An Unequivocal Synthesis of 1-Benzyl-3-ethyl-1,6-dihydropyridine and its Use for a Biogenetically Modelled Synthesis of (±)-Catharanthine

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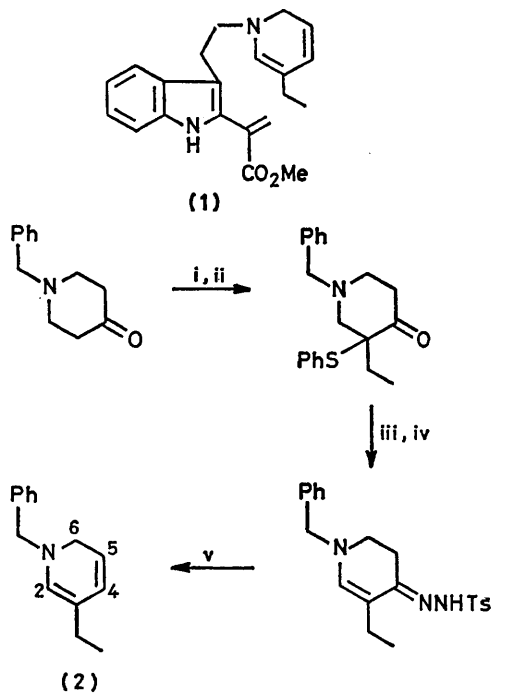
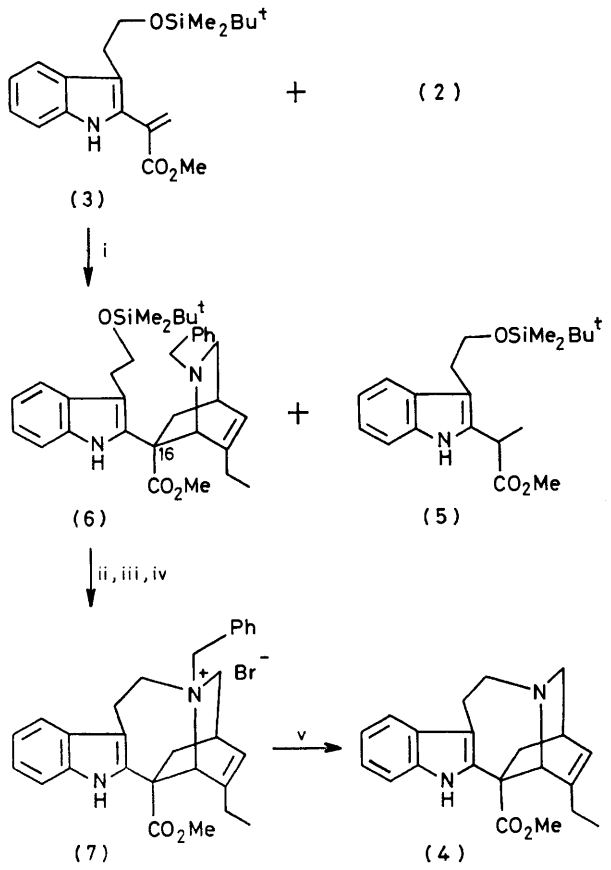
Summary The first unambiguous synthesis of an *N*-substituted 3-ethyl-1,6-dihydropyridine (**2**) and its use for a biomimetic synthesis of (±)-catharanthine (**4**) are described.

WHEREAS the role of 1,4-dihydropyridines in various biological systems is well established,[1] numerous investigations[2] during the past 12 years have implicated 1,2- and/or 1,6-dihydropyridines in the biosynthesis of certain indole alkaloids. Thus, dehydrosecodine B (**1**), containing an indole-2-acrylate moiety and a 3-ethyl-1,6-dihydropyridine system, is considered[2] as a possible biosynthetic intermediate which could undergo intramolecular cycloadditions leading to Aspidosperma and/or Iboga type indole alkaloids. Synthetic applications[3–7] of similar cycloadditions involving appropriate indole-2-acrylates and *N*-substituted 1,2-dihydropyridines or 3-ethyl-1,4,5,6-tetrahydropyridines have also been demonstrated. Although methods providing access to indole-acrylates[5–10] and *N*-substituted 1,2-dihydropyridines[11] are now available, no straightforward synthesis of an *N*-substituted 3-ethyl-1,6-dihydropyridine is known, except for the reported[12] formation of a tricarbonylchromium(0) complex by isomerisation during the complexation of the corresponding 1,2-dihydropyridines. However, in a recent report,[13] the occurrence (in 12% unisolated yield) of 1,3-dimethyl-1,6-dihydropyridine in an unresolved mixture of products obtained by sodium borohydride reduction of 1,3-dimethylpyridinium iodide in strongly alkaline medium was established only by a careful ^{1}H n.m.r. analysis. With dehydrosecodine B (**1**) as an eventual synthetic target, we were therefore interested in devising a suitable synthetic route to an *N*-substituted 3-ethyl-1,6-dihydropyridine.



SCHEME 1. *Reagents and conditions:* i, HMDSLi, Ph_2S_2, THF–HMPA, 75% yield; ii, NaH, EtI, THF–DMF, 72% yield (B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, 1976, **98**, 4887; R. M. Coates, H. D. Pigott, and J. Ollinger, *Tetrahedron Lett.*, 1978, 2139); iii, $TsNHNH_2$, AcOH; iv, AcOEt, 70 °C, 1 h, 75% yield (iii + iv); v, BuLi (2 equiv.), TMEDA–THF (20:80), −60 °C, 15 min, then 20 °C, 45 min, >95% yield (J. E. Stemke, and F. T. Bond, *Tetrahedron Lett.*, 1975, 1815). Abbreviations: THF = tetrahydrofuran; TMEDA = tetramethylethylenediamine; Ts = tosyl; DMF = dimethylformamide; HMPA = hexamethylphosphoric triamide; HMDSLi = lithium hexamethyldisilazane.



SCHEME 2. *Reagents and conditions:* i, Et_2O, N_2, 20 °C, 15 h; ii, THF–AcOH–H_2O, 48 h, 60% yield; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 100% (ref. 7); iv, LiBr, DMF, 60 °C, 17 h; v, PrSH, LiH, HMPA, 10 min, 0 °C (ref. 14), 10% yield (iv + v).

We now describe an unambiguous synthesis of 1-benzyl-3-ethyl-1,6-dihydropyridine (**2**) through the reactions outlined in Scheme 1. Compound (**2**), the single product of the final step, was isolated as an oil† and all its spectroscopic data, in particular the ^1H n.m.r. spectrum (80 MHz, $CDCl_3$): δ 7·25 (s, 5H, ArH), 5·85 (br. s, 1H, 2-H), 5·80 (dm, 1H, $J_{4,5}$ 10·2, $J_{4,6}$ 1·5 Hz, 4-H), 5·16 (dt, 1H, $J_{5,4}$ 10·2, $J_{5,6}$ 4 Hz, 5-H), 3·88 (s, 2H, CH_2Ph), 3·60 (dd, 2H, $J_{6,5}$ 4, $J_{6,4}$ 1·5Hz, 6-H), 1·93 (q, 2H, J 7 Hz, CH_2Me), and 0·94 (t, 3H, J 7 Hz, CH_2Me), point to the correctness of the structure.

Until now (**2**) appears to be the closest synthetic analogue of (**1**) with regard to the dihydropyridine part of the molecule. The availability of the 3-ethyl-1,6-dihydropyridine (**2**) as well as the previously reported[7] indole-2-acrylate (**3**) prompted us to elaborate a biogenetically modelled synthesis of catharanthine (**4**) (Scheme 2). The reaction of (**3**) with 1·5 equiv. of (**2**) in Et_2O at 20 °C for 15 h gave a mixture of compounds which could be resolved by column chromatography over silica gel. The major product (45% yield) was compound (**5**) [$M^{+\cdot}$ 361; ^1H n.m.r., δ 1·53 (d, J 7 Hz) and 4·1 (q, J 7 Hz; >CHMe)] thereby revealing the expected reducing character of the dihydropyridine (**2**). In addition to (**5**), two isomeric Iboga-type adducts (**6**; C-16 epimers) could be separated in 11 and 1·5% yield. Their ^1H n.m.r. spectra were different but did not provide any conclusive indication of the stereochemistry of the two adducts.[6,7] However, the major adduct was assigned the structure (**6**) on the basis of its transformation to (±)-catharanthine (**4**). The dequaternisation of the known *N*-benzyl-ammonium bromide salt (**7**) according to the method of Kutney *et al.*[14] gave (±)-catharanthine (**4**) (identical with an authentic sample; m.s., n.m.r., and t.l.c.), albeit in poor overall yield.‡

† Compound (**2**) could be stored for several weeks in an inert atmosphere over KOH pellets at −20 °C without isomerisation or disproportionation as shown by its unchanged ^1H n.m.r. spectrum.

‡ Satisfactory ^1H n.m.r. and mass spectral data were obtained for purified and chromatographically homogeneous samples of each synthetic intermediate.

The poor yield of the desired adduct (**6**) and also unexpected difficulty in the formation (iv, Scheme 2) of the quaternary salt (**7**) seem to be the limiting factors of this synthesis of catharanthine, but refinements of these crucial steps are under way. Although the total synthesis of (±)-catharanthine has been previously accomplished,[15] the strategy adopted here involves a simple approach closely resembling the postulated[2] biosynthetic pathway.

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