Configurational and Conformational Studies with Derivatives of 3-Azabicyclo[3,3,1]nonane

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CONSIDERABLE interest has recently developed in the stereochemistry of bicyclo[3,3,1]nonane (I) and its derivatives and heterocyclic analogues, partly because it has been demonstrated[1,2] by *X*-ray and other methods that, contrary to earlier qualitative expectations,[3] several compounds having two hydrogen atoms at the hindered *endo*-positions at atoms 3 and 7, or one hydrogen atom and one lone-electron pair, exist preferentially in conformations analogous to (I) (but with partly flattened chairs)

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[1] W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 1964, 57; W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1965, 1844; I. Laszlo, *Rec. Trav. chim.*, 1965, **84**, 251; N. W. Pumphrey and M. J. T. Robinson, *Chem. and Ind.*, 1963, 1903.

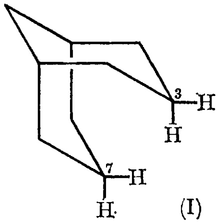
[2] M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, 1964, **47**, 695.

[3] P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson, *J. Chem. Soc.*, 1956, 1813; E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 296; G. H. Whitham, "Alicyclic Chemistry," Oldbourne Press, London, 1963, p. 94.

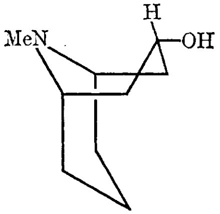
rather than in chair–boat arrangements (*cf* II; IV); the third possibility, a twin-twist–boat, has not usually been considered very probable. Chen and Le Fèvre, however, have concluded[4] that 3α-granatanol is a mixture of conformers in which the chair–boat (II) is preferred.

Examination of the n.m.r. spectra of the hydrochloride and the methiodide of 3-methyl-3-azabicyclo[3,3,1]nonane has now shown that the main configurational isomer in solutions of the hydrochloride has conformation (III; R=Me; R′ = H) corresponding to that found[2] (III; R = R′ = H) for 3-azabicyclo[3,3,1]nonane hydrobromide in the solid phase; the methiodide, however, is apparently almost exclusively (IV; R = R′ = Me). These conclusions follow[5] from the observed coupling constants (for the methiodide in pyridine–D_2O: $J_{AB} = 13\cdot5$; $J_{AX} = 10\cdot3$; $J_{BX} = 2\cdot1$ c./sec.; for the hydrochloride in trifluoroacetic acid; $J_{AX} = 0$—2; $J_{BX} = 2\cdot2$; $J_{AB} = 12\cdot8$; $J_{AM} = 3\cdot5$; $J_{BM} = 10\cdot4$ c./sec.) The boat-ring, like the chairs in (I) and (III), is probably partly flattened, a process which has little initial effect on torsional angles. The single boat in this bridged system cannot easily be twisted, and the n.m.r. evidence also excludes the possibility of an appreciable proportion of a twin-twist–boat conformation. The minor configurational isomer in solutions of the hydrochloride (small N^+- methyl doublet *ca.* 0·15 p.p.m. upfield from the main doublet in chloroform) we formulate with conformation (IV; R = H; R′ = Me) by analogy with that of the methiodide.

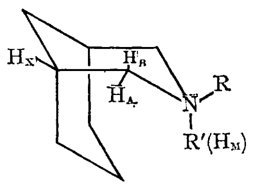
The stereochemistry of quaternisation of cyclic *N*-alkyl bases is also the subject of much current study[6a,b]. Methylation of 3-benzyl- or 3-ethyl-3-azabicyclo[3,3,1]nonane gives mixtures of diastereoisomeric quaternary salts, the stereoselectivity being higher (product ratios *ca* 8—10 : 1) than is observed (ratios 2—3 : 1) in corresponding alkylations of the 3-methyl base. The chief product obtained from benzylation of the 3-methyl base is slowly converted in boiling chloroform into the main product from methylation of the 3-benzyl base. These facts, taken with those given above, imply *boat–axial* attack of quaternising agent on the tertiary bases, analogous to the axial attack observed in several other systems[6a] where piperidine rings retain their normal chair conformations on quaternisation.



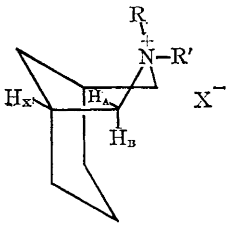
(I)



(II)



(III)



(IV)

The conclusions stated are being checked by *X*-ray analysis on some of the salts.

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[4] C.-Y. Chen and R. J. W. Le Fèvre, *Tetrahedron Letters*, 1965, 737.

[5] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

[6] *Inter alia* (*a*) J. McKenna, J. M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, 1965, **1711**, and following papers; (*b*) A. T. Bottini and R. L. Van Etten, *J. Org. Chem.*, 1965, **30**, 575; and references quoted.