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THE MECHANISM OF THE REDUCTION OF PYRIDINIUM IONS BY SODIUM BOROHYDRIDE, II.*

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Evidence that the mechanism for the conversion of pyridinium ions to tetrahydropyridines by sodium borohydride involves the protonation of a 1,2-dihydropyridine intermediate has been presented (1). The question of whether the proton attack occurred at the center or terminal position of the conjugated dienamine or produced an equilibrium mixture of the two resultant immonium cations was not answered. Evidence for the course of the protonation step is now available.

The protonation of a conjugated dienamine should be comparable to the protonation of the anion from an α,β-unsaturated acid and therefore predicted by the correlation, "Ingold's Rule" (2). The results of the investigation of the protonation of

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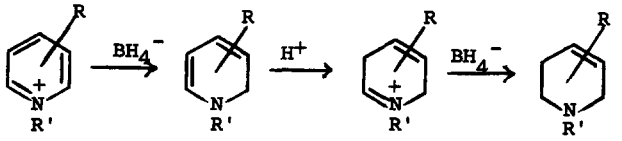
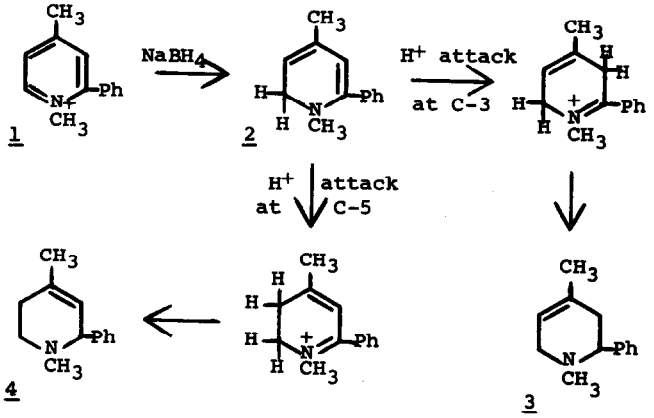
dienamines by Opitz and Merz (3) can be correlated by Ingold's Rule: weak acids lead to the kinetically-controlled product by proton attack at the central position of the enamine and stong acids or equilibrating conditions give the product of thermodynamic control by attack of the proton at the terminal position (4). The sodium borohydride reduction of the dimethylenamine of cholestenone, a close analog of a 1,2-dihydropyridine, produced β-N,N-dimethylamino-5-cholestene (5), predicted on the assumption that the intermediate formed by kinetically-controlled protonation would undergo reduction rapidly. These analogies lead to the formulation of the sodium borohydride reduction of pyridinium ions as:



A study of the sodium borohydride reduction of 1,4-dimethyl-2-phenylpyridinium iodide [1] confirmed the prediction based on Ingold's Rule as elaborated above. An intermediate dihyropyridine was isolated from the reduction of 1. The ultraviolet spectrum of this dihydropyridine (λ_{max} 350 mμ) required that the phenyl substituent be conjugated with the dienamine system and that it be the 1,6-dihydropyridine 2. Huisgen (6) has reported that the ultraviolet spectrum of 1-methyl-2-phenyl-1,2-dihydropyridine exhibited a maximum at 285 mμ.



The further reduction of 2 with sodium borohydride in aqueous medium produced 1,4-dimethyl-2-phenyl-1,2,3,6-tetrahydropyridine [3] (b.p. 85-87° /1 mm; picrate m.p 149-152°)

and not the isomeric 1,2,5,6-tetrahydropyridine 4. The catalytic hydrogenation of 3 gave two isomeric piperidines. The ultraviolet spectrum (fine structure of low intensity centered at 254 mμ) of the isolated tetrahydropyridine 3 eliminated the possibility of the structure being a 1,2,3,4- or 1,4,5,6-tetrahydropyridine, but this evidence did not distinguish between the 1,2,5,6-and 1,2,3,6-tetrahydropyridine structures. The choice of the latter structure 3 was readily made on the basis of the proton magnetic resonance spectrum of the reduction product in which the benzylic proton appeared as a quartet centered at 6.78 τ (J_{cis} = 5.4 cps, J_{trans} = 8.2 cps). The benzylic proton in the 1,2,5,6-tetrahydropyridine 4 would have been expected to appear as an unmistakable doublet. That the quartet was indeed due to the resonance of the benzylic proton was revealed by the integrated area of this peak (equivalent to one proton) and the fact that the quartet shifted to 5.92 τ in acidic medium, indicative of the fact that the proton must be adjacent to the nitrogen.

The spin-spin splitting of the benzylic proton into a quartet resulted from the non-equivalence of the C-3 protons arising from the asymmetry of carbon atom 2 (7). The non-equivalence of the C-3 protons may further reflect the greater population of the thermodynamically more stable conformer of 3 in which the 2-phenyl substituent is pseudo-equatorial. The remaining portions of the spectrum contained the resonance peak of the vinyl proton centered at 4.55 τ, the C-6 methylene peak

centered at 7.05 τ, the C-3 methylene resonance centered at 7.8 τ, and singlets due to the resonance of the C-methyl and N-methyl protons at 7.95 and 8.30 τ, respectively.

The formation of 3 from 2 requires that protonation occur at the center of the conjugated dienamine system as predicted by Ingold's Rule. The products of the reduction of other unsymmetrical pyridinium ions (8) and the failure of 1,3-disubstituted-1,6-dihydropyridines (9) to undergo further reduction are consistent with Ingold's Rule.

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