Tetrahedron. Vol. 26, pp. 2221 to 2228. Pergamon Press 1970. Printed in Great Britain

CONFORMATIONAL STUDIES ON CERTAIN 6-MEMBERED RING LACTONES

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(*Received in the UK 20 December* 1969; *Accepted for publication 2 February* 1970)

Abstract—The stereochemistry of 6-membered ring lactones in some naturally occurring steroids has been studied. Circular dichroism measurements in the $n \rightarrow \pi^*$ band region have shown that one of these lactones (VIb) exists in a half chair conformation, whereas three other lactones (Vb, VII and VIII) are in a half boat conformation. The configuration of the substituents α and β to the lactonic carbonyl has been determined by NMR solvent effects.

IN A previous publication,[1] we have described *inter alia* the structure of two new steroidal lactones (Ia, IIa) of the withanolide series, both having a saturated 6-membered ring lactone in the side chain. This is the first instance when such compounds are found in Nature, in all the withanolides isolated so far the 6-membered ring lactone being unsaturated (Δ^{24}). Saturated lactones have been obtained however in this series by catalytic hydrogenation of withaferin A^2 diacetate (IIIb). The reduction proceeded with the rapid consumption of two moles of hydrogen to yield the dihydrodesoxy derivative (IVb), followed by the slow absorption of a third mole of hydrogen which reduced the lactone double bond leading to the tetrahydrodesoxy derivative Vb. This compound (Vb) proved, however, to be different from the dihydro-derivative VII obtained by catalytic reduction of the Δ^2 in Ib.[1] In alkaline conditions compound Vb underwent epimerization at C-25 with the concomitant hydrolysis of the acetate function, affording the epimeric lactone VIa;[2a] the corresponding monoacetate VIb was still different from VII. Compound VII could not be however epimerized by exposure to alkaline conditions, the only reaction taking place being the hydrolysis of the acetate function.

Finally, acetylation of IIa followed by catalytic hydrogenation of the Δ^2 afforded[1] a new fully saturated withanolide VIII, possessing a tertiary OH group at C_{20}. This compound resisted as well to attempted epimerization in alkaline medium.

In the present paper the stereochemistry of the lactone rings in compounds Vb, VIb, VII and VIII is investigated.

The following analysis which was done for the three stereoisomeric compounds (Vb, VIb and VII) is based on the assumption that they possess the same configuration at C-22; indeed, CD measurements (*vide infra*) confirm the 22R configuration of Vb and VIb, the same as in withaferin A (IIIa). The NMR signals of the C-22H show the same multiplicity (double triplet) and appear at about the same position (δ 4·22, 4·37 and 4·33 respectively). Furthermore, one can safely assume that the C-20 atom, carrying the whole steroid skeleton is equatorially attached to the C-22 of the lactone ring.

Conformational studies on 6-membered lactones performed by X-ray analysis[3] have shown that the carbonyl, the ethereal oxygen and the two adjacent C atoms lie generally in the same plane. The lactone ring can therefore assume either a half chair or a half boat conformation. Both conformations have actually been found in the crystalline state, the energy difference between them not being therefore too large;[4] if flagpole interactions are however involved the half boat conformation cannot be adopted.

Circular dichroism measurements. Some time ago the configuration at C-22 of another withanolide, jaborosalactone A(IX) was determined,[5] by comparison of its CD with that of parasorbic acid. Since dihydrodesoxywithaferin A (IV) also shows a positive Cotton effect in the range of the R band of the conjugated lactone, at about 250 nm (Table 1) it should possess the same stereochemistry at C-22 (i.e. 22 R). The same conclusion was reached independently through the X-ray analysis of a bromobenzoate derivative of withaferin A.[6] Since withanolide D acetate (Xb)[7] has a similar CD band it follows that it possesses the same 22 R configuration.

The sign of the $n \rightarrow \pi^*$ band of nonplanar lactones in the region around 215 nm is determined by the torsion angle along the O=C—C—C system of the ring.[4,8] Considering the 22 R configuration and the equatorial orientation of the linkage between the lactone and the whole steroid skeleton, a half chair conformation of the lactone should lead to a positive, and a half boat conformation to a negative CD band in the aforementioned region.

Actually it was found that the $n \rightarrow \pi^*$ band in compounds Vb and VII is negative whereas in compound VIb is positive (Table 1).

NMR solvent shift measurements. The stereochemical implications of the solvent shifts ($\Delta^{CDCl_3}_{C_6H_6}$) of protons lying in the proximity of a ketone group are well documented.[9] It is known for instance that a proton (or a Me group) on a carbon adjacent to the ketone will exhibit a strong upfield solvent shift if axial, and a weak (usually downfield) shift if equatorial oriented. For lactones the available information is very limited.[10] In the case of 5-membered ring lactones (the study was performed on a whole series of sesquiterpene lactones) a *pseudo* equatorial Me group next to the lactonic CO shows an upfield solvent shift ($\Delta^{CDCl_3}_{C_6H_6}$) of $\sim$14 Hz, whereas a *pseudo* axial methyl has a shift of $\sim$28 Hz. Both shifts are upfield, but the trend is the same as in ketones: axial substituents have stronger upfield shifts than equatorial counterparts.

The solvent shifts ($\Delta^{CDCl_3}_{C_6H_6}$) measured for the C-25 Me in compounds Vb, VIb and VII (Table 2) are +4·5, +5 and +4 Hz, respectively. The conclusion is that in all these compounds the C-25 Me groups have to be similarly oriented with respect to the lactonic CO; to account for such a weak solvent effect, this orientation should be equatorial.

DISCUSSION

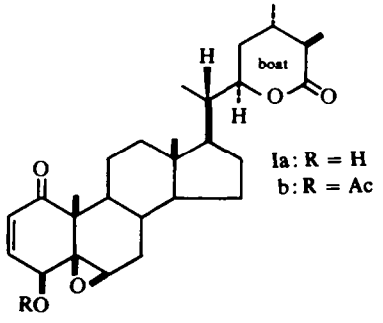
For the purpose of the present discussion the four theoretically possible δ-lactones are designated as A, B, C and D. In each case the *half chair* and *half boat* conformations are marked by the symbols c and b, respectively. The numbering of the C atoms is that used in steroids, and the substituents are referred to as α and β oriented; the skeleton attached equatorially at C-22 is always β oriented.

In the lactone ring of compound Vb which is obtained by catalytic hydrogenation

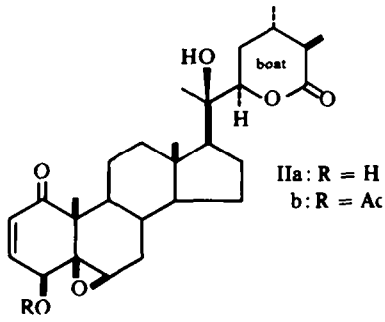
TABLE 1. CD-DATA OF CERTAIN WITHANOLIDES

Compound	Solvent	λ_{max} ($\Delta\varepsilon$)‡
IVb	ethanol	293(−4·37), 248(+3·54), ~200(+9).
Vb	ethanol	293(−4·56), 212(−1·8).
	dioxan	315i(−2·34), 303(−4·58), 294(−4·98), 284i(−4·01).
VIb	ethanol	293(−5·19), 223(+1·20).
	dioxan	316i(−1·96), 303i(−4·23), 294(−4·76), 228(+1·37).
VII	ethanol	293(−5·66), 216(−3·4).
	dioxan	315i(−2·20), 303i(−4·43), 294(−4·88), 284i(−3·96), 220(−3·0).
VIII	ethanol	303i(−3·62), 293(−4·59), 214(−4·84).
Xb	ethanol	344(+1·73), 292(−0·17), 254(+3·72), 216(+30·5), negative at shorter wavelengths.

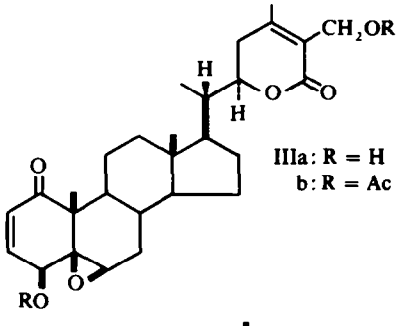
‡ Inflexions are indicated by i.



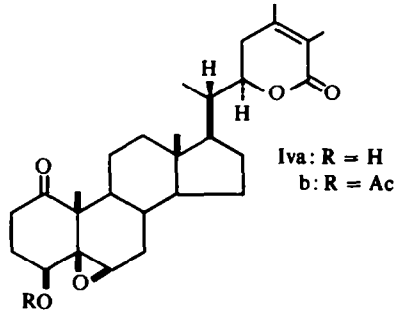
Ia: R = H
b: R = Ac



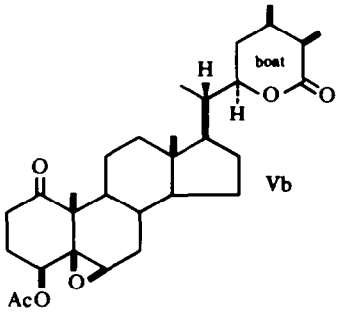
IIa: R = H
b: R = Ac



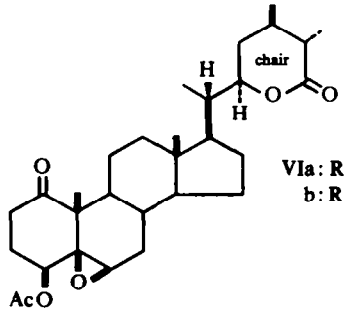
IIIa: R = H
b: R = Ac



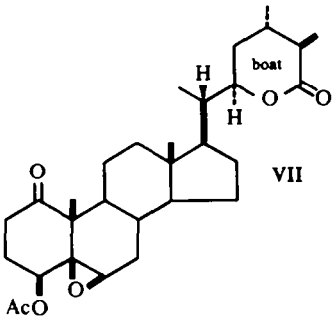
IVa: R = H
b: R = Ac



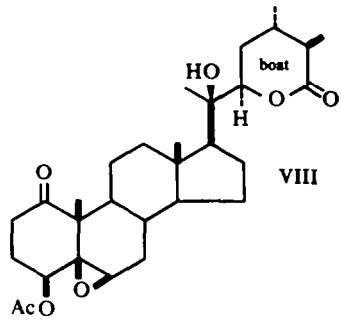
Vb



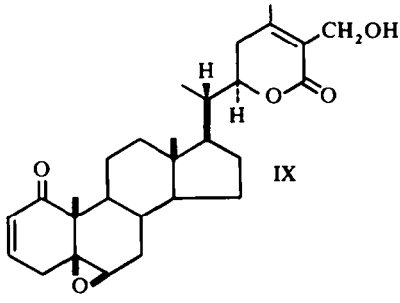
VIa: R = H
b: R = Ac



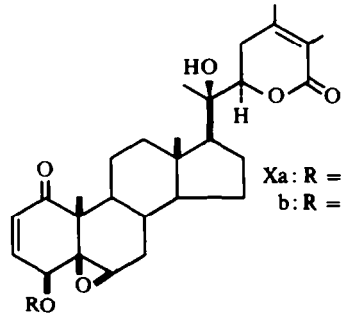
VII



VIII



IX



Xa: R = H
b: R = Ac

of IIIb[2b] the two Me groups at C-24 and C-25 should be in a *cis* relationship. In principle four possibilities are available for this lactone: with the two Me groups β oriented (structures A-c or A-b) or α oriented (structures D-c and D-b); since the Cotton effect in the 215 nm region is negative, the two chair possibilities (A-c and D-c) can be disregarded.

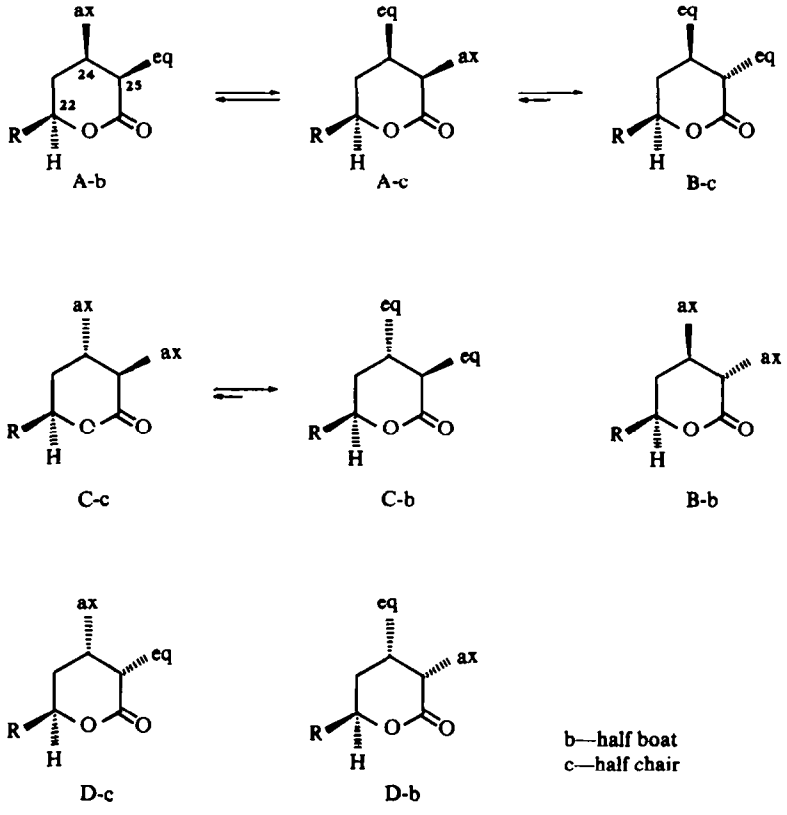
Conformation D-b is very improbable due to flagpole interactions; furthermore, the axial C-25 Me should be able to undergo epimerization in alkaline conditions to yield a compound in which this Me is equatorial; the product of such an epimerization would have the lactone in conformation C-b which is, however, incompatible with the positive sign of the Cotton effect (half chair conformation) measured for compound VI.

The last possibility left for the lactone in compound V is therefore conformation A-b, suggested both by the negative CD curve and by the equatorial orientation of the C-25 Me,* as deduced from the NMR solvent shifts data. Thus, the process of epimerization of compound V into VI can best be imagined through a sequence involving first the flipping of structure A-b to A-c, in which the C-25 Me becomes axially oriented, being therefore readily epimerized. The lactone ring in VI should be consequently assigned structure B-c with the two Me groups in a *trans* diequatorial relationship. This conclusion is supported by the positive Cotton effect of the latter in the $n \rightarrow \pi^*$ band region; since VI has been obtained in equilibrating conditions,

* The easy epimerization of the C-25 Me in V led us at the time[2b] to assume an axial orientation for this group.

TABLE 2. NMR SOLVENT SHIFTS DATA FOR THE C-24 AND C-25 Me GROUPS IN CERTAIN WITHANOLIDES (IN Hz AT 60 MHz.

Compound	C-25 CH_3			C-24 CH_3		
	$CDCl_3$	C_6H_6	$\Delta^{CDCl_3}_{C_6H_6}$	$CDCl_3$	C_6H_6	$\Delta^{CDCl_3}_{C_6H_6}$
Vb	68	63·5	+4·5	55·5	39·5	+16
VIb	79·5	74·5	+5	65	41·5	+23·5
VII	73	69	+4	67	42	+25
VIII	72·5	65	+7·5	69·5	38·5	+31



the equatorial orientation of the C-25 Me is obvious, being thermodinamically more stable. Furthermore, according to the solvent shifts data this Me group should indeed be very close to the plane of the lactonic CO. A boat conformation (B-b) for this lactone is highly improbable due to flagpole interactions.

The same analysis can now be done for compound VII which, in contrast to V and VI possesses a saturated 6-membered ring lactone of natural occurrence. The

negative sign of the Cotton effect associated with the lactone ring in VII excludes the possibility of a chair conformation, as represented by structures C-c and D-c; since the compound remains unchanged upon exposure to alkaline conditions, i.e. it does not undergo epimerization at C-25, structure D-b can be discarded as well, the last possibility being that described by C-b. Supporting evidence for this structure is found again in the weak solvent shift measured for the equatorial C-25 Me.

It is noteworthy that in all the structures proposed for the lactone in compounds Vb, VIb and VII (A-b, B-c and C-b, respectively) 1,3 diaxial repulsive interactions are reduced to minimum.

The lactone ring in compound VIII, obtained from the naturally occurring IIa, should possess structure C-b, by the same arguments used for compound VII. The CD of VIII in the range of the lactone n → π* band is negative, hence indicative for a half boat conformation, whereas the NMR solvent shift is close to that exhibited by the C-25 Me in VII. It is probably useful to recall that VIII also, cannot be epimerized.

Supporting evidence for the above conclusions can be found in a work due to Wolf,[4] showing that the CD maximum of a half chair conformation should lie at longer wavelengths than that of the corresponding half boat conformation. Indeed, λ_{max} (EtOH solution) for VI (structure B-c) is longer by 11 and 7 nm, respectively, than for compounds V and VII (structures A-b and C-b).

In connection with the NMR solvent shifts of these compounds there is still another observation which derseves further comment. The $\Delta^{CDCl_3}_{C_6H_6}$ values for the C-24 Me in V, VI, VII and VIII are +16, +23·5, +25 and +31 Hz, respectively (Table 2). According to the above analysis this Me group is axial in Vb and equatorial in the three other compounds. It follows therefore that a Me group on a C atom β to the lactonic CO experiences an upfield solvent shift; however, the shift of an equatorial group is larger than that of the axial counterpart. These observations made for shifts induced by benzene in 6-membered ring lactones are not without precedent in the cyclic ketones.

In a publication[11] concerned with the conformation of cyclic ketones of different ring sizes it has been shown that for 5, 6, and 7-membered rings, the solvent shifts ($\Delta^{CCl_4}_{C_6H_6}$) of protons on the α C atom are smaller than those of other protons in the molecule. These findings are rationalised in terms of the geometry of the aromatic solvent-solute collision complex; the α protons in rings of the above sizes are more remote from the benzene molecule than protons occupying other positions and are therefore less shielded. Although in such ketones there is an unequivocal trend to larger upfield solvent shifts for protons on C atoms other than α, these simple models are not suitable for a differential evaluation of the shifts experienced by axial and equatorial protons (or Me groups) in a β position to the CO. Data on the solvent shifts for such Me groups have been obtained by Fetizon *et al.*,[12] from the measurements ($\Delta^{CCl_4}_{C_6H_6}$) of the three Me groups in 3,5,5-trimethylcyclohexanone deuteriated at position 3; the two equatorial Me groups show solvent shifts of +18·4 and +19·3 Hz, whereas the axial Me is shifted upfield by only 11·6 Hz. The same situation is evident from the data available for more rigid systems such as 5α and 5β-cholestan-4-ones. The C-10 Me is axial towards ring A in the 5α compound and equatorial in the 5β isomer. The solvent shift ($\Delta^{CDCl_3}_{C_6H_6}$) for this group in the first compound is +7·5 Hz[13] (+7·2 Hz[14]) while in the latter is +14 Hz.[13]

The fact that the C-10 Me in steroidal 6-ones experiences almost similar shifts in the 5α as well as 5β series (+5·4 and +4·3 Hz, respectively[14]) is not surprising to our opinion,[15] since in both stereoisomers this Me group is axial towards the ring bearing the CO.

In the steroidal 4-ones the situation is quite different; while the shape of rings A/B is the same as in the 6-ones (5α and 5β respectively), the geometrical relationship between the C-10 Me and the CO is different.

These observations are consistent with the proposed aromatic solvent-solute collision complex in which the benzene molecule orients itself on the positive side of the CO dipole, at about right angles to it.[16] Inspection of models of the above steroidal 4-ones shows clearly that such a complex with the benzene molecule would predict a larger upfield shift of the C-10 Me in the 5β series, whereas for the 6-ones the C-10 Me should experience the same effect in both stereoisomers.

A similar model would explain also the larger upfield solvent shift experienced by the equatorial C-24 Me, in the lactones VI, VII and VIII as compared to the shift of the corresponding axial Me in the lactone V. According to the specific geometry of the aromatic solvent-solute complex, an equatorial methyl β to the CO is closer to the aromatic molecule than an axial Me. The fact that lactones give in general larger solvent shifts than ketones is undoubtedly due to the influence of the etheric oxygen in the lactones. Studies performed on cyclic ethers have substantiated such a view.[17]

Acknowledgement—G.S. thanks the Deutsche Forschungsgemeinschaft for financial support, Miss L. Penzien and Mr. E. Kirmayr for skilful technical assistance.

D. L. acknowledges an interesting discussion with Prof. E. Wenkert on his observations concerning solvent shift effects, previous to publication.

REFERENCES

[1] I. Kirson, E. Glotter, A. Abraham and D. Lavie, *Tetrahedron* **26**, (1970) preceding paper

[2] D. Lavie, E. Glotter and Y. Shvo; [a] *J. Org. Chem.* **30**, 1774 (1965); [b] *J. Chem. Soc.* 7515 (1965).

[3] J. F. McConnell, A. McL. Mathieson and B. P. Schoenborn, *Tetrahedron Letters* 445 (1962); A. McL. Mathieson, *Ibid.* **81**, 1963; K. K. Cheung, K. H. Overton and G. A. Sim, *Chem. Comm.* 634 (1965); G. A. Jeffrey and S. H. Kim, *Ibid.* 211 (1966)

[4] H. Wolf, *Tetrahedron Letters* 5151 (1966)

[5] G. Snatzke, H. Schwang and R. Welzel, *Some Newer Physical Methods in Structural Chemistry* (Edited by R. Bonnett and J. G. Davis), p. 159. United Trade Press, London (1967). Cf. also G. Snatzke, *Angew. Chemie* Internat. Ed. **7**, 14 (1968)

[6] A. T. McPhail and G. A. Sim, *J. Chem. Soc.* (B), 962 (1968).

[7] D. Lavie, I. Kirson and E. Glotter, *Israel J. Chem.* **6**, 671 (1968)

[8] M. Legrand and R. Bucourt, *Bull. Soc. Chim. Fr* 2241 (1967)

[9] See for instance N. S. Bhacca and D. H. Williams, *Tetrahedron Letters* 3127 (1964); D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 2021 (1965); J. D. Connolly and R. McCrindle, *Chem. & Ind.* 379 (1965)

[10] C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.* **33**, 3156 (1968), see also G. Di Maio, P. A. Tardella and C. Iavarone, *Tetrahedron Letters* 2825 (1966).

[11] T. Ledaal, *Ibid.* 651 (1968)

[12] M. Fetizon, J. Goré, P. Laszlo and B. Waegell, *J. Org. Chem.* **31**, 4047 (1966)

[13] E. Glotter and D. Lavie, *J. Chem. Soc.* (C), 2298 (1967)

[14] P. C. Cherry, W. R. T. Cottrell, G. D. Meakins and E. E. Richards, *Ibid.* (C), 181 (1967)

[15] For other views on this point see ref. 14, and M. Fetizon, M. Golfier and J. C. Gramain, *Bull. Soc. Chim., Fr.* 275 (1968)

[16] D. H. Williams and D. A. Wilson, *J. Chem. Soc.* (B), 144, 1966; K. M. Baker and B. R. Davis, *Ibid.* 261 (1968)

[17] C. R. Narayanan and N. R. Bhadane, *Tetrahedron Letters* 1557 (1968)