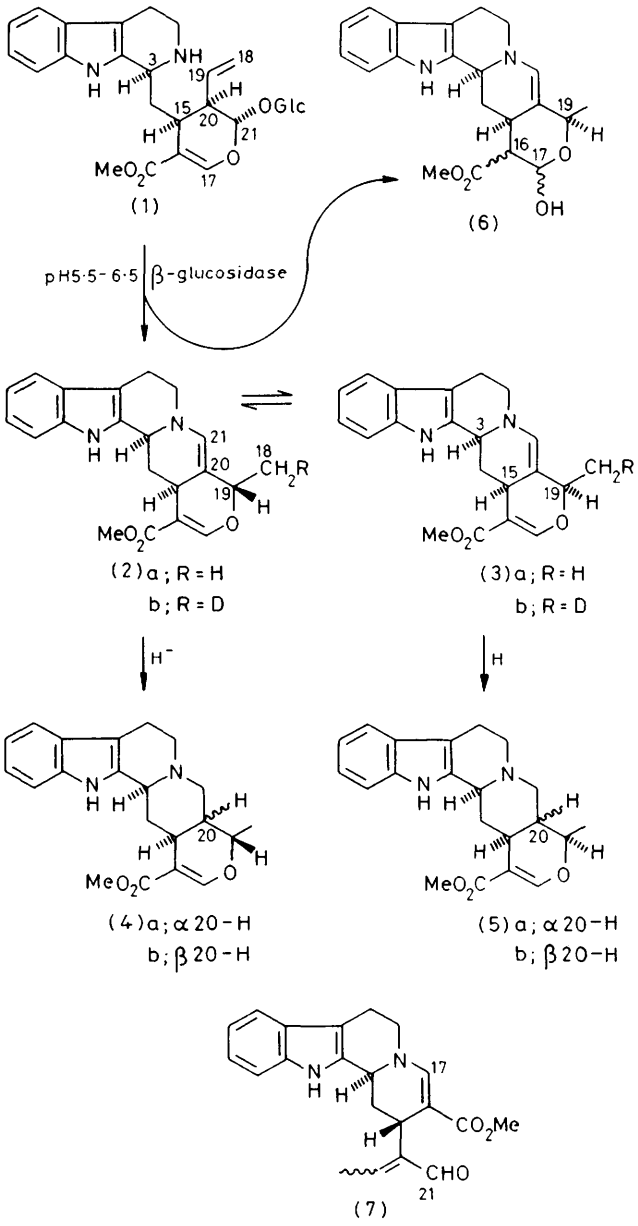
# Biomimetic Synthesis of Cathenamine and 19-Epicathenamine, Key Intermediates to Heteroyohimbine Alkaloids

By RICHARD T. BROWN* and JOHN LEONARD
(*Chemistry Department, The University, Manchester* M13 9PL)

*Summary* The previously unknown 19α-20,21-dehydroheteroyohimbine, 19-epicathenamine (**3a**), its water adducts (**6**), and cathenamine (**2a**) from which it is apparently formed, have been obtained by glucolysis of strictosidine (**1**); $^{2}H$ and $^{18}O$ studies indicate that the 19β/19α interconversion in water does not involve a dienamine (**8**) or (**6**).

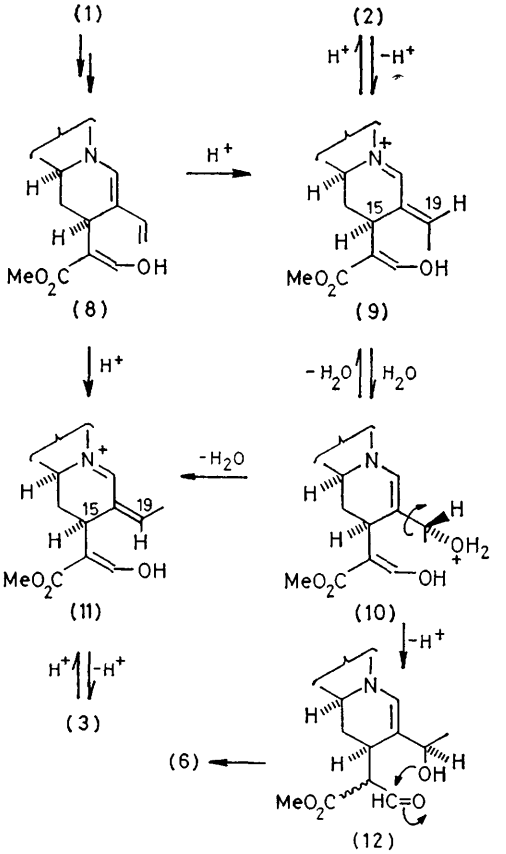
RECENTLY we have been able to achieve biomimetic syntheses of various indole alkaloids from strictosidine (**1**) in a 'one-pot' procedure with β-glucosidase and hydride reducing agents at pH 5—7.[1–3] One significant feature was that essentially the only heteroyohimbines obtained were the 19β-H (*S*)-tetrahydroalstonine (**4a**) and ajmalicine (**4b**), with negligible amounts of the 19α-H (*R*) isomers (**5**), in accord with the intermediacy of cathenamine[4] (20,21-dehydroajmalicine) (**2a**) which was subsequently trapped as the 21-cyano adduct by substituting cyanide for hydride.[5] This high degree of stereoselectivity was attributed to a kinetically controlled process involving

preferential formation of an *E*-alkene [*cf.* (**9**)] from the dienamine (**8**) followed by rapid cyclisation to (**2a**) and reduction to (**4**).[1,3] Such a mechanism would seem to be implicated *in vivo* since the 19β-alkaloids are certainly the most abundant. We have suggested that formation of the




less common 19α-alkaloids would require an equilibration period at the 20,21-dehydro stage in the absence of reducing agent to enable the *Z*-alkene (**11**) or equivalent to be formed.[3] Evidence is now adduced in support of this contention with the biomimetic formation from strictosidine of the previously unknown requisite 19α-intermediate, 19-epicathenamine (**3a**), together with its water adducts (**6**)[6] and cathenamine (**2a**).

β-Glucosidase was added to strictosidine in phosphate–citrate aqueous buffer (pH 6·0) at 37 °C, and after 3 h the solution was extracted with ether. T.l.c. and h.p.l.c. analysis showed that the extract (*ca.* 50% crude yield) comprised largely two isomeric compounds ($C_{21}H_{22}O_3N_2$) in a ratio of *ca.* 6 : 1, together with a trace of vallesiachotamine (**7**), which were separated by preparative t.l.c. The major product, $[\alpha]_D$ −67° (MeOH), was identified as (**2a**) from its u.v., c.d., n.m.r., and mass spectral data and by reduction to (**4a**) with $NaBH_4$.[4] The less polar product, $[\alpha]_D$ −11°, had u.v. and mass spectra identical with those of (**2a**), but, although generally similar, the 300 MHz n.m.r. spectrum showed differences in chemical shift at τ 3·01 (NH), 2·34 (bs, 17-H), 3·78 (bs, 21-H), 5·55 (q, *J* 6 Hz, 18-H), 5·66 (d + *J* 12 and 2·5 Hz, 3-H), fine coupling unresolved and 8·52 (d, *J* 6 Hz, 18-$H_3$). A full analysis with decoupling showed that, as expected, 3-H and 15-H were still *cis*, the c.d. spectrum confirmed that 3-H had retained the α(*S*) configuration, and hence the difference could only be in the C-19 chirality. Final confirmation of the novel structure (**3a**) was obtained when reduction with $NaBH_4$ in methanol afforded 19-epiajmalicine (**5b**) as the major product. Interestingly, with $NaCNBH_3$ in pH 6 buffer, (**3a**) gave mainly the C-20 epimer, rauniticine (**5a**), whereas (**2a**) gave again (**4a**) and only a small amount of its C-20 epimer, (**4b**).




When the glycolysis was left overnight (18 h) the proportion of (**3a**) relative to (**2a**) increased significantly to *ca.* 2 : 3, suggesting an interconversion. Accordingly, purified samples of the two alkaloids were also found to epimerise, even in organic solvents; for instance, after several hours in chloroform (**3a**) was 70% converted into the 19β epimer. Repetition of the glucolysis at pH 5·5 and

6·5 afforded, respectively, rather less and rather more (**3a**) than at pH 6·0, indicating some degree of pH dependence in its production.

The overnight reactions gave not only more vallesiachotamine (**7**), as expected, but also appreciable amounts of two isomeric water adducts, $M^+$ 368 ($C_{21}H_{24}O_4N_2$). Since reduction with $NaBH_4$ and subsequent dehydration with trifluoroacetic acid gave 19-epiajmalicine (**5b**), both have the general structure (**6**), corresponding to alkaloids isolated by Kan-Fan and Husson from *Guettarda eximia*.[6] However, in our case, dehydration of (**6**) with silica afforded largely (**3a**) rather than (**2a**) (*ca.* 6:1 ratio) in accordance with 19$\alpha$ chirality. As mentioned above, epimerisation of (**3**) can occur fairly rapidly and would probably better account for the formation of (**2**) rather than the presence of a water adduct of cathenamine.

We have previously indicated that (**2**) is derived from a dienamine (**8**) *via* a preferentially formed *E*-alkene (*cf.* **9**) by Michael addition of the enol, necessarily from the upper ($\beta$) face, and hence (**3**) would result from an analogous addition to a *Z*-alkene (**11**). The latter could be produced from (**2**) by either (a) direct protonation of the dienamine (**8**) regenerated from (**9**) or, (b) addition of water to (**9**) from the lower ($\alpha$) face to give (**10**), partial rotation about the 19,20 bond, and elimination of water. A variation of (b) would be formation of the cyclised water adduct (**6**) from (**10**) *via* (**12**), followed by dehydration to (**2**).

In order to distinguish between these two general mechanisms for the interconversion of (**2a**) and (**3a**), we repeated the glucolysis of (**1**) at pH 6·0 in $D_2O$. After 3 h the two epimers were isolated and both were found to contain essentially one deuterium atom at C-18, from mass spectra. After 24 h the proportion of (**3**) had greatly increased but still both were the [$^2H_1$]-species (**2b**) and (**3b**). Evidently no more deuterium had been incorporated from the water, the dienamine (**8**) had not been reformed, and thus could not be an intermediate. Hence the first mechanism is not valid (at least in water), and the actual process would seem to involve the addition of water at C-19 to achieve inversion. Of the two variants we considered that the rapid addition and loss of water (**9**) → (**10**) → (**11**) was much more likely. The cyclised water adducts (**6**) formed from (**10**) *via* (**12**) are really too stable to function as convenient precursors of (**3**) in as much as they apparently require an active dehydrating agent (silica, $CF_3CO_2H$) to liberate the $\beta$-alkoxyacrylate system. Cyclisation of (**10**)/(**12**) to (**6**) would appear to be not readily reversible in aqueous solution, and thus represents a competing rather than an intermediary process to the formation of (**2**) and (**3**). In this context it is noteworthy that they are not precursors for heteroyohimbine alkaloids in cell-free systems.[7] A conclusive distinction between the two variants was made by using $^{18}O$ water to establish that the ring oxygen in 19$\alpha$-heteroyohombine alkaloids is of intramolecular origin, since no $^{18}O$ was incorporated into (**2**) or (**3**).

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