

CHAIR-BOAT EQUILIBRIA IN FUSED CYCLOHEXANE SYSTEMS

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THE energy difference between a chair and a boat form in cyclohexanone¹ is only about 1 kcal/mole; for cyclohexane² this difference is very much larger, being in the order of 5 kcal/mole. Accordingly boat forms in cyclohexanone derivatives are of very wide occurrence³ whereas only very few authentic cases are known of boats in cyclohexane derivatives.⁴ In this note we report several examples of boat forms in fused cyclohexane systems as well as some semi-quantitative data on the chair-boat equilibria.

The compounds employed in this study are the five aminoalcohols Ia-Va and the five corresponding N,N-dimethyl derivatives Ib-Vb (cf. Fig. 2). The aminoalcohols were obtained from the appropriate epoxides^{5,6} by reaction with ethanolic ammonia at 180°. The dimethylaminoalcohols were analogously

¹ N.L. Allinger, *J. Amer. Chem. Soc.* **81**, 5727 (1959).

² K.E. Howlett, *J. Chem. Soc.* 4353 (1957); W.S. Johnson, V.J. Bauer, J.L. Margrave, M.A. Frisch, L.H. Dreger and W.N. Hubbard, *J. Amer. Chem. Soc.* **83**, 606 (1961); J.B. Hendrickson, *Ibid.* **83**, 4537 (1961).

³ J. Levisalles, *Bull. Soc. Chim. Fr.* 551 (1961).

⁴ R.D. Socolow, *J. Amer. Chem. Soc.* **83**, 2592 (1961).

⁵ A. Fürst and P.A. Plattner, *Helv. Chim. Acta* **32**, 275 (1949); L. Blunschy, E. Hardegger and L.H. Simon, *Ibid.* **29**, 119 (1946); A. Fürst and R. Scotoni, Jr., *Ibid.* **36**, 1332 (1953); I. Malunowicz, J. Fajkoš and F. Šorm, *Coll. Czech. Chem. Comm.* **25**, 1359 (1960).

⁶ The starting compound for the synthesis of the compounds IIa and IIb, 9-methyl- $\Delta^{6,7}$ -octal-1-one, was generously provided by Professor W.S. Johnson, Stanford University, Stanford, Calif.

prepared by reaction with dimethylamine and also by Clarke-Eschweiler methylation of the corresponding aminoalcohols; the samples prepared by the two procedures were identical. Certain of the compounds were found to exhibit rather unsatisfactory melting point behaviour. However, all the compounds, as well as their hydrochlorides, gave satisfactory analyses; the dimethylaminocholestanols IIIb-Vb were found to be homogeneous by the criterion of thin-layer chromatography on "alkaline" silica⁷ in several systems. Their structure and homogeneity was, moreover, demonstrated, on the case of IIIa, by converting this in very high yield to the appropriate epoxide, 2 α ,3 α -epoxycholestane, via the dimethylaminoalcohol IIIb, the corresponding methiodide and pyrolysis of the quaternary base; a sequence known to be stereospecific.⁸ The identity of the compounds studied cannot therefore be in doubt.

Spectroscopic determination of intramolecular hydrogen bond formation⁹ was used for following the chair-boat equilibria. In the chair forms, C, of our compounds intramolecular hydrogen bond formation between the hydroxyl and the amino function cannot take place and the chair conformer will hence exhibit a band of the free hydroxyl only. Two types of classical boats,¹⁰ B- β and B- α , and the intermediate twist conformer,¹¹ B-t, are possible in any substituted trans-decalin system (Fig. 1). In the boat forms of our compounds - and in the boat forms only - the geometric conditions for intramolecular hydrogen bond formation are fulfilled. A bonded hydroxyl band in the spectra of the compounds studied therefore unequivocally indicates

⁷ E. Stahl, Arch. Pharm. **292**, 411 (1959).

⁸ J. Sicher and M. Pánková, Coll. Czech. Chem. Comm. **20**, 1409 (1955).

⁹ For a review see M. Tichý, Chem. Listy **54**, 506 (1960).

¹⁰ The symbol B- β denotes the boat in which the flag-pole bonds are β and the symbol B- α that in which the flag-pole bonds are α .

¹¹ J.C.N. Ma and J. Levisalles, Bull. Soc. Chim. Fr. in press.

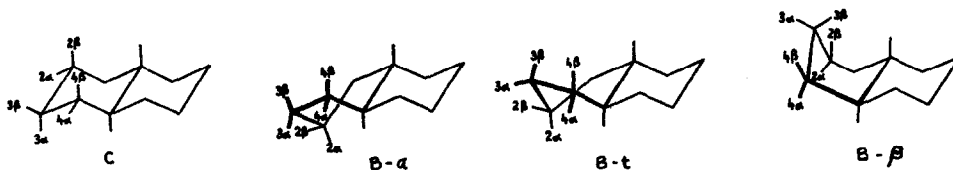


FIG. 1

the presence of a boat conformer.

No band due to bonded hydroxyl was found in the spectra¹² of the decalin derivatives Ia and Ib (Fig. 2), showing that these compounds exist as chair conformers exclusively.¹³ The presence of the two axial groups (OH and NH₂, and OH and NMe₂, respectively) is hence in itself not sufficient to induce the cyclohexane ring in a trans-decalin system to take up a boat conformation, even though the boat conformer would derive stabilization from intramolecular hydrogen bond formation.

The introduction of an angular methyl group 1,3 to one of the axial functional groups will make the chair conformer more strained and, indeed, the spectra of the aminoalcohols IIa-IVa and the dimethylaminoalcohols IIb-IVb exhibit both a free and a bonded hydroxyl band. This represents unequivocal proof for the presence of boat forms in these six compounds.

The spectra can be made to provide semi-quantitative data on the boat-chair compositions. Such evaluation is particularly straightforward in the dimethylaminoalcohols since these compounds - unlike the aminoalcohols - are

¹² The spectra were measured by Dr. M. Horák of this Institute. For the technique used see J. Sicher, M. Horák and M. Svoboda, Coll. Czech. Chem. Comm. **24**, 950 (1959).

¹³ The absence of a bonded OH band cannot, in general, be regarded as proof of the absence of a boat conformer because in certain special cases boat forms can be visualized in which hydrogen bond formation is prevented by restriction of rotation about the C-N and/or C-O bond. This, however, cannot be the case in the compounds Ia and Ib.

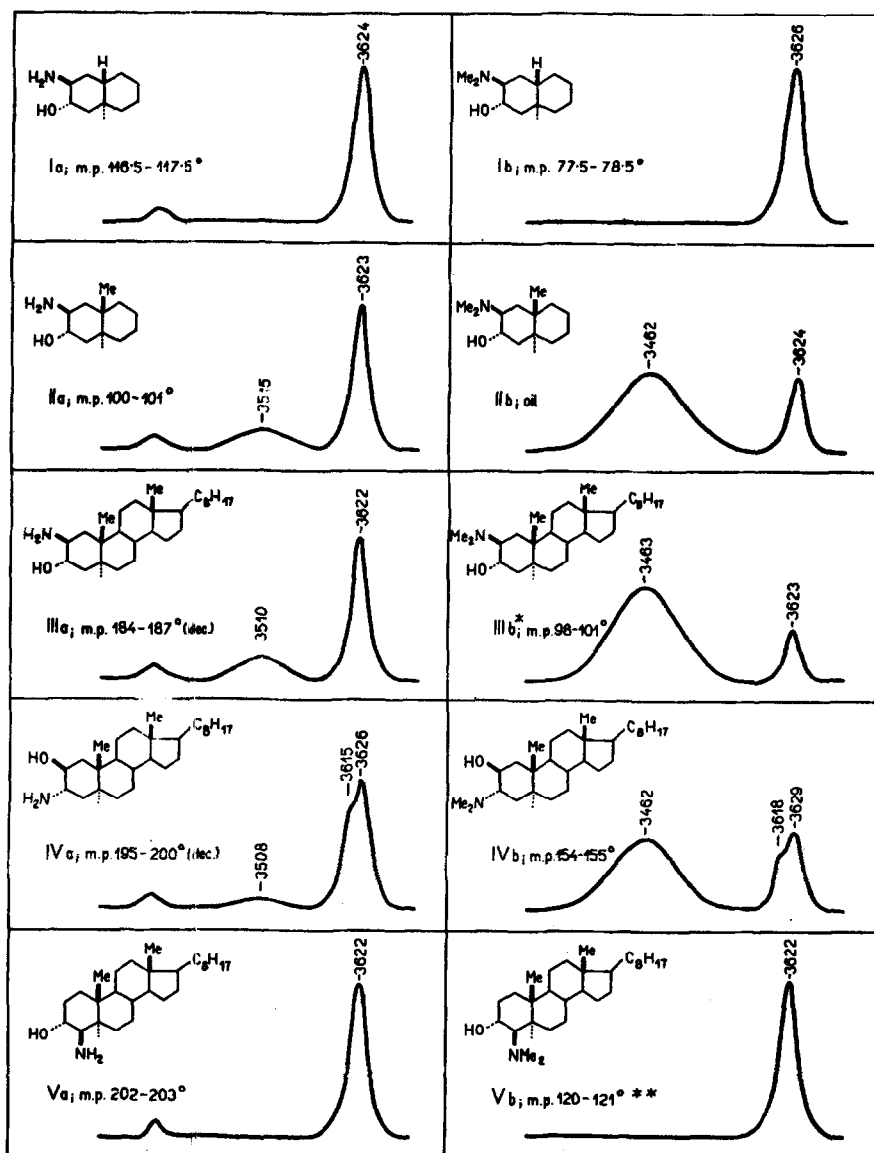


FIG. 2

* Double m.p.; melts first at about 50° and resolidifies.

** Double m.p.; melts first at about 55° and resolidifies.

probably fully hydrogen bonded in the boat conformer and any free hydroxyl is hence due to the chair form. The integrated area of the free hydroxyl band in Ib provides a reference value for 100 per cent chair content. The amount of the boat form in the 9-methyldecalin derivative IIb may thus be estimated to be about 55 per cent and that in the corresponding cholestane derivative about 70 per cent. The higher proportion of the boat form in the latter compound is plausibly interpreted by a difference in the stability of the corresponding chair forms: in the more flexible bicyclic system II the large 1,3-axial interactions between the methyl and the amino function can more readily be reduced by a flattening of the chair than in the tetracyclic system III. In the isomer IVb the amount of the boat form is estimated¹⁴ to be about 40 per cent, i.e. considerably lower than in IIIb. The difference in the conformational equilibria in IIIb and IVb reflects the difference of the sum of 1,3-interactions in the chair forms of these position isomers. As would be anticipated, the situation is dominated by the very large dimethylamino vs. methyl interaction in IIIb and the percentage of the chair form at equilibrium is hence considerably lower in this isomer than in IVb, with the large groups in the 1,4-positions.

In the derivatives Va and Vb the very large 1,3-methyl vs. amino interactions also operate in the chair form, yet their spectra were found to show bands of the free hydroxyl only. This can be explained by considering the two possible boat structures: in the B- α boat there would in this case be a very large angular methyl vs. 4 β -amino interaction and this form is hence energetically most unfavourable. In the B- β boat there would be a considerable 1,2-interaction between the bulky 4 β -amino-function and the eclipsed C₍₅₎-C₍₆₎ bond, also making the boat form very strained. The

¹⁴ Evaluated, in this instance, from the integrated band area of the bonded band, since the free hydroxyl band is an unresolved doublet, characteristic for hindered hydroxyl.

twist form B-t is intermediate between B- α and B- β and will hence partake of some of the strain of both the classical forms. Ring A would therefore preferentially exist in a chair form, probably achieving strain relief by flattening of ring A, a feature which would not be detected by intramolecular hydrogen bond determination. An alternative interpretation, namely that V does in part exist in a boat conformation of the type B- β but that hydrogen bond formation is precluded by restricted rotation about the C-N bond, cannot be altogether excluded but seems much less likely.

The separation between the bands due to the free and the bonded hydroxyl group, $\Delta\nu$, in the three amino-alcohol derivatives IIa-IVa is practically the same (about 112 cm^{-1}), showing that the geometry of the boat form in these three compounds is probably identical or very similar. The same holds true for the corresponding dimethylamino derivatives IIb-IVb where the $\Delta\nu$ value averages about 162 cm^{-1} . Both these values are somewhat higher than those recorded¹⁵ for trans-2-aminocyclohexanol and trans-2-dimethylaminocyclohexanol (97 and about 150 cm^{-1} , respectively). Arguments to be developed in the full publication suggest that, for the dimethylamino derivatives at any rate, this situation indicates a twist rather than a classical boat structure.

¹⁵ Unpublished results.