The Conformations of δ-Lactones

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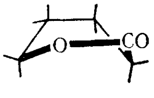
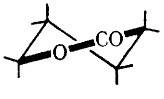
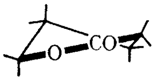
THERE has been general agreement that the C–O–CO–C group is planar in δ-lactones,[1–3] but disagreement on the preferred conformation of the lactone ring. Cheung, Overton, and Sim,[3] concluded from crystallographic data that although both half-boat (A) and half-chair (B) conformations were compatible with the planar lactone group, δ-lactones normally adopt the half-chair conformation if free to do so. The opposite conclusion was reached by Mathieson,[4] and an interpretation of optical rotatory dispersion data by Wolf[5] was held to support this latter view. However, other authors[6,7] have concluded that the o.r.d. curves of δ-lactones are but little affected by the conformation of the ring.



(A)



(B)



(C)

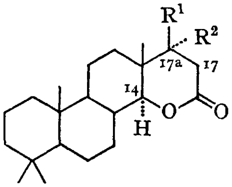
During another investigation,[8] we prepared a number of unstrained steroidal lactones whose substitution patterns made them particularly suitable for conformational study. We now report chemical and spectroscopic evidence which collectively strongly supports the assignment of half-chair type conformations to these compounds in solution.

It was noted that whereas the 17aβ-acetoxy-lactone (VI) was smoothly saponified by base, the epimeric 17aα-acetoxy-lactone (III) underwent elimination and yielded quantitatively the 17,17a-dehydro-lactone under the same mild conditions. The tentative inference that the 17aα-acetoxy-function in (III) was axially oriented was confirmed by its n.m.r. spectrum. The 17aα-hydroxy-, -acetoxy-, and -methoxy-substituted lactones all showed strong deshielding of the axial proton at C(14) [0·45—0·54 p.p.m. relative to the unsubstituted lactone (I)]. An average value of 0·45 p.p.m. for the deshielding of axial protons by adjacent (1 : 3) axial hydroxyl groups in other steroidal systems has been reported.[9] An axial orientation of the 17aα-substituent is possible only when the lactone ring adopts a half-chair type conformation; in the boat conformation the 17aα-substituent is directed away from the C(14) proton and indeed leads to the prediction that the 17aβ-acetoxy-lactone (VI) should undergo elimination more rapidly than its epimer.

These conclusions are confirmed by analysis of the ABX systems presented by the C(17,17a) protons in the lactones [(II), (III), and (VI)]. Even a qualitative examination of the observed vicinal coupling constants (Table) shows that boat-type conformations are inadmissible. Thus the two large couplings in the β-acetoxy-derivative (VI) require that the X proton [at C(17a) should lie *outside* the dihedral angle enclosed by the AB protons [at C(17)],[10] and conversely for the α-substituted lactones [(II) and (III)]. These orientations are possible only in half-chair type conformations. Although caution is necessary in any quantitative interpretation of the data in terms of simple Karplus theory the actual values of the observed coupling constants are in fact best accommodated in slightly flattened half-chair conformations (C), in which C(17a) becomes closer to the plane of the lactone group. The effect of this flattening is to give the C(17) protons "pseudoaxial" and "pseudoequatorial" character[11] as in the case of cyclohexene.

All the lactones examined had infrared carbonyl absorptions (Table) close to the normal range (1730—1750 cm.$^{-1}$) for δ-lactones thus supporting the suggestion[3] that normal i.r. frequencies are associated with half-chair conformations.

TABLE



	Lactone		τ, C(14)-H	J[C(17)-H, C(17a)-H] (c./sec.)	ν_{max}(cm.$^{-1}$)
(I)	Unsubstituted,	$R^1=R^2=H$	6·46		1731 (CCl_4)
(II)	17aα-Hydroxy,	$R^1=H$, $R^2=OH$	5·92	6·0, 1·5	1723 ($CHCl_3$)*
(III)	17aα-Acetoxy,	$R^1=H$, $R^2=OAc$	6·01	6·5, 1·3	1743 (CCl_4)
(IV)	17aα-Methoxy,	$R^1=H$, $R^2=OMe$	5·99		
(V)	17aβ-Hydroxy,	$R^1=OH$, $R^2=H$			1728 ($CHCl_3$)*
(VI)	17aβ-Acetoxy,	$R^1=OAc$, $R^2=H$	6·47	8·0, 8·7	1751 (CCl_4)

* (Solvent shifts, $CHCl_3$ to CCl_4, are 10—15 cm.$^{-1}$ for δ-lactones, see ref. 3).

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[1] J. F. McConnell, A. McL. Mathieson, and B. P. Schoenborn, *Tetrahedron Letters*, 1962, 445.
[2] A. McL. Mathieson and J. C. Taylor, *Tetrahedron Letters*, 1961, 590.
[3] K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Comm.*, 1965, 634.
[4] A. McL. Mathieson, *Tetrahedron Letters*, 1963, 81.
[5] H. Wolf, *Tetrahedron Letters*, 1966, 5151.
[6] G. Snatzke, H. Ripperger, Chr. Horstmann, and K. Schreiber, *Tetrahedron*, 1966, **22**, 3103.
[7] J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 7211.
[8] P. Johnston, R. C. Sheppard, C. E. Stehr, and S. Turner, *J. Chem. Soc.* (*C*), 1966, 1847.
[9] K. Tori and T. Komeno, *Tetrahedron*, 1965, **21**, 309.
[10] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 1963, 806.
[11] D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee, *Chem. and Ind.*, 1954, 21.