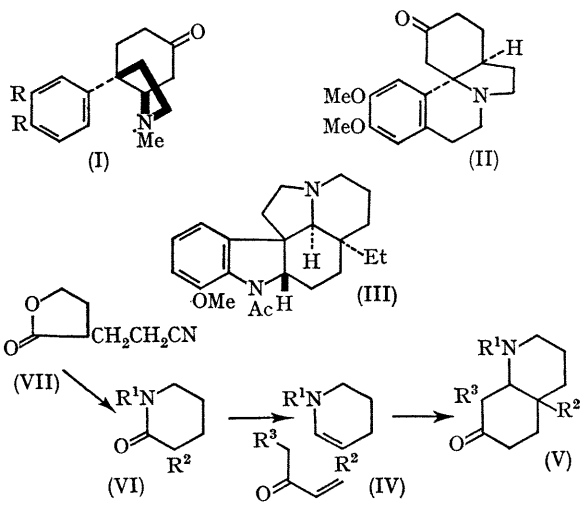
# Synthesis of *Aspidosperma* Alkaloid Precursors. A New Application of the Methyl Vinyl Ketone Annelation of Endocyclic Enamines in Alkaloid Synthesis

By R. V. STEVENS,* RAVINDRA K. MEHRA, and ROBERT L. ZIMMERMAN
(*Department of Chemistry, Rice University, Houston, Texas* 77001)

*Summary* A new, potentially general, method for the synthesis of angularly substituted hydroquinolones is presented.

WE recently reported syntheses of mesembrine model (I; R = H),[1] racemic mesembrine itself (I; R = OMe),[2] and the *Erythrina* alkaloid model (II).[3] Each of these syntheses featured the annelation of an endocyclic enamine with methyl vinyl ketone (MVK). We have investigated the scope of this unique annelation procedure as a potentially general method of synthesis for a variety of other alkaloid systems. Various angularly substituted hydroquinolones (V) can be approached by selection of an appropriate endocyclic enamine (IV) and MVK or a close equivalent. We selected as our initial test the known amino-ketone (V; $R^1 = R^3 = H$, $R^2 = Et$) whose subsequent conversion into aspidospermine (III) has already been reported.[4]

Whereas our previous work used $\Delta^2$-pyrrolines, obtained from the acid-catalysed, thermally induced rearrangement of cyclopropyl imines,[5] the present study required an equally general synthesis of $\beta$-substituted $\Delta^2$-piperidines (IV). The controlled reduction of an appropriately substituted lactam (VI) was therefore investigated. Benzylation of the readily prepared piperidone (VI; $R^1 = H$, $R^2 = Et$)[6] provided the corresponding lactam (VI; $R^1 = CH_2Ph$, $R^2 = Et$).† Carefully controlled di-isobutyl-aluminium hydride (DIBAL-H) reduction[7] and subsequent base work up yielded the desired endocyclic enamine (IV;




† Analytical and spectral data for all new compounds were in agreement with their formulation.

$R^1 = CH_2Ph$, $R^2 = Et$).[8] Admixture of a hot ethylene glycol solution of the enamine and a slight excess of MVK gave a practically quantitative yield of the desired hydroquinolone (V; $R^1 = CH_2Ph$, $R^2 = Et$, $R^3 = H$), m.p. 81·5—82°. Reductive debenzylation of the corresponding hydrochloride salt yielded the known[4a] amino-ketone (V; $R^1 = R^3 = H$, $R^2 = Et$). The spectral features of this substance as well as m.p. and mixed m.p. with an authentic sample‡ confirm the skeletal assignment.

Raney-nickel catalysed hydrogenation of the readily prepared lactone (VII)[9] provided lactam (VI; $R^1 = H$, $R^2 = CH_2{\cdot}CH_2OH$). Dibenzylation of this substance was best accomplished with dimsyl sodium in $Me_2SO$. DIBAL-H reduction of the resultant piperidone (VI; $R^1 = CH_2Ph$, $R^2 = CH_2{\cdot}Ph$, $R^2 = CH_2{\cdot}CH_2OCH_2Ph$) afforded enamine (IV; $R^1 = CH_2Ph$, $R^2 = CH_2{\cdot}CH_2OCH_2Ph$) whose MVK annelation was achieved as described above. Selective reductive *N*-debenzylation of the hydrochloride salt of (V; $R^1 = CH_2Ph$, $R^2 = CH_2CH_2OCH_2Ph$, $R^3 = H$) gave the desired hydroquinolone (V; $R^1 = R^3 = H$, $R^2 = CH_2{\cdot}CH_2OCH_2Ph$).

Although the stereochemical course of the MVK annelation of 3-aryl-$\Delta^2$-pyrrolines was predicted and found to favour *cis*-fused hydro-indoles, *e.g.* (1),[2] such a decision in the present cases cannot be made with confidence. Furthermore, the acid catalysis required in the subsequent debenzylation step could alter the stereochemistry of the ring fusion *via* a retro-Michael process.

The feasibility of employing $\beta$-substituted-$\Delta^2$-piperidines in combination with methyl vinyl ketone as a method of synthesis of angularly substituted hydroquinolones has been established. Application of this knowledge to the synthesis of *Aspidosperma* alkaloids is in progress.

We thank the Public Health Service, the Robert A. Welch Foundation, and Eli Lilly Company for support of this work. The n.m.r. spectrometer was purchased with funds provided by the National Science Foundation.

(*Received, June 3rd,* 1969; *Com.* 783.)

‡ We are grateful to Professor Stork for providing us with a sample of this substance. We found that the literature m.p. of 47—50° could be improved by subliming the sample at 35°/0·1 mm. Both our substance and that prepared by Stork melted at 51—51·5° when purified in this manner.

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