Tetrahedron Letters No.39, pp. 2911-2917, 1964. Pergamon Press Limited
Printed in Great Britain

COUPLING CONSTANTS AND THE CONFORMATION OF γ-LACTONES

J.B. Lowry and N.V. Riggs

Department of Organic Chemistry, University of New England,
Armidale, N.S.W., Australia

(Received 29 June 1964; in revised form 10 August 1964)

For comparison with the proton magnetic resonance (p.m.r.) spectra of some 2-substituted 2-hydroxybutyrolactones, the isomeric methyl piptodisinates and their 2-*O*-acetyl derivatives (1), we have examined those of a number of model compounds. Chemical shifts lie in the expected ranges, the signals for the 4-protons (δ 4·0-4·4) being well to low-field from those for the 2- and 3-protons (δ 2·2-2·8). Coupling constants from analysis of the *ABXY* (2) or *AB* spectra together with those for leucodrin tetra-acetate (3) and methyl *O*-acetyl-α-piptodisinate are collected in Table 1.

The "normal" geminal coupling constant, J^{gem}, in a saturated methylene group may be taken as that for methane, -12·4 ± 0·6 c/s (4). Values of J_2^{gem} are high[*] as previously found for methylene groups adjacent to carbonyl groups (3,5,6,7), whereas those of J_3^{gem} are essentially "normal", and those of J^{gem} low. Decreases of J^{gem} of the order of

---

[*] We assume that geminal coupling constants for saturated methylene groups are negative in sign (4) and use high, low, and cognate terms to refer to the magnitude of J^{gem}.

TABLE I

COUPLING CONSTANTS (c/s) FOR SOME γ-LACTONES

Compound [a]	$\underline{J}^{gem}_2$	$\underline{J}^{gem}_3$	$\underline{J}^{gem}_4$	Others
I	-	13·4	9·1	$\underline{N}$ = 7·0, $\underline{R}$ = 6·9 [b]
II	-	13·1	8·8	$\underline{N}$ = 6·8, $\underline{R}$ = 6·6 [b]
III	-	13·4	-	-
IV	-	-	8·9	-
V	18·0	-	10·5	-
VI	18·9	-	-	$\underline{J}_{23}$ = 5·9, $\underline{J}_{2'3}$ = -0·2 [c]
VII (lactone A) [d]	17·2	-	-	$\underline{J}_{23}$ =12·4, $\underline{J}_{2'3}$ = 7·8
VII (lactone B) [d]	-	-	-	$\underline{J}_{34}$ (*trans*) = 8·3
VIII	-	e	8·7	$\underline{N}$ = 8·1, $\underline{R}$ = 7·3 [b]

[a]
I : 2-hydroxy-2-methylbutyrolactone in pyridine
II : 2-hydroxy-2-phenylbutyrolactone in pyridine
III : 2-hydroxy-2,4,4-trimethylbutyrolactone in pyridine
IV : 2-hydroxy-3,3-dimethylbutyrolactone in pyridine
V : 3-acetoxy-3-methylbutyrolactone in $CDCl_3$
VI : 3,4-dibromo-γ-valerolactone in CCl_4
VII : leucodrin tetra-acetate (3) in $CDCl_3$
VIII : methyl *O*-acetyl-α-piptodisinate in $CDCl_3$ (1)

[b] $\underline{N} = \frac{1}{2}(\underline{J}_{34} + \underline{J}_{3'4})$; $\underline{R} = \frac{1}{2}(\underline{J}_{34'} + \underline{J}_{3'4'})$. Values of $\underline{N}$ and $\underline{R}$ may be interchanged.

[c] Uncertainty, ± 0·2; see text.

[d] Related compounds give similar values (3).

[e] $\underline{J}^{gem}_3$ cannot be obtained since $\delta_{33'} = 0$.

0·8 c/s per degree have been observed with increase in the HCH bond angle (8) although the accompanying theoretical treatment is in error in not predicting the negative sign for $\underline{J}^{gem}$ (4). In a γ-lactone for which the internal angles have been measured (9), although there is some distortion owing to a fusion to a decalin system, those at positions 3 and 4 are 9^{o} and 6^{o}, respectively, less than tetrahedral. The HCH angles at these positions are therefore presumably both somewhat greater than tetrahedral. Any decrease of $\underline{J}_3^{gem}$ from this cause is apparently compensated by the opposite effect of electronegative substituents attached to the adjacent carbon atoms, (10), the carbonyl group to C2 and the acyloxy group to C4. This compensating effect is also shown in the value of $\underline{J}_4^{gem}$ for compound V, in which an acetoxy group is attached to the adjacent C3, as compared with other values of $\underline{J}_4^{gem}$, uniformly low at ca. 9 c/s. Intermediate values of $\underline{J}^{gem}$ (10-12 c/s) occur for methylene groups attached to the ethereal oxygen atom in furanose (1) or pyranose (11) rings and for those in primary alcohol groups or their acetates attached to saturated carbon atoms (7), bond angles in these cases being unknown. The low values for the methyl halides, methanol, and dichloromethane (4) may however be "corrected", from the known HCH angles (by -0·8 c/s per degree), to the values expected at the tetrahedral angle. Corrected values for the limited series CH_3Br, CH_3Cl, CH_3F, and CH_2Cl_2 fall from 12·2 to 9·7 c/s in this order, that of increasing electronegativity (12) of the substituents, perhaps fortuitously since the values for

CH_3I (11·4 c/s) and CH_3OH (10·6 c/s) lie *ca.* 1 c/s below the line. Apart from any effect on bond angle, it seems likely that *direct* attachment of an electronegative hetero-substituent to a saturated methylene group *lowers* the value of $\underline{J}^{gem}$. Any explanation of this effect is not likely to lie in simple considerations of reduced electron densities in the C-H bonds as is intuitively associated with the term, electronegativity, since electronegativity induced in a saturated carbon atom attached to the methylene group is correlated with increase in $\underline{J}^{gem}$ (10).

In the crystal-state of γ-lactones, C3 lies out of the plane of C2-C1-O-C4 (13), and we have interpreted vicinal coupling constants in terms of such a conformation in solution. The values of $\underline{J}_{23}$ and $\underline{J}_{2'3}$ for 3,4-dibromo-γ-valerolactone (VI) in carbon tetrachloride at 35° are very close to those predicted by the original Karplus equation, $\underline{J} = 8{\cdot}5 \cos^2\phi - 0{\cdot}28$ (14) for $\phi = 30^\circ$ and 90°, respectively. Dihedral angles near these values lead to a conformation in which H2 (mid-field) is *pseudo*-axial, H2' (high-field) and H3 (low-field) are *pseudo*-equatorial, and the two bromine atoms (which we assume to have added *trans* to α-angelicalactone) are *pseudo*-axial (dihedral angle, *ca.* 150°) probably as a result of strong repulsive forces between them in the non-polar solvent. We note that the predicted small negative coupling near 90° arises in the theoretical treatment from approximate cancellation of two large terms (14), and believe that $\underline{J}_{2'3} = -0{\cdot}2$ c/s represents the first reported experimental value in agreement. There is however an uncertainty of ± 0·2 c/s in this value since the components of the observed high-field and low-field doublets consist of pairs of unresolved lines whose separation may be up to 0·4 c/s, as judged from widths at half-height.

As coupling constants are sensitive to substituent effects (10), modified Karplus equations (15) of form $J_{ij} = a_{ij} \cos^2 \phi_{ij}$ may be more appropriate but require sufficient information to fix a_{ij}, assumed for a given substitution pattern to have one of two values depending on whether $\phi_{ij} \gtrless 90^\circ$. Should the 3-phenyl group in lactone A of leucodrin tetra-acetate (VII) be *pseudo*-axial, the values of J_{23} and $J_{2'3}$ could be met with dihedral angles of 56° and 64°, respectively, and $a_{ij} = 40$ c/s. This value is improbably high and furthermore a Dreiding model of this conformation is severely (and inexplicably) strained. We conclude that the phenyl group is *pseudo*-equatorial in the conditions of measurement ($CDCl_3$ solution; temperature unstated (3)), but cannot determine the *a* values and dihedral angles without further knowledge.

The conformation of a pair of adjacent methylene groups may in principle be so calculated if at least three of the vicinal coupling constants are known and on the assumption implicit above that the projected geminal valence angles are near 120°. For compounds I, II and VIII insufficient lines in the *XY* portion of the *ABXY* spectra were resolved to allow completion of the analysis (2) but the near equality of *N* and *R*, readily obtained from the *AB* (low-field) portion at 40°, is sufficient to show either that the 3- and 4-methylene groups are nearly eclipsed or, more likely, that there is rapid conformational inversion about this mean position. At the lowest temperature (-35^{o}) so far available to us there was some broadening with loss of resolution of the lines in the *AB* spectrum of compound I but no clear evidence of conformational freezing.

We have confirmed the structure previously proposed (1) for piptosidin by its reduction with sodium borohydride to dihydropiptosidin whose p.m.r. spectrum shows that its only *structural* difference from leucodrin lies in the substituents attached to lactone A (16). The signal of the new proton, H3, on lactone B is a doublet at δ 4·80, J_{34} = 8·5 c/s, close to J_{34} in lactone B of leucodrin tetra-acetate. The 3-acetoxy and 4-diacetoxyethyl substituents in the latter are *trans* (17) and both may be assumed to occupy *pseudo*-equatorial positions, owing to non-bonded interaction of the 4- with a 2-substituent in the inverted conformation, the H3-H4 dihedral angle probably being near 160^{o}. Should these substituents be *cis* in dihydropiptosidin, the 4-substituent would probably remain *pseudo*-equatorial but suffer stronger non-bonded interaction with the 3-substituent. The H3-H4 dihedral angle would then probably be $>30^{o}$ and J_{34} (*cis*)$<$ 6 c/s (assuming *a* values near 10 and 8 c/s, respectively, for dihedral angles greater than, or less than, 90^{o}). It is likely that these substituents in dihydropiptosidin are *trans* as in lactone B of leucodrin.

P.m.r. spectra of compounds I - VI were measured at 35° on a Varian A 60 spectrometer at the University of Sydney by Mr. D.C. Dehlsen and Dr. A.V. Robertson whom we thank for their kind assistance.

REFERENCES

(1) N.V. Riggs and J.D. Stevens, Tetrahedron Letters, No.24, 1615 (1963).

(2) N.V. Riggs, Aust.J.Chem., **16**, 521 (1963).

(3) G.W. Perold and K. Pachler, Proc.Chem.Soc., 62 (1964).

(4) H.J. Bernstein and N.Sheppard, J.Chem.Phys., **37**, 3012, (1962).

(5) M. Barfield and D.M. Grant, J.Amer.Chem.Soc., **83**, 4726 (1961).

(6) M. Barfield and D.M. Grant, J.Amer.Chem.Soc., **85**, 1899 (1963).

(7) T. Takahashi, Tetrahedron Letters, No.11, 565 (1964).

(8) H.S. Gutowsky, M. Karplus, and D.M. Grant, J.Chem.Phys., **31**, 1278 (1959).

(9) J. Fridrichsons and A.McL. Mathieson, Acta Cryst., **15**, 119 (1962).

(10) K.L. Williamson, J.Amer.Chem.Soc., **85**, 516 (1963).

(11) R.U. Lemieux and J. Howard, Canad.J.Chem., **41**, 308 (1963).

(12) J.R. Cavanaugh and B.P. Dailey, J.Chem.Phys., **34**, 1102 (1961).

(13) A.McL. Mathieson and J.C. Taylor, Tetrahedron Letters, No.17, 590 (1961).

(14) M. Karplus, J.Chem.Phys., **30**, 11 (1959).

(15) K.L. Williamson and W.S. Johnson, J.Amer.Chem.Soc., **83**, 4623 (1961).

(16) J.B. Lowry and N.V. Riggs, to be published.

(17) R.D. Diamand and D. Rogers, Proc.Chem.Soc., 63 (1964).