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INTRAMOLECULAR CONDENSATIONS OF N-(5-OXOHEXYL) NITROGEN HETEROCYCLES; A NEW ANNULATION PROCEDURE

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It has been demonstrated that enolizable ketones condense with pyridinium salts *via* attack of the enolate anion on either the 2,4, or 6-position of the pyridinium salt. Attack at the 4-position affords isolable 1,4-dihydropyridines; however, attack at the 2- or 6-positions has never led to the isolation of the corresponding dihydropyridines as these compounds undergo further reaction with great facility (1). In this note we wish to report the isolation of a 1,6-dihydropyridine derivative and a related 1,2-dihydroisoquinoline derivative *via* a novel carbonyl cyclization reaction that takes place under physiological conditions.

The requisite N-(5-oxohexyl)-3-cyanopyridinium bromide (1), mp 121-122°, was prepared by reacting neat 6-bromo-2-hexanone (2) with 3-cyanopyridine at room temperature for 11 days resulting in a yield of 14% (3). The reaction of 1 with a weak base in a heterogeneous solvent system (ether-aqueous $NaHCO_3$) led to the rapid accumulation of the 1,6-dihydropyridine 2 (7-cyano-1-acetyl-1,2-dihydro- 3H, 4H, 9aH-quinolizine) in the organic phase. Isolation by chromatography on silica gel yielded 2 (72%) as a moderately unstable yellow solid which after recrystallization from t-butyl alcohol has mp 88.9-89.6°; I.R. ($CHCl_3$) 2189, 1710, 1645, and 1578 cm^{-1}; M^+/e = 202; Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.85. Found: C, 71.14; H, 7.24; N, 13.58.

The decision as to whether this product is 3, 4, or 2 which would arise from attack at the 2-, 4-, or 6-positions of the pyridine ring respectively rests on the following mechanistic and spectroscopic considerations. Attack at the 4-position to produce 4 would require a sterically unfavorable, eight-membered transition state which would not be expected to compete effectively with the two six-membered transition states leading to 3 and 2. The mass spectral and UV data are in support of this judgment. The mass spectrum shows an intense peak at M^+-1/e = 201 which could be due to the loss of the 9a hydrogen (4). The bicyclic system of 4 would not be expected to exhibit this behavior since the analogous hydrogen is at a bridgehead, and thus, no special stability would be imparted to the ion resulting from loss of this hydrogen. Furthermore, peaks at m/e 159, 158, 157 and 155 are indicative of a stepwise degradation to a cyanoquinolizinium ion (m/e = 155), and there is a lack of peaks at m/e = 176 and 151 which should occur in the spectrum of 4 from the loss of acetylenic fragments (5). The UV spectrum, λ_{max}^{MeOH} 240(8000) and 355 nm (ϵ = 4950), is nearly identical with that of the 1,6-dihydropyridine of 3-cyanopyridine methiodide, λ_{max}^{EtOH} 240(5400) and 349 nm (ϵ = 4950) (6). In contrast 4 would be expected to exhibit no long wavelength absorption, but only a moderately perturbed absorption similar to that of acrylonitrile. This is a consequence of the orthogonality between the lone pair on nitrogen and π-orbitals of the carbon-carbon double bond

which eliminates most of the charge-transfer contribution to excitation (7).

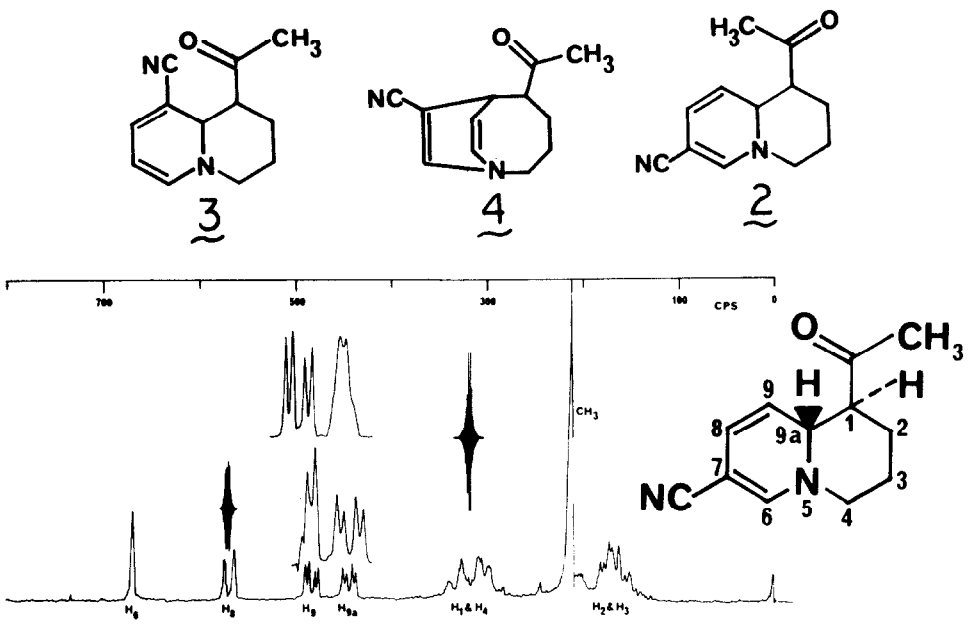
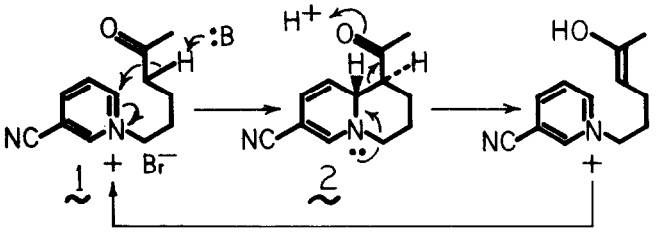


Figure 1. 100 MHz nmr spectrum of 2.

The distinction between the 1,2- and 1,6-isomers, 3 and 2 respectively, is afforded by the 100 MHz nmr spectrum and associated spin decoupling experiments shown in Fig. 1. The two pertinent features of this spectrum are the singlet at 669 cps (1H) which must be attributed to NC-C=CH-N, and the series of signals at 569 cps (1H), 482 (1H), 444 (1H), and 320 (3H). The double resonance experiments outlined in Fig. 1 establish the four carbon sequence -CH=CH-CH-CH-. Both of these features are consistent only with structure 2. Finally, the stereochemistry about centers 1 and 9a is probably trans as judged by the 10 cps coupling constant between the protons at these positions.



When 2 is treated with strong acid it is converted back to the original salt 1. Thus, methanolic HCl or CF_3CO_2H regenerate the nmr spectrum of 1 within the time required to record the spectrum; whereas, CH_3CO_2H is without effect even after standing several days. Complete deuteration of 2 in the 6-position is easily affected by cyclization of 1 in D_2O (8). Acid catalyzed regeneration of 1 yielded a product completely deuterated at the 2-position of the pyridine ring. These facile interconversions demonstrate the close structural relationship between 1 and 2, and tend to confirm the aforementioned nmr assignments. It may also be worth noting that this acid-base cycle bears an intriguing resemblance to the sequence of reactions thought to be instrumental in the conversion of nicotinamide to nicotine in vivo (9).

The utility of this annulation procedure has been demonstrated by extending the reaction to the analogous isoquinolinium salt 5, mp 140-141°. Reaction of 5 in aqueous $NaHCO_3$ afforded the highly unstable dihydroisoquinoline 6 (1-acetyl-1,2-dihydro-3H, 4H, 11bH-benzo[a]quinolizine) which was benzoylated to form a characterizable derivative 7, mp 188-189°; nmr ($CDCl_3$) δ 1.37 - 2.17 ppm (4H, m, H_2 and H_3), 1.73 (3H, s, $-CH_3$), 3.05-3.53 (3H, m, H_1 and H_4), 4.68 (1H, d, J=10 cps, H_{11b}), 6.72-7.72 (9H, m, H_6, H_8, H_{10}, H_{11}, and C_6H_5), 8.42 (1H, q, H_8) (10); M^+/e = 331; Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.52; H, 6.20; N, 4.14. The unsubstituted dihydroisoquinoline 6 can be isolated and preserved long enough to obtain an nmr spectrum (Fig. 2) if one lyophilized the organic phase. The assignments of

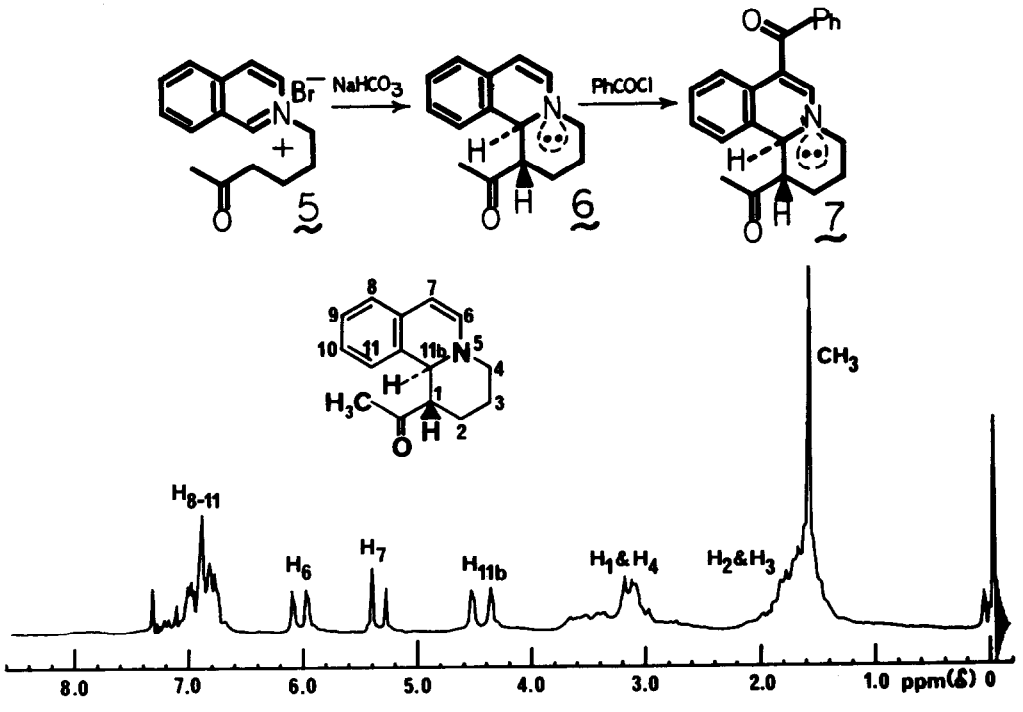


Figure 2. 60 MHz nmr spectrum of 6.

signals for protons 6, 7, 11b, and 1 were verified by double resonance. The 10 cps coupling between H_1 and H_{11b} would again seem to be indicative of a trans stereochemistry. Also of significance is the chemical shift of the methyl group (1.60 ppm) which represents an upfield shift of 0.82 ppm from that of 5. Models show that this very pronounced shielding could arise from the positioning of the acetyl group over the aromatic nucleus. However, this would happen only if the lone pair on nitrogen is cis to H_{11b}. If this stereochemistry were trans, the acetyl group would be brought into severe steric interaction with the aromatic ring hence the occurrence of the cis stereochemistry.

We are continuing to investigate the scope of this novel annulation and the chemistry of the resulting cyclization products.

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