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

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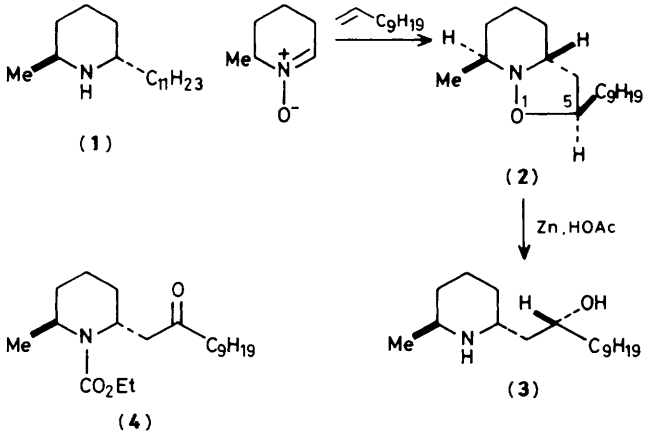
A convenient route to *trans*-2,6-dialkylpiperidines by cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine oxides followed by reductive cleavage of the resulting isoxazolidine is illustrated by a synthesis of the fire ant-venom alkaloid, solenopsin.

Recent reports[1] on the synthesis of *trans*-2,6-dialkylpiperidines from tetrahydropyridine oxide by cycloaddition reactions prompt us to record some of our own results[2] 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 nitrone 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 Gossinger[4] 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 ^{13}C 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 ^{13}C 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-butylstannane[7] 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.

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