STRUCTURAL INVESTIGATION OF VALEPOTRIATES ON THE BASIS OF ¹H-LANTHANIDE-INDUCED SHIFTS

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The ester iridoids isolated from *Valeriana* plants known as valepotriates (1) are a pharmacologically important class of compounds and have been extensively studied by chemical and physical methods (2). A structural feature which sometimes still presents a problem is the location of the acyloxy substituents (acetoxy, isovaleroxy, etc.) at C-1, C-7, and C-11.

This problem cannot be solved by ¹H-nmr spectra as shown in earlier 60-100 MHz studies of some valepotriates (1-3) as well as by 250 MHz data (this work). Use of ¹³C-nmr spectroscopy can be helpful {carbonyl shift differences of ca. 0.4 ppm (4)} when a sufficient amount of pure compound is available. Detailed mass spectral studies (5) have shown that cims with isobutane and amines as reactant gases can also solve the problem.

In the present work a series of valepotriates (mostly of the diene type) have been studied by ¹H nmr at 250 MHz using lanthanide shift reagents in an attempt to correlate the induced shifts with the positions of the acyloxy substituents.

The ¹H-nmr spectral parameters of ten valepotriates (Table 1) deduced from their 250 MHz spectra as well as the lanthanide-induced shifts (LIS) obtained via successive addition of solid Eu(fod)₃ to the valepotriate solutions in CDCl₃ are collected in Table 2. The induced shifts for valtrate [4] and isovaltrate [5] are also presented graphically in Figure 1 **a,b**.

The presence of several oxygen coordination sites in the valepotriate molecules practically excludes any exact determination of the complex geometry. Nevertheless, an inspection of the LIS

data reveals several features that may be helpful for determination of the position of the acetoxy substituents in similar compounds. In the case of diene valepotriates [4-10], the largest LIS-values are observed for the protons closest to the acetoxy substituents: H-11, H-11' for compounds **4,6,8,9,10**; H-7 for **5**; H-11, H-11', and H-7 for **7**, which leads to the assumption that the favored site of complexation is the acetoxy group, probably on steric grounds. This conclusion is supported also by the LIS-data for the monoene valepotriate **3**. Judging from the LIS-values for H-7, H-11, and H-11' as well as for the acetoxy protons, Ac-11 is preferred as a complexation site in comparison of Ac-7 (compound **7**). Also Ac-11 is favored with respect to the acetoxy group in the 7-substituent (compound **8**). This result offers an easy way to determine the position of acetoxy groups in valepotriates of the diene type.

The LIS results for the 5-OH monoenes [1 and 2] were hampered by the large signal broadening at Eu(fod)₃/ substrate ratios larger than 0.1. Here also the shifts for H-7 bearing the AcO group are larger than those for the protons located at the other acyloxy substituents (H-1, H-11, and H-11'), although the favored complexation site for those compounds is probably the 5-OH group. The latter is indicated by the larger LIS-values for the protons, closer to this group, H-6' (presumably *cis* to OH) and H-9, as well as for the acetoxy protons in the complex 11-substituent as compared to the Ac-7 protons. It is known that the hydroxyl group is normally strongly preferred as a lanthanide complexation site in comparison to ester groups (6) as was observed for desacetylvaltrate (3).

TABLE 1.   Chemical Structures of Investigated Valepotriates

Valepotriate	R^1	R^5	R^7	R^{11}
Monoenes				

1 IVHD-valtrate	i-Val	OH	Ac	α-i-Val-O-i-Val
2 AHD-valtrate	i-Val	OH	Ac	α-Ac-O-i-Val
3 Didrovaltrate	i-Val	H	Ac	i-Val

Dienes

4 Valtrate	i-Val		i-Val	Ac
5 Isovaltrate	i-Val		Ac	i-Val
6 7-Homovaltrate	i-Val		β-Me-Val	Ac
7 DIA-valtrate	i-Val		Ac	Ac
8 Acevaltrate	i-Val		β-Ac-O-i-Val	Ac

Diene Halohydrines

| 9   8-Hydroxy-10-bromo-valtrate X=Br | i-Val | | i-Val | Ac |
| 10 8-Hydroxy-10-iodo-valtrate X=I | i-Val | | i-Val | Ac |

i-Val=COCH$_2$CH(CH$_3$)$_2$
Ac=CH$_3$CO
α-i-Val-O-i-Val=COCHCH(CH$_3$)$_2$
$\qquad\qquad$ OCOCH$_2$CH(CH$_3$)$_2$
β-Me-Val=COCH$_2$CH(CH$_3$)CH$_2$CH$_3$

α-Ac-O-i-Val=COCHCH(CH$_3$)$_2$
$\qquad\qquad$ OCOCH$_3$
β-Ac-O-i-Val=COCH$_2$C(CH$_3$)$_2$
$\qquad\qquad$ OCOCH$_3$

It was rather unexpected to observe that the presence of an OH group in the diene halohydrins **9** and **10** does not change the order of induced shifts observed for compounds **4-8** lacking such a group. This result may be due to steric hindrance at the OH group in **9** and **10**.

In conclusion, it can be stated that the use of [1]H-nmr lanthanide-induced shifts offers a convenient and reliable method for determination of the position of acetoxy substituents in newly isolated valepotriates and related compounds with uncertain location of acetoxy substituents. The method has the advantage of using small amounts of substance (2-4 mg) and the ease in obtaining and interpreting the LIS data.

EXPERIMENTAL

The [1]H-nmr spectra were measured on a Bruker WM-250 spectrometer at normal probe temperature using 5 mm tubes. The estimated

TABLE 2. ^{1}H-nmr Parameters and Lanthanide Induced Shifts (LIS)[a] for Valepotriates **1-10** (solutions in $CDCl_3$)

Chemical shifts (δ, ppm), coupl. constr. (Hz), in parenthesis and LIS (in italics)

Compounds	1	3	5	6	6'	7	9	10	10'	11	11'	Ac-7	Ac-11
1	6.07 (2.0) *2.64*	6.66 *2.35*		2.79 (7.0;13.0) *4.71*	1.99 (10.0;13.0) *2.54*	4.90 (10.0;7.0) *3.63*	2.91 (2.0) *4.69*	3.12 (5.0) *0.57*	2.84 (5.0) *0.35*	4.90 (12.5) *3.70*	4.73 (12.5) *2.50*	2.04 *0.43*	2.14[b] *2.05*
2	6.08 (2.0) *2.00*	6.67 *1.98*	2.97	2.80 (13.0;7.0) *4.33*	1.99 (13.0;10.0) *1.75*	4.87 (10.0;7.0) *3.96*	2.90 (2.0) *4.85*	3.12 (5.0) *0.40*	2.83 (5.0) *0.42*	4.90 (12.5) *2.61*	4.72 (12.5) *2.35*	2.04 *0.06*	2.07 *0.62*
3	5.84 (5.5) *0.76*	6.52 *0.39*	m *0.58*		[c]	4.95 (5.5) *1.38*	2.72 (5.5;8.0) *0.51*	4.69 (12.5) *1.25*	4.46 (12.5) *1.09*	3.07 (5.0) *0.62*	2.82 (5.0) *0.34*		2.07 *1.94*
4	5.99 (10.0) *1.41*	6.70 *0.89*		5.87 (3.0;3.0) *1.63*		5.38 (3.0) *2.12*	3.44 (10.0;3.0) *0.95*	3.05 (5.0) *1.24*	2.91 (5.0) *0.84*	4.74 (12.0) *2.23*	4.66 (12.0) *2.25*		2.07 *1.42*
5	5.98 (10.0) *0.94*	6.71 *0.55*		5.86 (2.5;2.5) *1.39*		5.36 (2.5) *2.19*	3.43 (10.0;2.5) *0.78*	3.05 (5.0) *1.31*	2.91 (5.0) *0.73*	4.77 (12.0) *1.40*	4.66 (12.0) *1.39*	2.06 *1.36*	2.08 *2.47*
6	5.98 (10.0) *0.87*	6.70 *0.64*		5.87 (2.5;3.0) *1.16*		5.38 (3.0) *1.46*	3.44 (2.5;10.0) *0.67*	3.03 (5.0) *0.89*	2.91 (5.0) *0.61*	4.74 (12.5) *1.66*	4.66 (12.5) *1.67*	2.07	2.06 *2.14*
7	5.98 (10.0) *1.52*	6.71 *1.10*		5.87 (3.0;2.5) *2.39*		5.37 (3.0) *2.70*	3.44 (2.6;10.0) *1.31*	3.05 (5.0) *1.86*	2.91 (5.0) *1.14*	4.74 (14.0) *2.92*	4.70 (14.0) *2.96*	2.07	2.06 *1.07*
8	5.98 (10.0) *0.69*	6.72 *0.50*		5.86 (2.5;2.5) *1.04*		5.38 (2.5) *1.04*	3.42 (10.0;2.5) *0.60*	3.03 (5.0) *0.68*	2.91 (5.0) *0.47*	4.75 (12.0) *1.40*	4.67 (12.0) *1.36*	1.97[b] *1.43*	2.01 *2.73*
9	6.24 (10.0) *0.42*	6.68 *0.47*		5.74 (2.5;3.0) *0.86*		5.37 (3.0) *0.50*	3.04 (10.0;2.5) *0.28*	3.90 (10.5) *0.13*	3.69 (10.5) *0.11*	4.73 (12.5) *1.15*	4.63 (12.5) *1.18*		
10	6.22 (10.0) *1.20*	6.66 *1.24*		5.75 (2.5;3.0) *2.45*		5.22 (3.0) *1.90*	3.16 (2.5;10.0) *0.99*	3.71 (10.0) *0.84*	3.55 (10.0) *0.67*	4.67 (12.5) *3.83*	4.60 (12.5) *3.46*		

[a] LIS extrapolated to Eu(fod)$_3$/substrate molar ratio 1:1
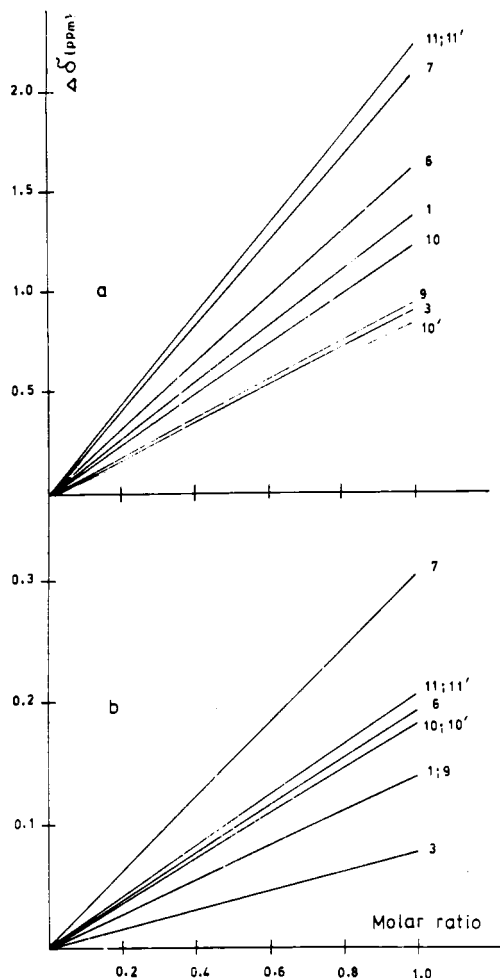[b] Ac group in the ester residue.
[c] Not observed due to overlap.

FIGURE 1.   Induced ^{1}H-nmr shifts for: (a) valtrate [**4**] and (b) isovaltrate [**5**] as a function of the Eu(fod)$_3$/
substrate molar ratio

accuracy of the chemical shifts and coupling con-
stants determination was 0.002 ppm and 0.5 Hz,
respectively.

The commercial shift reagent Eu(fod)$_3$ was
added in portions to the solution of valepotriate in
dry CDCl$_3$ (10^{-2}-5.10^{-2} molar), containing also
traces of TMS as internal standard. The maximal
molar ratio Eu(fod)$_3$/substrate used was 0.4 for
most compounds and 0.1 for **1** and **2**; excessive
line broadening was observed at higher ratios,
thus limiting the number of observations to 4 or
5. The induced shifts were plotted versus the
Eu(fod)$_3$/substrate ratio, and the extrapolated LIS
values for 1:1 ratio were calculated in the usual
way (6). The correlation coefficients obtained
were in the range 0.98-0.99, except for com-
pound **2** (0.92). For qualitative use of the
method, it would be sufficient to plot the induced
shifts versus weight of Eu(fod)$_3$ added.

The preparation and purification of the val-
epotriates **1-10** has been previously described (5).

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