

Synthesis of *trans*-2,6-Dialkylpiperidines by 1,3-Cycloaddition of Alkenes to 2-Alkyl-2,3,4,5-tetrahydropyridine Oxides

William Carruthers and Michael J. Williams

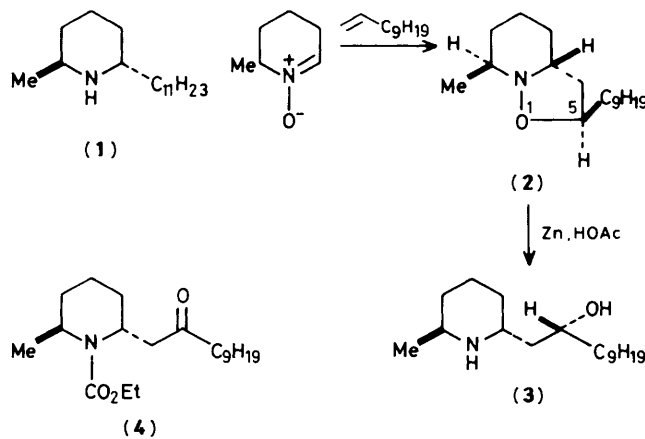
Chemistry Department, The University, Stocker Road, Exeter EX4 4QD, U.K.

A convenient route to *trans*-2,6-dialkylpiperidines by cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine oxides followed by reductive cleavage of the resulting isoxazolidine is illustrated by a synthesis of the fire ant-venom alkaloid, solenopsin.

Recent reports¹ on the synthesis of *trans*-2,6-dialkylpiperidines from tetrahydropyridine oxide by cycloaddition reactions prompt us to record some of our own results² in this area. We too had conceived the possibility that cycloaddition of an alkene to a 2-alkyl-2,3,4,5-tetrahydropyridine 1-oxide would take place preferentially by orthogonal approach of the alkene to the nitrene in a conformation in which the 2-alkyl substituent was equatorial, to give an isoxazolidine which would furnish a *trans*-2,6-dialkylpiperidine by reductive cleavage of the N–O bond. We have shown the validity of this supposition by a short stereocontrolled synthesis of solenopsin (1), one of the constituents of the venom of the fire ant *Solenopsis saevissima*.³ Related results were reported by Gossinger⁴ during the course of our work and he used the reaction in a neat synthesis of the alkaloid porantherilidine.

In our approach to solenopsin, 2-methyl-2,3,4,5-tetrahydropyridine 1-oxide, obtained from 2-methyl-1-hydroxypiperidine with mercuric oxide, was treated with undec-1-ene in chloroform at 50°C to give the isoxazolidine (2) in 47% yield after chromatography. Thin layer and gas-liquid chromatography and the ¹³C n.m.r. spectrum clearly indicated the formation of only one stereoisomer in this reaction, shown to be the *trans* compound (2) by conversion into solenopsin. The stereochemistry at C-5 in (2) is assigned by analogy.⁵ Reductive cleavage of the isoxazolidine ring with

zinc and acetic acid afforded the piperidine derivative (3), again as a single isomer. The chemical shifts of the α and α' carbon atoms (δ 46.0 and 47.7) in the ¹³C n.m.r. spectrum of (3) closely resembled those reported for solenopsin (δ 45.9 and 50.9) rather than those of isosolenopsin with *cis* alkyl substituents (δ 52.6 and 52.7).⁶ Conversion of (3) into solenopsin was effected by reduction of the corresponding phenoxythioxocarbonate with tri-*n*-butylstannane⁷ or, better, by desulphurisation of the thio-acetal of the derived ketone (4)



with Raney nickel and acid hydrolysis of the carbamate. None of the *cis* isomer was detected by g.l.c.

We thank the S.E.R.C. and I.C.I. Pharmaceuticals Division for a CASE award to M. J. W.

Received, 9th June 1986; Com. 791

References

- 1 D. Lathbury and T. Gallagher, *Tetrahedron Lett.*, 1985, **26**, 6249; J. J. Tufariello and J. M. Puglis, *ibid.*, 1986, **27**, 1489.
 - 2 M. J. Williams, Ph.D. Thesis, University of Exeter, 1984.
 - 3 J. G. MacConnell, M. S. Blum, and H. M. Fales, *Tetrahedron*, 1971, **26**, 1129. Solenopsin has been synthesised on a number of previous occasions, e.g. K. Takahashi, H. Kurita, K. Ogura, and H. Iida, *J. Org. Chem.*, 1985, **50**, 4368; K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumara, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 2831; M. Bonin, J. R. Romero, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, 1982, **23**, 3369.
 - 4 E. Gossinger, *Monatsh. Chem.*, 1980, **111**, 143.
 - 5 J. J. Tufariello and Sk. Asrof Ali, *Tetrahedron Lett.*, 1978, 4647.
 - 6 Y. Moriyama, D. Doan-Huynh, C. Monneret, and Q. Khuong-Huu, *Tetrahedron Lett.*, 1977, 825.
 - 7 M. J. Robbins and J. S. Wilson, *J. Am. Chem. Soc.*, 1981, **103**, 932.
-