Alternative Cyclisation of 3α- and 3β- Indole Alkaloid Glucosides

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Summary Under acidic conditions dihydromancunine (**2**) can be obtained directly from 3β-dihydrovincoside (**1c**) by cyclisation of N-4 to C-21, whereas 3α-strictosidine (**1a**) affords a novel N-1 cyclised derivative, nacycline (**6**).

THE synthesis of dihydromancunine (**2**) provided a satisfactory model for a hypothetical biosynthetic intermediate, which was readily converted into standard *Corynanthé* alkaloids.[1] A key feature was the use of (**1d**) containing an *N*-4 benzyl group to prevent spontaneous formation of the vallesiachotamine derivative (**3b**), which otherwise was the sole product when the sugar was removed from 18,19-dihydrovincoside (**1c**) by β-glucosidase in the usual pH 5 buffer. Subsequently we have found that if more acidic media are used dihydromancunine can be obtained directly from (**1c**) without using a blocking group; for example, at pH 4 after 48 h dihydromancunine constitutes *ca.* 10% of the product from dihydrovincoside. Since a much lower pH denatures the enzyme, alternative non-enzymatic methods for acid-catalysed cleavage of the sugar are being examined to improve the yield. In an extension of this investigation of the 3α-series, strictosidine (**1a**) was treated with methanolic HCl at room temperature for 5 days. Most of the starting material was recovered unchanged but a small amount of a new compound was isolated: nacycline, $C_{21}H_{22}N_2O_3$, $[\alpha]_D^{25}$ +220° (MeOH).

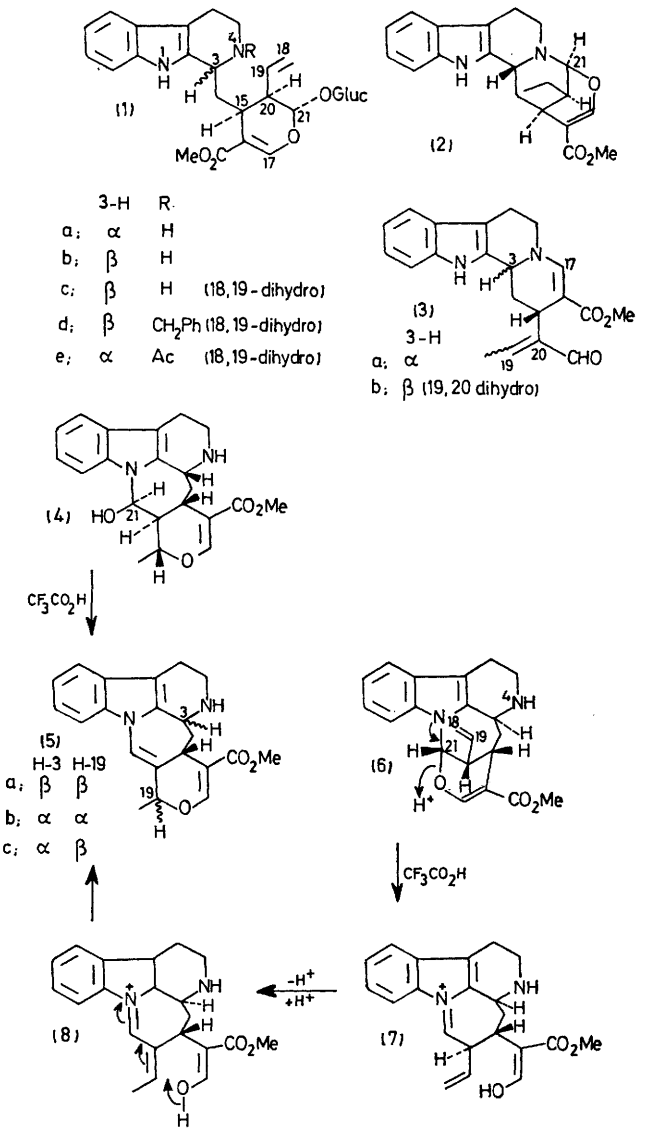
U.v., i.r., and n.m.r. spectral data indicated indole and methyl β-alkoxyacrylate chromophores. Since acetylation gave an acetamide, $C_{23}H_{24}N_2O_4$, the basic nitrogen function was still secondary, and subsequent catalytic hydrogenation to a dihydro-derivative together with appropriate n.m.r. signals established that the vinyl group had also been retained. However, although the formula of nacycline corresponded to simple loss of glucose, its mass spectrum

was totally unlike that of the glycoside, being dominated by a loss of 101 m.u. ($MeO_2C{\cdot}CH{\cdot}CHO$) from M^+ just as with dihydromancunine. Furthermore, no indolic NH could be detected in the n.m.r. or i.r. spectra of nacycline or its acetamide, whereas a signal at τ 3·65 was reminiscent of 21-H in the *N*-1 cyclised aglycone (**4**) derived from vincoside (**1b**), a correspondence which also extended to characteristic features of the mass spectra.[2] On the basis of these and other data structure (**6**) was provisionally assigned to nacycline.

Confirmation of structure for (**4**) had been obtained by its ready transformation to an *N*-vinyl indole (**5a**) on treatment with CF_3CO_2H and an analogous C–O bond cleavage seemed feasible for (**6**). After 2 h in CF_3CO_2H it was partially converted into two *N*-vinyl indoles, whose chemical and spectral behaviour corresponded to the same gross structure (**5**) as the vincoside derivative. One anticipated difference was in the c.d. spectra where the 3α-compounds exhibited negative Cotton effects in the 320—300 nm region in contrast to the positive effect of the 3β-isomer. The rearrangement of (**6**) presumably occurs by opening of the protonated ether to (**7**), a prototropic shift to (**8**), and conjugate addition to generate two C-19 epimers (**5b,c**). Finally, 18,19-dihydronacycline *N*-4-acetamide was obtained by removal of the sugar from (**1e**) with β-glucosidase at pH 4, or at pH 5 followed by CF_3O_2H treatment.

Since the vinyl group was still present in nacycline, the configuration at C-20, as with C-3 and C-15, must be the same as in strictosidine.[3] That at C-21 was necessarily inverted, presumably by backside displacement of a protonated hydroxy or glucoside residue by N-1. Any opening of the dihydropyran ring would have led to rearrangement either to vallesiachotamine[3] (**3a**) or to an *N*-vinyl indole as above, but traces of the latter only could be detected in the original reaction mixture. Therefore, nacycline is fully represented by structure (**6**), noteworthy in being formed by cyclisation of C-21 to N-1 even though the more reactive N-4 is available for bonding. This behaviour is in accord with previous arguments that a 3α-analogue of mancunine would not be readily formed because of severe stereochemical interactions;[4] further examination of models indicated that the 3β-vincoside series would be equally unlikely to cyclise to N-1.

We thank the S.R.C. for financial support (C.L.C. and A.G.L.).



(*Received, 12th February* 1975; *Com.* 177.)

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