# Synthetic Entry to the Hexacyclic *Aspidosperma* Alkaloids. Total Synthesis of (±)-4-Hydroxyaspidofractinine

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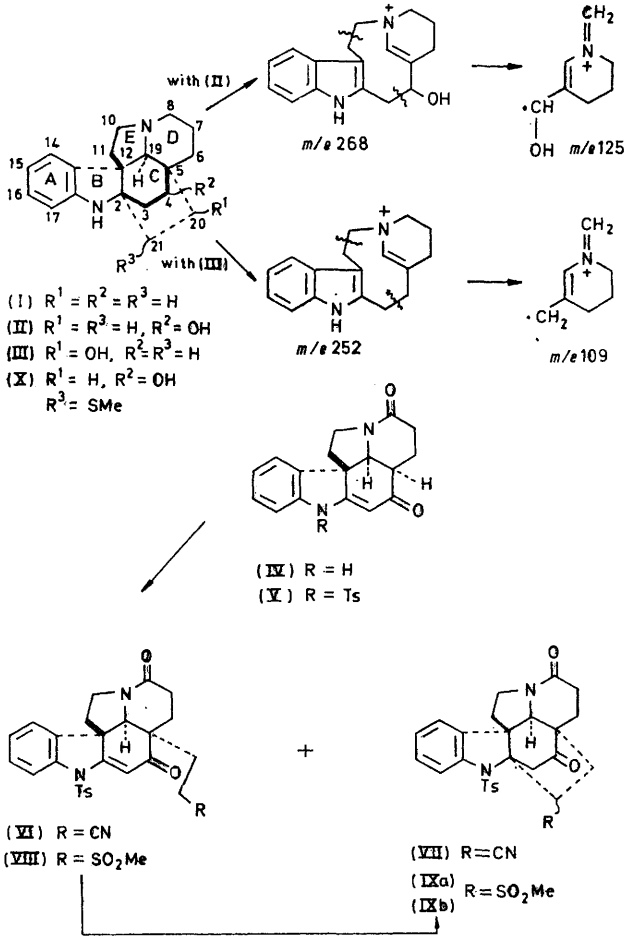
*Summary* The pentacyclic intermediate (V) underwent a new type of Michael cyclization on the vinylogous amide system with acrylonitrile and methyl vinyl sulphone to give regio- and stereo-specific bridge formation producing the hexacyclic compounds which constitute the aspidofractinine (I) skeleton.

THE hexacyclic *Aspidosperma* alkaloids,[1] whose fundamental skeleton is represented by aspidofractinine (I),[2] not only contain an interesting cage structure, but also may be an important intermediate in the conversion into the heptacyclic *Aspidosperma* species.[3] This hexacyclic ring system is derived from the aspidospermine skeleton by formation of a bond between C(2) and C(21) of the ethyl side chain, as was realized by Biemann in the conversion of (−)-minovincine into 20-hydroxyaspidofractinine (III).[4] We now report the two-fold Michael cyclization of the synthetic compound (V), which proceeded regio- and stereo-specifically to give the hexacyclic compounds (VII) and (IX).

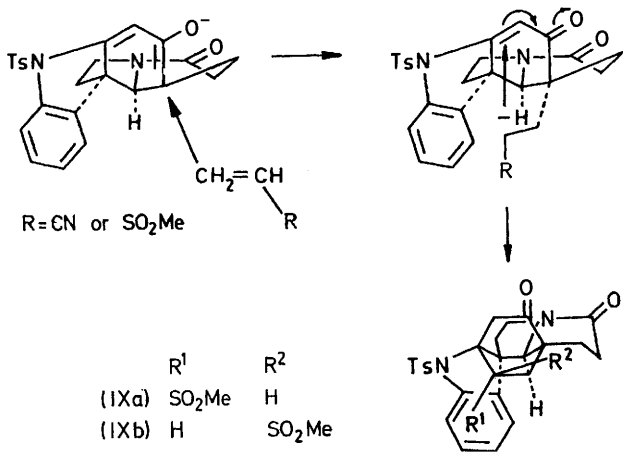
Compound (IV)[5a] (C/D ring junction *cis*, m.p. 247—249°) was prepared from 2-hydroxytryptamine and its stereochemistry fully elucidated.[5] It was treated with sodium hydride in boiling monoglyme for 2 h, and the mixture of the sodium salt and tosyl chloride then heated under reflux for 5 h to give the tosylate (V), colourless prisms, 44%, m.p. 240—241°, $M^+$ 434. The Michael reaction of (V) with acrylonitrile (10 mol equiv.) was effected in $Bu^tOH$ and $Me_2SO$ containing $Bu^tOK$ (room temp., 1 h) and chromatography on alumina gave two products (VI),† colourless prisms, 29%, m.p. 290—291°, $M^+$ 487, and (VII),† colourless prisms, 23%, m.p. 310—316°, $M^+$ 487. Compound (VI) was converted quantitatively into (VII) on further base treatment (room temp., 1·5 h). A possible reaction mechanism is shown in the Scheme.

This type of cyclization was also successful with methyl vinyl sulphone,[6] which provided the useful precursor (IX). The Michael addition was effected under the conditions described above to give a mixture of the two cyclization products (IXa) and (IXb), colourless prisms, 21%, m.p. 270—290°, two spots on t.l.c. The chemical shifts of the methylsulphonyl protons are δ2·96 for (IXa) and 3·22 for (IXb), This discrepancy, due to the anisotropy of the phenyl ring, suggests that the methylsulphonyl group lies above the aromatic ring in (IXa) and on the opposite side in (IXb) and in the open chain product (VIII), colourless prisms, 22%, m.p. 212—215°, $M^+$ 540. The isomer (IXb) is more stable than (IXa) because of lower steric interaction, as illustrated by the fact that (VIII) was converted on




† Structure confirmed by elemental analysis, and i.r., u.v., and n.m.r. data.

further base treatment (room temp., 1·5 h, and 40—50°, 1·5 h) into (IXb) as the sole product, colourless prisms, m.p. 280—284°.† A mixture of (IXa) and (IXb) was reduced




| | $R^1$ | $R^2$ |
|---|---|---|
| (IXa) | $SO_2Me$ | H |
| (IXb) | H | $SO_2Me$ |

SCHEME

with $NaH_2Al(OCH_2CH_2OMe)_2$ in boiling dioxan for 2·5 h to afford a crude product (X) as a resin (the absorptions due to lactam, ketone, and sulphone groups in the i.r. spectrum disappeared), which without purification, was subjected to desulphurization with Raney nickel in ethanol (reflux, 2 h). The product was purified by chromatography on silica gel to give (±)-4-hydroxyaspidofractinine(II),† colourless needles, m.p. 154—155°. It is well known that retro-Diels–Alder type fragmentations at the C(5)–C(20) and C(2)–C(21) bonds *cis* to C(19)–H are common for alkaloids of the refractine class.[4] Thus, the mass spectrum of 20-hydroxyaspidofractinine(III)[4] indicates the fragments of *m/e* 296($M^+$), 252($M$ − 44), 140, 109, of which the fragment (*m/e* 252) underwent bond fission to yield an ion of *m/e* 109, while the present synthetic product (II) afforded the fragment of *m/e* 268($M$ − 28), which then gave a fragment of *m/e* 125. Consequently, it is concluded that the synthetic compound (II) has the hydroxy-group at C-4 *trans* to the C(19)–H bond.

Financial support from the Ministry of Education is acknowledged.

(*Received*, 15*th February* 1973; *Com.* 212.)

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