CONFIGURATION OF SOME ALKALOIDS BY A CHIRAL NMR SHIFT REAGENT

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Abstract - The optically active lanthanide shift reagents was used to quickly solve the problem of configuration of some alkaloids. The S isomers give smaller induced shift than R isomers when the complex is formed with europium d-camphorate.

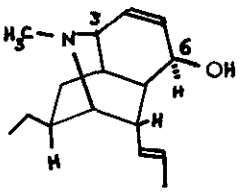
We report the use of Eu(facam)$_3$ — europium 3-trifluoracetyl d-camphorate — to find the absolute configuration of cannivonine b (1), (-) N-norlaudanosine (2) and N-methyl-1,2-dihydropapaverine (3). The structures of these bases and their relative configurations have been determined using shift reagents (1,2) as well as correlation through ozonolysis to a derivative of aspartic acid (3,4) (Table 1).

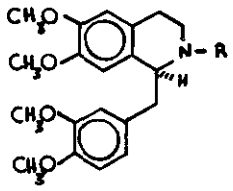
Amines and alcohols have been studied using chiral shift reagents because of their well-determined complexation site (on the lone pair) (5-8). A differential chemical shift of 0.5-0.7 ppm is observed for the CH-NH proton after addition of 0.5 mole of shift reagent, which is larger than for the corresponding alcohols. Application of optically active shift reagents is limited to the determination of configuration at centers near the complexation sites (9). However, the method does not permit direct identification of absolute configuration.

On the basis of our previous work (2) on compound 1, the centers C-3 and C-6 must have opposite configurations (3R, 6S or 3S, 6R). The 220-MHz NMR spectra of cannivonine b showed separation of the signals of the C-3 and C-6 protons. The H-3 signal (Table 1) has been split into two signals at δ 2.65 and 2.98 and the H-6 signal into two at δ 5.35 and 5.52. The corresponding integrated signals for the major enantiomer (4:1) were δ 2.98 and 5.35 and for the minor, δ 2.65 and 5.52. The major enantiomer, therefore, has a 3S, 6R configuration, since the H-6 has been shifted more and the H-3 less than the corresponding signals of the 3R, 6S isomer. This observation has been confirmed for two other alkaloids. Having

Table I

NMR of Selected Protons





			δ_0	δ_{LSR}*	
	1	H-6 (±)	4.20	5.35	5.52
		6S		5.35	
		6R			5.52
		H-3 (±)	2.15	2.65	2.98
		3S		2.65	
		3R			2.98
R=H	2	H-1 (±)	3.17	3.60	3.80
		1S		3.62	
		1R			3.78
R=CH$_3$	3	H-1 (±)	3.42	3.88	3.72
		1S	3.40	3.73	
		1R	3.38		3.90

* 0.25 M of Eu(facam)$_3$, 220 MHz, in $CDCl_3$, 10.0%

the separated isomers of laudanosine (2) and papaverine (3) we observed larger differential shifts $\Delta\delta_1$ for CH-N for the R-enantiomers (when complexed with a d-shift reagent) than for the S-enantiomers (8-10). The absolute configurations of the asymmetric centers of 2 and 3 have been successfully established by ozonolysis to L-asparaginate (3), by correlation to ushinsunine and crystallography (4). We have observed the same trend for several other pairs of tetrahydrocarboline and indolic alkaloids. However, the only suitable model for the cyclohexenol part of 1 was (-)-shikimic acid methyl ester. It has a 3R configuration and shows an H-3 signal after addition of 0.1 mole of Eu(facam)$_3$ at δ 4.92 (δ_0 4.40 $CDCl_3$), which confirmed our proposition for the cannivonine C-6 center (δ 4.72 for 3S configuration).

Our results suggest that prediction of induced shift for optical isomers is possible and the induced shift is smaller if compound S reacts with d-shift reagent (8.9). The theoretical calculations made with program SIMCON-2 on models of compounds 1-3 confirm this hypothesis. The relative slopes for α-to-nitrogen or oxygen R-protons are higher than for corresponding S-protons. The opposite trend for shift reagent-oxygen complexes has been observed by Mexican group (11) for

biphenyls, however these results are not supported by crystallographic data, the geometry involved is less rigid and the conformational equilibria is certainly in part responsible for the enanthiomeric shift difference.

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