

Synthesis and Conformational Study of Stereoisomeric 2-Phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,3,4-benzoxadiazines

Ari Rosling,^a Ferenc Fülöp,^b Curt-Peter Askolin^a and Jorma Mattinen^{*a}

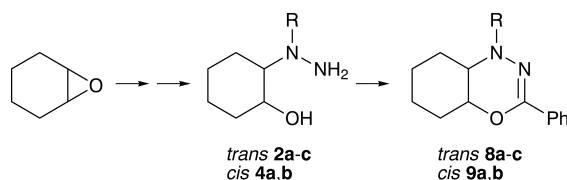
^aDepartment of Organic Chemistry, Åbo Akademi University, FIN-20500 Turku, Finland

^bInstitute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, Szeged, Hungary

New stereoisomeric hexahydro-4H-1,3,4-benzoxadiazines were synthesised and their conformational behaviour, ring and nitrogen inversion, was investigated by means of NMR spectroscopy and ¹H NMR simulation.

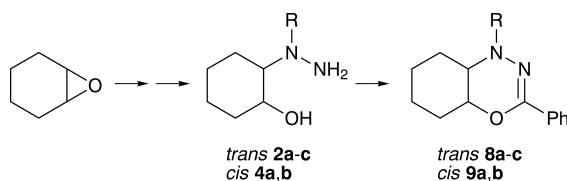
Although several papers have described the syntheses and conformational behaviour of saturated and partially unsaturated 1,3-oxazines condensed with a cyclohexane ring,¹ much less attention has been paid to the related bicyclic stereoisomeric cyclohexane-fused 1,3,4-oxadiazines.^{2a,c}

trans-Hydrazine alcohols **2a,b** were prepared from the *trans*-1,2-amino alcohols **1a,b**, obtained by ring opening of cyclohexane oxide with the appropriate amine. Nitrosation (NaNO₂, H⁺) of **1a,b** followed by reduction (LiAlH₄/THF) afforded *trans*-2-(1-R-hydrazino)cyclohexan-1-ol **2a,b** in moderate yields. *cis*-Hydrazino alcohols **4a,b** were prepared from the corresponding *trans*-1,2-amino alcohols **1a,b** (acetylation, ring closure with inversion using thionyl chloride, hydrolysis of the *cis*-oxazolidine, nitrosation and reduction).⁵ The attempted ring closure of the benzoylated derivatives of **2a,b** by applying thionyl chloride⁷ failed,⁸ whereas the acid-catalysed one-pot reaction of treating **2a-c** and **4a,b** with benzimidate⁹ afforded the desired 2-phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,3,4-benzoxadiazines **8a-c** and **9a,b** (Scheme A).



Scheme A

Estimation of the *O-in* and *O-out* conformational equilibrium in bicyclic *cis*-fused 1,3,4-heterocycles, using vicinal H–H coupling constants, encounters problems in the extraction of reliable ³J_{HH} values from complex ¹H NMR spectra of higher order. The ¹H NMR simulation program Perch⁴ proved most useful, resolving the vicinal H–H coupling constants for both the complex model compounds **8a-c** and those in equilibrium **9a,b** (Scheme B). However, the better



Scheme B

extraction of ³J_{HH} values using Perch brought to our attention new difficulties in the choice of correct model values for the estimation of the *O-in* and *O-out* conformational equilibrium in **9a,b**. The obvious deformation in the carbocycle ring of **9b** (R = Bn), as concluded from its vicinal coupling constant values, made the model values for vicinal H–H coupling constants of an ideal chair form not applicable. In low-temperature ¹³C NMR experiments two sets of ¹³C NMR signals for **9a,b** were obtained, as the signals of the *O-in* and *O-out* conformers readily separated at 193 K. Estimation of the equilibrium at room temperature, based on the ¹³C NMR signals [$\delta_{\text{obs}} = \delta_{\text{Major}}(x) + \delta_{\text{Minor}}(1-x)$], was not possible due to the rapid nitrogen inversion still taking place in the *O-in* and *O-out* conformers and which could not be frozen out. Only the equilibrium of the ring inversion at 193 K, based on the ¹³C signal integrals of the two conformers was measurable, showing the *O-in* form to be predominant in both isomers **9a,b** (70:30 ± 5 and 85:15 ± 5, respectively).

Techniques used: ¹H NMR, ¹H NMR simulation, low temperature ¹³C NMR

References: 18

Schemes: 4 (preparation of starting materials; ring closure reactions; conformational route map)

Tables: 5 (selected ¹H and ¹³C NMR chemical shifts; vicinal H–H coupling constants)

Figures: 1 (the observed spectrum of **9a** and the simulated spectrum of **9a**)

Received, 9th March 1998; Accepted, 26th May 1998
Paper E/8/01923A

References cited in this synopsis

- F. Fülöp, G. Bernáth and K. Pihlaja, *Adv. Heterocycl. Chem.*, 1998, **69**, 349.
- (a) T. Taguchi, J. Ishibashi, T. Matsuo and M. Kojima, *J. Org. Chem.*, 1964, **29**, 1097; (c) M. Forchiassin, A. Risaliti and C. Russo, *Tetrahedron*, 1981, **37**, 2921.
- R. Laatikainen, M. Niemitz, U. Wever, J. Sundelin, T. Hassinen and J. Vepsäläinen, *J. Magn. Reson., Ser. A*, 1996, **120**, 1.
- (a) W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, 1950, **72**, 2187; (b) R. A. B. Bannard, N. C. C. Gibson and J. H. Parkkari, *Can. J. Chem.*, 1971, **49**, 2064.
- F. Fülöp, G. Bernáth and P. Shár, *Tetrahedron*, 1985, **41**, 5981.
- F. Elliott, *J. Chem. Soc.*, 1949, 591.
- F. Bernáth, L. Fülöp, L. Gera, A. Hackler, Gy Argay Kálmán and P. Sohár, *Tetrahedron*, 1979, **35**, 799.

*To receive any correspondence.