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STRUCTURE AND CONFORMATION OF CIS AND TRANS-3,5-DIMETHYLVALEROLACTONES[1]

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The study of the structure and conformation of saturated δ-lactones has recently attracted considerable attention.[2-8] The relationship between the structure and conformation of these compounds to their NMR, IR, CD and ORD properties has been studied. There is general agreement that the $C-O-\overset{O}{\overset{\|}{C}}-C$ group is planar in δ-lactones;[5-7] however, there is disagreement on the preferred conformation of this ring. On the basis of x-ray analysis of a bromodilactone it was implied that the presence of the $C-O-\overset{O}{\overset{\|}{C}}-C$ group in a 6-membered ring produced a boat conformation,[6] and ORD data was interpreted as supporting this view.[8] More recently, however, the IR[7] and NMR[2,3] spectral data of some substituted δ-lactones are more consistent with a half-chair conformation. This growing interest in the stereochemistry of δ-lactones prompted us to prepare and examine the NMR properties of cis and trans-3,5-dimethylvalerolactone (I), a diasteroisomeric pair of lactones, which has a combination of substitutes that has not previously been studied.* The NMR spectra of the two lactones in CCl_4 are shown in Figures Ia and IIa. Significant aspects of the spectra are the shifts in the two spectra of the C_3-CH_3 (δ 1.01 to 1.09) and C_5-H (δ 4.29 to 4.46) and the appearance of the C_5-CH_3 group at δ 1.33 in both spectra. These results can be explained if the NMR spectrum having the highest field resonance for the C_3-CH_3 is assigned to the cis-isomer and the cis and trans isomer are represented by half-chair conformation. The cis-isomer has the C_3-CH_3 and C_5-CH_3 groups in a cis-1,3 relationship and may be expected to exist preferentially in conformation IA which avoids diaxial opposition of these groups.** Since the cis and trans isomer have the same resonance for the C_5-CH_3 group, the trans isomer is assigned conformation IB which has this group in an equatorial position.**

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*The synthesis of these lactones and their conversion to 5-alkyl-5-(3'-hydroxy-1'-methylbutyl)-barbituric acids will be reported elsewhere.

**Only one of the optical isomers is shown.

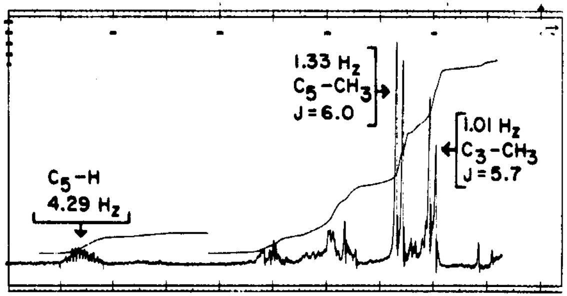


Figure Ia - 100 MHz spectrum of IA

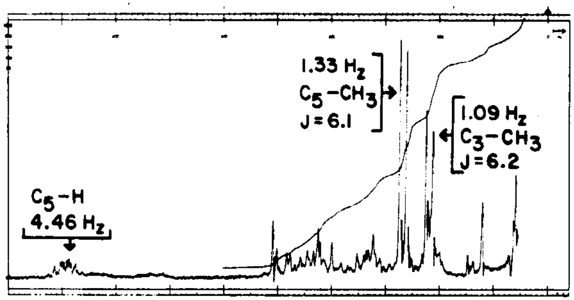


Figure IIa - 100 MHz spectrum of IB

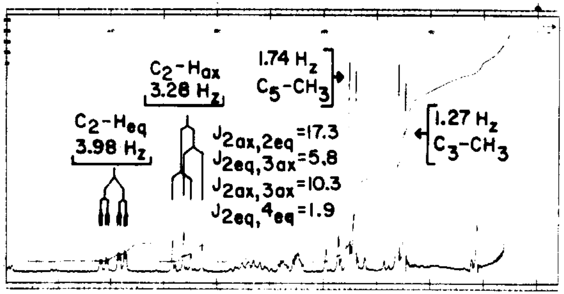


Figure Ib - 100 MHz spectrum of IA with 0.23 mole % of Eu(DPM)$_3$ added

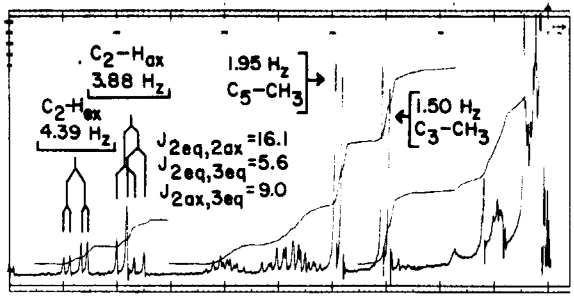
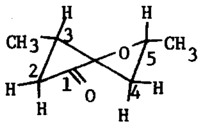
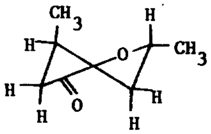


Figure IIb - 100 MHz spectrum IB with 0.24 mole % of Eu(DPM)$_3$ added

The shift of δ 1.01 to 1.09 and the increase in J_{H,CH_3} for the C_3-CH_3 group is the results expected on going from an equatorial to an axial CH_3-group,[9,*] and the shift of 4.29 to 4.46 Hz of the C_5-H can be explained by the cis 1,3-diaxial interaction of the C_3-CH_3, C_5-H of IB which is absent in IA.[10,**] Proof for the correctness of these assignments was sought by observing the NMR spectra of IA and IB in the presence of tris-(dipivalomethanato)europium [Eu(DPM)$_3$]. The addition of this reagent to the CCl_4 solution of IA or IB shifted the C_2-methylene group into a spectral region where the spin-spin splitting of the C_2-H's with the C_3-H becomes amenable to first-order analysis. (Figure Ib and IIb)[11,***] According to Barfield and Grant, J_{gem} is dependent upon the dihedral angle between the methylene group and the π lobes of adjacent π bonds.[12] Assuming this type of relationship to exist in the present case, the J_{gem} of 17.3 Hz for the C_2-methylene in IA can only be explained with a conformation in which the C=O group bisects the C_2-methylene group.[+] This stereochemistry in combination with a planar lactone grouping necessitates that the cis isomer exist in the half-chair conformation IA. The vicinal coupling



IA



IB

$J_{2ax,3ax}$=10.3, $J_{2ax,3eq}$=5.8, and the long range coupling of 1.9 Hz observed between C_2-Heq and C_4-Heq are also in accord with this assignment. The large long range coupling between C_2-Heq and C_4-Heq is particularly revealing since the geometry in the half-chair conformation IA has these protons in the planar W configuration necessary for maximum effect.[13] The geometry of a boat or half-boat conformation for the cis-isomer is not favorable for the observation of such a large long range $J_{2eq,4eq}$ coupling. In the case of the trans-isomer the slightly lower $J_{2eq,4eq}$ 16.1, the slightly larger J_{vic} (9.0 and 5.6 Hz) than expected and the absence of C_2-H_{eq}, C_4-H_{eq}

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[*] Johnson, Starkovsky and Gurowitz have reported that in cyclohexanones, equitorial methyl groups appear at higher field and have coupling constants smaller than axial methyl groups.[9]

[**] Deshielding in the order of 0.18 ppm has been observed in cyclohexanols in going from 1,3-H,H to 1,3-CH_3,H interactions.[10]

[***] Coupling constants are not significantly changed by the addition of Eu(DPM)$_3$ in the concentration range reported.

[+] The sign of J_{gem} in these lactones is opposite the J_{vic} and is assumed to be negative.

long-range coupling is best accounted for if IB has a slightly flatten half-chair conformation similar to the structure proposed by Sheppard and Turner to explain the spectral properties of some steroidal Lactones.[2] This flattening causes the C_3-CH_3 and the C_2-methylene protons to adopt a "pseudoaxial" and "pseudoequatorial" character in order to relieve the unfavorable steric interaction of the axial C_3-CH_3 group in IB. The vicinal, geminal and long range coupling of IA and IB as well as the observation that the NMR spectra ($CDCl_3$) are not significantly changed in the temperature range of -55 to 30° are consistent with a fixed conformation for these lactones, rather than a rapidly equilibrating set of conformers.* Both the cis and trans lactones I had infrared carbonyl absorption (CCl_4) at 1736 cm^{-1} which is within the range (1730-1750 cm) suggested for the normal frequency for δ-lactones having a half-chair conformation.[7]

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*The J_{gem} and J_{vic} of IB might be accounted for by a rapidly equilibrating system. However, the fact that the C_5-CH_3 appears at δ1.33 in both IA and IB would be inconsistent with this interpretation.

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