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A REINVESTIGATION OF 1,2-DIHYDROPYRIDINE FORMATION BY CONDENSATION OF ALDEHYDES WITH ANILINE: REVISION OF A STRUCTURAL ASSIGNMENT

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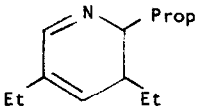
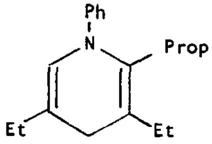
The recent discovery of Charman and Rowe (1) that aldehydes can be condensed with ammonium salts to give 2,3-dihydropyridines 1 prompts us to report our similar investigations on the acetic acid catalyzed formation of dihydropyridines from aldehydes and aromatic amines. The present paper also endeavors to correct some confusion in the literature which has resulted from an erroneous structural assignment 2 to the dihydropyridine formed from aniline and butanal.



1[a]



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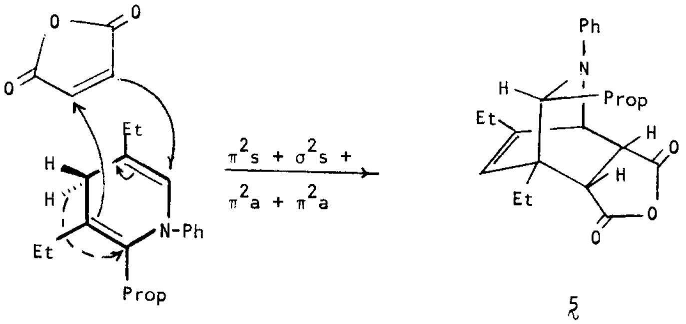
It has been reported (2,3) that 2 reacts with maleic anhydride to form a single diene adduct 5. To explain the isolation of a single isomer it was postulated (3) that a 1,3-hydrogen shift occurred on the back side of the 1,4-dihydropyridine 2 in concert with dienophile addition to the front side. The bicyclic amine 5 would thus have the propyl group and anhydride moiety, presumably endo, on the same side of the molecule. This reported reaction has been cited as evidence that 1,4-dihydropyridines undergo a diene reaction (4). Because of skepticism regarding the above thermally disallowed concerted $\pi^{2}s + \pi^{2}a + \sigma^{2}s + \pi^{2}a$ process (5) in conversion of 2 to 5, we have reinvestigated this problem.

[a] Formed by reaction of butanal and ammonium acetate.

Three dihydropyridines 2, 3, 4 can be considered as possible structures for the acetic acid catalyzed condensation of three moles of butanal and one mole of aniline, based upon mechanistic considerations, oxidation of the adduct to a pyridinium salt, and degradation products reported by Craig (2,3).



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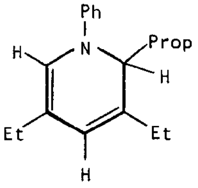

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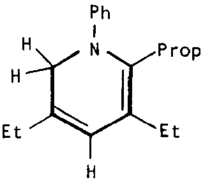

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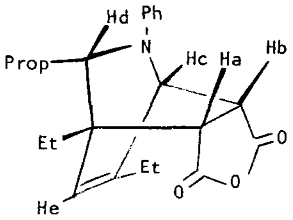
In order to distinguish these possibilities, the dihydropyridine was synthesized as reported previously (2) and spectral parameters were determined. The ultraviolet spectrum of the light yellow oil, λ_{max} (MeOH) 340nm, ε 9600; 240nm, ε 8800 [lit. (2) λ_{max} 340nm, ε 12,600, λ_{max} 240 nm, ε not given] is consistent with either 1,2-dihydropyridine 3 or 4, but not with 1,4-dihydropyridine 2 (6). The nmr spectrum ($DCCl_3$) of the adduct showed δ6.90 (phenyl) δ5.58 and δ5.96 (2H, vinyl singlets); δ4.20 (J = 5Hz, CH-N, broad triplet) δ2.10 and δ1.50 (8H, broad multiplets); and 1.04 (9H, sharp multiplets). The presence of two vinyl protons and the triplet characteristic of the single hydrogen next to nitrogen and n-propyl is consistent with only structure 3.

On the basis of mechanistic considerations for Diels-Alder $\pi^{2}s + \pi^{4}s$ cycloadditions, maleic anhydride should add to the less hindered face of 3 to form the endo adduct 6 (7) with the propyl group on the side of the molecule away from the anhydride moiety (Hd syn). Crystalline adduct 6, mp 119-120° [lit(2)mp 120°], showed nmr ($DCCl_3$): δ6.90 phenyl; δ 5.63 He (singlet); δ4.70 Hc (doublet, J_{bc} = 4 Hz); δ3.50 Hb (quartet, J_{ab} = 8 Hz, J_{bc} = 4 Hz); δ3.30 Hd (broad); δ3.10 Ha (doublet, J_{ab} = 8 Hz); δ0.8-2.2 (broad mult., 17 H). $Eu(DPM)_3$ induced signal shifts (mole ratio $Eu(DPM)_3$/6 of 0.6) for single hydrogens were in cps, Ha(33), Hb(32), Hc(25), Hd(13), He(15).

The $Eu(DPM)_3$ induced signal shifts are in tentative agreement with the stereochemical assignments in 6. Examination of molecular models using a europium-oxygen bond distance of 3.0-3.5 A° (8) indicates that it is only when the europium is coordinated exo to the oxygen of the anhydride in 6 that the relative Eu-H internuclear distances are in the same order as the relative pseudo-contact shifts. Estimated relative Eu-H distances in 6 are Ha = Hb(1.0) < Hc(1.25) < He(1.4) ≅ Hd syn(1.4) < Hd anti(1.7). The nearly equal Eu-He and Eu-Hd syn internuclear distances result in similar pseudo-contact shifts. The estimated Eu-Hd anti distance would indicate a smaller pseudo-contact shift than observed; however, in the absence of the isomer with Hd anti, the possibility of contributions to the shift values from minor amounts of $Eu(DPM)_3$ coordination with nitrogen, and uncertainty caused by angular and internuclear distance variables (9), the assignment to 6 is regarded as tentative.

On the basis of the reassigned 1,2-dihydropyridine structure 3 to the butanal-aniline adduct, it must be concluded; there is no present evidence that 1,4-dihydropyridines are



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capable of taking part in a concerted diene synthesis (4). The scope of the synthesis of 1,2-dihydropyridines from aldehydes and aromatic amines and the reactions of dihydropyridines to form bicyclic amines are being further investigated.

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References

1. H. Charman and J. Rowe, Chem. Commun., 1971, 476.
2. D. Craig, A. Kuder and J. Efroymson, J. Am. Chem. Soc., 70, 1624 (1948).
3. ibid., 72, 5236 (1950).
4. A.S. Onishchenko, Diene Synthesis, Daniel Davey and Co., Inc., N.Y., 1964, 579.
5. R. B. Woodward and R. Hoffmann, Angew. Chem. internat. Edit., 8, 781 (1969).
6. a) M. Saunders and E. Gold, J. Org. Chem., 27, 1439 (1962) report 239nm (log ε 3.9) and 350nm (log ε 4.1) ethanol for N-phenyl-1,2-dihydropyridine and 286nm (log ε 4.2) for N-phenyl-1,4-dihydropyridine, correcting the assignment in 6b.

   b) P. Karrer, G. Schwarzenbach and G. Utzinger, Helv. Chim. Acta., 20, 72 (1937) incorrectly assigned the N-phenyl-1,2-dihydropyridine structure to N-phenyl-1,4-dihydropyridine.
7. F.Liberatore, A. Casini, V. Carelli, A. Arnone, R. Mondelli, Tetrahedron Lett., 1971, 2381, have shown endo addition in the $\pi^{4}s + \pi^{2}s$ dimerization of N-methyl-4-cyano-1,2-dihydropyridine.
8. W. Walter, R. Becker, J. Thiem, Tetrahedron Lett., 1971 (1971).
9. P. Demarco, T. Elzey, R. Lewis, E. Wenkert, J. Am. Chem. Soc., 92, 5734 (1970).