A New Synthesis of (±)-Mesembrine

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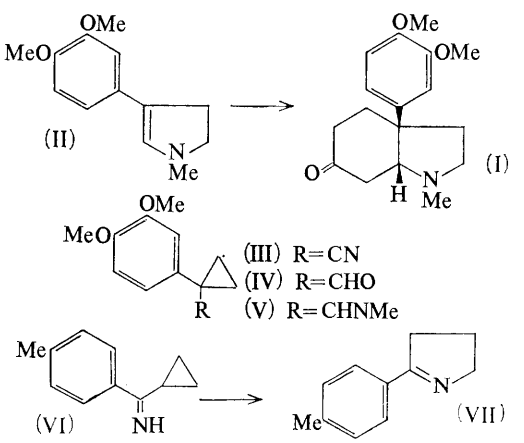
IN the Stork modification of the venerable Robinson annellation procedure, the reaction between an enamine and methyl vinyl ketone presumably produces a β-aminoketone which then loses dialkylamine to form an αβ-unsaturated carbonyl compound.[1] This first step suggests that the Stork modification might be applicable to the synthesis of certain alkaloids. If the nitrogen of the enamine intermediate used to introduce a new ring in the annellation reaction were so positioned that it could also ultimately become the nitrogen of the alkaloid, an expeditious synthesis might be possible. A route to mesembrine (I),[2,3] for example, could be envisaged as involving in the final key-step the reaction between methyl vinyl ketone and pyrroline (II). In fact, both the preparation of (II) and its conversion by this method into mesembrine have been realized.

Substituted cyclopropane (III) was prepared from 3,4-dimethoxyphenylacetonitrile and 1,2-dibromoethane using dimethyl sulphoxide and its anion as the solvent and base respectively.[4] Diisobutylaluminium hydride[5] effected the conversion of (III) into aldehyde (IV) and reaction of the latter with $MeNH_2$ yielded imine (V).



† On the basis of steric considerations, the addition of methyl vinyl ketone to (II) to form the isomer of (I) in which the perhydroindole moiety contains a *trans* ring fusion seems unlikely. In any event, that material has neither been sought nor isolated from the complex mixture of products obtained in the addition reaction.

Cloke[6,7] has reported the ready thermal isomerisation of (VI) to pyrroline (VII) at temperatures below 200° but attempts to convert (V) into (II) in this manner failed. Subsequently the rearrangement was found to be catalysed by acid (as suggested by Cloke's work and confirmed by a more recent study by Stevens).[6-8] At 160° in the presence of a small amount of NH_4Cl, pure imine (V) isomerizes to (II). The condensation of (II) with methyl vinyl ketone in refluxing 1,2-dimethoxyethane yielded (±)-mesembrine.† The structure of the synthetic material was established by comparison of its n.m.r. and i.r. ($CDCl_3$ solution) spectra with those obtained from an authentic sample of the alkaloid.‡

The further application of this general approach to the synthesis of alkaloids is currently under investigation.

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‡ The authentic sample of the alkaloid in the form of the hydrochloride was obtained from S. B. Penick & Co., N.Y.C., U.S.A. Its i.r. spectrum was identical with that reported in the literature (K. Bodendorf and W. Kreiger, *Arch. Pharm.*, 1957, **290**, 30). Correct analytical data have been obtained on all new substances reported. Spectral data are in accord with the assigned structures. We thank Professor R. V. Stevens, Department of Chemistry, Rice University, Houston, Texas, for recently communicating to us his results, before publication, on an independent model study of the mesembrine synthesis described here. His observations, which are analogous to our own, are to appear in *Tetrahedron Letters*.

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