

Isolation and Biomimetic Conversion of 4,21-Dehydrogeissoschizine

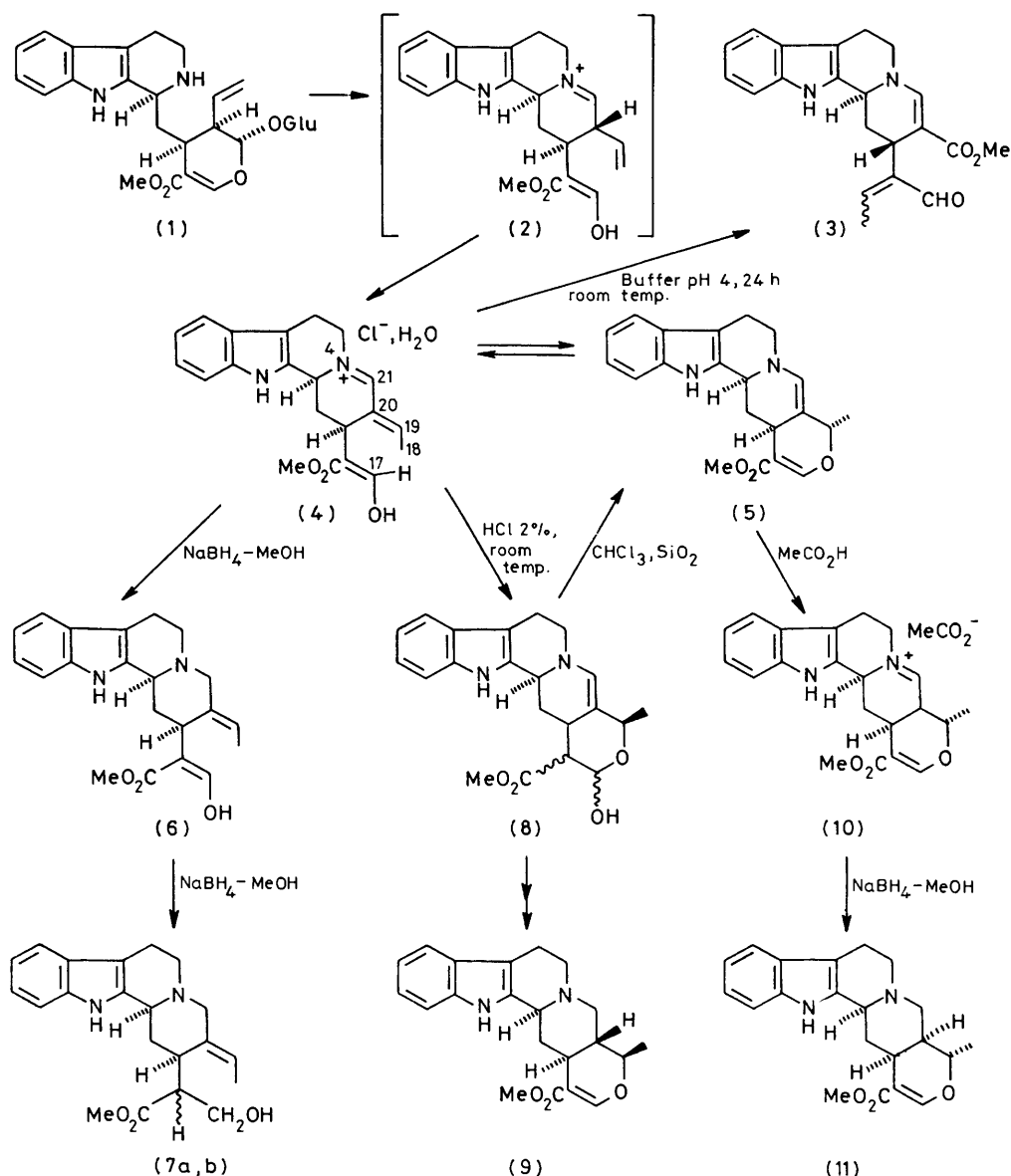
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Summary 4,21-Dehydrogeissoschizine hydrochloride (4), a postulated intermediate in the biosynthesis of heteroyohimbine alkaloids, has been isolated from a plant source; it has been converted into cathenamine (5) and isovallesiachotamine (3), in addition 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 $\text{C}_{21}\text{H}_{23}\text{O}_3\text{N}_2$, 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.‡ NaBH₄ 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 NaBH₄.

Moreover, cathenamine (5) yields tetrahydroalstonine (11) quantitatively on reduction using the same conditions as above in the presence of traces of MeCO₂H.

These results indicate that the equilibrium (4) ⇌ (5) is involved in the NaBH₄ 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 [Me₄Si, CD₃OD, δ = 0, 400 MHz¶] of (4): 2.05 [d, *J* 6 Hz, C(18)H₃] and 3.35 (s, CO₂Me) and of (10),

derived from the protonation of (5): 1.38 [d, *J* 6 Hz, C(18)H₃] and 3.70 (s, CO₂Me) clearly demonstrates that (4) and (10) are different and that the C(18)H₃ 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 shown² (8) leads to 19-epiajmalicine (9) on reduction with NaBH₄ in methanol followed by dehydration (*p*-MeC₆H₄SO₃H). 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 conversions⁵ 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 ¹³C n.m.r. spectrum of cathenamine (5). We are grateful to Dr. A. Ahond for interpreting it.

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¶ 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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³ 'Indole and Biogenetically Related Alkaloids,' eds J. D. Phillipson and M. H. Zenk, Academic Press, London, in the press; R. Besselièvre and H. P. Husson, unpublished results.

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