HETEROCYCLES, Vol. 20, No. 4, 1983

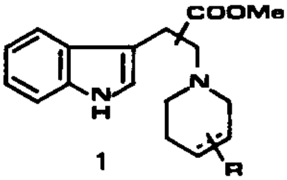
NMR SPECTROSCOPIC STUDIES OF TRYPTOPHAN DERIVATIVES

Ari Koskinen, Pekka Somersalo and Mauri Lounasmaa*

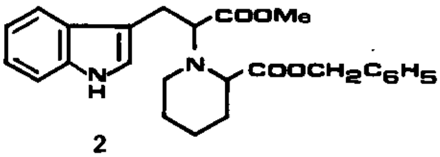
Technical University of Helsinki, Department of Chemistry,
SF-02150 Espoo 15, Finland

Abstract - Proton and carbon-13 nuclear magnetic resonance spectra of some tryptophan derivatives are reported along with their analysis. The spectral parameters reveal new sensitive probes for structure elucidation of indole alkaloids.

In a purely synthetical context[1] we required a facile method for the identification of different structural isomers of ß-indolylethylpiperidine derivatives of the type 1. Since compounds of this type have not previously been aptly characterised by nuclear magnetic resonance, we became interested in studying their NMR spectral characteristics.



1

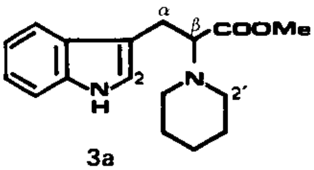


2

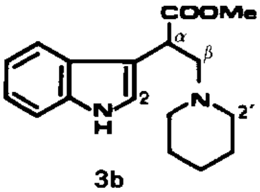
Our studies proved extremely fruitful yielding new information not only on the compounds studied *per se* but also on some new and characteristic sensitive probes for studying the substitution patterns in various indole alkaloids.

^{1}H NMR Spectroscopy

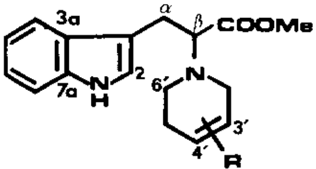
The only reported ^{1}H NMR spectrum for compounds of the type **1** was in a recent publication by Rapoport[2] for compound **2**. Even this paper, however, left the NMR shifts unassigned in implicit form. Comparison of the ^{1}H NMR spectra of **3a**, **4a** and **5a** with those of **3b**, **4b** and **5b** presented in Table 1, respectively, reveal that:



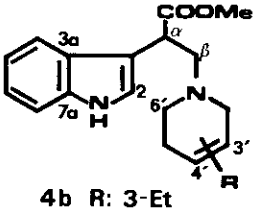
3a



3b



4a R: 3-Et
5a 4-Me



4b R: 3-Et
5b 4-Me

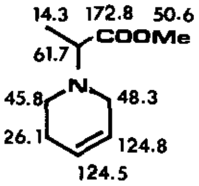
TABLE 1. ^{1}H NMR data of compounds 3 - 5.

	3a	4a	5a	3b		4b		5b	
H-α	3.15 m	3.15 m	3.19 m	4.23 dd	4.4 Hz 10.0 Hz	4.29 dd	4.0 Hz 9.6 Hz	4.26 dd	4.4 Hz 9.8 Hz
COOC$\underline{H}_3$	3.44 s	3.54 s	3.52 s	3.54 s		3.56 s		3.62 s	
H-β	3.55 m	3.60 m	3.55 m	2.63 dd	4.4 Hz 12.0 Hz	2.60 dd	4.0 Hz		
				3.27 dd	10.0 Hz 12.0 Hz			3.29 dd	9.8 Hz
H-2	6.84 d	6.97 d	6.96 d	6.95 d		7.00 s		7.06 d	
N-H	8.55 br s	8.23 br s	8.22 br s	8.90 br s		8.88 br s		8.79 br s	

- the indolic N-H absorbs at lower field in the b series indicating increased acidity of the proton. The high-field shift of the a series is explained by *the enhanced possibility of hydrogen bonding between the indole N-H and* the carbomethoxy group. In the b series, such hydrogen bonding is prohibited on steric grounds.
- the ester methyl signal is shifted to higher field in the a series as compared to the b series manifesting a larger effect due to the anisotropic ring current of the aromatic indole nucleus. This observation is comprehensible on the same reasoning as the previous item.
- the H-2 of the indole unit exhibits sharper doublet fine structure or even singlet (**3b**) in the **b** series. This phenomenon is explained by the diminished four-bond H-C=C-C-H coupling: The ester carbonyl tends to align the C=O π-bond nearly in the plane of the aromatic system causing the α-hydrogen to be displaced farther from the plane. This results in the diminution of the $^4J_{HH}$ which is a function of $\cos^2\Theta$ (Θ = the torsion angle between the π-system and the axis of the C-H bond).[3]
- in the a series, H-ß, i.e. the proton α to the ester unit, resonates at δ3.55 with its fine structure partially hidden under the ester methyl signal. The H-α protons resonate at δ 3.15 and are virtually undifferentiated.
- the clearest distinction between the a and b series can be made on the observation of the signal due to H-α in the b series at lower field approximately at δ 4.25 with three bond $^3J_{HH}$ coupling constants 4 Hz and 10 Hz to the ß-hydrogens at approximately δ 2.60 and δ 3.30.

^{13}C NMR Spectra

Peak assigments are based on chemical shift correlation[4] and SFORD spectra recorded to reveal the multiplicities of the signals. The indole carbon resonances were assigned based on established literature data[5], and the piperidine carbons were identified by the use of model compounds[6]. For the tetrahydropyridine derivative 6, the carbons 2 and 6 were differentiated by the endocyclic homoallyl effect[7] exhibited by C-6.



6

The ^{13}C NMR spectra of the compounds **3a**, **4a**, **5a**, **3b**, **4b** and **5b** are presented in Table 2.

TABLE 2. ^{13}C NMR spectral assignments.

C	**3a**	**3b**	Δδ	**4a**	**4b**	Δδ	**5a**	**5b**	Δδ
2	122.5	122.1	−0.4	122.6	122.4	−0.2	122.6	122.3	−0.3
3	111.9	111.7	−0.2	111.6	111.6	0	111.6	111.9	+0.3
3a	127.1	126.2	−0.9	127.3	126.2	−1.1	127.3	126.3	−1.0
4	118.2	118.6	+0.4	118.5	118.6	+0.1	118.5	118.8	+0.3
5	118.7	119.3	+0.3	119.1	119.3	+0.2	119.1	119.4	+0.3
6	121.3	121.8	+0.5	121.7	121.9	+0.2	121.7	121.9	+0.2
7	111.2	111.3	+0.1	111.1	111.4	+0.3	111.0	111.4	+0.4
7a	135.8	136.0	+0.2	136.0	136.1	+0.1	136.0	136.1	+0.1
α	24.8	41.0	+16.2	26.3	41.2	+14.9	25.2	41.2	+16.0
β	69.2	61.7	−7.5	68.3	60.6	−7.7	68.2	60.5	−7.7
2'	50.8	54.5	+3.7	52.1	55.6	+3.5	49.0	52.5	+3.5
3'	26.0	25.8	−0.2	137.8	137.3	+0.5	125.2	124.7	−0.5
4'	24.2	24.2	0	117.5	117.5	0	132.6	132.5	−0.1
5'	26.0	25.8	−0.2	27.7	27.7	0	31.2	30.3	−0.9
6'	50.8	54.5	+3.7	46.7	49.9	+3.2	46.7	50.2	+3.5
$\underline{C}OOCH_3$	172.2	174.8	+2.6	172.3	174.7	+2.4	172.3	174.5	+2.2
$COO\underline{C}H_3$	50.6	51.7	+1.1	50.9	51.8	+0.9	51.0	51.9	+0.9
$3'-\underline{C}H_2-CH_3$	-	-	-	25.3	25.3	0	-	-	-
$3'-CH_2-\underline{C}H_3$	-	-	-	12.1	12.0	−0.1	-	-	-
$4'-\underline{C}H_3$	-	-	-	-	-	-	22.9	22.9	0

- The resonances of the indole nucleus remain nearly independent of the substitution in the side chain. Carbons 2 and 3a make an exception, however, in being shifted to higher field in the **b** series as compared to the **a** series. The effect is less diagnostic for C-2 but the observed Δδ ≈ − 1 ppm for C-3a.
- In the **b** series, the chemical shift of the ester carbonyl is shifted 2.5 ppm to lower field and the ester methyl 1.0 ppm to lower field. These effects are also taken as the manifestation of the aromatic ring current effect (vide supra).

- Disregarding the effects on the multiplicities of the signals due to C-α and C-ß, the most dramatic effect is observed in the heterocyclic carbons α to the non-indolic nitrogen, i.e. C-2' and C-6' equalling $\Delta\delta \approx +3.5$ ppm. This effect is attributable to the release of steric congestion caused by the carbomethoxy group in the members of the **a** series[4].
- Changing from the **a** series to the **b** series also affects the side chain carbons C-α and C-ß in a regular manner. A paramagnetic shift of 15-16 ppm is observed for C-α, as one would expect from simple considerations of α and ß-effects [4]. On the other hand, the observed shift of C-ß ($\Delta\delta \approx -7.5$ ppm) is nearly 9 ppm units smaller than one might expect. This is, however, easily apprehended by considering the added γ-effects in the **a** series.

EXPERIMENTAL

The NMR spectra were recorded at r.t. on a Jeol JNM-FX 60 spectrometer operating at 15.04 MHz in Fourier transform mode. The resonances were measured downfield (δ) from the internal standard TMS (δ 0.00) in approximately 0.5 M $CDCl_3$ solutions. For ^{13}C NMR spectra, 10000 scans of 4 kHz were accumulated with 8 k data points (FID) using 5 μsec pulse width (9 μsec ≙ 90° pulse) and 1.50 sec pulse repetition time. The data were processed using Fourier self-convolution[8] to increase resolution.

REFERENCES

1. A. Koskinen, P. Somersalo and M. Lounasmaa, to be published.
2. J.E. Johansen, B.D. Christie and H. Rapoport, J. Org. Chem., 1981, **46**, 4914.
3. H. Günther, NMR spectroscopy, John Wiley and Sons, New York, 1980.
4. F.W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden and Son Ltd., London, 1978.
5. M. Shamma and D.M. Hindenlang, Carbon-13 NMR Shift Assignments of Amines and Alkaloids, Plenum Press, New York, 1979.
6. M. Lounasmaa and A. Koskinen, Tetrahedron Lett., 1982, **23**, 349.
7. E. Wenkert, D.W. Cochran, E.W. Hagaman, F.M. Schell, N. Neuss, A.S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H.Mehrli, J. Poisson, N. Kunesch and Y. Rolland, J. Am. Chem. Soc., 1973, **95**, 4990.
8. J.K. Kauppinen, D.J. Moffatt, D.G. Cameron and H.H. Mantsch, Appl. Opt., 1981, **20**, 1866.

Received, 24th November, 1982