Biomimetic Inversion of C-3 in Monoterpenoid Indole Alkaloids

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Summary An inversion of 3-H analogous to that required *in vivo* has been found to occur spontaneously under mild conditions during a synthesis of Corynanthé-type alkaloids from a vincoside derivative.

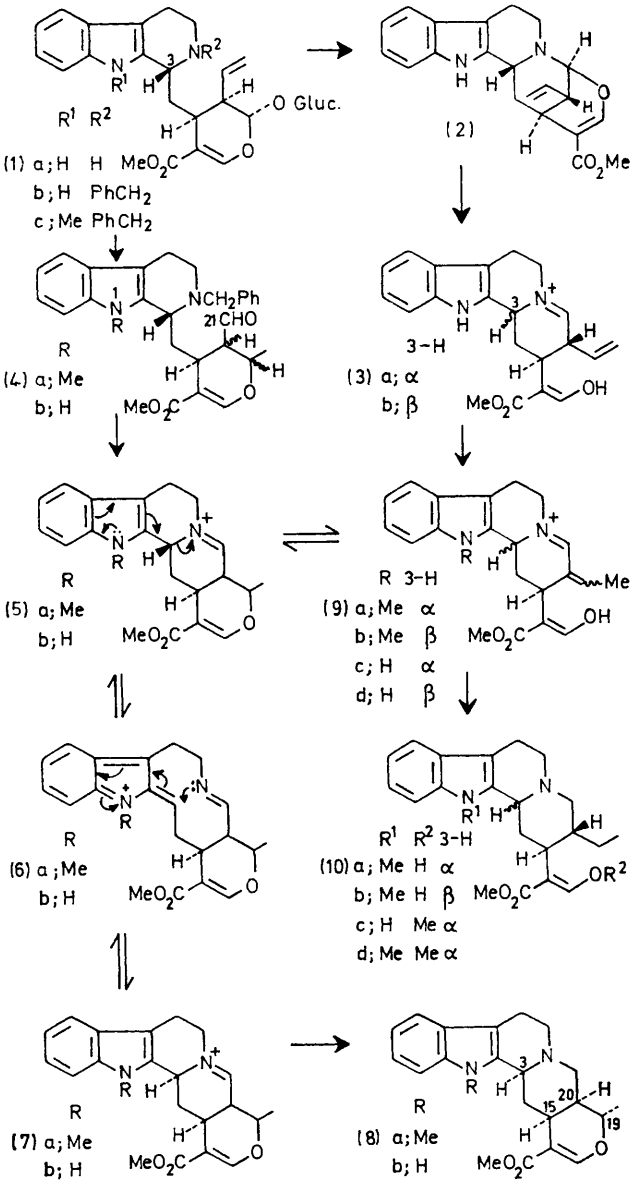
Two intriguing points to emerge from biosynthetic studies on monoterpenoid indole alkaloids were (i) that even for the Corynanthé type with 3α(*S*) stereochemistry the exclusive precursor was a 3β(*R*) epimer, vincoside (**1a**), and (ii) that the consequent inversion of C-3 occurred with retention of hydrogen.[1] The former has been rationalised by invoking a hypothetical intermediate, mancunine (**2**), which was substantiated by synthesising a closely related structure readily converted into known alkaloids.[2,3] We now report the synthesis from a vincoside derivative of two 3α Corynanthé alkaloids— N^1-methyltetrahydroalstonine (**8a**) and N^1-methyl-20β-dihydrogeissoschizine (**10a**) in a sequence which provides a satisfactory analogy and mechanism for the latter process.

A recent synthesis[4] of heteroyohimbine alkaloids from (**1b**) was forced to deviate from the presumed biogenetic route because (**4b**) could not be isolated owing to cyclisation of the indolic NH on to the C-21 aldehyde. Hence it was repeated with a methyl blocking group on N-1. Removal of the sugar from N^4-benzyl-N^1-methylvincoside (**1c**), m.p. 219–221°, $[\alpha]_D^{25}$ − 87° (MeOH) gave two major products, isomeric with a simple aglycone but lacking the characteristic *rapid* shift in the u.v. spectrum on addition of alkali. However, both eventually gave a base shift when left and were assigned the gross structure of a rearranged aglycone (**4a**), supported *inter alia* by n.m.r. signals for aldehydic protons at τ 0·50 and 0·62 and *C*-methyl doublets at τ 8·44 and 8·56. Hydrogenation of the mixture with Pd–C in MeOH–AcOH afforded mainly two compounds together with a small amount of a third.

One major product, $C_{22}H_{26}N_2O_3$, $[\alpha]_D^{25}$ − 163° (MeOH), [picrolonate, m.p. 176° (decomp.)] did not exhibit a u.v. base shift, and its mass spectrum suggested a heteroyohimbine structure which was substantiated by appropriate n.m.r. signals. Furthermore, since 3-H was above τ 6·2, and 19-H appeared at τ 5·5 with a *trans*-diaxial coupling (8 Hz) to 20-H,[5] the stereochemistry was 3α, 15α, 19β, 20α, corresponding to that of tetrahydroalstonine (**8b**). Methylation of the latter with MeI–NaOMe–Me_2SO in a modification of Heaney's method[6] afforded a good yield of N^1-methyltetrahydroalstonine (**8a**) which was identical with the previous compound.

On the other hand, the second major product, $C_{22}H_{28}N_2O_3$, $[\alpha]_D^{25}$ + 92° (MeOH) gave an *immediate* u.v. base shift typical of a β-hydroxyacrylate chromophore, and the mass and n.m.r. spectra were consistent only with a dihydrogeissoschizine structure. A negative Cotton effect in the c.d. spectrum between 260 and 300 nm, and an n.m.r. absorption at τ 5·46 showed that 3-H was still β. After methylation of the enol with diazomethane, an oxidation–reduction sequence with $Pb(OAc)_4$ and $NaBH_4$ afforded the 3α isomer. This proved identical with N^1-methyldihydrocorynantheine (**10d**), prepared from dihydrocorynantheine (**10c**) as above, and also with the methyl ether obtained by treatment of the minor product ($C_{22}H_{28}N_2O_3$) with diazomethane. Hence the second major compound must be 3β,20β-N^1-methyldihydrogeissoschizine (**10b**) and the minor its 3α epimer (**10a**).

Inversion of 3-H has thus occurred readily in two cases, and since nothing similar had been observed in previous



reactions,[2-4] it could neither be caused by the Pd–C catalyst nor take place after reduction of C-21. Deuteriation studies confirmed that 3-H was retained throughout. We therefore postulate the following mechanism: cleavage of the C-3–N-4 bond in the obligatory immonium intermediate (**5a**) is promoted by electron release from N-1 and gives the imine (**6a**); re-closure can then occur by attack of N-4 on C-3 from the opposite side to afford the more stable structure (**7a**), which is subsequently reduced to (**8a**). Formation of the dihydrogeissoschizine derivatives is presumably *via* retro-Michael cleavage of (**5a**) to (**9b**), and a similar conversion of (**7a**) into (**9a**) or epimerisation of (**9b**) prior to reduction.

Since C-H is not lost at any stage this sequence furnishes an apposite model for the *in vivo* process: opening of the ether bridge in mancunine (**2**) generates the immonium ion (**3b**), convertible by inversion of 3-H as above into demethyldehydrocorynantheine (**3a**). From this all the 3α Corynanthé alkaloids can be derived by various combinations of reduction, methylation, tautomerism, and conjugate addition. Obviously the epimerisation could occur at other stages, *e.g.* (**9b**) or (**5b**), but the essential mechanism would remain the same. The Ipecac alkaloids could presumably be epimerised in a similar manner but with electron release from oxygen rather than nitrogen.

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