Synthesis of 3-Halomethyl-2,3,4,5-tetrahydro-2,5-methano-1*H*-2-benzazepines and their Rearrangement to 4-Halo-1,2,3,4,5,6-hexahydro-2,6-methano-2-benzazocines

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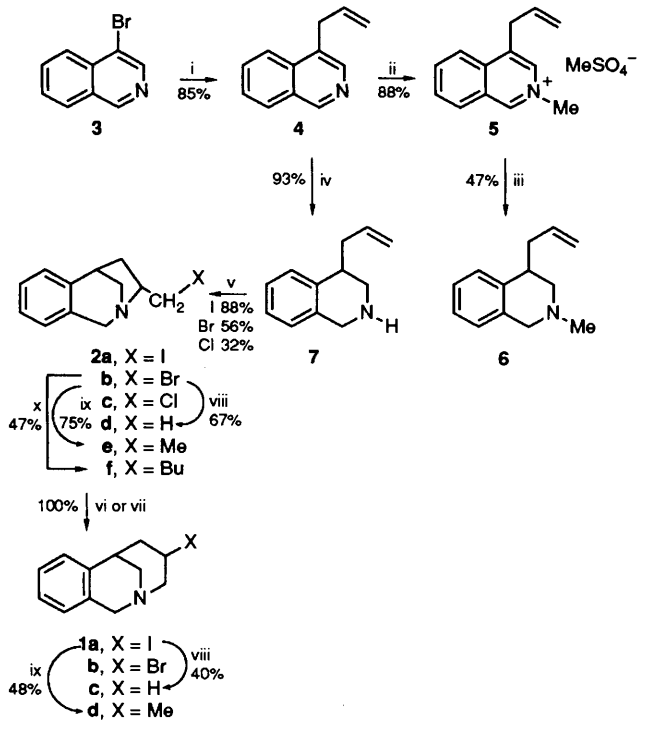
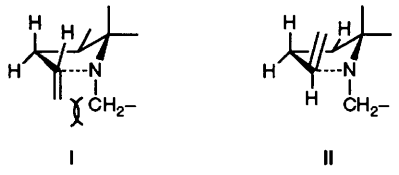
This study reports a three-step synthesis of 3-halomethyl-2,3,4,5-tetrahydro-2,5-methano-1*H*-2-benzazepines **2a–c** and the rearrangement of **2a–b** to 4-iodo- and 4-bromo-1,2,3,4,5,6-hexahydro-2,6-methano-2-methano-2-benzazocines **1a–b**.

As part of a programme aimed at the synthesis of novel *N*-methyl-D-aspartic acid (NMDA) noncompetitive antagonists, we required access to the 4-halo-1,2,3,4,5,6-hexahydro-2,6-methano-2-benzazocines **1a–b** and 3-halomethyl-2,3,4,5-tetrahydro-2,5-methano-1*H*-2-benzazepine **2a–c**. Intermediates **1** and **2** can be coupled with alkylcopper reagents to provide 3-substituted and 2-substituted analogues, respectively. In this report we describe a three-step synthesis of **2a–c** which proceeds *via* a new method for the reduction of isoquinolines to 1,2,3,4-tetrahydroisoquinolines and report that **2a–b** can be rearranged to **1a–b**.

Scheme 1 outlines the route devised to prepare **1a–d** and



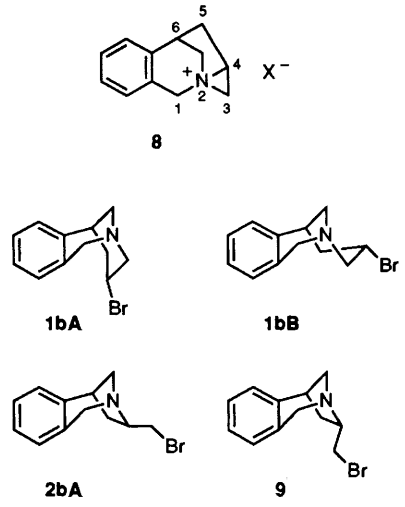
Scheme 1 *Reagents and conditions*: i, CH_2=$CHCH_2Sn(Bu)_3$, $[Pd(PPh_3)_4]$, toluene, 110 °C; ii, Me_2SO_4; iii, $LiBH_4$, MeOH; iv, $LiEt_3BH$, THF; v, *N*-halosuccinimide (halo = chloro, bromo or iodo), THF, 0–25 °C; vi, NaI or KBr, THF, 50 °C; vii, heat; viii, $LiAlH_4$, THF, reflux; ix, $Me_2CuCNLi_2$, THF, −78 °C → 0 °C; x, $Bu_2CuCNLi_2$, THF, −78 °C → 0 °C



Scheme 2 Partial structures of the transition states in the conversion of **2** to **1**

2a–f. Commercially available 4-bromoisoquinoline **3** was coupled with allyltributylstannane using tetrakis(triphenylphosphine)palladium(0) catalyst in refluxing toluene to give an 85% yield of 4-allylisoquinoline **4**. Although Ishikura *et al.*[1] reported that **3** can be converted to **4** in 61% yield *via* a borate intermediate using copper(I) cyanide, attempts to repeat this reaction were unsuccessful. Since there were no reported methods for the selective reduction of isoquinolines to 1,2,3,4-tetrahydroisoquinolines in the presence of an isolated double bond, **4** was converted to the *N*-methyl quaternary salt **5** (88%) which was readily reduced to the *N*-methyltetrahydro derivative **6** (47%) using lithium borohydride in methanol. However, attempts to demethylate **6** to 4-allyl-1,2,3,4-tetrahydroisoquinoline **7** were complicated by cleavage of the more labile benzyl–nitrogen bond. Fortunately, we discovered that **4** could be reduced directly to **7** in 93% yield using two equivalents of lithium triethylborohydride in tetrahydrofuran (THF) followed by quenching the reaction with methanol.†

† Quenching the reduction reaction with $[^2H_4]$methanol gave $[4^2H]$-**7** whereas reduction of **4** using lithium triethylborodeuteride with methanol quenching gave $[1,3\text{-}^2H_2]$-**7**. Mechanistically, we propose that hydride addition occurs first at C-1 followed by attack at C-3 with quenching of the resulting C-4 anion.



Halocyclization of **7** using *N*-halosuccinimides produced the azabicyclo[3.2.1]heptanes **2a–c** as the only products.[2] The cyclization proceeded *via* the 5-*exo-trig* route to give the kinetically favoured five-membered ring product.[3] The stereochemistry of amines **2a–c** can be rationalized by considering the two possible transition states depicted as envelopes **I** and **II** in the partial structures shown in Scheme 2. In transition state **I** which would lead to the *endo*-halomethylene product the terminal olefinic and benzyl methylene substitutents of the incipient cyclopentane ring are forced into an eclipsing *syn* relationship. In transition state **II**, which leads to the observed *exo*-halomethylene group, the olefin is free from steric congestion.

Compound **2a** was found to rearrange thermally to the thermodynamically favoured azabicyclo[3.3.1]octane **1a** which would have been the product of an initial 6-*endo-trig* cyclization of **7**. Amine **1a** and **1b** were more efficiently prepared by treating **2a** and **2b**, respectively, with sodium iodide or potassium bromide in acetone. Apparently, rearrangement occurs *via* the aziridinium ion **8** which subsequently reacts with the iodide or bromide ions. Reaction of **8** at C-4 gives the rearranged products **1a** and **1b**, whereas reaction at C-3 gives **2a** and **2b**. The chloride **2c** failed to rearrange under these conditions. The observation that the azabicyclo[3.2.1]heptanes are the kinetic and azabicyclo[3.3.1]octanes are the thermodynamic products is supported by the relative values of the calculated heats of formation of these compounds. Using AM1[4] semi-empirical quantum mechanics calculations isomers **1bA** and **B** were calculated to have heats of formation of 26.03 and 31.79 kcal mol^{-1} (1 cal = 4.184 J), respectively, while the *exo*- and *endo*-bromomethyl azabicyclo[3.2.1]heptanes, **2bA** and **9**, yielded calculated heats of formation of 37.41 and 38.27 kcal mol^{-1}, respectively. The lowest energy azabicyclo[3.3.1]octane **1bA** is therefore 11.38 kcal mol^{-1} more stable than the lowest energy azabicyclo[3.2.1]heptane **2bA**.

NMR studies including ^1H COSY and ^{13}C DEPT NMR analyses were used to confirm the structures of **2a–c** and **1a–c**. Both ring systems had similar ^1H and ^1H COSY NMR spectra which made the structural assignment difficult. The primary spectroscopic difference between these compounds is that in one ring system the C-4 methine is adjacent to the amine, and the C-3 methylene is adjacent to the halide while in the other system, the opposite is true. These differences could be proved by ^{13}C DEPT NMR. The spectra of bromides **2b** and **1b** indicated a change of the methine resonance from δ 66 in **2b** to δ 45 in **1b**, while a methylene moved from δ 37 to δ 65. Spectra of iodides **2a** and **1a** showed even greater shift differences. They showed that a methine moved from δ 66 to δ 24, while the corresponding methylene changed from δ 12 to δ 65. An additional observation from the spectra of iodides **2a**

and **1a** was that the carbons bearing the iodide substituent were shifted as if the substituent were protons instead of iodides. Both atoms are known to shift ^{13}C NMR resonances similarly.

Reductive dehalogenation of **2b** and **1a** using lithium aluminium hydride in THF produced **2d** and **1c**, respectively.‡ The ^{1}H NMR spectrum of compound **2d** possessed an exocyclic methyl substituent as indicated by a methyl doublet resonance at 1.4 Hz, whereas amine **1a** showed a new methylene resonance. These spectral data for **2d** and **1c** provide additional support for the structural assignments for **2b** and **1a–c**. The picrate salt of **1c** has m.p. 150–151 °C (lit.[5] m.p. 150–152 °C). The observation that **1a** did not undergo dehydroiodination even when treated with 1,5-diazabicyclo[5.4.2]undec-5-ene (DBU) in refluxing toluene is also consistant with an equatorially oriented iodide

The halides **1b** and **2b** could be coupled with methyl and butyl cuprates to provide the substituted analogues **1d** and **2e**, respectively.[6] The bromide **2b** gave higher yields and cleaner products since it was less prone to rearrange to **1b** than the more reactive iodide **2a**. Iodide **1a** was coupled with methyl cuprate which formed **1d**. This reaction was not as facile as with the benzazepines, possibly because of a hindered secondary halide. Assuming a nucleophilic type of cuprate attack, the alkyl cuprate would be required to approach the C-3 carbon from the *endo*-face of the ring system. The coupling reactions in both ring systems also caused partial elimination back to amine **7**.

The biological activity of **1e**, **1f**, **1d** and related compounds will be reported in due course.

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‡ Reductive dehalogenation conditions with **2a** caused partial rearrangement prior to displacement. A similar mixture was also seen when coupling with cuprates.

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