

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

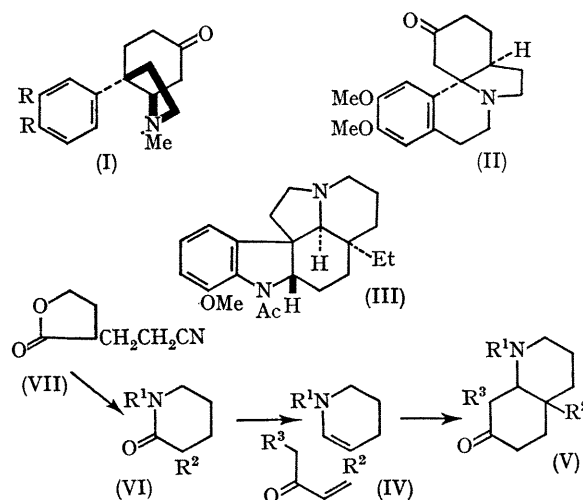
By R. V. STEVENS,* RAVINDRA K. MEHRA, and ROBERT L. ZIMMERMAN

(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 annellation of an endocyclic enamine with methyl vinyl ketone (MVK). We have investigated the scope of this unique annellation 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; R¹ = R³ = H, R² = Et) whose subsequent conversion into aspidospermine (III) has already been reported.⁴

Whereas our previous work used Δ^2 -pyrrolines, obtained from the acid-catalysed, thermally induced rearrangement of cyclopropyl imines,⁵ the present study required an equally general synthesis of β -substituted Δ^2 -piperidines (IV). The controlled reduction of an appropriately substituted lactam (VI) was therefore investigated. Benzyla-



R² = Et)⁶ provided the corresponding lactam (VI; R¹ = CH₂Ph, R² = Et).† Carefully controlled di-isobutyl-aluminum hydride (DIBAL-H) reduction⁷ 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.

$R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Et}$).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; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Et}$, $R^3 = \text{H}$), m.p. 81.5–82°. Reductive debenzoylation of the corresponding hydrochloride salt yielded the known^{4a} amino-ketone (V; $R^1 = R^3 = \text{H}$, $R^2 = \text{Et}$). 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; $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{CH}_2\text{OH}$). Dibenzoylation of this substance was best accomplished with dimethyl sodium in Me_2SO . DIBAL-H reduction of the resultant piperidone (VI; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$) afforded enamine (IV; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$) whose MVK annelation was achieved as described above. Selective reductive *N*-debzoylation of the hydrochloride salt of (V; $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$, $R^3 = \text{H}$) gave

the desired hydroquinolone (V; $R^1 = R^3 = \text{H}$, $R^2 = \text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$).

Although the stereochemical course of the MVK annelation of 3-aryl- Δ^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 debenzoylation step could alter the stereochemistry of the ring fusion *via* a retro-Michael process.

The feasibility of employing β -substituted- Δ^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.

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[†] 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.

¹ R. V. Stevens and M. P. Wentland, *Tetrahedron Letters*, 1968, 2613.

² R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, 1968, **90**, 5580; see also F. C. Tahk and S. L. Keely, jun., *ibid.*, p. 5584; T. J. Curphey and H. L. Kim, *Tetrahedron Letters*, 1968, 1441.

³ R. V. Stevens and M. P. Wentland, *Chem. Comm.*, 1968, 1104.

⁴ (a) G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872; (b) Y. Ban, Y. Sato, I. Inove, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanoako, *Tetrahedron Letters*, 1965, 2261.

⁵ R. V. Stevens and M. C. Ellis, *Tetrahedron Letters*, 1967, 5185; R. V. Stevens, M. C. Ellis and M. P. Wentland, *J. Amer. Chem. Soc.*, 1968, **90**, 5576.

⁶ C. F. Koelsch, *J. Amer. Chem. Soc.*, 1968, **65**, 2548.

⁷ L. I. Zakharkin and I. M. Khorlina, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1959, 2146 (*Chem. Abs.*, 1960, **54**, 10932).

⁸ This enamine has recently been prepared by an entirely different method: F. E. Ziegler and P. A. Zoretic, *Tetrahedron Letters*, 1968, 2639.

⁹ W. A. W. Cummings and A. C. Davis, *J. Chem. Soc.*, 1964, 4591.