Tetrahedron Letters No.22, pp. 2613-2615, 1968. Pergamon Press. Printed in Great Britain.

THERMAL REARRANGEMENT OF CYCLOPROPYL IMINES.
II. SYNTHESIS OF A MESEMBRINE MODEL (1)

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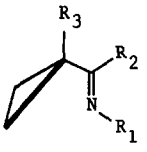
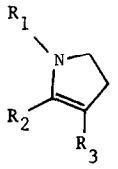
(Received in USA 1 February 1968; accepted for publication 1 March 1968)

We recently reported (3) the total synthesis of the simple pyridine alkaloids myosmine [3] and apoferrorosamine [4] by means of the thermally induced, acid catalyzed, rearrangement of cyclopropyl ketimines [1]. The success and efficiency of these experiments has prompted us to further investigate the crucial rearrangement step, [1] to [2], as a general method of alkaloid synthesis. We wish now to report the synthesis of a model [5, R = H] of the Amaryllidaceae alkaloid mesembrine [5, R = OCH_3].



[1]



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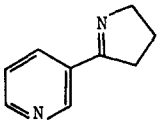
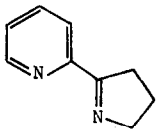
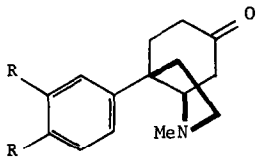


[3]



[4]



[5]

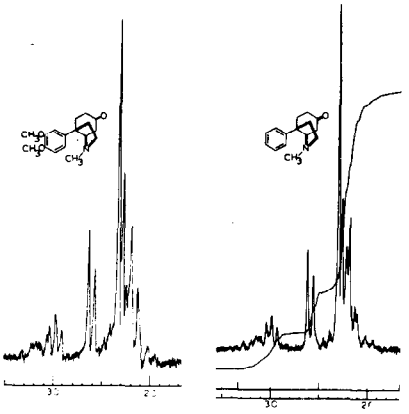
1-Phenylcyclopropane carboxaldehyde (4) reacted smoothly with an equimolar benzene solution of methylamine and suspended magnesium sulfate to give aldimine [i, R_1 = CH_3, R_2 = H, R_3 = Ph] in 96% yield, bp 53°/0.23 mm, IR: 1661 cm^{-1}, PMR: one-proton quartet, δ 7.57 (J = 1.5 cps); five-proton singlet, δ 7.21; three-proton doublet, δ 3.17 (J = 1.5 cps);

four-proton multiplet, δ 1.19. This somewhat unstable colorless liquid formed a beautifully crystalline picrate (5) of mp 167.5 - 168.5°.

The rather hygroscopic hydrobromide of this aldimine was precipitated from an etheral solution and, without isolation, the ether and excess HBr removed. The resultant solid residue, which melted at 65-67°, was carefully heated to 120° over the course of one-hour and the resulting clear yellow melt dissolved in dilute acid and extracted with ether to remove neutral materials. Pyrroline [2, R_1 = CH_3, R_2 = H, R_3 = Ph] was secured as a solid residue by basification of the acidic solution and ether extraction. The sublimate (5), obtained in 59% yield melted sharply at 61 - 61.5°, IR: 1613 cm^{-1}, UV: $\lambda_{max}^{95\% \text{ EtOH}}$ 306.5 mμ (ε = 11,390), PMR: five-proton singlet, δ 7.09; one-proton triplet, δ 6.32 (J = 1.4 cps); four-proton multiplet, ca. δ 2.99 three-proton singlet, δ 2.57.

We now took advantage of the nucleophilic properties associated with the β-carbon of pyrroline [2] to complete the synthesis. Admixture of this reagent and methyl vinyl ketone (6) in hot ethylene glycol produced a dark red solution which was dissolved in dilute acid and extracted with ether. The mesembrine model [5, R = H] was secured in 47% crude yield from the neutralized acidic solution by ether extraction and subsequent preparative layer chromatography. Rechromatography of the impure material and subsequent distillation, bp 109° (bath temp)/0.1 mm. gave a pure sample by TLC, IR 1719 cm^{-1}, picrate (5) mp 168-170° (d).

Confirmation of the structural and stereochemical assignment was easily made by comparison of the PMR spectra of the model and mesembrine itself (7,8). The success of these experiments has prompted us to continue an examination of this interesting process and will be the subject of future communications.



REFERENCES

1. The authors are indebted to the Petroleum Research Fund administered by the American Chemical Society (PRF # 925 G-1) and to the Rice University Research Sponsors for financial support of this work.
2. Public Health Service Predoctoral Research Fellow, 1967 - .
3. R. V. Stevens and M. G. Ellis, Tetrahedron Letters, 5185 (1967).
4. D. I. Schuster and J. D. Roberts, J. Org. Chem., 27, 51 (1962).
5. Combustion data for this substance were in agreement with its formulation.
6. Whereas annelations involving this reagent and exocyclic enamines are common, its formulation here with an endocyclic enamine is apparently unique.
7. We are most greatful to Professor P. Jeffs of Duke University for supplying us with the PMR Spectrum of mesembrine.
8. The cis ring fusion of the octahydroindole nucleus of mesembrine has been derived from degradative and synthetic evidence, cf., A. Popelak, G. Littenbauer, E. Haack, and H. Springler, Naturwissenschaften, 47, 231 (1960).