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THE SYNTHESES OF PARTIALLY REDUCED INDOLO AND BENZOQUINOLIZINES VIA 1,4-DIHYDROPYRIDINE INTERMEDIATES*

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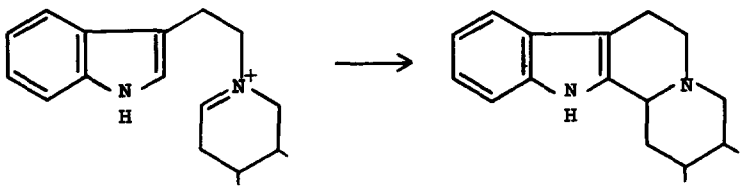
Recently a number of cyclizations have been reported which result from the electrophilic attack of a protonated enamine on an electron rich aromatic ring as indicated below:



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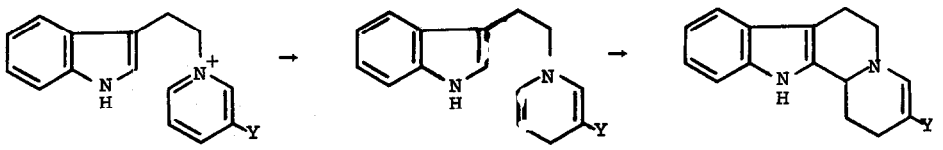
**Jerome H. Supple was an Eastman Kodak Fellow, 1961-1962. The present address of David Nelson is the Department of Chemistry, University of Wyoming, Laramie, Wyoming. ***Author to whom inquiries should be directed.

This system has been generated by lithium aluminum hydride reduction of isoquinolinium salts (1), reduction of pyridinium ion over Raney nickel in base (2), dehydrogenation of a piperidine derivative with palladium catalyst (3) or mercuric acetate (4), and reduction of the pyridinium salt by lithium aluminum hydride or sodium borohydride in diglyme (5). An important route to this system, the protonation of a 1,4-dihydropyridine formed by sodium dithionite reduction (6), has not previously been investigated. This report describes the successful cyclization of 1,4-dihydropyridines under mildly acidic conditions.

The reaction of 3-(β-bromoethyl)indole with 3-cyanopyridine or 3-benzoylpyridine produced the corresponding pyridinium salts. The reaction of the quaternary salt of 3-benzoylpyridine (1a) with sodium dithionite gave a compound, m.p. 160-163°, the elemental analyses of which corresponded to the dihydropyridine plus an extra atom of oxygen. The infrared ($\bar{\nu}$ 1670, 1650, and 1537 cm^{-1}) and ultraviolet [λ_{max} 384 mμ (ϵ 5900)] absorption spectra of this product were consistent with the expected 1,4-dihydropyridine (2a). The reaction of 2a with glacial acetic acid gave a product whose properties (m.p. 250-255°, $\bar{\nu}$ 1615 cm^{-1}, λ_{max} 308 mμ) (7), and elemental analyses corresponded to 1,2,6,7,12,12b-hexahydro-3-benzoylindolo[2,3a]-quinolizine (3a).



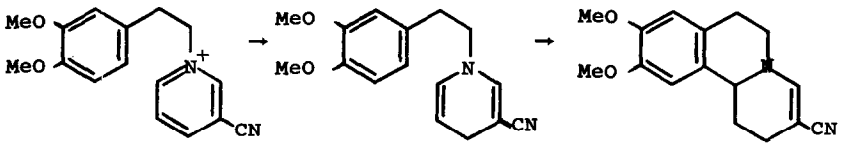
1a Y=PhCO-
1b Y=CN

2a Y=PhCO-
2b Y=CN

3a Y=PhCO-
3b Y=CN

The reaction of 1-[β-(3-indolyl)-ethyl]-3-cyanopyridinium bromide (1b) with sodium dithionite in aqueous methyl alcohol yielded a solid (3b) without acidification whose properties [m.p. 223-225°, $\bar{\nu}$ 2190, 1630 cm^{-1}, λ_{max} 280 mμ (ε 20,460) and 223 mμ (ε 20,830)] corresponded to those of a 1,4,5,6-tetrahydropyridine such as 1-methyl-3-cyano-1,4,5,6-tetrahydropyridine reported by Schenker and Druey (8). The elemental analyses eliminated the possibility that 3b was the acyclic tetrahydropyridine and supported the fact that cyclization had occurred in the very slightly acidic reduction medium. Using a reduction medium buffered with sodium bicarbonate the intermediate 1,4-dihydropyridine (2b) could be isolated, and 2b was shown to undergo cyclization to 3b on treatment with acid.

The cyclization of papavarine to pavine (9) and the synthesis of 2,3-dimethoxyberbine (10) indicated the possibility that the dimethoxyphenyl nucleus would be sufficiently nucleophilic to allow attack on the protonated enamine system of a 1,4-dihydropyridine. To confirm this possibility the β-(3,4-dimethoxyphenylethyl)-pyridinium salt of 3-cyanopyridine (4) was prepared, and on reduction with sodium dithionite in buffered medium led to the 1,4-dihydropyridine which readily cyclized to 5 on treatment with hydrochloric acid. The elemental analyses, spectral properties ($\bar{\nu}$ 2195, 1630 cm^{-1}, λ_{max} 280 mμ and 231 mμ), and proton magnetic resonance spectrum [3 singlets, 1 proton each at 6.67, 6.75, and 6.90 ppm (aromatic and vinyl hydrogens); broad, unresolved doublet, 1 proton centered at 4.32 ppm (bridge-head proton); singlet, 6 protons at 3.90 ppm (methoxyl protons); and multiplet, 7 protons between 2.0 and 3.5 ppm] of 5 confirmed the cyclization. The sodium dithionite reduction of 4 in the absence of a buffer led to the cyclization product, 5, directly due to the acidity of the reduction mixture.



4 5

The cyclizations described in this report occurred in high yield and under mildly acidic conditions. These results in combination with the ubiquitous occurrence of the 1,4-dihydropyridine system in nature make this reaction of interest as a synthetic and potential biosynthetic method of formation of alkaloids.

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