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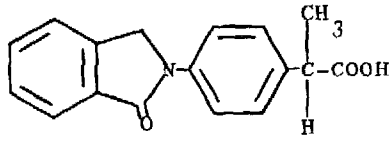
DETERMINATION OF ABSOLUTE CONFIGURATION OF THE DERIVATIVE FROM 2-[4-(1-oxo-2-isoindolinyl)-phenyl]-propionic acid AND R-(+)-1-phenylethylamine BY ^{1}H-NMR SPECTROSCOPY; USE OF SHIFT REAGENT WITH DIASTEREOISOMERIC AMIDES

Sergio DE MUNARI, Giuseppe MARAZZI, Angelo FORGIONE*, Antonio LONGO and Paolo LOMBARDI

Ricerca e Sviluppo Chimico, Farmitalia Carlo Erba S.p.A.
Via Imbonati 24, Milano, Italy

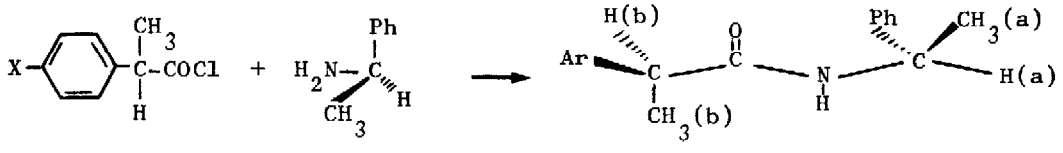
SUMMARY. The assignment of the S-(+), R-(-) absolute configuration of Indoprofene, an analgesic and anti-inflammatory drug, has been made via an NMR configurational correlation of diastereoisomeric phenylethylamides with the aid of Eu(fod)$_3$.

2-[4-(1-Oxo-2-isoindolinyl)-phenyl]-propionic acid (IPP) is an analgesic and anti-inflammatory agent, commercially known as Indoprofene. The chemistry[1], biological activity[2], presence and determination in body fluids[3,4] of this substance have been already reported.

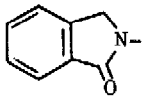


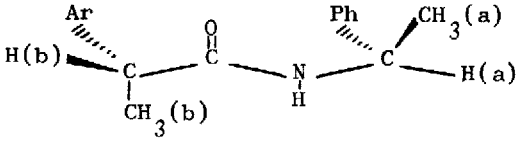
INDOPROFENE

In the present communication we establish the absolute configuration of each enantiomer of IPP[5] [R-(-), S-(+)] in two different ways: (a) by exploiting the phenomenon of the chemical shift non-equivalence of the three diastereoisomeric phenylethylamides 2, 3, 4, of known configuration[6] and of 5; (b) by measurement of the lanthanide induced shift (LIS) PMR values for the same amides, which have been prepared by coupling partially resolved α-phenylpropionic acid chlorides, suitably substituted in the *para* position, with excess of (R)-phenylethilamine 1.



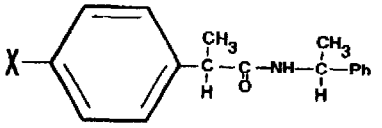
R,S 1 (S,R)

Substituent	Amides
X = H-	2
CH_3CONH-	3
NH_2-	4
	5



(R,R)

The PMR values for individual diastereoisomers are listed in Table 1 while Fig. 1 reproduces the characteristic pattern shown by the signals corresponding to CH_3(a) and H(b). The proton resonances for these substituents in one diastereoisomer appear in all the four spectra at lower field with respect to the values for the same groups in the alternative diastereoisomer. This same sense of non-equivalence observed for the amides (R,R)-2, (R,R)-3, (R,R)-4 and (-,R)-5 with a downfield CH_3(a) - downfield H(b) pattern, as well as for the amides (S,R)-2, (S,R)-3, (S,R)-4 and (+,R)-5 with upfield CH_3(a) - upfield H(b) pattern of signals[7] (Table 1, columns 3 and 5) suggests that IPP has the R-(-), S-(+) absolute configuration. Moreover, additional evidence arises from a regularity in the relative magnitude of the $Eu(fod)_3$ induced shift (LIS) values for the CH_3(a) signals observed in the alternate diastereoisomeric phenylethylamides. Table 1 (column 7) shows that the PMR signals for this substituent in the S,R series and in (+,R)-5 are shifted further downfield, with a given molar ratio, than in the R,R series and in (-,R)-5. Therefore there are two different and convergent correlations between the (+) and (-) 2-[4-(1-oxo-2-isoindolinyl)-phenyl]-propionic acid and, respectively, the S and R configurations of the three arylpropionic acids (X = H, CH_3CONH, NH_2), of known stereochemistry. In the first case we find positive chemical shift differences of the diastereotopic groups $\Delta\delta_{CH_3(a)}$ = 0.05 ppm and $\Delta\delta_{H(b)}$ = 0.05 ppm between the (-,R)-5 and (+,R)-5, in agreement with the same differences observed in the reference



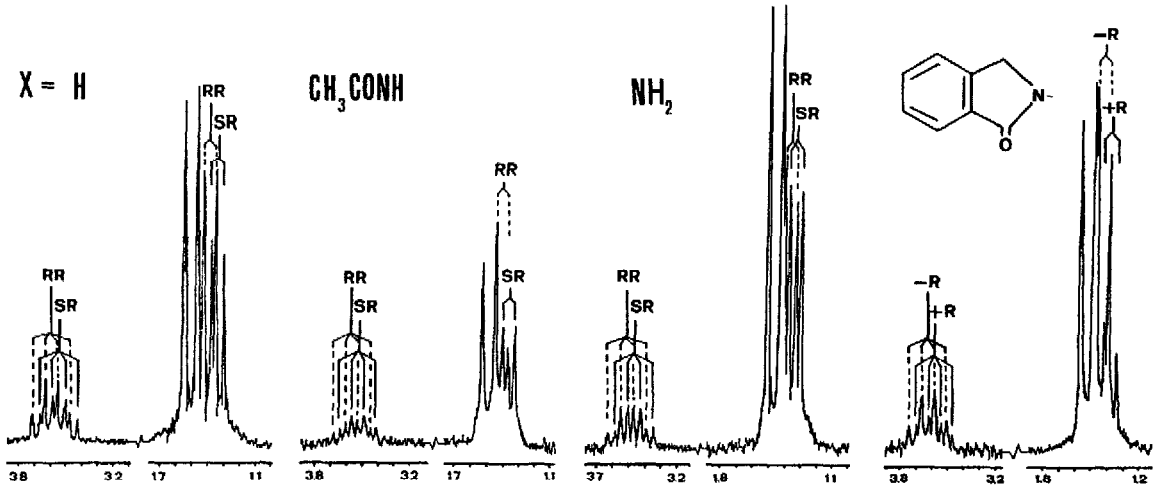


Figure 1. ^{1}H-NMR spectra, 90 MHz, of diastereoisomeric phenylethylamide mixtures. Resonances (ppm from TMS) of CH_3(a) and H(b) diastereotopic groups are reported.

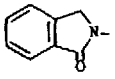
entry	substituent	$\delta_{CH_3(a)}$	$\Delta\delta_{CH_3(a)}$	$\delta_{H(b)}$	$\Delta\delta_{H(b)}$	LIS*	ΔLIS*	LIS* ratios	config. of acid moiety
2	H-	1.34	0.05	3.55	0.06	4.39	1.05	1.31	S
		1.39		3.61		3.34			R
3	CH_3CONH-	1.37	0.05	3.52	0.05	3.18	0.69	1.28	S
		1.42		3.57		2.49			R
4	NH_2-	1.34	0.03	3.47	0.05	4.13	1.05	1.34	S
		1.37		3.52		3.08			R
5		1.38	0.05	3.58	0.05	2.56	0.61	1.31	S
		1.43		3.63		1.95			R

Table 1. Chemical shifts (ppm from TMS) of diastereotopic groups CH_3(a) and H(b), and $LIS_{CH_3(a)}$ data in diastereoisomeric phenylethylamides.

* LIS = lanthanide induced shift of CH_3(a) proton resonance when molar ratio $\frac{Eu(fod)_3}{substrate} = 1$

$\Delta LIS = LIS_{S,R} - LIS_{R,R}$ or $LIS_{+,R} - LIS_{-,R}$

LIS ratio = $LIS_{S,R}/LIS_{R,R}$ or $LIS_{+,R}/LIS_{-,R}$

diastereoisomeric amides (Table 1, columns 4 and 6) between the R,R and S,R configurations. These small chemical shift differences find consistency, in the second case, on the $LIS_{CH_3(a)}$ values, $\Delta LIS_{CH_3(a)}$ and LIS ratios (Table 1, columns 7, 8, 9). The magnitude of the LIS for the $CH_3(a)$ group of the phenylethylamides of (+)-IPP is larger than that of (-)-IPP: this behaviour is consistent with the change from the S to the R configuration in the acid moiety of the reference compounds.

However, the lanthanide chemical shift reagent $Eu(fod)_3$ causes a dramatic separation of proton signals for the $CH_3(b)$, H(a) and H(b) of diastereoisomeric phenylethylamides; we shall rationalize these empirically correlated data in terms of a proposed configurational correlation model in a subsequent paper.

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References and footnotes

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