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

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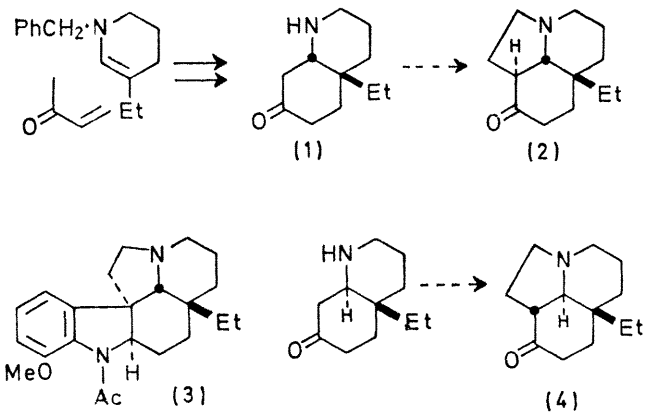
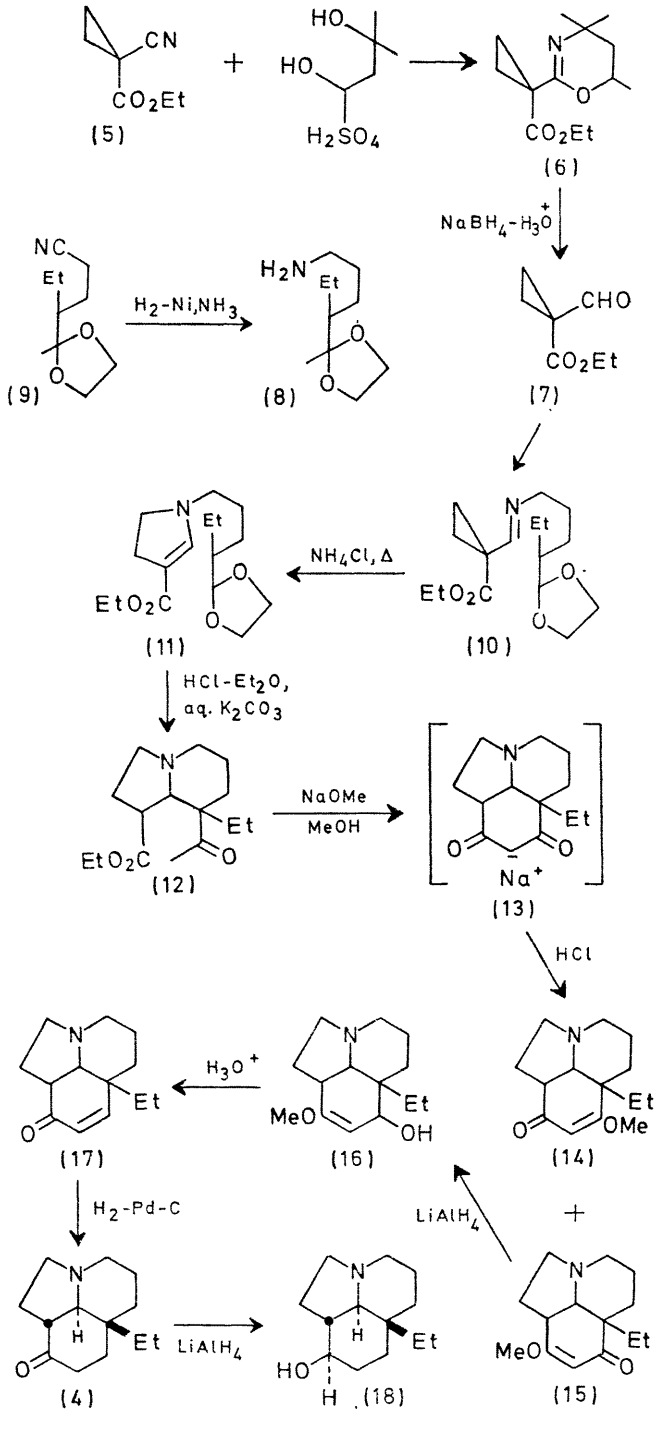
Summary A new method for the synthesis of an established hydrolulolidone *Aspidosperma* alkaloid precursor, (**4**), is presented which involves the acid-catalysed thermal rearrangement of a cyclopropyl-imine (**10**) to a 2-pyrroline (**11**) as a key stage.

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**).

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