

THE DETERMINATION OF THE STEREOCHEMISTRY OF FIVE-MEMBERED α,β -UNSATURATED LACTONES WITH AN EXOMETHYLENE DOUBLE BOND BASED ON THE ALLYLIC LONG-RANGE COUPLINGS OF EXOMETHYLENE PROTONS

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An appreciable number of natural sesquiterpenic compounds contain an α,β -unsaturated γ -lactone ring with an exomethylene double bond of the type I. The elucidation of the nature of ring fusion of I was usually carried out either by chemical correlation or by X-ray analysis. The use of p.m.r. spectroscopy for the solution of this problem was based on the magnitude of the vicinal coupling $^3J_{A,B}$ predominantly in dihydroderivatives. Pinhey and Sternhell¹ have shown that this coupling is less characteristic of the cis-trans isomerism and that it can be utilised with advantage only in the case of six-membered rings^{1,2} where the correspondence of Dreiding models with the probable real conformations is relatively good. However, the relative increase in the significance of $^3J_{A,B}$ when I is transformed to suitable derivatives is charged by a potential complication caused by the possible epimerisation of the allylic carbon due to an H-shift taking place simultaneously. This necessitates the determination of the fusion of rings directly and independently. From the point of view of p.m.r. in the case of I the magnitude of the transoid and cisoid allylic couplings $^4J_{b,A}$ and $^4J_{a,A}$ remains to be discussed. It becomes clear that these couplings also can serve as an additional indication of the cis-trans isomerism of the ring fusion of I.

The idea of using the allylic coupling for the solution of this problem is based on following assumptions. Recent X-ray studies^{2,3,4} have shown that the resonance structure $-O^+(C=O^-)-$ contributes appreciably to the ground state of the lactone group $-O(C=O)-$. In the case of I this structure can be stabilised by conjugation with the exomethylene double bond. In consequence an appreciable limitation of the conformational mobility of the γ -lactone ring can be expected and hence also a limitation of the variability of the allylic dihedral angle θ (see Fig. 1) which predominantly determines the magnitude of the allylic coupling^{5,6}. In view of the possi-

bility that different strains of cis- and trans-fused γ -lactone rings manifest themselves by different degrees of perturbation of relative configuration of orbitals of C-atoms forming intervening bonds, and in view of the fact that the transoid and the cisoid couplings do not differ very much^{5,6} a certain characteristic ranges of both 4J can be expected.

TABLE 1

No	Compound	lactone fusion	size of fused ring	δ (ppm) H_a, H_b		$ ^4J $ (Hz)		ref.
				cisoid	transoid	cisoid	transoid	
II	Asperilin	cis	6	5.48	6.01	1	1	8
III	Ivasperin	cis	6	5.59	6.24	1.0	1.0	8
IV	Dehydromicrocephalin	cis	6	5.55	6.08	1.0	1.0	9
V	Yomogin	cis	6	5.72	6.20	1.5	1.5	10
VI	Arglanin	trans	6	5.52	6.18	3.0	3.0	11
VII	Tuberiferin	trans	6	5.45	6.12	3.0	3.0	12
VIIIa	Helenaalin	cis	7	5.78	6.24	3.0	3.0	13,14
VIIIb	Acetate VIIIa	cis	7	6.11	6.42	2.8	2.8	13
IX	Balduilin	cis	7	5.80	6.33	2.0	2.0	13,15
X	Amaralin	trans	7	5.46	6.17	3.3	3.3	16
XI	Ligustrin	trans	7	5.63	6.38	3.5	3.5	17
XII	Monobromgaillardin	trans	7	5.55	6.22	3.0	3.0	18
XIIIa	Tamaulipin A	trans	10	5.58	6.30	3.2	3.8	19
XIIIb	Acetate XIIIa	trans	10	5.58	6.30	3.6	3.6	19
XIV	Tamaulipin B	trans	10	5.55	6.25	3.2	3.5	20
XVa	Cnoporopicrin	trans	10	5.65	6.03	3.0	3.2	21
XVb	Cnicin	trans	10	5.72	6.08	3.0	3.3	22

A comparative study of a large number of published p.m.r. data of sesquiterpenic lactones of type I, as well as our unpublished measurements⁷ have indicated that these suppositions may be justified. It seems that the following rules are applicable:

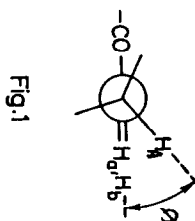
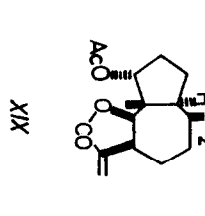
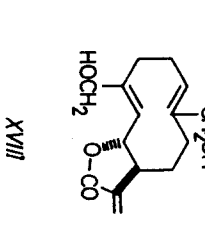
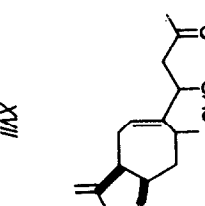
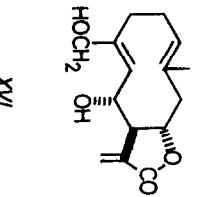
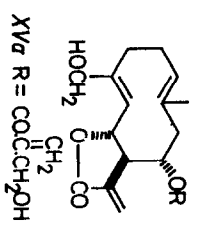
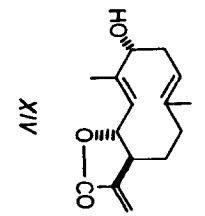
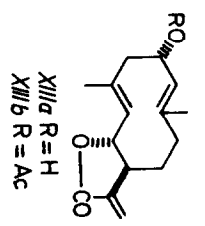
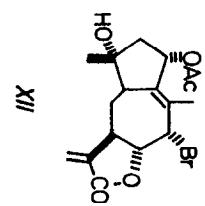
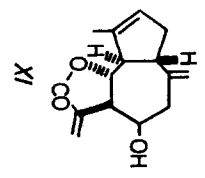
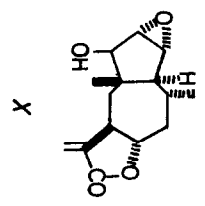
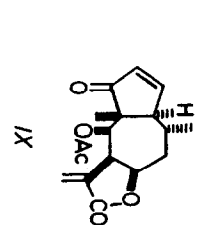
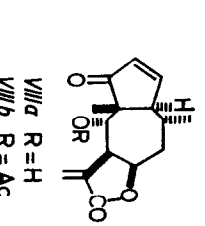
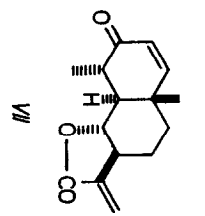
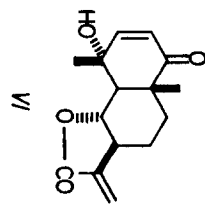
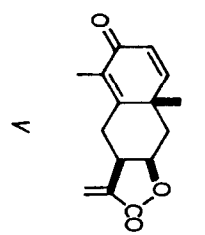
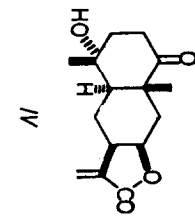
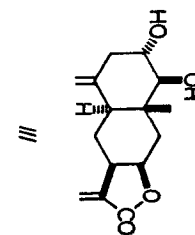
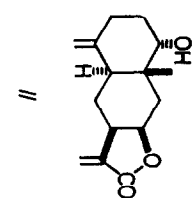
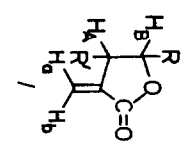


Fig.1



XVd R = COC(CH₂)₂OH
 XVb R = COC(CH₂)₂OH

XVII

XVIII

XIX

XIIIa R = H
 XIIIb R = Ac

VIIIa R = H
 VIIIb R = Ac

- 1) trans-lactones I have larger $|^4J_{\text{cisoid}}|$ and $|^4J_{\text{transoid}}|$ than cis-lactones,
- 2) $|^4J_{\text{(trans)}}| \geq 3 \text{ Hz} \geq |^4J_{\text{(cis)}}|$.

A few representative cases of lactones of eudesmane, guaiane, pseudoguaiane and germacrane types with a defined stereochemistry of the lactone ring are listed in Table 1. The assignment of protons in Table 1 (II-XIV measured in CDCl_3 , XVa and XVb in d_6 -DMSO) was carried out under the assumption that a proton at a lower field is closer to the carbonyl group and hence is $H_b = H_{\text{transoid}}$. This question is presently less important because in the majority of substances the reported doublet splittings of exomethylene protons are of the same magnitude (II-XII, XIIIb). In those cases where the splittings are different (e.g. XIIIa, XIV, XVa and XVb) the assignment agrees with the rule $|^4J_{\text{transoid}}| > |^4J_{\text{cisoid}}|$, found in analogous systems⁶. However, salonitenolide (XVI)²³ with H_b at 6.35 ppm and H_a at 6.16 ppm and with $^4J_{b,A} = 3.0 \text{ Hz}$ and $^4J_{a,A} = 3.45 \text{ Hz}$ (in d_6 -DMSO) is an exception. The question of the correctness of the given magnitude of the doublet splittings and of their assignment to allylic couplings is more problematic because the assignment was not corroborated by double resonance in most cases. In despite of this circumstance this assignment can be considered as very probable because the detailed analyses carried out till now (e.g. XIII-XV) indicate that the geminal coupling $^2J_{a,b}$ in I is usually zero or very small²⁴ (salonitenolide XVI²³ with $^2J = 2.2 \text{ Hz}$ represents an exception).

In view of these circumstances a more detailed discussion of the validity of rules 1 and 2 is premature²⁵. The cases with $|^4J_{\text{transoid}}| > 3 \text{ Hz}$ and $|^4J_{\text{cisoid}}| < 3 \text{ Hz}$, as for example xanthumin (XVII)²⁶ or albicolid (XVIII)²⁷ and all cases with $|^4J| \approx 3 \text{ Hz}$ (e.g. VIIIa and XII) are problematic²⁵. The only exception which is in strict contradiction to rule 2 is hysterin (XIX)²⁸ which is described as a cis-lactone with doublet splittings 3.5 Hz. However, in addition to vicinal coupling $^3J_{A,B}$ the use of allylic couplings based on rules 1 and 2 could contribute considerably to an easy indication of ring fusion in I and thus also to the solution of the stereochemistry of sesquiterpenic lactones. As this problem will also be important in future and its study will remain limited for the time being to unique natural materials, the main aim of this communication consists in focusing attention on these possibilities of the application of p.m.r., and to stimulate thus a more precise analysis of p.m.r. spectra of natural occurring lactones of the type I in this direction.

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- 7) This problem is presently under study but there are certain difficulties, both because the determination of the sign of 4J is difficult, and because at present ideas on the geometry of the majority of substances studied are not sufficiently founded (recent X-ray studies have shown appreciable discrepancies in comparison with Dreiding models, cf. ref. 14). At the moment it is obvious that the determined absolute values of 4J cannot be explained simply on the basis of a mere dependence on the allylic angle θ (Fig. 1), because this dependence is insufficient even in its revised form (cf. ref. 6). The dependence of 4J on the polarity of the solvent, which could affect $\sigma - \pi$ contact mechanism has not yet been observed in the case of I.
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- 24) The dependence of 2J on the solvent was found. It was also observed in some cases that with substances having a substituent of the OR-type on the carbon of the fused ring adjacent to C_A in I 2J is different for R=H and R=Acyl. The reason consists probably in a different deformation of the geminal angle caused by van der Waals interaction. This problem will be a subject of subsequent communication.
- 25) This material is not reliable at present and it is very incoherent. From the point of view of the dependence on θ (Fig. 1) the equality of cisoid and transoid 4J would correspond to the planar or envelope conformation (with ring-oxygen out of plane), in which θ is about $\pm 60-70^\circ$, which corresponds also, in principle, to theoretical ideas concerning $40-60^\circ$ range (cf. ref. 6). Different values can correspond a priori to the theory⁶ but they can be only apparent (because of inaccurate measurements, for instance) or also depending on substitution (cf. ref. 24 and XIIIa and XIIIb in Tab. 1). The tendency to the puckering of the ring should be characteristic of the trans-fusion and should be a reason for the increase of the vicinal dihedral angle H_A-H_B , and simultaneously also of the increase of θ toward 90° and hence also of the rule 1.
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