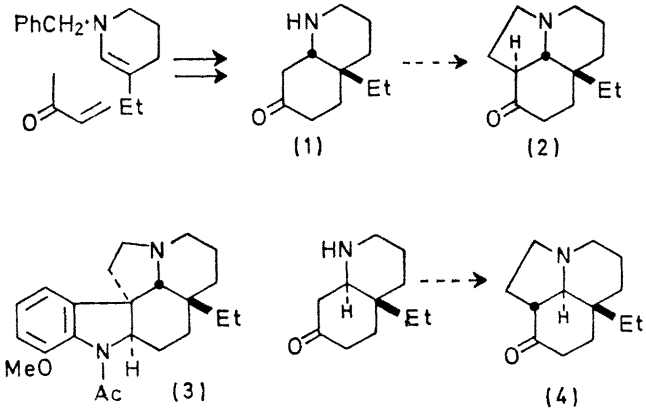
General Methods of Alkaloid Synthesis. A New Approach to Functionalized Hydrolulolidone *Aspidosperma* Alkaloid Precursors. A Formal Synthesis of (±)-Aspidospermine

By R. V. STEVENS,* J. MICHAEL FITZPATRICK, MORRIS KAPLAN, and ROBERT L. ZIMMERMAN

(*Department of Chemistry, Rice University, Houston, Texas* 77001)

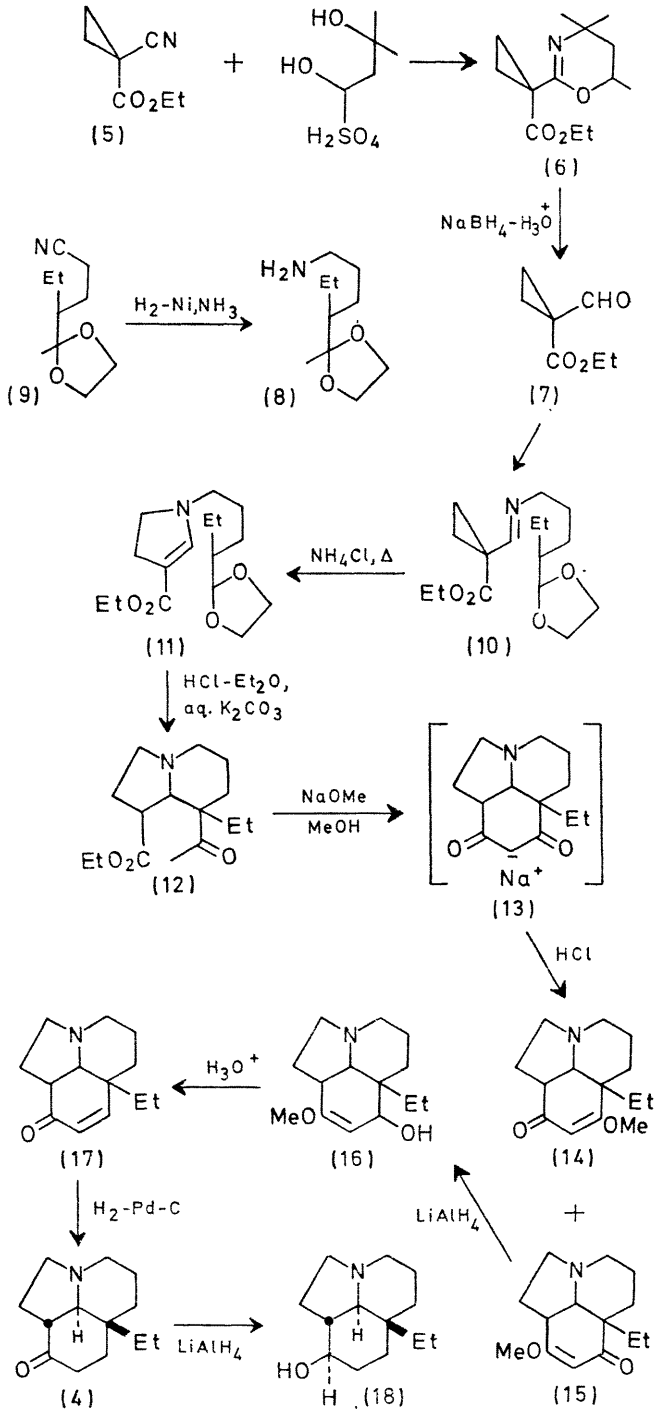
Summary A new method for the synthesis of an established hydrolulolidone *Aspidosperma* alkaloid precursor, (**4**), is presented which involves the acid-catalysed thermal rearrangement of a cyclopropyl-imine (**10**) to a 2-pyrroline (**11**) as a key stage.

IN developing new, hopefully general, synthetic methods for a variety of alkaloid systems[1] we studied several members of the *Aspidosperma* group by two approaches. The first involves the methyl vinyl ketone annelation of appropriately substituted endocyclic enamines[1] and was successfully used in synthesis of angularly substituted hydroquinolones, *e.g.* (**1**).[2] This had been converted previously[3] into hydrolulolidone (**2**) and thereafter into aspidospermine (**3**) itself. The diastereoisomeric ketone (**4**) was then synthesised[4] and converted into (**3**) and the synthesis[5] of the remaining two possible diastereoisomeric tricyclic ketones followed.



We now report a second, fundamentally different approach to the hydrolulolidone system which involves the acid-catalysed thermal rearrangement of a cyclopropyl-imine, (**10**), to an appropriately substituted 2-pyrroline, (**11**), as a key stage. The readily prepared cyano-ester (**5**)[6] was smoothly converted into the dihydro-oxazine (**6**) (64%),† b.p. 89—91° at 0·5 mmHg, and thereafter to the aldehyde (**7**) (61%), b.p. 102—103° at 46 mmHg, (2,4-dinitrophenylhydrazone, m.p. 136·5—137°) by reduction with $NaBH_4$ and hydrolysis of the intermediate tetrahydro-oxazine.[7]

Condensation of 2-pentanone and acrylonitrile yielded a keto-nitrile[8] which quantitatively gave the acetal (**9**), b.p. 79—82° at 0·4 mmHg. Subsequent reduction (Raney-nickel) of this substance yielded the amine (**8**) (87%), b.p. 75—78° at 0·25 mmHg, which was condensed with aldehyde (**7**) in benzene under reflux (Dean–Stark). The resultant cyclopropyl-imine (**10**) (86%), b.p. 142—145° at



† Each intermediate reported has been subjected to i.r. and n.m.r. analysis. Supporting data were obtained from low-resolution mass spectral and/or combustion data.

0·2 mmHg, was smoothly rearranged (82%) to the endocyclic enamine (**11**), b.p. *ca.* 170° at 0·1 mmHg, with NH_4Cl as the acidic catalyst at 160°. Closure of the second ring was achieved by treatment of (**11**) with ether saturated with dry HCl gas.[9] The acetal function could be detected in the crude product (90%) but was readily hydrolysed with aqueous acid to the unprotected keto-ester (**12**) (86%). Treatment of crude (**12**) with methoxide and acidification of the basic methanolic solution with dry HCl yielded two crystalline tricyclic enol-ethers (**14**), m.p. 94—95°, and (**15**), m.p. 116—117° in a ratio of 28 : 72 (93% yield). Reduction with $LiAlH_4$ of the major isomer, (**15**), gave (**16**) (96%), m.p. 114—114·5°, which was hydrolysed and dehydrated to the enone (**17**) (70%), m.p. 42—42·5°, in hot aqueous acid. The structure of (**17**) and its precursors was confirmed by reduction to the known[4] hydrolulolidine (**4**) and the corresponding alcohol (**18**). In addition to correct analytical and spectral data each of these substances was converted into its corresponding crystalline picrate and compared directly with authentic specimens.‡ The obtention of (**4**) also constitutes a formal total synthesis of (±)-aspidospermine (**3**).

We thank the Public Health Service, the National Cancer Institute, the National Science Foundation, and the Robert A. Welch Foundation for support. The n.m.r. and mass spectrometers were purchased with funds provided by N.S.F. A Sloan Fellowship (to R.V.S.) is gratefully acknowledged.

(*Received, May 11th*, 1971; *Com.* 747).

‡ Kindly provided by Professor Y. Ban.

[1] See R. V. Stevens and L. E. DuPree, jun., *Chem. Comm.*, 1970, 1585 and references cited therein.
[2] R. V. Stevens, R. K. Mehre, and R. L. Zimmerman, *Chem. Comm.*, 1969, 877.
[3] G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872.
[4] Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Letters*, 1965, 2261; *cf.* also Y. Ban and I. Inoue, *J. Chem. Soc.* (*C*), 1970, 602.
[5] M. E. Kuehne and C. Bayha, *Tetrahedron Letters*, 1966, 1311.
[6] L. W. Jones and A. W. Scott, *J. Amer. Chem. Soc.*, 1922, **44**, 407; a far more reproducible procedure is given by E. L. Mitch, Ph.D. Thesis, Rice Institute, 1959, p. 73.
[7] J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, *Organic Preparations and Procedures*, 1969, **1**, 193.
[8] N. P. Shusherina, R. Ya. Levina, and Z. S. Sidenko, *Zhur. obshchei Khim.*, 1959, **29**, 398; *Chem. Abs.*, 1960, **54**, 5191.
[9] E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Amer. Chem. Soc.*, 1968, **90**, 6177.