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A NEW SYNTHETIC APPROACH TO THE AMARYLLIDACEAE ALKALOIDS. APPLICATION TO THE SYNTHESIS OF MESEMBRINE AND MESEMBRININE.

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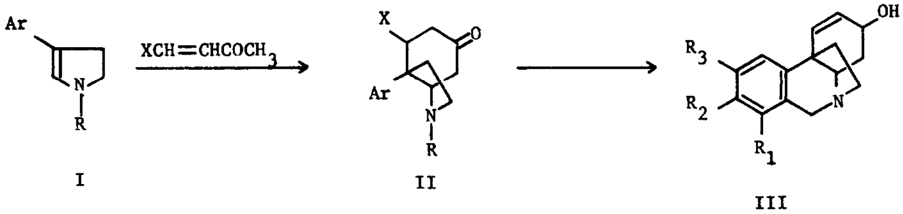
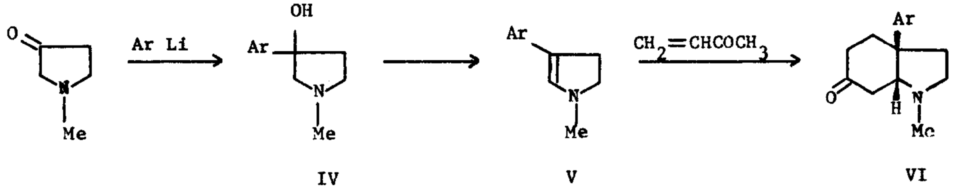
In considering synthetic routes to the Amaryllidaceae alkaloids(1) we were especially struck by the simplicity and potential generality of the following apparently unexplored transformations:



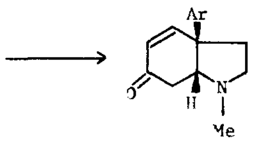
By virtue of its enamine-like structure the pyrroline (I) should react with vinyl ketones to yield substances of general structure (II).(2) Conversion of (II) to alkaloids possessing the 5,10b-ethanophenanthridine structure, for example crinine (III, R_1 = H; R_2,R_3 = methylenedioxy)(3 a,b) or powelline (III, R_1 = OMe; R_2,R_3 = methylenedioxy),(3 b,c) can then readily be envisaged. We now wish to report that successful application of the first part of this scheme has led to a simple synthesis of mesembrine (VI)(4) and of mesembrinine (VIII).(5) The sequence of reactions employed was as follows:



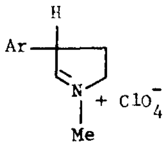
V + XCH=CHCOCH$_3$

VII

Ar = 3,4-dimethoxyphenyl-



VIII

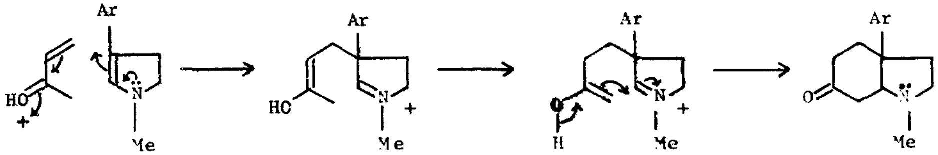


IX

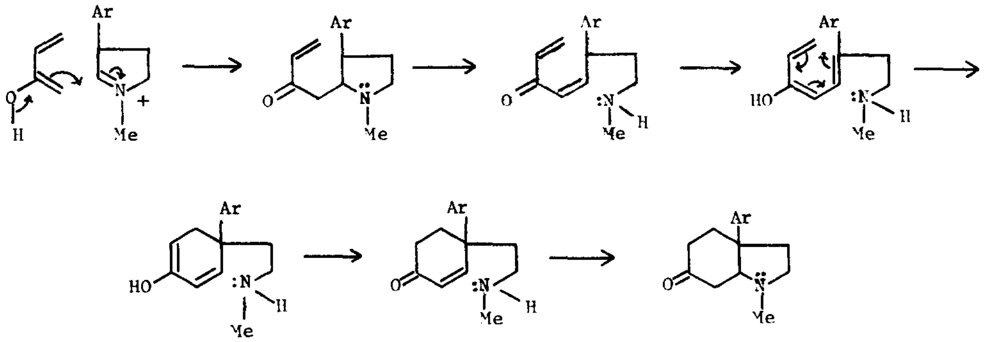
Reaction of 4-lithioveratrole(6) with 1-methyl-3-pyrrolidone(7) gave the crystalline amino alcohol (IV) in 44% yield.(8) Dehydration of (IV) proceeded smoothly in boiling 6N sulfuric or hydrochloric acid(9) to give a single crystalline base, further characterized as its crystalline perchlorate and oily hydrochloride. Structure (V) was assigned to this dehydration product on the basis of its spectral properties. Thus the perchlorate of this base showed no IR absorption in the $\overset{+}{\gtrless}$N-H region, suggesting that it had the C-protonated structure (IX). Moreover the double bond absorption in the free base at 1615 cm^{-1} shifted to 1680 cm^{-1} in the perchlorate, a behavior characteristic of enamines.(10) Further support for structure (V) came from the NMR spectrum of this base, which showed the protons of the pyrroline ring in an A_2B_2X pattern, the vinyl hydrogen appearing as a triplet (J = 1.3 Hz) at 6.35δ and the four remaining ring protons as a multiplet at 3δ. Matching of this multiplet to computer simulated spectra led to a value for the A-B coupling constants (between protons at the 4- and 5- positions of the pyrroline ring) of $J_{cis} = J_{trans} = 9.2$ Hz, in close agreement with the results for a similar molecule, 1-methyl-2-phenyl-2-pyrroline, in which $J_{cis} + J_{trans}$ was reported to be 18.4 Hz.(11)

When (V) was condensed with methyl vinyl ketone in refluxing water a 14% yield of d,l-mesembrine (VI), isolated and identified as its hydrochloride, was obtained.(12) On the other hand, reaction of (V) with methyl ethynyl ketone, methyl β-chlorovinyl ketone (VII, X = Cl), or β-acetylvinyltrimethylammonium chloride (VII, X = $\overset{+}{N}Me_3$) under the same conditions failed to yield any detectable (by TLC) amount of mesembrinine (VIII). Reactions attempted in solvents other than water led to no fruitful results. Closer scrutiny of the reaction between (V) and methyl vinyl ketone, however, showed that it was strongly subject to acid catalysis. Thus condensation of the hydrochloride of (V) with methyl vinyl ketone in refluxing acetonitrile gave mesembrine hydrochloride directly in 85% overall yield from (IV). A similar reaction employing methyl β-chlorovinyl ketone gave mesembrinine *hydrochloride*(13) *in 44% overall yield from (IV).*

Several possible explanations may be advanced for the involvement of a proton in the condensation of (V) with vinyl ketones. One possibility is that the protonated form of the vinyl ketone, being a more potent electrophile than the vinyl ketone itself, attacks (V) in a manner analogous to that usually proposed for the reaction of enamines with electrophilic olefins.(2, 14)



Another possibility is that the reaction follows a course in which the initial bond forming step is a Mannich reaction between the vinyl ketone and the iminium salt of (V).



At present we have little information which would lead us to favor any one path over another.(15, 16)

The synthesis of mesembrine and mesembrinine which we have described illustrates in part the utility and versatility of the synthetic scheme outlined at the beginning of this communication. Work is continuing to extend this synthesis to the Amaryllidaceae alkaloids.

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References and Footnotes.

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8. Satisfactory elemental analyses have been obtained for all new crystalline substances reported in this communication.
9. For a similar dehydration see A.R. Lepley, W.A. Khan, A.B. Giumanini, and A.G. Giumanini, *J. Org. Chem.*, **31**, 2047 (1966).
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11. R.J. Abraham and W.A. Thomas, *Chem. Commun*. 431 (1965).
12. Identity was established by comparison of IR and NMR spectra and of TLC behavior with a sample of natural mesembrine hydrochloride.
13. Identity was established by comparison of m.p., m.m.p., IR spectrum, NMR spectrum and TLC behavior with a sample of natural mesembrinine hydrochloride.
14. For recent work on this reaction see I.Fleming and M.H. Karger, *J. Chem. Soc.(C)*, 226 (1967). The formation in the reaction at hand of the dihydropyran or cyclobutane intermediates known to be involved in similar reactions may occur. It seems likely, however, that such intermediates would represent only momentary excursions from the path of reaction leading to the alkaloids.
15. Either of the two mechanisms outlined can accommodate the loss of HCl which must have occurred in the formation of mesembrinine from methyl β-chlorovinyl ketone.
16. We are investigating the possibility raised by this work that other reactions between electrophilic olefins and enamines may be subject to electrophilic catalysis.