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SYNTHESES OF SOME INDOLIC IMINO-ETHERS AND THEIR CYCLIZATION STUDIES

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Abstract. Acetyltryptamine and benzoyltryptamine react with triethyloxonium tetrafluoroborate to afford the corresponding imino-ethers which do not undergo intramolecular cyclization to the corresponding β–carbolines. Tryptamine reacts with chlorobutyryl chloride to afford the imide (X). With excess tryptamine, the chloroimide (XI) is obtainable which cyclizes to the lactam (XII) with sodium hydride. The lactam (XII) afforded the enamino ether (XV) on treatment with triethyloxonium tetrafluoroborate which also failed to cyclize to the corresponding β-carboline. These results are rationalised in the light of the facile intramolecular cyclization of 3-(2-succinimido-ethyl) indole (I).

We have recently described[1] a novel cyclization reaction involving the use of triethyloxonium tetrafluoroborate[2] for *o*-alkylation followed by an intramolecular attack of the indole 2-position of 3-(2-succinimido-ethyl)indole (I) to afford the fluoroborate salt (II) in over 80% yields. With base, spontaneous deprotonation of this salt takes place to provide the enamide(III), an attractive intermediate for indole alkaloid syntheses.

When acetyl tryptamine (IV) was treated with excess of triethyloxonium tetrafluoroborate in dichloromethane, it was completely converted to the iminoether (V). A variety of conditions, including the use of acid and base catalysts, were investigated but the ketimine (VI) could not be obtained.

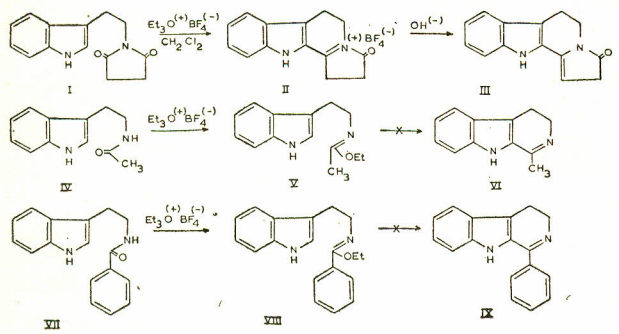
N_b-Benzoyl tryptamine (VII) was prepared by the Schotten–Baumann procedure. Treatment with triethyloxonium tetrafluoroborate afforded the corresponding imino-ether (VIII). This again did not cyclize when refluxed in various solvents, with or without catalysts.

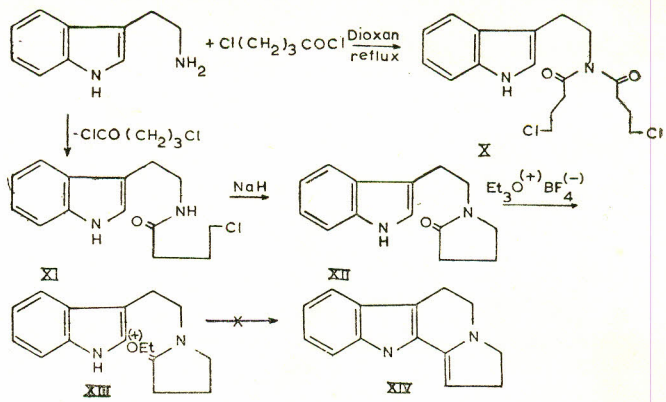
In both the above examples, a secondary amide was used to generate the imino-ether. It was thought that with a tertiary amide, a significant contribution of the immonium ion may exist which would make the carbon atom being attacked considerably more electrophilic and, therefore, more susceptible to intramolecular attack.[3,4] The lactam (XII) appeared an attractive compound to attempt this reaction and its preparation from tryptamine and chlorobutyryl chloride was attempted.

When equimolar portions of 4-chlorobutyryl chloride and tryptamine were dissolved in dioxan, there was an initial precipitation. The precipitate then gradually redissolved and prolonged reflux afforded a new substance which showed the molecular ion in its mass spectrum at *m/e* 368, corresponding to the diacylated structure (X).

The alternative method used for preparing the monoacylated compound was to use 2 moles tryptamine with 1 mole 4-chlorobutyryl chloride and filter and recycle the tryptamine hydrochloride precipitated. This provided the amide (XI) in quantitative yields which when treated with sodium hydride for 22 hr at 25°C, cyclized in over 80% yield to the desired lactam (XII).

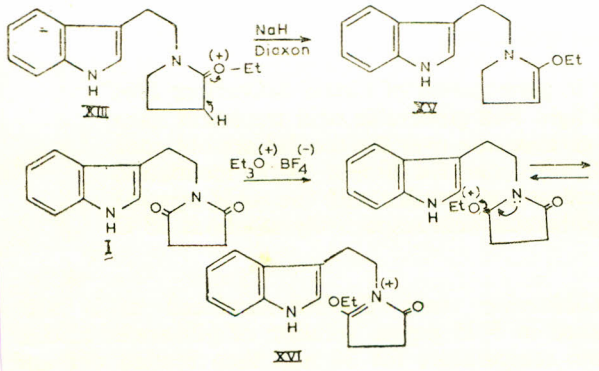
When the lactam (XII) was treated with triethyloxonium tetrafluoroborate in dichloromethane, it was readily converted to the corresponding alkylated salt (XIII). However, inspite of prolonged reflux, no cyclization product (XIV) was discernible. On refluxing in methanol/acetic acid, gradual decomposition to polar materials was observed. Attempted generation of anion at the indole nitrogen with sodium hydride in dioxan, in order to make the indole





2-position more nucleophilic, resulted in preferential deprotonation at the α-carbon in the lactam ring to afford the corresponding enamine (XV).

The above results indicate the weak nucleophilic character of the indole 2-position. The high yield cyclization of the imide (I) to the fluoroborate salt (II) may be rationalized in terms of the highly electrophilic nature of the intermediate iminium compound



(XVI) since the sp^2 carbon β- to the carbonyl group would be highly electron deficient in analogy with acrylates and vinyl ketones. Moreover, the destablization of the structure (XVI) on account of two adjacent electropositive groupings would also assist the cyclization reaction.

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