Isolation and Biomimetic Conversion of 4,21-Dehydrogeissoschizine

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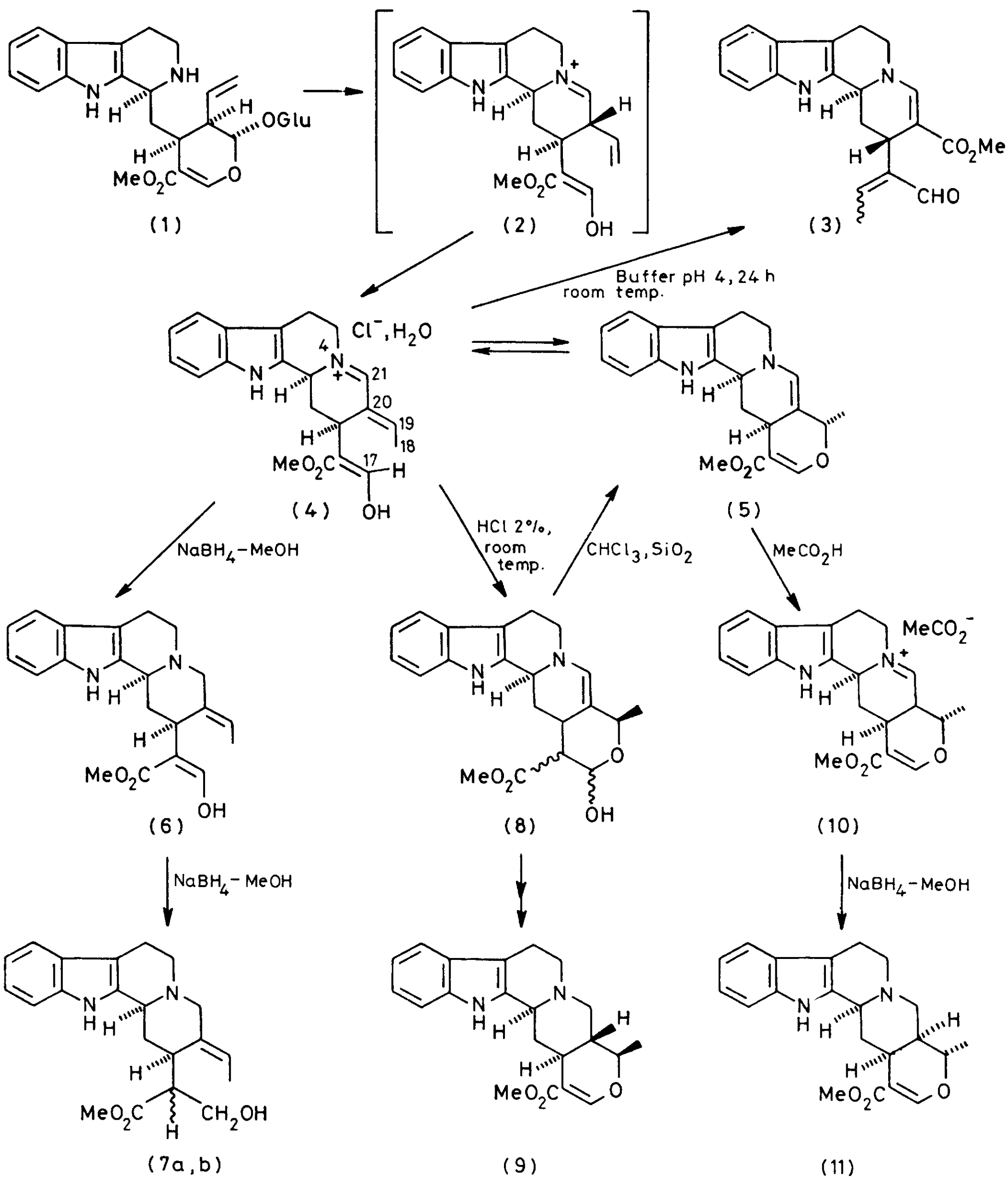
Summary 4,21-Dehydrogeissochizine hydrochloride (**4**), a postulated intermediate in the biosynthesis of heteroyohimbine alkaloids, has been isolated from a plant source; it has been converted into cathenamine (**5**) and iso-vallesiachotamine (**3**), in addition to heteroyohimbine and geissoschizine-type alkaloids, (**9**), (**11**) and (**6**), (**7**), respectively.

WE recently isolated cathenamine (**5**) and 17-hydroxy cathenamine (**8**) from the leaves of *Guettarda eximia* (*Rubiaceae*).[1,2]

We now report the isolation of 4,21-dehydrogeissoschizine hydrochloride (**4**) from the same plant. Alkaline treatment of the plant (10% aq. Na_2CO_3) was followed by ether extraction at room temperature. The ether solution was concentrated and extracted with a 2% aqueous solution of hydrochloric acid. After 12 h the precipitated crystals of (**4**) were filtered off (yield 3·45 g per kg of dry leaves), m.p. 250 °C decomp., and analysed for the formula $C_{21}H_{22}$-O_3N_2, HCl, H_2O. The salt (**4**), when treated with aqueous alkaline solution (Na_2CO_3 or NaOH) gives pure crystalline cathenamine (**5**) (ether–methanol, m.p. 176 °C) in quan-



titative yield.† This experiment affords information concerning the structure of (**4**) and shows that it was the precursor of cathenamine (**5**) in the previous isolation,[1] where the aqueous acid solution was made alkaline and immediately extracted with ether to obtain the crude alkaloid mixture containing, as the major product, cathenamine (**5**).

Proof of the structure of (**4**) is based on spectral data and chemical transformations.‡ $NaBH_4$ reduction of (**4**) in methanol leads to a mixture of geissoschizine (**6**) 10%, isositsirikine (**7a**) 30%, 16-epi-isositsirikine (**7b**) 50%, and tetrahydroalstonine (**11**) $<10\%$.§ The formation of (**6**) and (**7**) possessing an ethylidene type double bond of *E* configuration is in agreement with the reduction of the conjugate iminium ion of type (**4**) by the 1,2-addition of a hydride ion.[3] The same mixture of (**6**) + (**7**) + (**11**) is obtained on reduction of cathenamine (**5**) in methanol with $NaBH_4$.

Moreover, cathenamine (**5**) yields tetrahydroalstonine (**11**) quantitatively on reduction using the same conditions as above in the presence of traces of $MeCO_2H$.

These results indicate that the equilibrium (**4**) $\rightleftharpoons$ (**5**) is involved in the $NaBH_4$ reduction in methanol and that a cyclised structure of type (**10**) could not be rejected *a priori* for the new isolated product. The examination of the ^1H n.m.r. spectra [Me_4Si, CD_3OD, $\delta = 0$, 400 MHz¶] of (**4**): 2·05 [d, *J* 6 Hz, $C(18)H_3$] and 3·35 (s, CO_2Me) and of (**10**), derived from the protonation of (**5**): 1·38 [d, *J* 6 Hz, $C(18)H_3$] and 3·70 (s, CO_2Me) clearly demonstrates that (**4**) and (**10**) are different and that the $C(18)H_3$ resonances are in agreement with the proposed structures.

Some biomimetic conversions of 4,21-dehydrogeissoschizine (**4**) have been achieved. Thus 17-hydroxy-cathenamine (**8**) is obtained (yield 40%) from (**4**) treated in 2% aqueous hydrochloric acid solution for 12 h at room temperature after dissolution by heating on the steam bath.

As we have previously shown[2] (**8**) leads to 19-epiajmalicine (**9**) on reduction with $NaBH_4$ in methanol followed by dehydration (p-$MeC_6H_4SO_3H$). However, (**4**) yields a mixture of vallesiachotamine (traces) and isovallesiachotamine (**3**)[4] in a buffered solution at pH 4 (yield 20%).

All the chemical transformations herein described mimic biosynthetic steps and complement conversions[5] carried out from strictosidine (**1**) the common precursor of the indole alkaloids. The role of 4,21-dehydrogeissoschizine (**4**) in the enzymatic synthesis of heteroyohimbine alkaloids is given in the following paper.[6]

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† Up until the present time cathenamine had only been isolated in an amorphous form.

‡ It has been possible to record a ^{13}C n.m.r. spectrum of cathenamine (**5**). We are grateful to Dr. A. Ahond for interpreting it.

§ We thank M. Damak, M. Úrrea, G. Robert, A. Ahond, C. Poupat, and P. Potier for the communication of the following results (unpublished): $NaBH_4$ controlled reduction of geissoschizine (**6**) leads to isositsirikine (**7a**) and epi-isositsirikine (**7b**) in the same ratio as for (**4**); this is in agreement with the pathway (**4**) $\rightarrow$ (**6**) $\rightarrow$ (**7a, b**).

¶ We thank Dr. S. K. Kan, Institut d'Electronique Fondamentale, Université de Paris-Sud, 91405, Orsay, for recording all ^1H n.m.r. spectra with his 400 MHz machine.

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