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STRUCTURE AND CONFORMATION OF HETEROCYCLES. I.
CONFORMATIONAL INVERSION IN A cis-1,4-DIOXANO-1,4-DIOXANE

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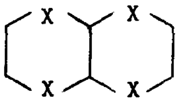
The conformational analysis of six-membered heterocycles has recently received considerable attention (1). Thus, oxygen, nitrogen and sulphur containing six-membered rings have been studied by various methods, most of which had been well established in the course of extensive conformational analyses (2) of cyclohexane and its substituted derivatives.

In the dioxane series, the 1,2 (3) - and 1,3 - isomers (4-7) and/or their substituted derivatives have been studied. These systems have been thoroughly scrutinized and interesting results have emerged, concerning conformational equilibria and substituent conformational preferences (3-5) as well as ring inversion (6-7). The 1,4 dioxanes, however, proved themselves less prone and unequivocal to conformational analysis. Actually, so far, only painstaking X-ray and NMR analysis, mainly done in the Leiden laboratories (8), led to conclusive conformational assignments (9); moreover, apparently none but qualitative evidence (8c) has, so far, been presented concerning barriers to ring inversion in this system.

In the frame of a research project on 1,4,5,8-tetrahetero-decalins I, we investigated the corresponding oxa-derivatives, viz. 1,4-dioxano-1,4-dioxanes II. The latter, accompanied by the bi(dioxolan-2-yl) isomers III can generally be obtained by the known (10) acid-catalyzed condensation of appropriate α-diketones with ethylene glycol (Eq. 1). Since the excellent



I

X
O
NR
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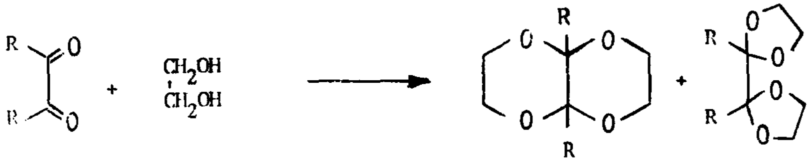
PR

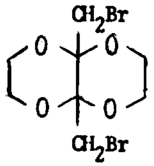


II III

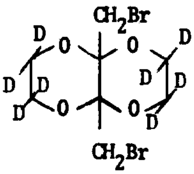
pioneering work of Boeseken and his group, one can find controversial or sometimes inconclusive data in the literature concerning structural as well as conformational assignments in the series (10,8c).

While we sought and achieved reliable criteria for structure and geometry assignments (11), difficulties were encountered in attempts to evaluate barriers to ring inversion in the cis-II system. This bears resemblance to the situation in cis-decalins (12). The apparent reason for these difficulties is to be found in the following facts. In cis-II the peripheral 4-proton system is too complex for temperature dependent NMR spectral analysis which is the only practical method as yet available for this purpose (13,14); furthermore, two identical substituents (or protons) on the junction are chemically and magnetically equivalent, this property being inherent to the cis-decalin system bearing two identical cis-substituents which are then in identical environment (15).

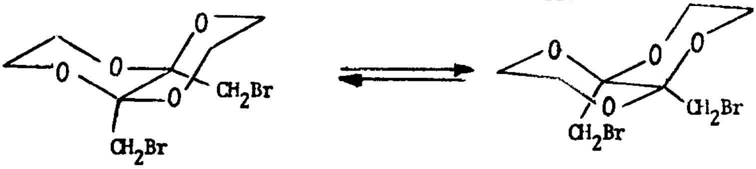
This impasse was obviated by choosing the di(bromomethyl) derivative IIa (11) as subject for the present study.



IIa



IIb



A variable temperature NMR spectral investigation of IIa was undertaken in order to freeze out and analyze the two conformers which bear mirror-image relationship (Eq.2). The molecule is in that case chiral and the bromomethylene protons magnetically nonequivalent (15,16). The room temperature NMR spectrum of IIa exhibits a sharp singlet at δ3.74 ppm due to the bromomethylene protons, overlapped by an AA'BB' multiplet, due to the peripheral protons (Fig.1). By using ethyleneglycol-d_4-1,1,2,2 in the above mentioned condensation, the corresponding octadeuterated product IIb was i.al.secured. As the temperature is lowered, its NMR spectrum at 60 Mc reveals a developing AB quartet unchanged down from -60°C with $\Delta\delta_{AB}$=36.8 Hz and J_{AB}=12.0 Hz (Fig.1). The coalescence temperature is -38°C. An analysis of this intramolecular two-site problem (17) was performed using a computer program kindly supplied by Prof. M. Saunders (17b). A plot of (2C-J) i.e. the separation of the inner lines, vs. -ln τ yielded the experimental τ-values. At coalescence τ_c was found to have the value of 0.01 corresponding to an inversion rate of 50 $\sec^{-1}$. Using the absolute reaction rates theory (14,18), the free energy of activation was calculated from the expression $k = \frac{k_B f}{h} T \exp(-\Delta G^{\ddagger}/RT)$ to give $\Delta G^{\ddagger}$=11.5±0.5 kcal/mole. A plot of ln $^k/_T$ vs. $^1/_T$ yielded $\Delta H^{\ddagger}$=11.1±0.9 kcal/mole and $\Delta S^{\ddagger}$=0±1 e.u.

A comparison of these results with those obtained in corresponding carbocyclic systems is called for. Thus, for cis-decalin and its 9-substituted derivatives the reported $\Delta G^{\ddagger}$values exceed 12 kcal/mole (12,13); moreover, for 9,10-di(bromomethyl)-decalin (which is analogous to the subject of the present study) $\Delta G^{\ddagger}$=14.7 kcal/mole, with even higher values for other 9,10-substituted derivatives (16,19). The lower barrier in the 1,4,5,8-tetraoxadecalin molecule may be attributed to the lower C-O torsonial barrier (1). By drawing a parallel, 1,4-dioxane should invert more rapidly than cyclohexane and even than the other isomeric dioxanes (6,7).

A detailed account and final conclusions are, however, deferred until additional results become available; experimentation along similar and other lines is now underway.

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16. For a similar situation in the decalin system, cf. J. Altman, H. Gilboa, D. Ginsburg and A. Lowenstein, Tetrahedron Letters, 1329 (1967).
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19. Unusually large differences in the various reported $\Delta S^{\ddagger}$ values (12,13,16) are worthy of note. This discrepancey is hardly accountable by symmetry arguments alone (16,20). On the other hand, the determination of $\Delta S^{\ddagger}$ by the method used in this and the cited studies are said to involve considerable uncertainty (13,14). We chose, therefore, not to elaborate on this theme, as yet.

20. For a discussion pertinent to this problem, cf. R.W. Murray, P.R. Story and M.L. Kaplan, J. Am. Chem. Soc. 88, 526 (1966).

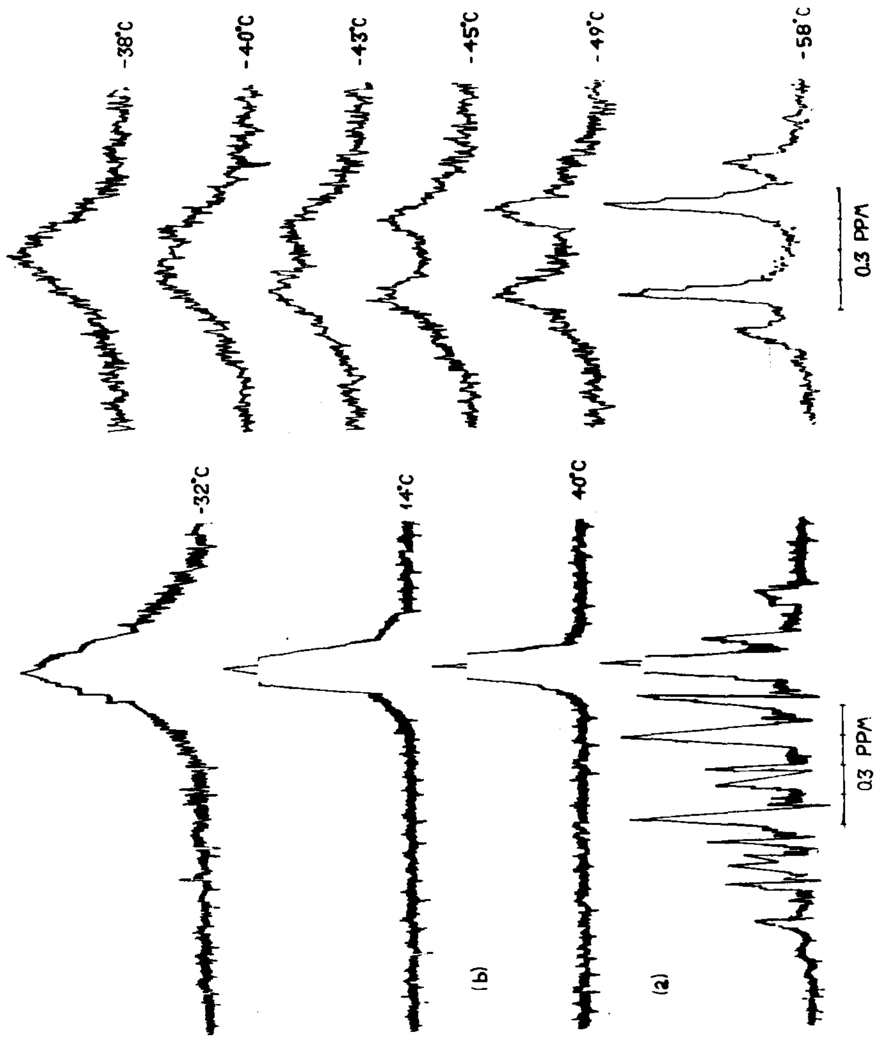

Fig.1 - Temperature dependent NMR spectra of IIb, taken at 60 Mc in $CDCl_3$ ca. 5% solution with TMS as internal reference. The r.t. spectrum of IIa is also displayed.