

## Synthesis of *trans*-2,6-Dialkylpiperidines by Intramolecular Amidomercuration

William Carruthers,<sup>a</sup> Michael J. Williams,<sup>a</sup> and Michael T. Cox<sup>b</sup>

<sup>a</sup> Chemistry Department, The University, Stocker Road, Exeter EX4 4QD, U.K.

<sup>b</sup> I.C.I. Ltd., Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

Intramolecular amidomercuration of *N*-methoxycarbonyl-6-aminohept-1-ene and reaction of the resulting organomercurial with sodium borohydride in the presence of acrylonitrile or decen-3-one has been used to prepare *trans*-2,6-dialkylpiperidines, including solenopsin A, a constituent of the venom of the fire-ant.

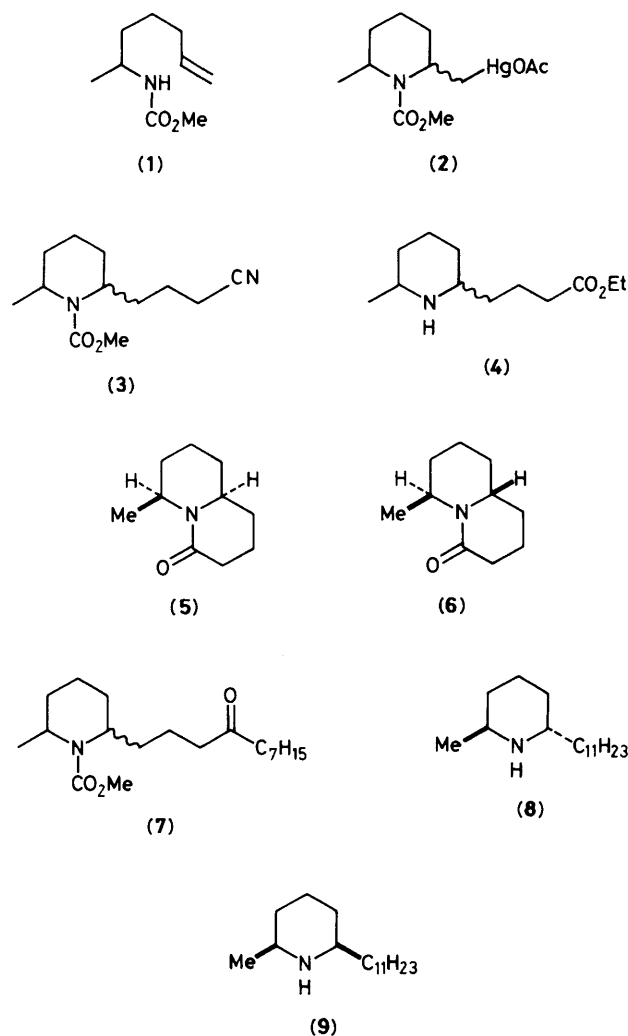
Recent reports<sup>1</sup> on the synthesis of nitrogen heterocycles by intramolecular amidomercuration of *N*-protected unsaturated amines prompts us to record our own experiments in this area. We have been exploring the possibility of employing this reaction to prepare *trans*-2,6-dialkylpiperidines. A number of natural products contain this structural feature, but there are few good general methods of synthesis.<sup>2</sup>

Reaction of *N*-methoxycarbonyl-6-aminohept-1-ene (**1**) with mercuric acetate in tetrahydrofuran, according to Harding and Burks,<sup>3</sup> gave a crude organomercurial (**2**), reduction of which with sodium borohydride and methanol, without isolation, led to a mixture of *cis*- and *trans*-*N*-methoxycarbonyl-2,6-dimethylpiperidine (62% overall) in the ratio of about 1:2 (g.l.c.). The isomers were separated by preparative g.l.c. and identified by conversion into the crystalline hydrochlorides of the corresponding 2,6-dimethylpiperidines (*cis*-2,6-dimethylpiperidine hydrochloride, m.p. 286–287 °C, lit.<sup>4</sup> m.p. 289–291 °C, *trans*-2,6-dimethylpiperidine hydrochloride, m.p. 240–242 °C lit.<sup>4,5</sup> m.p. 236–238, 240–242 °C). The formation of a mixture of stereoisomers in this cyclisation contrasts with results obtained with *N*-acyl derivatives of 5-aminohept-1-ene, which gave entirely *trans*-2,5-dimethylpyrrolidine.<sup>3</sup>

Giese<sup>6</sup> has shown that reaction of organomercurials with borohydride in the presence of derivatives of acrylic acid

affords coupled products through a free radical chain reaction. Following this, reaction of the mercurial (**2**) with sodium borohydride and acrylonitrile smoothly gave the coupled product (**3**) (75%) as a mixture *cis* and *trans* isomers (ratio *cis*:*trans* = 2:3). The isomers were separated by preparative g.l.c. and their stereochemistries established by conversion into the known *cis*- and *trans*-4-methylquinolizidines.<sup>7</sup> Heating the individual nitriles with ethanolic hydrogen chloride led to the unstable amino esters (**4**) which were separately cyclised to the quinolizidones (**5**) and (**6**) in boiling xylene. Reduction with lithium aluminium hydride gave the corresponding quinolizidines. The *cis* isomer [as (**5**)] was identified by comparison of its i.r. spectrum with that of an authentic specimen, and by mixed melting point of its picrate (m.p. 191–192 °C, lit.<sup>7</sup> m.p. 197.5–199 °C, the specimen we used had m.p. 193–195 °C). The picrate of our other isomer [as (**6**)] had m.p. 191–192 °C but a specimen of the picrate of *trans*-4-methylquinolizidine (lit.<sup>7</sup> m.p. 198.5–200 °C) was not available for comparison. The amino esters (**4**) could also be obtained directly from (**2**) by reaction with sodium borohydride and ethyl acrylate, but in much poorer yield (40%) than by the acrylonitrile route.<sup>8</sup>

We have used this sequence to prepare the *trans*-2,6-dialkylpiperidine solenopsin A (**8**), a constituent of the venom of the fire ant *Solenopsis saevissima*.<sup>9</sup> Reductive coupling of



(2) with decen-3-one in the usual way gave the *cis* and *trans* isomers (7) but in noticeably poorer yield (25%) than in the reactions with acrylonitrile and ethyl acrylate. The ratio of isomers formed was about 3:2 but we cannot say which was which because we were unable to separate them by preparative g.l.c., because of decomposition, or by h.p.l.c. Reduction

of the carbonyl group in the mixture by hydrogenolysis of the derived thioacetals with Raney nickel, and cleavage of the methoxycarbonyl group with ethanolic hydrogen chloride gave solenopsin (8) and isosolenopsin (9) [77% from (7), ratio 2:3]. The isomers were separated by preparative g.l.c. and distinguished through their  $^1\text{H}$  n.m.r. spectra, particularly by the downfield chemical shift of the signal due to the C-2 and C-6 protons in solenopsin<sup>9</sup> (br.  $\delta$  3.08—2.85) compared with that of isosolenopsin<sup>10</sup> (br.  $\delta$  2.72—2.44), and by their crystalline hydrochlorides (solenopsin hydrochloride, m.p. 113—114 °C, lit.<sup>11</sup> m.p. 114 °C; isosolenopsin hydrochloride, m.p. 154 °C, lit.<sup>9</sup> m.p. 154—155 °C).

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