Biomimetic Synthesis of Brevicolline from Tryptophan, Acetaldehyde, and *N*-Methyl-Δ^1-pyrrolinium Acetate

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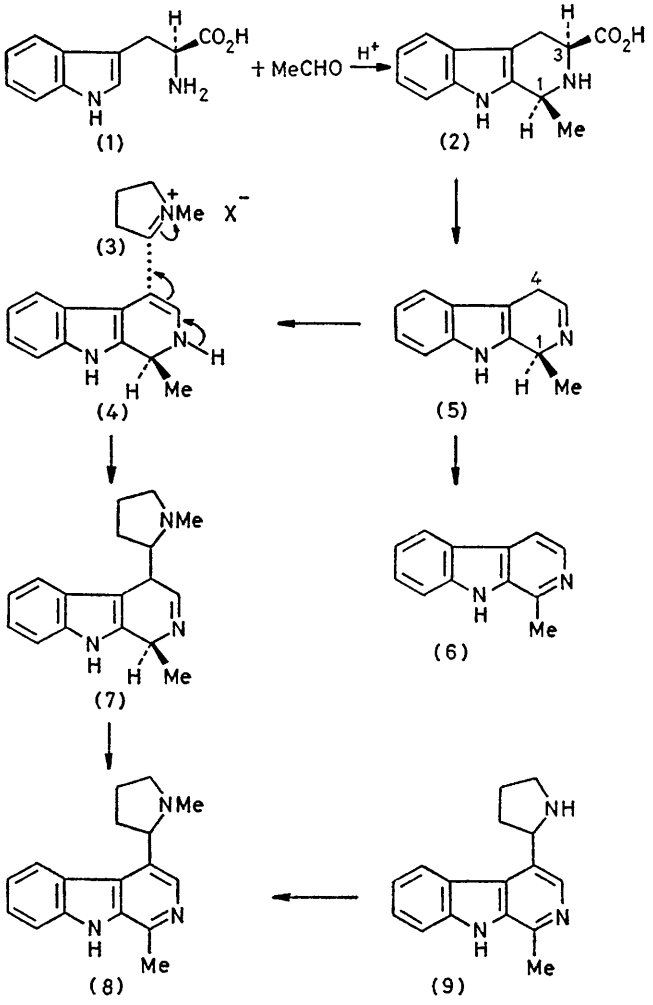
Summary 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, produced *in situ* from tryptophan and acetaldehyde, was oxidatively decarboxylated with sodium hypochlorite affording a dihydro-β-carboline which on condensation with *N*-methyl-Δ^1-pyrrolinium acetate and subsequent aerial oxidation afforded brevicolline.

BREVICOLLINE (**8**) is the major alkaloid of the plant *Carex brevicollis* DC., native to the southwestern part of the U.S.S.R.[1] It has been established that the β-carboline part of this alkaloid is derived from tryptophan and pyruvic acid.[2] Putrescine and related compounds (arginine, glutamic acid, and proline), were precursors of the pyrrolidine ring.[3] Formate served as a precursor of the *N*-methyl group.[2]

The Scheme illustrates our proposal for the biosynthesis of brevicolline. A Mannich reaction between L-tryptophan (**1**) and acetaldehyde affords 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (**2**), the major product *in vitro* being the (1*S*,3*S*)-isomer.[4] In nature the condensation could involve pyruvic acid which would yield (**2**) after decarboxylation. An oxidative decarboxylation of (**2**) yields the 1,4-dihydro-β-carboline (**5**). The 1,2-dihydro-β-carboline (**4**) is then formed by a tautomeric shift. This enamine condenses with the *N*-methyl-Δ^1-pyrrolinium salt (**3**) which is derived from ornithine *via* putrescine and *N*-methylputrescine. This reaction is analogous to the biosynthesis of nicotine which involves a condensation between (**3**) and a dihydropyridine.[5] Oxidation of the product (**7**) then yields brevicolline.

We have been able to obtain brevicolline by reactions which simulate the ones in this proposed scheme. L-Tryptophan (3·6 mmol) and acetaldehyde (13 mmol) were dissolved in 0·2 N HCl (30 ml) and the mixture was shaken for 18 h at room temperature. The solution was adjusted to pH 10 with sodium hydroxide and 5% sodium hypochlorite (4·0 mmol) added, followed, 5 min later, by a solution of *N*-methyl-Δ^1-pyrrolinium acetate[6] (3·6 mmol) in water (100 ml). The mixture was stirred at room temperature in an open beaker for 7 days. A chloroform extraction of this solution afforded an 8/3 mixture of harmane (**6**) and brevicolline, which was readily separated by t.l.c. This racemic brevicolline (**1**—2% yield) was identical (u.v., high resolution mass spectrum, t.l.c.) with an authentic specimen



SCHEME

of the natural alkaloid. The formation of harmane was not unexpected since it is readily formed by the oxidative decarboxylation of (**2**).[7] Norbrevicolline (**9**) was obtained by adding sodium hypochlorite to a mixture of (**2**) and

proline. An oxidative decarboxylation of the latter produces Δ^1-pyrroline[8] which presumably condenses in an analogous fashion with the dihydro-β-carboline (**4**) ultimately to yield (**9**). Methylation of (**9**) with formaldehyde and formic acid yielded brevicolline. Brevicolline and its *N-ind*-methyl derivative have been previously synthesized;[9,10] however a multi-step sequence of reactions was required, none of which could be described as physiological.

This investigation was supported by a research grant from the National Institutes of Health, U.S. Public Health Service. The author thanks Dr. M. Ya. Lovkova, Bach Institute of Biochemistry, Moscow for a sample of brevicolline.

(*Received*, 18*th June* 1979; *Com.* 646.)

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