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THERMAL REARRANGEMENT OF CYCLOPROPYL IMINES. I. TOTAL SYNTHESIS OF MYOSMINE AND APOFERROROSAMINE.

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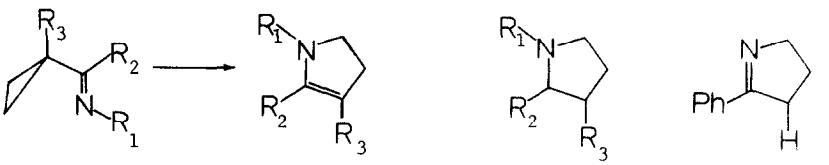
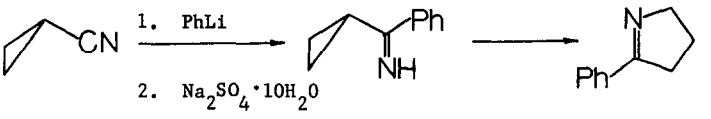
We were impressed by the fact that such structurally dissimilar alkaloid families as the Strychnos, Aspidosperma, Senecio, Amaryllidaceae, and Tobacco all incorporate various perturbations of the pyrrolidine ring system [3]. Reasoning that any potentially general synthetic adventure into this vast array should, in principle, benefit from the nucleophilic properties associated with the β-carbon of a Δ^2-pyrroline [2] the synthetic task was reduced to this central character. Furthermore, the thermally induced rearrangement of cyclopropyl imines [1] seemed admirably suited for this assignment, and we were pleased to discover that an example of the proposed rearrangement [$R_2 = C_6H_5$, $R_1 = R_3 = H$] had been reported by J. B. Cloke in 1929 (2).



[1] [2] [3] [4]

The product of this rearrangment was later (3) shown to be the Δ^1-pyrroline [4] rather than the Δ^2-isomer, a fact in consonance with a growing body of information dealing with these potentially tautomeric substances (4).

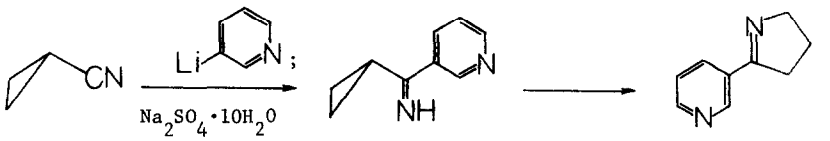
In order to gain experience with the proposed rearrangement we repeated the Cloke experiment employing phenyl lithium in place of the Grignard reagent and water to decompose the intermediate lithium salt rather than the tedious acid work-up prescribed by Cloke. Ketimine [5] was obtained as a water-white liquid which distilled at 58°/0.25 mm. and slowly decomposed upon standing (5). We were surprised to discover that this material did not readily yield the pyrroline [4] when heated under a variety of conditions but rather mainly resinified. However, upon admixture with a catalytic amount of the corresponding hydrochloride, m.p. 101-103°, ketimine [5] readily yielded the pyrroline [4]. We have been unable in this and other work in our laboratory to induce smooth rearrangement of cyclopropyl imines in the absence of added acid catalyst. Fortified with this experience we turned our attention to the synthesis of the Tobacco alkaloid myosmine [6].



[5] [4]

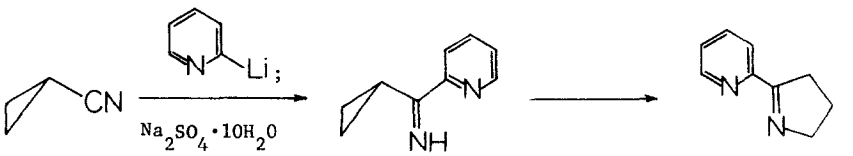
Cyclopropane carbonitrile was added at -70° to an etheral solution of 3-pyridyl lithium prepared by the method of Gilman (6). The resulting orange-brown solution was allowed to warm to room temperature and carefully decomposed with $Na_2SO_4 \cdot 10\ H_2O$ and filtered. Additional lithium salts were removed by concentration and trituration with benzene. Distillation of this dark oil gave a fraction boiling at 60-90°/ 0.15 mm., redistillation of which yielded ketimine [7] of b.p. 78-80°/0.15 mm., yield 30% (5).

This material slowly decomposed upon standing. A small amount of base [7] was converted to its hydrochloride which proved to be exceedingly hygroscopic. Admixture of ketimine [7] and a catalytic amount of its hydrochloride and heating at 100° for 20 minutes followed by distillation gave mainly myosmine [6], b.p. 77°/0.15 mm., yield 65%. The pure natural product was obtained by preparative layer chromatography and subsequent vacuum sublimation. Myosmine obtained in this manner melted at 45-46° [lit. (7) m.p. 44-45°], and displayed IR, NMR and UV spectra which were identical with published spectra (8).



[7] [6]

Synthesis of the unstable ketimine [8] was accomplished in 35% yield in an analogous manner and distilled at 69°/0.08 mm. (5). Admixture of this base and its hydrochloride and heating for 20 minutes at 100° followed by distillation gave nearly pure apo-ferrorosamine [9] of b.p. 65°/0.3 mm. as a nearly colorless liquid which solidified upon standing, yield 75%. The pure natural product was secured by preparative layer chromatography and subsequent vacuum sublimation and melted at 55-55.5°; lit. (9) m.p. 46-49°. The IR, NMR and UV spectra of this material were identical with published spectra (8). The success of these experiments has prompted us to examine more complex systems and will be the subject of further communications.



[8] [9]

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