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STRUCTURE AND SYNTHESIS OF ALAMARIDINE, A NOVEL BENZOPYRIDOQUINOLIZINE ALKALOID FROM ALANGIUM LAMARCKII

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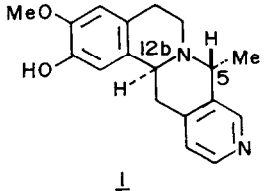
Abstract: Synthesis of (±)-alamaridine (1) from the N-pyridylmethyl dihydroisoquinolinium salt 3 via pivaloyl chloride induced cyclisation to 4 and subsequent reduction with sodium cyanoborohydride in acetic acid established the structure and relative stereochemistry at the chiral centres of this unique 5-methylbenzopyridoquinolizine alkaloid isolated from A.lamarckii Thw.

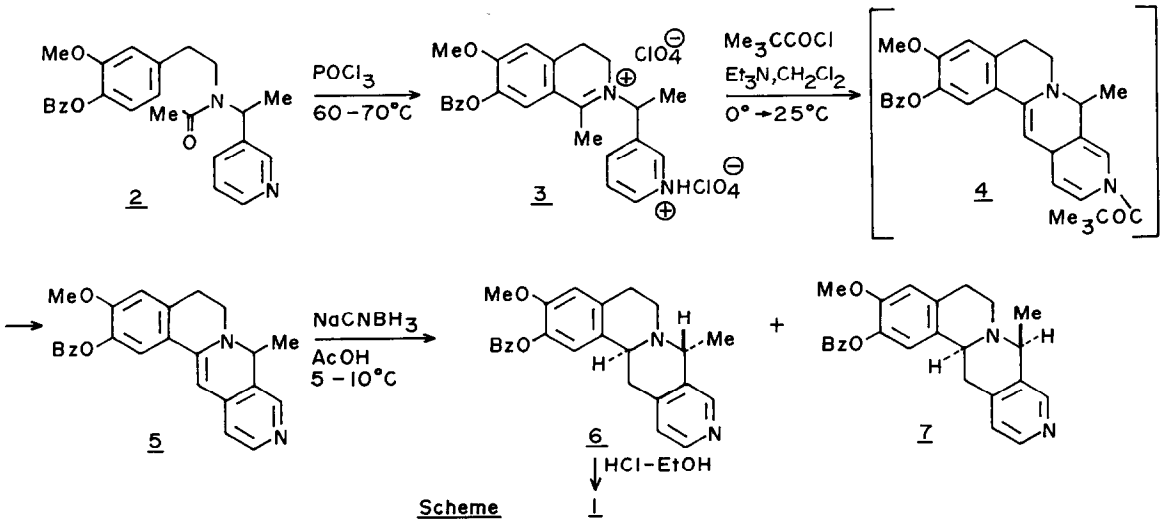
We earlier published[1,2] the isolation and characterisation of a number of benzopyridoquinolizine alkaloids from the weakly basic fraction of the methanolic extract of the seeds of Alangium lamarckii Thw. (Alangiaceae). The same source further yielded yet another novel base designated as alamaridine. In a preliminary report[3], we put forward a tentative structure for this alkaloid with a unique 5-methylbenzopyridoquinolizine skeleton based primarily on the spectral data and biogenetic considerations. The total synthesis (Scheme) of (±)-alamaridine which forms the subject matter of the present communication not only confirms the structure but also establishes the relative stereochemistry at the chiral centres, viz. C-5 and C-12b as 1.



1

The amide 2 on cyclisation with $POCl_3$ afforded the isoquinolinium salt 3 isolated as the bis-perchlorate (60%). The required benzopyridoquinolizine skeleton was then constructed from 3 by pivaloyl chloride induced cyclisation presumably through the nucleophilic attack of the enamine (generated in situ by Et_3N used) on the N-pivaloylpyridinium moiety as expected. The intermediate N-pivaloyldihydropyridine 4, however, could not be isolated since it apparently underwent spontaneous oxidation to O-benzyldehydroalamaridine 5 (20%).

Although initial attempts (catalytic hydrogenation or $NaBH_4$ in methanol) for the reduction of 5 were unsuccessful, it was eventually achieved by sodium cyanoborohydride in acetic acid to obtain a mixture of diastereoisomers 6 and 7 in 1:3 ratio. The relative stereochemistry of C-12b hydrogen and C-5 methyl in 6 and 7 was established on the basis of the ^{1}H-NMR chemical shifts of known 8-methyltetrahydroprotoberberines[4]. Thus, the minor isomer exhibiting a methyl



Scheme

doublet at δ 1.40 and a methine quartet at δ 4.14 was assigned the structure 6, while structure 7 was ascribed to the major one showing a methyl doublet at δ 1.58. Finally, both 6 and 7 were debenzylated and the product derived from 6 was found to be exactly identical (IR, MS and NMR) with the natural product.

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