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¹H and C-13 Nuclear Magnetic Resonance of Tiaprofenic Acid

Said E. Ibrahim^{ab}; Mahmoud H. A. Hassan^a

^a Medicinal, Aromatic and Poisonous Plants, Research Centre, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia ^b Department of Research and Quality Control, Egypt. Int. Pharm. Indust. Co, Cairo, Egypt

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¹H- AND C-13 NUCLEAR MAGNETIC RESONANCE
OF TIAPROFENIC ACID

SAID E. IBRAHIM* and MAHMOUD M.A. HASSAN

Medicinal, Aromatic and Poisonous Plants, Research Centre,
College of Pharmacy, King Saud University,
Riyadh-11451 (Saudi Arabia)

Key Word Index - ¹H-NMR of tiaprofenic acid; proton chemical shifts of tiaprofenic acid; ¹³C-NMR of tiaprofenic acid; carbon chemical shifts of tiaprofenic acid.

Abstract - ¹H-NMR spectrum of tiaprofenic acid in CDCl₃ was obtained and proton chemical shifts from tetramethylsilane were assigned to each proton and set of equivalent protons of the molecule. The hydroxy proton of the carboxylic acid group was confirmed by deuterium exchange. The natural abundance C-13 nuclear magnetic resonance spectrum of the compound in CDCl₃ was recorded using Fourier transform technique. The chemical shifts of carbon resonances have been assigned on the basis of the chemical shift additivity theory and the signal multiplicity observed in the single frequency off-resonance decoupled (SFORD) spectrum. Also comparison with carbon chemical shifts of model compounds were useful.

INTRODUCTION

Tiaprofenic acid (I), α -(5-benzoyl-2-thienyl)propionic acid is new anti-inflammatory and analgesic drug with a marked therapeutic effect (1-3). Literature review has revealed the absence of any data regarding its spectral characteristics particularly the ¹H- and C-13 NMR spectral data. So, it was of interest to study its nuclear magnetic resonance spectra and to assign chemical shifts for its protons and carbons to make such data available. Confirmation of its structure as

*Present address: Department of Research and Quality Control, Egypt.
Int. Pharm. Indust. Co, Cairo (Egypt)

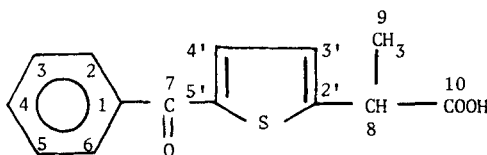
well as chemical shift additivity for disubstituted aromatics will be achieved. The PMR and C-13 NMR spectra are specific means for identification of tiaprofenic acid.

EXPERIMENTAL

^1H -NMR spectra of tiaprofenic acid in CDCl_3 and after deuterium exchange using tetramethylsilane as a reference standard were recorded on a Varian T60-A-60 MHz NMR spectrometer. Proton noise decoupled and single frequency off-resonance decoupled (SFORD) C-13 NMR spectra were recorded on a Varian FT-80A-80 MHz spectrometer operating at 20.00 MHz. The sample was prepared in 10 mm o.d. tubes in approximately 10% solution in CDCl_3 with tetramethylsilane as internal reference. Spectra were recorded with 8K data points at a probe temperature of 23°C . For an average spectral width of 5000 Hz, a 10 μs pulse width corresponding to a tilt angle of 30° was employed with 2S interval between pulses.

RESULTS AND DISCUSSION

The ^1H -NMR spectrum of tiaprofenic acid in CDCl_3 using tetramethylsilane as internal reference shows a α -methyl doublet centred at 1.6 ppm, a CH-methene quartet at 4.11 ppm, an aromatic five protons multiplet (for benzoyl moiety) at 7.70 - 7.43 ppm and two thiophene protons at 7.77, 6.97 ppm (doublet) for H-3' and H-4' respectively. This agrees with that found for thiophene protons in 2-thiophene carboxaldehyde (4). The hydroxyl proton of the carboxylic acid group shows up at 11.33 ppm which disappeared on deuterium exchange.



I

Table 1. Carbon Chemical Shifts of Tiaprofenic Acid.

Carbon No.	Chemical Shift δ ppm	multiplicity
C-1	137.75	s
C-2	129.07	d
C-3	128.40	d
C-4	132.31	d
C-5	128.40	d
C-6	129.07	d
C-7	188.25	s
C-9	18.44	q
C-10	177.91	s
C-2'	142.21	s
C-3'	135.14	d
C-4'	126.53	d
C-5'	152.03	s

s = singlet; d = doublet; q = quartet.

The carbon chemical shifts for tiaprofenic acid are shown in Table 1. The carbon resonances have been assigned in accordance with:

- A) Chemical shift considerations (5), particularly about substituent effects in benzene series (6).
- B) Signal multiplicities determined from off-resonance decoupling.
- C) Peak intensities.
- D) Comparison of the carbon chemical shifts of structurally related model compounds such as benzoyl chloride, benzophenone, acetophenone, thiophene and thiophen 2-carboxaldehyde.

The assignment of the carbon chemical shifts of the benzene ring were based on the chemical shift additivity rules for monosubstituted benzenes (7-10). Thus the effect of $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-Ph}$ function on C-1, C-2, C-3 and C-4 of benzene was considered knowing that benzene and thiophene are isoteres.

	C-1	C-2	C-3	C-4
Calculated:	137.90	130.20	128.30	132.10
Found :	137.75	129.07	128.40	132.31

The calculated chemical shift values are in good agreement with that found for the benzene ring. However, applying the same rules for assigning the carbon resonances of the thiophene ring system C-2', C-3', C-4' and C-5', the calculated values were not in agreement with that found. This is expected because of the effect of the C-2' substituent. Also the carbonyl group shielding effect in 2-thiophene carboxaldehyde is more than that in case of benzaldehyde (11,12) (Table 2).

However, the carbon chemical shift values found for thiophene ring system in tiaprofenic acid are more than that anticipated from a 2-carbonyl substituent. This could be attributed the 2'-side chain substituent and the effect of the benzoyl function in the 5- position. The found and the calculated carbon chemical shifts and the difference (Δ) are shown in Table 3.

These differences (Δ) could be considered as the net effect of both the 2'- α -propionic acid side chain and the 5'-benzoyl function.

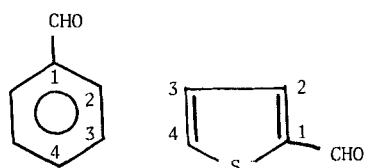
Regarding the α -propionic acid side chain substituent, the α -carbon (C-8) would suffer the effect of the β -carbon (C-9) and the internal carboxylic function (C-10). The carbon chemical shift would be:

$$16.3 + 9.4 + 16.0 = 41.7$$

This is in agreement with the found value for C-8 which is 41.30.

For the methyl function (C-9) which would suffer the effect of both

Table 2. Shielding Effect of the Carbonyl Group in Benzene and Thiophene.



Compound	Carbon No.			
	C-1	C-2	C-3	C-4
Benzaldehyde	+ 8.6	+ 1.3	+ 0.6	+ 5.5
2-Thiophene carboxaldehyde	+19.00	+10.20	+ 1.9	+10.20

Table 3. Incremental Shifts of the Aromatic Carbon Atoms of Disubstituted Thiophene.

	C-2'	C-3'	C-4'	C-5'
Found	142.21	135.14	126.53	152.03
Calculated	134.90	136.70	128.40	143.70
Difference (Δ)	+ 7.31	- 1.56	- 1.87	+ 8.33

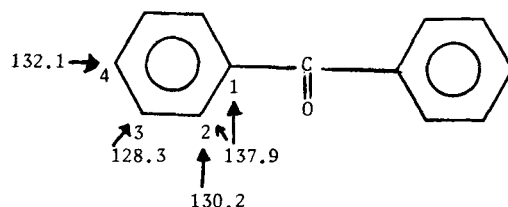
the -CH and -COOH functions, the calculated carbon chemical shift is:

$$15.8 + 3 = 18.30$$

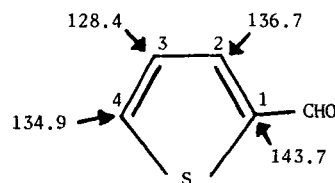
This is in good agreement with the found value for C-9 (CH_3) which is 18.44.

Regarding the carbon resonances of C-7 and C-10 carbonyl functions, the found values are in agreement with the reported ones.

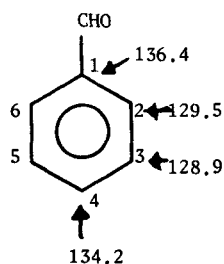
The data derived in this study could be very useful in studying the carbon chemical shifts of similar compounds.



Benzophenone



2-Thiophene carboxaldehyde



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