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REACTIONS OF DIHYDRONICOTINAMIDES

II. THE ACID-CATALYZED DIMERIZATION OF 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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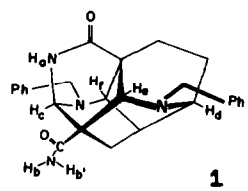
We would like to report the dimerization of 1-benzyl-1,4-dihydronicotinamide in acidic aqueous suspension to form the polycyclic cage molecule 1 in high yield. Although one can write a stepwise mechanism for this reaction involving known enamine chemistry, the high yields of one particular product, and other experimental observations, suggest the possibility of a concerted mechanism.



1

It has long been recognized that dihydronicotinamides are unstable to acid, and several workers have identified 6-hydroxy-1,4,5,6-tetrahydronicotinamides or their derivatives as major products of their destruction in homogeneous solution (1). We attempted to prepare such a hydration product by suspending 1 g of finely powdered benzyldihydronicotinamide (2) in 400 ml 0.05 N HCl. The dihydronicotinamide is very slightly soluble in this mixture, and goes into solution only after three hours. Upon neutralization of the solution with $NaHCO_3$, 650 mg of crude dimer precipitate. After recrystallization from ethanol, the dimer has mp 202-205° (dec). The elemental analysis, uv (end absorption) ir, nmr, and high resolution mass spectra (3) are in accord with structure 1, and allow no alternative structures. The 100 mHz nmr spectrum reproduced here has some interesting features. On exchanging the sample with D_2O, the peaks due to three protons at 5.92, 6.27,

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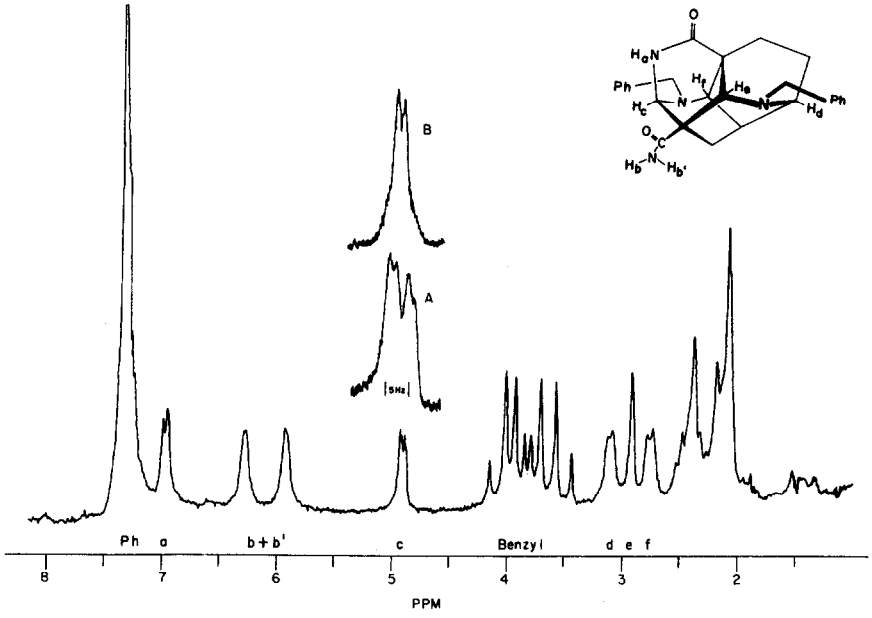
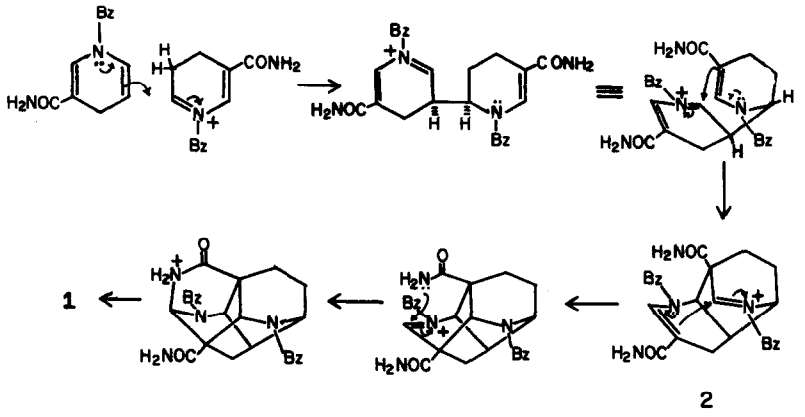
and 6.96 δ disappear, and the peak due to H_c (4.89 δ) collapses to a doublet (J = 1.8 Hz, spectrum B). By decoupling, H_c was shown to be coupled to H_f (2.75 δ), an example of four-bond coupling between protons in a relation very close to the "planar W" required for strong interaction (4).



100 mHz proton nmr spectrum of 1 in deuterochloroform. A: peak at 4.89 δ on expanded scale. B: same peak after exchange with D_2O.

Upon elucidation of the structure 1 for the dimer, we came upon the completely analogous crystal structure reported by Ammon and Jensen in 1966 for the dimer of 1-methyldihydronicotinamide (5). Karrer (6) had obtained this dimer in 10% yield, in addition to monomeric products, upon acidification of an aqueous acetone solution of methyldihydronicotinamide. The crystallographers did not consider this structure surprising, and their work has not been widely noticed by organic chemists. Indeed, one can rationalize the formation of a structure such as 1 by the stepwise sequence of reasonable reactions shown on the next page. Three alkylations of enamines by iminium cations are followed by the alkylation of the carboxamido group, whose proximity makes up for its low nucleophilicity.

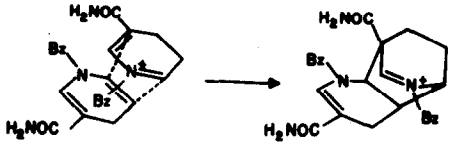


The great specificity with which this product is formed leads to some questions about this mechanism, however. The dimer is formed in 61-65% yield in aqueous 0.05 N HCl suspensions, independent of dihydronicotinamide/solvent ratio (absolute yields determined by isotopic dilution using addition of ^{14}C-dimer before workup). When the reaction is run in 0.05 N DCl in D_2O, the dimer is 74% d_1, and only 22% d_2 and 4% d_3 after removal of exchangeable deuterium. This requires that protonated nicotinamide react with neutral starting material faster than it is attacked by water or loses a proton, that the initial alkylation be stereospecific (syn), and that the product of the first alkylation close faster than it can lose a proton, if the mechanism is indeed stepwise.

We considered the possibility that the reaction occurs at the surface of the suspended solid and is controlled by the crystal structure of the starting material. The formation of the dimer in homogeneous solution, albeit in lower yields (for instance, 29% in 0.011 M solution in 25% aqueous acetone brought to 0.05 N in HCl), seems to rule this out. The crystal structure of benzyldihydronicotinamide (7) does not support this hypothesis in any case.

We suggest, rather, that the stereospecificity of initial bond formation and lack of subsequent proton exchange could be explained by a concerted cycloaddition between protonated and neutral dihydropyridine molecules. The process would be a "Diels-Alder cyclization with inverse electron demand" (8), the dienophile being an electron-rich enamine and the diene an eniminium cation. The principals of maximum overlap of π bonds

and polar interactions in diene additions (9,10) predict the specific formation of 2, which is so rigid that closure of the next two bonds without deprotonation or attack by water is to be expected. The results are further rationalized if the neutral dihydronicotinamide itself is associated in saturated aqueous solution, so that protonation



3 2

leads directly to the complex 3 which precedes the cyclization (10). We have found evidence for the involvement of π-complexes of dihydronicotinamides in a different reaction (11) and are continuing to investigate this question.

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