Biomimetic Synthesis of Anatabine from 2,5-Dihydropyridine Produced *in Situ* by the Action of Sodium Hypochlorite on Baikiain

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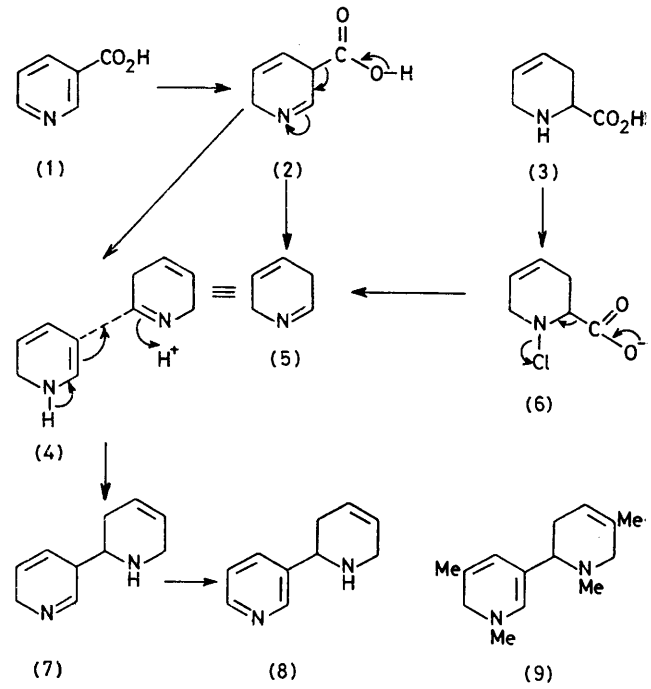
Summary Anatabine [2-(3-pyridyl)-1,2,3,6-tetrahydropyridine] and pyridine were produced when sodium hypochlorite was added to an aqueous solution of baikiain (1,2,3,6-tetrahydropyridine-2-carboxylic acid), this result being consistent with the intermediate formation of 2,5-dihydropyridine.

ANATABINE (**8**) is found in several species of tobacco, and we have established that nicotinic acid (**1**) serves as a precursor of both rings of this alkaloid.[1–3] It was proposed that its biosynthesis involves the intermediate formation of 3,6-dihydronicotonic acid (**2**) which undergoes decarboxylation to yield 2,5-dihydropyridine (**5**). Tautomerism of this compound affords 1,2-dihydropyridine (**4**) which could be formed directly from (**2**) as illustrated in the Scheme. Condensation of the enamine (**4**) with 2,5-dihydropyridine yields 3,6-dihydroanatabine (**7**) from which anatabine is produced by a dehydrogenation.

Despite a vast amount of work on dihydropyridines,[4,5] little is known of the chemistry of the simple dihydropyridines which lack substituents. 1,4-Dihydropyridine, out of the five possible isomers, is the only one which has been well characterised.[6,7] *N*-Alkylated 1,2- and 1,4-dihydropyridines are also known.[7–10] Cyclic imines have been obtained by the oxidative decarboxylation of α-amino acids, *e.g.*, Δ^1-pyrroline from proline.[11] Thus a plausible synthetic precursor of 2,5-dihydropyridine would be the natural product baikiain (**3**).[12] Accordingly (**3**), dissolved in aqueous buffers at pH 7, 8, and 10, was treated with sodium hypochlorite (1 equiv.), which resulted in the formation of strong u.v. absorptions at 255—265 nm, characteristic of pyridine derivatives. After 3 h the reaction mixtures were acidified and evaporated, and the residues subjected to t.l.c. Anatabine (10, 18, and 26% yield at pH 7, 8, and 10 respectively) and pyridine were isolated, the former being identical (mass spectrum, ^{13}C n.m.r.,[2] u.v., and i.r.) with an authentic specimen of (*RS*)-anatabine.[13]



SCHEME

It is proposed that reaction of baikiain with sodium hypochlorite yields the *N*-chloro-derivative (**6**) which

undergoes decarboxylation and loss of chloride ion to afford 2,5-dihydropyridine. Dimerization as previously discussed and oxidation (by air or sodium hypochlorite) then yields anatabine. This ready production of anatabine in aqueous solution provides strong support for the intermediacy of 2,5-dihydropyridine in its formation from nicotinic acid in the tobacco plant. The dihydroanatabine derivative (**9**) was obtained by the reduction of 1,3-dimethylpyridinium iodide with sodium borohydride in alkaline solution.[14] Its formation, involving dihydropyridines, is probably analogous to our reported synthesis of anatabine.

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