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STRUCTURE AND CONFORMATION OF HETEROCYCLES *III*[1]. ANGULARLY AND PERIPHERALLY SUBSTITUTED CIS-1,4,5,8-TETRAOXADECALINS.

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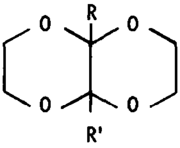
In previous communications (1,3) we have described approaches for structural (1) and dynamic conformational analysis (3) of the interesting cis-1,4,5,8-tetraoxadecalin system (4). We now wish to present results of the application of these procedures to mono-angularly and peripherally substituted derivatives. A new method for synthesis of the latter has been developed.

The approach to the evaluation of barriers to inversion of the bicyclic system under scrutiny involves temperature dependent NMR studies of protons in the range between high-and nil exchange. In this context, one well-known procedure (5) consists in starting with two interconverting substituents and slowing down the ring inversion until one reaches frozen conformations. The second, less conventional method relies on having a prochiral substituent in the angular position. This center becomes observably chiral when the molecule assumes a fixed dissymetric conformation at low enough a temperature and the protons on the angular substituents become magnetically non-equivalent (3,6). Making use of well established rate study techniques, one may then derive the activation parameters for conformational interconversion (5).

Following the successful application of the second of these procedures to the 9,10-di(bromomethyl) derivative *I* (3), it was of interest to investigate some mono-angularly substituted derivatives, especially in view of somewhat puzzling results recorded for the decalin analogs (5a,d, 6c).

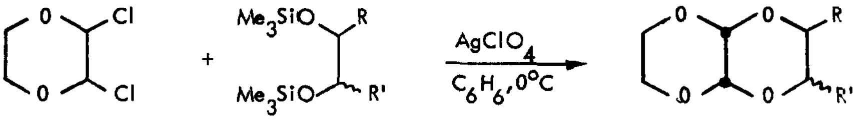


		m.p.,C°
I	: $R=R'=CH_2Br$	
II	: R= -⌬- CMe_2H; R'=H.	100
III	: R= -⌬- CMe_2D; R'=H.	100
IV	: R= -⌬- CMe_2Br; R'=H	99
V	: R= - CH_2-Ph; R'=H.	75

A first such attempted investigation of compounds *II*-*IV*(7) was unproductive since no appreciable line broadening, let alone splitting of the cumyl methyl signals was detected on cooling down to -100°C. The methyl groups are apparently too remote from the chiral center, for their protons to show magnetic non-equivalency. However, the study of 9-benzyl-cis-1,4,5,8-tetraoxadecalin V was rewarding. Its room temperature NMR spectrum (100 MHz; Acetone-d_6) exhibits a sharp singlet at τ 6.94 due to the benzylic protons. On cooling down to -90°C one registers broadening, splitting and finally an AB system, with $\Delta\delta_{AB}$=61 Hz and J_{AB}=14.7 Hz (8a), with the coalescence temperature, Tc= -78°C. The rate of inversion at Tc is approximated from $k_c = \pi(\Delta\delta^2 + 6J^2)^{\frac{1}{2}}/\sqrt{2} = 79\ \mathrm{sec}^{-1}$ (i.e. without intrinsic line-width correction) (5,9) and hence $\Delta G^{\ddagger}_{195} = 9.5$ kcal/mole (8b).

We now turn to peripherally substituted 1,4,5,8-tetraoxadecalins. The only such reported derivatives are, to our knowledge, cis-1,4,5,8-tetraoxadecalin-trans-2,3-dicarboxylic acid and its dimethyl and diethyl esters (10). The reason is apparently that the standard synthetic procedures for securing the system are under thermodynamic control viz. 1,2-diketones + α-glycols under acid catalysis or 2,3-dichlorodioxanes + α-glycols with hydrogen chloride evolution (1,10 and references therein). Thus, derivatives of relatively high energy content are not likely to form in these processes (11). Preparative methods which obviate conditions of thermodynamic control were therefore sought.

While attempted condensations of dichlorodioxane with alkali salts of α-glycols failed, the use of their bis-trimethylsilyl derivatives led to the desired products. The scope of this new method is currently being explored and hopefully it will provide otherwise unattainable compounds in the series.



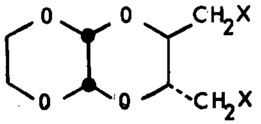
VI VII VIII

	a	b	c	d	e
R	H	Me	CO_2Me	Me	CO_2Me
R'	H	H	CO_2Me	Me	CO_2Me
Config.		?	trans; (R), (R)	trans	cis-anti
m.p., C°	133-134	67-69	77-78	oil	93-94

We were able, so far, to prepare in moderate yields, the peripherally substituted derivatives *VIII*a-e (7b). The new cis-dicarbomethoxy derivative *VIII*e was also prepared by a modification of Boeseken's method (10) viz., direct condensation of *VI* and meso-dimethyltartarate with continuous entrainment of the HCl formed in a stream of nitrogen. Since *VIII*e is thus shown to be formed also in a thermodynamically controlled process, it is tentatively assigned the more stable anti-configuration.

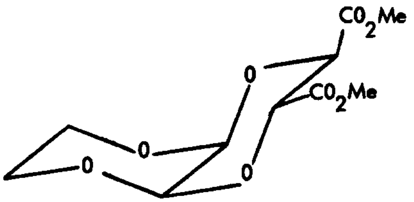
Both cis-and trans-dichlorodioxanes give similar results in the above reaction indicating that it probably proceeds by an S_N1 type mechanism. On the other hand, the glycols as well as their bis-trimethylsilyl derivatives react with complete retention of configuration. This was confirmed by chemical corelation of the dicarbomethoxy derivative *VIII*c with the dimethyl derivative *VIII*d via the conversions:

$$VI + VIIc \longrightarrow VIIIc \xrightarrow{LiAlH_4} IX_\alpha \xrightarrow{Ph_3MeP^+I^-} IX_\beta \xrightarrow{LiAlH_4} VIIId$$

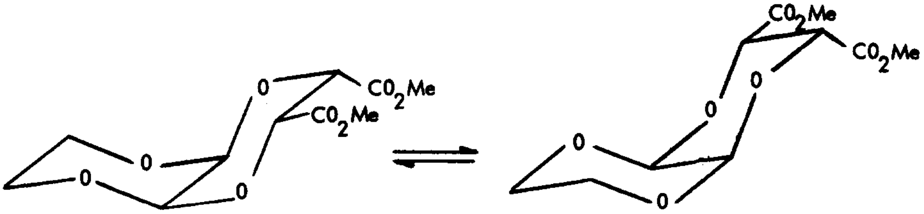


α: X=OH

IX β: X=*I*



VIIIc



VIIIe

The esters *VIII*c,e were subjected to dynamic conformational analysis. *VIII*c exhibited an unchanged NMR spectrum between $-80^{\circ}$and $+150^{\circ}$C,as expected, since the diequatorial conformation should be stable in this temperature range. Not so with the axial-equatorial isomer *VIII*e, where conformational interconversion occurs at rates amenable to variable temperature NMR study (100 MHz, Acetone-d_6/Pyridine). Thus the carbomethoxy singlet at τ 6.35 broadens on cooling and eventually splits with $\Delta\delta$=6Hz at -96°C. Coalescence occurs at -80°C. The rate constant of exchange at T_c is evaluated from $k_c = \pi\, \Delta\delta/\sqrt{2}$ and leads to $\Delta G^{\ddagger}_{193}$ 10.0 kcal/mole (8b).

The conformational analysis of heterocyclic compounds has been quite extensively documented in recent years (13), including the dynamic aspects (5a, 14). Nevertheless, surprisingly little is known in this context, on hetero-bicyclic and polycyclic systems. We can now conclude that a consistent picture for the inversion barriers in cis-1,4,5,8-tetraoxadecalins obtains. The $\Delta G^{\ddagger}$ values for the compounds V and *VIII*e are lower than that of the angularly disubstituted derivative *I* (3). The difference is, though, small and can be understood in terms of alleviation of strenuous eclipsing of angular substituents at the peak (transition state) in the inversion profile of the system (15). Furthermore, the free energies of activation are lower than those recorded for a variety of decalins (5a,d;6c). A first order explanation of this observation is suggested by the fact that the torsional barriers of C-O bonds are lower than those of C-C bonds in comparable systems (13a). However, additional factors, such as partial mitigation of 1,3-dioxial interactions and the "anomeric effect" undoubtedly play an important role but will be discussed in the full paper.

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4. Only cis fused derivatives of this bicyclic system are known so far. For leading references cf. (1a,3).
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7. a. Compounds *II* and V were prepared by the classical condensation of the corresponding ketoaldehydes with ethylene glycol under acid catalysis. *II* was brominated to *III* which was further reduced to *IV* by $LiAlD_4$.
   b. Satisfactory elemental analyses as well as spectral data were secured. The latter corroborate in full the previously established correlations (1a).
8. a. The chemical shift lacks high accuracy since the low field branch of the AB pattern partly overlaps the peripheral proton resonances.
   b. A detailed analysis for evaluation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ will be reported in the full paper.
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15. For a pertinent discussion on this aspect cf. (5d).