

The Meliacins (Limonoids). Tris(dipivalomethanato)europium-induced Upfield and Downfield Shifts in the Nuclear Magnetic Resonance Spectra of the Meliacins

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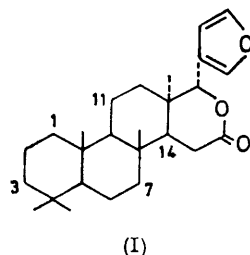
The methyl signals in the n.m.r. spectra of a number of meliacins have been assigned by the use of tris(dipivalomethanato)europium-induced shifts. While most of the compounds examined gave downfield shifts, both downfield and upfield shifts were observed for 3-deacetylkhivirin.

THE value of tris(dipivalomethanato)europium as a shift reagent for the n.m.r. spectra of compounds containing a lone-pair-bearing functional group has been demonstrated.¹ We have applied the technique to the study of the n.m.r. spectra of the meliacins (limonoids), which, although highly oxygenated polyfunctional compounds, give useful shifts because of the differences in the strength of co-ordination of the reagent with different functional groups. Thus it has been suggested that the strength of co-ordination decreases in the series OH >

C=O > -O- > CO₂R, and a recent study of bifunctional compounds has demonstrated significant differences in the co-ordination strengths of ethers, thioethers, ketones, and esters.¹ Taking advantage of this and of the dependence of the induced shift on the distance of the proton from the centre of co-ordination, we have assigned the methyl shifts in the n.m.r. spectra of a number of

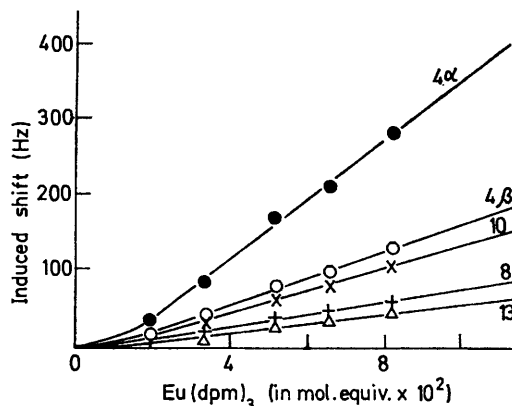
¹ See, for example, J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641, and references cited therein; H. Hart and G. M. George, *Tetrahedron Letters*, 1971, 625.

meliacins by adding increasing amounts of the reagent and observing the progressive increase in the induced



shifts. The spectra were recorded at 60 MHz for 0.11M-solutions of the compounds in $[^2\text{H}]$ chloroform with tetramethylsilane as internal standard. Within the range of molar ratio (reagent to compound) 0.25—1, the induced shifts were proportional to the amount of reagent added (see, for example Figure). Some of the assignments are given in Table 1. With a few important exceptions they are in good agreement with the assignments of Taylor and Ohochuku,² which were based on deduced 'incremental terms' for functional groups depending on their nature and position in the molecule. We find that for 3β -hydroxy- and acetoxy-compounds the 4α - and 4β -methyl groups had been reversed by Taylor and

450—500 Hz. But in 3α -hydroxy-compounds, while the 4α -methyl groups give signals in the same range, the 4β -methyl signals appear further upfield, at 230—280 Hz. All the 3-hydroxy-compounds examined gave the



Eu(dpm)₃-induced shifts of methyl signals for 3-deacetylkhivorin (Ig) (0.11M-solution)

other methyl signals in the ranges 150—170 (C-8), 210—265 (C-10) and 105—140 Hz (C-13). The chemical shifts of the principal characteristic protons in some of the

TABLE 1
Assignment of n.m.r. signals (in Hz; 60 MHz spectra)

Compound	Substituents in (I)	Methyl positions					15-H	17-H	OAc	Furan H
		4 α	4 β	8	10	13				
(Ia)	3 α -OH-7 α -OAc-14,15-epoxy	49	49	63	56	74	210	335	126	380, 442
(Ib)	3 α -OH-7 α -OAc- Δ^{14}	50	50	69	57	74	339	296	118	384, 445
(Ic)	3 β -OH-7 α -OAc-14,15-epoxy	52	45	63	55	73	210	335	125	379, 443
(Id)	3 β -OH-7 α -OAc- Δ^{14}	54	47	75	56	69	339	296	118	385, 445
(Ie)	3 β ,7 α -(OAc) ₂ -14,15-epoxy	50	45	63	57	73	209	333	121, 125	378, 441
(If)	1 α ,3 α ,7 α -(OAc) ₃ -14,15-epoxy	48	55	64	60	74	211	335	120, 120, 128	378, 444
(Ig)	3 α -OH-1 α ,7 α -(OAc) ₂ -14,15-epoxy	55	51	64	60	73	210	334	123, 128	377, 442
(Ih)	1 α ,3 α ,7 β -(OAc) ₃ -14,15-epoxy	54	54	62	59	75	221	330	118, 121, 127	378, 443
(Ii)	7 β -OH-1 α ,3 α -(OAc) ₂ - Δ^{14}	56	56	74	69	60	420	299	118, 120	383, 445

TABLE 2
Chemical shifts (in Hz at 60 MHz) under the influence of Eu(dpm)₃ †

Compound (see Table 1)	Methyls					15-H	17-H	OAc	Furan H
	4 α	4 β	8	10	13				
(Ia)	502	275	167	231	131	298	378	182	393, 447
(Ib)	404	272	161	226	113	422	340	169	398, 455
(Ic)	481	513	156	244	109	272	368	147	394, 447
(Id)	510	550	167	263	113	404	343	159	404, 460
(Ie)	114	128	80	73	88	239	342	129, 141	378, 442
(If)	189	125	131	151	179	320	381	363, 388, 240	397, 453
(Ig)	462	236	151	214	138	281	375	89,* 170	395, 453
(Ih)	157	113	123	132	151	311	373	281, 340, 200	397, 458
(Ii)	96	83	143	131	106	550	361	212, 223	410, 466

* Upfield shift. † Molar ratio (reagent to substrate) = 1.

Ohochuku. Furthermore in compound (Ib) the values for the C-8 and C-13 methyl signals have been interchanged, as have those of the 4α - and 4β -methyl groups in 3-deacetylkhivorin (Ig).

The chemical shifts at a molar ratio (reagent to substrate) of 1 show certain regular features which may be useful in structural determination. For 3β -hydroxy-compounds the C-4 methyl signals appear in the range

meliacins under the influence of the reagent are summarised in Table 2.

Although a hydroxy-group when present in the molecule takes up most of the reagent and therefore dominates the induced shifts, a significant proportion of the reagent is simultaneously co-ordinated at other lone-pair centres.

² N. S. Ohochuku and D. A. H. Taylor, *J. Chem. Soc. (C)*, 1969, 864; 1970, 2396.

This may explain the relatively low shifts obtained for 3-deacetylkhivorin (Ig), on account of its three ester/lactone carbonyl groups. The low shifts [also observed for (Ii)] may be partly accounted for by steric factors which affect the concentration of the bulky reagent around the co-ordination site. We find that, in the absence of a hydroxy, aldehydic, or ketonic function, complexing at the ester carbonyl group does lead to considerable shifts. In khivorin for example, the acetoxy methyl signals suffer large downfield shifts of 268, 243, and 112 Hz, respectively. This could arise from reagent co-ordination on the ester carbonyl groups. Two of the ester signals suffer shifts each about twice that of the third, suggesting a mutual reinforcement of the effect of the complex on the two ester groups, which may therefore be the C-1 and C-3 acetoxy-groups. This is supported by the spectrum of compound (Ih).

The induced shifts have been shown to be governed by the equation of McConnell and Robertson:³ $\Delta H_i/H_p = K(3 \cos^2 \phi_i - 1)/r_i^3$,³ in which the angle term is usually considered to be of little importance. Consequently the induced shifts are expected to be dependent mainly on the distance of the proton from the europium atom and should be downfield. The expected downfield shift

was observed in nearly all the compounds examined. Surprisingly however, in 3-deacetylkhivorin (Ig), while all the other protons showed downfield shifts one of the acetoxy methyl signals suffered an upfield shift. To relieve steric interaction between the bulky reagent (co-ordinated at 3 α -OH) and the 1 α -OAc, the acetoxy-group might have adopted a conformation for which the angle term was sufficiently important to change the sign of the induced shift. Two other examples of compounds showing Shim downfield and upfield shifts have recently been reported.⁴

EXPERIMENTAL

The meliacins examined were either known natural products or known derivatives prepared by standard methods, and have been reported elsewhere. The spectra were recorded with a Varian A56/60 spectrometer at 60 MHz for solutions in [²H]chloroform with tetramethylsilane as internal standard. The solvent was dried over calcium chloride and calcium carbonate.

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³ H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, 1958, **29**, 1361.

⁴ P. H. Mazzochi, H. J. Tamburin, and G. R. Miller, *Tetrahedron Letters*, 1971, 1819; T. H. Siddall, *Chem. Comm.*, 1971, 452.