixture of aglucones (**4a**) and (**4b**) which could be separated by t.l.c. but readily interconverted in solution. Brief treatment



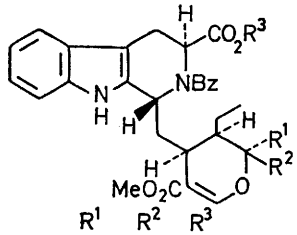
R
(1)a; $-CH=CH_2$
b; Et



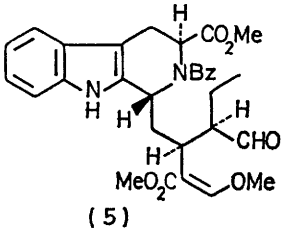
	R^1	R^2	R^3
(2)a;	H	$H-CH=CH_2$	
b;	CO_2H	$H-CH=CH_2$	
c;	CO_2H	H	Et
d;	CO_2H	Bz	Et



3-H R
(3)a; α H
b; β H
c; β Me



	R^1	R^2	R^3
(4)a;	OH	H	H
b;	H	OH	H
c;	OH	H	Me
d;	H	OH	Me



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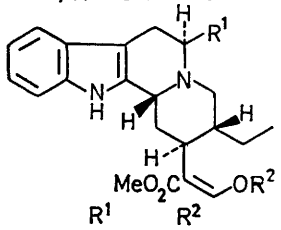
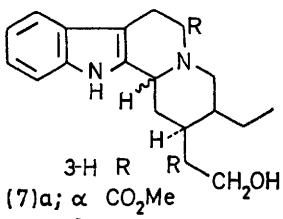


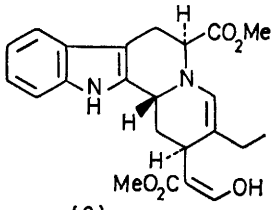
	R^1	R^2
(6)a;	CO_2Me	Me
b;	H	Me
c;	CO_2Me	H

with diazomethane gave the methyl esters (**4c**) and (**4d**), and more prolonged methylation afforded the ring opened aldehyde (**5**) containing an enol ether function, whose purpose was to hamper nucleophilic attack by N-4 on C-17. Catalytic hydrogenation of (**5**) with Pd–C in methanolic acetic acid achieved the remaining stages in one step: hydrogenolysis of the benzyl group was followed by cyclisation of N-4 to C-21, subsequent reduction of the resulting carbinolamine gave a compound with the *Corynanthé* skeleton—5-methoxycarbonylhirsutine (**6a**) $[\alpha]_D^{22}$ + 77° (MeOH). This structure and stereochemistry was fully substantiated by mass, u.v., i.r., n.m.r., and c.d. spectra, which showed a striking correspondence to the known alkaloid hirsutine[5] (**6b**). Finally, cleavage of the enol ether with acid and reduction with sodium borohydride provided a compound (**7b**) whose mass spectrum was identical to that of adirubine, and indicated that they differed only in stereochemistry.

Direct hydrogenolysis of the mixture of methylated aglucones (**4c**) and (**4d**) in methanolic acetic acid had an interesting consequence, since only a small amount of the expected vallesiachotamine derivative (**3c**) was obtained. The major product $[\alpha]_D^{22}$ + 216° (MeOH) was isomeric but was not an aldehyde and retained the β-alkoxyacrylate chromophore. Since there was no base shift in the u.v.



3-H R R
(7)a; α CO_2Me CH_2OH
b; β CO_2Me
c; β CH_2OH



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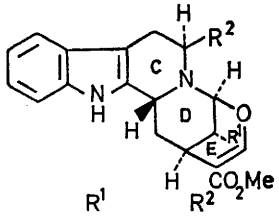
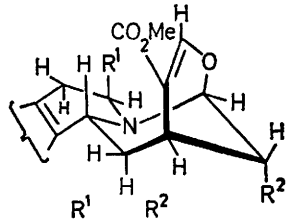
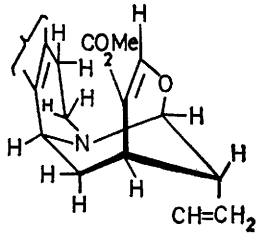


	R^1	R^2
9)a;	Et	CO_2Me
b;	$-CH=CH_2$	H



	R^1	R^2
(10)a;	CO_2Me	Et
b;	H	$-CH=CH_2$



(11)

spectrum and borohydride had no effect the enamine (**8**) was eliminated, but reduction with $LiAlH_4$ afforded a compound whose mass and c.d. spectra corresponded to a triol (**7c**). The structure consistent with these data was the aminoether (**9a**), which was confirmed by analysis of the n.m.r. spectrum where, with the aid of decoupling, virtually every proton could be assigned, and furthermore, the observed coupling constants established a chair conformation for ring D (**10a**). Since (**2c**) gave *only* the vallesiachotamine derivative (**3c**), which was associated with opening of the cyclic hemiacetal, it would be reasonable to suppose that the amino-ether (**9a**) might be derived from (**4**) by an alternative route without ring opening *via* intramolecular displacement of the protonated C-21 hydroxy by N-4 at some stage. No compound could be detected corresponding to (**6c**), which would have supported the intermediacy of (**8**) or its immonium derivative.

The formation of the novel structure (**9a**) suggests a possible explanation of the necessity for a 3β-configuration in the biosynthetic precursor (**2a**). There seems no reason why the general sequence we have followed from the 3β-glucoside (**2**) to the *Corynanthé* skeleton *via* a ring-opened enol ether should not also be followed by the corresponding 3α-isomers. However, if one postulates a biosynthetic aminoether intermediate (**9b**) formed analogously to (**9a**), then only with 3-H in the β-configuration can ring D have a chair conformation (**10b**) with minimal interactions. If 3-H is α, the conformational choice is between a chair (**11**) with severe 1,3-diaxial interactions between rings C and E, and a boat with a bowsprit-flagpole interaction between 3-H and the vinyl group, so that formation of such an intermediate would not be favoured. Subsequent stages would involve opening of the ether bridge when different combinations of methylation, tautomerism, reduction, and C-3 epimerisation[6] could provide the various *Corynanthé* type alkaloids.

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[1] J. Staunton, in 'The Alkaloids,' ed. J. E. Saxton, Specialist Periodical Reports, The Chemical Society, London, 1972, vol. 2, p. 1 and refs. therein.
[2] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1193.
[3] G. N. Smith, *Chem. Comm.*, 1968, 912.
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[6] *E.g.* J. A. Joule and A. J. Gaskell, *Tetrahedron*, 1967, **23**, 4053.