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SYNTHESIS OF 4-(1-METHYL-2-PYRROLIDINYL)ISOQUINOLINE UNDER PHYSIOLOGICAL CONDITIONS : A MODEL FOR THE BIOSYNTHESIS OF 4-PYRROLIDINYLISOQUINOLINE ALKALOIDS

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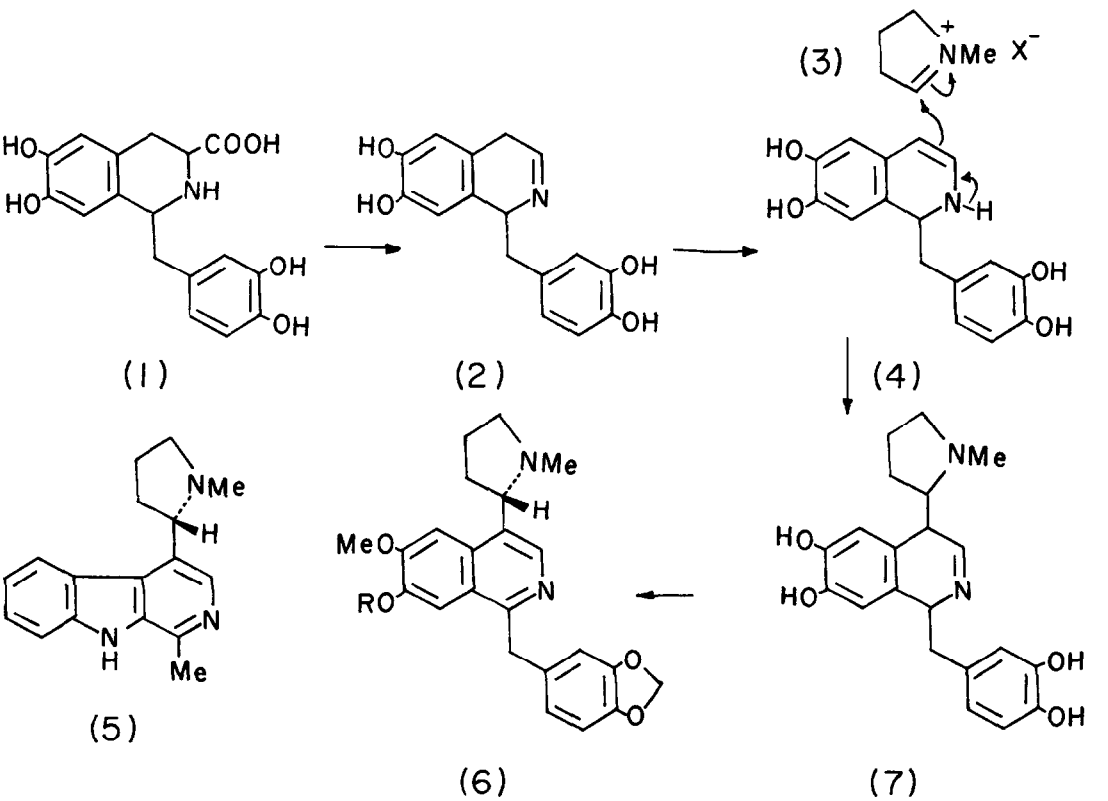
Abstract.— 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid was oxidatively decarboxylated with sodium hypochlorite, affording a dihydroisoquinoline which on condensation with N-methyl-Δ^1-pyrrolinium acetate, and subsequent aerial oxidation yielded 4-(1-methyl-2-pyrrolidinyl)isoquinoline.

Arenine (6, R = H) and macrostomine (6, R = Me) are novel isoquinoline alkaloids which have been isolated from *Papaver arenarium*[2] and *P. macrostomum*[3] respectively. Although no biosynthetic experiments have been carried out on these alkaloids, which contain a pyrrolidine ring at the 4-position of the isoquinoline nucleus, we consider that these alkaloids are formed from norlaudanosoline-3-carboxylic acid (1) which is formed from dopa and 3,4-dihydroxyphenylpyruvic acid. It is suggested that this compound undergoes an oxidative decarboxylation af-



fording the 1,4-dihydroisoquinoline (2) which tautomerizes to the 1,2-dihydroisoquinoline (4). This enamine then condenses with the N-methyl-Δ^1-pyrrolinium salt (3), which is presumably formed from ornithine. This reaction is analogous to one involved in the biosynthesis of nicotine where (3) condenses with a dihydropyridine.[4] Oxidation and suitable methylations of (7) then yield the alkaloids (6). We have been able to simulate these reactions in this proposed scheme, starting with 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (8).[5] This compound was dissolved in dilute NaOH (pH 10) and treated with an equivalent of NaOCl. After 5 minutes an equivalent of (3)[6] was added and the solution (pH 7.5) stirred for 7 days in an open beaker at room temperature. A $CHCl_3$ extract of this solution yielded a mixture of isoquinoline and 4-(1-methyl-2-pyrrolidinyl)isoquinoline (9). This latter compound which could also be named benzo[d]nicotine was obtained as a pale yellow oil, IR (neat) 2830 cm^{-1} (NMe); UV (95% EtOH) λ_{max} (Log ε) 219 (4.68), 262 (3.36), 272 (3.40), 285 (3.31), 310 (3.38), 318 sh (3.40), 323 (3.52) MS m/e 212 (M^+), 84 (N-methylpyrrolinium ion); ^{13}C NMR ($CDCl_3$) ppm from Me_4Si 151.6 (C-1), 141.1 (3), 134.7 (4a), 131.8 (6), 129.8 (8a), 128.3 (8), 128.1 (7), 126.6 (5), 123.3 (4), 66.9 (2'), 57.2 (5'), 40.8 (NMe), 34.0 (3'), 22.9 (4').[7] This product was identical with a sample prepared from ethyl isoquinoline-4-carboxylate[8] using a method analogous to Späth's synthesis of nicotine,[9] and the synthesis of benzo[e]nicotine from ethyl quinoline-3-carboxylate.[10,11] Brevicolline (5), using similar physiological conditions, has been recently prepared from 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and (3).[12]

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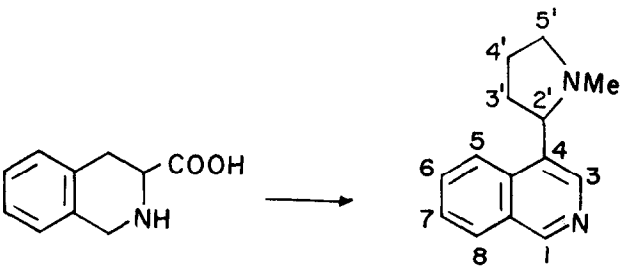

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