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STEREOCHEMICAL STUDIES BY PMR SPECTROSCOPY V - A SIMPLE METHOD TO FIND THE STEREOCHEMISTRY OF THE SIDE CHAIN OF γ-LACTONES*+

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Several natural and synthetic γ-lactones fused to cyclohexane systems are known since long, as santonin, artemisin, alantalactone etc. and new ones are also being found or made. All of these have a methyl side chain next to the lactone carbonyl. There is no simple or direct chemical, nor was there any physical method to find its stereochemistry. As a result there was much confusion in the literature about this point. The C_{11}-CH_3 in α-santonin (I, Table 1) was deduced to be β-oriented on some stability considerations (1,2,3) based on the equilibration reactions of this methyl group in the lactone. The other lactones mentioned above and several others also were assigned stereochemistry at C_{11}, after chemically relating them to an α-santonin derivative. However recent chemical (4) and X-Ray studies (5) have shown that the C_{11}-CH_3 in α-santonin is actually α-oriented. Hence the stereochemical assignment at C_{11}, in all the other lactones had to be reversed. We are presenting below a simple method by which the stereochemistry of the side chain of any such γ-lactone can be directly and independently determined.

In the trans-lactones like α or β-santonin or their hydrogenation products, the B-ring has no flexibility and

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+Part III Tetrahedron Letters 3639 (1965), ibid.3741 (1965) will be considered as Part IV.

TABLE I -(QUASI-EQUATORIAL)

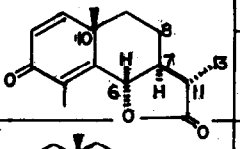
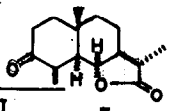
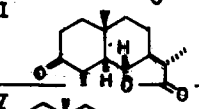
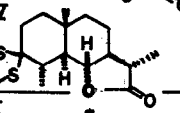
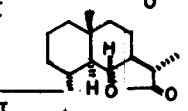
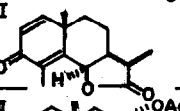
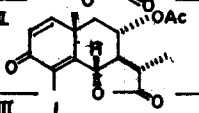
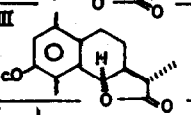
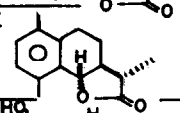
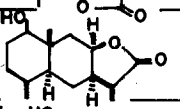
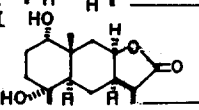
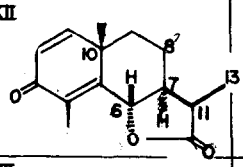
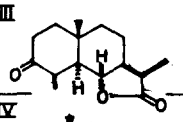
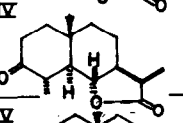
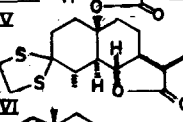
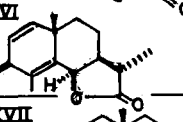
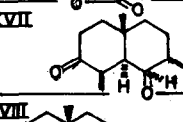
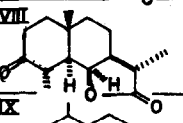
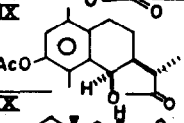
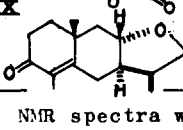
Compound	Chemical Shift of the C_{11}-CH_3 in		'c' $\delta CDCl_3-\delta C_6H_6$ ($\delta CDCl_3-\delta C_5H_5N$)
	'a' $CDCl_3$	'b' Benzene and (pyridine)	
I 	1.28	0.99 (1.23)	+0.29 (+0.05)
II 	1.25	1.05 (1.19)	+0.20 (+0.06)
III 	1.24	1.02 (1.16)	+0.22 (+0.08)
IV 	1.18	0.96 (1.13)	+0.22 (+0.05)
V 	1.19	1.02 (1.16)	+0.17 (+0.03)
VI 	1.26	0.98 (1.21)	+0.28 (+0.05)
VII 	1.29	1.06 (1.34)	+0.23 (-0.05)
VIII 	1.28	1.03 (1.23)	+0.25 (+0.05)
IX 	1.26	1.01 (1.21)	+0.25 (+0.05)
X 	1.21	1.03 (1.19)	+0.18 (+0.02)
XI 	1.23	- (1.18)	- (+0.05)

TABLE II -(QUASI-AXIAL)

Compound	Chemical Shift of the C11-CH_3 in		'c' $\delta CDCl_3-\delta C_6H_6$ ($\delta CDCl_3-\delta C_5H_5N$)
	'a' $CDCl_3$	'b' Benzene and (Pyridine)	
XII 	1.26	0.71 (1.16)	+0.55 (+0.10)
XIII 	1.27	0.79 (1.14)	+0.48 (+0.13)
XIV 	1.26	0.78 (1.10)	+0.48 (+0.16)
XV 	1.16	0.76 (-)	+0.40 (-)
XVI 	1.39	0.96 (1.29)	+0.43 (+0.10)
XVII 	1.31	0.84 (1.18)	+0.47 (+0.13)
XVIII 	1.32	0.88 (1.23)	+0.44 (+0.09)
XIX 	1.37	1.00 (1.28)	+0.37 (+0.9)
XX 	1.26	0.81 (1.18)	+0.45 (+0.08)

NMR spectra were taken on a Varian A-60 spectrometer in 10% solution in the solvents given. The figures given in parenthesis, in column 'b' are the chemical shifts in pyridine soln. and in 'c' the chemical shifts in $CDCl_3$ solution minus those in pyridine solution (a-b). The other figures given in column c are the chemical shifts in $CDCl_3$ minus those in C_6H_6 (a-b).

is rigidly held due to the trans fusion of the lactone. In 6-epi-α-santonin and its hydrogenation products the B ring is capable of existing in a boat conformation. But if it were so, models would show that the lactone carbonyl would strongly shield the C_{10} angular methyl group (6). Virtually the same chemical shifts of about δ 1.33 observed in α and 6-epi-α-santonin (I, XVI), and about δ 1.20 for tetrahydro-α, and tetrahydro-6-epi-α-santonin (III, XVIII) show that the B-ring is in the chair conformation in the cis-lactones also. Then in the trans-angular (I to V, VII to IX and XII to XV) or linear (XX) lactones, the $C_{11}\beta$-CH_3 would be pseudo-axial and $C_{11}\alpha$-CH_3 pseudo-equatorial. In the cis-angular (VI, XVI to XIX) and linear lactones (X,XI) the β and α-C_{11}-CH_3 would have the opposite conformations.

It has been observed before that axial and equatorial methyl groups adjacent to ester carbonyls, show different types of solvent shifts in benzene when compared to those in chloroform (6). Based on this analogy NMR spectra of 20 γ-lactones of different types, as trans, cis, angular and linear, were determined in $CDCl_3$, benzene and pyridine solutions and the chemical shifts of the C_{11}-CH_3 in these compounds tabulated.

The pseudo-equatorial methyl groups show an upfield shift of ∽ 0.23 ± 0.06 P.P.M. in benzene, when compared to that in chloroform (Table I), whereas the pseudo-axial ones under the same conditions show a very large upfield shift of 0.46 ± 0.06 P.P.M. (Table II). The difference in the solvent shifts are so large that the conformations of the methyl groups could not be mistaken. Interestingly these shifts are somewhat different in magnitude and direction from those observed for methyl groups adjacent to ketones (14).

The Tables also show that C_{13}-protons are affected by the carbonyl and double bonds in ring A (compare I to V in column 'a'). The C_3-carbonyl alone deshields C_{13} by 0.05 P.P.M. although they are 7 carbon-carbon single bonds

away (compare III and V column 'a'). When this distant methyl group comes little closer and pseudo-axial, the deshielding is more, ∽ 0.1 P.P.M. (compare XV with XIII or XIV, column 'a'), and when little more like this, the deshielding rises to 0.16 P.P.M. (compare XV with XVII or XVIII, column 'a'). In all these cases, the same separation of 7 carbon-carbon single bonds is kept up between them. This would indicate that the downfield shift of this distant protons is to be attributed to the deshielding effect of the carbonyl, rather than its inductive effect. It is interesting to note that in III, the distance between them on Dreiding models is over 7Å.

But the solvent shifts observed (column 'c') do not seem to be seriously affected by the C_3-ketone or the double bonds. Thus between XV and XVI, which show the largest difference of 0.23 in their chemical shifts in $CDCl_3$ (Column 'a'), the difference in $\delta CDCl_3 - \delta C_6H_6$ is only 0.03 P.P.M. (column 'c') and between III and IV, having a Δ 0.06 P.P.M. in $CDCl_3$ (column 'a') there is no difference in $\delta CDCl_3 - \delta C_6H_6$ (column 'c'). Thus, these large shifts appear to be mostly brought about by the lactone group alone. Pseudo-equatorial methyl groups seem to be sufficiently away from an adjacent benzenoid ring to be affected by it (e.g. VIII and IX). But the pseudo-axial one appears to come just within its effective deshielding zone, that in compound (XIX) the signal is slightly brought down from its normal value of 0.46 ± 0.06 P.P.M.

Since the cis or trans nature of the lactone will be easily revealed from the J values of the C_6 or C_8-H as the case may be, these solvent shifts would directly lead to the stereochemistry of the C_{11}-CH_3. Spectra in pyridine solution also shows similar shifts, though of small magnitude (∽ +0.05 P.P.M. for pseudo-equatorial and ∽ +0.1 P.P.M. for pseudo-axial ones), and could be used when the compound is insoluble in benzene, as is the case with (XI) (15).

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REFERENCES

1 R.B.Woodward and P. Yates, Chem. and Ind. 1391(1954).

2 E.J. Corey, J.Amer.Chem. Soc. 77, 1044(1955).

3 N.M.Chopra, W.Cocker and T.T.Edward, Chem.and Ind. 41 (1955).

4 M. Nakazaki and H. Arakama, Bull. Chem. Soc. Japan 37, 464 (1964); see also Y.Abe, T.Miki, M. Sumi and T.Toga, Chem. and Ind. 953 (1956).

5 J.D.M. Asher and G.A.Sim, J.Chem.Soc. 6041 (1965).

6 C.R. Narayanan and N.K.Venkatasubramanian, Tetrahedron Letters 3639 (1965).

7 W. Cocker and T.B.H.McMurray, Tetrahedron 8, 181(1960)

8 D.H.R.Barton, J.E.D.Levisalles and J.T.Pinhey, J.Chem. Soc. 3472 (1962).

9 W.Herz and V.Viswanathan, J.Org.Chem. 29,1022 (1964).

10 W. Herz, G. Hogenauber and A.R.Devivar, J.Org.Chem. 29 1700 (1964).

11 Ishikawa, J. Pharm. Soc. Japan, 76, 504 (1956).

12 W.Cocker, H. Gobinsingh, T.B.H.McMurray and M.A.Nisbet, J. Chem. Soc. 1432 (1962).

13 W.Cocker and M.A. Nisbet, J.Chem.Soc. 534 (1963).

14 N.S. Bhacca and D.H. Williams, Tetrahedron Letters 42, 3127 (1964).

15 Since this manuscript was prepared for publication, the copy of Tetrahedron Letters No.25, 2825 (1966) received in our Library contained an article by Di. Maio, P.A.Tardella and C.Lavarone, giving some examples of solvent shifts of methyl groups in δ-lactones.

I, santonin; II, γ-tetrahydrosantonin; III, α-tetrahydrosantonin; IV, α-tetrahydrosantonin thioketal; V,deoxo-α-tetrahydrosantonin; VII, Artemisin acetate; VIII, 6-epi-desmotropsantonin acetate; IX, hyposantonin; XII, β-santonin; XIII, γ-tetrahydroβ-santonin; XIV, α-tetrahydro-β-santonin; XIX, desmotroposantonin acetate; vide ref.(7); VI, 6-epi-β-santonin, ref.(8): X, tetrahydroasperlin, ref.(9): XI, dihydromicrocephalin, ref.(10): XV, α-tetrahydro-β-santonin-thioketal, m.p. 155°C. $[\alpha]_D^{29} = +75^\circ$: XVI, 6-epi-α-santonin, ref.(11): XVII, γ-tetrahydro-6-epi-α-santonin, ref.(12): XVIII, α-tetrahydro-6-epi-α-santonin, ref.(12): XX, An artemisin derivative, ref.(13).