Stereochemical Control in the Biomimetic Conversion of Heteroyohimbine Alkaloid Precursors. Isolation of a Novel Key Intermediate

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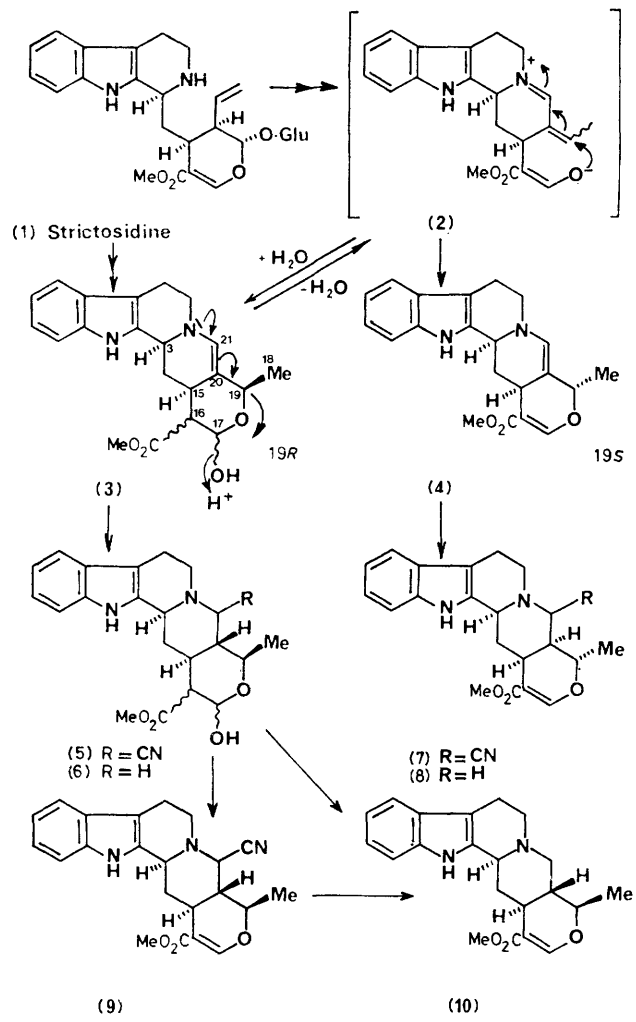
Summary The isolation of a novel key intermediate (**3**) related to cathenamine (**4**) and its conversion in a stereoselective sequence of reactions into tetrahydroalstonine (**8**) and 19-epiajmalicine (**10**) afford new information concerning the biosynthesis of heteroyohimbine alkaloids.

THE eight possible heteroyohimbine alkaloids have been isolated.[1] However, the factors which govern the stereochemistry at C(3), C(19), and C(20) during their biosynthesis are still not well known. C(3) epimerisation has been achieved *in vitro*[2] and biomimetic syntheses starting from closely related precursors[3,4] show that the stereoselectivity is dependent on the kind of precursor and the experimental conditions employed. Until our isolation of cathenamine (**4**),[5] this postulated precursor of heteroyohimbine alkaloids had not been available. It has been shown that (**4**) is an intermediate in the cell-free biosynthesis of ajmalicine and related indole alkaloids,[6] leading mainly to the 19*S* series (ajmalicine and tetrahydroalstonine). The configuration at C(20) is dependent on the side of protonation of the enamine to give an immonium ion which is subsequently reduced. A biomimetic synthesis[4] leads to the same results *via* cathenamine (**4**).[7]

We describe herein the isolation and structure elucidation of a novel intermediate (**3**), related to cathenamine (**4**), hydroxylated at C(17). 20,21-Didehydroheteroyohimbine (**3**) was isolated, together with cathenamine (**4**),[5] from



Guettarda eximia (Rubiaceae)† as an inseparable mixture of two epimers at C(16) and/or C(17). The structure determination of (**3**) is based on spectral data and chemical properties: *m/e* 368 ($M^{+\cdot}$, 10%), 350 ($M - H_2O$; 50), and 249 (100); λ_{max} (EtOH) 228, 274, 280, and 290 nm; ^1H n.m.r.[8] δ ($CDCl_3$; Me_4Si; 240 MHz) two sets of Me signals are observed: 1·33 and 1·42 [each d, J 6 Hz, C(18)H_3], 3·83 and 3·86 (each s, CO_2Me), 6·18 (s, 21-H), and 8·22 and 8·30 (NH). The presence of the enamine function was confirmed by its trapping as the α-cyano-derivative (**5**) as in the case of cathenamine (**4**).‡ Compound (**5**) was dehydrated in benzene solution by *p*-$MeC_6H_4SO_3H$ to give only (**9**): m.p. 260 °C (ethanol), $[\alpha]_D^{20}$ + 21° ($CHCl_3$); *m/e* 377 ($M^{+\cdot}$, 100%), 156 (78), and 144 (50); ^1H n.m.r.[8] 1·40 [d, J 6 Hz, C(18)H_3], 3·85 (s, CO_2Me), 7·75 (s, 17-H), and 8·10 (NH).

Reduction ($NaBH_4$) of (**3**) leads to (**6**) and to 19-epi-ajmalicine (**10**) in high yield after dehydration (*p*-$MeC_6H_4SO_3H$). This result establishes the configuration at C(3), C(15), and C(19) for (**3**) and proves conclusively the proposed structures for (**3**), (**5**), (**6**), and (**9**). According to another route (**5**) gives (**9**) (dehydration) and then 19-epi-ajmalicine (**10**) ($NaBH_4$ reduction).

Treatment of the derivative (**3**) for 1 h in chloroform solution in the presence of silica gel 60 PF 254 (used for preparative layer chromatography) afforded cathenamine (**4**) in nearly quantitative yield. This result shows that the biogenetic intermediate (**3**) is able to fragment into the conjugated imminium species (**2**) which can be equilibrated at C(19), *via* the corresponding dienamine, into the 19*S* series. It is noteworthy that this configuration is the most commonly obtained in biomimetic synthesis.[4] The configuration at C(3) and C(15) being the same, the protonation at C(20) depends, *in vitro*, on the configuration at C(19). Indeed, the protonation takes place in such a manner that C(18)H_3 ends up in the energetically more favourable equatorial position.

Isolation of the labile compound (**3**) shows the existence of a novel biogenetic intermediate which can be stereoselectively converted into both 19*S* and 19*R* series indicating its possible involvement in a similar *in vivo* process. Such a conversion was not possible starting from cathenamine (**4**) indicating that the conversion (**2**) → (**4**) is probably irreversible and that stereochemical control could not occur at this stage.

Our results thus lead us to propose an alternative sequence for the early steps of the biosynthesis of the heteroyohimbine alkaloids.

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‡ In a typical procedure addition of CN^- was carried out at pH 4 in acetate buffer in the presence of KCN during 12 h. Independently R. T. Brown and J. Léonard have recently isolated cathenamine (**4**) as the cyano adduct (**7**).[7] We thank Mr. J.-P. Paccioni for the development of this procedure.

[1] J. Melchio, A. Bouquet, M. Païs, and R. Goutarel, *Tetrahedron Letters*, 1977, 315 and references cited therein. We thank Mlle. M. Païs for gifts of alkaloids.
[2] R. T. Brown, C. L. Chapple, and R. Platt, *J.C.S. Chem. Comm.*, 1974, 929.
[3] R. T. Brown and C. L. Chapple, *J.C.S. Chem. Comm.*, 1974, 740.
[4] R. T. Brown, J. Léonard, and S. K. Sleigh, *J.C.S. Chem. Comm.*, 1977, 636.
[5] H.-P. Husson, C. Kan-Fan, Th. Sévenet, and J. P. Vidal, *Tetrahedron Letters*, 1977, 1889.
[6] J. Stöckigt, H.-P. Husson, C. Kan-Fan, and M. H. Zenk, *J.C.S. Chem. Comm.*, 1977, 164.
[7] R. T. Brown and J. Léonard, *Tetrahedron Letters*, 1977, 4251.
[8] P. Gonord, C. Duret, C. Vibet, J. Salset, and S. K. Kan, *Rev. Sci. Instrum.*, 1973, **44**, 1725. We thank Dr. S. K. Kan and his colleagues (Institut d'Electronique Fondamentale, Université de Paris-Sud, 91405 Orsay) for allowing us to use their machine.