

A NEW INDOLIZINE SYNTHESIS
INVOLVING HETEROCYCLIC RING MODIFICATION

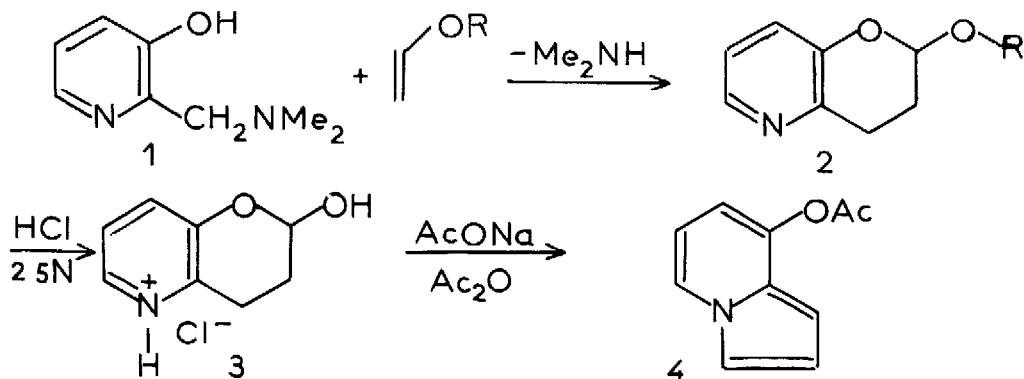
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Despite the fact that indolizine derivatives have been investigated as potential pharmacological agents ¹, no methods have been described for the synthesis of monosubstituted indolizines in the 8-position. These compounds may be considered as isosteric with 4-substituted indoles, some of which are known to have interesting medicinal properties ².

We wish to publish our preliminary results in this field, dealing more particularly with the synthesis of 8-acetoxy indolizine, that we have realized, starting from the Mannich base of 3-hydroxypyridine (1) and using the following original scheme.



We have recently reported ³ that the Mannich base of 3-hydroxypyridine can be condensed with vinyl ethers to yield 2-alkoxy-5-aza-chromans (2). The latter were readily hydrolyzed to 5-aza-2-chromanol isolated as the hydrochloride 3 in 95 % yield (mp 213°5 C)

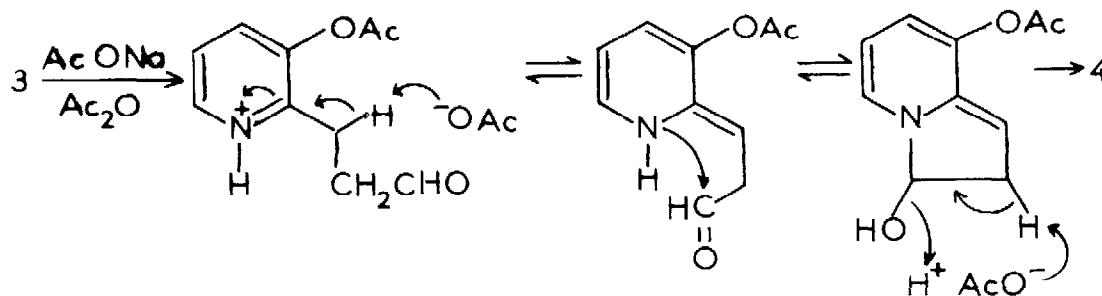
The hemiacetalic structure of the pyridinium salt 3 was confirmed in the solid state (no IR carbonyl absorption in KBr) as well as in aqueous solution (no aldehydic proton in nmr)

Nevertheless overnight treatment of 3 with one equivalent of AcONa in Ac₂O, at room tem-

perature, provided 8-acetoxy indolizine (4) isolated in a 70 % yield by distillation, bp/0 mm = 82°C, $n_D^{20} = 1.5853$, mp = 29°C

The structure of this last compound was established by elemental analysis and the following spectral data: μ s 175 (M^+), 133 ($M^+ - CH_2CO$), ν (cm⁻¹) 1770 (aromatic acetate), 1635 and 1540 (ring), 1200 (ν C-O-C asymmetric), pmr (δ , CDCl₃) 7.65 (2 d d, H-5, $J_{5-6} = 6.2$ Hz, $J_{5-7} = 1.4$ Hz, $J_{5-1} = 1$ Hz), 7.22 (d d, H-3, $J_{2-3} = 2.6$ Hz, $J_{3-1} = 1.4$ Hz), 6.70 (d d, H-2, $J_{2-3} = 2.6$ Hz, $J_{2-1} = 4$ Hz), 6.2-6.5 (m, H-1, H-6 and H-7), 2.26 (s, CH₃). The observed chemical shifts and apparent coupling constants (first order analysis as AMX) fit very well with the reported spectrum of indolizine ⁴

Although complete mechanistic details are uncertain at this time, and others paths conceivable, the following scheme can be proposed to account for the formation of the indolizine 4 ⁵



It should be pointed out that the behaviour of 5-aza-2-chromanol towards Ac₂O differs from that of 2-chromanol, which in similar conditions yields 2-acetoxy-chroman without suffering ring opening ⁶, while the hemiacetal 3 acts as a masked aldehydic function. In fact 3-(2'-pyridyl)propionaldehyde is known to be unstable ⁷, and its involvement in the synthesis of indolizine itself has been outlined by V. Boekelheide and R. J. Windgassen who prepared indolizine in a 50 % yield by heating 3-(2'-pyridyl)-1-propanol at 280°C in the presence of a palladium on charcoal catalyst ⁸

In conclusion this work provides a convenient entry, under mild conditions, to 8-substituted indolizines that were up to now unknown, the scope of this synthesis is presently under investigation

References and Notes

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