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BIOMIMETIC SYNTHESIS OF YOHIMBINE AND HETEROYOHIMBINE ALKALOIDS FROM 4,21-DEHYDROGEISSOSCHIZINE

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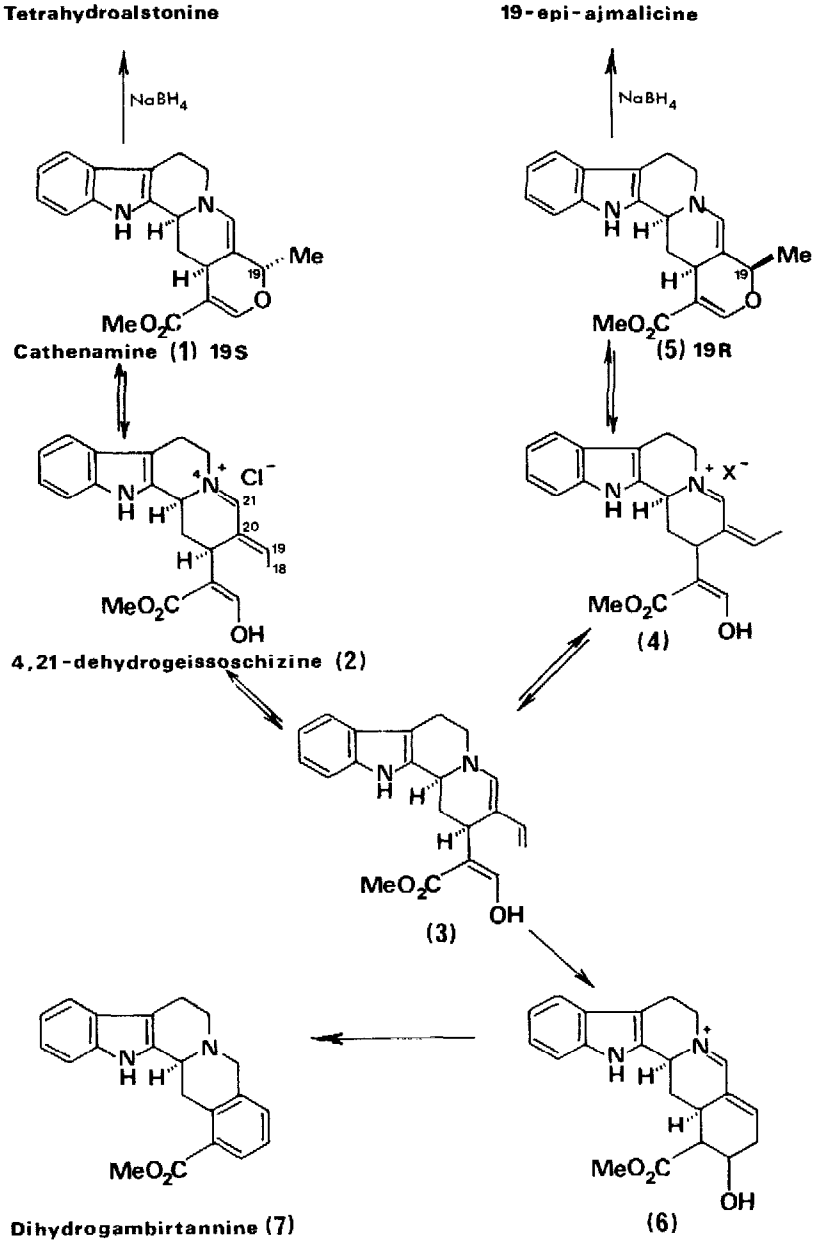
Summary : The first biomimetic synthesis of the yohimbine skeleton (7) from a Corynanthé-type precursor (2) is reported as well as the transformation of the latter into both the 19 R and 19 S heteroyohimbine series. Reactions were performed on an alumina surface.

We have recently been able to isolate the previously unknown 4,21-dehydrogeissoschizine (2) from a plant source[1]. It was then proven that (2) is a metabolic intermediate in enzymatic synthesis of heteroyohimbine alkaloids[2].

In this communication we wish to report that this pivotal intermediate can be transformed in a biomimetic manner into both 19 S (1) and 19 R (5) heteroyohimbine alkaloids and more interestingly can lead to the yohimbine series.

Indeed it has been postulated for a long time that the latter could be biosynthesised from the Corynanthé-type alkaloids[3]. However, among the numerous syntheses of the yohimbines[4,5], none of them took advantage of the biomimetic cyclisation of the intermediate dienamine (3)[4], probably because of the difficulty of synthesising such an enamine. 4,21-dehydrogeissoschizine (2) represents the protonated form of (3) but until now it appeared[1] that 1,4 addition of the enol function onto the conjugated iminium salt was the only reaction to occur under deprotonation conditions (aqueous NaOH, Na_2CO_3 or $(Et)_3N$) to give cathenamine (1)[6] in quantitative yield. Several attempts at different pH in buffered solution afforded (1) or rearranged products[1,6]. The generation of (3) in classical conditions was therefore a problem due to the competing reactions.

It is known that some organic reactions can be performed on alumina surfaces under very mild conditions[7]. Our observation of the nucleophilicity of the indole C-3 position catalysed by alumina during the total synthesis of an indole alkaloid[8] led us to try these reaction conditions on (2). One could indeed expect on the alumina surface deprotonation of (2) and activation of the reactivity as a dienamine which by nucleophilic attack on the aldehyde function would yield the yohimbine skeleton.


Tetrahydroalstonine
19-epi-ajmalicine
NaBH4
NaBH4
Me
MeO2C
Cathenamine (1) 19S
(5) 19R
Cl⁻
X⁻
4,21-dehydrogeissoschizine (2)
(4)
OH
(3)
(6)
Dihydrogambirtannine (7)

Scheme 1

To a suspension of (2) (1 g) in chloroform (300 ml) was added basic aluminoxid 90 Merck act. 1 (100 g). After 24 h stirring at room temperature the solid was filtered off and the organic solution distilled to dryness. The residue (0,3 g)[9] was immediately reduced with $NaBH_4$ in methanol in the presence of traces of acetic acid. $NaBH_4$ treatment was necessary in order to reduce the unstable enamines (1) and (5) before separation of the mixture. The crude extract showed, apart from polar products [silicagel thin layer chromatography (tlc), $CHCl_3$-CH_3OH 1 % for elution] , three compounds of decreasing polarity which have been identified as tetrahydroalstonine (reduction product of (1)), dihydrogambirtannine (7) and 19-epi-ajmalicine (reduction product of (5)). After tlc purification, pure dihydrogambirtannine (7) (5 mg) was isolated as a crystalline product and shown to be identical with a sample of the natural product (Rf, MS, IR, UV, NMR) [10,11].

The notorious instability of (7) [11] explains the poor yield of pure isolated product compared with the estimation on tlc.

No $NaBH_4$ reduction product of the intermediate (6) was isolated indicating that this product must afford (7) quickly on the alumina by dehydration and 1,3 hydride shift.

Another experiment with alumina was stopped after 4 h and the ^1H NMR spectrum [12] of the crude material (two spots on tlc) implied a 50/50 mixture of cathenamine (1)[6] and 19-epi-cathenamine (5) [13]. Furthermore cathenamine (1), obtained by aqueous basic treatment of (2)[1], was stable in chloroform solution [14], but also led to 19-epi-cathenamine (5) in the presence of alumina. The latter epimerised in chloroform even in the absence of alumina indicating its lower stability.

These results demonstrated that 4,21-dehydrogeissoschizine can be in equilibrium with the dienamine (3) which leads to the yohimbine series and to the 19 R heteroyohimbine series via the epimeric (Z) conjugated iminium salt (4).

The alumina surface thus mimics very well what could occur in enzymatic reactions and the equilibria indicated on scheme I are likely to be reminiscent of the possible pathways accounting for the formation of yohimbine and 19 R and S heteroyohimbine alkaloids in vivo.

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9 - Elution of the alumina with polar solvents (alcohols) allowed the recovery of more material but it has been observed that these solvents quickly decomposed the reaction products on heating.

10 - The authors thank Drs M. HESSE and G. NASINI for a sample of dihydrogambirtannine.

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12 - 400 MHz NMR spectra of some alkaloids in these series will be discussed later : C. KAN-FAN, M. LOUNASMAA, S.K. KAN and H.-P. HUSSON to be published.

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We thank Dr. R.T. BROWN for communication of the ^{1}H NMR spectrum of (5).

14 - No change in the spectrum after 3 days in the NMR tube.

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