

Biomimetic Synthesis of Nicotine

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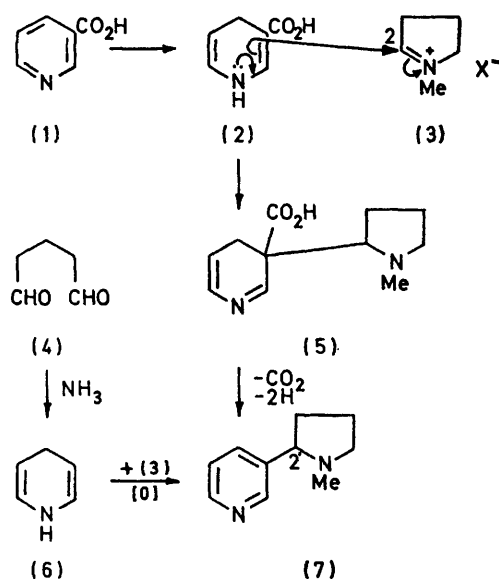
Summary Nicotine is formed at room temperature by stirring an aqueous solution of glutaraldehyde, ammonia, and 1-methyl- Δ^1 -pyrrolinium acetate in the presence of air, maximum yields being obtained at an alkaline pH.

mediate since the enamine system in such a compound would be expected to react with the pyrrolinium salt (3) to yield (5), which would then be converted into nicotine by an oxidative decarboxylation.

It has been established that the precursors of nicotine (7) in *Nicotiana* species are 1-methyl- Δ^1 -pyrrolinium salt (3)¹ and nicotinic acid (1).² Some modification of nicotinic acid is necessary prior to its incorporation into nicotine and various suggestions have been made,³ one being illustrated in the Scheme. 1,4-Dihydropyridinic acid (2) is a plausible inter-

Prior to the examination of reduced forms of nicotinic acid as potential precursors of nicotine, we decided to examine the ability of simple dihydropyridines to react with the pyrrolinium salt (3). Authentic 1,4-dihydropyridine (6) has been prepared,⁴ however we considered that small amounts of (6) or its tautomers would be present in an aqueous solution of glutaraldehyde (4) and ammonia.⁵ Accordingly, glutaraldehyde, ammonia, and [2-¹⁴C]-1-methyl- Δ^1 -pyrrolinium acetate¹ were mixed together in aqueous solution at various pHs. After standing for 24 h at room temperature inactive nicotine was added to the mixture. The reisolated nicotine was purified by distillation, and was crystallized to constant activity as its dipchlorate and dipicrate. The radiochemical yield of nicotine obtained at various pHs (indicated in parentheses) were: 1.8% (3.3), 5.8% (4.9), 8.0% (5.6), 10.8% (6.1), 17.4% (8.9), 21.2% (10.3). The radioactive nicotine was systematically degraded,^{1a} and all the activity was found at C-2', as expected. The reaction mixture (pH, 10.3) which gave the highest yield of nicotine consisted of the following: conc. NH₃ (5 ml), water (5 ml), 25% aqueous glutaraldehyde (2 ml), and 5 ml of an aqueous solution of [2-¹⁴C]-1-methyl- Δ^1 -pyrrolinium acetate (1.0 mmol). Increasing these reagents ten-fold, and stirring the mixture in air for 3 days resulted in the formation of (\pm)-nicotine (7%) identical (i.r., u.v., t.l.c., mixed m.p.) with an authentic specimen.

I thank the National Institutes of Health, U.S. Public Health Service for financial support.



SCHEME

(Received, 22nd August 1972; Com. 1473.)

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