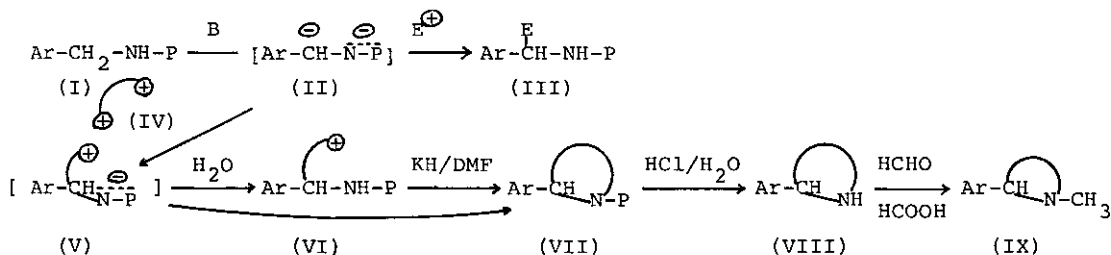


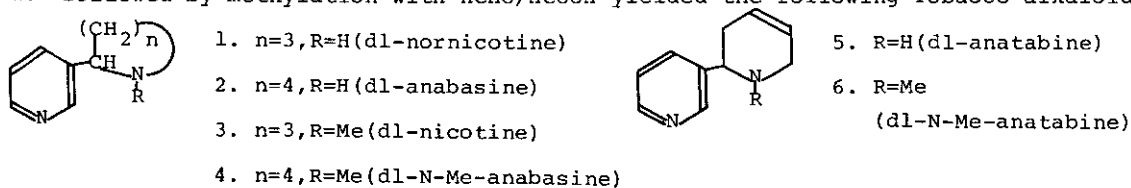
NOVEL SYNTHETIC METHOD OF TOBACCO ALKALOIDS : FORMATION OF N, α -DILITHIATED
N-PYRIDYLMETHYLBENZAMIDES AND THE REACTION WITH DIELECTROPHILES

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We have investigated the formation of N, α -dianion(II) bearing a heteroaromatic ring(Ar: furan, thiophen, pyridine) and the reaction with various electrophiles(E⁺) to give α -alkylated amine derivatives(III). This method was applied to the synthesis of Tobacco alkaloids bearing a pyridine ring.



3-Aminomethylpyridine derivative(I), N-protected with benzoyl group, underwent efficient and regioselective lithiation on treatment with LDA/THF(-70~-85°C) to give N, α -dilithium salts(II), which reacted with α,ω -dielectrophiles(IV) such as Br-(CH₂)_n-X or Cl-CH₂CH=CHCH₂-Cl(cis) to yield N-(3-pyridyl- α -halogenoalkylmethyl)benzamides(VI). The cyclization of (VI) to azacycloalkanes(VII) via intramolecular C-N bond formation was achieved with KH/DMF(-10~-15°C). (VII) could also be obtained by one-pot reaction from (II) without isolation of (VI). Hydrolysis of N-benzoyl derivatives(VII) with 6N-HCl followed by methylation with HCHO/HCOOH yielded the following Tobacco alkaloid:



Similar procedure was applied not only to the synthesis of 2- and 4-pyridyl derivatives but also to the formation of other derivatives with 4- and 7-membered azacycloalkanes(n=2,5).